

Towards Stereocontrol in Radical Polymerization

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**Australian
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University**

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Declaration

This thesis presents my own original work, and, to the best of my knowledge, contains no material written or published by any other person, except where due reference has been made. This work has not been previously submitted for any other degree or diploma at any university or institution.

A handwritten signature in black ink, reading "Benjamin Noble". The signature is written in a cursive style with a large, stylized initial 'B'.

Benjamin Brock Noble

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“The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are completely known, the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.”

— Paul Dirac

Abstract

Despite over 50 years of research, control of the stereochemistry in free-radical polymerization using simple and scalable methods remains elusive for most common monomers. An attractive strategy, which has received considerable attention, is the use of Lewis acids to coordinate and constrain the terminal and penultimate side-chains of the growing polymer radical. Unfortunately, the control achieved to date usually is modest at best. In this work, a combination of theory and experiment has been used to explore why current methods are not optimal, with a view to designing better control strategies. In the course of this work, the dramatic effects of Lewis acids on other radical processes, such as photoinitiation, were also explored, along with other aspects of control in radical polymerization. The main findings of this work are as follows.

Theoretical calculations revealed that a key problem with current Lewis acid-based control agents is their binding selectivity. Even when they bind the terminal and penultimate side-chains selectively, this binding mode stabilizes and deactivates the propagating radical. Moreover, it was found that a non-stereocontrolling terminal-monomer binding mode catalyses propagation and dominates the reaction. This propagation catalysis, which is useful in its own right, was confirmed experimentally using pulsed laser polymerization. On this basis, a better control strategy, targeting simultaneous binding of the monomer, terminal and penultimate side-chains, was proposed. Indeed, a further theoretical examination of methacrylic acids salts established that the reasonably high isospecificity reported results from the formation of bridging scaffolds. The use of methacrylic salts as ionic auxiliaries is suggested as one potential route to isotactic polymer, and an improved method for the conversion of calcium methylate to poly(methyl methacrylate) was designed for this purpose.

Among the other important findings of this work was the discovery of dramatic effects of Lewis acids on photoinitiators. While these effects hampered pulsed laser polymerization experiments with strong Lewis acids, strategies for avoiding them were devised. While the effects of Lewis acids on photoinitiation were shown to be very complex, the results presented raise the exciting prospect of a simple route to visible light photoinitiation. Lewis acid/ base interactions were also shown to have dramatic effects on the redox activity of surface tethered nitroxide radicals, work that lays a basis for ongoing research on the use of electric fields to control nitroxide mediated polymerization.

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1. Why is Stereocontrol the “*Holy Grail*” of Radical Polymerization?

1.1 Prologue

The objective of synthetic chemistry is to precisely construct complex molecular species, while maximizing the yield, step-efficiency, cost-effectiveness and safety of the requisite procedures. The aim of polymer synthesis is to assemble macromolecules with carefully tailored microstructures, so that specific bulk-properties (i.e. those that maximize utility for a given application) can be targeted. Over the last century, synthetic polymers have become both ubiquitous and indispensable; finding a diverse range of applications from generic construction and packaging materials to customizable highly specialized drug-delivery systems,¹⁻⁴ biosensors⁵ and artificial muscles.⁶ Much current research has focused on the synthesis and applications of stimuli sensitive ‘smart polymers’, which can respond to externally induced physical or (bio)chemical stimuli.⁷⁻⁹ Smart polymers have found applications ranging from medicine¹⁻⁵ (in drug/protein-delivery systems and diagnostic sensors) to high-performance engineering^{10, 11} (in self-healing coatings and actuators). Many of the other potential applications of these innovative materials have yet to be realized.

Only a few decades ago, many synthetic chemists viewed radicals with apprehension and disdain. Generally, chemists believed radicals were ‘too reactive’ to have much synthetic utility and their reactions were considered to be “*messy, unpredictable, unpromising and essentially mysterious*”.¹² Consistent with this perception, standard free-radical polymerization offers very limited control over the microstructure of the resultant polymer; with poor control of the chain-end functionality (because of irreversible termination by combination and disproportionation), very broad molecular weight distributions (typically $\bar{D} > 2$) and no tacticity regulation (usually only atactic polymer is obtainable). Despite these significant deficiencies, radical-based polymerizations are generally favoured by industry because of their robust nature and high functional group compatibility. Radical polymerization is undoubtedly the most broadly applicable chain polymerization process, as the neutral propagating radical species is able to polymerize both nucleophilic and electrophilic monomers. Additionally, the insensitivity of radicals to a diverse array of chemical functionality makes radical polymerization remarkably tolerant of reagent/solvent impurities. Radical polymerization can also be performed under relatively mild conditions and employs initiators that are significantly less hazardous than those used anionic and coordination polymerization.

Because of these characteristics, standard free-radical polymerization was viewed as a convenient route to high-volume commodity plastics but seen as inappropriate for precision polymer synthesis, where significantly more structural control is required (see **Figure 1** for a detailed comparison).

Over the last few decades, synthetic polymer chemistry has been revolutionized by the discovery and subsequent development of ‘living’ radical polymerization; including most notably, atom-transfer radical polymerization (ATRP),¹³⁻¹⁵ nitroxide-mediated polymerization (NMP)¹⁶⁻¹⁸ and reversible addition-fragmentation chain-transfer (RAFT)¹⁹⁻²⁵ polymerization. Living-radical methodologies have overcome many of the supposed limitations of radical-based polymerizations, and so redefined their scope and utility. These methodologies can be used to synthesize polymers with a narrow molecular distribution ($\bar{D} \sim 1.1$) and offer precise chain-end control. Moreover, these chain-ends are ‘living’ towards further polymerization and can be extended to construct block copolymers and/or grafted into novel topologies.^{26, 27} The synthesis of highly complex molecular architectures by radical-based polymerization, which was thought to be impossible, is now highly practical.^{26, 27} As the propagating species in living-radical polymerization is radically-based, it retains all the advantages of conventional free-radical polymerization (see **Figure 1**), such as a remarkable tolerance of different chemical functionalities.²⁸ Unfortunately, the reversible deactivation-activation reactions utilized in living-radical polymerization have no effect on stereospecificity, which is poorly regulated in most monomer systems.

Free-Radical	Living-Radical	Ionic and Coordination
✓ Suitable for a wide variety of monomers. ✓ Initiators are easily handled and reasonably oxygen/moisture stable. ✓ Compatible with various additives (fairly insensitive to impurities). ✗ Broad molecular weight distribution ($\bar{D} > 2$). ✗ No effective chain-end control. ✗ No effective stereocontrol.	✓ Suitable for a wide variety of monomers. ✓ Initiators are easily handled and reasonably oxygen/moisture stable. ✓ Compatible with various additives (fairly insensitive to impurities). ✓ Narrow molecular weight distribution ($\bar{D} \sim 1.1$). ✓ Precise chain-end control (highly customizable). ✗ No effective stereocontrol.	✗ Incompatible with some (polar) monomers. ✗ Initiators are usually pyrophoric and highly moisture sensitive. ✗ Demands very high purity (up to ppb) reagents and solvents. ✓ Narrow molecular weight distribution ($\bar{D} \rightarrow 1.0$). ✓ Precise chain-end control (highly customizable). ✓ Precise stereocontrol.

Figure 1 The advantages and disadvantages of various chain polymerization methodologies.

1.2 Introduction and background

Polymer tacticity (or stereochemistry) is the relative configuration of adjacent stereocentres along the macromolecular C–C backbone, or equivalently, the relative orientation of adjacent side-chains with respect to this backbone (see **Figure 2**). Tacticity has a very significant influence on a polymer's physical properties; including (but not limited to) its melting point, mechanical strength, solubility, thermal stability and crystallinity. Consequently, tacticity control has been described by one of the codevelopers of RAFT, as the “*holy grail*” of radical polymerization.²⁹ Moreover, tacticity also has a significant effect on many polymeric structural changes that are often exploited in ‘smart’ polymer systems. For instance, poly(*N*-isopropylacrylamide) is of significant interest in drug delivery and its phase-transition behaviour is strongly dependent on tacticity; with isotactic-rich polymer having a significantly lower coil-to-globule transition temperature (17 °C) than the atactic polymer (31 °C).³⁰ Other important properties of poly(*N*-isopropylacrylamide), including its solubility, glass-transition temperature, thermal stability and solution-phase viscosity also have a notable tacticity dependence.³¹⁻³⁸

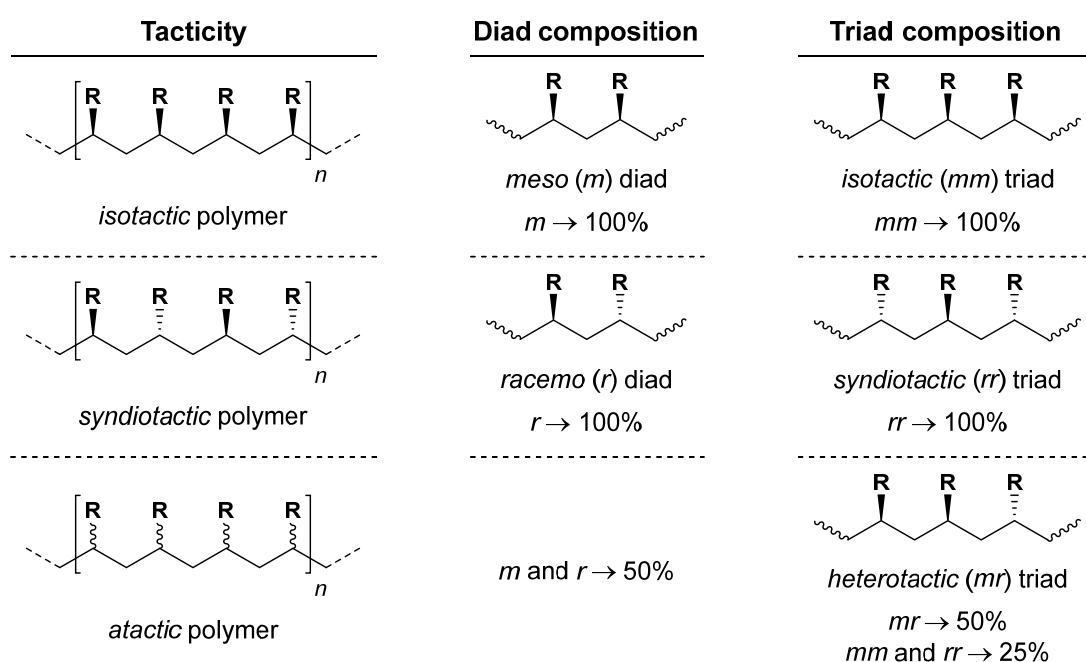


Figure 2 *Isotactic*, *syndiotactic* and *atactic* polymer derived from a mono-substituted alkene of the general form, $\text{H}_2\text{C}=\text{CHR}$. The component diad and triad structures, and respective compositions of each stereoconfiguration are also shown.

While tacticity control is a prized goal in the radical polymerization field, it has proven to be an enormously challenging endeavour. The first attempts to control tacticity in radical polymerization date from the 1960s and despite over 50 years of pioneering and innovative research, the level of stereocontrol currently obtainable in most monomer systems is fairly limited; particularly in comparison to the near perfect control achieved in ionic and coordination polymerizations.³⁹ Indeed, as Satoh and Kamigaito noted in their excellent and comprehensive 2009 review “*stereocontrol in radical polymerization has not reached satisfactory levels for applications to other areas*”.³⁹ With the development of highly versatile and efficient living-radical methodologies, sub-optimal stereocontrol has become the last remaining disadvantage of radical-based polymerization. Many important monomers, perhaps most notably NH-substituted (meth)acrylamides and (meth)acrylic acid, cannot be polymerized directly by non-radical chain processes, so the development of effective tacticity regulation is of particular importance for these systems.

From a mechanistic perspective, regulation of tacticity in radical polymerization is a daunting problem. Indeed, in 1976 Pino and Suter noted that “*the perspectives for stereocontrol in free radical polymerization are not very promising*”.⁴⁰ In radical polymerization, the planar (sp^2 hybridized) propagating polymer radical is pro-chiral and its stereochemistry is determined during monomer addition. In contrast to the highly regulated environments found at the polymer terminus in an anionic or coordination polymerization, the flexible radical terminus does not usually discriminate (significantly) between *meso* and *racemo* forms of propagation. Many pioneering researchers have explored a diverse array of different stereocontrol strategies in radical polymerization over the last 50 years. Some strategies attempt to exploit interactions between the pendant side-chains of the polymer terminus and added stereocontrol agents, while others modify the inherent chemical structure of the monomer (prior to polymerization) or confine the propagating polymer chains to the surface of (or within) specialized structures. The strategies can be loosely categorized as indicated in **Figure 3**. For a more compressive account of each strategy the reader is directed to Satoh and Kamigaito’s excellent 2009 review.³⁹

Confinement Techniques	Monomer Modification	Chemical Additives
☒ Organic frameworks (urea crystals, cyclodextrins etc.). ☒ Stereoregular polymer templates. ☒ Inorganic frameworks (zeolites). ☒ Metal-organic frameworks (MOFs).	☒ Bulky auxiliaries. ☒ Chiral auxiliaries. ☒ Ionic auxiliaries. ☒ Self-assembling auxiliaries. ☒ Multiple H-bonding auxiliaries.	☒ Lewis acids. ☒ Bulky polar solvents. ☒ Chiral living radical polymerization agents (chiral nitroxides and ATRP complexes). ☒ π -stacking solvents. ☒ Ionic liquids.

Figure 3 The different strategies that have been employed in an attempt to control tacticity in radical polymerization. The successful manipulation of tacticity is denoted with ☒, while ☒ indicates no significant (or a very limited) effect on stereochemistry has been observed using this strategy.

It is worth noting that some of the strategies listed in **Figure 3** have been found to be remarkably effective. For instance, *isotactic-rich* poly(acrylonitrile) ($mm = 87\%$) can be synthesized by confining acrylonitrile within the channels of crystalline urea.⁴¹ Moreover, highly *syndiotactic* poly(methyl methacrylate) ($rr = 97\%$) can be synthesized using *isotactic* poly(methyl methacrylate) ($mm = 96\%$) as a template.⁴²⁻⁴⁴ The problem with confinement and templating strategies, aside from their fairly limited scope, is their impracticality. Monomer must first be included within, or on the surface of, the host clathrate/polymer template and then the resultant polymer must be subsequently removed and recovered following the polymerization. Depending on the host and guest system, isolation of the resultant polymer may be facile or quite challenging. Regardless, these extra confinement and recovery steps somewhat negate the usual advantages of radical-based polymerization. Given practicality considerations and the additional requirement that stereocontrol be compatible with existing living-radical methodologies, the focus of this thesis is on monomer modification and chemical additive strategies; in particular Lewis acid-mediated radical polymerization and the use of ionic auxiliaries in the polymerization of methacrylic acid salts.

In parallel to improving stereocontrol, increasing interest has been directed at another important frontier of radical polymerization; using propagation catalysts and termination inhibitors to enhance structural control.⁴⁵ Living-radical polymerizations are not actually true ‘living’ polymerizations, as some amount of bimolecular termination, by radical-radical combination and/or disproportionation, is unavoidable. While lowering the active chain-end concentration will decrease the amount of bimolecular termination,

it also reduces the overall polymerization rate. Thus, living-radical polymerization must carefully balance the requirements for good microstructural control against the need to synthesize polymer within practical reaction time-frames. For a given monomer system, the propagation to termination rate coefficient (k_p/k_t) ratio will determine the maximum permissible concentration of active chain-ends; with higher radical concentrations leading to significant bimolecular termination and consequently poor molecular weight and chain-end control. Increasing the k_p/k_t ratio would enhance the amount of structural control that is attainable in a given time-frame, or equivalently, allow similar levels of structural control to be achieved in shorter time-frames.

In addition to improving chain-end and molecular weight control, propagation catalysts may also be able to reduce the concentration of defect structures in the resultant polymer. While living-radical polymerization enables exceptional levels of microstructural control in many systems, reactive monomers are still susceptible to chain-transfer, head-to-head addition and backbiting (1,5-hydrogen atom transfer) reactions.³⁹ Indeed, radical-based polymerizations are generally more prone to side-reactions and consequently higher concentrations of defect structures are usually observed in the resulting polymer.³⁹ In some systems, defect structures are present at exceptionally low concentrations and will scarcely affect the bulk properties of the polymer. Indeed, for many applications, the presence of certain defects may even have a desirable effect on the polymer's physical and chemical properties (e.g. by improving degradability). However, for other types of applications, even small concentrations of defects can be highly detrimental, as they can have a disproportionately negative effect on polymer stability.⁴⁶ As modulation of defects can influence a polymer's bulk properties, the development of synthetic strategies to reduce their concentration is of significant interest.

Over 10 years ago, Matyjaszewski and Davis identified increasing k_p/k_t ratios as an important area for future research.⁴⁵ While several studies have examined the effect of ionic liquids on k_p and noted significant catalysis in some instances,⁴⁷⁻⁵³ Lewis acids have remained relatively underexplored. In this regard, pulsed laser polymerization (PLP) combined with size-exclusion chromatography (SEC) is a well-established and highly accurate means of determining k_p .⁵⁴⁻⁵⁶ Unfortunately, PLP-SEC studies of Lewis acid-mediated polymerization are rare. This thesis also examines the kinetics of Lewis acid-mediated radical polymerization using PLP-SEC methodology.

1.3 Objectives

The objectives of this thesis are as follows:

- 1) To examine tacticity control in radical polymerization from a fundamental mechanistic perspective and so determine the most likely reason(s) why current methods are delivering suboptimal levels of stereocontrol. Lewis acid-mediated radical polymerization will be a particular focus of this thesis.
- 2) To clarify the mechanism for tacticity determination in unmediated radical polymerization and establish accurate theoretical methodology for the first principles prediction of tacticity.
- 3) To apply pulsed laser polymerization (PLP) to study the kinetics of Lewis acid-mediated radical polymerization and so accurately quantify the effects of Lewis acids on propagation rate coefficients (k_p). Moreover, to examine if Lewis acid complexation has an activating or deactivating effect on propagation and hence whether competition from uncomplexed propagating chains is a source of failure for stereocontrol.
- 4) To establish the likely effects of Lewis acids on photoinitiation and determine how PLP conditions might need to be modified to obtain consistent and reproducible results (related to the previous aim).
- 5) To better understand the origins of stereocontrol in strategically chosen monomer systems.

1.4 General methodology

Over the last few decades, computational chemistry has become invaluable for assessing the thermodynamic and kinetic feasibility of individual chemical processes within the context of complex multi-step reactions. Computational chemistry can provide detailed insights into stability and reactivity, allowing macroscopic observations to be rationalized in terms of fundamental molecular interactions. While it is possible to predict propagation rate coefficients and tacticity theoretically, it requires significant computational resources. In contrast, it is very straightforward to use experimental techniques, such as NMR and PLP-SEC, to accurately quantify tacticity and k_p of a particular polymerization. Unfortunately, these techniques provide fewer insights into the underlying chemistry of these processes.

To examine stereocontrol in radical polymerization thoroughly, this thesis employs a combination of computational and experimental methodologies. As part of this thesis, the methodological requirements for modelling polymerization reactions are reviewed in **Chapter 3**, while an additional summary of computational theory is provided in the appendix. A brief outline of PLP is provided in **Chapter 4**, where the extension of this kinetic methodology to Lewis acid-mediated polymerizations is also examined.

1.5 Outline of this thesis

This thesis by publication is composed of several accepted, submitted and draft manuscripts that have been collated into chapters as follows:

Chapter 2 is devoted to a comprehensive literature review that summarizes the use of Lewis acids, for both polymer and small-molecule radical synthesis, and contrasts these two processes from a mechanistic perspective [*Publication 1*]. It examines the probable mechanistic requirements for stereocontrol in Lewis acid-mediated radical polymerization and comprehensively assesses the potential reasons why Lewis acids might fail as stereocontrol agents. By drawing on results from small-molecule studies, the likely importance of each of these factors is discussed and evaluated.

Chapter 3 is a methodological literature review that covers the application of theoretical quantum chemistry to reactions of direct relevance to radical polymerization [*Publication 2*]. This review extensively discusses and analyses methodological aspects of modelling polymerization reactions with computational chemistry; examining model choice, electronic structure procedures, partition function evaluation, conformational searching and solvation modelling. This chapter also critically examines the mechanism of tacticity determination in unmediated radical polymerizations, with styrene and methyl methacrylate chosen as monomers for an illustrative case study.

Chapter 4 explores the application of pulsed laser polymerization (PLP) to study the kinetic effects of Lewis acids on radical polymerization. Firstly, this chapter presents a combined quantum chemistry/PLP study of the effect of lithium bis(trifluoromethanesulfonyl)imide (LiNTf_2) on the propagation kinetics of methyl methacrylate (MMA) [*Publication 3*]. Secondly, the initiation efficiency of benzoin (a common PLP photoinitiator) and several of its analogues are critically evaluated using a combination of theory and experiment [*Publication 4*]. Thirdly, the effects of two Lewis acids, zinc chloride (ZnCl_2) and aluminium chloride (AlCl_3), on photoinitiation of two common initiators, methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA), are explored using high-level theory and experiment [*Publication 5*].

Chapter 5 examines the origins of the highly variable tacticity obtained during the radical polymerization of methacrylic acid (MAA) and methacrylate salts. Firstly, the tacticity of MAA is predicted from first-principles using theoretical calculations and the effect of ionizing the carboxylic acid side-chains in aqueous-solution is examined [*Publication 6*]. Secondly, the radical polymerization of calcium methacrylate is thoroughly examined in a detailed theoretical study [*Publication 7 Draft*]. Isotactic regulation in this novel monomer system is re-examined, with high-level calculations used to study the mechanistic origins of stereocontrol.

Chapter 6 is a brief stand-alone chapter on nitroxide chemistry that is separated into two parts. The first part reports the successful nitroxide-mediated polymerization (NMP) of vinyl chloride [*Publication 8*] and highlights the invaluable mechanistic information computational chemistry can provide. This work also demonstrates the value of persistent experimentation and this seemingly infeasible NMP serves as inspiration and encouragement for the continued exploration of stereocontrol strategies. The second part of this chapter examines the effect of Lewis acid/base interactions on the oxidation potential of TEMPO monolayers [*Publication 9*]. The electrostatic effect of different electrolytes on these monolayers is evaluated with both experimental and theoretical techniques. This work provides a starting point for future studies on the effect of electric fields on NMP.

Chapter 7 summarizes the key findings of this thesis, discusses potential directions for future work and concludes with an outlook for this challenging but crucially important area of research.

Appendices present a facile procedure for converting poly(calcium methacrylate) to poly(methyl methacrylate). Moreover, a brief description of the theoretical foundation of quantum chemistry, with a particular focus on some of the practical issues that arise when undertaking computational work is provided. Full electronic supporting information for the experimental and theoretical studies are supplied as separated appendices on the attached CD-ROM at the back of this thesis.

1.6 List of publications

The following published works, submitted and draft manuscripts are incorporated into this thesis by publication:

1. Noble, B.B.; Coote, M.L., **Mechanistic Perspectives on Stereocontrol in Lewis Acid-Mediated Radical Polymerization: Lessons from Small-Molecule Synthesis** *Adv. Phys. Org. Chem.*, 2015, 49, 189-258.
<http://dx.doi.org/10.1016/bs.apoc.2015.07.002>
2. Noble, B.B.; Coote, M.L., **First Principles Modelling of Free-Radical Polymerization Kinetics** *Int. Rev. Phys. Chem.*, 2013, 32, 467-512.
<http://dx.doi.org/10.1080/0144235X.2013.797277>
3. Noble, B.B.; Smith, L.M.; Coote, M.L., **The Effect of LiNTf₂ on the Propagation Rate Coefficient of Methyl Methacrylate** *Polym. Chem.*, 2014, 5, 4974-4983. <http://dx.doi.org/10.1039/c4py00190g>
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<http://dx.doi.org/10.1021/acs.macromol.5b02336>
5. Noble, B.B.; Mater, A.C.; Smith, L.M.; Coote, M.L., **Insights into the Effects of Lewis acids on Type I Radical Photoinitiators and Implications for Pulsed Laser Polymerization** *Polym. Chem.*, 2016, 7, 6400–6412.
<http://dx.doi.org/10.1039/c6py01445c>
6. Noble, B.B.; Coote, M.L., **Effects of Ionization on Tacticity and Propagation Kinetics in Methacrylic Acid Polymerization In Controlled Radical Polymerization: Mechanisms**, Matyjaszewski, K.; Sumerlin, B.S.; Tsarevsky, N.V.; Chiefari, J., Eds., American Chemical Society Publications, United States, 2015, pp. 51-72. <http://dx.doi.org/10.1021/bk-2015-1187.ch003>

7. Noble, B.B.; Coote, M.L., **Isotactic Regulation in the Radical Polymerization of Calcium Methacrylate: Is Multiple Chelation the Key to Stereocontrol?** *Draft Manuscript (In Prep)*
8. Abreu, C.; Mendonca, P.; Serra, A.C.; Noble, B.B.; Guliashvili, T.; Nicolas, J.; Coote, M.L.; Coelho, F.J. **Nitroxide-Mediated Polymerization of Vinyl Chloride at Low Temperature: Kinetic and Computational Studies** *Macromolecules*, 2016, 49, 490–498,
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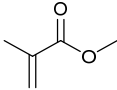
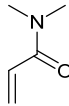
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2. Mechanistic Perspectives on Lewis Acid-Mediated Radical Polymerization

2.1 Overview

Lewis acids are arguably the most practical and widely applicable of all the stereocontrol agents that have been examined to date. In Lewis acid-mediated radical polymerization, a coordinating Lewis acid is added in an attempt to enhance the stereospecificity of propagation. While Lewis acids afford reasonable levels of isotactic stereocontrol in some monomer systems, this control is generally not comparable to that obtained via ionic and coordination polymerization (see **Table 1**). Moreover, as the precise mechanistic origins of tacticity control are unclear, it is impossible to improve these polymerizations in a rational manner. The formidable challenge of selecting an effective Lewis acid and appropriate polymerization conditions is excellently illustrated by the pioneering study of Okamoto and co-workers.⁵⁷ This study assessed more than 40 Lewis acids and examined polymerization temperatures ranging from -30 to 150 °C, in conjunction with various common cosolvents.⁵⁷ Despite this exhaustive screening process, the amount of isotactic control obtained for methyl methacrylate (MMA) was modest (with *m* increasing from around 22 to 45%).⁵⁷ More than a decade later, no subsequent study has been able to improve Lewis acid-mediated control in this system.

Table 1 The isotactic control achieved in Lewis acid-mediated radical polymerization compared to anionic/coordination polymerization for methyl methacrylate and *N,N*-dimethyl acrylamide.

Monomer (Mon)	Lewis acid (LA)	[LA] ₀ /[Mon] ₀	Temp (°C)	Solvent	<i>m</i> (%)	Ref
 methyl methacrylate	None	-	60	Toluene	22	58
	MgBr ₂ ·(OEt) ₂	0.05	80	Benzene	29	58
	Sc(OTf) ₃	0.38	60	Toluene	45	57
	anionic/coordination polymerization				>99	59
 <i>N,N</i> -dimethyl acrylamide	None	-	0	MeOH	49	60, 61
	Yb(OTf) ₃	0.10	0	MeOH	88	60, 61
	Y(OTf) ₃	0.05	30	MeOH	86	62
	anionic/coordination polymerization				>99	63

It is perhaps tempting to view Lewis acid-mediated radical polymerization as an attempt to imitate anionic or coordination polymerization, as these processes also utilize metallic cations to regulate stereochemistry. However, unlike in anionic or coordination polymerization, the basicities of side-chains in radical polymerization are not well differentiated and so Lewis acids will interact far less selectively with the polymer terminus. For instance, in the radical polymerization of methyl methacrylate and *N,N*-dimethyl acrylamide, the neutral ester/amide of the propagating polymer radical is only marginally more basic (~ 2 pK_b units) than the side-chains of the monomer and polymer (see **Figure 4**). While this low basicity confers a high tolerance towards protic impurities, unfortunately it also means that the Lewis acid can be sequestered by the other species in the polymerization. Contrastingly, in the anionic (and coordination) polymerization of these same monomers, the enolate ester/amide of the propagating polymer terminus is (a staggering) 30 pK_b units more basic than the other side-chains in the polymerization. This high basicity results in the very selective association of the metallic cations at the polymer terminus but also makes these polymerizations highly intolerant of trace protic impurities.

Methyl methacrylate				
	Active chain-ends		Other species present	
model species				
	anionic	radical	monomer	chain
pK_b	-12.5	17.5	19.5	19.1
<i>N,N</i> -dimethyl acrylamide				
	Active chain-ends		Other species present	
model species				
	anionic	radical	monomer	chain
pK_b	-14.9	13.4	15.4	14.9

Figure 4 Aqueous Brønsted basicities (pK_b) for model species of relevance to the anionic and radical polymerization of methyl methacrylate and *N,N*-dimethyl acrylamide. pK_b values were calculated via a proton-exchange approach, employing G3(MP2)RAD(+)//M06-2X/6-31+G(d,p) methodology and SMD solvation corrections.

The pK_b values given in **Figure 4** present what may seem like a fundamental (and insurmountable) obstacle to achieving high levels of stereocontrol in radical processes. However on the contrary, Lewis acids can afford very high levels of diastereocontrol (> 99%) in small-molecule radical synthesis.⁶⁴⁻⁷¹ This chapter [*Publication 1*] reviews and summarises the application of Lewis acids as stereocontrol agents in both radical polymerization and small-molecule radical synthesis. As a preface, some of the key features of radical reactivity are discussed and rationalized, by employing prototypical reactions as illustrations. Next, pivotal examples of successful and unsuccessful stereocontrol in radical polymerization and small-molecule synthetic reactions are presented (an example is illustrated in **Figure 5**). Finally, fundamental mechanistic insights are drawn from small-molecule radical reactions and the resulting implications for polymer synthesis are discussed in detail. This chapter not only reviews literature of relevance to Lewis acid-mediated radical polymerization (and small-molecule radical synthesis) but also presents a detailed systematic assessment of the underlying mechanistic aspects of these processes.

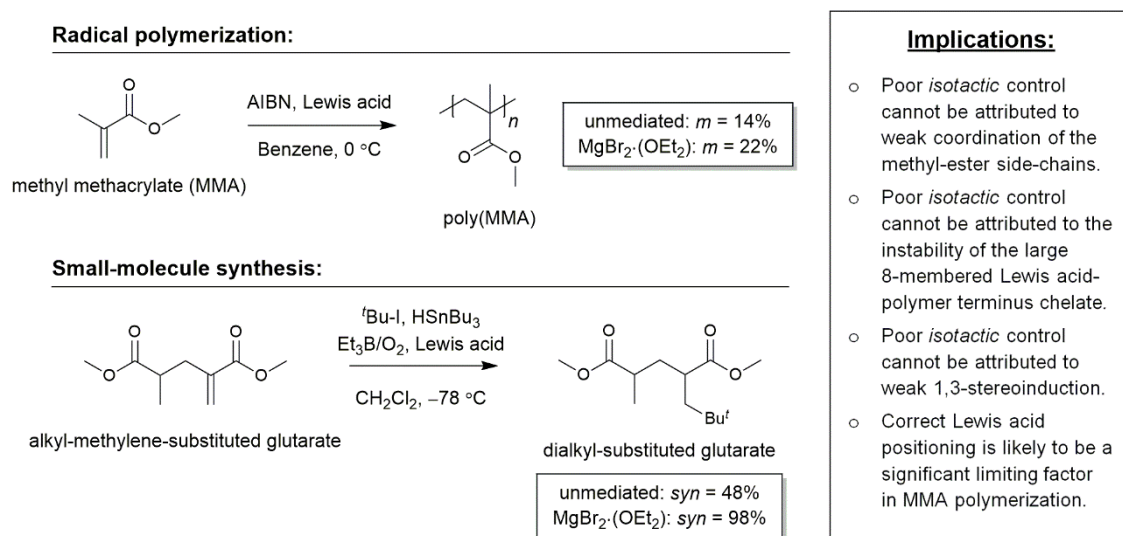


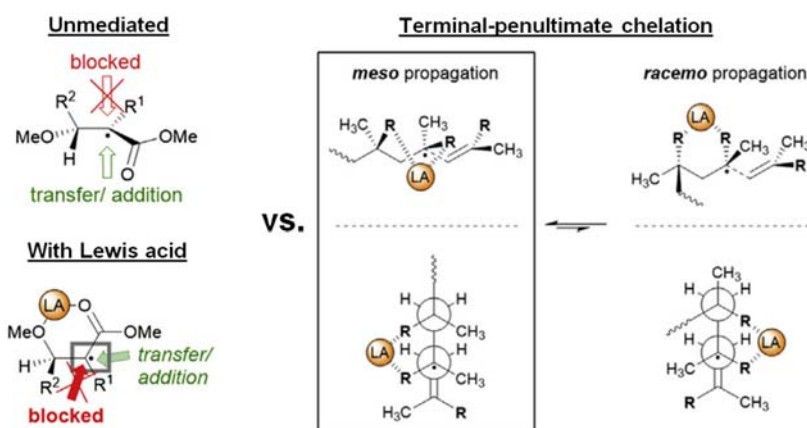
Figure 5 An example of the contrasting stereocontrol afforded by the same Lewis acid, $\text{MgBr}_2 \cdot (\text{OEt}_2)$, in radical polymerization (Ref 58) and a small-molecule radical addition reaction (Ref 72, 73).

2.2 Publication 1

Mechanistic Perspectives on Stereocontrol in Lewis Acid-Mediated Radical Polymerization: Lessons from Small-Molecule Synthesis.

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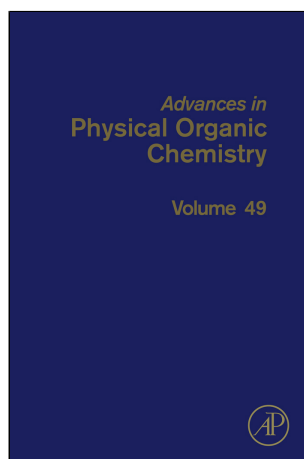


The following manuscript is a peer-reviewed book chapter that was published in *Advances in Physical Organic Chemistry*. The literature review, discussion and resulting mechanistic insights presented in this manuscript are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas, provided me with valuable suggestions and extended and corrected my drafts.

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Mechanistic Perspectives on Stereocontrol in Lewis Acid-Mediated Radical Polymerization: Lessons from Small-Molecule Synthesis

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Abstract

The regulation of stereochemistry in radical polymerization has thus far proved enormously challenging, being the subject of more than 50 years of intense and innovative research. The relatively recent development of living radical polymerization has revitalized interest in stereocontrol, as the lack of tacticity control is now the greatest obstacle to the synthesis of precisely controlled macromolecules by highly versatile and efficient radical-based processes. Lewis acids (LAs) have been employed in an attempt to

overcome the relatively poor stereoselectivity of unmediated radical polymerization, although the level of stereocontrol achieved is highly variable and condition dependent. We examine the use of LAs in radical polymerization from a mechanistic perspective, considering the underlying mechanism of tacticity determination and the likely requirements for effective stereocontrol. Concurrently, we examine the use of LAs in synthetic radical transformations, where they can facilitate very high levels of diastereocontrol but similar variability and condition dependencies are also noted. This chapter outlines and assesses some of the key factors likely to underlie the success or failure LA-mediated isotactic control in radical polymerization.



1. INTRODUCTION

The objective of polymer synthesis is to efficiently assemble macromolecules with precisely controlled structures, so as to maximize their utility for a given application. Over the last century, synthetic polymers have become ubiquitous, used in areas ranging from medicine through to construction. Some of the notable applications of synthetic polymers are as varied as drug-delivery systems,^{1–4} artificial muscles,⁵ adhesives,⁶ coatings,^{7–9} lubricants,¹⁰ catalysts¹¹ and catalyst supports,¹² and high-performance engineering materials.¹³ Much current research has focused on developing stimuli-sensitive polymers, which can respond to externally induced physical or (bio)chemical stimuli, including light, heat, magnetic or electric fields, pH or the presence of various analytes.^{14–16} These so-called “smart polymers” already have numerous applications, ranging from diagnostic biosensors¹⁷ to self-healing coatings.^{18,19} Undoubtedly, many other innovative applications for these remarkable polymers will be realized in the near future. To fully capitalize on the potential benefits of these smart materials, existing polymerization processes must continually be refined and new processes explored so that structural control and productivity can be maximized.

In the decades after their discovery, radicals were viewed as “too reactive” for precision synthesis and their reactions were viewed by many chemists as “messy, unpredictable, unpromising, and essentially mysterious.”²⁰ Despite this initial pessimism, free-radical polymerization rapidly became an important industrial process, responsible for the production of approximately half of all commodity plastics. Compared with other more sophisticated polymerization processes, free-radical polymerization has the often understated advantages of being highly robust and versatile, as the neutral radical-based propagating species is tolerant of a variety of solvent and/or monomer impurities and can facilitate the (co)polymerization of a wide-array of monomer

functionalities. In contrast, coordination and ionic polymerization generally requires extensive purification of both monomer and solvent to remove trace impurities that can adversely react with either the initiator or the propagating species. Indeed, many of the initiators and catalysts used in anionic and coordination polymerization are not only highly moisture sensitive but also pyrophoric and so these processes generally demand very inert reaction conditions. The versatility of anionic and coordination processes is also restricted, as many monomer systems have inherent functional incompatibilities with the initiating systems and so cannot be polymerized directly. However, provided the necessary purification procedures are performed and suitable reaction conditions are maintained, ionic and coordination polymerization offers precise control of polymer microstructure. Unfortunately in contrast, conventional free-radical polymerization affords quite poor control of microstructure, with limited molecular weight, chain-end and tacticity control.

While radical polymerization was long seen as an attractive and efficient route to commodity plastics, prior to the development of “living” radical processes it was thought to be inappropriate for precision polymer synthesis. Over the last few decades, the advance of living radical polymerization, including most notably atom-transfer radical polymerization (ATRP),^{21–23} nitroxide-mediated polymerization (NMP),^{24–26} and reversible addition-fragmentation chain-transfer polymerization (RAFT),^{27–33} has redefined the scope and utility of radical polymerization. Living radical polymerizations combine the versatility and robust nature of conventional free-radical polymerization with a narrow molecular weight distribution and precise chain-end control; enabling the facile synthesis of a remarkable array of polymers with precisely controlled compositions, topologies, and functionalities.^{34,35} Macromolecules with highly complex architectures, including (co)polymer networks, combs, brushes, and stars, can now be routinely assembled through highly efficient radical-based processes.^{34,35} While living radical polymerization has undoubtedly revolutionized polymer synthesis, unfortunately these approaches do not regulate the tacticity (stereochemistry) of the polymer.

Polymer tacticity is the relative arrangement of side-chains with respect to the macromolecular C–C backbone (Figure 1). Tacticity is an important aspect of microstructure that has a dramatic influence on many of the polymer's physical properties; including melting point, mechanical strength, and crystallinity, as well as its ability to assemble into ordered nanostructures. For instance, the melting point of atactic poly(propylene) (<0 °C) is more than 130 °C lower than either the isotactic (165 °C) or syndiotactic form

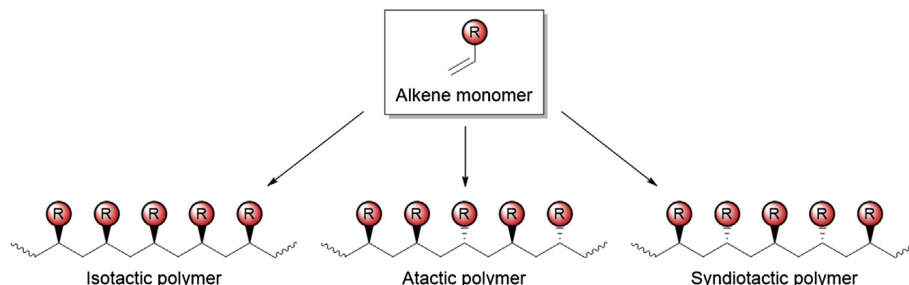


Figure 1 Isotactic, atactic, and syndiotactic polymers derived from a monosubstituted alkene of the general form, $\text{H}_2\text{C}=\text{CHR}$.

(130 °C).³⁶ Unfortunately, unmediated radical polymerization almost invariably yields atactic polymer, which obviously precludes its use for niche applications that may require stereoregular polymer.^{37,38} Much pioneering work over the last 50 years has sought to address this deficiency and develop effective tacticity control, a goal that has been described as the “holy grail”³⁹ of radical polymerization. Indeed, attempts to control polymer stereochemistry predate the development of living radical polymerization by several decades, with the first unsuccessful attempts reported in the early 1960s. Since these initial reports, many chemists have remarked on the difficulties associated with obtaining stereoregular polymers via radical polymerization. For instance, Pino and Suter noted in their 1976 review that “the perspectives for stereocontrol in free radical polymerization are not very promising.”⁴⁰ Indeed, compared to the remarkably rapid advancements made in molecular-weight and chain-end control, progress in stereocontrol has been much more modest. As Satoh and Kamigaito noted in a recent review, “stereocontrol in radical polymerization has not reached satisfactory levels for applications to other areas.”⁴¹

While effective stereochemical control has remained enormously challenging and elusive in all but a few monomer systems, remarkably high levels of diastereo- and enantioselectivity have been reported in radical-based transformations in organic synthesis. Indeed, diastereoselectivities of >99% have been reported in many radical-based synthetic transformations. Given that very high levels of diastereocontrol can now be routinely obtained for many substrates, much effort in organic radical synthesis is now directed toward diversifying the substrates amenable to such control strategies and establishing protocols for enantioselective transformations. Given the high productivity and functional group tolerance of these radical transformations, many have already found utility in natural product synthesis.^{42–44}

Several excellent reviews have summarized stereoselectivity in radical polymerization^{41,45} and radical synthesis.^{46–53} In particular, the relatively recent review of Satoh and Kamigaito provides an excellent summary of stereocontrol strategies in radical polymerization.⁴¹ Instead of rechronicling all of this expansive literature, our article is focused on Lewis acid (LA)-mediated radical polymerization, which is one of the most practical and promising stereocontrol strategies. As such, we provide a detailed overview of LA-mediated radical polymerization that also highlights the utility of LAs in some relevant synthetic transformations. By drawing on insights made from small-molecule transformations, we examine the underlying mechanism of LA-mediated stereocontrol in detail and discuss some of its difficulties and limitations when applied to radical polymerization. Instead of merely examining why isotactic content might vary with LA identity and reaction conditions, we aim to identify the current limitations of isotactic control in relatively “successful” optimized systems. Given that understanding radical reactivity and the underlying mechanism of these processes is imperative to this discussion, an overview of radical reactivity, radical polymerization, and some important radical-based synthetic transformations is also provided. For a more general summary of stereocontrol in radical polymerization, the reader is directed to Satoh and Kamigaito’s excellent review.⁴¹

We should also briefly comment on the use of stereospecific and stereoselective nomenclature in radical reactions and polymerization. As outlined by Chen,⁵⁴ the IUPAC use of stereospecific and stereoselective varies (somewhat confusingly) between fundamental reactions and polymerizations. For fundamental reactions, *stereoselectivity* is defined as “the preferential formation in a chemical reaction of one stereoisomer over another,”⁵⁵ while a process is termed *stereospecific* “if starting materials differing only in their configuration are converted into stereoisomeric products.”⁵⁵ In contrast, *stereoselective polymerizations* are defined as “polymerization in which a polymer molecule is formed from a mixture of stereoisomeric monomer molecules by incorporation of only one stereoisomeric species,”⁵⁵ while *stereospecific polymerization* is a “polymerization in which a tactic polymer is formed.”⁵⁵ If the definition for “normal” reactions is applied to polymerizations, one could reasonably argue that the polymerization of prochiral vinyl monomers to form either isotactic or syndiotactic polymer should be termed *stereoselective polymerization*, because one stereoisomeric configuration is favored (but is not formed exclusively). In contrast, the polymerization definition would imply the process is *stereospecific* but not *stereoselective*. Because of this somewhat counterintuitive terminology,

nomenclature derived from stereoselective and stereospecific, such as *isoselective*- and *isospecific*-polymerization, is often used interchangeably in polymer literature. To avoid confusion, we will apply the fundamental reaction definition of *stereoselective* and *stereospecific* to both the small-molecule transformations and polymerizations discussed in this chapter. As such, polymerizations where isotactic stereostructures are formed preferentially (but not exclusively) are termed *isoselective*, and *stereoselectivity* is used to describe the tendency of a polymerization to form tactic stereoregular polymer.



2. IMPORTANT FEATURES OF RADICAL REACTIVITY

Radicals can promote an enormously diverse array of chemical transformations that are of relevance not only to organic and polymer synthesis, but to combustion,⁵⁶ atmospheric⁵⁷ and biological⁵⁸ chemistry as well. Free radicals can react with a variety of different substrates, often forming multiple products and so controlling their chemoselectivity can be problematic. These reactions include bimolecular radical combination and disproportionation, transfer (substitution) and addition reactions with spin-paired molecules, or fragmentation and ring opening. Arguably, radical processes are more complex and less intuitive than their ionic counterparts, which is the predominant reason why radical reactions were initially viewed as “unpredictable” and “messy.” However, many of the important subtleties of radical reactivity are now well understood and as such they are now widely employed in chemical synthesis. While radical reactivity is certainly quite distinct from that of ionic reagents, radical processes are actually reasonably predictable and their reactions can be highly selective; provided sensible reagent substrates and conditions are utilized. As understanding radical reactivity is imperative to this discussion (and the design of efficient and selective radical processes), a brief summary of some of the most important aspects of their reactivity is provided. For a more comprehensive account of radical reactivity, the reader is directed to Refs 59–65.

Free radicals can be stabilized through conjugation with either electron-donating and/or electron-withdrawing groups. The effect of substituents can be rationalized using Frontier Molecular Orbital Theory, which qualitatively describes the interactions between the SOMO of radical and the π^* orbital (LUMO) of an electron-withdrawing group or the n orbital (HOMO) of an electron-donating group (Figure 2). Electron-withdrawing groups, such as $-\text{C}=\text{O}$ and $-\text{C}\equiv\text{N}$, possess a relatively low-energy

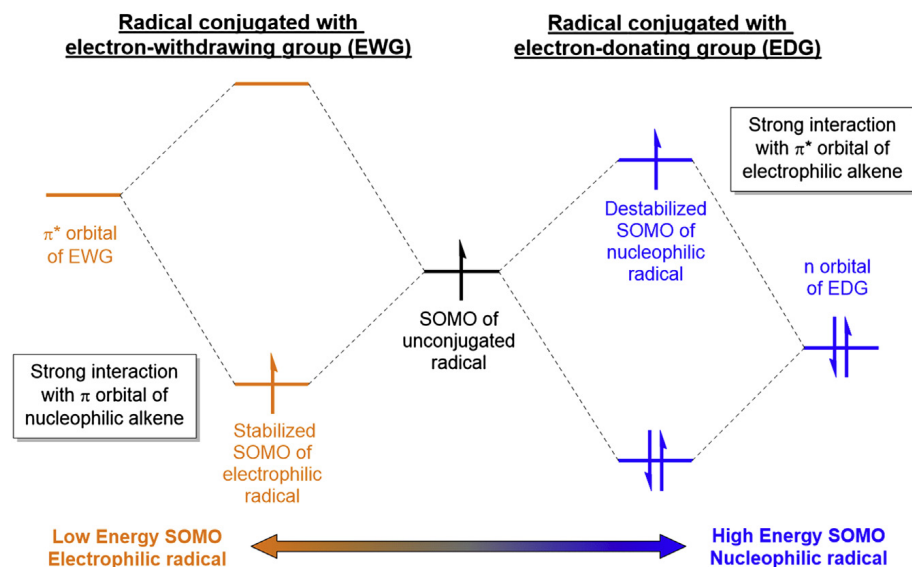


Figure 2 The Frontier Molecular Orbitals of a radical species conjugated to an electron-withdrawing or electron-donating group. (See color plate.)

unoccupied π^* orbital, so interaction of the frontier orbitals will stabilize the SOMO of the radical (resulting in overall net stabilization). In contrast, electron-donating groups, such as $-\text{OR}$ and $-\text{NR}_2$, possess a relatively high-energy occupied n orbital, so interaction of the frontier orbitals will destabilize the SOMO of the radical but stabilize the nonbonding pair (resulting in net stabilization of the 3-electron system).

These frontier interactions have important consequences for radical reactivity as they effectively give radicals polar (electrophilic or nucleophilic) character according to their substitution. High-energy SOMOs will interact more effectively with the π^* orbitals of electrophilic alkenes, while low-energy SOMOs will preferentially interact with the π orbitals of nucleophilic alkenes. Thus, radicals are effectively ambiphilic and their addition reactions will be particularly kinetically favorable if the radical substrate and alkene acceptor have a “matched” electronic character; that is if electrophilic radicals are reacted with nucleophilic alkenes or vice versa. The importance of polar effects can be illustrated by considering the rate coefficients for the addition of the “nucleophilic” 2-hydroxy-2-propyl radical and “electrophilic” cyanomethyl radical to acrylonitrile (AN) and ethyl vinyl ether (Figure 3). At $\sim 25^\circ\text{C}$, the rate of addition of the 2-hydroxy-2-propyl radical to the “electrophilic” alkene AN is three orders magnitude faster than the comparable addition of the cyanomethyl radical.^{66,67} Conversely, the

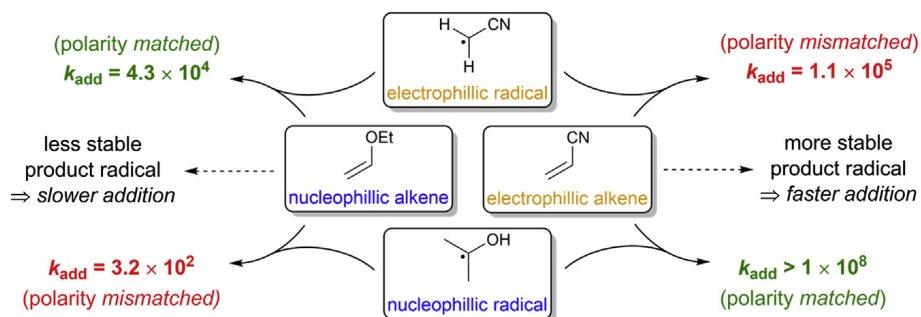


Figure 3 Illustrative examples of polar and radical stability effects in radical addition reactions. Addition rate coefficients (k_{add}) are given in $\text{L mol}^{-1} \text{s}^{-1}$ and were measured at $\sim 25^\circ\text{C}$.^{66,67}

addition of the cyanomethyl radical to the “nucleophilic” alkene ethyl vinyl ether is over two orders of magnitude faster than the addition of the 2-hydroxy-2-propyl radical.^{66,67} Analogous polar effects have also been noted in transfer reactions.^{68,69} The importance of polar effects in radical reactions is exemplified by the copolymerization of styrene (STY) and maleic anhydride.^{70,71} This copolymerization affords highly alternating copolymer, as the relatively nucleophilic styrene radical reacts preferentially with the highly electrophilic maleic anhydride monomer and vice versa.^{70,71} Similar alternating preferences have also been observed in the radical copolymerization of STY and AN.⁷²

Stabilization and thermodynamic effects also significantly influence radical reactivity. In accordance with the Bell–Evans–Polanyi principle, an approximately linear correlation between the activation barrier and reaction enthalpy is observed in many radical reactions (including addition to alkenes and transfer).^{60,61} Thus, the relative stabilities of the substrate and product radicals can influence not only the thermodynamics but also the kinetics of radical reactions. Generally, reactions in which an unstable substrate radical reacts to form a stabilized acceptor radical will have highly negative reaction enthalpies and consequently low reaction barriers. Conversely, reactions in which a stable radical substrate reacts to form an unstable acceptor radical will be disfavored, both kinetically and thermodynamically. Radical stability effects can be observed in the rate coefficients listed in Figure 3. Indeed, contrary to the reactivity predicted according to polar effects alone, the addition of the cyanomethyl radical to AN is actually slightly faster than addition to ethyl vinyl ether. In this instance, polar effects are counteracted by radical stability, which favors the formation of the relatively stable product radical derived from addition to AN, rather than the less stable product

radical derived from addition to ethyl vinyl ether. Indeed, the addition of the 2-hydroxy-2-propyl radical to the AN forms a stabilized radical species and is thus favored by both polar and radical stability effects. Remarkably, this addition reaction is so rapid that it is virtually diffusion limited ($k_{\text{add}} > 1 \times 10^8 \text{ L mol}^{-1} \text{ s}^{-1}$).^{66,67} If the alkene acceptor is changed to ethyl vinyl ether, then the reaction becomes disfavored by both polar and radical stability arguments and the rate of addition is reduced by more than five orders of magnitude ($k_{\text{add}} = 3.2 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$).^{66,67}

Steric interactions significantly affect radical reactivity, although these factors are usually fairly intuitive, simply depending on the proximity and size of the interacting groups. For instance, in radical addition reactions with substituted alkenes, the importance of steric effects depends of the size and proximity of substituents attached to radical and alkene. Quite intuitively, steric bulk in the α -position (relative to the point of addition) of an alkene slows the rate of radical addition more dramatically than the presence of the same group in the β -position, because of the closer proximity of the interacting groups. This importance of steric effects is nicely illustrated by considering the relative rate coefficients for the addition of cyclohexyl radicals to methyl acrylate, methyl crotonate, methyl methacrylate (MMA), methyl (*E*)-3-isopropylacrylate, and methyl 2-isopropylacrylate (Figure 4).⁷³ At 20 °C, the rate of addition of the cyclohexyl radical to methyl crotonate is nearly two orders of magnitude slower than comparable addition to methyl acrylate.⁷³ In contrast, the addition of the cyclohexyl radical to MMA is also slower than comparable addition to methyl acrylate, but only by around 30%.⁷³ While the presence of a CH₃ group slows the rate of cyclohexyl radical addition to both alkenes, a much more dramatic rate reduction is observed for methyl crotonate because the substituent is much closer to the adding radical. Unsurprisingly, as the steric bulk of the substituent increases, the rate of addition decreases. At 20 °C, the rate of addition of the cyclohexyl radical to methyl (*E*)-3-isopropylacrylate is slower than comparable addition to methyl acrylate by a factor of around 600.⁷³ For comparison, the addition of the cyclohexyl radical to methyl 2-isopropylacrylate is slower than comparable addition to methyl acrylate but only by 60%.⁷³

Regioselectivity in radical addition reactions to substituted alkenes is determined by a combination of steric, polar, and thermodynamic effects. Radicals will react selectively with the more accessible (less substituted) carbon center of alkenes, forming the more stabilized product radical and affording anti-Markovnikov addition products. Regioselectivity is dependent on the steric differentiation of the C atoms of the C=C bond and

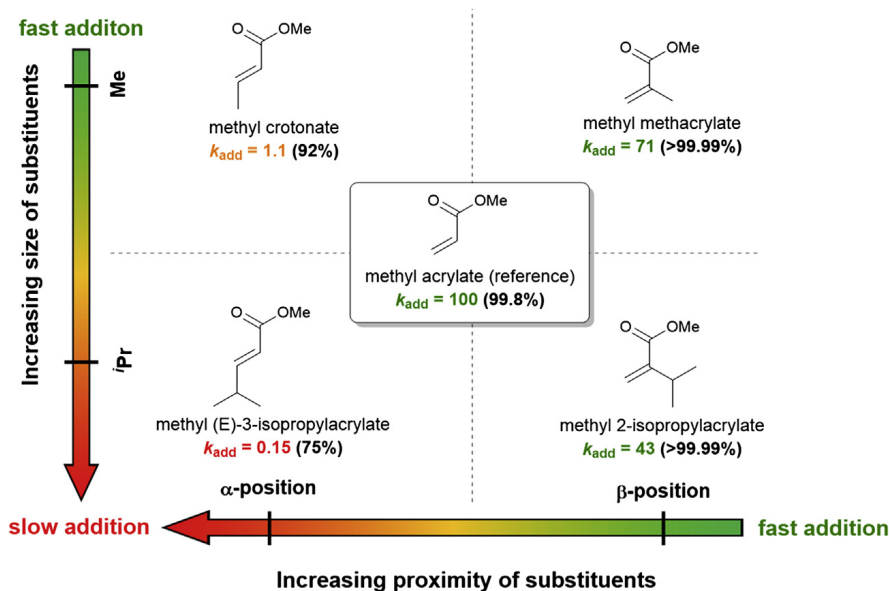


Figure 4 Illustrative examples of steric effects in the addition of the cyclohexyl radical to various alkenes. Relative addition rate coefficients (k_{add}) for the major isomer (anti-Markovnikov) were measured at 20 °C, and regioselectivity for this isomer is given in parentheses.⁷³ (See color plate.)

on the stability of the product radicals formed from addition. Radical addition reactions to 1,2-disubstituted alkenes tend to have lower levels of regioselectivity than analogous 1-substituted or 1,1-disubstituted alkenes. This lower regioselectivity results from less steric differentiation between the C atoms of C=C bond and the increasing stability of the “alternative” minor product radical, which results from substitution. The influence of steric and radical stability effects on regioselectivity can also be seen in Figure 4. At 20 °C, the addition of cyclohexyl radicals to methyl acrylate is very regioselective, affording 99.8% of the anti-Markovnikov product. However, the regioselectivity for methyl crotonate is substantially lower (92%) and progressively decreases as the steric bulk of the substituent increases.⁷³ Indeed, under identical conditions, methyl (E)-3-isopropylacrylate shows rather poor regioselectivity (75%).⁷³ In contrast, these same effects enhance regioselectivity for 1,1-disubstituted alkenes compared with monosubstituted analogues. At 20 °C, the regioselectivity of cyclohexyl radical addition to MMA and methyl 2-isopropylacrylate is extremely high (>99.99%).⁷³

The coordination of an LA to the conjugate side-chain of either an alkene or radical can significantly influence reactivity by altering the underlying polar

characteristics of the substrates. Coordination of LAs to electron-withdrawing groups, such as $\text{C}=\text{O}$ and $\text{C}\equiv\text{N}$, will effectively lower the energy of the π^* orbital, which lowers the radical SOMO and will thus increase its electrophilic character. Coordination of LAs to electron-donating groups, such as OR and NR_2 , will effectively lower the energy of the n orbital, which lowers the radical SOMO and decreases its nucleophilic character (and lowers its overall stability). Analogously, coordinating an LA to the conjugate donor of an electron deficient alkene will effectively increase its electron withdrawing ability and stabilize the π^* orbital, further increasing its electrophilic character, while coordinating an LA to the electron donating group of nucleophilic alkene will decrease its nucleophilic character. The influence of LAs on polar effects is excellently demonstrated by several copolymerization studies.^{74–79} While monomers with well-differentiated polar characteristics will copolymerize in an alternating fashion, copolymerization of monomers with similar polar characteristics, such as MMA/STY, usually affords random copolymer.⁸⁰ However, the inclusion of LAs, such as ZnCl_2 or BCl_3 , can afford alternating copolymer in MMA/STY copolymerization by altering the underlying polar characteristics of MMA.^{77–79} By coordinating to the conjugate methyl ester moiety, LAs can enhance the electrophilic character of MMA monomer and radicals, which leads to better polar differentiation and thus alternating propagation in copolymerization with STY.^{77–79} These strategies can even be employed in conjugation with living radical polymerization to synthesize well-defined alternating copolymers with precisely controlled molecular weights and chain-ends.^{81,82}

In addition to polar effects, LAs can also interact with radicals directly via electrostatics, the so-called “odd-electron bonding” or distonic radical–cation interactions. These interactions were initially explored using ab initio calculations by Clark over 25 years ago.⁸³ Clark reported that the addition of methyl radicals to alkenes could be catalyzed by the complexation of Li^+ to the $\text{C}=\text{C}$ bond.⁸³ While some might have questioned the experimental significance of such results (given the nontrivial challenge of solubilizing Li^+ in nonpolar solutions), it was later demonstrated experimentally by Michl and coworkers that Li salts of noncoordinating carborane anions could facilitate the radical polymerization of various 1-alkenes, such as propene and 1-butene.^{84–86} In the absence of specific additives, the radical polymerization of such monomers would normally result in the formation of low-molecular-weight oligomers due to degenerative H-transfer. However, as Clark later confirmed with more detailed theoretical calculations,⁸⁷ Li^+ can catalyze propagation and comparatively inhibit H-transfer, thus

facilitating the formation of high-molecular-weight polymer. While the elegance and novelty of these studies is unquestionable, the potential importance of distonic radical–cation interactions in polar systems has not been thoroughly explored. While one might reasonably question the generality of such effects (and specifically their applicability to polar systems), we should emphasize that much of the odd-electron catalysis reported by Clark has electrostatic origins.^{87,88} Indeed, it is interesting to note that in the gas phase the interaction energy between the methyl radical and Li^+ is over 50 kJ mol^{-1} .⁸⁷ More recent work has confirmed that Li^+ exerts a modest stabilizing effect on unimeric MMA radicals,⁸⁹ although it is unclear to what extent this stabilization may simply reflect polar effects.



3. RADICAL POLYMERIZATION

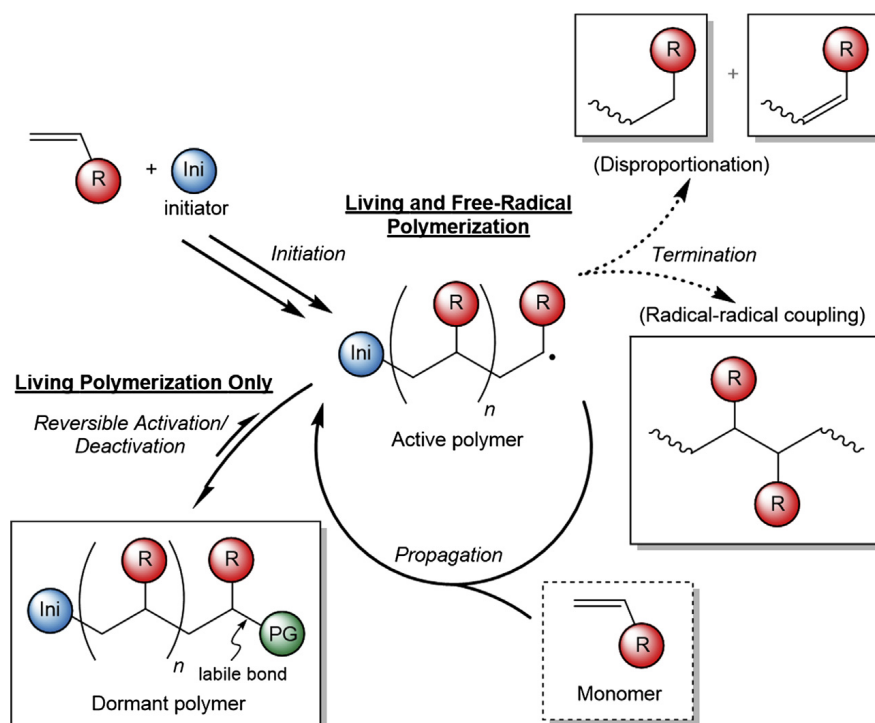
Living and conventional radical polymerization are both chain processes, proceeding via a sequence of initiation, propagation, chain transfer, and termination reactions. Initiator radicals are generated from the physically or chemically induced decomposition of an appropriate radical initiator. These radicals initiate chain growth by adding to the $\text{C}=\text{C}$ bond of monomer, forming a new $\text{C}-\text{C}$ bond and radical center, which can then undergo further propagation. Termination of polymer chain growth occurs via radical coupling and/or disproportionation. These reactions exist in competition with propagation and lead to the broad molecular-weight distributions characteristic of conventional radical polymerization. Depending on the termination mode, the resulting chain-ends consist of initiator fragments (combination) or a 1:1 mixture of saturated and unsaturated monomer units (disproportionation) or some mixture of the two. Either way, the chain-ends are not suitable for further polymerization (e.g., to make block copolymers) or functionalization (to construct stars, brushes, etc.). The growing polymer radicals can also undergo intramolecular chain transfer (backbiting) as well as intermolecular chain-transfer reactions with solvent, monomer, polymer, and/or other additives. These transfer reactions stop chain growth at the polymer terminus but form a new radical center that can propagate. Depending on the transfer agent and the application, chain-transfer reactions can either be desirable as a means of reducing the molecular weight, or undesirable reactions that lead to defect structures in the resulting polymer.

Living radical polymerization does not alter the inherent propagation step of free-radical polymerization but lowers the effective concentration

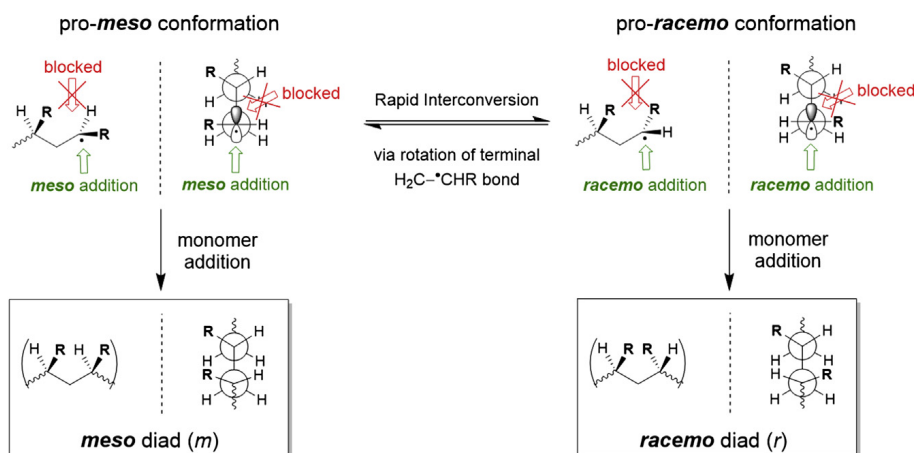
of propagating radicals by reversibly storing them in a dormant form. While these dormant species are unable to propagate, they are also protected from irreversible termination reactions. By carefully tuning the stability and reactivity of the dormant form, termination reactions (which are second order with respect to radical concentration) can be suppressed, relative to chain growth (which is first order with respect to radical concentration). This allows a low polydispersity index ($PDI < 1.2$) to be achieved within practical reaction timeframes and as the product polymer can be isolated in its dormant form, its chain-ends remain “active” toward further polymerization with another monomer (e.g., as in block copolymer synthesis) and/or can be functionalized as desired (e.g., to produce stars, brushes, etc.). As the active propagating species is unchanged, living radical polymerization retains most of the advantages of free-radical polymerization. However, the use of living radical initiating systems does not affect tacticity, as the underlying propagation step is identical to that of free-radical polymerization. Indeed, even the use of chiral initiating systems, including chiral nitroxides^{90–93} and ATRP agents,^{94–97} has no appreciable effect on main-chain polymer tacticity. The underlying reactions of both living and nonliving radical polymerization are outlined in [Scheme 1](#).

To develop better stereocontrol agents, it is crucial to understand stereo-selection at a fundamental mechanistic level and appreciate the subtle but crucial differences between tacticity determination in ionic and coordination versus radical processes. As previously outlined, the propagation step of living radical polymerization is identical to that of free-radical polymerization and so the mechanism of tacticity determination in these processes is also identical. In radical polymerization, the planar (sp^2 hybridized) carbon radical of the polymer terminus is prochiral, and its stereochemistry is determined during subsequent monomer addition. The addition of monomer occurs exclusively to the *anti*-face of the radical, as the *syn*-face is shielded by the steric bulk of the penultimate group ([Scheme 2](#)). Hence, the prochiral polymer terminus can adopt either *pro-meso* or *pro-racemo* arrangements; defined by the relative orientation of the terminal and penultimate side-chains with respect to the macromolecular C–C backbone.

Addition of monomer to a *pro-meso* conformation will lead to formation of a *meso* diad (*m*), while addition to a *pro-racemo* configuration forms a *racemo* (*r*) diad. The polymer terminus can interconvert between *pro-meso* and *pro-racemo* conformations via rotation of the terminal ($\sim CH_2-CHR\cdot$) sp^3-sp^2 bond. This torsion does not disrupt stabilizing conjugation between the radical and terminal side-chain (R). Thus, it is anticipated that for most



Scheme 1 The underlying initiation, propagation, activation/deactivation, and termination reactions for living and free-radical polymerization (chain transfer is not shown).

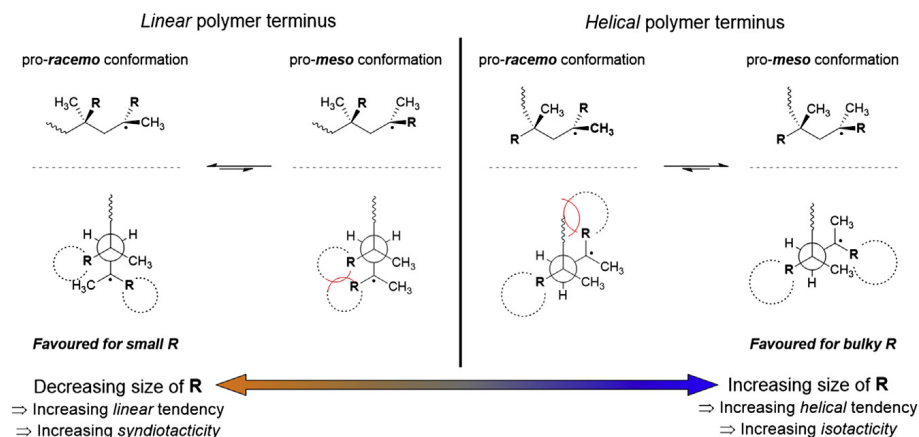


Scheme 2 Idealized stereoselection in free-radical polymerization of a monosubstituted alkene, $\text{H}_2\text{C}=\text{CHR}$. The polymer terminus is shown in a linear conformation.

ordinary monomers rotation around the terminal bond is very rapid compared with propagation. We have recently confirmed this postulate in theoretical studies on methacrylic acid propagation⁹⁸ and would argue that it should be applicable to most “ordinary” monomer systems, including (meth)acrylates and (meth)acrylamides. For most monomers, pro-*meso* and pro-*racemo* configurations are nearly degenerate and similarly reactive and hence radical polymerization affords predominantly atactic polymer. However, dipole–dipole and steric repulsion leads to moderate syndiotactic preferences in many common monomers, such as methacrylates and methacrylamides.

While radical polymerization under typical conditions almost invariably affords either atactic polymer or mildly syndiotactic polymer, it is worth briefly discussing two notable exceptions, where highly stereoregular polymer can be obtained in homogenous solution-phase polymerizations without additional stereocontrol agents. Firstly, somewhat counterintuitively, the radical polymerization of bulky methacrylates and methacrylamides affords highly isotactic polymers.^{99–102} The mechanism is thought to be due an amplification of the repulsive interactions between the bulky terminal and penultimate side-chains.^{41,103} In relatively small monomers, such as MMA, these interactions force the ester side-chains to locate on opposite sides of the main chain during propagation, leading to the mild syndiotactic preferences observed.^{41,103} In exceptionally bulky chains, these interactions also force the side-chains to adopt conformations in which their interactions are minimized.^{41,103} However, in contrast to the smaller monomers, the bulky ester side-chains also force the main chain itself to assume a helical conformation, and in this helical conformation the repulsive steric interaction is minimized in a pro-*meso* (rather than pro-*racemo*) configuration (see Scheme 3).^{41,103} Interestingly, correspondingly bulky acrylates and vinyl ethers do not show this isotactic tendency and afford atactic (or moderately syndiotactic) polymer instead.^{104–111} More generally, this highlights an additional complication in the design of reagents for stereoregulation in radical polymerization: the need to take into account the chain structure as well as the interactions between the side-chains themselves.

Secondly, radical polymerization of monomers possessing a chiral auxiliary can also afford highly isotactic rich polymer. In such monomer systems, tacticity is not determined by relative 1,3-interactions between the stereogenic center of the penultimate unit and the prochiral radical center. Instead, the (enantiomerically pure) chiral auxiliary imposes a preference for the formation of either (*R*) or (*S*) absolute stereogenic centers at the prochiral



Scheme 3 The favored linear pro-*racemo* and helical pro-*meso* conformations adopted by “normal” and “bulky” methacrylates/methacrylamides. Note that only the terminal and penultimate units are shown for clarity.

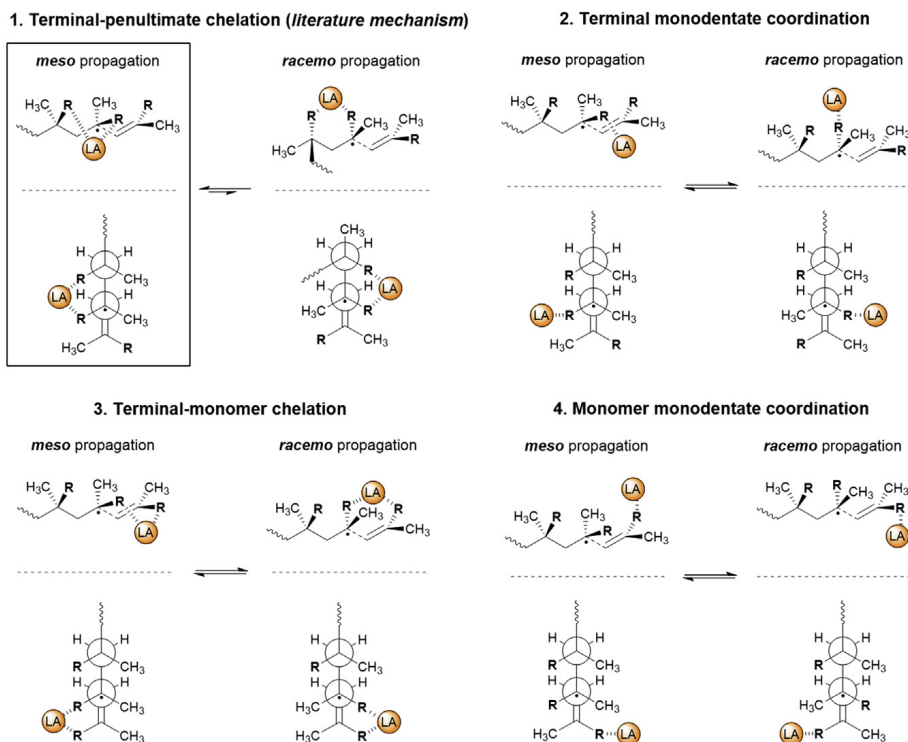
radical center; imparting so-called “facial selectivity.” Repeated formation of stereogenic centers with the same absolute stereochemistry on the main chain C–C backbone will automatically result in isotactic polymer. There are several notable examples of chiral auxiliary stereocontrol in radical polymerization, for which the reader is directed to Refs 112–114. While very bulky or chiral monomers can afford highly isotactic-rich polymer, the monomers are expensive and the resultant polymers subsequently need to have this additional bulky or chiral functionality removed. Thus, there is still substantial interest in stereocontrol of ordinary monomers through the use of chemical additives. The use of such additives can be divided into two areas, LA-mediated processes (which are the focus of this work) and solvent-mediated processes.

While it is not the focus of this chapter, we will provide a brief outline of solvent-mediated stereocontrol for context. Generally, solvent-mediated processes employ bulky fluoroalcohols or other novel solvents to influence the structure of the polymer terminus through H-bonding with the pendant side-chains. These processes can enhance the inherent syndiotactic preference of monomers, such as MMA,^{115–119} methacrylic acid,^{120,121} *N*-vinylpyrrolidone,¹²² *N*-methyl methacrylamide,¹²³ and vinyl acetate.^{124,125} However, in some systems these additives cause modest increases in isotactic or heterotactic content instead.^{126–128} While obtaining syndiotactic-rich polymer is certainly not trivial and normally requires the use of low temperatures, these processes facilitate the synthesis of poly(MMA) and poly(MAA) with a

syndiotactic triad fractions of $rr = 93\%$ and $rr = 95\%$, respectively.^{115,116,120} While most of these strategies capitalize on the inherent syndiotactic preference of the parent monomer, they do offer a relatively convenient route to syndiotactic-rich polymer and are compatible with living radical polymerization processes, such as RAFT and ATRP (although the use of very low temperatures may complicate these processes). Given the reasonable progress in syndiotactic control, we instead focus instead on isotactic control strategies through the use of chelating LAs.

LA-mediated radical polymerization attempts to overcome the low stereoselectivity of unmediated radical polymerization by the inclusion of a coordinating LA. Most studies to date have focused on the use of metallic chelating LAs, that is, metal cations with more than one empty coordination site. The most intuitive and frequently cited mechanism of LA-mediated isotactic control is via the chelation of the terminal and penultimate groups of the polymer terminus. The terminal-penultimate chelate mechanism assumes the formation of a kinetically labile chelate complex between the terminal and penultimate side-chains of the polymer terminus and the LA (Scheme 4, scenario 1). By coordinating the terminal and penultimate side-chains, the LA supposedly imparts an energetic preference for *meso* propagation. After monomer addition, the kinetically labile LA then detaches from the penultimate and antepenultimate groups, before (re)coordinating at the terminus-penultimate position of the polymer terminus to regulate the stereochemistry in subsequent propagation steps. This basic mechanism was first proposed by Matsumoto¹²⁹ and has since been frequently cited in other studies on LA-mediated radical polymerization.^{41,130–138} Unfortunately, this simplistic mechanism conceals various complexities and so potential modes of failure.

The most obvious requirement for isotactic regulation is the stability of the Lewis acid–base adducts. If these coordinate bonds are not sufficiently stable then very high Lewis-acid loadings would be required to ensure that the majority of polymer termini are chelated. While in principle isotactic control could still be achieved at high Lewis-acid loading, this would be quite impractical (in terms of waste, solubility, compatibility with living radical processes etc.). Assuming, sufficient stability of the Lewis acid–base adduct, the next requirement is that the terminal-penultimate chelate forms selectively over other nonchelated (monodentate) adducts (scenario 2 and 4 in Scheme 4). If the terminal-penultimate adduct is not stable compared to other monodentate adducts, it is unlikely that high levels of isotactic control would be observed. Another potential limitation of this

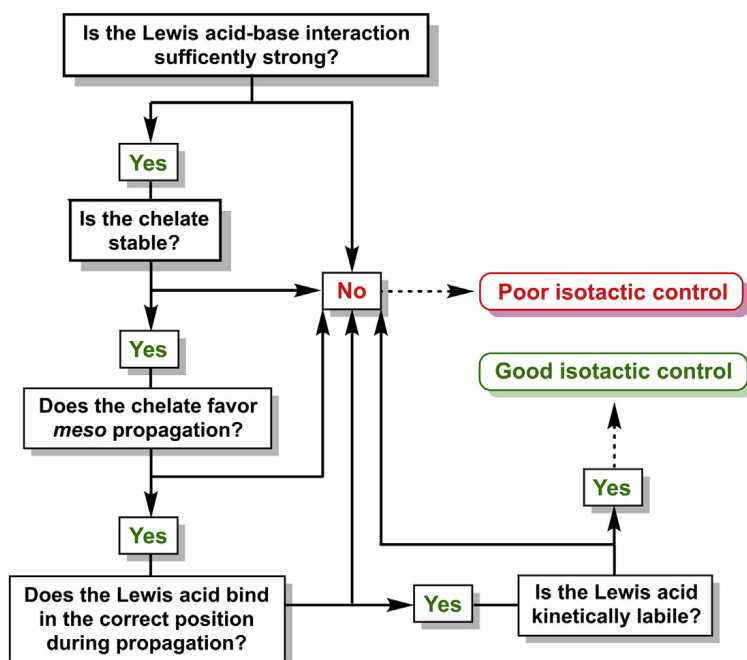


Scheme 4 Stereoselectivity during radical polymerization of a disubstituted alkene ($\text{CH}_2=\text{CCH}_3\text{R}$), in the presence of a Lewis acid (LA): scenarios (1)–(4) illustrate the likely stereochemical effect of LA coordination in different positions.

mechanism is the level of isotactic control afforded by the terminal-penultimate chelate itself. While it is usually implicitly assumed that chelation in this position favors *meso* addition, this argument is derived assuming the polymer terminus preferentially adopts a linear conformation. If helical conformations are considered, then terminal-penultimate complexation will actually favor *racemo* propagation. Thus, LA-mediated isotactic control relies on the polymer terminus having a sufficient linear/helical preference, otherwise competitive propagation of pro-*racemo* complexes will reduce the level of isotactic control.

Another crucial requirement of LA-mediated isotactic control is that the LA remains in the terminal-penultimate position during propagation; that is, that the terminal-penultimate binding position is the most reactive in the polymerization. However, chelation can occur not only at the terminal-penultimate position but at any other point along the polymer chain, including the penultimate-antepenultimate and/or the terminal-incoming

monomer side-chains (Scheme 4, scenario 3). If there is no selectivity for propagation with the LA in the terminal-penultimate position, then alternative complexes would likely undermine the isotactic control afforded by the terminal-penultimate chelate. Lastly, it is usually assumed that the LA is kinetically labile; that is, that exchange of LA is faster than propagation. To be effective at catalytic concentrations, the LA must be released from the polymer chain after propagation so that it can reassociate with the terminal and penultimate groups of the polymer terminus. While some isotactic control may be observed even if the LA is not labile, it would require very high loading of LA. We should note that at higher LA loading, the basic complexes depicted in Scheme 4 would still persist, but uncoordinated R groups would be bound by additional LA. Under limiting conditions where all R groups are bound, the complexes in scenario 2 and 4 would become equivalent but remain distinct from those of scenario 1 and 3 (which would also still be nonequivalent with each other). The basic requirements for LA-mediated isotactic control are summarized in Scheme 5.



Scheme 5 The necessary requirements for effective isotactic control in Lewis acid-mediated radical polymerization.



4. LEWIS ACIDS IN RADICAL-BASED POLYMER SYNTHESIS

The first attempts to control stereochemistry in radical polymerization by the use of LAs were reported over 50 years ago. In the early 1960s, Bovey examined the effect of catalytic amounts of zinc chloride (ZnCl_2) on the radical polymerization of MMA, noting no significant stereochemical effects.¹³⁹ Otsu et al. later found that stoichiometric amounts of ZnCl_2 slightly increased the isotacticity of the resulting poly(MMA).¹⁴⁰ Given these initially underwhelming results, LA-mediated radical polymerization remained relatively unexplored, with few investigations reported in the 1970s and 1980s. However, following the successful application of LAs in small-molecule radical transformations throughout the 1990s, Matsumoto et al. examined the use of $\text{MgBr}_2 \cdot \text{OEt}_2$ in the radical polymerization of MMA.¹²⁹ Unfortunately, contrary to the high levels of diastereoselectivity achieved in various synthetic transformations, Matsumoto only noted a slight increase in isotacticity with the inclusion of $\text{MgBr}_2 \cdot \text{OEt}_2$ in the polymerization.¹²⁹

Following this work, Okamoto and coworkers successfully synthesized isotactic- and syndiotactic-rich polymers of various α -(alkoxymethyl)acrylates by including various LAs.¹⁴¹ The pioneering study by Okamoto and coworkers¹⁴² excellently demonstrates the daunting challenge of finding effective stereocontrol agents and suitable reaction conditions for LA-mediated radical polymerization. This work screened over 40 different LAs and a range of reaction conditions; polymerization temperatures from -30 to 150°C and various common cosolvents, including CHCl_3 , Toluene, DMF, and THF.¹⁴² Even after such an exhaustive study, only moderate isotacticity ($mm = 21\%$) could be obtained for MMA under optimized conditions (see Table 1).¹⁴² Likewise ethyl methacrylate (EMA) also proved challenging, with only small increases in isotacticity observed with the inclusion of $\text{Sc}(\text{OTf})_3$ or $\text{Yb}(\text{OTf})_3$. While several other authors have demonstrated that $\text{Sc}(\text{OTf})_3$ -mediated MMA polymerizations are compatible with living radical polymerization,^{133,143,144} none of these studies has been able to improve the underlying isotactic control.

Developing stereocontrol for the radical polymerization of acrylamides and methacrylamides is of particular interest, as accessing the corresponding poly(acrylamides) and poly(methacrylamides) by ionic or coordination polymerization is in some instances difficult or even impossible. Unsubstituted and monosubstituted acrylamides cannot be synthesized by anionic or

Table 1 Illustrative examples of isotactic control in Lewis acid-mediated radical polymerization of some common polar monomers

Monomer (Mon)	Lewis acid (LA)	[LA] ₀ /[Mon] ₀	Solvent	Temperature (°C)	Triad Tacticity (%)			Diad (%)		References
					mm	mr	rr	m	r	
 MMA	None	—	Benzene	80	4	36	60	22	78	129
	MgBr ₂ ·OEt ₂	0.05	Benzene	80	8	41	51	29	71	129
	None	—	Toluene	60	3	34	63	20	80	142
	Sc(OTf) ₃	0.08	Toluene	60	14	46	40	40	60	142
	Sc(OTf) ₃	0.38	Toluene	60	21	48	31	45	55	142
 EMA	None	—	CHCl ₃	60	3	32	65	19	81	142
	Sc(OTf) ₃	0.08	CHCl ₃	60	9	44	47	31	69	142
	Yb(OTf) ₃	0.08	CHCl ₃	60	10	35	55	28	72	142
	HfCl ₄	0.08	CHCl ₃	60	8	33	58	25	75	142
	None	—	CH ₃ OH	0	22	49	29	46	54	146,147
 AM	Sc(OTf) ₃	0.10	CH ₃ OH	0	40	43	17	62	38	146,147
	Yb(OTf) ₃	0.10	CH ₃ OH	0	65	29	6	80	20	146,147
	Y(OTf) ₃	0.10	CH ₃ OH	0	58	33	9	75	25	146,147
	None	—	CH ₃ OH	60	—	—	—	46	54	146,147
	Yb(OTf) ₃	0.10	CH ₃ OH	60	—	—	—	84	16	146,147
 DMAM	None	—	CH ₃ OH	0	—	—	—	49	51	146,147
	Yb(OTf) ₃	0.10	CH ₃ OH	0	—	—	—	88	12	146,147
	None	—	CH ₃ OH	30	—	—	—	50	50	134
	Y(OTf) ₃	0.05	CH ₃ OH	30	—	—	—	86	14	134
	None	—	Benzene	60	—	—	—	58	42	165
 DEAM	None	—	Bulk	60	—	—	—	55	45	165
	Y(OTf) ₃	0.05	Bulk	60	—	—	—	75	25	165
	Y(OTf) ₃	0.05	CH ₃ OH	60	—	—	—	82	18	165

(Continued)

Table 1 Illustrative examples of isotactic control in Lewis acid-mediated radical polymerization of some common polar monomers—cont'd

Monomer (Mon)	Lewis acid (LA)	[LA] ₀ /[Mon] ₀	Solvent	Temperature (°C)	Triad Tacticity (%)			Diad (%)		References
					mm	mr	rr	m	r	
 NIPAM	None	—	CH ₃ OH	−20	—	—	—	44	56	146,147
	Yb(OTf) ₃	0.08	CH ₃ OH	−20	—	—	—	90	10	146,147
	Yb(OTf) ₃	0.20	CH ₃ OH	−20	—	—	—	92	8	146,147
	None	—	CH ₃ OH	60	—	—	—	47	53	157
	Yb(OTf) ₃	0.12	CH ₃ OH	60	—	—	—	88	12	157
 MAM	None	—	CH ₃ OH	60	7	39	54	27	73	148,149
	Yb(OTf) ₃	0.08	CH ₃ OH	60	33	49	18	58	42	148,149
	Yb(OTf) ₃	0.10	CH ₃ OH	0	50	35	15	68	32	148,149
 NIMMAM	None	—	Toluene	60	8	42	50	29	71	148,149
	Yb(OTf) ₃	0.10	Toluene	60	10	43	47	32	68	148,149
	None	—	CH ₃ OH	60	2	29	69	17	83	148,149
	Yb(OTf) ₃	0.10	CH ₃ OH	60	46	44	10	68	32	148,149
	MgBr ₂	0.10	CH ₃ OH	60	4	36	60	22	78	148,149
 NIPMAM	None	—	CH ₃ OH	20	<1	20	80	10	90	148,149
	Yb(OTf) ₃	0.10	CH ₃ OH	20	63	33	4	80	20	148,149
	Yb(OTf) ₃	0.10	CH ₃ OH	−20	67	29	4	82	18	148,149
	Yb(OTf) ₃	0.10	CH ₃ OH	60	58	37	5	77	23	148,149

coordination polymerization without prior protection of the protic amide hydrogens; as these processes yield polymers with an alternative nylon primary structure. In addition, acyclic methacrylamides cannot currently be polymerized by either anionic or coordination polymerization regardless of their substitution¹⁴⁵ which is likely attributable to the instability of the propagating enolate species. Given the difficulties associated with alternative polymerization processes for these monomers, the pioneering work of Okamoto and coworkers in these monomers systems is particularly noteworthy. These authors investigated the use of various rare earth metal triflates in the polymerizations of an array of acrylamides^{146,147} and methacrylamides (Table 1).^{148,149}

Remarkably, for the radical polymerization of *N,N*-disubstituted acrylamides, such as DMA (which are polymerizable directly with anionic and coordination processes), the isotactic control afforded by LAs is comparable to that obtained via anionic polymerization under much more demanding conditions.^{150,151} For instance, Okamoto and coworkers reported that an isotactic content of $m = 88\%$ could be obtained during the radical polymerization of DMA in methanol at 0 °C by using 10 mol% Yb(OTf)₃ as a control agent.^{146,147} Subsequent work by Matyjaszewski and coworkers demonstrated that either RAFT or ATRP could be used concurrently with either Y(OTf)₃ or Yb(OTf)₃ to simultaneously control the tacticity, molecular weight distribution, and chain-end functionality.¹³⁴ Moreover, the presence of only 5 mol% of Yb(OTf)₃ or Y(OTf)₃ was found to be sufficient to induce an isotactic content of $m = 86\%$ in CH₃OH at 30 °C.¹³⁴ Moreover, stereoblock poly(DMA) could be obtained by ATRP polymerizations in the presence of Y(OTf)₃. While initially the level of isotactic control afforded by LAs for DMA was unprecedented, Chen and Mariott subsequently reported near perfect levels of isotactic control ($mm > 99\%$) in the coordination polymerization of DMA by a cationic chiral *ansa*-zirconocene complex.¹⁵² More recently, Hirano and coworkers examined the use of high concentrations of alkali metal triflates and triflimides (MNTf₂), finding that the relatively weak LA, NaNTf₂, in a 1:1 ratio with monomer increased isotactic content to $m = 85\%$ in DMA polymerizations.¹⁵³ While this example of isotactic control is intriguing, it is probably more readily attributed to electrostatic repulsion between the side-chains rather than a chelation mechanism.

Particular biomedical interest is focused on poly(*N*-isopropylacrylamide), because in aqueous solution it undergoes a coil-to-globule transition at around body temperature and so it could have numerous applications as a

thermally responsive smart polymer. In the presence of $\text{Y}(\text{OTf})_3$ in methanol at -20°C , *N*-isopropylacrylamide (NIPAM) could be radically polymerized to afford polymer with an isotactic content of $m = 90\text{--}92\%$, while almost atactic polymer was obtained in the absence of LA ($m = 44\%$).^{146,147} Subsequently, numerous studies demonstrated that LA tacticity control can be used in conjunction with either RAFT^{135,154–159} or ATRP¹⁶⁰ to yield isotactic-rich poly(NIPAM) with controlled molecular weights and chain-ends. Other authors have used RAFT and LA-mediated stereocontrol to synthesize novel stereoblock poly(NIPAM)s.^{135,161–163} It should be noted that in some initial studies, minor degradation of the molecular-weight control (P.D.I > 1.6) was observed in the presence of the LA.¹⁵⁴ However, under more favorable conditions, poly(NIPAM) with an isotacticity of $m = 88\%$ and a P.D.I of < 1.3 could be obtained in the presence of $\text{Y}(\text{OTf})_3$.¹⁵⁷

LAs were also found to quite effective in the radical polymerization of unsubstituted acrylamide (AM). Okamoto noted that the isotactic content of poly(AM) could be increased from $m = 46$ to 80% by including $\text{Yb}(\text{OTf})_3$ as a mediator in CH_3OH . Lu and coworkers later demonstrated that isotactic rich polymer could be obtained in aqueous ATRP polymerizations of AM, using either $\text{Y}(\text{OTf})_3$ or AlCl_3 as mediators.¹³⁸ Lu also demonstrated that isotactic-rich poly(AM) could be on a silicon wafer by immobilizing the ATRP initiator.¹⁶⁴ Interestingly, Li and coworkers reported that AM undergoes a spontaneous stereogradient RAFT polymerization in the presence of $\text{Y}(\text{OTf})_3$.¹³¹ Li noted that in the initial stages of the polymerization, $\text{Y}(\text{OTf})_3$ was ineffective and predominantly atactic poly(AM) formed.¹³¹ However, he noted that isotacticity progressively increased with monomer conversion.¹³¹ Because of the living nature of this polymerization system, poly(AM) with a stereogradient tacticity (atactic to isotactic) was formed.¹³¹

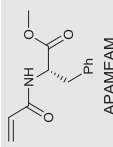
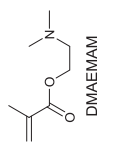
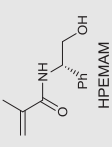
Analogous isotactic control was also noted in both unsubstituted and variously *N*-substituted methacrylamides. Okamoto and coworkers found that the mild syndiotactic preference of MAM ($m = 27\%$) could be reversed by the presence of $\text{Y}(\text{OTf})_3$ to afford isotactic-rich poly(MAM) ($m = 68$).^{148,149} Good levels of isotactic control were also observed for NMMAM in the presence of $\text{Yb}(\text{OTf})_3$, while MgBr_2 was found to be ineffective. In the absence of any mediator, poly(NMMAM) with an isotactic content of $m = 17\%$ was obtained in CH_3OH , while addition of $\text{Yb}(\text{OTf})_3$ afforded isotactic-rich polymer ($m = 68\%$). Interestingly, Okamoto found that stereoregulating effect of $\text{Yb}(\text{OTf})_3$ was much lower in toluene than CH_3OH . This is contrary to the preference observed for MMA, where polar solvents are found to be detrimental to isotactic control. Matyjaszewski and

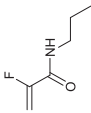
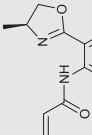
coworkers also demonstrated that either RAFT or ATRP could be used concurrently for molecular weight control of NMMAM polymerizations.¹³³ In the presence of $\text{Yb}(\text{OTf})_3$ or $\text{Y}(\text{OTf})_3$, ATRP or RAFT could be used to synthesize isotactic-rich poly(NMMAM) ($m = 64\text{--}67\%$) with a narrow P.D.I. (<1.20).¹³³ Excellent isotactic control was also observed in NIPMAM, with the high syndiotactic preference of the unmediated polymerization ($m = 10\%$) nearly completely reversed by the inclusion of $\text{Yb}(\text{OTf})_3$ ($m = 80\text{--}82\%$).^{148,149}

We should also briefly discuss attempts to control stereochemistry of several more novel monomers with LAs (Table 2). Endo and coworkers examined the RAFT polymerization of an acrylamide with a chiral L-phenylalanine auxiliary (APAMEAM).¹⁶⁶ In the absence of LA, the polymerization was found to afford nearly completely atactic polymer $m = 49\%$.¹⁶⁶ However, in the presence of high concentrations of $\text{Y}(\text{OTf})_3$ the isotacticity increased to $m = 69\%$.¹⁶⁶ Tenhu and coworkers reported that the presence of $\text{Y}(\text{OTf})_3$ could enhance isotactic content in the radical polymerization of dimethylaminoethyl methacrylate (DMAEMA).¹⁶⁷ The isotactic content of the resulting polymer increased from $m = 18$ to 35% with the inclusion of 0.25 equivalents of $\text{Y}(\text{OTf})_3$.¹⁶⁷ Xu and coworkers recently reported that tacticity in the radical polymerization of a methacrylamide substituted with a chiral 2-hydroxy-1-phenylethyl auxiliary (HPEMAM) could be influenced by the inclusion of LA.¹³² The presence of $\text{Pr}(\text{OTf})_3$ increased the isotactic content of the resulting polymer from $m = 14$ to 62% .¹³² We should note that it is possible that this isotactic control partially results from the presence of the chiral 2-hydroxy-1-phenylethyl auxiliary. HPEMAM could potentially coordinate to chelating LA through both the amide and hydroxyl O atoms simultaneously to afford a 7-membered ring. Such chelation would likely lead to facial discrimination of the prochiral center by the Ph group and hence the overall isotactic content could be enhanced by chiral auxiliary control. Indeed, consistent with this argument, we note that the triad tacticity in the presence of LA is fairly non-Bernoullian ($mm/mr/rr = 42/40/18$),¹³² with a relative excess of mm and rr triads.

Hirano and coworkers investigated isotactic control of *N,n*-propyl- α -fluoroacrylamide (NPFAM) by various LAs.¹⁶⁸ In contrast to the quite high levels of isotactic control reported for ordinary acrylamides and methacrylamides, LAs had very little effect on the isotactic content of the resulting fluorine-containing polymers.¹⁶⁸ Interestingly, Shen and coworkers reported that LAs were highly effective for the isospecific polymerization of an acrylamide bearing a chiral oxazolidine auxiliary (MOPAM).¹⁶⁹ In the

Table 2 Illustrative examples of isotactic control in Lewis acid-mediated radical polymerization of some novel polar monomers

Monomer (Mon)	Lewis acid (LA)	[LA] ₀ /[Mon] ₀	Solvent	Temperature (°C)	Triad Tacticity (%)			Diad (%)		References
					mm	mr	rr	m	r	
 APAMEAM	None	—	Dioxane	60	—	—	—	49	51	166
	Y(OTf) ₃	0.05	Dioxane	60	—	—	—	62	58	166
	Y(OTf) ₃	0.20	Dioxane	60	—	—	—	68	32	166
	Y(OTf) ₃	0.50	Dioxane	60	—	—	—	69	31	166
	Yb(OTf) ₃	0.20	Dioxane	60	—	—	—	66	34	166
	Sc(OTf) ₃	0.05	Dioxane	60	—	—	—	61	39	166
 DMAEMAM	None	—	DMF	60	0	35	65	18	82	167
	None	—	ⁱ PrOH	60	0	33	67	17	83	167
	Y(OTf) ₃	0.12	ⁱ PrOH	60	3	40	57	23	77	167
	Y(OTf) ₃	0.25	ⁱ PrOH	60	16	37	47	35	65	167
 HPENAM	None	—	CH ₃ OH	60	3	25	72	16	84	132
	Y(OTf) ₃	0.20	CH ₃ OH	60	29	36	35	47	53	132
	Pr(OTf) ₃	0.20	CH ₃ OH	60	34	39	27	54	46	132
	Ce(OTf) ₃	0.20	CH ₃ OH	60	35	38	27	54	46	132
	La(OTf) ₃	0.20	CH ₃ OH	60	36	39	25	56	44	132
	LaCl ₃	0.20	CH ₃ OH	60	18	33	49	35	65	132
	ZnCl ₂	0.20	CH ₃ OH	60	6	22	72	17	83	132
	None	—	ⁿ BuOH	60	4	19	77	14	86	132
	Pr(OTf) ₃	0.20	ⁿ BuOH	60	42	40	18	62	38	132

 NPFAM	None	—	CH ₃ OH	−40	9	50	41	34	66	168
	Sc(OTf) ₃	0.10	CH ₃ OH	−20	12	52	36	38	62	168
	Y(OTf) ₃	0.10	CH ₃ OH	−20	13	53	34	39	61	168
	Li(OTf)	0.10	CH ₃ OH	−20	10	51	38	36	64	168
	Sm(OTf) ₃	0.10	CH ₃ OH	−20	9	58	33	38	62	168
	None	—	ⁿ BuOH	60	—	—	—	36	64	169
	Y(OTf) ₃	0.10	ⁿ BuOH	60	—	—	—	71	29	169
	Y(OTf) ₃	0.30	ⁿ BuOH	60	—	—	—	85	15	169
	Y(OTf) ₃	0.50	ⁿ BuOH	60	—	—	—	91	9	169
	Y(OTf) ₃	1.00	ⁿ BuOH	60	—	—	—	95	5	169
 MOPAM	None	—	CH ₃ OH	60	—	—	—	15	85	169
	Y(OTf) ₃	0.50	CH ₃ OH	60	—	—	—	48	52	169

absence of any additive, the radical polymerization of MOPAM afforded syndiotactic-rich atactic polymer ($m = 36\%$). However, in the presence of a stoichiometric amount of $Y(OTf)_3$, polymer with an isotactic content of $m = 95\%$ was obtained.¹⁶⁹ As with the previous chiral monomer examples, it is possible that the excellent isotactic control obtained for MOPAM partially reflects concurrent chiral auxiliary control. Indeed, in contrast to the LA-mediated radical polymerizations of ordinary achiral monomers, $Y(OTf)_3$ was required in stoichiometric quantities, otherwise isotactic content progressively decreased.

Most of the studies reported to date have focused on the polymerization of (meth)acrylamides and methacrylates. Okamoto and coworkers examined the use of nonchelating LAs including, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), in the radical polymerization of vinyl acetate and vinyl pivalate.¹⁷⁰ Unfortunately, the LAs were found to be fairly ineffective in these vinyl ester systems, with no significant tacticity changes observed.¹⁷⁰ Significant stereochemical effects were noted by Kuwahara in the radical polymerization of vinyl acetate and AN in the presence of a stoichiometric amount of Mg or Co halides.^{171,172} However, such effects are more readily attributed to geometric confinement of the propagating species within the heterogeneous reaction mixture. Lu and coworkers examined the ATRP of AN in the presence of a low concentration of $AlCl_3$, finding minor increases in isotactic content.¹³⁷ More recently, Chen performed ATRP polymerizations of AN in the presence of YBr_3 and also noted minor increases in isotactic content.¹³⁶

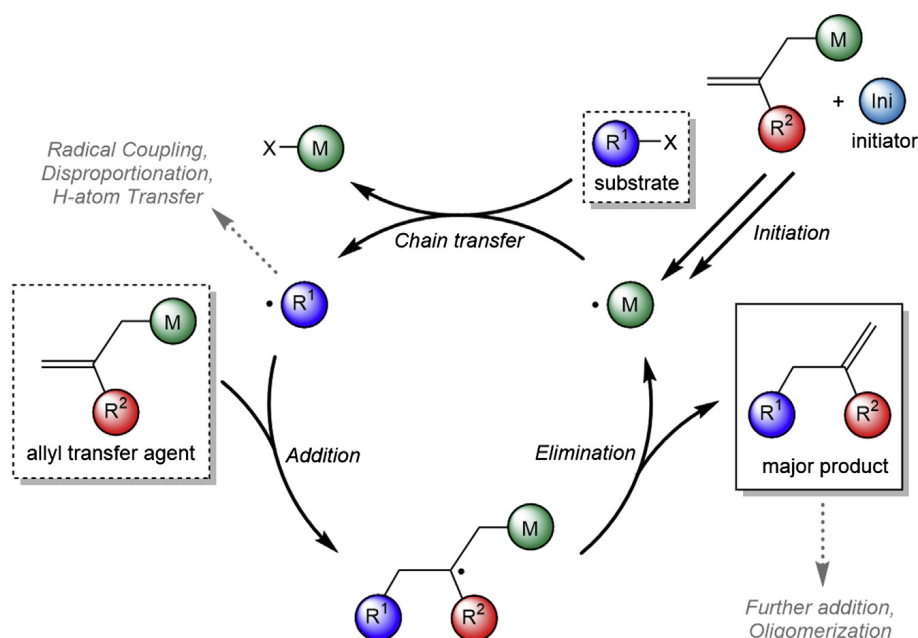


5. SYNTHETIC RADICAL TRANSFORMATIONS

Radicals have become increasingly popular in synthesis over the last few decades, as they can promote a diverse array of transformations under mild conditions with high productivity; often allowing multiple functional groups to be installed, converted and/or removed in a single synthetic step. Such versatile reactivity is exemplified by radical cascade reactions, which use both inter- and intramolecular reactions to rapidly create complex frameworks for natural product synthesis, often without the need to use protecting groups.¹⁷³ A plethora of useful synthetic transformations involving radicals has been developed including, dehalogenation,²⁰ allylation,^{174–176} conjugate addition,^{47,50} decarboxylation,^{177–180} deoxygenation,^{181–183} and various coupling reactions.^{184–186} As this work is primarily concerned with

radical polymerization, we will limit our discussions of these synthetic transformations to chain processes involving C-centered radicals: particularly, reduction, allylation, and alkene addition reactions. The development of efficient radical-based processes over the last few decades can largely be attributed to a better understanding of radical reactivity and selectivity and detailed kinetic analysis. Given the importance of understanding the underlying mechanism of transfer and addition reactions, a general summary of these processes is provided below.

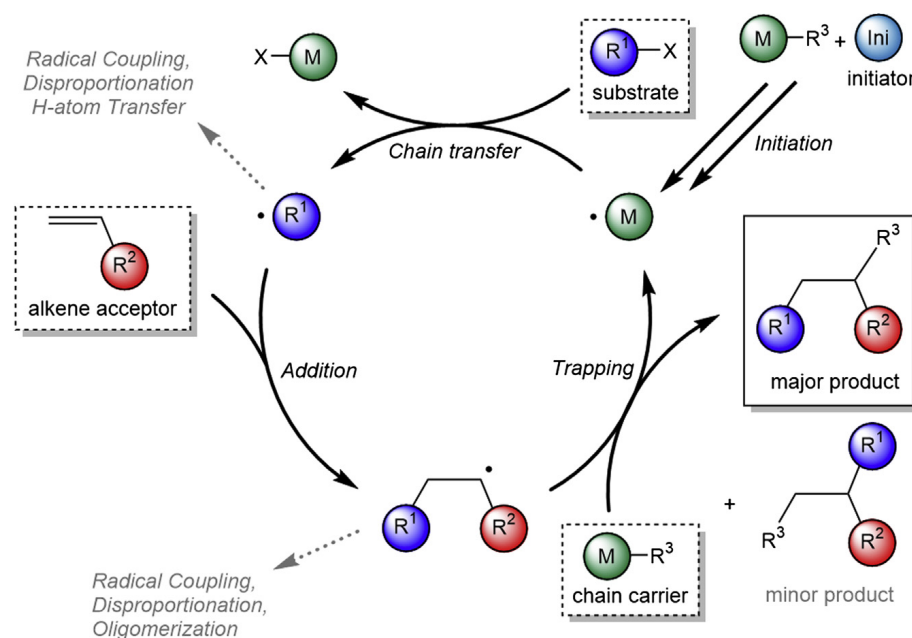
A majority of synthetically useful radical transformations, including addition and transfer, occur via chain processes that are comprised of elementary initiation, propagation, and termination reactions. Radical allylations are chain-based group-transfer reactions in which a radical substrate adds to an allyl-based transfer agent, with the product radical undergoing β -fragmentation to afford an allyl-substituted substrate. Classically, allylstannanes or allylsilanes are used as the transfer agent; however pioneering work has demonstrated the viability of alkyl sulfones as well.^{174–176} In most radical allylations, the allyl acceptor also functions as a source of radical chain carrier (mediator). A general scheme for a radical allylation with a substituted allyl transfer agent ($\text{H}_2\text{C}=\text{CR}^2-\text{CH}_2\text{M}$) is shown in Scheme 6. Many of the unwanted side-reactions in radical allylations can be suppressed by the



Scheme 6 A general scheme for radical allylation.

appropriate choice of initiator, allyl transfer agent, and radical substrate concentrations. Arguably, the most significant limitation of these reactions is the need to prevent further addition to the allyl-substituted product. Polar effects are also frequently employed to ensure rapid allylation and minimize side-reactions.

Radical addition to alkenes can be regarded as a small model for the propagation step in radical (co)polymerizations, but one in which the product radical is then deliberately trapped by atom or group transfer. Contemporary radical addition reactions are carefully designed to minimize side-reactions and maximize productivity and selectivity. Conjugate radical additions to α,β -unsaturated carbonyl acceptors are particularly popular, because in contrast to many ionic transformations they display excellent functional group tolerance and 1,4-chemoselectivity. A general reaction scheme for a synthetic radical addition reaction of a monosubstituted alkene ($\text{H}_2\text{C}=\text{CHR}^2$) is shown in Scheme 7. These reactions normally couple a radical substrate to an alkene acceptor via a radical chain process, trapping the product radical with an appropriate atom or group transfer agent. Well-designed synthetic addition reactions can suppress oligomerization (or polymerization) and direct reduction by carefully modulating the reactivity of the alkene



Scheme 7 A general scheme for radical addition reaction to an alkene followed by atom or group transfer.

acceptor, radical substrate, and transfer agent. Other side-reactions, including radical coupling and disproportionation, can be limited by maintaining low radical concentrations. As previously noted, radical addition reactions are usually fairly regioselective, with preferential addition to the more accessible C atom of the C=C bond to yield the more substituted and stabilized radical. These reactions also usually capitalize on polar effects by matching the electronic character of the radical substrate and alkene acceptor.



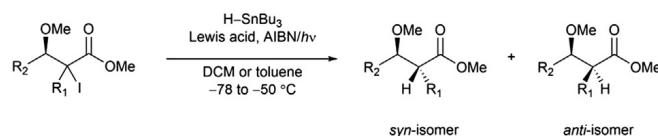
6. LEWIS ACIDS IN RADICAL-BASED SYNTHETIC TRANSFORMATIONS

While synthetic radical transformations, such as atom and group transfer and conjugate addition, can be highly productive and extraordinarily versatile, diastereoselectivity is quite variable. In some systems, underlying steric and/or dipolar interactions can lead to surprisingly high levels of diastereoselectivity, even in the absence of specific control agents. However, for many substrates these transformations are not appreciably diastereoselective, which obviously limits their synthetic utility. Over last few decades, several pioneering researchers have discovered that LAs can facilitate extraordinary high levels of diastereocontrol in radical-based atom transfer, allylation and addition reactions, in some cases exceeding 99%. As already noted, many synthetic reactions capitalize on polar effects by matching the electronic character of the radical substrates to the accepting species. Thus, the inclusion of LAs in such transformations can also increase yields, as LAs can enhance the polar differentiation between radicals and different alkenes or allyl traps. We should emphasize that our aim is not to exhaustively outline all of the LA-mediated radical transformations that have been reported in the literature. Rather, we select a few pivotal studies to illustrate some of the important discoveries that have been made in small-molecule systems over the last two decades, prior to discussing their relevance to LA-mediated radical polymerization. For a more comprehensive summary of radical transformations and the application of LAs in radical synthesis, the reader is directed to some excellent reviews.^{46–53}

Chelation-based stereocontrol utilizes the coordinative interaction between a chelating LA and two Lewis base donor groups to fix the conformation of the radical substrate (or alkene) in a rigid cyclic adduct. Steric or dipolar interactions between the substituents of the remote stereocenter(s) and the incoming reagents can then alter the underlying diastereoselectivity of the transformation. Arguably, the first example that convincingly

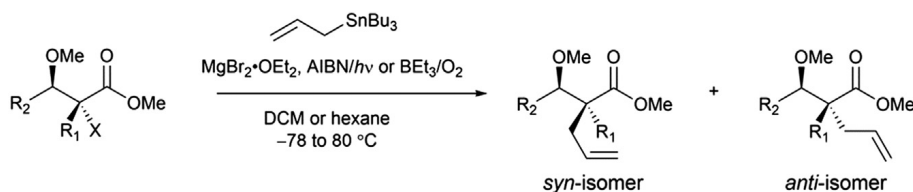
demonstrated the utility of LAs as stereocontrol agents in acyclic radical synthesis was reported by Guindon and coworkers in the early 1990s.¹⁸⁷ Guindon found that the high *syn*-selectivity preference of unmediated radical reductions of various α -iodo- β -methoxy esters^{188,189} could be inverted by addition of various LAs (Scheme 8).¹⁸⁷ For instance, when the radical-promoted reduction of the *anti*-isomer of the 1-iodo-1-methyl-2-methoxy-2-phenyl methyl ester was performed in the presence of MgI_2 , $\text{MgBr}_2 \cdot \text{OEt}_2$ or AlCl_3 high selectivity for the *anti*-product isomer (*anti* = 96% *ds*) was observed, in contrast to the high *syn*-selectivity of the unmediated reaction (*syn* = 96% *ds*). Interestingly, MgI_2 and $\text{MgBr}_2 \cdot \text{OEt}_2$ were found to afford high selectivity even at catalytic concentrations, while AlCl_3 was significantly less effective at substoichiometric concentrations. In the unmediated reaction, no difference in diastereoselectivity is observed between *syn*- and *anti*-isomers of the substrate, confirming that the conformational equilibration of the intermediate radical species is rapid. Interestingly, chelate control was found to be significantly more effective for the *anti*-isomer of the substrate iodides compared to the *syn*-isomers. Guindon later demonstrated that α -alkoxy- or α -hydroxyl-methylacrylates could be used as alkene substrates in radical addition reactions, with stereoselective H-transfer occurring in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$.¹⁹⁰

Guindon also subsequently demonstrated that $\text{MgBr}_2 \cdot \text{OEt}_2$ afforded excellent diastereocontrol in the radical allylation of these α -iodo- β -methoxy esters substrates (Scheme 9).¹⁹¹ At high temperatures in the absence of LA, these allylations were found to be modestly selective for the *syn*-isomer depending on the substitution (see R_1 and R_2 in Scheme 9). However, at low temperatures with three equivalents of $\text{MgBr}_2 \cdot \text{OEt}_2$, very high



substrate isomer	R_1	R_2	Temp ($^\circ\text{C}$)	Solvent	$[\text{MgI}_2]_0/[\text{substrate}]_0$	<i>syn:anti</i> (product)
<i>anti</i>	Me	Ph	-78	Toluene	None	96/4
<i>syn</i>	Me	Ph	-78	Toluene	None	96/4
<i>anti</i>	Me	Ph	-50	DCM	2	4/96
<i>syn</i>	Me	Ph	-50	DCM	2	80/20
<i>anti</i>	^tPr	Ph	-78	Toluene	None	96/4
<i>anti</i>	^tPr	Ph	-50	DCM	2	4/96
<i>syn</i>	^tPr	Ph	-50	DCM	2	70/30

Scheme 8 Radical reduction of various 1-iodo 2-methoxy esters in the presence and absence of MgI_2 .



R ₁	R ₂	Temp (°C)	[MgBr ₂ ·OEt ₂] ₀ /[substrate] ₀	<i>syn:anti</i>
H	Ph	70-80	None	83/17
H	Ph	-78	3.0	3/97
H	Me	70-80	None	75/25
H	Me	-78	3.0	2/98
H	<i>c</i> -C ₆ H ₁₁	70-80	None	78/22
H	<i>c</i> -C ₆ H ₁₁	-78	3.0	1/99
H	<i>t</i> Pr	70-80	None	77/23
H	<i>t</i> Pr	-78	3.0	1/99
Me	Ph	70-80	None	94/6
Me	Ph	-78	3.0	1/99
Me	Me	70-80	None	82/18
Me	Me	-78	3.0	1/99
Me	Et	70-80	None	83/17
Me	Et	-78	3.0	1/99

Scheme 9 Radical allylation of 1-iodo-2-methoxy esters in the presence and absence of MgBr₂·OEt₂.

anti-selectivity was obtained, ranging from 97 to 99%, depending on the substituents of the 1-iodo 2-methoxy ester framework. The remarkable effectiveness of this chelation-based stereocontrol is best demonstrated by the 1-methyl 2-phenyl substrate, as the high *syn*-selectivity of the unmediated allylation (*syn* = 94% *ds*) is completely reversed by the addition of MgBr₂·OEt₂, which affords exceptional *anti*-selectivity (*anti* >99% *ds*). As with the previously reported radical reductions, Guindon noted that chelation control was significantly more effective for the *anti*-isomer of the starting iodide substrate compared with the *syn*-isomer. However, in contrast to the reduction reactions, the allylation of these substrates required stoichiometric amounts of MgBr₂·OEt₂ to obtain high diastereoselectivity. These reactions could also be performed with the bromide and phenyl selenium analogues of these iodo-ester substrates. Subsequent work also demonstrated the effectiveness of an alternative tin-free transfer agent, allyltrimethylsilane, for allylation reactions with these substrates.¹⁹²

Given the dramatic reversal of diastereoselectivity that LAs induce in these reductions and allylations, it is worth examining the mechanism of this regulation. To minimize A^{1,2}/A^{1,3} strain and dipole–dipole repulsion

(between the COOMe and OMe groups), the uncomplexed radical substrate adopts the conformation shown in Figure 5. H-transfer and allyl addition to the top face of the radical is disfavored by steric interaction with the R^2 group. Thus, addition and transfer occurs preferentially to the bottom face, selectively affording *syn*-isomers. Incorporating a chelating LA reverses this preference by simultaneously coordinating the COOMe and OMe groups in a 6-membered chelate. This coordination leads to the substrate conformation depicted in Figure 5, where addition and transfer to the top face is disfavored because of steric interactions between the incoming reagent and R^2 . In this case, addition and transfer occurs on bottom face of the radical to afford the *anti*-isomers as shown.

The effect of substrate stereochemistry on chelation control has not yet been fully explained. Computational studies of the unmediated reactions have confirmed that conformational equilibration of some of the relevant radical species are significantly faster than H-transfer from a model of H-SnBu₃,¹⁹³ which is consistent with the experimental results. The differing selectivity of substrate isomers under chelation conditions seemingly suggests that in the presence of LA, conformational equilibration of the radical intermediate is slower than trapping by the relevant atom or group transfer agents. Thus, the population of radical conformations would be under kinetic control and hence would be dependent on the stereochemistry of the substrate isomer and its tendency to chelate MgBr₂·OEt₂.

One of the first studies that examined the effect of LAs on diastereoselectivity in intermolecular radical additions reactions was reported by Toru and coworkers in 1993 (Scheme 10).¹⁹⁴ In the absence of any additive, the addition of ^tBu radical to the cyclic chiral alkene (*R*)-(-)-2-((3,5-di-*tert*-butyl-4-methoxyphenyl)-sulfinyl)-2-cyclopentenone was found to be relatively unselective, affording diastereomers **I** and **II** in roughly equal proportions. However, the inclusion of TiCl₂(OⁱPr)₂ afforded isomer **I** with

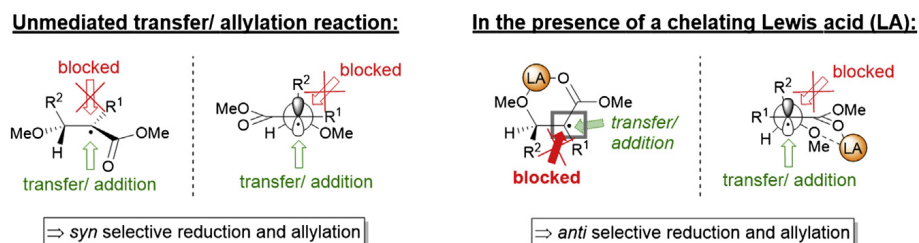
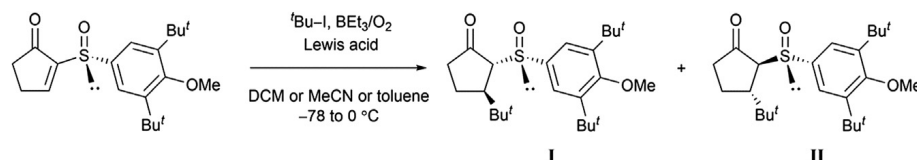


Figure 5 A simplified depiction of the mechanism of diastereoselection in 2-methoxy ester systems in the absence and presence of a chelating Lewis acid (LA).



Scheme 10 Radical conjugate addition to the sulfinyl-substituted 2-cyclopentenone.

high diastereoselectivity (95% *ds*). Interestingly, other LAs, namely ZnBr_2 and $\text{Ti}(\text{O}^i\text{Pr})_4$, afforded virtually no selectivity. The reaction solvent was also found to have a minor influence on stereoselectivity with dichloromethane (DCM) affording better control than acetonitrile or toluene. Interestingly, significantly better control was observed at higher temperatures, with *ds* increasing from 75% to 95% as temperature was increased from -78 to 0°C .

A probable mechanism for this regulation is depicted in Figure 6. In the absence of chelating LA, the substrate alkene probably exists as a mixture of *s-cis* and *s-trans* conformations. In the *s-trans* conformation, the bulky group (3,5-di-*tert*-butyl-4-methoxyphenyl) shields the bottom face of the alkene and addition of $t\text{Bu}$ radicals would occur from the opposite (top) face yielding isomer **I**. However, in *s-cis* conformation, this bulky group is shielding the top face of the alkene and so addition would occur at the bottom face

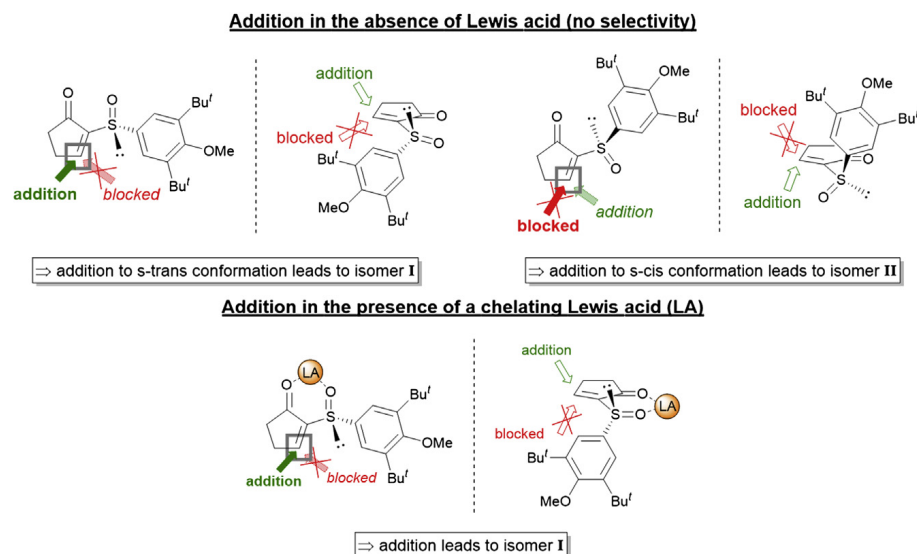
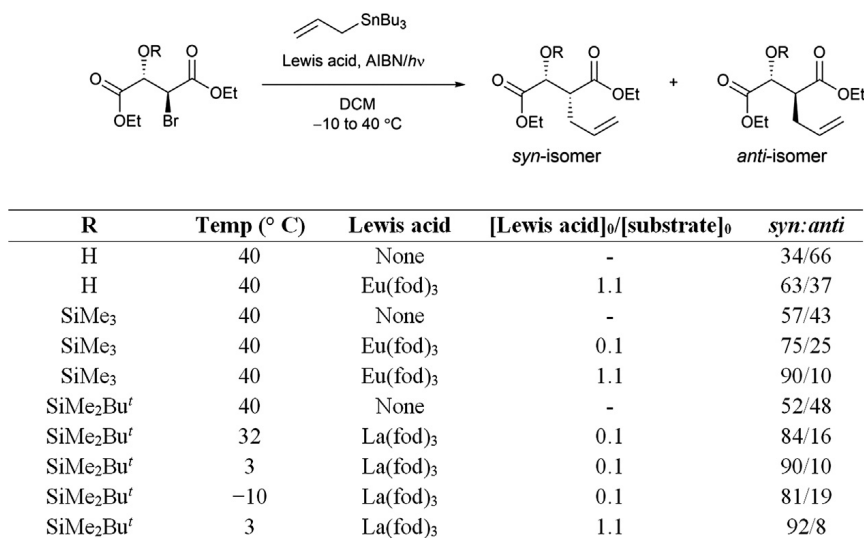


Figure 6 Probable conformations for the sulfinyl-substituted 2-cyclopentenone in the absence and presence of a chelating LA.

to yield isomer **II**. The absence of any control in the unmediated reaction seemingly implies that both conformations are nearly degenerate and similarly reactive. However, addition of a chelating LA would enforce the *s-trans* conformation and lead to high selectivity for isomer **I**.

Nagano and coworkers reported that diastereoselectivity during the allylation of various α -bromo- β -siloxy diester frameworks by allyltributylstannane could be influenced by the addition of various LAs (Scheme 11).^{195,196} In the absence of stereocontrol agents, allylations on these substrates were not stereoselective and afforded roughly equal quantities of the *syn*- and *anti*-isomers.^{195,196} However, in the presence of lanthanum tris(6,6,7,7,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione) (La(fod)₃), allylations on the R=SiMe₂Bu^f isomer were highly *syn*-selective (90–92% *ds*), even at catalytic LA loading.^{195,196} Similarly high levels of diastereoselectivity could be obtained on the R=SiMe₃ substrate by employing Eu(fod)₃.^{195,196} Interestingly, LAs were found to be relatively ineffective for stereocontrol in allylations of the hydroxyl substrate (R=H).^{195,196} Nagano also showed that when the β -ethyl ester group was replaced with a noncoordinating methyl group, the diastereoselectivity afforded by LAs was reversed and the *anti*-isomer was obtained with 80% *ds*; as would be anticipated from the earlier work of Guindon and coworkers.

From these experiments, Nagano concluded that the *syn*-selectivity observed for the siloxy diesters results from chelation of both of the ethyl



Scheme 11 Radical allylation of 3-bromo-2-oxysuccinate frameworks in the presence and absence of La(fod)₃.

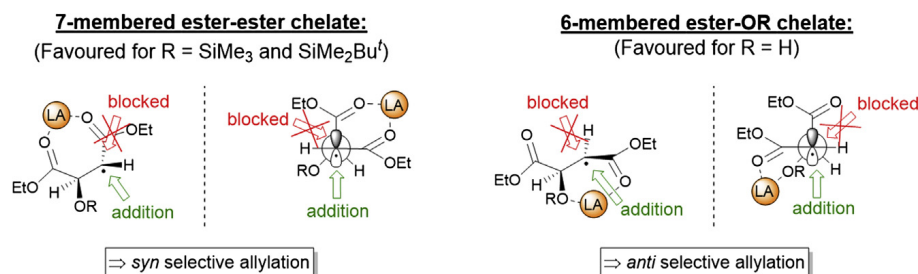
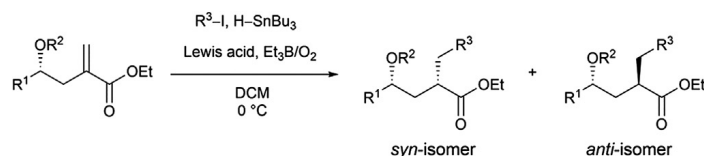


Figure 7 A simplified depiction of the mechanism of diastereoselection in α -bromo- β -oxy diester frameworks in the presence of a chelating Lewis acid (LA).

ester groups by La(fod)₃ to form a 7-membered ring (see Figure 7). He concluded that the bulkiness of the silyl R groups (R = SiMe₃, SiMe₂Bu^t) prevents the siloxy (OR) moiety from coordinating to the LA and so prevents the formation of an *anti*-selective 6-membered chelate (see Figure 7). Thus, the relatively poor control observed for the hydroxyl substrate (R = H) probably reflects competitive formation of both 6- and 7-membered chelates, which have divergent selectivity preferences.

Nagano also studied alkyl radical addition to variously substituted 3-hydroxyl and 3-alkoxy-1-methylene ethyl esters (Scheme 12).^{195,196} In the absence of LA, this transformation was found to be essentially unselective. However, the addition of various LAs, including MgBr₂·OEt₂, MgBr₂,



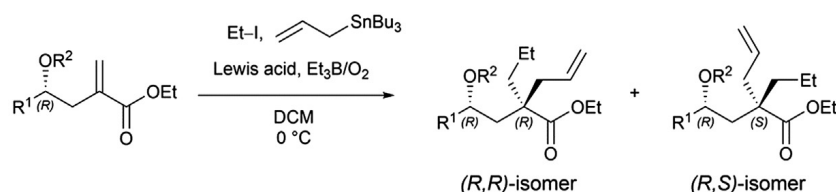
R ¹	R ²	R ³	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	<i>syn:anti</i>
Ph	H	^t Pr	None	-	42/58
Ph	H	^t Pr	MgBr ₂ ·OEt ₂	3.0	71/29
Ph	Me	^t Pr	MgBr ₂ ·OEt ₂	3.0	81/19
Ph	Me	^t Pr	MgBr ₂	3.0	82/18
Ph	Me	^t Pr	ZnCl ₂	3.0	82/18
Ph	Me	^t Pr	Eu(fod) ₃	1.0	82/18
Ph	Me	^t Pr	La(fod) ₃	1.0	92/8
Ph	Me	^t Bu	MgBr ₂ ·OEt ₂	3.0	21/79
Ph	Me	^t Bu	La(fod) ₃	1.0	13/88
Ph	CH ₂ OMe	^t Pr	MgBr ₂ ·OEt ₂	3.0	74/26
Ph	CH ₂ OMe	^t Pr	La(fod) ₃	1.0	76/24
^t Bu	CH ₂ OMe	^t Pr	MgBr ₂ ·OEt ₂	3.0	91/9
^t Bu	CH ₂ OMe	^t Pr	La(fod) ₃	1.0	67/33

Scheme 12 Radical addition to 3-hydroxyl and 3-alkoxy-1-methylene ethyl esters in the presence and absence of Lewis acids.

ZnCl₂, Eu(fod)₃, and La(fod)₃, was found to improve *syn*-diastereoselectivity for most substrates, as would be anticipated from previous allylations of α -bromo- β -siloxy diesters. The selectivity afforded by La(fod)₃ and MgBr₂·OEt₂ was substrate dependent. The addition of the ⁱPr radical to the 3-phenyl-3-methoxyl ester (R¹=Ph, R²=Me) proceeded with selectivity for *syn*-isomer of 92% in the presence of La(fod)₃. Interestingly, when an analogous addition reaction was performed with the ^tBu radical, the selectivity afforded by chelate control was reversed and *anti*-selectivity of 88% was observed.

Nagano also investigated allylations of the intermediate radicals formed from the addition of ethyl radicals to these alkoxy-1-methylene ethyl esters (Scheme 13).¹⁹⁷ Contrary to the H-transfer reactions reported above,^{195,196} allylation of these substrates (after ethyl radical addition) did not proceed cleanly in the absence of LA and afforded a complex mixture of products. The inclusion of LAs afforded the (*R,R*) isomers in modest yield (~50%) and with high diastereoselectivity (up to 94% *ds*). Interestingly, MgBr₂·OEt₂ was found to be a more effective stereocontrol agent than MgBr₂, which Nagano attributed to the increased solubility in the reaction mixture. Some of the important factors influencing stereoselectivity in these reactions were later clarified by conformational analysis of the 7-membered radical chelate intermediates.¹⁹⁸ It should also be noted that these reactions can be performed with steroidal R¹ groups.¹⁹⁹

Metzger and coworkers reported that diastereoselectivity in the addition of various alkyl radicals to 1-methylene-3-alkyl-dimethyl glutarate (followed

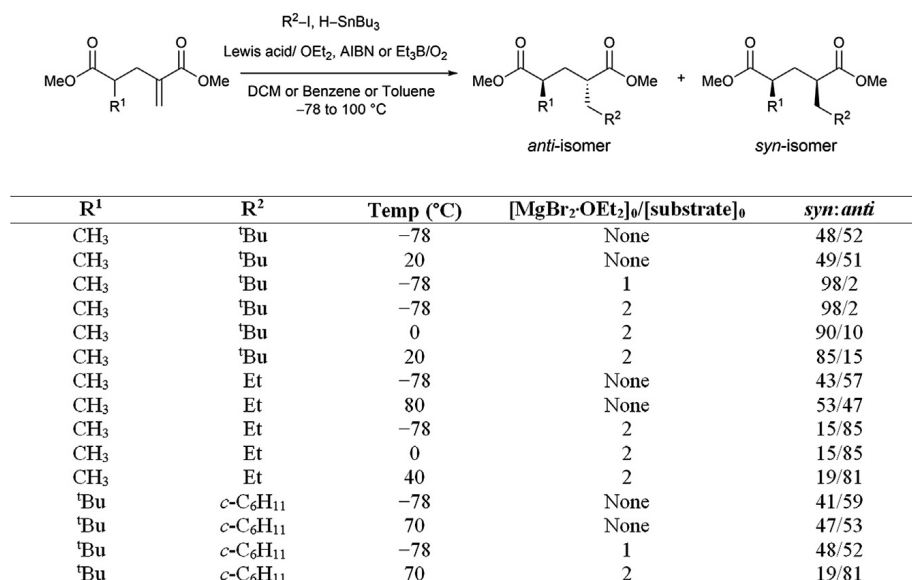


R ¹	R ²	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	(<i>R,R</i>):(<i>R,S</i>)
Ph	Me	MgBr ₂ ·OEt ₂	3.0	92/8
Ph	Me	MgBr ₂	3.0	86/14
Ph	CH ₂ Ph	MgBr ₂ ·OEt ₂	3.0	94/6
Ph	CH ₂ Ph	MgBr ₂	3.0	89/11
Ph	CH ₂ Ph	MgBr ₂ ·(OEt ₂) ₃	3.0	93/7
Ph	CH ₂ Ph	Et ₂ AlCl	1.2	50/50

Scheme 13 Radical addition to 3-hydroxyl and 3-alkoxy-1-methylene ethyl esters followed by allylation in the presence of various Lewis acids.

by trapping with tributyltin hydride) could be controlled by the addition of LAs (Scheme 14).^{200,201} Metzger thoroughly examined the influence of the reaction conditions on diastereoselectivity; performing these reactions at different temperatures with various LAs and solvents.²⁰¹ Metzger also examined the effect of different alkyl substitutions of the adding radical and the alkene substrate.²⁰¹ Interestingly, good yields and diastereoselectivity were obtained with LiClO_4 , MgBr_2 , $\text{MgBr}_2 \cdot \text{OEt}_2$, MgI_2 , and $\text{Sc}(\text{OTf})_3$, while other LA mediators, such as AlCl_3 , $\text{Al}(\text{O}^i\text{Pr})_3$, AlMe_3 , CeCl_3 , ZnBr_2 , and InCl_3 , resulted in either low yield and/or selectivity.²⁰¹ High selectivity was obtained with diethyl ether, DCM, or toluene as solvents, but selectivity was significantly lower in THF and pentane.²⁰¹ Interestingly, temperature was found to have a variable effect on selectivity depending on the size of the adding radical species (R^2). With $\text{R}^2 = ^i\text{Bu}$, the selectivity afforded by $\text{MgBr}_2 \cdot \text{OEt}_2$ was found to noticeably decrease with increases in temperature; decreasing from 98% *syn*-selectivity at -78°C to 54% at 100°C . With $\text{R}^2 = \text{Me}$, this selectivity was found to be essentially temperature independent. Finally, with $\text{R}^2 = c\text{-C}_6\text{H}_{11}$, selectivity increased with reaction temperature; with *anti*-selectivity improving from 52% at -78°C to 81% at 70°C .

As Metzger and coworkers outlined, the divergent diastereoselectivity afforded by $\text{MgBr}_2 \cdot \text{OEt}_2$ for different R^2 groups is likely attributable to



Scheme 14 Radical addition reactions to 1-methylene-3-alkyl-dimethyl glutarates in the presence and absence of a chelating Lewis acid.

variations in the conformation of the chelated radical. With small R^2 groups such as Me and Et, it is likely that the chelate adopts a conformation where the R^2 substituent shields the top face of the radical, with H-transfer occurring at the bottom face (Figure 8). Provided there is a sufficient preference for the “linear” chelate conformation, H-transfer would afford the *anti*-isomer. For much larger R^2 groups, namely Bu^t , it is probable that the chelate would adopt a conformation where the R^2 substituent shields the bottom face of the radical, with H-transfer now occurring at the top face (Figure 8). Assuming a “linear” conformation, H-transfer would afford the *syn*-isomer as shown. The higher absolute diastereoselectivity of the $R^2 = Bu^t$ examples could reflect greater steric interactions between the incoming $H\text{SnBu}_3$ and the R^1 substituent in the competing helical pathway.

The pioneering work of Sibi and coworkers has elegantly demonstrated the use of chiral and achiral oxazolidinones in synthetic radical transformations. In the mid-1990s, Sibi and coworkers reported that LAs could facilitate very high levels of diastereoselectivity in radical allylations of bromide substrates carrying chiral oxazolidinone auxiliaries (Scheme 15).²⁰² In the absence of any mediator, these allylation reactions were found to be essentially unselective. By using chelating LAs, such as $MgBr_2$, to control the conformer populations, Sibi found that exceptional levels of diastereoselectivity (>99%) could be obtained. When the size of the R group was reduced from $R = CHPh_2/CH_2Ph$ to $R = CHMe_2/Ph$, selectivity afforded by $MgBr_2$ was significantly reduced.

Sibi also investigated radical addition to chiral oxazolidinone acrylamides and diastereoselectivity in the subsequent allylation of the product radical (Scheme 16).²⁰³ In the absence of LA, the allylations were found to be unselective.²⁰³ However, for the $R = \text{alkyl}$ substrates, the inclusion of $MgBr_2 \cdot OEt_2$ afforded excellent diastereocontrol (>99%) for the

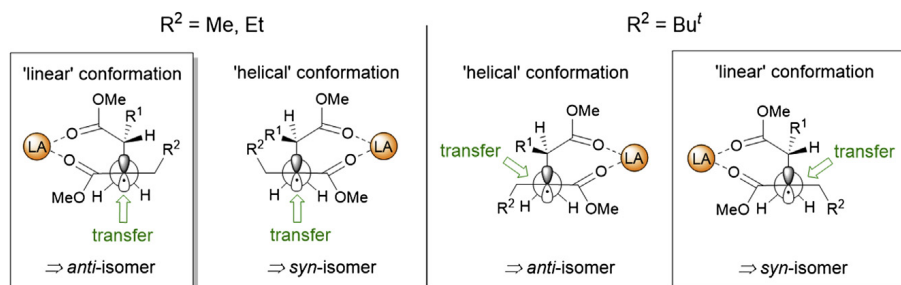
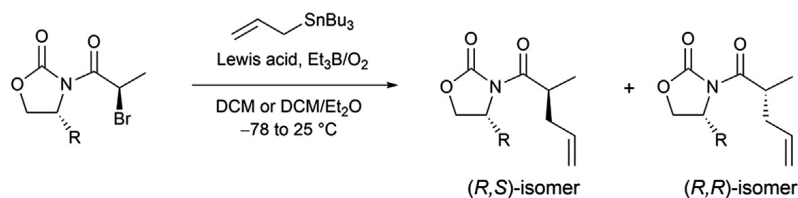


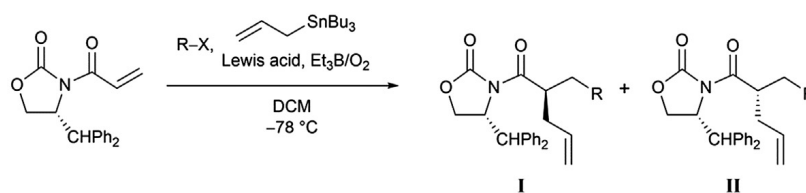
Figure 8 Possible intermediate radical conformations for the substituted glutarates in the presence of $MgBr_2 \cdot OEt_2$.



R	Temp (°C)	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	(R,S):(R,R)
CHPh ₂	-78	None	-	36/64
CHPh ₂	-78	BF ₃ ·OEt ₂	2.0	42/58
CHPh ₂	-78	ZnCl ₂	2.0	86/14
CHPh ₂	-78	Zn(OTf) ₂	2.0	88/12
CHPh ₂	-78	MgI ₂	2.0	>99/1
CHPh ₂	-78	MgBr ₂	2.0	>99/1
CHPh ₂	25	MgBr ₂	2.0	97/3
CHPh ₂	-78	Yb(OTf) ₃	1.0	94/6
CHPh ₂	-78	Sc(OTf) ₃	1.0	>99/1
CH ₂ Ph	-78	None	-	50/50
CH ₂ Ph	-78	MgBr ₂	2.0	94/6
CH ₂ Ph	-78	Sc(OTf) ₃	1.0	98/2

Scheme 15 Radical allylation of various chiral oxazolidinones substrates in the presence and absence of chelating Lewis acids.

I-isomer.²⁰³ Interestingly, when a nucleophilic radical source was utilized ($R = \text{MeOCH}_2$), MgBr_2 was found to be much less effective but high levels of selectivity could be obtained with Yb(OTf)_3 .²⁰³ This lower selectivity might be attributable to competing coordination of the methoxy substituent



R	X	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	I:II
Et	I	None	-	50/50
Et	I	MgBr ₂	2.0	>100/1
ⁱ Pr	I	MgBr ₂	2.0	>100/1
^t Bu	I	MgBr ₂	2.0	>100/1
MeOCH ₂	Br	MgBr ₂	2.0	64/36
MeOCH ₂	Br	Yb(OTf) ₃	1.0	98/2
MeCO	Br	MgBr ₂	2.0	98/2
PhCO	Br	MgBr ₂	2.0	98/2

Scheme 16 Radical addition and subsequent allylation of various chiral oxazolidinone substrates in the presence and absence of chelating LAs.

to MgBr_2 to form a 7-membered chelate. Such chelation could prevent the formation of the “normal” 6-membered bis(carbonyl) complex (see Figure 9 below) and so degrade the conformation control of the radical intermediate. $\text{Yb}(\text{OTf})_3$ may either selectively form the 6-membered chelate or it could feasibly coordinate to both the carbonyl groups and the methoxy group simultaneously. Interestingly, MgBr_2 was still effective for diastereocontrol in transformations with acid bromides ($\text{R} = \text{MeCO}$ and PhCO).

Sibi and coworkers also thoroughly investigated substituted allylations of α -bromooxazolidinone imides in the presence of LAs (Scheme 17).²⁰⁴ Consistent with previous work, Sibi et al. noted that the stereochemistry of the starting bromide significantly influenced the effectiveness of the LA control.²⁰⁴ Moreover, they found that the diastereoselectivity obtained in the presence of LAs improved as the reaction temperature increased from -78 to 25°C and/or the reactivity of the allylating agent was reduced from $\text{R} = \text{COOMe}$ to $\text{R} = \text{H}$.²⁰⁴ As Sibi outlines, these dependencies are likely caused by the slow rotational equilibration of the substrate radical, which limits the conversion of monodentate coordinated radical species into the more thermodynamically favorable (and stereocontrolling) bidentate chelate.²⁰⁴ Increasing the temperature or reducing the reactivity of the allylating agent facilitates formation of this bidentate chelate by allowing rotation around the amide bond to compete with allylation.²⁰⁴ Interestingly, Sibi found that $\text{Yb}(\text{OTf})_3$ was significantly less effective than $\text{MgBr}_2 \cdot \text{OEt}_2$

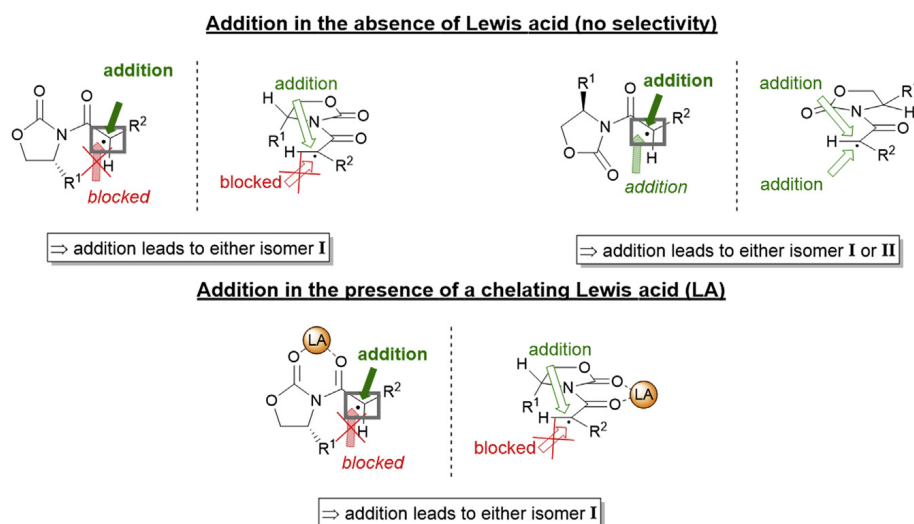
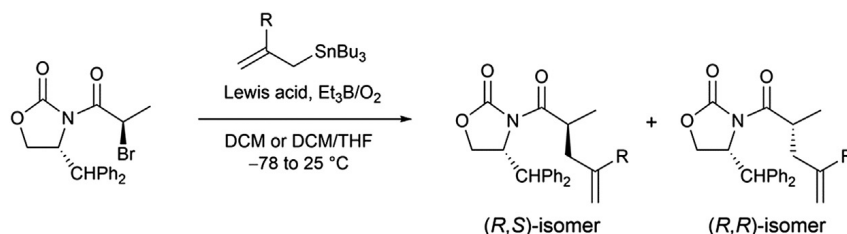


Figure 9 The mechanism of diastereoselective allylation of chiral oxazolidinones substrates in the presence and absence of chelating Lewis acids.



R	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	Temp (°C)	(<i>R,S</i>):(<i>R,R</i>)
H	None	-	-78	64/36
H	MgBr ₂ ·OEt ₂	1.0	-78	98/2
H	Yb(OTf) ₃	1.0	-78	67/33
H	MgBr ₂ ·OEt ₂	1.0	0	>98/2
H	Yb(OTf) ₃	1.0	0	>98/2
H	MgBr ₂ ·OEt ₂	1.0	25	>98/2
H	Yb(OTf) ₃	1.0	25	>98/2
Me	MgBr ₂ ·OEt ₂	1.0	-78	96/4
Me	Yb(OTf) ₃	1.0	-78	50/50
Me	MgBr ₂ ·OEt ₂	1.0	0	>98/2
Me	Yb(OTf) ₃	1.0	0	>98/2
Me	MgBr ₂ ·OEt ₂	1.0	25	>98/2
Me	Yb(OTf) ₃	1.0	25	>98/2
COOMe	MgBr ₂ ·OEt ₂	1.0	-78	75/25
COOMe	Yb(OTf) ₃	1.0	-78	33/67
COOMe	MgBr ₂ ·OEt ₂	1.0	0	98/2
COOMe	Yb(OTf) ₃	1.0	0	80/20
COOMe	MgBr ₂ ·OEt ₂	1.0	25	98/2
COOMe	Yb(OTf) ₃	1.0	25	83/17

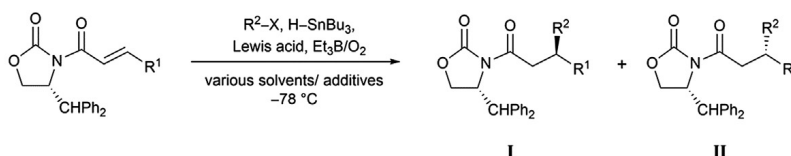
Scheme 17 Radical allylation of a chiral oxazolidinones substrate in the presence of Lewis acids.

for allylations with the methyl ester reagent ($R = \text{COOMe}$).²⁰⁴ However, this poor selectivity could be overcome by employing 6 equivalents of $\text{Yb}(\text{OTf})_3$.²⁰⁴ It is not currently clear why $\text{Yb}(\text{OTf})_3$ is less effective at normal concentrations, although it may be sequestered by the methyl ester moiety of the allyl tin reagent more favorably than $\text{MgBr}_2 \cdot \text{OEt}_2$.

LA-mediated diastereocontrol in radical transformations involving chiral oxazolidinone substrates originates from the formation of a rigid 6-membered chelate complex. In the absence of LA, the oxazolidinone substrate radical (or alkenes) can adopt two conformations, in which the two carbonyl groups are either syn- or antiperiplanar (Figure 9). In the synperiplanar conformation, the R^1 substituent of the oxazolidinone is in close proximity to the α -prochiral radical and shields the bottom face from allylation. However, in the antiperiplanar conformation, the R^1 substituent is

probably located too far away from the radical center to significantly influence the diastereoselectivity of this allylation. Incorporating a chelating LA enforces the synperiplanar conformation and leads to diastereoselective addition of the allyl tin reagent. The lower diastereoselectivity observed for substrates with small oxazolidinone substituents probably results from less effective steric differentiation of the two radical faces.

Sibi and coworkers also showed that diastereoselectivity in the radical addition reactions of chiral α,β -unsaturated *N*-enoyloxazolidinones can be controlled through the use of chelating LAs (Scheme 18).^{205,206} In the absence of LAs, these radical additions are not appreciably diastereoselective and afford both isomers **I** and **II** in roughly equal quantities.^{205,206} Remarkably, the inclusion of LAs (even at catalytic concentrations) leads to reasonably high selectivity for the **I** isomer, despite the greater distance between the forming β -prostereogenic center of the alkene and the existing stereogenic of the chiral auxiliary. For instance, the addition of ^{*i*}Pr radical to the $R^1 = \text{Me}$ substrate proceeded with 96% diastereoselectivity for the **I** isomer in the presence of 1.0 equivalent of Yb(OTf)₃.²⁰⁶ Even with only 0.1 equivalent of Yb(OTf)₃, excellent diastereoselectivity (94%) was observed for this radical addition reaction.²⁰⁶ In contrast, even at stoichiometric concentrations, MgBr₂·OEt₂ was found to be significantly less effective, while the inclusion of ZnCl₂ had no effect on diastereoselectivity.²⁰⁶ For addition of the ^{*i*}Pr radical to $R^1 = \text{Ph}$ substrate, 1 equivalent of Yb(OTf)₃ afforded

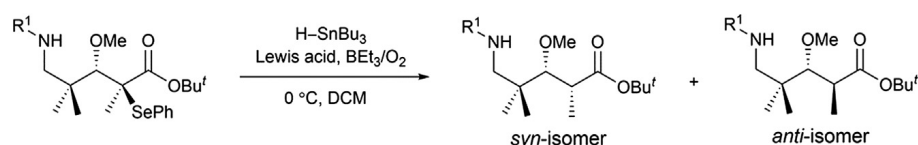


R ¹	R ²	X	Lewis acid	[Lewis acid] ₀ /[substrate] ₀	I:II
Me	^{<i>i</i>} Pr	I	None	-	57/43
Me	^{<i>i</i>} Pr	I	Yb(OTf) ₃	1.0	96/4
Me	^{<i>i</i>} Pr	I	Yb(OTf) ₃	0.1	94/6
Me	^{<i>i</i>} Pr	I	MgBr ₂ ·OEt ₂	2.0	86/14
Me	^{<i>i</i>} Pr	I	ZnCl ₂	2.0	57/43
Me	MeOCH ₂	Br	Yb(OTf) ₃	1.0	93/7
Me	MeCO	Br	Yb(OTf) ₃	1.0	88/12
Ph	^{<i>i</i>} Pr	I	Yb(OTf) ₃	1.0	98/2
Ph	^{<i>i</i>} Pr	I	Yb(OTf) ₃	0.1	91/9
Ph	MeOCH ₂	Br	Yb(OTf) ₃	1.0	91/9
Ph	MeCO	Br	Yb(OTf) ₃	1.0	89/11

Scheme 18 Radical allylation to chiral oxazolidinones alkene substrates in the presence of Lewis acids.

even higher diastereoselectivity (98%).²⁰⁶ Interestingly, for both $R^1 = \text{Me}$ and Ph substrates, employing a radical source bearing a coordinating group ($R^2 = \text{MeOCH}_2$ or MeCO) leads to a notable reduction in the level of diastereocontrol, even at stoichiometric $\text{Yb}(\text{OTf})_3$ loadings.²⁰⁶ The origin of this reduction is unclear but we should note that $i\text{Pr}$ radicals add more selectivity to $\text{Yb}(\text{OTf})_3$ complexed substrate than other alkyl radicals (such as ethyl and cyclohexyl radicals) and hence this lower selectivity may simply result from steric effects.

In the late 1990s, Guindon investigated the influence of LAs on the stereoselectivity of radical reductions for various δ -amino- β -hydroxyesters (Scheme 19).²⁰⁷ These substrates are particularly noteworthy, as they possess three Lewis-basic donor moieties and so can chelate LAs to form either endo- or exocyclic radicals. Chelation can occur at either the O-acyl of the ester and the β -hydroxyl group to form an endocyclic radical (*syn*-selective) or at the δ -amine and β -hydroxyl groups resulting in an exocyclic radical (*anti*-selective). Guindon investigated the stereochemical effect of adjusting the R^1 substituent, which alters the Lewis basicity of the N-donor and the tendency for endo- or exocyclic radical chelate formation. When $R^1 = \text{Et}$, the reduction was found to have relatively poor *syn*-selectivity under chelation conditions, which can be attributed to the relatively high basicity of the amine and hence competitive formation of an exocyclic radical chelate. In contrast with $R^1 = \text{COOBu}^t$, $\text{MgBr}_2 \cdot \text{OEt}_2$ afforded high *syn*-selectivity, which suggests that the reduced basicity of the N-donor favored endocyclic radical complexation. Possible structures for these exo- and endocyclic radical chelates are depicted in Figure 10.



R^1	$[\text{MgBr}_2 \cdot \text{OEt}_2]_0 / [\text{substrate}]_0$	<i>anti:syn</i>
Et	None	93/7
Et	1.1	25/75
CH_2Ph	None	83/17
CH_2Ph	1.1	7/93
COOBu^t	None	58/42
COOBu^t	1.1	4/96

Scheme 19 Radical reductions of various δ -amino- β -hydroxyesters in the presence of a chelating LA. Note that some products were isolated as δ -lactams.

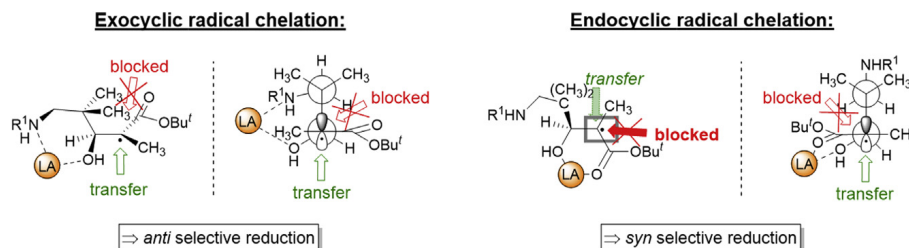
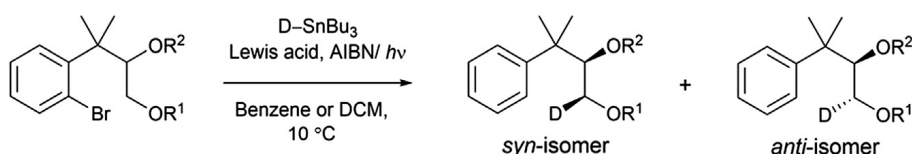


Figure 10 Exo- and endocyclic radical chelate complexes derived from the δ -amino- β -hydroxyester substrates.

Most of the transformations reported above utilize coordination sites on either electrophilic radicals or alkenes. However, Renaud and Gerster reported that LAs can facilitate high levels of diastereocontrol in the reduction of 1,2-dioxy-substituted substrates (Scheme 20), which proceed via a nucleophilic radical intermediate.²⁰⁸ For instance, the unmediated reduction with 1,2-dimethoxy ($R^1 = R^2 = \text{Me}$) substrate was found to moderately *syn*-selective (71% *ds*) but the inclusion of 2.2 equivalents of $\text{MgI}_2 \cdot \text{OEt}_2$ afforded high *anti*-selectivity (94% *ds*).²⁰⁸ Interestingly, alternative LAs, such as $\text{ZnCl}_2 \cdot \text{OEt}_2$ and $\text{Ti}(\text{O}^i\text{Pr})_3\text{Cl}$, were noted to be ineffective for chelation control. The proposed mechanism for this reduction is outlined below. Initial bromine abstraction forms an unstable aryl radical that then undergoes 1,5-hydrogen atom transfer, forming the more stable oxy-substituted radical depicted in Figure 11. In the absence of LA, this intermediate radical would preferentially adopt the conformation shown in Figure 11 to minimize dipole repulsion between the oxy groups. Deuterium transfer to the accessible face of this radical would afford the *syn*-isomer. Simultaneous coordination of both oxy groups by a chelating LA would lead to the 5-membered ring depicted below. Transfer to the accessible bottom face of this radical would lead to the *anti*-isomer. The significance of this reaction is that it demonstrates that chelation control can be effective, even for nucleophilic radicals.



Scheme 20 Radical reductions of 1,2-dioxy-substituted substrates in the presence of a chelating Lewis acid.

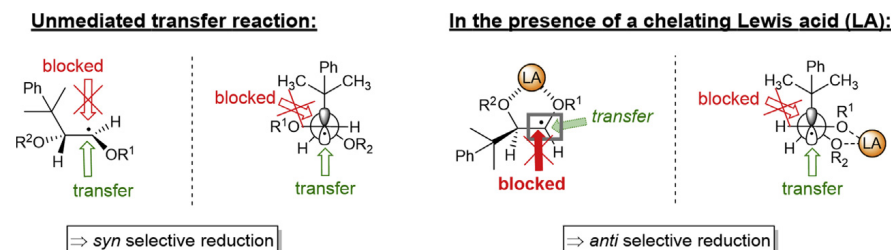


Figure 11 A simplified depiction of the mechanism of diastereoselection in 1,2-dioxy substituted reduction reactions in the absence and presence of chelating Lewis acid.

7. SOME LESSONS FROM SYNTHESIS

Currently the highest level of isotactic control in radical polymerization that has been promoted by Lewis acids is $m = 92\%$ achieved by the addition of $\text{Y}(\text{OTf})_3$ to NIPAM polymerization. While this level of control is a vast improvement on non-LA-mediated polymerization, it is not of the level achieved in small-molecule synthesis. Moreover, the isotactic control more typically achieved in polymerization of acrylamides and methacrylamides in the presence of effective LAs falls in the range of $m = 60\text{--}80\%$, while the control for methacrylates is even worse, with $m = 40\text{--}50\%$. However, many of the synthetic transformations reported above achieve very high diastereoselectivities ($>99\%$) through chelation control. We should also note that unlike mixtures of diastereoisomers in small-molecule synthesis, the m and r diads (and mm , mr , and rr triads etc.) that comprise atactic polymer cannot be separated or isolated. In small-molecule organic synthesis, poor to modest levels of diastereocontrol may be acceptable, provided the starting substrates are easily accessible and the desired product isomer can be readily separated from the crude mixture of product diastereoisomers. Indeed, in small-molecule synthesis, diastereocontrol is of interest mainly to reduce waste and improve the overall yield of a desired synthetic target. However, in polymeric systems the stereocenters themselves are covalently linked and so no separation technique can be used to isolate the stereoregular portions of each chain.

Considering the proposed mechanism of LA-mediated isotactic control (Scheme 4), the reported synthetic radical transformations provide some useful insights into its potential modes of failure (Scheme 5). We reexamine these potential modes of failure while concurrently drawing on synthetic literature where relevant. We should clarify that our goal is not simply to highlight the factors that likely cause LA and condition dependencies but

also to examine current limitations in some of relatively successful LA-mediated radical polymerizations.

7.1 Is the Lewis Acid–Base Interaction Too Weak?

The strength of Lewis acid–base interactions is dependent on the identity of the Lewis acid and base donors and is highly variable; ranging in strength from that of weak hydrogen bond or dispersive forces (4 kJ mol^{-1}) to significantly stronger than some covalent bonds ($>100 \text{ kJ mol}^{-1}$). A fundamental requirement of any LA stereocontrol strategy is that the respective Lewis acid–base adducts be sufficiently stable so as to modify the conformation of the radical substrate and/or alkene. Arguably, the simplest explanation for suboptimal levels of isotactic control is that the Lewis acid–base interactions are too weak and so allow unbound polymer termini to propagate competitively. Given a sufficiently strong Lewis acid–base interaction is a necessary but not sufficient condition for successful stereocontrol, it is worth considering if any correlation can be found between isotactic control and coordinative bond strength. As already noted, relatively high levels of isotactic control can be achieved with the inclusion of LAs in acrylamides and methacrylamides polymerizations (typically $m = 70\text{--}80\%$), while methacrylates have remained relatively challenging systems ($m = 45\%$). It is perhaps tempting to attribute the poor stereocontrol observed for methacrylates to a weak interaction between the component ester side-chains and the mediating LA. Conversely, it seems intuitive that the improved control of acrylamides and methacrylamides could result from the stronger Lewis base coordination sites of these monomers.

The most direct method to determine if the strength of coordinative interactions is limiting stereocontrol would be to directly examine relevant binding energies of the respective species. Unfortunately, there are relatively few binding energies reported in the literature that are directly relevant to LA-mediated radical polymerization. While there are some binding enthalpies for similar donor species that have been quantified via calorimetry,²⁰⁹ these are often for 1:1 complexes that are not necessarily reflective of the adducts adopted in polymerizations. Several authors have proposed scales to quantify both Lewis acidity and basicity, perhaps most notably the Donor²¹⁰ and Acceptor^{211,212} numbers of Gutmann and Beckett. While such scales are undoubtedly useful, we should caution that Lewis acid–base interactions are dependent on both the identity of the acid and base, which makes them highly specific and often nontransferable. Given these difficulties in direct assessment of the coordinative bond strength of Lewis

adducts in radical polymerization, small-molecule synthetic transformations can provide very useful insights that can help assess this potential mode of failure. The synthetic studies outlined above clearly demonstrate that significant stereochemical changes can be observed for substrates possessing weak donor sites, such as esters and ethers, and that moderate LAs, such as $\text{MgBr}_2 \cdot \text{OEt}_2$, are sufficiently strong to impart high levels of diastereocontrol (sometimes even at high temperatures). Such high levels of diastereocontrol demonstrates implicitly that the underlying coordinative interactions between esters and/or ethers and typical LAs ($\text{MgBr}_2 \cdot \text{OEt}_2$ and $\text{Sc}(\text{OTf})_3$) are sufficiently strong.

We should also briefly note that unlike assessing the effectiveness of various LAs for the *same* monomer system, comparing the effectiveness of stereocontrol between *different* monomer systems is actually somewhat ambiguous. Up to this point, we have been pragmatically defining effectiveness of isotactic control agents based purely on the absolute values of *m* or *mm* obtained in the presence of control agents. However, this definition neglects any consideration of the inherent tacticity preference of the monomer. Arguably, a more objective measure of effectiveness would be to examine the free energy difference between *meso* and *racemo* propagation ($\Delta G^\ddagger_{m/r}$) with and without added LA (under otherwise consistent conditions). Illustrative $\Delta G^\ddagger_{m/r}$ values for some typical LA-mediated polymerizations are presented in Table 3.

Table 3 clearly illustrates the ambiguities that arise when attempting to compare the effectiveness of LA-mediated radical polymerization in different monomer systems. Although the highest absolute *m* value in Table 3 is observed for NIPAM polymerization with $\text{Yb}(\text{OTf})_3$ in CH_3OH (*m* = 90%), LA control in this system benefits from the inherent atactic preference of NIPAM ($\Delta G^\ddagger_{m/r} = -0.5 \text{ kJ mol}^{-1}$). In contrast, DMMAM polymerization with $\text{Yb}(\text{OTf})_3$ in CH_3OH is less successful in absolute terms (*m* = 68%), which can be attributed to the inherent syndiotactic preference of the monomer ($\Delta G^\ddagger_{m/r} = -4.4 \text{ kJ mol}^{-1}$), but the LA actually induces a larger $\Delta G^\ddagger_{m/r}$ energetic change. Indeed, it could be reasonably argued that the most effective example of isotactic control is actually that of NIPAM polymerization with $\text{Yb}(\text{OTf})_3$ in CH_3OH , because although the *m* value of the polymer obtained was only 80%, the LA counteracted the strong syndiotactic preference of the unmediated system ($\Delta G^\ddagger_{m/r} = -5.4 \text{ kJ mol}^{-1}$). Thus, conclusions regarding the effectiveness of stereocontrol across different monomer systems must be made with some degree of caution. Based on this revised assessment, it could be reasonably argued that the isotactic control

Table 3 Free energy differences between *meso* and *racemo* propagation for various common monomers, in the absence and presence of a mediating Lewis acid

Monomer ^a /Lewis acid/Solvent	Temperature (°C)	<i>m</i> (%)	References	$\Delta G^\ddagger_{m/r}$ (kJ mol ⁻¹)	$\Delta(\Delta G^\ddagger_{m/r})$ (kJ mol ⁻¹)
MMA/None/Toluene	60	20	142	-3.8	+3.3
MMA/Sc(OTf) ₃ /Toluene	60	45		-0.6	
AM/None/CH ₃ OH	0	46	146,147	-0.4	+3.5
AM/Yb(OTf) ₃ /CH ₃ OH	0	80		3.1	
DMAM/None/CH ₃ OH	60	46	146,147	-0.4	+5.0
DMAM/Yb(OTf) ₃ /CH ₃ OH	60	84		4.6	
NIPAM/None/CH ₃ OH	-20	44	146,147	-0.5	+5.1
NIPAM/Yb(OTf) ₃ /CH ₃ OH	-20	90		4.6	
MAM/None/CH ₃ OH	60	27	148,149	-2.8	+3.6
MAM/Y(OTf) ₃ /CH ₃ OH	60	58		0.9	
NMMAM/None/CH ₃ OH	60	17	148,149	-4.4	+6.5
NMMAM/Yb(OTf) ₃ /CH ₃ OH	60	68		2.1	
NIPMAM/None/CH ₃ OH	20	10	148,149	-5.4	+8.7
NIPMAM/Yb(OTf) ₃ /CH ₃ OH	20	80		3.4	

^aMethyl methacrylate (MMA), acrylamide (AM), *N,N*-dimethyl acrylamide (DMAM), *N*-isopropylacrylamide (NIPAM), methacrylamide (MAM), *N*-methyl methacrylamide (NMMAM), *N*-isopropyl methacrylamide (NIPMAM).

achieved for MMA with $\text{Sc}(\text{OTf})_3$ is nearly identical in energetic $\Delta G_{m/r}^\ddagger$ terms to that obtained for AM and MAM with $\text{Yb}(\text{OTf})_3$ and $\text{Y}(\text{OTf})_3$, respectively. For these three monomers/LA systems, differences in the m % of the resulting polymers are mainly attributable to the variable inherent tacticity preference of the respective monomers rather than significant variations in the effectiveness of the control agent. While LA acidity should be carefully considered, it seems unlikely that the strength of LA interactions is the dominant factor limiting current levels of isotactic control in “successful” methacrylate and (meth)acrylamide systems.

7.2 Is the Chelate Unstable?

All chelation-based stereocontrol strategies rely on the inherent thermodynamic stability of chelate complexes relative to potential monodentate adducts. Chelation involves the coordination of an LA to a polydentate ligand through more than one coordination site to form a cyclic adduct. The chelate effect refers to the empirically observed preference for the coordination of a polydentate ligand to an LA through multiple donor sites simultaneously, rather than the analogous coordination of comparable monodentate ligands. We should also note that the chelate effect is predominantly an entropic effect, and so the favorability of chelated complexes compared with analogous monodentate species actually increases with increasing temperature. While 5- and 6-membered chelate rings are ubiquitous in coordination chemistry and their inherent stability is well known, chelation of adjacent acyl O-atoms in the radical polymerization of important monomers, such as (meth)acrylates and (meth)acrylamides, leads to relatively large 8-membered rings. One might reasonably attempt to use the instability of this larger chelate ring to rationalize the suboptimal effectiveness of LAs in the radical polymerization of these monomers.

However, as demonstrated by the synthetic transformations of Nagano and Metzger, high levels of diastereoselectivity (of up to 98%) can be obtained via “nonstandard sized” 7- and 8-membered chelate rings. More recently, Sibi and coworkers reported that chiral LA complexes can be utilized to achieve high levels of enantioselectivity in radical addition reactions with a variety of β -substituted acrylates; transformations that also involve an 8-membered chelate ring.^{213,214} In addition, we note that chelation of adjacent carboxylate groups of ionized poly(methacrylic acid) has been used to rationalize the dependence of metal binding affinities on tacticity. Studies by Morawetz,²¹⁵ Morcellet,²¹⁶ and Bello²¹⁷ have demonstrated that the metal binding affinities have a significant tacticity dependence, which the authors

attribute quite intuitively to 8-membered chelation of adjacent carboxylate (or carboxylic acid) side-chains. Collectively, these studies indicate that the relatively poor stereocontrol obtained in radical polymerization is probably not attributable solely to low selectivity for the larger chelate complexes, although this may be responsible for some of the variation in the effectiveness of LAs. However, the extra conformational flexibility of larger rings may complicate diastereocontrol. We should also note that for transformations where monodentate complexes are undermining diastereocontrol, higher reaction temperatures may actually increase the effectiveness of chelate control.

7.3 Does the Chelate Favor *Meso* Propagation?

Another fundamental requirement for isotactic regulation is that the terminal-penultimate chelate complex has a significant selectivity preference for *meso* propagation. Polymers of 1-alkenes ($\text{H}_2\text{C}=\text{CHR}$) and 1,1-disubstituted alkenes ($\text{H}_2\text{C}=\text{CR}^1\text{R}^2$) have a primary structure in which the stereogenic centers ($-\text{CHR}-$ or $-\text{CR}^1\text{R}^2-$) are separated by methylene ($-\text{CH}_2-$) groups. For a polymerization to yield stereoregular polymer, the configuration of the previous stereogenic center must significantly influence that of the forming center, so-called “1,3-stereocontrol.” Such control was initially thought to be more difficult than 1,2-stereocontrol because of the greater separation between the existing and forming stereogenic centers. While successful 1,3-stereocontrol in radical synthesis is undoubtedly less common than 1,2-stereocontrol, there are still numerous examples of successful chelation control in 1,3-systems. Specifically, Nagano and Metzger reported high levels of 1,3-diastereocontrol in transformations on 3-alkoxy-1-methylene ethyl esters and 1-methylene-3-alkyl-dimethyl glutarate, respectively. The transformations reported by Metzger are particularly noteworthy because they rely on a linear/helical preference of the glutarate radical chelate. These studies seemingly indicate that high levels of 1,3-stereocontrol is feasible, provided there is sufficient differentiation between diastereotopic faces of the radical.

Very recently, we investigated the *meso/racemo* selectivity preference resulting from terminal-penultimate chelation of MMA trimer radicals by Li^+ using high-level *ab initio* calculations.⁸⁹ Although LiNTf_2 was found to be ineffective for isotactic control experimentally, these calculations suggest that under normal polymerization conditions, terminal-penultimate chelation infers a modest selectivity preference of around 5 kJ mol^{-1} for linear *pro-meso* conformations of the polymer terminus compared with

helical pro-*racemo* configurations.⁸⁹ If this level of selectivity was retained in the respective *meso* and *racemo* transition states, it would result in a highly isotactic-rich polymer at 25 °C ($m = 90\%$).⁸⁹ While the generality of this result is yet to be confirmed in other monomer/LA systems, we would cautiously argue that *meso/racemo* selectivity of the terminal-penultimate chelate should be even higher in monosubstituted acrylamides and acrylates; because the absence of CH₃ groups should lead to better steric differentiation between the linear pro-*meso* complex and the helical pro-*racemo* adduct. While preliminary work suggests that *meso/racemo* selectivity of the terminal-penultimate chelate could be a fundamental restriction on the effectiveness of isotactic control, it seems unlikely that it is the principal limiting factor in any of the systems studied to date (with the possible exception of methacrylamides). Indeed, in the LiNTf₂ MMA system mentioned above, the failure of stereocontrol is primarily due to deactivation of the transition state by the terminal-penultimate binding mode in favor of a nonstereocontrolling binding mode (see below). We should note that linear (*meso*)/helical (*racemo*) selectivity is likely to have a significant enthalpic component and so would probably decrease with increasing reaction temperature (in contrast to the favorability of chelation).

7.4 Does the Lewis Acid Bind in the Correct Position during Propagation?

Undoubtedly, one of the most challenging limitations of LA-mediated isotactic control is the requirement for the position-specific coordination of the terminal and penultimate groups of the polymer terminus by LA. This requirement is fairly polymerization specific and has only limited synthetic parallel, as generally substrates for small-molecule transformations are deliberately selected so as to eliminate (or at least minimize) the potential formation of alternative chelates. Indeed, the vast majority of successful LA-mediated chelation control has been reported for substrates that only possess two donor groups and hence only one potential site for chelation. In contrast, in a typical radical polymerization there are a multitude of different sites of chelation, not only at the polymer terminus but at any point along the polymer chain. While this aspect of selectivity is only pertinent in a few of the reported synthetic transformations, these few studies do offer some very useful insights that highlight issues that may arise for polymerization processes.

In synthetic transformations, multiple sites of chelation are almost invariably associated with deterioration in the effectiveness of stereocontrol. This

is perhaps unsurprising, as if there are multiple points of chelation then different chelate complexes with potentially divergent stereoselectivity preferences can react to afford different diastereoisomers. In instances where the Lewis basicities of these donor groups are poorly differentiated, competitive formation of alternative chelate complexes can significantly lower the diastereocontrol afforded by LAs. This quite intuitive observation has been demonstrated by the work of Guindon et al. on radical reductions of δ -amino- β -hydroxyesters and Nagano et al. in allylations of α -bromo- β -siloxy diesters. Additionally, some issues with LA-mediated diastereocontrol were also noted in Sibi's work on allylations of a α -bromooxazolidinone imide substrate with a methyl ester substituted tin allylating agent.

In radical polymerization there are a multitude of potential coordination sites that only differ in their extended substitution and so would be expected to have similar basicities (to a first approximation). In contrast, in anionic and coordination polymerization, the propagating enolate species has a significantly higher Lewis basicity than other side-chains and hence the cationic metallic complexes are strongly associated (specifically) with the polymer terminus. We should clarify that it is not only a requirement that the LA coordinates the terminal and penultimate groups simultaneously but also that this binding mode dominates propagation (Scheme 4, scenario 1). In this regard, we note that the LA could preferentially coordinate to the terminal-penultimate groups but also deactivate the polymer terminus toward propagation, in which case no significant isotactic control would be observed (as other less stable but more reactive complexes would dominate propagation). It is also unlikely that adding higher loadings of LA would overcome this positioning problem, although it may influence the speciation of the complexes. Considering the different binding positions given in Scheme 4, specifically scenario 1 and 3, it is unclear if there would be a notable preference for either form of propagation. While coordination of the LA to either the radical or the alkene (but not both simultaneously; as in terminal-penultimate propagation pathway) would be expected to maximize polar stabilization, distonic radical-cation interactions would favor pathways with short distances between the LA and the forming radical (terminal-monomer pathway). It is somewhat unclear which pathway (if any) thermodynamic and steric effects would favor.

Recently, we explicitly examined the energetics of Li^+ coordination at different positions of the polymer terminus using high-level ab initio calculations.⁸⁹ These calculations suggested that while there was a modest thermodynamic preference for Li^+ chelation at the terminal-penultimate

position, unfortunately this mode of complexation also kinetically deactivated the polymer terminus toward monomer addition.⁸⁹ Indeed, a less thermodynamically stable terminal-monomer adduct was found to be more kinetically reactive, with (pseudo)cyclization of this complex being the most favorable overall propagation pathway.⁸⁹ While we are uncertain as to the generality of terminal-penultimate versus terminal-monomer preferences, we simply note that LA positioning is likely to be a significant limitation in LA-mediated radical polymerization.

7.5 Is the Lewis Acid Kinetically Labile?

One crucial aspect of LA-mediated stereocontrol that has received relatively little attention is the kinetic lability of the Lewis acid–base adducts. To be effective at catalytic concentrations, these Lewis adducts must be kinetically labile; otherwise the LA will be sequestered within the polymer chains and so will be unable to regulate stereochemistry at the polymer terminus. In this context, “kinetic lability” implies that the exchange of the LA is significantly faster than the rate of propagation in the polymerization. LAs, such as $\text{Sc}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$, and $\text{Yb}(\text{OTf})_3$, are generally effective at catalytic concentrations for (meth)acrylamide and methacrylate polymerization, which seemingly suggests that the metal ions are (at least somewhat) kinetically labile. Nevertheless, it is interesting to consider some of the available exchange rates around various metal cations. Indeed, aqueous exchange rates span nearly 20 orders of magnitude at 25 °C, with very rapid ligand exchange in the $[\text{Eu}(\text{H}_2\text{O})_7]^{2+}$ complex ($k_{\text{exh}} \sim 5 \times 10^9 \text{ s}^{-1}$)²¹⁸ and nearly no exchange in the $[\text{Ir}(\text{H}_2\text{O})_6]^{3+}$ complex ($k_{\text{exh}} \sim 1 \times 10^{-10} \text{ s}^{-1}$).²¹⁹ We should emphasize that measuring ligand exchange rates is usually quite challenging, requiring the use of very high-pressure NMR measurements. As such, relatively few systems have been examined and no direct data are available for actual LA-mediated polymerization systems (or synthetic transformations). Notwithstanding, we will briefly discuss some of the available data and make some more qualitative general observations.

Firstly, we note that available data indicate rapid ligand exchange ($k_{\text{exh}} \sim 10^{10} \text{ s}^{-1}$) around all alkali metal cations and alkali earth metal cations, with the exception of Be^{2+} and Mg^{2+} .²²⁰ Ligand exchange rates around $[\text{Mg}(\text{solvent})_6]^{2+}$ vary with solvent identity, with rapid exchange in DMF ($k_{\text{exh}} = 6.2 \times 10^6 \text{ s}^{-1}$)²²¹ and much slower exchange in CH_3OH ($k_{\text{exh}} = 4.7 \times 10^3 \text{ s}^{-1}$).²²² Ligand exchange rates are also dependent on the identity of the diluting cosolvent, with DMF ligand exchange on $[\text{Mg}(\text{DMF})_6]^{2+}$ over an order of magnitude more rapid in deuterated

DCM ($k_{\text{exh}} = 6.2 \times 10^6 \text{ s}^{-1}$)²²¹ diluent compared with deuterated nitromethane ($k_{\text{exh}} = 4.3 \times 10^5 \text{ s}^{-1}$).²²³ Given the success of rare earth metal triflates in mediating (meth)acrylamide polymerizations, it is particularly interesting to consider available exchange rates for trivalent lanthanide cations, such as Yb^{3+} , Y^{3+} , and Sc^{3+} . Unfortunately, ligand exchange rates around these metal cations have only been quantified for a limited number of solvents. With DMF as a ligand, 8-coordinate complexes are observed for Yb^{3+} and other trivalent lanthanides.²²⁰ At 25 °C, DMF exchange around these 8-coordinate complexes is fairly rapid, varying from $4 \times 10^6 \text{ s}^{-1}$ for $[\text{Ho}(\text{DMF})_8]^{3+}$ to $1 \times 10^8 \text{ s}^{-1}$ for $[\text{Yb}(\text{DMF})_8]^{3+}$.²²⁴ For 1,1,3,3-tetramethyl urea (TMU), trivalent lanthanides adopt 6-coordinate complexes and a notable decrease in the rate of ligand exchange is observed.²²⁰ At 25 °C, the exchange rates of $[\text{Sc}(\text{TMU})_6]^{3+}$, $[\text{Yb}(\text{TMU})_6]^{3+}$, and $[\text{Y}(\text{TMU})_6]^{3+}$ are ~ 1 , 60, and 300 s^{-1} , respectively.^{225–227} Remarkably, the exchange of TMU ligand around Yb^{3+} cations is over six orders of magnitude slower than that of DMF, which is mainly attributable to the lower coordination number of the TMU complex.

Given this variability, gauging even rough qualitative estimates of exchange rates around Yb^{3+} , Y^{3+} , and Sc^{3+} in meth(acrylamide) polymerizations is highly problematic. It could be argued quite reasonably that DMF rates should be used as rough guide for monomers such as *N,N*-dimethyl acrylamide (DMA); because both compounds are *N,N*-dimethyl amides. However, we note that because of the extra $\text{H}_2\text{C}=\text{CH}$ substitution of DMA, it is significantly bulkier than DMF and hence may not form 8-coordinate complexes with Yb^{3+} , Y^{3+} , and Sc^{3+} . Arguably, the TMU exchange rates may be more relevant for meth(acrylamide) polymerizations, as TMU is more sterically comparable to a typical meth(acrylamide). However, we note that the Donor Number of TMU is significantly higher than corresponding amides such as DMF or *N,N*-dimethylacetamide, indicating that TMU is considerably more Lewis basic.²²⁸ As such, it is not clear that the electronic properties of TMU are comparable to that of a typical (meth)acrylamide. More generally, it is not possible to straightforwardly relate ligand exchange rates to specific characteristics (size, dielectric constant, donor number, etc.) of the ligand or solvent. We also note that the exchange rates given above for Yb^{3+} , Y^{3+} , and Sc^{3+} were measured in deuterated acetonitrile as a diluent, while the most effective meth(acrylamide) polymerizations are performed using CH_3OH as a cosolvent. Thus, it is very difficult to use quantified exchange rates to ascertain even a rough order of magnitude estimate of the kinetic lability of metal ions in

LA-mediated radical polymerizations. The effectiveness of some LAs at catalytic concentrations seemingly implies that the respective mediating metal cations are kinetically labile (under those specific conditions). However, kinetic lability may be the cause of unexpected condition dependencies, as it would likely be influenced by the reaction conditions; including LA, monomer and cosolvent concentration (and identity), polymerization temperature, etc.

7.6 Summary and Outlook

Small-molecule synthesis provides many mechanistic insights of relevance to LA-mediated radical polymerization:

- Is the Lewis acid–base interaction too weak?
The interaction between modestly strong LAs and relatively weak Lewis bases affords excellent stereocontrol in many synthetic radical transformations. While weak coordinative interactions may limit the effectiveness of weak LAs for isotactic control, it is unlikely to be a limiting factor in many of the LA-mediated radical polymerizations investigated to date; particularly those that employ strong LAs (such as rare earth metal triflates).
- Is the chelate unstable?
There are several examples of 7- and 8-membered chelates yielding excellent levels of diastereo- and enantioselectivity in radical synthesis. For typical carbonyl monomers chelate stability is unlikely to be limiting isotactic control, although it could explain why isotactic control varies with different LAs.
- Does the chelate favor *meso* propagation?
There are several successful examples of 1,3-stereocontrol in radical synthesis, demonstrating that remote stereogenic centers can sufficiently influence forming centers to afford high levels of diastereoselectivity. In polymerization systems, terminal-penultimate chelation would most likely significantly favor pro-*meso* configurations and in the absence of other complicating factors yield isotactic polymer. While the *meso*/*racemo* selectivity of the terminal-penultimate chelate is unlikely to be the sole cause of suboptimal levels of isotactic control, it may be the most significant limitation in some of the more successful LA-mediated polymerizations.
- LA positioning
Multiple chelation sites in substrates have been associated with deteriorating levels of stereocontrol in several synthetic reactions. Moreover,

it is unclear if the problems associated with multiple chelation sites can be overcome with higher LA loadings. Theoretical studies have confirmed that LA positioning is likely a key limitation of current isotactic control strategies.

- Kinetic lability

No data are available which unambiguously quantify exchange rates around typical LAs in radical polymerization systems. In many polymerization systems, moderate isotactic control is observed at catalytic loadings suggesting that the LA is at least somewhat kinetically labile. However, the extent to which LA lability may be undermining isotactic control is currently unclear.

It is interesting to note that almost all of the monomer systems investigated thus far have been electrophilic alkenes, with comparatively few studies of nucleophilic systems, such as vinyl esters and ethers. While LA control of such systems may be problematic, the study of Renaud and Gerster seemingly suggests that chelate control is feasible for nucleophilic radical systems.



8. CONCLUSION

From humble beginnings as unpredictable curiosities, radicals are now utilized in an increasingly diverse array of synthetic transformations. While radical reactions were initially thought to be quite unselective, pioneering work has demonstrated that very high diastereo- and enantioselectivity can be obtained in many radical transformations, in some cases rivaling selectivity obtained with ionic reagents. While stereocontrol in radical polymerization has thus far proved enormously difficult, given the unprecedented advancements in of the last few decades it is likely that significant improvements in stereoregulation are possible. In particular, it is likely that this field will continue to benefit from insights made in synthetic studies and a more comprehensive understanding of these processes. Moreover, the continuing development of novel LA catalysts, weakly coordinating anions, and highly structured chiral ligands offers a nearly limitless combination of as yet untested potential stereocontrol agents. While stereocontrol in radical polymerization remains a daunting challenge, understanding the underlying mechanism of LA-mediated radical polymerization and its subtleties will hopefully enable further improvements to tacticity control in the near future.

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2.4 Supporting information

Supporting information for the calculated pK_b values presented in **Figure 4** can be found on the CD-ROM attached at the back of this thesis.

3. Computational Modelling of Free-Radical Polymerization

Kinetics

3.1 Overview

To elucidate the underlying mechanistic effects of stereocontrol agents using computational chemistry, the accuracy and reliability of computational methodology must be established. The main emphasis of this chapter [Publication 2] is the application of theoretical quantum chemistry to model reactions relevant to radical polymerization. It systematically reviews and assesses various methodological approaches that have been used to predict propagation rate coefficients in radical polymerisation (see **Figure 6**). The importance of the chemical model, electronic structure method, solvation modelling and the coupled issues of partition function evaluation and conformational analysis are examined. By comparing theoretical and experimental values, it is shown that accurate and reliable computational predictions are possible but require appropriate precautions. The practical value of computational chemistry is then showcased by three representative case studies drawn from polymer literature: copolymerisation kinetics; defect structure formation in vinyl chloride; and RAFT reactivity.

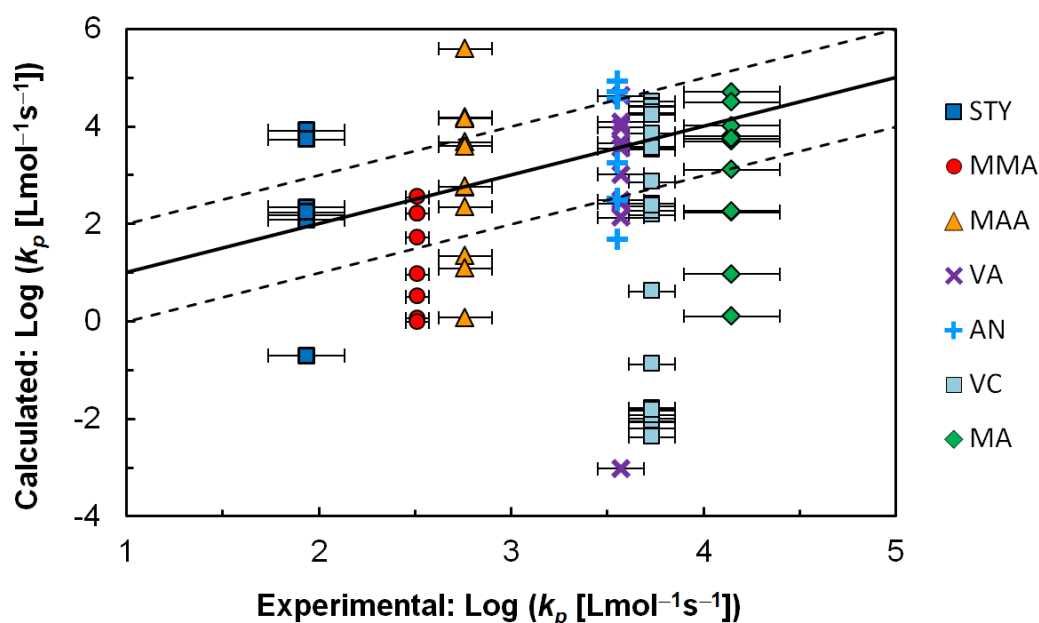


Figure 6 Theoretically predicted and experimentally determined propagation rate coefficients for the radical polymerization of: styrene (STY), methyl methacrylate (MMA), methacrylic acid (MAA), vinyl acetate (VA), acrylonitrile (AN), vinyl chloride (VC) and methyl acrylate (MA). Values were taken from Refs 74-103.

Before attempting to elucidate the mechanistic effects of stereocontrol agents, it is necessary to first clarify the kinetic scheme underlying tacticity selection in unmediated radical polymerization. In the remaining part of this chapter, the previously evaluated theoretical approaches are used to study tacticity determination in styrene (STY) and methyl methacrylate (MMA). Two possible mechanisms can be envisaged, depending on the relative rates of propagation and conformational equilibration. The first is the *rapid interconversion* scheme presented in **Figure 7**, which is envisioned as the correct mechanism for tacticity determination throughout this thesis. In this scheme, tacticity is determined by the orientation of the terminal and penultimate side-chains during monomer addition. The second mechanism, adopted by several other authors (designated here as the *slow interconversion* scheme, see **Figure 7**) has been employed (in conjunction with quantum chemical calculations) to make quantitative tacticity predictions and rationalize the effect of stereocontrol agents.¹⁰³⁻¹⁰⁵ In the *slow interconversion* scheme, tacticity is determined by the orientation of the side-chains of the terminal unit and the incoming monomer.

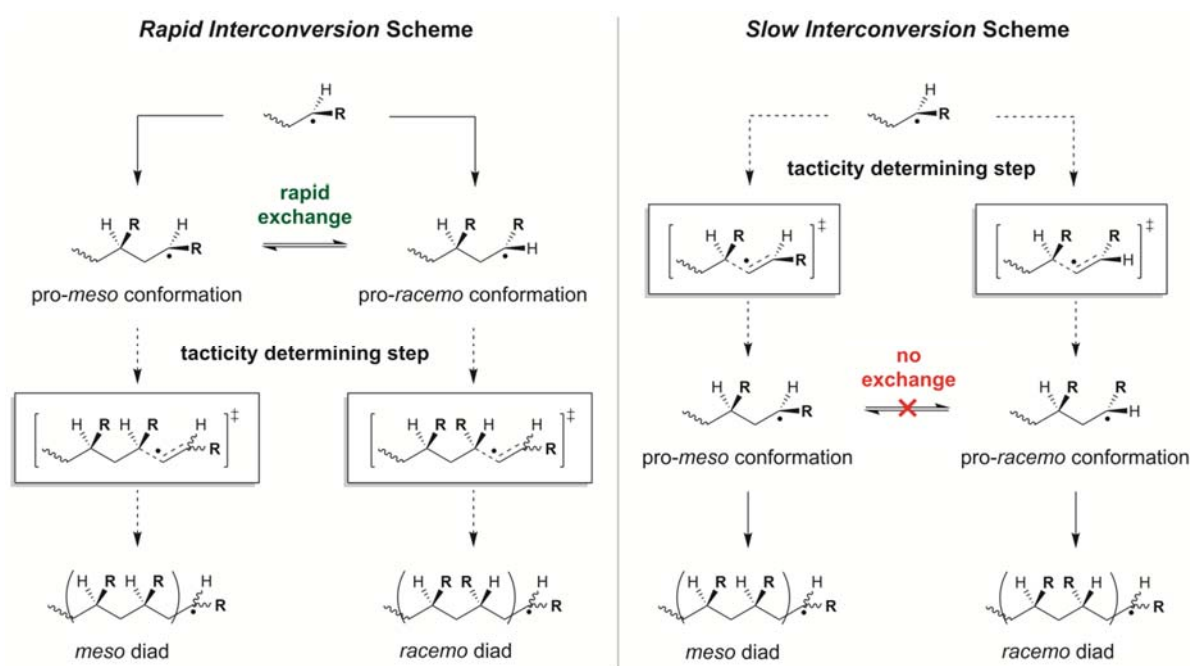


Figure 7 The *rapid* and *slow interconversion* schemes for tacticity determination in radical polymerization. In the *rapid interconversion* scheme, the *pro-meso* and *pro-racemo* conformations can rapidly interconvert and so the rate of their formation is irrelevant. In the *slow interconversion* scheme, these conformations are unable to equilibrate and so tacticity is predetermined before the *meso* or *racemo* diad actually forms.

These two conflicting mechanistic schemes originate from a divergent assumption regarding the relative rates of rotation around the terminal bond ($\sim\text{CH}_2\text{-C}^*\text{HR}$) and of propagation. In the *rapid interconversion* scheme, rotation around the terminal bond is presumed to be significantly faster than propagation; consequently *pro-meso* and *pro-racemo* type conformations are able to equilibrate after each propagation step. Under this scheme, the orientation of the terminal radical unit only becomes fixed during subsequent monomer addition and thus tacticity is determined by the orientation of the terminal and penultimate side-chains during propagation. In contrast, the *slow interconversion* scheme makes the converse assumption that rotation around the terminal chain bond is significantly slower than propagation; thus *pro-meso* and *pro-racemo* type conformations are unable to equilibrate following propagation. This scheme assumes that the orientation of the terminal side-chain is fixed, in which case tacticity is determined in the preceding propagation step by the orientation of the side-chains of the terminal unit and incoming monomer.

By establishing which of the two respective assumptions is valid, the correct mechanistic scheme can be identified. Rotation of the terminal bond does not disrupt conjugation between the radical and its side-chain, although it does disrupt (relatively minor) hyperconjugation interactions between the radical and adjoining H atoms of the $-\text{CH}_2-$ group. Nevertheless, one would intuitively assume that this rotation should be very rapid in most monomer systems and orders of magnitude faster than propagation. Perhaps somewhat surprisingly, the authors who employ the *slow interconversion* scheme do not justify its use, nor do they calculate the barrier to this terminal bond rotation. To demonstrate the unreasonableness of the *slow interconversion* scheme, rotational barriers around the terminal bond for propagating STY and MMA models were calculated from first principles (see **Figure 8**). As the lowest energy *pro-meso* and *pro-racemo* poly(MMA) structures adopt different chain structures, the barrier for linear/helical conversion was also calculated.

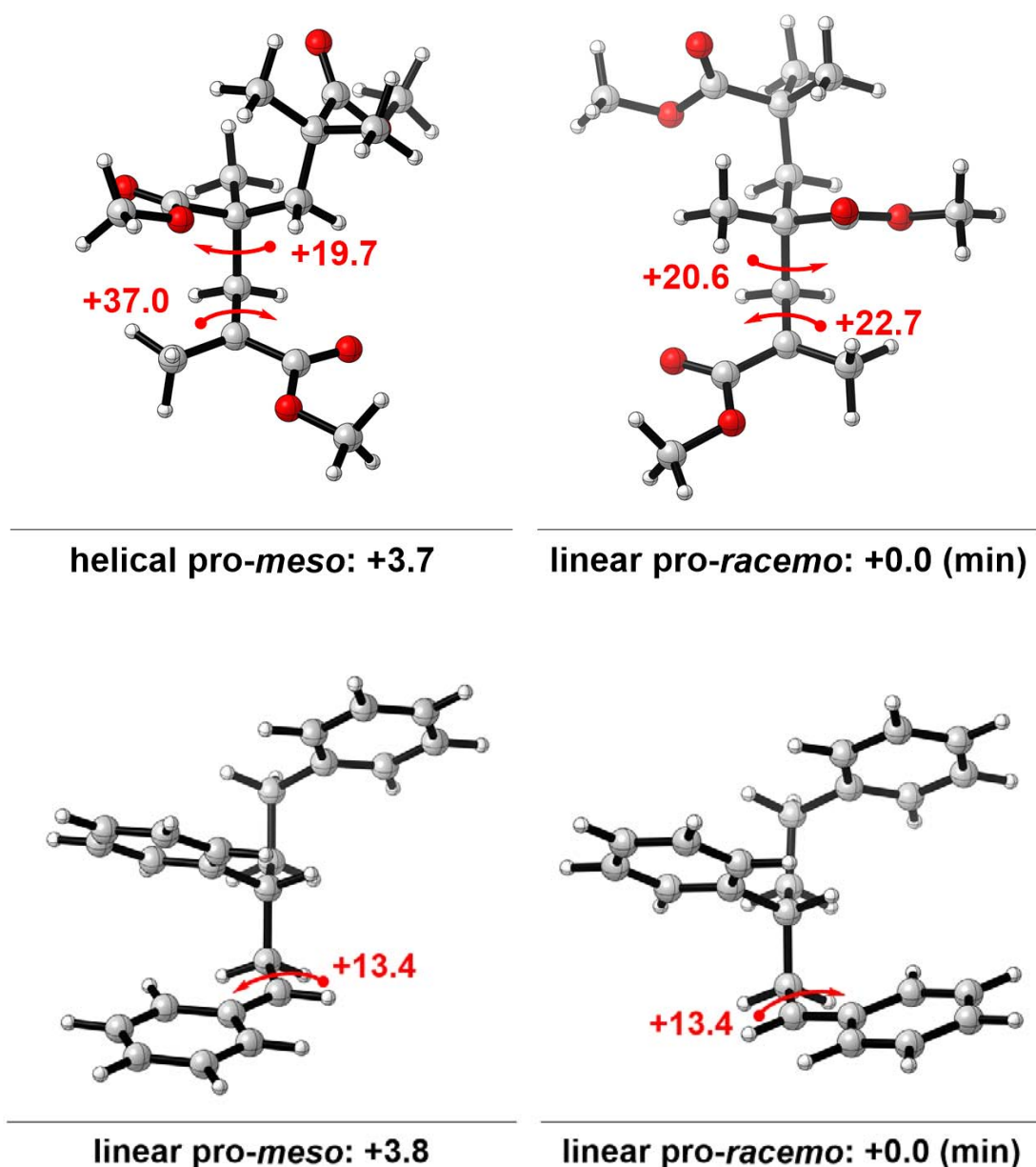


Figure 8 Rotational barriers in (kJ mol⁻¹) around the various C–C bonds of propagating poly(MMA) and poly(STY) radicals. Calculated at 25 °C using the G3(MP2)RAD//M06-2X/6-31+G(d,p) level of theory, in conjunction with an ONIOM approximation and SMD solvation corrections.

As illustrated by **Figure 8**, the rotational barrier around the terminal bond is very small in both systems in comparison to the barrier for propagation (> 55 kJ mol⁻¹). Unsurprisingly, smaller barriers are observed in the monosubstituted poly(STY) radical compared to the disubstituted poly(MMA) radical. The barrier for terminal bond rotation is somewhat larger for the helical poly(MMA) radical than for the linear radical, although it is still fairly modest and significantly smaller than the barrier for propagation. Moreover, the interconversion of helical pro-meso conformations to linear pro-racemo

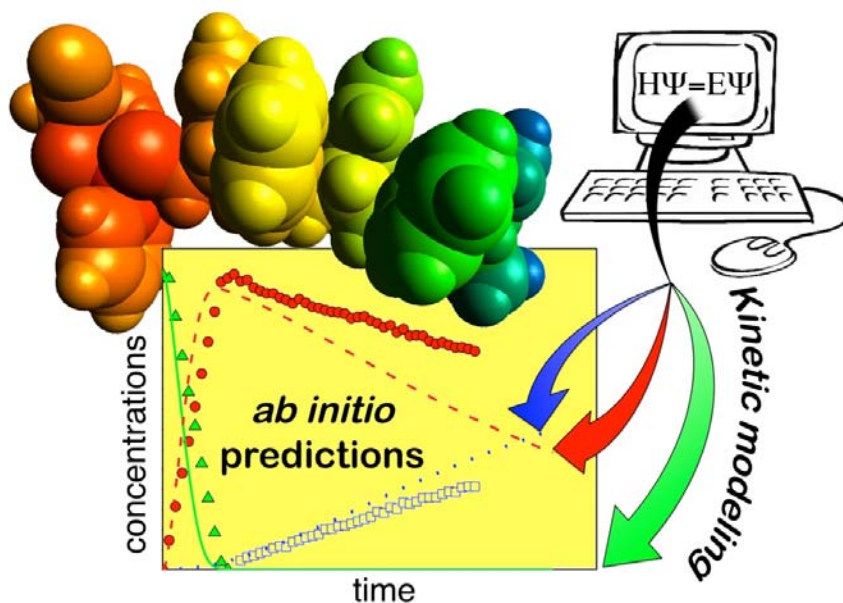
conformations would proceed via an initial helical to linear rotation (to form a linear pro-*meso* configuration, which can more readily undergo pro-*meso*/pro-*racemo* conversion). In any case, the *rapid interconversion* scheme is the correct mechanism for STY and MMA. This scheme is also tested and verified for methacrylic acid (MAA) in **Chapter 5**. The alternative *slow interconversion* scheme was found to be invalid in all the monomer systems examined thus far (STY, MMA and MAA). Moreover, this scheme is based on a dubious kinetic assumption, which is almost certainly incorrect under normal polymerization conditions. Incorrectly employing the *slow interconversion* scheme would lead to erroneous tacticity predictions and its use is strongly discouraged.

3.2 Publication 2

First Principles Modelling of Free-Radical Polymerization Kinetics

Noble, B.B. and Coote, M.L.

Int. Rev. Phys. Chem., **2013**, 32, 467-512.



The following manuscript is a peer-reviewed literature review article that was published in *International Reviews in Physical Chemistry* and featured on the cover. The literature review and discussion presented are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas, provided valuable suggestions and extended and corrected my drafts.

First principles modelling of free-radical polymerisation kinetics

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Computational quantum chemistry can make valuable contributions to modelling and improving free radical polymerisation. At a microscopic level, it can assist in establishing reaction mechanisms and structure-reactivity trends; at a macroscopic level it can be used in the design and parameterisation of accurate kinetic models for process optimisation and control. This review outlines and critically evaluates various methodological approaches that have been employed in first principles prediction of rate coefficients in free radical polymerisation, examining in turn the choice of chemical model, electronic structure method, solvation modelling and the coupled issues of partition function evaluation and conformational analysis. It is shown that accurate and reliable predictions are possible but only if necessary precautions are taken into account. The practical value of accurate computational modelling of radical polymerisation kinetics is then illustrated through three representative case studies from the literature in which theory has been used to develop accurate kinetic models: free radical copolymerisation kinetics; defect structure formation in radical suspension polymerisation of vinyl chloride; and reversible addition fragmentation chain transfer polymerisation.

Keywords: quantum chemistry; molecular orbital calculations; density functional theory; kinetic modelling; radical polymerisation; free-radical copolymerisation; poly(vinyl chloride) defect structures; reversible addition fragmentation chain transfer (RAFT) polymerisation

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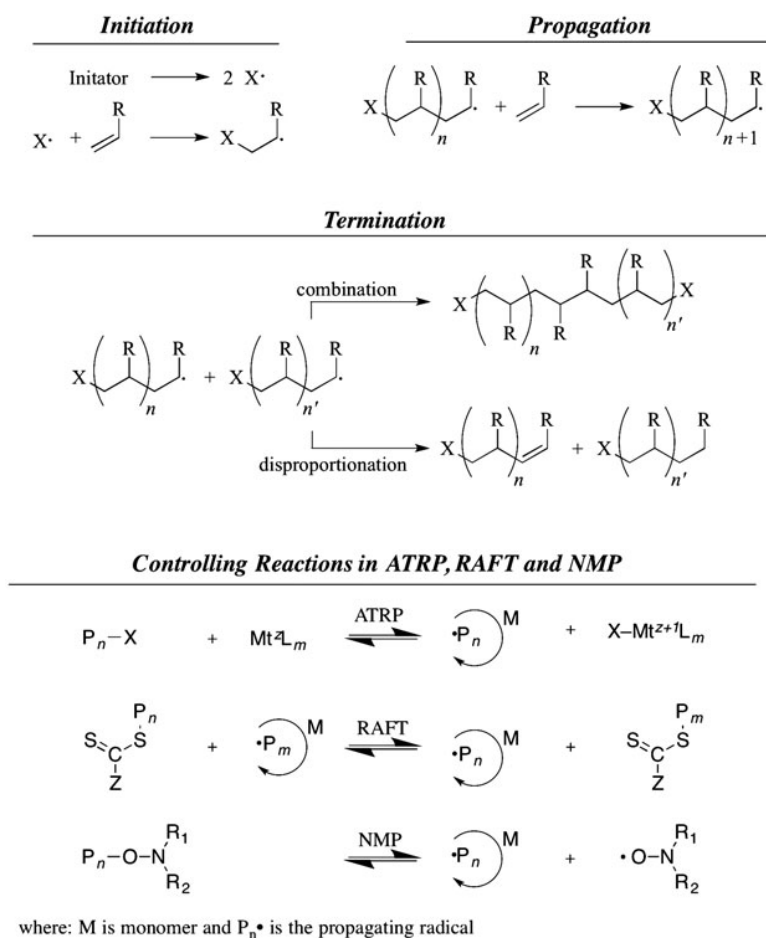
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1. Introduction

Free-radical polymerisation is the most commercially significant polymerisation process utilised in the production of approximately 50% of all synthetic polymers [1]. It is a form of chain polymerisation proceeding via a sequence of initiation, propagation, chain transfer and termination reactions (see Scheme 1(a)). In contrast to other chain polymerisation methods, such as ionic and coordination polymerisation, it has the advantage of being tolerant of mild conditions, reagent/solvent impurities and a broad range of monomer functionalities, thus making it an attractive option for industry. However, the limited control of molecular weight distribution, chain end composition and other aspects of polymer microstructure have previously restricted the utility of radical-based polymerisation, as many applications require precise control over these properties. The development of controlled radical polymerisation (CRP) procedures, notably, atom transfer radical polymerisation (ATRP) [2–4], nitroxide-mediated polymerisation (NMP) [5–7] and reversible addition fragmentation chain transfer (RAFT) [8–10] (Scheme 1(b)), has resolved many of the previous limitations of radical-based processes, combining the versatility and robust nature of conventional free-radical polymerisation with a narrow molecular weight distribution and precise end group control. The effectiveness of CRP relies on delicately balancing the rates of several competing reactions. Because of the complexity of these processes, the correlation between the initial conditions and the reaction outcomes is often very complicated and unintuitive. Thus, selecting a compatible control agent and appropriate reaction conditions for a given monomer can be problematic.

Kinetic modelling is central to developing more effective control agents and establishing optimal reaction conditions. Accurate kinetic models are capable of predicting the reaction outcomes such as the molecular weight distribution, composition and microstructure of the resulting polymer as a function of the initial conditions, such as reagent concentrations and temperature. Such models also provide valuable insights into the influence of chemical structure on reactivity, allowing for more effective control agents to be selected or designed. However, constructing a kinetic model requires the accurate rate coefficients of the principal reactions to be known. Radical polymerisation is comprised of a multitude of discrete reactions occurring within the context of a complex multistep process. Generally, there are no experimental techniques for studying these individual reactions in isolation and so obtaining



Scheme 1. Initiation, propagation and termination reactions for the free-radical polymerisation of a mono substituted alkene of the general form $\text{CH}_2=\text{CHR}$, along with key equilibria in various CRP processes.

accurate measurements for the rate coefficients, many of which are chain length dependent, can be problematic.

Over the last few decades, the development of elegant pulsed laser polymerisation (PLP) techniques [11–13] has allowed for the deduction of the propagation rate coefficient in most free-radical homopolymerisations with relative ease, and comparatively few model-based assumptions. These pseudostationary techniques allow for the propagation and termination rate coefficients to be determined by effectively separating the initiation and termination reactions from propagation in time. In a PLP experiment, a sample of monomer and photoinitiator is subjected to periodic laser irradiation. This irradiation rapidly generates photoinitiator radicals, which propagate during the dark time between laser pulses. At each laser pulse, the rapid increase in radicals terminates the growth of the existing polymer chains, while new photoiniti-

ator radicals commence chain growth. Whilst bimolecular termination occurs throughout the dark time between pulses, it is possible to optimise the reaction conditions (laser pulsing rate, laser power and initiator concentration) such that the termination that occurs at each laser pulse is much more significant, and hence the polymer that is initiated and terminated by successive laser pulses is clearly visible as a peak in the molecular weight distribution. Under these optimised conditions, the polymer that is initiated by one laser pulse survives the next one, and is terminated by the subsequent one which should also be visible in the molecular weight distribution as a second peak at twice the molecular weight of the primary peak. Provided these peaks are visible, the propagation rate coefficient can be deduced from the low-molecular weight side inflexion point of the primary peak in the molecular weight distribution (with knowledge of the monomer concentration and the time between successive laser pulses). Once the propagation rate coefficient is known, the termination rate coefficient can be determined by analysis of the reaction rate between more widely spaced laser pulses in a technique known as single-pulse PLP. For more details regarding the theory and application of these PLP techniques, the reader is directed to Refs. [11–13]. In some systems, the measurement of the propagation rate coefficient may be hindered by monomer absorbance of the laser radiation, excessive amounts of chain transfer or non-size exclusion behaviour in the molecular weight distribution. Moreover, for more complicated processes, such as copolymerisation or CRP, even sophisticated techniques such as PLP, cannot be used to extract individual rate coefficients without resorting to model-based assumptions.

The deficiencies and limited scope of current experimental methods make computational chemistry a particularly valuable tool for studying radical polymerisation, providing a useful complement to experimental studies. At the macroscopic level, computational chemistry can be used to predict the various rate and equilibrium constants of relevance to radical polymerisations including propagation, chain transfer and reactions involving the control agents. This allows for the accurate simulation of these polymerisation processes under varying conditions. At the microscopic level, computational chemistry can be used to clarify reaction mechanisms and model the interactions between substituents and control agents. This enables the rational selection or design of these agents through structure-reactivity studies. This review focuses on the macroscopic applications of computational chemistry to radical polymerisation. For some examples of microscopic applications of quantum chemistry in understanding radical polymerisation, the reader is directed to the previous mechanistic and structure-reactivity studies of self initiation [14–17], thioketone-mediated polymerisation [18,19], cobalt-mediated polymerisation [20], RAFT [21–37], NMP [38–45] and ATRP [46–53].

To exploit the full potential of computational chemistry, it is imperative that accurate and reliable methodology is applied to the polymerisation reactions. Inaccurate computational methodology may result in erroneous conclusions such as false predictions of optimal conditions or control agents. Moreover, the use of unreliable and inaccurate computational theory can undermine confidence in computational chemistry more generally. In this work, we review some of the alternative approaches to quantitative modelling of radical polymerisation with a view to assessing their accuracy and reliability. For this purpose, we focus primarily on propagation kinetics, for which reliable experimental data are available for comparison. We then draw on case studies from the literature to show how quantum chemistry can aid the derivation and parameterisation of accurate kinetic models for radical polymerisation.

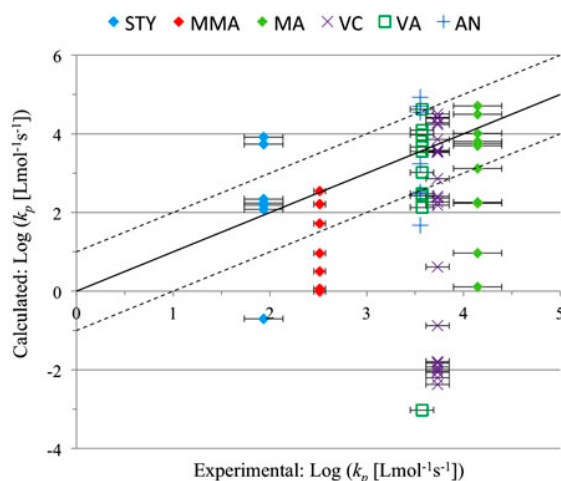


Figure 1. (Colour online) Calculated propagation rate coefficients for STY, MMA, MA, VC, VA and AN with respective experimental values at 298 K. Solid line corresponds to correct prediction of rate coefficient (calculated $\text{Log } k_p = \text{experimental } \text{Log } k_p$). Dashed lines indicate chemical accuracy from the actual propagation rate coefficient. Error bars indicate precision (95% confidence) in experimental values.

2. Computational procedures for studying radical polymerisation

Open-shell systems are generally more challenging to study computationally than comparable closed-shell systems. However, given the broader relevance of radical reactivity to fields varying from organic synthesis, combustion and atmospheric chemistry to biological chemistry, much effort has been directed to establishing and assessing theoretical procedures for modelling odd-electron species. Prototypical reactions, such as radical addition to alkenes and hydrogen abstraction, have been studied extensively [54–56]. In the radical polymer field, initial quantum-chemical studies examined qualitative aspects of radical reactivity such as probing the presence of penultimate effects in copolymerisation [57–64]. Over the last decade, increases in computing power and the development of highly cost-effective composite *ab initio* procedures have allowed the thermodynamic and kinetic properties for a wide variety of radical reactions to be predicted to within ‘chemical accuracy’ (*ca.* 4 kJ mol^{-1} in reaction energies and barriers or an order of magnitude in a rate coefficient or equilibrium constant at 298 K).

Given these advances and the unique chemical insights that can be provided by quantum chemistry, much current research has been directed towards establishing reliable theoretical methodology that can be applied quantitatively to radical polymerisation. The accuracy and reliability of such methodology are usually assessed by comparing predicted propagation rate coefficients for homopolymerisations with experimentally derived values, usually from PLP studies. In the literature, a multitude of different theoretical procedures have been applied to radical polymerisation reactions, with varying success at predicting experimental propagation rate coefficients (see Figure 1). This is illustrated in Tables 1–6, which summarise the variously calculated (and selected experimental) propagation rate coefficients of important monomers such as styrene (STY) [65–72], methyl methacrylate (MMA) [67,68,70,73–75], methyl acrylate (MA) [67,69,70,73,74,76–78], vinyl acetate (VA) [67,70,75,78–82], acryloni-

Table 1. Theoretically predicted and experimentally derived propagation rate coefficients at 298 K, activation barriers and Arrhenius factors for STY.

Kinetic parameters			Methodology					Ref.	
k_p (L mol ⁻¹ s ⁻¹)	E_a (kJmol ⁻¹)	log A	Model	Level of theory	Conformation searched	Vibrational partition function approximation	Phase/solution model		
8.60×10^3	32.5	7.63			Experiment: PLP-MWD		Bulk	[65]	
8.24×10^3	35.3	10.1	Hexamer	B3LYP/6-31G(d,p)//PM3	ONIOM	Yes ^a	HO	gas/NA	[66]
1.99×10^{-1}	41.5	6.57	NR ^b	BP86/cc-PVTZ corrected with (T)/cc-PVDZ	CCSD	NR ^b	HO	Bulk/COSMO-RS	[67]
1.54×10^2	34.6	8.25	Unimer	B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p)		Yes ^c	HO	gas/NA	[68]
1.20×10^2	34.6	8.14	Unimer	B3LYP/6-31G(d,p)		Yes ^c	HO	gas/NA	[69]
2.19×10^2	34.7	8.42	Trimer	B3LYP/6-31G(d,p)		No ^d	HO	gas/NA	[70]
5.43×10^3	26.8	8.43	Unimer	B3LYP/6-31G(d,p)		Yes ^c	1-D hindered rotor (Torsion eigenvalue summation)	gas/NA	[71,72]

^aDetails not provided.

^bAbbreviation: not reported.^cFull search.^d Straight chain conformation used.

Table 2. Theoretically predicted and experimentally derived propagation rate coefficients at 298 K, activation barriers and Arrhenius factors for MMA.

Kinetic parameters			Methodology					
k_p ($\text{L mol}^{-1} \text{ s}^{-1}$)	E_a (kJ mol^{-1})	$\log A$	Model	Level of theory	Conformation searched	Vibrational partition function approximation	Phase/solution model	Ref.
3.26×10^2	22.3	6.42			Experiment: PLP-MWD		Bulk	[65]
5.22×10	27.7	6.57	Unimer	MPWB1K/6-31G(d,p)//B3LYP/6-	Yes ^a	1-D Hindered rotor (Torsion eigenvalue summation)	gas/NA	[73,74]
9.22×10	28.0	6.87	Dimer	31G(d)				
1.63×10^2	22.7	6.19	Trimer					
3.51×10^2	26.0	7.10	Unimer	B3LYP/6-311+G(d,p)//B3LYP/6-	Yes ^b	HO	gas/NA	[68]
				31G(d,p)				
3.19×10	26.0	6.06	NR ^c	BP86/cc-PVTZ corrected with CCSD(T)/cc-PVDZ	NR ^c	HO	Bulk/COSMO-RS	[67]
1.15×10	36.7	7.49	Unimer	B3LYP/6-311+G(d,p)	Yes ^a	HO	gas/NA	[75]
9.77×10^{-1}	42.3	7.40	Dimer					
1.63×10^2	33.1	8.01	Trimer	B3LYP/6-31G(d,p)	No	HO	gas/NA	[70]

^aLinear search.^bFull search.^cAbbreviation: not reported.^dStraight chain conformation used.^eEnergy directed tree search.

Table 3. Theoretically predicted and experimentally derived propagation rate coefficients at 298 K, activation barriers and Arrhenius factors for MA.

Kinetic parameters			Methodology			
k_p ($\text{L mol}^{-1} \text{s}^{-1}$)	E_a (kJ mol^{-1})	$\log A$	Model	Level of theory	Conformation searched	Vibrational partition function approximation
$(1.4 \pm 0.8) \times 10^4$	18.5 ± 0.9	7.4 ± 0.2			Experiment: PLP-SEC	
1.72×10^2	26.4	6.86	Unimer	MPWB1K/6-31G(d,p)	Yes ^a	1-D Hindered rotor
6.39×10^3	22.8	7.80	Dimer			(Torsion eigenvalue summation)
1.03×10^4	21.5	7.78	Trimer			HO
1.83×10^2	24.3	6.52	Dimer	MPWB1K/6-311+G(3df,2p)	Yes ^b	gas/NA
1.28×10	22.8	5.10	Dimer	31+G(d)		Bulk/COSMO- RS
5.11×10^4	10.5	6.54	Unimer	G3(MP2)-RAD//B3LYP/6-31G(d)	Yes ^c	gas/NA
3.15×10^4	5.2	5.41	Dimer			1-D Hindered rotor
5.01×10^3	21.8	7.50	Dimer			(Torsion eigenvalue summation)
						Bulk/COSMO- RS
9.34×10	23.8	6.14	NR ^d	BP86/cc-PVTZ corrected with CCSD (T)/cc-PVDZ	NR ^d	Bulk/COSMO- RS
1.31×10^3	31.0	8.55	Unimer	B3LYP/6-31G(d,p)	Yes	gas/NA
5.62×10^3	27.4	8.55	Trimer	B3LYP/6-31G(d,p)	No ^e	gas/NA

^aLinear search.^bFull conformational search.^cEnergy directed tree search.^dAbbreviation: not reported.^eStraight chain conformation used.

Table 4. Theoretically predicted and experimentally derived propagation rate coefficients at 298 K, activation barriers and Arrhenius factors for VA.

Kinetic parameters			Methodology					
k_p ($\text{L mol}^{-1} \text{s}^{-1}$)	E_a (kJ mol^{-1})	$\log A$	Model	Level of theory	Conformation searched	Vibrational partition function approximation	Phase/solution model	Ref.
4.06×10^3	20.5	7.20			Experiment: PLP-SEC		Bulk	[79]
3.40×10^3	19.8	7.00			Experiment: PLP-SEC		Bulk	[80]
9.54×10^3	16.1	6.80	Unimer	B3LYP/6-31G(d)//UHF/6-31G(d)	Yes ^a	HO	gas/NA	[81]
3.53×10^3	14.8	6.14	Dimer					
9.48×10^{-4}	30.1	2.25	Unimer	B3LYP/6-31+G(d)	No ^b	HO	gas/NA	[82]
2.65×10^2	23.9	6.61	NR	BP86/cc-PVTZ corrected with CCSD(T)/cc-PVDZ	NR ^c	HO	Bulk/COSMO-RS	[67]
1.23×10^4	11.7	6.14	Unimer	G3(MP2)-RAD//B3LYP/6-31G(d)	Yes ^d	1-D Hindered rotor (Torsion eigenvalue summation)	gas/NA	[78]
4.61×10^3	7.4	4.96	Dimer					
1.04×10^3	17.6	6.10	Dimer				Bulk/COSMO	
3.02×10^2	27.8	7.35	Unimer	B3LYP/6-311+G(d,p)	Yes ^a	HO	gas/NA	[75]
1.34×10^2	29.7	7.33	Dimer					
4.21×10^4	15.5	7.34	Trimer	B3LYP/6-31G(d,p)	No ^b	HO	gas/NA	[70]

^aFull search.^bStraight chain conformation used.^cAbbreviation: not reported.^dEnergy directed tree search.

Table 5. Theoretically predicted and experimentally derived propagation rate coefficients at 348 K, activation barriers and Arrhenius factors for AN.

Kinetic parameters			Methodology					
k_p ($\text{L mol}^{-1} \text{ s}^{-1}$)	E_a (kJmol^{-1})	$\log A$	Model	Level of theory	Conformation searched	Vibrational partition function approximation	Phase/solution model	Ref
8.70×10^3	15.4	6.25			Experiment: PLP-SEC		Propylene carbonate	[83]
4.60×10^3	—	—			Experiment: Nitroxide trapping		Bulk	[84]
2.37×10^2	27.7	6.53	Unimer	G3(MP2)-RAD//B3LYP/6-31G	Yes ^a	HO	gas/NA	[85]
1.26×10^3	23.0	6.55	Dimer	(d)				
1.09×10^3	22.4	6.40	Trimer					
4.02×10^3	—	—	Dimer			1-D hindered rotor (Torsion eigenvalue summation)	Bulk/COSMO	
4.88×10^5	39.4	11.6	Unimer	B3LYP/6-311+G(d,p)	No ^b	HO	gas/NA	[86]
3.42×10^5	39.1	11.4	Dimer					
7.47×10^5	37.5	11.5	Trimer					
1.07×10^4	31.4	8.74	Trimer	B3LYP/6-31G(d,p)	No ^b	HO	gas/NA	[70]

^aEnergy directed tree search.^bStraight chain conformation used.

Table 6. Theoretically predicted and experimentally derived propagation rate coefficients, activation barriers and Arrhenius factors for VC.

Kinetic parameters			Methodology				Ref.
k_p ($\text{L mol}^{-1} \text{s}^{-1}$)	E_a (kJ mol^{-1})	$\log A$	Model	Level of theory	Conformation searched	Vibrational partition function approximation	Phase/solution model
$(5.4 \pm 1.4) \times 10^3$	NR	NR		Experiment: electron spin resonance spectroscopy			
3.13×10^3	NR	NR		Experiment: rotating sector	No ^a	HO	Benzene THF gas/NA
4.14	29.7	5.82	Unimer	B3LYP/6-311G(d,p)			
1.52×10^{-2}	34.7	4.26	Dimer				
6.31×10^{-3}	35.9	4.09	Trimer				
7.25×10^2	21.8	6.68	Unimer	G3(MP2)-RAD//B3LYP/6-31G(d)	Yes ^b	HO	gas/NA
3.32×10^3	18.2	6.71	Dimer				
3.77×10^3	17.2	6.59	Trimer				
7.15×10^3	—	—	Dimer				
3.53×10^3	—	—	Dimer				
1.01×10^{-2}	33.6	3.89	Unimer				
8.67×10^{-3}	33.4	3.79	Dimer	B3LYP/6-31+G(d)	No ^a	HO	gas/NA
4.25×10^{-3}	34.6	3.69	Trimer				
1.33×10^{-1}	27.2	3.89	Unimer	BMK/6-311+G(3df,2p)//B3LYP/6-31+G(d)			
1.64×10^{-2}	31.6	3.75	Dimer				
8.93×10^{-3}	32.7	3.68	Trimer		No ^a	HO	gas/NA
1.18×10^{-2}	33.2	3.89	Tetramer				
1.48×10^{-2}	32.7	3.90	Pentamer				
2.57×10^2	22.6	6.37	Unimer	B3LYP/6-31G(d,p)	No ^a	HO	gas/NA
1.53×10^2	23.6	6.32	Dimer				
1.85×10^2	23.7	6.42	Trimer				
2.33×10^2	23.7	6.52	Tetramer				
3.19×10^4	24.0	5.79	Unimer	MPWB1K/6-31G(d,p)	No ^a	HO	gas/NA
2.61×10^4	23.1	5.55	Dimer				
2.55×10^4	23.0	5.53	Trimer				
2.51×10^4	23.0	5.53	Tetramer				
1.89×10^4	23.5	5.48	Pentamer				
1.73×10^4	23.5	5.44	Hexamer				

^aStraight chain conformation used.^bEnergy directed tree search.

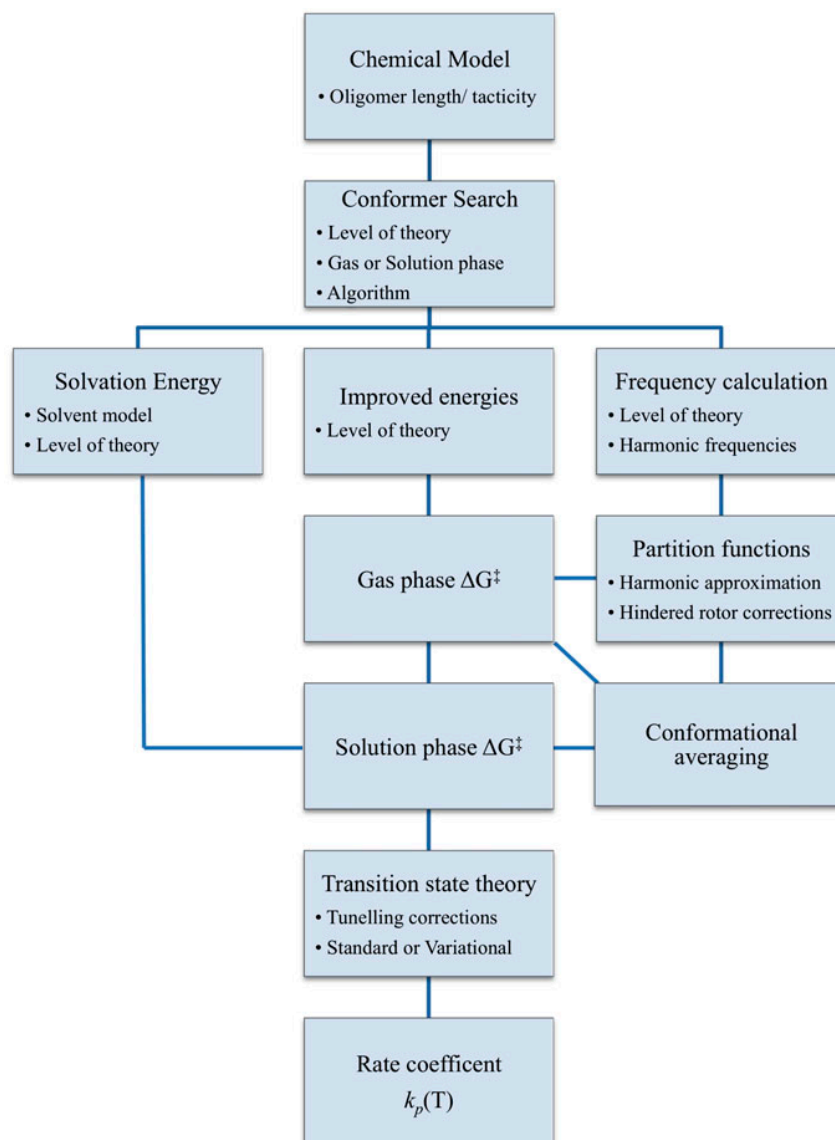


Figure 2. The methodology utilised for the prediction of propagation rate coefficients.

trile (AN) [70,83–86] and vinyl chloride (VC) [82,85,87–92]. From these tables, it is apparent that the methodology has a large effect on the accuracy of the predicted propagation rate coefficients. Some theoretical procedures fail to predict qualitative trends in reactivity with respect to monomer functionality, while others predict propagation rate coefficients that differ from experimental results by more than six orders of magnitude at 298 K. At the same time, more robust methods are able to reproduce experimental propagation rate coefficients at

298 K to within an order of magnitude and correctly predict monomer reactivity trends. As illustrated in Figure 1, experimental precision of propagation rate coefficients is typically high compared to the variation in the calculated data. However, due to relatively narrow temperature range accessible for experimental studies, the precision of the Arrhenius parameters (E_a and A) is often highly correlated and generally lower than precision of the k_p values.

To use theory to predict the thermochemistry of simple compounds in the gas phase, there are relatively few procedural decisions or approximations to make beyond the choice of electronic structure method, and so evaluating the methodology by comparison with experiment is straightforward. However, predicting a solution-phase propagation rate coefficient in a polymerisation is much more complicated and requires multiple calculations and approximations, many of which are intrinsically coupled. Thus, if there is a disagreement with experimental data, it is often difficult to identify which calculation or approximation is responsible for it. Moreover, agreement with experimental results does not necessarily validate the accuracy of the theoretical procedures because of the potential for fortuitous error cancellation between the different components of the calculation. Thus, to test the reliability and robustness of a theoretical procedure, it is desirable to assess the various aspects of the methodology individually. As shown in Figure 2, there are four broad components of the methodology that can influence the accuracy of the calculated rate coefficients: the chemical model of the propagation reaction, the accuracy of the various electronic structure calculations, the accuracy of the solvation modelling, and the approximations used in the kinetic and thermodynamic treatment of the model system (including the related problems of conformer averaging and calculation of partition functions). This section discusses and evaluates these components systematically, with references to previous studies that highlight some of the considerations and challenges associated with modelling radical polymerisation.

2.1. Chemical model design

Free-radical polymerisation is dominated by addition reactions between monomers and relatively long polymer radicals, typically longer than 100 monomer units. However, studying such long polymer chains using quantum chemistry, even with relatively low-cost methods, is impractical. To study propagation and other polymerisation reactions computationally, it is necessary to use a truncated oligomer model. In principle, short-chain models should be valid provided there is no conjugation along the polymer backbone, as the effect of remote substituents on propagation diminishes rapidly with distance from the reaction centre and at some point these effects become negligible. However, as detailed below, the validity of using oligomeric models to simulate chemically controlled reactions has been questioned by some researchers. It is generally agreed that, depending on the system, the addition rate coefficient may vary significantly during the first few propagation steps. For instance, Fischer *et al.* used EPR experiments to show that the rate coefficient for the addition of the benzyl radical to STY is an order of magnitude faster than the addition of the polystyryl radical to STY at 298 K [93]. But the extent of these chain length effects has been a matter of some debate, centred around the observed dependence of the propagation rate coefficient on the laser pulsing rate in some PLP experiments.

On the basis of careful PLP experiments, Olaj *et al.* observed that the measured propagation rate coefficients of STY and MMA increased with higher laser pulsing rates, which the authors ascribed to a significant long-range chain length dependency that extended beyond

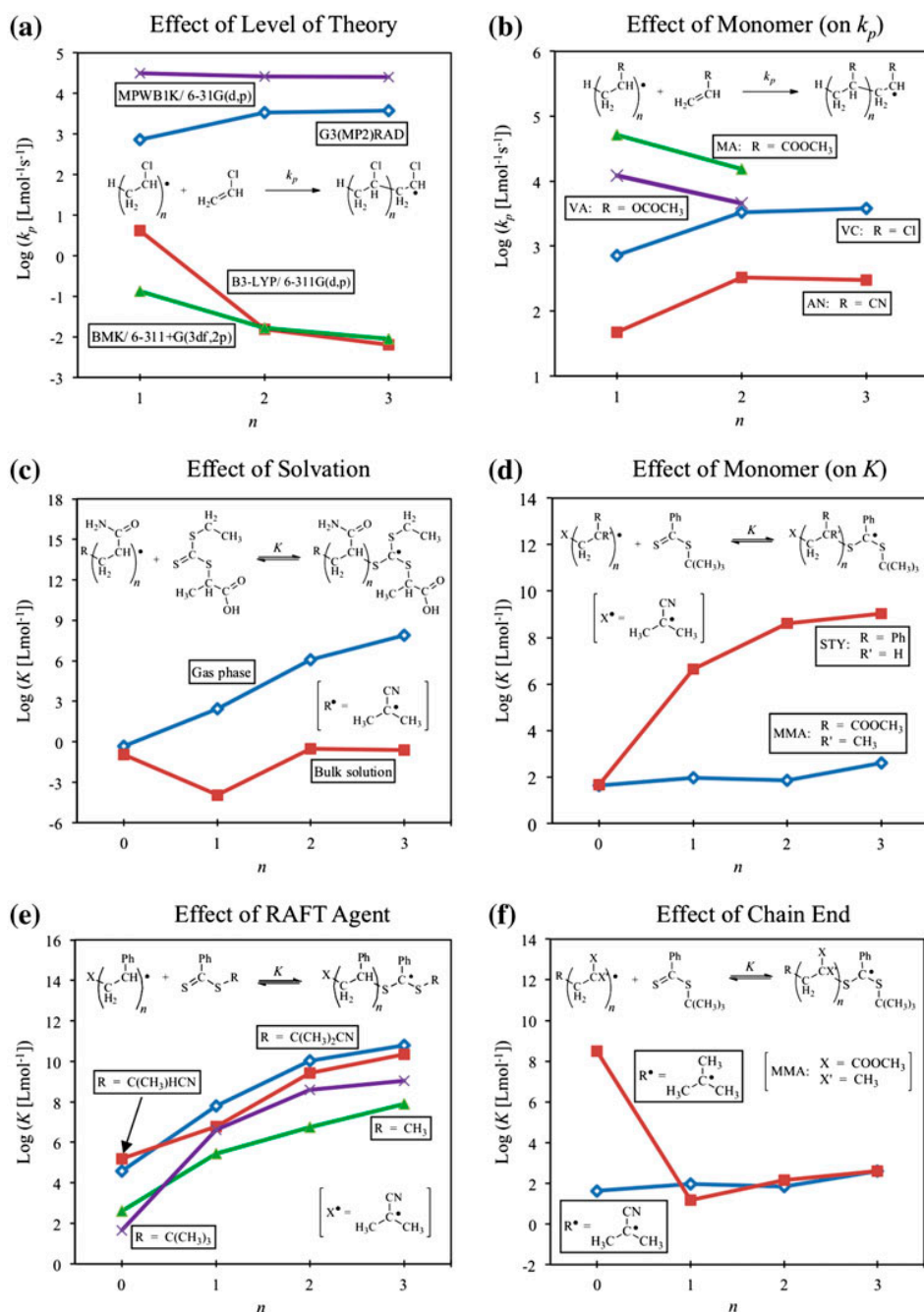


Figure 3. (Colour online) The chain length convergence of different polymerisation systems at 298 K. (a) Gas-phase propagation rate coefficients at 298 K, data taken from [85,89,90,92]. (b) Gas-phase propagation rate coefficients at 298 K, data taken from [78,85]. (c) Gas- and solution-phase equilibrium constants at 298 K, data taken from [37]. (d)–(f) Solution-phase equilibrium constants at 298 K, gas-phase data taken from [19,35,37] and corrected with the COSMO-RS solvent model using bulk monomer as a solvent.

100 propagation steps [94]. However, Willemse *et al.* argued that this effect was an artefact caused by band broadening in the size-exclusion chromatography (SEC) analysis, concluding that chain length dependency is limited to the first 10 propagation steps [95]. Subsequently, Olaj *et al.* found that long-range chain length dependency persisted even after distortions caused by the SEC analysis were corrected [96]. Recently García *et al.* suggested that the observed dependence of the propagation rate coefficient on laser pulsing rate could be adequately explained by varied heating of the sample [97]. Additionally, García *et al.* noted that authors who reported quasi-isothermal conditions typically observed no significant variation in the propagation rate coefficient with laser pulsing rate. Small molecule studies of chain length effects via elegant nitroxide trapping techniques generally suggest that convergence to the long chain limit is rapid [98]. According to a recent review of these studies by Heuts *et al.* [99], most available evidence suggests that the chain length dependence of the propagation rate coefficient is characterised by a high value for the initial addition step followed by approximately exponential decay to the long chain value. Given the results of these small molecule studies, and doubts cast by García *et al.* [97] on the PLP evidence for long-range chain length effects, we conclude that the use of *appropriate* oligomeric models for computational studies is justified. However, it is also clear that there are strong-chain length effects for the first few steps and hence very short oligomers (especially unimers) do not provide an adequate model of polymeric propagating radicals.

To establish the minimum chain length necessary to model a polymerisation reaction, the propagating radical can be systematically extended until an acceptable level of convergence is obtained. While a majority of studies have focused on structures no larger than dimer or trimer radicals, van Speybroeck *et al.* examined the propagation rate coefficient of ethylene to much longer chain lengths, though by necessity at a relatively low level of theory, B3-LYP/6-31G(d) [100]. In this study [100], a significant chain length effect was noted during the initial few propagation steps, however, the rate coefficient was found to have largely converged by the trimer (hexyl radical) stage. Figure 3 summarises the results of other theoretical studies in the literature for propagation [78,85,89,90,92], and also for a related process, radical addition to RAFT agents [19,35,37]. From Figure 3 it is immediately obvious that consistent with experimental results, unimeric radical reactions are not suitable models for corresponding polymeric reactions. Thus, when close ‘agreement’ between experimental propagation rate coefficients and those calculated using unimeric models is reported, it is almost certainly the result of fortuitous error cancellation. It is also clear from Figure 3 that the rate at which chain length effects converge depends on the chemical reaction being studied, whether the reaction is studied in the gas- or solution-phases, and also (unfortunately) the level of theory used. In particular, when non-dispersion corrected density functional theory (DFT) methods (such as B3-LYP) are used even the qualitative chain length dependencies are not well modelled, as dispersion is often an important contributor to longer range substituent effects in these reactions. The large differences between the gas- and solution-phase behaviour in Figure 3 are due to the contribution of hydrogen bonding to the remote substituent effects. These interactions are significant in the gas phase, in which most theoretical calculations on polymerisation have been performed, but are considerably less significant in the solution phase [37,78]. Thus, chain length convergence should be studied for experimentally realistic conditions using theoretical procedures that are able to model these effects accurately. Modelling these effects with unreliable methodology or under non-representative reaction conditions may lead to erroneous conclusions regarding the required model size and the use of models

that are either too small or unnecessarily large. Notwithstanding these complexities, the collected studies in Figure 3 indicate that in most cases dimers or trimers provide reasonable approximations to their long-chain equivalents, although the exact model size should be evaluated on a case-by-case basis.

2.2. Electronic structure calculations

Electronic structure calculations are pivotal to the accurate prediction of rate coefficients and are arguably the source of the largest errors. Within quantum chemistry there exists a hierarchy of different methods that address the competing demands of accuracy and model size. While the most sophisticated *ab initio* methods can provide chemical accuracy, they can only be applied to small models because of their high computational expense. Alternatively, less sophisticated methods can be applied to more realistic models; however, their accuracy may be limited to semi-quantitative or qualitative predictions. Thus, it is necessary to compromise between designing a realistic chemical model and simultaneously restricting its size to facilitate the use of sufficiently accurate methodology.

Our focus here is the prediction of propagation rate coefficients, which are dependent on the activation barrier for a radical addition reaction. However, it is prudent to assess prospective theoretical procedures not only on their ability to predict activation barriers but also the overall reaction energies; the reliability of a procedure that can reproduce experimental kinetics but fails for thermodynamics is questionable. In any case, the accurate prediction of both these properties is necessary for studying reversible processes, e.g. the propagation of stabilised monomers close to their ceiling temperatures. Moreover, we aim not only to assess various theoretical methods for calculating propagation rate coefficients via benchmarking against experiments, but also to identify reliable methodology for predicting the energetics of other relevant reactions where reliable experimental data may not be available (e.g. the controlling reactions in RAFT, NMP and ATRP). Thus, we wish to identify theoretical procedures that are equally capable of modelling hydrogen and halogen abstraction, reversible radical addition to thiocarbonyl compounds and bond homolysis of alkoxyamines.

Central to the prediction of accurate kinetics and thermodynamics is obtaining accurate geometries, frequencies and single-point energies. Since the accuracy of these respective properties at a given level of theory may differ significantly, we need to examine each of these properties in turn to identify reliable theoretical procedures.

2.2.1. Geometry optimisation and frequency calculations

When assessing different levels of theory for geometry optimisations and frequency calculations, the absolute accuracy of the obtained molecular geometries and frequencies themselves may not be directly significant. Rather, this assessment should examine the effect of any inaccuracies in geometries and frequencies on the resulting kinetics and thermodynamics. To examine the influence that the level of theory has on the accuracy of the molecular geometries, activation and reaction energies can be calculated using the geometries optimised at various levels of theory but utilising a consistent high-level method for the single-point energies. The influence that the molecular geometry has on the rotational component of the entropy of activation and reaction can also be examined at the various levels of theory. To assess the

accuracy associated with molecular frequencies, the zero-point vibrational energies, vibrational entropies and thermal corrections should be calculated at varying levels of theory.

Early benchmarking studies of hydrogen abstraction [101,102] and addition to C=C [103,104] and C=S [105] bonds suggested that relatively low levels of theory, such as B3-LYP/6-31G(d) or MPW1K/6-31+G(d,p), are generally appropriate for geometry optimisations and frequency calculations. Due to the high computational cost associated with obtaining the benchmark CCSD(T) geometries, only relatively simple models, such as the addition of the methyl radical to ethylene, could be considered. For radical addition, these studies concluded that while DFT calculations underestimate the forming bond length in the transition states of radical additions, this underestimation had a relatively minor influence on the calculated reaction barrier, with the notable exception of addition to C=S bonds. For addition to C=S bonds, the use of the IRCMax technique [106,107] was necessary to correct transition structures optimised at a low level of theory [105]. The prototypical models examined in these studies were necessarily simplistic and so it is questionable whether the conclusions drawn are more generally applicable to radical polymerisation systems.

Contemporary low-cost procedures (including HF and various DFT methods) are generally able to describe structural aspects of covalent bonding, such as bond lengths and angles, reasonably well. However, some more recent studies found that these procedures fail to predict accurate geometries in systems where intermolecular (see for instance [108]) and intramolecular (see for instance [109]) dispersive interactions are significant. While dispersion is typically weaker than electrostatic and inductive interactions, and much weaker than covalent bonding, it can still have a significant influence on structure. In novel systems where intermolecular dispersion is the dominant interaction, such as benzene or helium dimers, low-cost procedures typically do not even predict stable minima and clearly cannot be used to predict accurate structures (see for instance [108]). Generally, in systems of interest to radical polymerisation, covalent bonding, electrostatic and inductive interactions rather than dispersion are the dominant interactions and so it might be assumed that the latter interaction has only a minor influence on structure, an assumption supported by the aforementioned prototypical benchmarking studies [101–105]. However, as a counter example, in some larger systems of biological interest, intramolecular dispersion was found to have a significant influence on the conformational profile and consequently the resulting thermochemistry (see for instance [109]). Moreover, a recent study on the RAFT process noted that at low levels of theory (such as B3-LYP), various sulfonyl addition intermediates were unstable and fragmented spontaneously. However, higher levels of theory, such as M06-2X, predicted stable addition structures with modest barriers to fragmentation [110]. Thus, the importance of intramolecular dispersive interactions in determining structure in larger oligomer systems is somewhat unclear; however, preliminary work suggests such interactions can make a significant contribution to single point energies (see Section 2.2.2). For monomers and propagating radicals where non-covalent interactions are significant, using low-cost methods for geometry optimisations and frequency calculations could potentially lead to significant error. To address these shortcomings, new DFT functionals capable of accurately describing dispersive interactions are being actively developed and tested [111,112]. While the importance of non-covalent interactions on structure may be diminished in solution, it is advisable to examine prospective optimisation procedures cautiously, particularly in systems where these interactions are expected to be significant.

2.2.2. Single-point energy calculations

DFT methods are frequently utilised for single-point energy calculations due to their low computational cost, however, their accuracy and reliability are often questionable. Generally, the accuracy of DFT calculations can vary from very poor to fairly good, depending on the chemical system and choice of basis set and density functional. Unfortunately, as the exact density functional is unknown, there is no systematic method for improving DFT results. Typically, prospective functionals are evaluated against high level *ab initio* procedures for relatively small models. However, many highly parameterised DFT methods may deliver excellent results for small prototypical reactions only to fail unexpectedly for larger systems. For instance, in a study of VC propagation [85], it was shown that the error in the calculated reaction barrier at the B3-LYP level of theory was less than 4 kJ mol^{-1} for unimer addition, how-

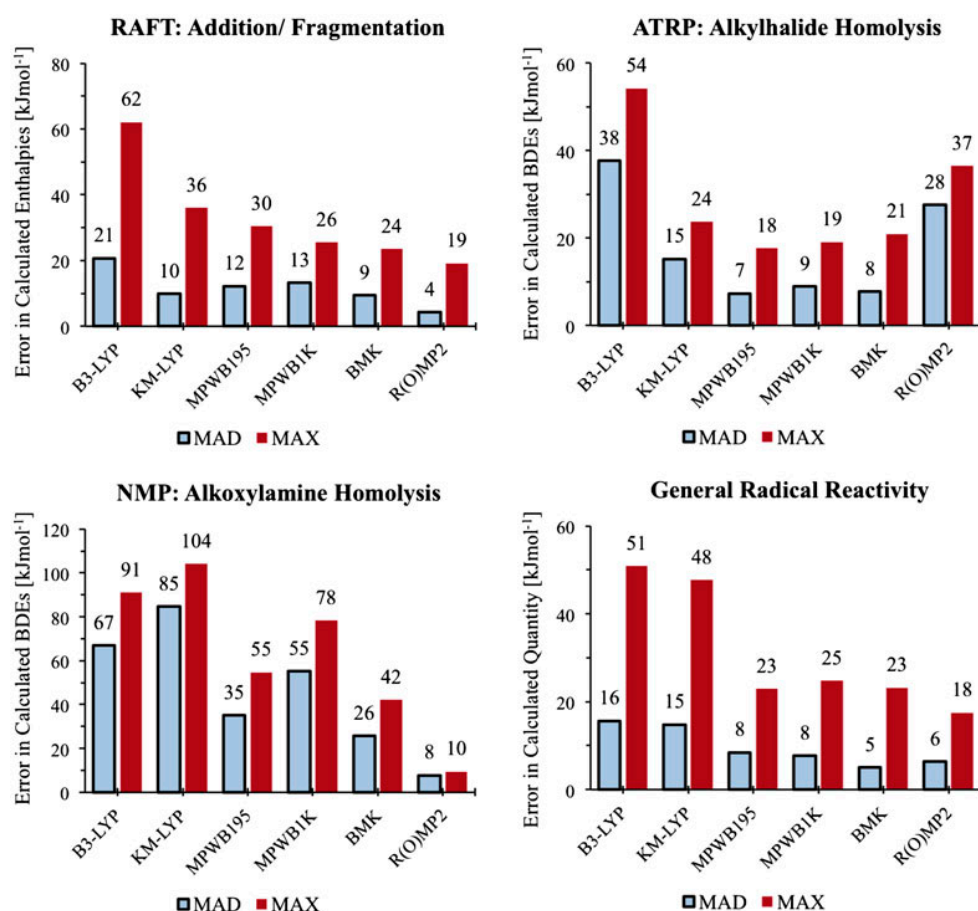


Figure 4. MADs and maximum deviations (MAX) of various levels of theory from G3(MP2)-RAD reaction energies at 0 K. Single-point calculations at specified level of theory were made using a 6-311+G(3df,2p) basis set on structures optimised at B3-LYP/6-31G(d) level. All data taken from Refs. [115,116].

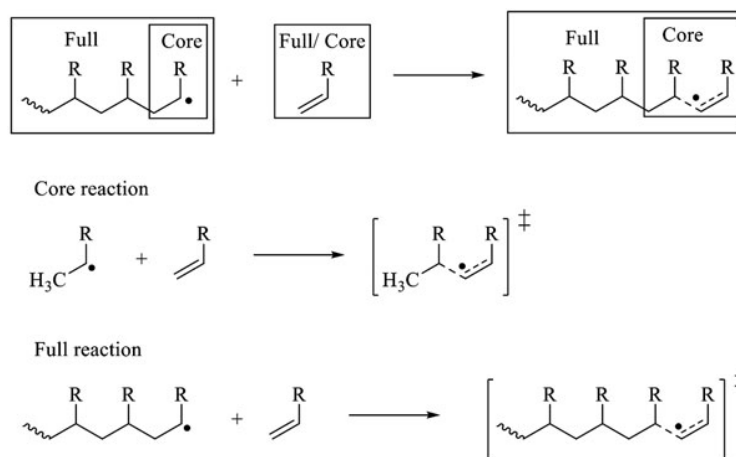
ever, this error increased to around 16 kJ mol^{-1} when a larger dimer model was considered. Presumably, the 'accurate' result for the unimer was due to fortuitous error cancellation and/or the poor result for the dimer was because of the failure of B3-LYP to model the remote substituent effects correctly (in this case the dispersive and hyperconjugative interactions). Either way, it emphasises the dangers of relying upon simplified chemical models for benchmarking studies, and, as a corollary, low levels of theory for chain length and substituent effect studies.

Given these problems, it is helpful to look beyond the immediate radical polymer field for benchmarking studies. It has been widely noted [113–126] that a large number of contemporary DFT functionals fail dramatically for organic reactions in which the extent of substitution changes significantly. Even for the study of isodesmic reactions, which are subject to a high degree of intrinsic error cancellation, several popular DFT functionals have been found to have errors of as much as 90 kJ mol^{-1} for predicting thermodynamic properties [113]. Previous studies [113–126] have shown that some popular DFT methods are unable to calculate reaction barriers and energies to within chemical accuracy and fail to reproduce even qualitative trends in some radical reactions. For instance, one such study [114] found that functionals such as B3-LYP and MPWB1K fail to predict qualitative experimental trends in some simple R–X bond dissociation energies (where X=H, CH₃, OCH₃, OH, F) when the alkyl substitution was altered (from R=Me to Et, *i*-Pr, *t*-Bu). Other rigorous studies [115,116] that tested the performance of theoretical procedures for predicting bond dissociation energies, β -scission energies and the enthalpies of radical addition, ring opening, and hydrogen and halogen transfer reactions concluded that all the DFT methods that were examined fail to provide an accurate description of reaction energetics. Most of the functionals examined showed highly unpredictable deviations from the benchmark values. In other words, they fail to predict not only the absolute energies but also the correct trends, thus preventing their use even in semi-quantitative studies. While the relevance of such prototypical reactions to radical polymerisation may not be immediately obvious, they encompass many of the principal reactions in CRP including halogen transfer (in ATRP), addition to thiocarbonyls (RAFT) and homolysis of alkoxyamines (NMP).

Figure 4 illustrates the mean and maximum absolute deviations of B3-LYP, KM-LYP, MPW1B95, MPWB1K, BMK and R(O)MP2 methods from benchmark G3(MP2)-RAD calculations for model reactions of relevance to RAFT, ATRP and NMP, as well as a supplementary test set of 'general' radical reactions [115,116]. This 'general' test set is composed of R–H bond dissociation energies, enthalpies of abstraction, ring opening, addition and β -scission (excluding any C=S systems included in the RAFT set). As Figure 4 indicates, none of the DFT functionals tested are able to reliably reproduce the benchmark G3(MP2)-RAD results in any of the test sets examined. This poor performance not only highlights some of the erratic failures of DFT-based methods, but also emphasises why such methods should not be used to study CRPs or radical chemistry in general. While the spectacular failure of the popular B3-LYP functional (from at least 21 kJ mol^{-1} in mean to over 90 kJ mol^{-1} maximum absolute deviation) is no longer surprising, the poor performance and inability to reach the chemical accuracy of all other tested functionals is more disturbing. It is very difficult, if not impossible to predict when a particular functional might fail and it is this variability that makes DFT unsuitable for high accuracy work. While the R(O)MP2 method also has large maximum deviations from the benchmark data, most of these deviations are predictable and systematic. In particular, the worst errors occur when highly delocalised (spin contaminated) radicals are involved.

As a consequence of these failures, much research has been directed toward developing new general-purpose functionals with improved accuracy and reliability [97,98]. As previously noted, a major shortcoming of traditional DFT methods is their inability to adequately model dispersion interactions, which can influence both absolute and relative reaction energies. For instance, in elimination (or, conversely, addition) reactions, dispersive attraction stabilises the associated fragments within a single molecule, a stabilisation then disappears as the fragments are separated. Thus, by failing to accurately model this dispersive stabilisation, DFT may underestimate the energy required to separate these fragments. For instance, Check and Gilbert noted that compared to experiment, B3-LYP increasingly underestimates the C–C bond dissociation energy in a set of progressively substituted alkanes [120]. Subsequently, Kong and co-workers found that correcting B3-LYP for dispersion with the exchange-dipole moment model (XDM) reduced this underestimation [127]. However, it should be emphasised that their B3-LYP-XDM results still underestimated these bond dissociation energies by between 10 and 17 kJ mol⁻¹, suggesting that there are remaining deficiencies in the B3-LYP functional. Various strategies to correct DFT for dispersion have been adopted, including the addition of empirical parameters to existing functionals, separately calculating the dispersion interaction based on physical arguments and including dispersion bound complexes in the training sets of new DFT functionals during optimisation. For more details regarding the theory and application of these corrections, which is beyond the scope of this work, the reader is directed to a recent review [128]. While dispersion corrected functionals such as M06-2X [112] and wB97XD [129], as well as XDM corrected functionals [127,130–133] show great promise, their reliability has yet to be thoroughly tested on reactions relevant to radical polymerisation.

In contrast to the variable performance of DFT, several studies have shown that composite *ab initio* procedures offer excellent intrinsic accuracy for radical reactions, albeit at a higher computational cost. Composite *ab initio* procedures approximate high-level correlated calculations with a large basis set using a series of lower cost calculations combined with additivity and/or extrapolation routines. These procedures, which include most notably the *G_n* [134–140], CBS [141] and *W_n* families of methods [142,143], are considerably more cost-effective than traditional *ab initio* methods of comparable accuracy. In addition, the explicitly correlated CCSD(T)-F12 approximations [144–146] have also demonstrated outstanding accuracy at significantly reduced computational cost. Of these composite *ab initio* procedures, G3(MP2)-RAD [147] provides excellent intrinsic accuracy for the prediction of thermochemistry in most radical systems and is feasible for systems of up to 20 non-hydrogen atoms in an open-shell configuration. G3(MP2)-RAD approximates CCSD(T) calculations with a large triple- ζ basis from calculations with a double- ζ basis set, via basis set corrections carried out at the R(O) MP2 level of theory. Several studies have verified the robust performance of G3(MP2)-RAD for predicting a wide range of thermochemical properties to within chemical accuracy, including enthalpies of radical addition [148], hydrogen/halogen transfer [50,51,148,149], ring opening and cyclisation [150–152] and bond homolysis [43,44,149,153,154]. In a few systems, most notably radical addition to thiocarbonyls, G3(MP2)-RAD calculations are not sufficient for chemical accuracy and even higher level calculations, such as W1, are required [105]. Moreover, all of these computational methods are based on a single Hartree Fock determinant and may fail in systems that possess significant multireference character, such as organic biradicals. However, for most of the reactions of interest to radical polymerisation, single-reference procedures are sufficiently accurate [44].



Scheme 2. The ONIOM approximation applied to the propagation of a mono substituted alkene of the general form $\text{CH}_2=\text{CHR}$.

In radical polymerisations involving monomers with small side chains, such as polyvinyl chloride (PVC), high-level calculations such as G3(MP2)-RAD are feasible for models as large as dimers and trimers. However, for monomers with large side chains, such as MMA, these calculations may only be feasible for unimeric addition. Where full G3(MP2)-RAD calculations are impractical, an ONIOM [155,156] inspired approximation can be utilised [115,116,148]. In this approximation a 'core' segment of a reaction is selected, which incorporates all forming and breaking bonds and principal substituents attached to these atoms (including any groups conjugated with the reaction centre). In forming the core any secondary substituents are exchanged for hydrogen atoms. Both the core reaction and full reaction are fully optimised at the same level of theory, with the ONIOM approximation only used to correct the single-point energies of the full reaction. In this way, the method is similar to the isodesmic methods used for pKa prediction [157]. The core system is studied at the highest level of theory possible, as well as a second lower level of theory. The full reaction is studied using the same lower level of theory to determine the effect of remote substituents on the core reaction. The energy of full system at the high level of theory is then approximated as the energy of the core system at the high level plus a correction for the remote substituent effects, obtained as the energy difference of the full and core systems at the lower level of theory (Equation (1)).

$$E_{\text{Full}}^{\text{High}} \cong E_{\text{Full}}^{\text{Low}} + E_{\text{Core}}^{\text{High}} - E_{\text{Core}}^{\text{Low}} \quad (1)$$

This procedure is illustrated in Scheme 2.

Provided the ONIOM layers are selected appropriately and treated consistently, the accuracy of this approximation is limited only by the inherent accuracy of the high-level method and the capacity of the low-level method to model the remote substituent effects on the core reaction. In that regard, it is important to note that non-dispersion corrected DFT methods are usually poor choices for modelling even the remote substituent effects, whereas R(O)MP2

with a triple- ζ basis is usually adequate, even when it is not capable of modelling the primary substituent effects correctly [115,116]. For instance, using G3(MP2)-RAD to study a core reaction and incorporating remote substituent effects at R(O)MP2/G3MP2, large level was shown to approximate the full G3(MP2)-RAD values for a test set of 112 radical reactions to within a mean absolute deviation (MAD) of less than 1 kJ mol^{-1} and a maximum absolute deviation of 5 kJ mol^{-1} , at a fraction of the computational cost of the full G3(MP2)-RAD calculations [115]. Using B3-LYP in place of R(O)MP2 for the ONIOM layer increased the maximum errors to 15 kJ mol^{-1} over the same set, further illustrating its decreased ability to model remote substituent effects. Nonetheless, it is worth noting that for the same test set, both R(O)MP2 and B3-LYP used without an ONIOM correction had maximum errors of 91 and 41 kJ mol^{-1} , respectively. Thus, the ONIOM approach substantially improves the accuracy of lower cost methods. For problematic systems where even G3(MP2)-RAD is not sufficiently accurate for the reaction core, such as radical addition to thiocarbonyls, further correcting the G3(MP2)-RAD energies with a W1 core (i.e. an extra ‘inner core’ that includes only the reaction centre and can thus be studied at an even higher level of theory) provides a close approximation to full W1 [148], again at a fraction of the computational cost. Thus, by using the ONIOM approximation at R(O)MP2 level in combination with composite *ab initio* procedures, it is feasible to study systems with as many as 40 heavy atoms to within chemical accuracy. This strategy allows dimer and trimer models of most common radical polymerisations to be studied at a high level of accuracy.

2.3. Reaction rate theories

2.3.1. Transition state theory

While it is possible to calculate gas-phase rate coefficients very accurately by running classical or quantum trajectory simulations on a high level *ab initio* potential energy surface, the enormous computational cost involved limits this approach to systems of only a few atoms. Clearly, using such sophisticated simulations is not practical for modelling reactions of relevance to radical polymerisation. Transition state theory (TST) evaluates a chemical reaction as a stationary one-way flux at the transition state, implying that the rate coefficient can be obtained without any explicit consideration of reaction dynamics [158]. TST assumes that the number of molecular collisions with an energy greater than or equal to the activation energy can be predicted by Maxwell–Boltzmann statistics, i.e. that the transition state is in quasi-equilibrium with the reactants. There are several different formulations of TST that vary in sophistication [159–161]. In conventional TST the dividing surface is chosen for convenience as the maximum point of the electronic zero-point vibrational energy corrected potential energy surface along the minimum energy path (MEP). This assumes that reactants reaching the transition state react irreversibly, without ‘re-crossings’.

From these assumptions, a simple equation relating the rate coefficient as a function of temperature, $k(T)$, to the properties of the reactant(s) and transition state is obtained [162]. This is provided below in two equivalent forms (Equations (2) and (3)).

$$k(T) = \kappa(T) \frac{k_b T}{h} (c^\circ)^{1-m} \exp \left[-\frac{\Delta G^\ddagger}{RT} \right] \quad (2)$$

$$k(T) = \kappa(T) \frac{k_B T}{h} (c^\circ)^{1-m} \frac{Q_{\ddagger}}{\prod_{\text{reactants}} Q_i} \exp \left[-\frac{\Delta E_{\ddagger}}{RT} \right] \quad (3)$$

In these equations: $k(T)$ is the tunnelling correction factor, T is the absolute temperature, R is the universal gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$), k_B is Boltzmann's constant ($1.380658 \times 10^{-23} \text{ J mol}^{-1} \text{ K}^{-1}$), h is Planck's constant $6.6260755 \times 10^{-34} \text{ J s}$, $c^\circ (= \frac{pR}{T})$ is the standard unit of concentration mol L^{-1} , m is the molecularity of the reaction, $Q_{\ddagger}$ and Q_i are the molecular partition functions of the transition structure and reactant i , respectively (discussed below), $\Delta G_{\ddagger}^\ddagger$ is the Gibbs free energy of activation and $\Delta E_{\ddagger}^\ddagger$ is the 0 K, zero-point energy corrected electronic energy barrier for the reaction. The value of c° depends on the standard-state concentration assumed in calculating the thermodynamic quantities. The tunnelling coefficient $\kappa(T)$ corrects for quantum effects in motion along the reaction path and can be assumed to be unity in the addition of carbon-centred radicals to alkenes, due to the large masses of the reacting fragments, but would be expected to be non-negligible in electron and hydrogen transfer reactions. The reaction path degeneracy is implicitly treated through the symmetry numbers of the reacting species that are included in the external rotational partition function (Q_{rot}).

The main distinction between conventional and variational TST is the choice of the dividing surface or the 'point of no return' of the reaction [159–161]. As noted above, in conventional TST, this dividing surface is chosen for convenience as the maximum point of the electronic potential energy surface along the MEP. In variational transition state theory (VTST), this dividing surface is chosen more accurately as the maximum point on the Gibbs free energy surface along the MEP. Thus the conventional TST rate coefficient is an upper bound to the VTST rate coefficient. As most radical addition reactions have a large electronic barrier and variational effects are minimal, the conventional TST rate coefficient is a reasonable approximation. However, for reactions proceeding via small electronic barriers, variational effects become increasingly important and thus locating the variational transition state is desirable. An example where variational effects are important for radical polymerisation is the controlling reaction in in RAFT polymerisation, which involves carbon-centred radical addition to dithioesters. Depending on the substituents involved, many of these reactions have low or negligible enthalpic barriers but modest free energy barriers due to entropic effects. For these reactions, Coote *et al.* [28,33] have compared VTST with conventional TST finding that the variational transition state geometry can differ substantially from the conventional one, though due to the flatness of the potential energy surface the errors in energetic terms are usually only of the order of 5 kJ mol^{-1} or less.

2.3.2. Partition functions

The molecular partition function links the thermodynamic properties of a system to its quantum mechanical states and is given by Equation (4).

$$Q = \sum_i g_i \exp \left(-\frac{\varepsilon_i}{k_B T} \right), \quad (4)$$

where ε_i and g_i are the energy level and degeneracy of the i^{th} state, respectively. In theory this equation should be solved for all active modes using the Schrödinger equation. However, in practice, evaluation of partition functions can be greatly simplified through factorising into translational, rotational, vibrational and electronic terms as follows (Equation (5)).

$$Q = Q_{\text{trans}} \times Q_{\text{rot}} \times Q_{\text{vib}} \times Q_{\text{elec}} \quad (5)$$

This assumption is reasonable provided the reaction occurs on a single electronic surface. By making the further assumption that each species is an ideal gas and conforms to the harmonic oscillator (HO) and rigid-rotor approximation, simple analytical formulae (Equations (6)–(9)) can be obtained for the independent translational, (external) rotational, vibrational and electronic partition functions [163–165].

$$Q_{\text{trans}} = V \left(\frac{2\pi M k_b T}{h^2} \right)^{\frac{3}{2}} = \frac{RT}{P} \left(\frac{2\pi M k_b T}{h^2} \right)^{\frac{3}{2}} \quad (6)$$

$$Q_{\text{rot(non-linear)}} = \frac{\pi^{\frac{1}{2}}}{\sigma_r} \frac{T^{\frac{3}{2}}}{(\Theta_{r,x} \Theta_{r,y} \Theta_{r,z})^{\frac{1}{2}}}, \quad \text{where } \Theta_{r,i} = \frac{h^2}{8\pi^2 I_i k_b} \quad (7)$$

$$Q_{\text{vib}} = \prod_i \frac{1}{1 - \exp(-\frac{h\nu_i}{2kT})} \quad (8)$$

$$Q_{\text{elec}} = \omega_0. \quad (9)$$

In these equations: M is the molecular mass of the species, V and P are the reference volume and pressure, respectively, T is the absolute temperature, σ_r is the symmetry number of the molecule, while I_x , I_y and I_z are the principal moments of inertia about the x , y and z axes, respectively and ν_i are the vibrational frequencies of the molecule. The information required to calculate these analytical gas-phase partition functions is accessible from the optimised

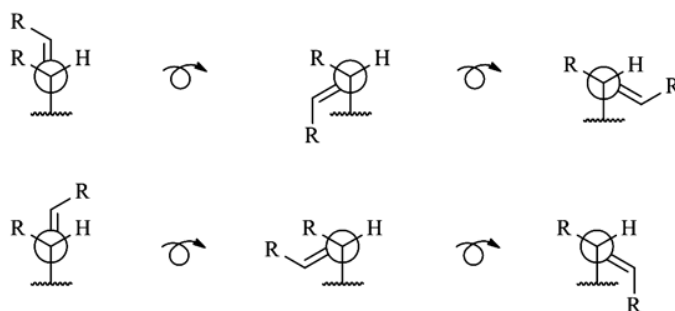


Figure 5. Newman projections illustrating the various *syn* and *anti* transition-state conformations for the propagation of mono substituted alkene of the general form $\text{CH}_2=\text{CHR}$.

geometries and frequencies. The electronic partition function is evaluated by assuming all excited states are inaccessible and hence ω_0 is the ground-state spin multiplicity. Equivalent formulae for evaluating the translational, rotational, vibrational and electronic components of the entropy and thermal corrections to the energy and enthalpy are also available in most physical chemistry textbooks [163–165].

Evaluation of the vibrational partition function using the above formula requires the implicit assumption that each vibrational mode can be treated under the HO approximation. For bond stretching modes, these assumed parabolic wells are a close approximation of the true potential energy surface. However, for torsional modes, the potential energy surface may have multiple minima (conformations) separated by varying barriers and thus are better described as hindered internal rotations [166–169]. Radical addition reactions proceed via up to six discrete transition-state conformations, as shown in Figure 5. For highly symmetric systems some of these transition state conformations are degenerate and are automatically accounted for in the symmetry number of the rotational partition function and/or through the inclusion of a chirality correction. For unsymmetrical systems these six transition-state conformations are discrete but generally near degenerate and thus calculating a rate coefficient using a single conformation of the transition state can underestimate the rate coefficient by up to a factor of six. In addition to these multiple reaction pathways, the reacting oligomer chain can itself access multiple conformations, each of which may react with monomer at a different rate. There are various techniques for addressing these conformational and torsional effects that range in accuracy and sophistication, which we now outline in turn [151,170].

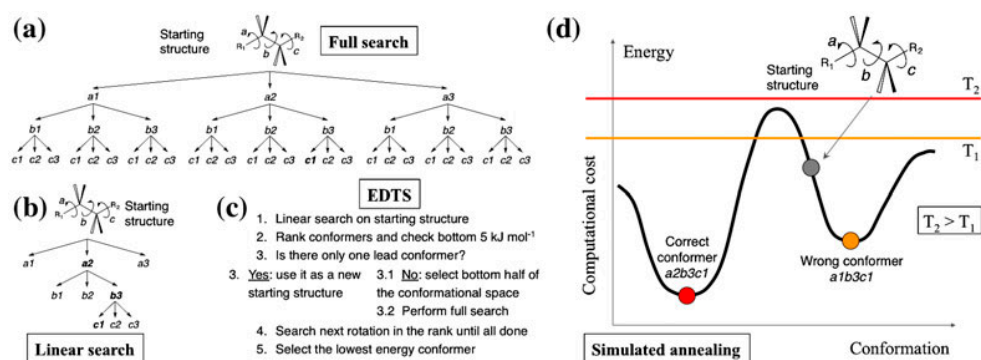
The most basic approach is to treat all vibrations as HOs. This approach neglects any explicit consideration of conformational effects or torsional anharmonicity. While it greatly simplifies the computational efforts involved in calculating rate coefficients, it can introduce significant error, particularly if the approach is not combined with accurate conformational searching. Statistically, only the lowest energy conformations will be significantly populated and so these conformations will make the dominant contribution to the observed physical properties. Geometry optimisations only locate the nearest local minimum on the potential energy surface to a given input structure and thus generating an input structure at random (such as simply using a fully extended oligomer chain) could yield structures tens or even hundreds of kJ mol^{-1} above the global minimum, and any thermochemistry calculated using such a conformation is thus erroneous. Hence, if all torsional modes are treated under the HO approximation, it is crucial to identify the lowest energy conformation of both the reacting oligomer and the transition state. As discussed below, there are many algorithms for locating lowest energy conformers that vary in reliability and cost and are also sensitive to the level of theory at which they are carried out. Provided the lowest energy conformer is correctly identified, the overall rate coefficient can generally be approximated to within 1–2 orders of magnitude by calculating the rate coefficient using this single conformation of the propagating radical and transition state, while treating all vibrations as HOs (see Refs. [24,26,59,85,104,171] for examples of assessment studies relevant to polymerisation). The remaining error then arises from the neglect of near degenerate reaction pathways and other conformational effects, and the neglect of torsional anharmonicity. Its success and cost will depend heavily on the accuracy of the conformational searching algorithm (see Section 2.3.3).

A more rigorous but significantly more computationally expensive approach is to calculate propagation rate coefficients for each conformation of the reacting oligomer, accounting for

the presence of multiple reaction channels, but still treating all vibrations under the HO approximation. The observed rate coefficient is then the Boltzmann weighted average of the individual propagation rate coefficients for each conformation of the oligomer chain. While this approach fully accounts for conformational effects, it is limited to fairly small systems, usually dimers, due to the enormous increase in conformational space with increasing molecular size. This approach also completely neglects torsional anharmonicity, as each vibration is treated under the HO approximation, which may cause significant errors in some systems.

An excellent compromise between accuracy and cost is to apply one-dimensional hindered internal rotor corrections (1D-HR) to the lowest energy conformation of the reacting oligomer and transition state [59]. Under this approach, a relaxed potential energy scan is performed around various rotatable bonds within the molecule, noting that these rotations need not lead to distinct conformations. A Fourier series is then fitted to the resulting rotational potential and a new partition function is calculated via torsional eigenvalue summation. To mitigate the effects of coupling between the modes, the HO approximation is still applied to all internal modes of a molecule, and then the resulting vibrational partition function is multiplied by a correction factor for each internal hindered rotor partition function [172]. This factor is calculated as the ratio of the hindered rotor partition function to the corresponding ‘pure’ vibrational partition function, as calculated from the second derivative of the rotational potential at the starting minimum. 1D-HR has the advantage of correcting for torsional anharmonicity as well as sampling all conformations within one bond rotation of the global minimum conformation. While this approach samples the dominant conformations, it neglects any conformation more than one bond rotation away from the global minimum. Combined with suitably high levels of theory and appropriate treatment of solvation effects, this approach has been successful in predicting chemically accurate propagation rate coefficients for a range of monomers [78,85].

The most accurate and expensive method for correcting conformational effects and torsional anharmonicity is multistructural transition-state theory (known as MSTor) [173]. This approach treats the full conformational space of the reacting oligomer and transition state, but unlike Boltzmann average also accounts for torsional anharmonicity. While MSTor is highly sophisticated, it is also very expensive (requiring not only energies and geometries



Scheme 3. (Colour online) Schematic representation of alternative approaches to lowest energy conformer searching: (a) full tree search; (b) linear search; (c) energy-directed tree search; (d) simulated annealing (see text for further details).

but also harmonic frequencies for every conformation of the oligomer and transition state) and thus limited to relatively small systems. To date there have been no assessment studies relevant to radical polymerisation in which MSTor is compared systematically with some of the simpler approaches described above; however, recent work on other reactions suggests that the corrections for multiple structures and torsional anharmonicity can affect the results by as much as an order of magnitude [174]. Crucially, the errors are non-systematic and thus can also affect the qualitative conclusions. It would certainly be desirable to test this technique on propagation reactions and in particular assess whether it offers a substantial improvement in accuracy over the global minimum 1D-HR approach for these reactions. More generally, it is clear from Tables 1–6 that relatively few literature studies of propagation have even included rigorous conformational searches, let alone used hindered rotor corrections for low-frequency torsional modes, and that failure to do this is clearly a very large source of potentially erratic error.

2.3.3. Conformational searching

Conformational isomerism is a form of stereoisomerism in which different isomers are separated by hindered internal rotations around one or more of their single and double bonds. The conformational space of a molecule is the set of all stable conformers, which can expand very rapidly with increasing molecular size. Locating the minimum energy conformations can be challenging, particularly for large systems. In principal, it is possible to search molecule's conformational space by optimising all structures generated from all combinations of the various bond rotations at appropriate resolutions, usually 120° and 180° for sp^3 and sp^2 centres, respectively. Provided the resolution of the bond rotations is appropriate, this full tree search method (as in Scheme 3(a)) generates and searches the full conformational space of the molecule. For relatively small structures performing a full tree search is feasible. However, the C–C backbone of a typical oligomer possesses multiple threefold rotation axes, leading to an approximately exponential increase in the conformational space with respect to increasing chain length. For instance, a VC dimer radical has just three C–C rotations and hence 2^3 or eight potential conformers (some of which may be equivalent); however, this grows to 32 (2^5) for trimer and 128 (2^7) for the tetramer. Moreover, the addition transition structures have 32, 128 and 512 potential conformers if the same resolution is used for the forming and breaking bonds. If the side chains of the oligomer can also access multiple conformations, then this increase is even more considerable. For instance, at the same resolution, the potential conformational space of a MA propagating radical is 128 even for the dimer radical and 2048 for its propagation transition structure. Although some simplifying assumptions (such as in this case the assumption that all of the ester side chains are *cis*) may be justifiable in some cases, it is clear that full conformational searches rapidly become impractical, even for relatively modest chemical systems.

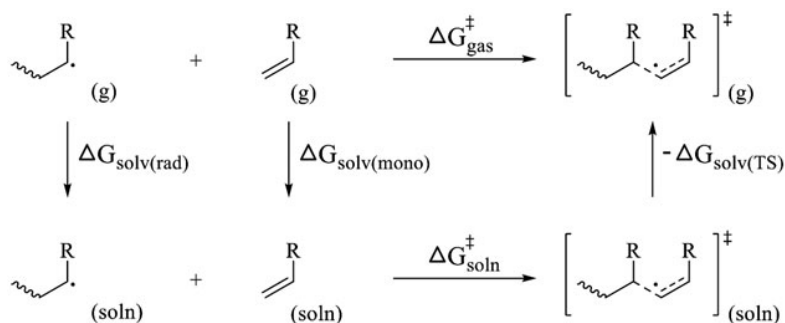
To identify the minimum energy conformation in such systems it is necessary to rely on algorithms, which search only a fraction of the full conformational space. The majority of the available algorithms, such as simulated annealing (as in Scheme 3(d)), are stochastic algorithms – rather than systematic searches – and randomly examine only a very small fraction of the conformational space. They were designed for biological systems containing much larger conformational spaces than typical oligomeric propagating radicals and understandably cannot reliably identify the lowest energy conformer with the accuracy necessary for the quantitative kinetic studies. A mini-review of these algorithms is provided in Ref. [175].

To bridge the divide between the (economical but inaccurate) stochastic algorithms and the full systematic tree search algorithm (which is accurate but impractical), Izgorodina *et al.* [175] have developed a semi-systematic algorithm called the energy directed tree search (EDTS, see Scheme 3(c)). It is based on a simpler ‘linear search’ algorithm (as in Scheme 3 (b)) in which the lowest energy conformer for each rotatable bond in a molecule is optimised in turn, whilst keeping every other bond in its starting conformation. Having optimised one bond, it is adjusted to its lowest conformation, and the next bond is then optimised, and so on. In this way, if one has n rotatable bonds at a resolution of 120° , there would be $3n$ conformers to investigate rather than 3^n in a corresponding full search. The problem with the linear search method is that it is based on the assumption that the preferred conformation of each bond is independent on the structure of the rest of the molecule. This assumption is sometimes reasonable (e.g. most esters usually prefer *cis* conformations rather than *trans* regardless of their environment), but not always. In these latter cases, the accuracy of the linear search depends heavily on the random starting structure, and the order in which the bonds are examined. The EDTS algorithm addresses these deficiencies by using an initial linear search to improve the starting structure for a subsequent linear search. Crucially, the initial linear search is also used to define the order in which the various bonds are examined on the second linear search. This ordering is based on the effect that their rotations have on the energy so that, for example, rotations where there is a dramatic difference in the relative energies of conformers are refined first and rotations that have very little impact on the energy are refined last. A range of additional checks and balances, implemented in a deterministic manner, are also included in the algorithm. In particular, there is a provision for a complete search of the lower half of the conformational space if there are multiple low-lying conformers after the initial search. In its most expensive form it scales as 2^n in systems that would otherwise scale as 3^n for an equivalent complete tree search; in its best-case scenario it is linear scaling. It has been tested against corresponding complete tree searches for a very broad range of open- and closed-shell molecules, with a variety of functional groups, and in all cases it correctly identified the lowest energy conformer, or a species within less than 4 kJ mol^{-1} of it [175]. Algorithms such as this are still too expensive to apply to polymeric species, but do make possible chemically accurate calculations on the types of oligomeric propagating radicals needed to model polymerisation accurately.

Finally, it is worth noting that, in addition to the algorithm used, the choice of electronic structure method at which it is implemented is also crucial. Generally, to reduce computational cost, conformational searches are performed at the level of theory used for geometry optimisations and only the lowest energy conformation that is identified at this low level of theory is used for the subsequent high-level single point calculations. However, in systems where dispersion and hydrogen bonding are important for determining relative conformational energies, it is advisable to perform conformational selection at a level of theory that adequately models these interactions.

2.4. Modelling solvent effects

Polymerisations are generally performed in condensed phase, usually in bulk monomer or in a mixture of monomer and additional solvent. In systems where the interactions between side chains are weak, solvation may only have a minor influence on reactivity and gas-phase calculations can thus correctly reproduce solution-phase rate coefficients [85]. However, if



Scheme 4. The Hess's law thermocycle used to calculate solution-phase free energy barriers.

these interactions are strong, such as in systems that undergo hydrogen bonding, then using gas-phase calculations to predict solution-phase rate coefficients is potentially inaccurate (see e.g. Refs. [67,78]). Solvation effects can be modelled by the inclusion of a large number of explicit solvent molecules through either Monte Carlo or molecular dynamics simulations. While ideally such simulations would use an appropriate molecular orbital-based method to describe the interactions between the molecules, generally the enormous computational cost involved is prohibitive and so molecular mechanics is used to describe intermolecular interactions. Even using molecular mechanics, these approaches are computationally intensive and results are often highly dependent on the number of explicit solvent molecules in the calculation as well as the imposed periodic boundary conditions.

As explicit treatment of large numbers of solvent molecules is problematic, continuum solvation models have become increasingly popular for modelling solution-phase thermochemistry [176]. Such models mimic solvation by surrounding a cavity containing the molecule with an electric field, the dielectric constant of which is dependent on solvent polarity. While continuum solvation models aim to recreate average solvation effects from underlying physical principles, they rely heavily on empirical parameters that are determined from test sets. When using such highly parameterised models, it is imperative that the calculations are carried out using the theoretical procedures at which they were parameterised. It is also essential to ensure that such models are used to calculate what they were parameterised for, namely total free energies of solvation rather than the total Gibbs free energies in solution, usually at 298 K. Calculation of total Gibbs free energies in solution can be achieved by adding the solvation energies to the most accurate available gas-phase Gibbs free energies via a simple thermodynamic cycle, and applying an appropriate change of state term to account for the differing standard states in gas and solution phases [177]. This approach is outlined schematically in Scheme 4. Any continuum solvation model can only recreate the average effect of solvation in a system and thus will perform poorly if explicit solvent interactions are significant. In such situations, explicit solvent molecules should be included in electronic structure calculations and the resulting complex treated with a continuum solvation model. An overview of applying both implicit and explicit solvation corrections to propagation is provided in Ref. [178].

As is clear from Tables 1–6, most computational studies of radical polymerisation to date have been performed in the gas phase, and this may occasionally be justified [85]. However, a recent theoretical study by Coote *et al.* [78] highlighted the importance of solvation effects in

accurate modelling of polymerisations involving hydrogen bonding monomers. In this study, *ab initio* calculations suggested that propagation of MA and VA in the gas phase occurred predominantly via gauche addition pathways. The calculated gas-phase data significantly underestimated both the activation barrier and frequency factor, compared with the solution-phase experimental results, leading to large self-cancelling errors of 2–3 orders of magnitude. Although the gauche transition states are more sterically crowded than the anti ones, they are also subject to more stabilising hydrogen bonding interactions. However, in solution the importance of these stabilising interactions is diminished, as solvent is able to compete effectively to form hydrogen bonds with the component monomer and radical. When solvation effects were included via the COSMO-RS solvation model, anti addition was found to be the dominant pathway, with calculated activation barriers within 4 kJ mol^{-1} of experiment. This study highlights that the use of standard gas-phase calculations to study solution-phase reactions can lead to large errors, and thus should be avoided for solvent sensitive systems.

It is worth noting that an earlier gas-phase DFT study [77] of the same reaction, MA propagation, found that the MPWB1K functional appeared to predict the experimental solution-phase propagation rate coefficient to within two orders of magnitude at 298 K. However, when compared with the higher level *ab initio* calculations, MPWB1K had actually overestimated the barrier for gauche addition by around 18 kJ mol^{-1} . This overestimation fortuitously leads to close agreement between the gas-phase barrier for gauche addition and the experimental solution-phase barrier. This intrinsic error in the electronic energies was masked by an equivalent error due to neglect of solvation; when solvation corrections were included, the resulting solution-phase rate coefficients at 298 K differed from the experimental solution-phase rate coefficients by more than four orders of magnitude. It seems likely that MPWB1K underestimates the strength of hydrogen bonding in the gauche transition state, which fortuitously causes the gas-phase barrier height to resemble the solution-phase experimental data. As many popular DFT functionals fail to describe long-range interactions properly, it would be anticipated that gas-phase calculations using such methods might often fortuitously resemble solution-phase results, where these stabilising interactions are less significant. However, relying on such error cancellation is dubious and hinders the physical understanding of solvent sensitive systems. This further highlights the need to decouple the different methodological contributions to overall kinetic predictions and study their accuracy independently, so as to ensure that the right answer is obtained for the right reasons.

3. Selected examples

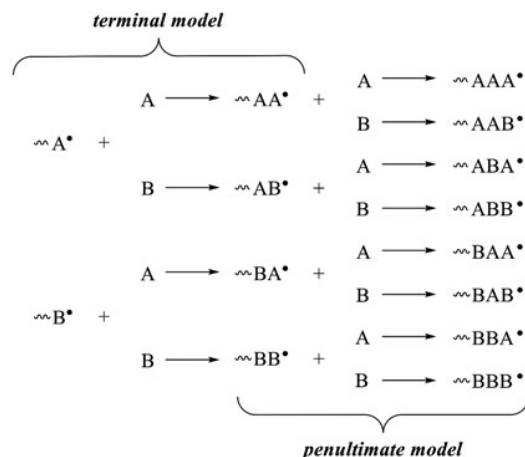
Free-radical homopolymerisation is a complex multistep process encompassing a variety of reactions and side-reactions, many of which have some degree of chain length dependence. The situation is further complicated in free-radical copolymerisation where the propagating radicals can also differ from one another in their compositions and sequence distributions and in CRP where (potentially chain length dependent) reactions and side-reactions with the control agent also need to be taken into account. Competition between these various reactions and side reactions determines important properties of the resulting polymer such as the chain end composition, the nature and concentration of any defect units and branch points, the molecular weight distribution and (where relevant) the copolymer composition and sequence distribution. Thus, understanding how this competition changes with the nature and concentration of various reagents is essential for controlling these processes. Unfor-

tunately, the more complex the process, the less intuitive the links are between the outcome and the various reagent reactivities and concentrations; hence, quantitative kinetic models are usually required for process optimisation and control. This complexity not only creates the need for accurate kinetic models but also presents challenges in deriving and parameterising them.

In principle, a kinetic model should be derived by solving the coupled differential equations corresponding to the rate expressions of each kinetically distinct reaction. However, a complete kinetic model for radical polymerisation would not only be extremely complex but would contain many thousands of unknown rate parameters corresponding to the various individual reactions of polymeric species of different chain lengths. In practice, simplifying assumptions are made, which might include ignoring certain side reactions, ignoring the chain length dependencies of all but the diffusion-controlled termination reactions (which are instead approximated by an empirical model) and treating most reactions as being irreversible. While many of these assumptions are reasonable, testing their validity experimentally is problematic.

Using experimental techniques it is difficult (if not impossible) to detect and measure the time dependent concentrations of all of the individual species (of different compositions and chain lengths) within a polymerising medium, and so the available experimental data are generally limited to a few observables such as the monomer, polymer and initiator concentration, the polymer molecular weight distribution and the total radical concentration. Typically, the experimental ‘measurement’ of the individual rate coefficients within a complex multistep process like radical polymerisation is reliant on treating these coefficients as adjustable parameters and fitting an assumed kinetic model to measured experimental data. Frequently, multiple models can be fitted equally well because of the limited degrees of freedom in the available experimental data. This encourages the use of over-simplified models where increasingly dubious assumptions are employed until the number of unknown rate parameters matches the degrees of freedom in the available experimental data. This parameterisation also makes it difficult to determine if a model’s good fit is because of its correct assumptions or merely the adjustable parameters.

Computational chemistry can be of great assistance in the derivation and parameterisation of kinetic models for radical polymerisation. Firstly, computational chemistry can be used to test the validity of model-based assumptions directly. For instance, the importance of chain length effects can be assessed by comparing calculated rate coefficients for model reactions of varying chain length; likewise, side reactions can be included or removed from a kinetic scheme on the basis of their calculated rate coefficients. Secondly, computational chemistry can be used to supply the values of some of the individual rate parameters within a kinetic scheme and thereby reduce the number to be estimated by model fitting. This circumvents the need to over-simplify models and allows for side reactions and chain length dependencies to be incorporated. Moreover, computational chemistry can in principle supply all of the missing parameters in a kinetic model, allowing for the first principles predictions of the observables in a polymerisation process. These predictions can then be compared with experiment so as to test the model’s validity. Because the *ab initio* model predictions are not fitted to the experimental data, such testing is much more likely to detect an invalid model, and hence model discrimination is improved. In this section, we will present three examples that highlight how some of the previous limitations of conventional (experimentally based) kinetic modelling have been overcome with the aid of computational chemistry.



Scheme 5. Terminal and penultimate models of propagation in a binary copolymerisation.

3.1. Copolymerisation

One of the first applications of computational chemistry in the radical polymer field was in helping to assess the validity of alternative models for copolymerisation kinetics [57–64, 179]. A copolymerisation is a polymerisation of two or more monomers, and the properties of the resulting copolymer are highly dependent upon its composition (the fraction of each monomer incorporated in the copolymer) and sequence distribution (the microscopic arrangement of the respective monomer units within a polymer chain). Copolymerisation models are used to predict these properties as a function of the monomer feed fractions, and are derived by considering all of the reactions that affect the concentration of the monomers and the propagating radicals. These include the propagation reactions of each type of propagating radical, which can differ in chain length, composition and sequence distribution, as well as side reactions that alter radical and/or monomer concentrations. Copolymerisation kinetics is made more complicated by the very large number of different species present. To simplify the kinetic analysis it is usually assumed that the reactivity of the propagating radical is affected not by the chain length or microstructure but simply by the local chemical structure. In the simplest and most widely used model, the terminal model [180–182], it is assumed that only the chain end composition affects the reactivity. Thus, in a binary copolymerisation, there are only four kinetically distinct reactions, corresponding to the two types of radical adding to either of the two types of monomer (see Scheme 5). More complex models account for the contribution of remote substituent effects on the propagation rates. For instance, the penultimate model [183] assumes that the composition of the penultimate unit affects the reactivity and so there are eight kinetically distinct propagation reactions in a binary copolymerisation (see Scheme 5).

Two versions of the penultimate model have been proposed [184], a general or explicit penultimate model in which no restrictions are placed on the nature of the penultimate unit effect, and an implicit penultimate model in which it is assumed that the penultimate unit affects the rate of the propagation but not its selectivity. More specifically, under this implicit penultimate model, the penultimate unit causes the so-called radical reactivity ratios ($s_i = k_{jii}/$

k_{iii} where k_{abc} is the rate coefficient for a radical with penultimate unit a and terminal unit b to add to monomer c) to deviate from unity ($s_i \neq 1$), while the monomer reactivity ratios ($r_i = k_{iii}/k_{ijj}$ and $r'_1 = k_{jii}/k_{jij}$) remain unaffected by the penultimate effect and are thus equal to each other and hence their terminal model values ($r_i = r'_1 = k_{ii}/k_{ij}$). Under this assumption it can be shown that the penultimate unit does not affect the copolymer composition and sequence distribution (which depends only values of the monomer reactivity ratios and hence collapses to the terminal model), but does affect the average propagation rate coefficients and radical concentrations through values of $s_i \neq 1$.

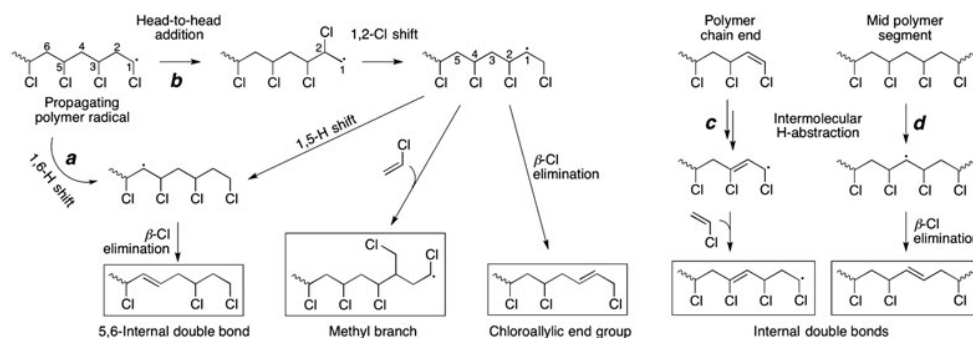
Both the terminal and penultimate models can be extended to account for additional side reactions. These extensions can incorporate various types of depropagation [185–192] and solvent effects ranging from monomer partitioning (where one of the monomers preferentially solvates the growing polymer chains) [193–195], monomer–monomer complex formation (where the complex can be inactive, propagate as a single unit or dissociate upon propagation) [196–202] to radical–solvent complex formation (where complexed and uncomplexed radical are assumed to propagate at a different rate) [203,204]. These various models are reviewed in detail elsewhere [205,206]; for current purposes, we merely note that they cover a wide range of different assumptions about what influences the chemistry of copolymerisation kinetics, and their resulting model parameters correspond to the rate and equilibrium constants of very different chemical reactions depending on the model used. It is also worth noting that the ‘simplest’ model in terms of the number of model parameters, the terminal model, actually makes the most assumptions about the underlying propagation kinetics and is thus arguably the least simple on scientific grounds.

For approximately 40 years following its initial publication in the 1940s [180–182], the terminal model was assumed to provide an accurate description of copolymerisation kinetics for all but a few ‘exceptional’ systems. This consensus originated from the ability to *fit* the terminal model (specifically the monomer reactivity ratios) to experimental composition data for a wide range of copolymerisation systems. However, for more than 40 years, these fit parameters (monomer reactivity ratios) were not used to make falsifiable predictions that could test the model’s validity. In 1985, Fukuda and co-workers [207] compared the average propagation rate coefficients for STY/MMA copolymerisation to the values predicted using the corresponding reactivity ratios, and revealed a comprehensive failure of the terminal model. Subsequent work confirmed that the terminal model was unsuitable for STY/MMA copolymerisation [208–211] and most other copolymerisations [75], [207], [212–225], [68], [226–229]. Indeed, only a few systems were found that actually follow this model [212,222,230,231]. Following these revelations, there was a flurry of activity to find a replacement for the terminal model [205]. There was particular interest in establishing whether the failure of the terminal model to predict the correct propagation rate coefficients implied that the terminal composition equation and associated large database of monomer reactivity ratios (stretching back to the 1940s) was invalid. As noted above, it is possible to construct an implicit penultimate model in which the terminal model breaks down for propagation rate coefficients but not composition – provided one can assume that the penultimate unit affects radical reactivity but not selectivity. Unfortunately, owing to their additional adjustable parameters, both implicit and explicit penultimate models (and any number of more complicated models incorporating various types of solvent effect) can be made to fit the available data in most cases.

Computational quantum chemistry can help discriminate between these alternative kinetic models by directly testing their underlying assumptions. In the mid 1990s, Heuts *et al.* [57–60] used theory to predict the rate coefficients for ethyl and *n*-propyl radical addition to ethylene. While these attacking radicals were not large enough to model penultimate unit effects on attacking polymeric radicals (effectively they differed in their beta rather than gamma substituents), the results provided a sufficient qualitative insight into effects of chemical structure on the frequency factor of the propagation reaction for Heuts *et al.* [57–60] to conclude that penultimate unit effects on the frequency factor were likely to be significant. They also argued that these penultimate effects, which arose in the hindered internal rotations around the backbone of the propagating radical, were likely to be most pronounced in radical reactivity ratios (where the backbone substituents were different). Provided the substituents at the penultimate position were not too dissimilar in steric bulk, they could be expected to cancel from monomer reactivity ratios. Hence, such entropic penultimate unit effects could conceivably lead to implicit penultimate effects, rather than explicit effects, provided no other complicating penultimate effects (e.g. on the barrier height) were present. However, as the model reactions were relatively small, the work was unable to rule out these complicating effects for typical copolymerisations, and comment on the likely generality of implicit or explicit penultimate effects.

To explore whether penultimate units could affect the barrier height, and whether such effects were implicit or explicit, Coote *et al.* [61–64] then conducted a series of high-level *ab initio* molecular orbital theory calculations on the barrier heights for a series of model propagation reactions in which attacking radicals differing in the nature of their gamma substituent (and hence penultimate unit) added to different types of monomer. The gamma substituents studied (H, F, CN and NH₂) were chosen to cover a range of electronic properties whilst maintaining the size small enough for accurate calculations. It was found that significant penultimate unit effects were possible and that the magnitude and direction of these effects depended upon the monomer with which the radical was reacting. For instance, a CN-substituent at the gamma position raises the reaction barrier for addition of X–CH₂–CH₂–CH₂• to CH₂=CH–CN by 2.9 kJ mol^{–1} (vs an X=H substituent), lowers the barrier marginally (by 0.7 kJ mol^{–1}) if monomer is CH₂=CH₂ and more substantially (by 4.6 kJ mol^{–1}) if the monomer is changed to CH₂=CH–NH₂ [61]. These trends were interpreted and generalised in terms of a polar origin for penultimate unit effects on barrier heights [62], and were shown to be further complicated by conformational effects [63]. Thus, it was concluded on the basis of these calculations that the assumption that a penultimate unit could affect radical reactivity without also affecting selectivity was unlikely to hold. Namely, the theoretical justification of an implicit penultimate model did not appear to be valid. Thus it was concluded that the experimentally demonstrated failure of the terminal model to predict the correct rate coefficients for most copolymerisations should be taken as evidence for its failure to predict the correct composition and sequence distribution [64].

More recently, other groups have used theory to test the underlying assumptions of models for copolymerisation kinetics in larger systems that are more representative of common copolymerisations involving STY, acrylates and methacrylates and their derivatives [73,74,68,86]. Admittedly, the increase in model size has come at the expense of calculation accuracy with B3-LYP and MPWB1K methods used in place of high-level *ab initio* procedures. Nonetheless, with this caveat the calculations have confirmed that penultimate unit effects are significant. Moreover, higher level *ab initio* calculations on realistic models of propagating radicals in reactions relevant to CRPs such as RAFT [19,35–37] and ATRP [49]



Scheme 6. Mechanistic pathways leading to various defect structures in PVC.

have also indicated strong penultimate and antepenultimate unit effects are possible, further confirming that the terminal model may be the exception rather than the rule.

3.2. The origin of defect structures in PVC

Free-radical polymerisation is rarely a 'perfect' process and the basic initiation, propagation and termination steps occur in competition with various side reactions. These side reactions usually result in the formation of 'defect structures' – that is, functional groups within the polymer chain (including end groups) that differ from the standard chemical structure of the polymer. Despite their relatively low concentration, defect structures have a profound effect on the stability and reactivity of polymers [232]. Thus understanding how such structures form and how to minimise their concentration is important for improving polymer lifetimes. Indeed, recent theoretical work suggests that the degradation of most fully saturated polymers is very slow, but the presence of unsaturated defect structures and end groups in typical polymers greatly increases susceptibility to autoxidation [233]. Modern experimental techniques such as NMR and mass spectrometry are capable of providing detailed information on the nature and concentration of defect structures in various types of polymers. However, establishing how such structures form, particularly when multiple reaction pathways are possible, is much more difficult.

Taking the radical suspension polymerisation of VC as a case study, a range of defect structures have been observed experimentally, including branches of various lengths, with and without tertiary chlorine atoms, as well as chloroallylic end groups and internal double bonds [232,234,235] (Scheme 6). The tertiary chlorine atoms are particularly significant in the initiation of autoxidation, while the various unsaturated structures are likely to play a significant role in propagating the damage. The nature and concentration of defect structures is highly dependent of the conversion regime. In 2005, Purmova *et al.* [235] noted significant increases in the formation of branched and internal unsaturated structures in polymers formed at high conversions (>85%) and a concurrent decrease in their stability. Moreover, the concentration of chloroallylic end groups was found to decrease with increasing monomer conversion. To rationalise these experimental results, the rate coefficients of various reactions and side-reactions were predicted using high-level *ab initio* theory with sophisticated diffusion

corrections [235]. These were then incorporated into a kinetic model of radical suspension polymerisation and used to predict the concentrations of defect structures resulting from each of the pathways. This theoretical work highlighted the importance of intramolecular chain transfer at high conversions (pathways *a* and *b* in Scheme 6). These processes, despite their low rate coefficients, become competitive with propagation above critical conversion, as propagation is slowed by a combination of monomer starvation and diffusion effects. Copolymerisation of chloroallylic end groups also becomes competitive at high conversions, explaining their decreased concentration. These conclusions have since been reaffirmed in more sophisticated kinetic modelling studies based in part on these computational parameters [236].

A complementary theoretical study by Van Cauter *et al.* [90] employed lower level DFT calculations to study possible side-reaction pathways in VC polymerisation at sub-critical conversions (<85%). Under these conditions, where diffusion effects are less significant, they concluded that head-to-head addition is responsible for the most abundant defect structures (methyl branches) followed by 1–5 backbiting to produce butyl branches. Intermolecular hydrogen abstraction leading to internal unsaturations was concluded to be of only minor significance and likewise the less favourable 1–6 hydrogen transfer was deemed insignificant. The contrast between these results for sub-critical conversions and the earlier work of Purmova *et al.* [235] for post-critical conversions highlights the crucial roles that monomer starvation and diffusion control of propagation have in the rapid increase in key defect structures beyond the critical conversions.

In 2008, Purmova *et al.* [234] conducted a follow-up experimental study to further explore the origin of defect structures in PVC. This study examined the simultaneous effects of chain length and conversion on the concentration of internal unsaturations. It had been assumed that internal unsaturations formed primarily from mid-chain intermolecular H-abstraction (pathway *d* in Scheme 6) and thus should have a reasonably constant concentration per total VC linkages. However, Purmova *et al.* noted the concentration of these defects increased only slightly with molecular weight, despite the significant increase in VC linkages. That is, the concentration of these defects per linkage sharply decreased with increasing molecular weight rather than remaining constant as anticipated. Moreover, ^{13}C NMR revealed that these unsaturations are predominantly located at 5, 6 position from the chain end, which suggested a backbiting mechanism rather than intermolecular H-abstraction was responsible for their formation. While the experimental results were able to clearly discount mid-chain intermolecular H-abstraction, *ab initio* calculations including diffusion corrections were necessary to identify through which mechanism these defects formed. This work compared an alternative (chain-end based) intermolecular H-abstraction pathway that could account for concentration behaviour of these unsaturations (pathway *c* in Scheme 6), as well as the aforementioned intramolecular processes (pathways *a* and *b* in Scheme 6). The intramolecular pathways (pathway *a* in particular) were found to be the dominant source of internal unsaturations, even at low conversions. Interestingly, if diffusion effects are completely neglected, the intermolecular pathways *c* and *d* are (incorrectly) predicted to dominate. This work highlights the importance of diffusion corrections, particularly at high conversions, a conclusion reaffirmed in more recent kinetic modelling studies [236].

The joint experimental and theoretical work concluded that minimising backbiting would help improve the thermal and photostability of PVC. This could potentially be achieved through restricting the mobility of the polymer radical by, for example, radical–solvent complexation, limiting the conversion or increasing monomer mobility at post-critical conversions

(through various additives). More generally, this case study demonstrates how theory can be used in conjunction with experiment to help understand underlying mechanistic behaviour, determine the origin of defect structures and help to construct more realistic kinetic models. These kinetic models can then improve the properties of the resultant polymers by optimising the reaction conditions to minimise defect formation.

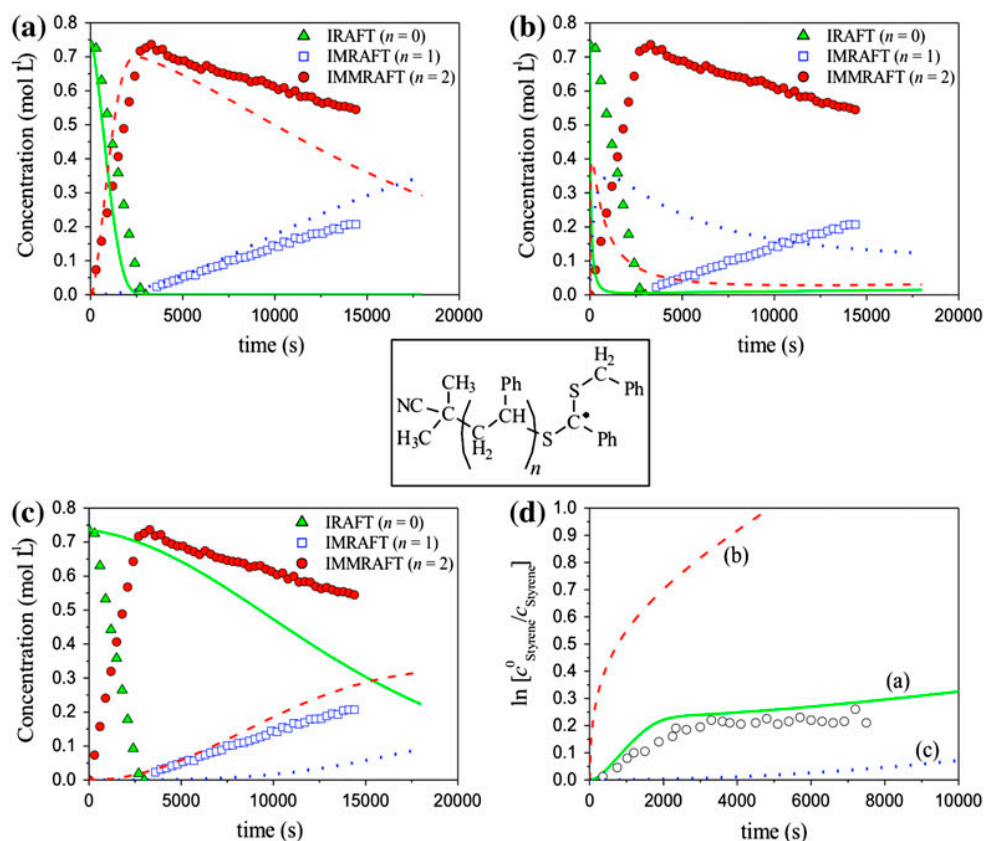


Figure 6. (Colour online) Comparison of the experimental (symbols, from Ref. [242]) and simulated (lines, from Ref. [243]) time dependent concentrations of the initial RAFT agent (cyanoisopropyl dithiobenzoate, IRAFT, full line), and the RAFT agents having one monomer unit (IMRAFT, dashed line) and two monomer units (IMMRAFT, dotted line) in the RAFT polymerisation of STY at 70 °C in deuterated benzene, initiated by AIBN. The simulation (a) uses *ab initio* predicted chain length dependent rate coefficients for various addition and fragmentation reactions; simulation (b) and (c) uses standard models from the literature in which either (b) fast fragmentation [240] or (c) slow fragmentation [241] rate and equilibrium constants has been obtained by fitting a chain length independent model to alternative sets of experimental data. The graphs are based on Figure 1 in Ref. [243], to which the reader is directed for more details regarding these simulations.

3.3. CRP kinetics

Perhaps the most exciting application of computational chemistry in the radical polymer field is assisting the optimisation of CRP. Over the last few decades, the development of strategies for controlling the molecular weight and architecture of polymers produced in free-radical polymerisation has revolutionised the polymer field. These strategies combine the advantages of conventional free-radical polymerisation (e.g. its broad scope, mild reaction conditions, tolerance of protic impurities) with the ability to synthesise a wide range of complex macromolecules with intricately controlled microstructures [237]. In conventional free-radical polymerisation, competition between bimolecular termination reactions, initiation and propagation produces polymers with a broad molecular weight distribution and end groups that are generally unsuitable for further functionalisation. In CRP, propagating radicals are reversibly stored as dormant or protected species that are unable to propagate or terminate. This dynamic equilibrium is used to reduce the ratio of termination to propagation (without directly interfering with propagation), and thus produce polymers with a narrow molecular weight distribution. Subsequent isolation of polymer chains in their dormant form allows for end group functionalisation, such as the production of block, graft or star assemblies. Unfortunately, the success of CRP relies upon delicately balancing the rate of several competing reactions, which requires careful optimisation of the control agent and the reaction conditions.

There has been enormous interest in developing accurate kinetic models for CRP and modelling the underlying structure-reactivity trends of the various kinetic parameters. However, the inclusion of the additional reactions and side reactions involving the control agent complicate the kinetic scheme and thus a complete model usually contains more unknown rate parameters than the degrees of freedom in experimental data [19]. This has led to problems where, depending on the type of observable that is fitted, the same kinetic scheme yields widely differing estimates for the rate coefficients of the principal reactions. For instance, estimates for the fragmentation rate coefficient and associated equilibrium constant in the dithiobenzoate-mediated RAFT polymerisation [238] of STY, derived from a simple chain length independent model, were found to differ by as much as six orders of magnitude [239], depending on whether the model was fitted to the total radical concentrations [240] (scenario *b* in Figure 6), or overall polymerisation rate [241] (scenario *c* in Figure 6). Moreover, this simple model, regardless of whether it is parameterised with either of the widely differing rate parameters, fails to predict the experimental concentration profiles [242] of the successive oligomeric dithioesters produced and consumed during the early stages of a RAFT process, as seen in Figure 6 [243]. Clearly, the underlying model is too simplistic; however, as noted above, inclusion of additional reaction steps that account for chain length dependencies is problematic as it introduces additional adjustable parameters, making the model-fitting process indeterminate.

Quantum chemistry is extremely valuable in these situations as it can be used to calculate the rate coefficients for key steps in the process without recourse to model fitting. To date, the majority of quantitative quantum-chemical modelling of CRP has focused on the RAFT process [19,56]. Initially, calculations were used to study the addition-fragmentation equilibrium in small model dithiobenzoate reactions to discriminate between alternative experimental estimates for the fragmentation rate coefficients. As noted above, two model-based estimates differed by six orders of magnitude [19,21,24,25,27,28]. Calculations showed that β -scission of cumyl radical (as in cumyl dithiobenzoate) and unimeric styryl radicals (as a model of

polystyryl dithiobenzoate) was associated with a high equilibrium constant for addition (and hence a slow fragmentation rate coefficient), in accordance with one set of experimental values [21,27]. However, the equilibrium constant (and also the fragmentation rate coefficient) was shown to vary over 12 orders of magnitude, as the leaving group and RAFT agent substituent was changed over a range of typical experimental structures, with only certain species undergoing slow fragmentation [24,26,28,32].

This wide variability suggested that significant chain length dependency in the early stages of the RAFT process was complicating the various experimental measurements (which were based on fitting chain length independent models to the data). This suggestion was confirmed in subsequent *ab initio* studies of the effects of chain length on the addition-fragmentation equilibrium [32,35–37]. Moreover, once the kinetic model was extended to allow for the most significant chain length dependencies, the predicted concentration profiles for the successive oligomeric dithioesters produced and consumed during the early stages of a RAFT process were brought into line with experiment, as seen in Figure 6 (scenario *a*) [243]. Crucially, the theoretical predictions in scenario *a* were made without recourse to model fitting and the good agreement with experiment thus provides mutual verification for the accuracy of the *ab initio* calculations, carried out using a multilayer ONIOM approximation to W1 theory [116,148], as well as the kinetic model. Further validation of the accuracy of the calculations at this level of theory was subsequently provided through comparison with more direct experimental measurements, derived from spin trapping experiments in model RAFT systems [244] and closely related thioketone reactions [18,245], and PLP experiments carried out on the RAFT polymerisations [36,246].

The underlying motivation of these quantitative studies is to provide an understanding of the design criteria for optimal control agents and an accurate database of kinetic parameters for use in structure-reactivity analysis and reagent design. As noted earlier, a review of the use of quantum chemistry in structure-reactivity analysis and reagent design is beyond the scope of the present work. However, it is worth noting that the use of quantum chemistry to either substitute or complement experimental data in structure reactivity studies of CRP is becoming routine. At one end of the spectrum, theory has been used to provide simple descriptors of polar, steric and resonance effects that can then be used in analysing experimental or computational kinetic parameters. Such analyses can take the form of quantitative linear free energy relationships [43,53] or more qualitative descriptions of reagent reactivities [19,22,23,29,30,44,50–52]. For the case of RAFT at least, such analyses have led directly to the first principles design of new classes of reagents [18,29,31]. Computational theory has also been used to provide a quantitative assessment of the suitability of control agents for a given monomer (and associated reaction conditions) as a pre-screening stage prior to experiment [33,247,248].

4. Summary and outlook

Within quantum chemistry, there is a multitude of ever improving theories and approximations for studying chemical processes. Over the last decade, the development of more efficient computational theory has allowed for the accurate first principles prediction of propagation rate coefficients in free-radical polymerisation as well as a multitude of other kinetic and thermodynamic properties of interest to copolymerisation and CRP. As detailed in the preceding sections, the choice of procedure has a critical effect on the accuracy of not only quantitative

results but also qualitative trends. To exploit the power of computational chemistry fully, and effectively direct future developments towards more efficient and effective polymerisation processes, it is essential that only accurate and reliable theoretical procedures are used. Some of the most important considerations in this regard are summarised below:

- *Model size:* Oligomers are suitable models for chain end processes such as propagation, RAFT agent addition and fragmentation, etc. Generally, dimer or trimer models are sufficient to model these processes; however, chain length convergence is *very* system dependent and should ideally be assessed under the specific conditions of interest until convergence is obtained. Unimeric models are too small to accurately model polymerisation processes and their use for such purposes should be avoided.
- *Electronic structure calculations:* Low-cost computational methods are generally acceptable for geometry optimisations and frequency calculations. For single-point energy calculations, the use of DFT without thorough prior assessment (to both *ab initio* procedures and experiment) is strongly discouraged, given the associated large and often non-systematic errors found. New generation dispersion corrected DFT procedures show promise but are yet to be rigorously evaluated for these systems. Given the reliability issues of DFT, composite *ab initio* procedures, such as G3(MP2)-RAD, applied in conjunction with the ONIOM approximation are advised. These procedures allow for the study of 'large' trimer and tetramer systems with high accuracy.
- *Reaction rate theories:* Proper treatment of conformational effects is essential to obtain physically meaningful reaction energies. Calculated thermochemistry should always be based on the lowest energy conformation, and for high accuracy work, anharmonic corrections and a more rigorous treatment of conformational near degeneracy, via 1D-HR or multidimensional methods such as MSTor, should be considered.
- *Solvation corrections:* In most systems, solvation significantly affects both quantitative and qualitative reactivity. Continuum solvation models can generally recreate average solvation effects, although heavy parameterisation makes their reliability in more novel systems somewhat questionable. Continuum solvation models should only be used to calculate free energies of solvation at the theoretical level at which they were parameterised.

Future increases in computing power and the development of more efficient computational algorithms will enable either the use of higher levels of theory to study of similarly sized systems or the study of larger systems at a similar level of theory. Given the excellent inherent accuracy of existing composite procedures, it is generally expected that the latter approach, i.e. more realistic modelling of complex polymerisation systems, would be preferential to simply improving the theory used for existing models. These developments will further aid the optimisation of CRP processes and radical polymerisation more generally. While computational studies can never replace the valuable role of experiment, such studies offer unique insights into fundamental processes, which can be of enormous practical value. As the cost of computer power, relative to experiment, continues to decrease, we expect to see this computer-guided approach to experiment becomes further embedded in the radical polymer field.

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3.4 Supporting information

Supporting information for the rotational barriers presented in **Figure 8** can be found on the CD-ROM attached at the back of this thesis.

4. Lewis Acids as Propagation Catalysts in Radical Polymerization

4.1 Overview

Since they were first utilized in radical polymerization of acrylonitrile,¹⁰⁶ Lewis acids have been touted as polymerization catalysts for polar monomers. However, a significant number of these claims are based on observations of simultaneous increases in the overall polymerization rate (R) and molecular weight (P_n). In free-radical polymerization, the overall polymerization rate under steady state conditions can be described by the following textbook¹⁰⁷ formula:

$$R = k_p[M] \sqrt{\frac{fk_d[I]}{< k_t >}} \quad [1]$$

In *Equation 1*, k_p , k_t and k_d are the propagation, termination and initiator decomposition rate coefficients, respectively. $[M]$ and $[I]$ are the (time-dependent) monomer and initiator concentrations, respectively and f is the initiator efficiency. Similarly, molecular weight in the absence of any kind of chain-transfer is given by the following formula⁴⁵:

$$P_n = \frac{2}{(1 + \delta)} \frac{k_p[M]}{2\sqrt{fk_d < k_t > [I]}} \quad [2]$$

In *Equation 2*, δ is a coefficient that is determined by the contribution of disproportionation to overall polymer chain termination. The effect of various types of chain-transfer on P_n can be described using the Mayo-Lewis equation.⁴⁵

Using these equations and making several other assumptions, the k_p to k_t ratio can be deduced in the presence and absence of added Lewis acids by measuring the overall polymerization rate and molecular weight of the resultant polymer. The drawback of using molecular weight and/or monomer conversion measurements to deduce k_p is that the accuracy of this approach hinges on the validity of the assumed kinetic model. Even in the absence of Lewis acids, it is very difficult to accurately determine k_p using measurements of molecular weight and monomer conversion alone. Moreover, Lewis acids may also affect other kinetic parameters aside from k_p (such as k_d , f and k_t).

Pulsed laser polymerization (PLP) in combination with size-exclusion chromatography (SEC) is an elegant method for determining k_p with very high accuracy and precision.⁵⁴⁻⁵⁶ In a PLP-SEC experiment, consecutive laser pulses generate radicals at regular intervals via the photolysis of an added photoinitiator. These fragment radicals rapidly initiate polymer propagation, which continues until these chains are terminated by analogous photoinitiator fragments that are generated from subsequent laser pulses. Some of these growing polymer chains will not be terminated by the immediately following laser pulse and will continue to propagate (until eventual termination by subsequent laser pulses). This regular termination leads to a characteristic multimodal molecular weight distribution, which can be analysed by SEC to determine k_p in a relatively model-free manner. The value of k_p can then be determined by the following formula⁵⁴⁻⁵⁶:

$$L_{0,n} = nk_p[M]t_0 \quad [3]$$

In *Equation 3*, $L_{0,n}$ is the kinetic chain length at the inflection point of the n^{th} molecular weight peak (on the low molecular weight side), $[M]$ is the initial monomer concentration and t_0 is the ‘dark time’ between laser pulses. PLP-SEC is the IUPAC recommended method for k_p determination.¹⁰⁸⁻¹¹¹

The first publication in this chapter [*Publication 3*] explores the application of PLP-SEC kinetic experiments to the lithium bis(trifluoromethanesulfonyl)imide (LiNTf₂) mediated polymerization of methyl methacrylate (MMA). This work establishes the catalytic effect of LiNTf₂ on the k_p of MMA. This publication also employs high-level theory to assess the potential reasons why LiNTf₂ delivers sub-optimal stereocontrol in MMA polymerizations. Interestingly, these calculations suggest a modest thermodynamic preference for chelation to the terminal and penultimate side-chains of the propagating polymer terminus. This coordination mode should impart a significant preference for *meso* propagation and thus isospecific polymerization. Unfortunately, terminal-penultimate chelation also deactivates the polymer terminus to such an extent that the terminal-monomer coordination mode is actually the dominant propagation pathway. That is, propagation is predicted to occur via the (pseudo)cyclization of a terminal-monomer complex. In this pathway, the terminal and penultimate side-chains are not simultaneously chelated and thus it is unlikely to propagate in an isospecific manner.

The second publication in this chapter [*Publication 4*] explores the contributing factors that collectively determine photoinitiation efficiency. This work employs both theoretical and experimental procedures to quantitatively assess and rationalize the efficiency of several substituted benzoin analogues. Criteria that are required for high efficiencies include: a small extinction coefficient at the excitation wavelength, rapid inter-system crossing, fewer than two triplet states below the lowest singlet state (with at least one of these possessing $n\pi^*$ character) and rapid α -cleavage. Interestingly, photoinitiators that form highly reactive radicals may not be optimal because of poor photoexcitation characteristics. This work demonstrates that it is not possible to select a ‘good’ acetophenone Type I initiator without properly considering all aspects of photoinitiation.

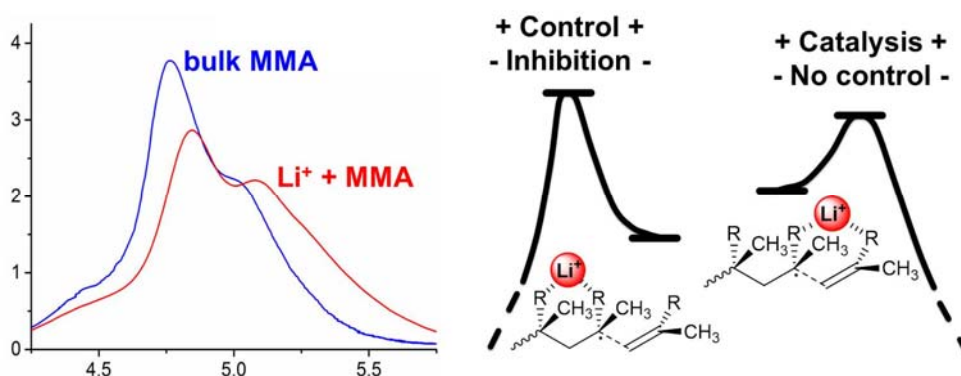
While PLP-SEC experiments of the LiNTf₂-mediated polymerization of MMA were successful, analogous kinetic studies with stronger Lewis acids were hampered by the loss of PLP characteristics in the corresponding molecular weight distributions. The final publication in this chapter [*Publication 5*] examines the effect of Lewis acid coordination on the efficiency of two common photoinitiators, methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA). In this work, the effect of two prototypical Lewis acids, zinc chloride (ZnCl₂) and aluminium chloride (AlCl₃) on the photoexcitation of MMMP and DMPA are contrasted. High-level theoretical results reveal that Lewis acid coordination can have both significant and divergent effects on the individual processes that comprise radical photoinitiation. Lewis acids not only affect the absorption profile of MMMP and DMPA but also significantly alter the stability of their excited states as well as the reactivity of the resulting radical fragments.

4.2 Publication 3

The Effect of LiNTf_2 on the Propagation Rate Coefficient of Methyl Methacrylate

Noble, B.B.; Smith, L.M. and Coote, M.L.

Polym. Chem., **2014**, 5, 4974-4983.



This manuscript is a peer-reviewed regular original research article that was published in *Polymer Chemistry*. The literature overview, computational results and discussion presented are my own work. I obtained the experimental results for this manuscript jointly, with the assistance of Dr. Leesa Smith. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.



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The effect of LiNTf₂ on the propagation rate coefficient of methyl methacrylate†

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In the present work we use accurate Pulsed Laser Polymerization (PLP) to measure the influence of various concentrations of lithium bis(trifluoromethane)sulfonamide (LiNTf₂) on the propagation rate coefficient of methyl methacrylate (MMA). We also perform ¹H-NMR analysis to evaluate the effect of LiNTf₂ on poly(MMA) stereochemistry. Additionally, we perform high-level quantum-chemical calculations to model the interactions between Li⁺ and the MMA monomer and propagating radical. Across a broad range of concentrations, LiNTf₂ only slightly increases the isotacticity of the resultant poly(MMA). However, a significant increase in the propagation rate coefficient was noted upon addition of LiNTf₂. The magnitude of this increase was found to be dependent on the LiNTf₂ concentration and temperature. Theoretical calculations reveal the complexities associated with Lewis acid-mediated stereocontrol. On the basis of this theoretical work, we suggest that the potential stereocontrol afforded by Lewis acids is being hindered by their action as propagation catalysts though non-stereoselective binding modes.

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Introduction

The objective of polymer synthesis is to control the assembly of macromolecules to facilitate precise adjustments to their structure and properties. Since they were first employed in radical polymerization over 50 years ago, Lewis acids have been used to alter monomer reactivity and control various aspects of polymer microstructure. Arguably, the most exciting function of these additives is their influence on main-chain stereostructure (tacticity), which is usually poorly regulated in their absence. The integration of effective stereocontrol with living radical polymerization would revolutionise polymer synthesis by providing a convenient radical-based route to precisely controlled stereoregular polymers. Over the last few decades, much pioneering work has sought to realise this goal,¹ which has been described as the “holy grail”² of radical polymerization.

More than 50 years ago, Bovey examined the effect of low concentrations of zinc chloride (ZnCl₂) on the radical polymerization of methyl methacrylate (MMA), noting no significant stereochemical effects.³ Otsu *et al.* later reported that employing high concentrations of ZnCl₂ slightly increases the isotacticity of the resulting poly(MMA).⁴ Subsequently, Matsumoto *et al.* utilised magnesium bromide (MgBr₂) in the radical

polymerization of MMA, also noting a slight increase in isotacticity, particularly on the solid surface of the partially insoluble MgBr₂.⁵ More recently, Okamoto and co-workers successfully synthesised isotactic rich polymers of various methacrylates,⁶ α -(alkoxymethyl)acrylates,⁷ acrylamides,^{8,9} and methacrylamides^{10,11} by employing rare earth metal triflates (M(OTf)₃, M = Sc, Y, Yb, Lu) as stereocontrol agents.

Unfortunately, even with these novel additives, the stereocontrol achieved in most systems is modest, compared with the high stereoregularity of polymers synthesised *via* anionic or coordination polymerization. Although reasonable isotactic control has been reported for acrylamides^{8,9} and to a lesser extent methacrylamides,^{10,11} this stereocontrol has not yet been replicated for other polar monomers, such as methacrylates, acrylates, vinyl esters, vinyl amides and vinyl halides. For instance, the best isotactic control reported for the radical polymerization of MMA is an isotactic triad fraction (*mm*) of 22%,⁶ compared to *mm* > 99% *via* anionic polymerization (albeit under much more demanding reaction conditions).¹² In Lewis acid-mediated radical polymerization, polymer stereochemistry is highly dependent on the reaction conditions (*i.e.* the identity and concentration of the Lewis acid, ligands, monomer and solvent). Unfortunately, the development of more effective stereocontrol is hindered by a poor understanding of the interactions between the Lewis acid and growing polymer terminus that regulate stereochemistry.

Stereocontrol mechanism?

In contrast to anionic and coordination polymerization, stereochemistry in radical polymerization is not determined by

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† Electronic supplementary information (ESI) available: Additional tables, figures and schemes, details of computational procedures and full set of obtained results, individual energy components and optimised geometries (in the form of Gaussian archive entries) for all species in this study. Includes a detailed description of the experimental methodology and PLP traces. See DOI: 10.1039/c4py00190g

the orientation of incoming monomer, but by the relative orientation of the terminal and penultimate side-chains of the polymer terminus during propagation (scenario (1) in Scheme 1). The pro-chiral polymer terminus can rapidly interconvert between pro-*meso* and pro-*racemo* conformations, which in the absence of stereocontrol agents, are nearly degenerate and similarly reactive towards propagation. Thus, radical polymerization is generally not stereoselective and affords atactic polymer. Since it was first proposed by Matsumoto,⁵ the literature mechanism of isotactic regulation has been frequently cited,^{1,13,14} although its complexities and limitations are neither widely appreciated nor well understood. The proposed mechanism of isotactic regulation is *via* the formation of a kinetically labile chelate complex between the terminal and penultimate side-chains of the polymer terminus and the Lewis acid (scenario (2a) in Scheme 1).⁵ It is assumed that such coordination imparts an energetic preference for *meso* propagation; thus leading to isotactic regulation. However, this simplistic mechanism conceals a layer of complexity and so potential modes of failure.

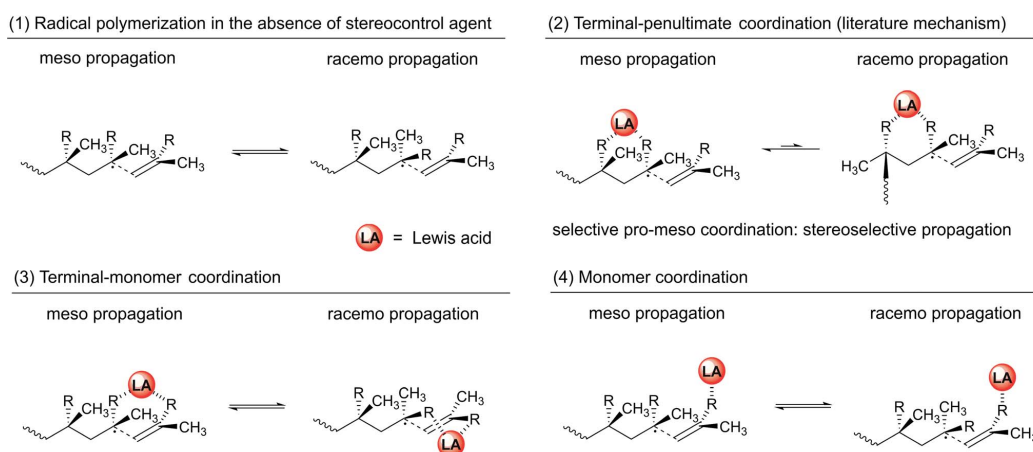
Firstly, this mechanism assumes terminal-penultimate complexes prearrange the polymer terminus exclusively into pro-*meso* configurations. However, helical polymer conformations could potentially accommodate such chelate complexes in pro-*racemo* configurations, which might competitively propagate and reduce the level of isotactic control (scenario (2) in Scheme 1).¹⁵ Secondly, this mechanism implicitly assumes that the terminal-penultimate complex is formed selectively over other monomer/polymer adducts. However, non-stereo-regulating complexes could form and compete with this terminal-penultimate complex to reduce the effectiveness of this stereocontrol. Specifically, coordination of the Lewis acid to the terminal side-chain and incoming monomer (scenario (3) in Scheme 1), exclusively to incoming monomer (scenario (4) in

Scheme 1) or to the main polymer chain would not be expected to impart significant isotactic control. Such complexes could readily accommodate both pro-*meso* and pro-*racemo* conformations, as the terminal and penultimate side-chains are not coordinated simultaneously. These conformations would be expected to rapidly interconvert (*via* rotation about the terminal chain bond) and possess similar stability and reactivity; thus leading to non-stereoselective propagation of the parent complexes. Most of these complications are unique to radical polymerization and are unlikely to be pertinent in synthetic intermolecular radical addition reactions, where coincidentally Lewis acids have been utilised to achieve very high diastereoselectivities.¹⁶

Catalysis?

Intriguingly, in addition to influencing polymer tacticity, Lewis acids can catalyse radical homopolymerizations^{3,6,17} and alter sequence distribution and composition in copolymerizations.^{18–20} Remarkably, some novel Lewis acids facilitate the radical polymerization of 1-alkenes,²¹ presumably by catalysing propagation and limiting the degenerative hydrogen transfer reactions which normally impede the production of high polymer. Indeed, such catalysis was first predicted by Clark on the basis of *ab initio* calculations carried out over 25 years ago,²² prior to being confirmed experimentally by Michl *et al.*²¹ Clark attributed these rate accelerations to electrostatic effects, suggesting such catalysis does not require covalent interaction between Li^+ and the $\text{C}=\text{C}$ bond and so can be observed even at long distances ($>4.5 \text{ \AA}$) when the cation is fully solvated.²³

Although Clark's theoretical work provides a satisfactory rationale for the catalysis reported in 1-alkenes, the origin of propagation rate enhancement in polar systems, where Lewis acid coordination presumably occurs at the conjugated side-chain rather than the $\text{C}=\text{C}$ bond, is more speculative.



Scheme 1 Stereoselectivity during radical polymerization of a mono substituted alkene ($\text{CH}_2=\text{C}(\text{CH}_3)\text{R}$), in the absence (1) and presence (2)–(4) of a Lewis acid (LA): scenarios (2)–(4) illustrate different positions of Lewis acid coordination to the polymer terminus and incoming monomer.

Simultaneous increases in the initial polymerization rate and the polymer's molecular weight confirm that Lewis acids are catalysing propagation, although the extent of these increases is uncertain. Initial polymerization rate is a function of monomer and initiator concentrations and rate coefficients for initiator decomposition, propagation and termination. However, extracting propagation rate coefficients from initial polymerization rate measurements can be problematic as Lewis acids are known to catalyse the thermal decomposition of radical initiators and can even catalyse the addition of 'unconventional' initiators, such as triplet oxygen (O_2^3), to alkenes.²¹ Although Pulsed Laser Polymerization (PLP) can be used to extract very accurate propagation rate coefficients in a relatively model free manner, to date we are unaware of any PLP studies of the effect on Lewis acids on the kinetics of radical polymerization of MMA. Recently, Pedron *et al.* used PLP to study the effect of LiOTf on the radical polymerization of ethoxy methacrylates and revealed significant propagation catalysis in these systems.^{24a} Very recently, Calle *et al.* suggested on the basis of ESR kinetic analysis that LiOTf inhibited propagation of MMA.^{24b}

Objectives

Undoubtedly, there is a lack of understanding of Lewis acid-mediated polymerization, particularly the mechanistic aspects of stereoselectivity, yet this information is crucial improving stereocontrol. As the mechanism of isotactic regulation is fairly speculative, it is difficult to suggest modifications that could improve existing stereocontrol, which leads to trial and error experimentation rather than rational design of stereocontrol agents. Clearly it would be desirable to clarify the mechanism underlying isotactic regulation; unfortunately doing so would require discriminating between scenarios (2)–(4), which is difficult or even impossible using experimental techniques. Although 1H and ^{13}C NMR has been employed to examine the relative binding affinity of polymer and monomer to Lewis acids,⁶ such techniques cannot readily observe coordination to the polymer terminus (such as scenarios (2) and (3) in Scheme 1) because of the very low concentration of radical chain-ends in the polymerising medium. Moreover, it is not clear if the most thermodynamically stable complex would also be the most reactive towards propagation.

This is a situation where theoretical chemistry can provide meaningful insight into the underlying interactions occurring at the polymer terminus, which is inaccessible directly from experiments. In the present work we aim to assess a new potential stereocontrol agent – lithium bis(trifluoromethane) sulfonamide (LiNTf₂) – in the radical polymerization of MMA and examine its effect on polymerization kinetics using appropriate PLP-SEC analysis. Concurrently, we aim to examine the importance of the proposed binding scenarios (2)–(4) with state-of-the-art quantum-chemical calculations. To the best of our knowledge this is the first time PLP has been used to accurately quantify the effect of Lewis acids on propagation kinetics of MMA and additionally the first time theoretical calculations have been used to clarify the mechanisms underlying stereoselectivity in such systems.

Methodology

Materials

Methyl methacrylate (MMA) (Aldrich, 99%) was passed through a column of basic alumina to remove the inhibitor. Benzoin (Aldrich, 98%) was purified by recrystallization from hot ethanol. Lithium bis(trifluoromethanesulfonimide) (LiNTf₂) (Aldrich, 99.9%), 2-methyl-4'-(methylthio)-2-morpholinopropiophenone (Aldrich, 98%), chloroform-*d* ($D = 99.8\%$, Cambridge Isotope Laboratories), methanol (GC grade, Merck), tetrahydrofuran (THF) (GC/GPC grade stabilized with BHT, Honeywell Burdick & Jackson) were used as received.

Experimental procedures

To determine accurate propagation rate coefficients of MMA in the presence of LiNTf₂, we performed PLP-SEC analysis. Particular attention was given to IUPAC-recommended consistency criteria to demonstrate the reliability of the k_p values.²⁵ Accordingly, the ratio of inflection point positions, L_1/L_2 , was found to be close to 0.5, and k_p was shown to be independent of pulse energy, of pulse repetition rate, and of photoinitiator identity and concentration. To measure k_p , solutions of MMA (~1.5 mL) containing LiNTf₂ (0–1.50 M) and photoinitiator (1–2 mM) were transferred to a quartz vial and each sealed with a rubber septa. Each sample was purged with nitrogen and then subsequently placed into a temperature controlled sample holder. The temperature was measured directly inside the sample and allowed to reach thermal equilibrium. Polymerization was then initiated by laser pulsing (at 355 nm, ~20 mJ per pulse) at repetition rates of up to 25 Hz. During polymerization, the temperature inside the sample was logged and the average temperature during the polymerization was used when determining Arrhenius parameters. The temperatures used were 10, 25 °C and 40 °C and the variation during an experiment did not exceed 3 °C. After polymerization, the sample was poured into methanol to precipitate the polymer generated. Subsequently, excess methanol was decanted and the samples were dried in a vacuum concentrator. The molecular weight distribution of the samples was analysed using (THF-phase) SEC and selected samples were analysed by 1H -NMR (in chloroform-*d*) to determine triad tacticities. A more detailed description of the experimental procedure, including PLP traces and can be found in the ESI.†

Theoretical procedures

Discriminating between the binding scenarios proposed above is very difficult, if not impossible *via* experimental techniques; therefore, we have employed quantum chemistry to determine binding affinities from first principles. Specifically, we used the high-level composite *ab initio* G3(MP2)-RAD method in conjunction with an ONIOM inspired approximation^{26,27} and M06-2X²⁸ thermochemistry to obtain accurate gas-phase energies. The SMD²⁹ method was used to model implicit solvation effects using methyl propanoate as the solvent to mimic bulk MMA. Similar methodology has been previously shown to predict accurate values for the kinetics and thermodynamics of

a wide range of radical reactions, including propagation.^{30–32} We should emphasize that the focus of the present theoretical work is to determine the relative binding affinities of very similar chemical species; thus a large degree of intrinsic error cancellation would be anticipated. All standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were carried out using Gaussian 09 (ref. 33) and Molpro 2009 (ref. 34) software packages. A detailed description of all the computational procedures, conformational searching, as well as full set of obtained results can be found in the ESI.†

Experimental results

To investigate the effect of LiNTf₂ on MMA polymerization kinetics we performed PLP-SEC analysis at varying concentrations and temperatures. An overlay of two typical PLP-SEC traces is shown in Fig. 1, which illustrates the increases in the molecular weight inflection points upon addition of LiNTf₂. The average k_p values across temperature range of 10 °C to 40 °C and

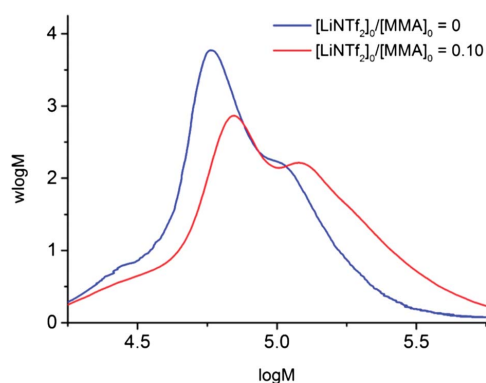


Fig. 1 PLP-SEC traces run at 10 Hz and 40 °C in the presence and absence of LiNTf₂.

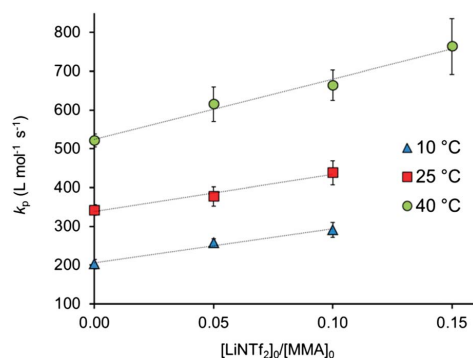


Fig. 2 Average k_p values in the presence and absence of LiNTf₂ determined by PLP-SEC. Error bars indicate 95% confidence intervals.

Table 1 MMA tacticity in the presence and absence of LiNTf₂

[LiNTf ₂] ₀ /[MMA] ₀	Temp. (°C)	Triad tacticity (%)			Diad (%)
		<i>mm</i>	<i>mr</i>	<i>rr</i>	
0	10	1.7	26.8	71.4	15.2
0.05	10	1.8	29.5	68.7	16.5
0.10	10	2.2	29.2	68.5	16.9
0	25	2.3	27.5	70.1	16.1
0 ^a	25	2.2	29.6	68.2	17.0
0.05	25	2.6	30.4	67.0	17.8
0.10	25	2.9	31.5	65.6	18.7
0	40	3.0	31.7	65.3	18.9
0 ^a	40	3.2	31.6	65.2	19.0
0.05	40	3.9	33.4	62.7	20.6
0.10	40	3.7	33.2	63.1	20.3
0.10 ^a	40	3.8	32.9	63.3	20.3
0.15	40	3.7	34.2	62.1	20.8

^a Indicates a duplicate sample was tested.

for a ratio of LiNTf₂ to MMA of 0 to 0.15 are illustrated in Fig. 2. These results clearly illustrate that k_p increases with increasing LiNTf₂ concentration. More detailed data included laser flashing rates, inflection points and conversions can be found in Tables S1–S4 in the ESI.†

Unfortunately, the addition of LiNTf₂ had little effect on poly(MMA) tacticity across a range of concentrations and temperatures (Table 1). The reasonably consistent tacticities of duplicate samples demonstrates the high precision of this analysis. Disappointingly, across all the conditions studied in this work, the isotactic triad fraction (*mm*) of the resultant poly(MMA) never exceeded 4%.

Theoretical results and discussion

From the experimental work undertaken, it is clear that LiNTf₂ increases the propagation rate coefficient of MMA, although there is no significant effect on polymer stereochemistry. The presence of propagation catalysis suggests that LiNTf₂ is interacting with the pendant ester groups of the polymer terminus and/or incoming monomer during propagation, though the absence of isotactic control indicates that these interactions are not stereoselective. These observations raise several questions regarding the interactions occurring at the polymer terminus: what coordination mode is the most favoured for polar monomers? Is there an electronic preference for coordination to a particular ester moiety within a polymerization? What is the relative binding affinity of monomer, the polymer terminus and the polymer chain? Which scenario (2)–(4) is responsible for the experimentally observed catalysis and perhaps most crucially, why does LiNTf₂ have no significant effect on polymer stereochemistry?

To address these questions we have used accurate quantum chemistry to clarify the nature of interactions between Li⁺ and the polymer terminus. To perform accurate calculations on these complex systems we need to make some simplifications. Thus, only relatively small oligomeric models are considered so

that high levels of theory can be used. These models are too small to allow for a quantitative first principles prediction of tacticity, which would require at least tetramer transition state models. Instead, our objective here is to use theory as a tool to understand the interactions underlying stereoselectivity. We aim to determine if the literature mechanism of isotactic regulation is applicable in the present system and identify the underlying cause of the low stereoselectivity. Results of this computational investigation are now presented and discussed in turn.

Binding modes

Prior to considering more complex systems, the coordination of Li^+ to MMA monomer was rigorously examined. The coordination of 'hard' Lewis acids, such as Li^+ , would be expected to occur predominantly at the *O*-acyl group of the ester side-chain. Nevertheless for completeness, Li^+ coordination to each ligation site of MMA monomer was investigated: the $\text{C}=\text{C}$ bond, the *O*-acyl group and *O*-methoxy group of the ester and both ester heteroatoms simultaneously in a chelate arrangement (*O,O'*-bis).

In total six discrete Li^+ monomer complexes were identified: *s-trans* and *s-cis* conformations of the *O*-acyl, *O*-methoxy and *O,O'*-bis coordination modes (Fig. 3). Interestingly, no stable minima with Li^+ complexed directly to the $\text{C}=\text{C}$ bond were found and attempts to optimise reasonable starting geometries

afforded *O*-acyl or *O*-methoxy bound complexes. The relatively short $\text{C}-\text{Li}$ distances ($<2.6 \text{ \AA}$) in the *s-trans* *O*-methoxy complex are suggestive of an interaction between the cation and the $\text{C}=\text{C}$ bond. Similar screening was performed on unimeric MMA radical Li^+ complexes to investigate the possibility of a direct C radical Li^+ interaction rather than coordination to the ester moiety. No stable minima with Li^+ complexed directly to the radical were found and attempts to optimise reasonable starting geometries afforded similar *O* bound complexes. Given the large electronic preference for *O*-acyl coordination in all systems considered, other sites of ligation were excluded henceforth.

Ester binding selectivity

It is well known that Lewis basicity is dependent not only on the functional identity of the coordination site but also its extended substitution.^{35,36} In a bulk MMA polymerization, there are 3 functionally distinct methyl ester moieties: those of the monomer, the radical terminus and polymer side-chains. To examine if there was an underlying electronic preference for coordination to a particular ester group, binding enthalpies of various unimeric models (Fig. 4) were calculated as Li^+ was progressively solvated by MMA monomer (Table 2). In the presence of a similarly sized organic ligand, tetrahydrofuran (THF), Li^+ forms a four coordinate complex.³⁷ Thus, consistent with previous theoretical work,^{23b} coordination numbers up to four were considered in the present study. As NTf_2^- is weakly coordinating anion, it is expected to be readily displaced from Li^+ by monomer in solution and so was not included in these calculations.

These calculations suggest that there is a modest enthalpic preference for Li^+ coordination to the terminal (radical) ester moiety, which is reduced as the cation is progressively solvated

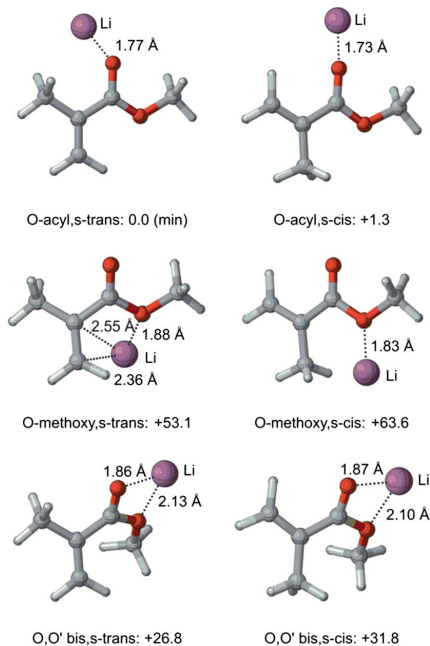
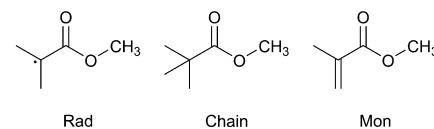


Fig. 3 Optimised geometries and relative free energies (kJ mol^{-1}) of different coordination modes of MMA monomer to Li^+ . Contact distances of coordinating atoms are also shown.



Structures of unimeric MMA models

Fig. 4 Unimeric models of the MMA polymer terminus (Rad), polymer chain (Chain) and the structure of MMA monomer (Mon).

Table 2 Relative binding enthalpies of unimeric MMA models to $\text{Li}^+(\text{Mon})_n$

Model ^a	Rad	Chain	Mon ^b
$n = 0$	0.0 (min)	+3.9	+10.9
$n = 1$	0.0 (min)	+3.6	+8.5
$n = 2$	0.0 (min)	+5.0	+8.3
$n = 3$	0.0 (min)	+4.4	+4.6

^a Here n is the number of solvating MMA monomer units. ^b Note that because Mon is also used to solvate Li^+ the product complex can be written as $\text{Li}^+(\text{Mon})_{n+1}$. Binding enthalpies were calculated at 25°C and are reported in kJ mol^{-1} .

by monomer. The conjugated radical is stabilised by coordination of Li^+ to the ester moiety, with the radical stabilisation energy (RSE) increasing relative to the corresponding uncoordinated species by between 5 to 8 kJ mol^{-1} , depending on the extent of cation solvation (see Table S7 in ESI†). These results suggest that saturated ester moieties are more basic than comparable α,β -unsaturated esters, which is consistent with previous experimental¹³⁵ and theoretical studies.³⁶ Although these results could be indicative of a modest preference for coordination to the ester group of the polymer terminus, this preference is too modest and the models considered too simplistic to allow for any conclusions regarding the position of Li^+ coordination.

Polymer binding selectivity

To account for the isotactic control of Lewis acids, a chelate terminal-penultimate complex is frequently invoked.^{1,13,14} Generally, chelate complexes that are composed of five or six membered rings are particularly stable compared with analogous monodentate complexes. However, chelation of adjacent ester groups on a poly(MMA) chain will form a relatively large eight membered ring. Although such large rings are usually enthalpically disfavoured because of transannular strain, all conformations of the highly substituted poly(MMA) chain are strained on the basis of optimal van der Waals radii and bond angles. Thus, in contrast to comparable unsubstituted systems, the enthalpic cost of prearranging poly(MMA) chains into chelating conformations should be minimal. Unfortunately, chelation can occur not only at the polymer terminus, but at any point along the polymer chain. If there is no selectivity for coordination at the polymer terminus, then competitive chelation of the penultimate side-chain in 'mid-chain' complexes will inhibit terminal-penultimate complexation. To examine these aspects of selectivity, the relative binding affinity of dimeric models of the polymer terminus and a polymer mid-chain segment were calculated, as Li^+ was progressively solvated by monomer.

These results are summarised in Fig. 5, which illustrates the structures and the best estimates (using a fully solvated cation)

of the relative binding affinities (see Table S10 of ESI† for more detailed results†). The calculated thermochemistry is consistent with qualitative arguments presented above, as the energy required to organise the model polymer terminus and polymer segment into precursor conformations for chelate binding is small ($>4 \text{ kJ mol}^{-1}$). However the relatively rigid coordination geometry of these dimeric models leads to lower gas-phase binding enthalpies compared to the corresponding monomer complex. Despite these lower binding enthalpies, the more favourable binding entropies of the dimeric models results in greater overall binding affinities compared with the corresponding monodentate monomer species. There is a clear preference for chelating coordination to the model dimeric polymer terminus compared with chelating coordination to the dimeric mid-chain segment and complete solvation by monomer (Fig. 5).

We should note that the Harmonic Oscillator/Rigid Rotor (HO/RR) approximation used in this work may overestimate binding entropies, particularly of monomer solvated complexes where rotation around the coordinate bond would probably be more accurately described as a hindered internal rotation. Although it is difficult to quantify this overestimation in the present systems, theoretical assessments of radical propagation reactions (in which the transition states possess a similarly long forming bond) have found the error associated with the HO/RR approximation is generally less than 4 kJ mol^{-1} at 298 K.³⁰ A more sophisticated (and more accurate) treatment of entropic effects, which would probably require molecular dynamic simulations, is beyond the scope of the present work.

Pro-meso/pro-racemo selectivity

Given the apparent preference for coordination to the terminal and penultimate ester groups of the polymer terminus, it is now worth considering if such coordination is selective for pro-meso conformations, which is the implicit assumption underlying the literature mechanism of isotactic control. The various conformations of a polymer terminus can be classified as either pro-meso or pro-racemo depending on the orientation of the terminal and penultimate side-chains with respect to the

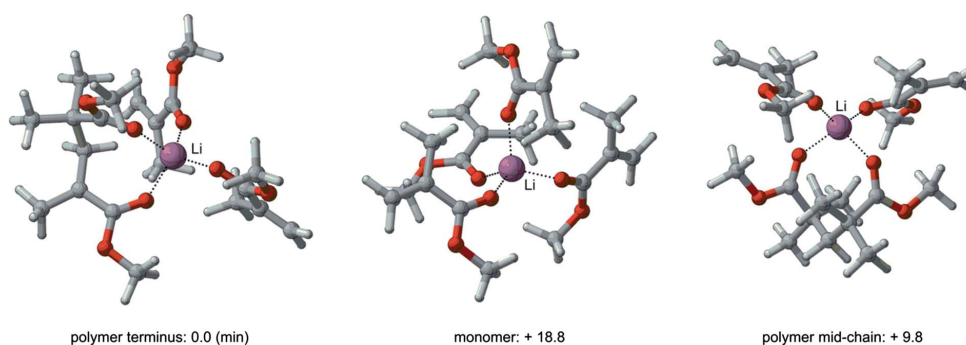


Fig. 5 Optimised geometries and relative binding free energies (kJ mol^{-1}) of $\text{Li}^+(\text{Mon})_2$ to models of the polymer terminus, mid-chain and monomer.

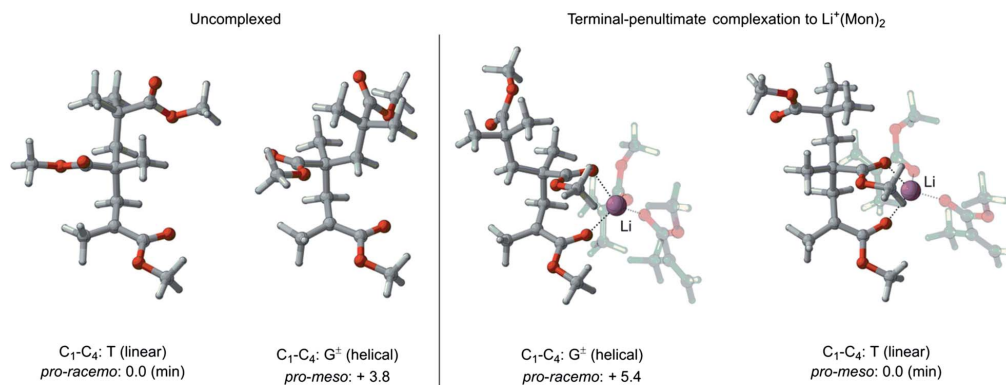


Fig. 6 Optimised geometries and relative free energies (kJ mol^{-1}) of *pro-meso* and *pro-racemo* conformations of the polymer terminus, in the absence of Lewis acid (uncomplexed, left) and with $\text{Li}^+(\text{Mon})_2$ complexed to the terminal and penultimate side-chains (right). Solvating monomer units on Li^+ have been made transparent for clarity.

backbone $\text{C}_1\text{--C}_4$ atoms. Considering a simplified linear (anti-periplanar, T) representation of the polymer terminus, such as is depicted in Scheme 1, it is usually assumed that the proximity of the side-chains in the *pro-meso* arrangement would result in a stronger binding affinity. However, the polymer terminus can also position the ester groups in similar proximity in *pro-racemo* arrangements by adopting helical (synclinal, $\text{G}^\pm$) conformations. The polymer terminus has to be at least trimeric for conformations to be classified as linear ($\text{C}_1\text{--C}_4$: T see Fig. 6) or helical ($\text{C}_1\text{--C}_4$: $\text{G}^\pm$ see Fig. 6) and more significantly, *pro-meso* or *pro-racemo*. To examine this selectivity, coordination of Li^+ to the terminal and penultimate ester groups of a trimeric polymer terminus was examined. Rigorous assessment of *pro-meso*/*pro-racemo* selectivity would require the calculation of the reactivity of these conformations rather than just their stabilities *i.e.* an explicit first principles calculation of tacticity. However, given the early position of these transition states and the similar coordination position of Li^+ in these complexes, the relative conformer energies should provide a reasonable estimate for this selectivity.

The geometries and relative energies of the lowest energy *pro-meso* and *pro-racemo* conformations of the chelated terminal-penultimate polymer complex and the parent (uncomplexed) species are illustrated in Fig. 6. In the absence of Li^+ , the polymer terminus preferentially adopts a linear *pro-racemo* conformation, by approximately 3.8 kJ mol^{-1} , which is consistent with the syndiotactic preference observed for MMA.³⁸ Chelation of Li^+ at the terminal and penultimate groups reverses this inherent preference of the polymer terminus, favouring a linear *pro-meso* conformation by 5.4 kJ mol^{-1} . If this level of selectivity was retained in the respective transition states, then the corresponding *meso* diad content (*m*) would be 90% and the isotactic triad (*mm*) content of the polymer (assuming Bernoullian statistics) would be approximately 80% at 25°C . The results presented above suggest that the underlying assumption of the literature mechanism, namely that

chelating terminal-penultimate coordination of a Lewis acid favours *pro-meso* conformations, is valid – at least in the present system.

The origin of propagation catalysis

Given that these calculations have demonstrated a binding affinity preference for selective *pro-meso* coordination of Li^+ to the polymer terminus, the poor level of isotactic selectivity found experimentally may initially seem surprising. However, the experimentally observed propagation catalysis indicates that the Li^+ is influencing not only the conformer energies of the polymer terminus but also its reactivity. Thus, it is necessary to consider if a thermodynamically less favourable Li^+ polymer or monomer complex is actually more reactive towards propagation and thus undermining the expected stereocontrol of the terminal-penultimate chelate complex. To investigate the position of Li^+ during monomer addition, the propagation barriers for the terminal-penultimate complex (scenario 2, Scheme 1), terminal-monomer complex (scenario 3, Scheme 1) and the monomer complex (scenario 4, Scheme 1) were calculated. Unfortunately, due to the size of these transition structures no explicit solvating monomer units were included in these calculations, with the exception of the monomer complexation pathway, where 1 solvating monomer unit was used to ensure all pathways had a consistent Li^+ coordination number (of 2).

The calculated kinetics and thermodynamics of these reactions are illustrated in Fig. 7. It should be noted that all energies in this diagram are calculated on the same absolute scale and are directly comparable. It is clear that, while the terminal-penultimate complex is the most stable, this stabilization deactivates it toward propagation to such an extent that it is kinetically disfavoured overall. At the same time, coordination to the Li^+ in the terminal-monomer and complexed-monomer pathways activates the propagation reaction. In the case of the terminal-monomer pathway, this activation is so significant that its propagation becomes the dominant pathway overall,

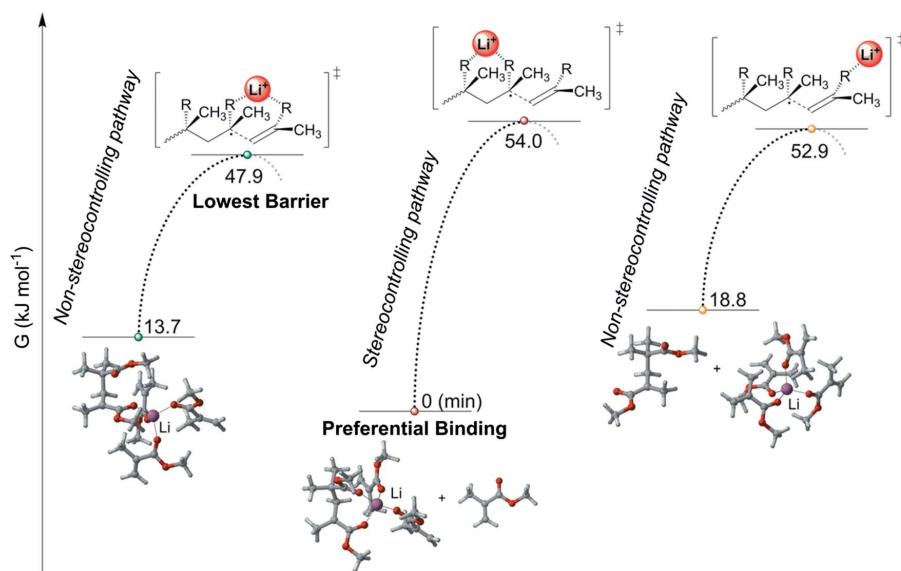


Fig. 7 Relative free energies (kJ mol^{-1}) of four coordinate Li^+ complexed polymer terminus and monomer with estimates of the propagation barriers based on two coordinate Li^+ calculations.

despite the relatively high energy of the precursor complex. This terminal monomer complex is non-stereoccontrolling, as it does not directly influence the relative orientation of the terminal and penultimate ester groups. Hence the kinetic favourability of this pathway explains the lack of stereocontrol in this system.

While it is clear that simultaneous coordination of Li^+ to the terminal and monomer chains catalyses propagation, the origin of this catalysis is likely a combination of multiple factors. Li^+ coordination would not only alter underlying polar effects, but our preceding calculations indicate a modest effect on radical stability as well. Additionally, the electrostatic catalysis reported by Clarke, which is based on odd electron interactions and determined by C and Li^+ proximity, could also contribute to the observed catalysis. Thus the barriers for the reactions considered above probably reflect different contributions from conjugate polar effects, radical stability, odd-electron electrostatic catalysis, chelation and binding geometries. The most successful Lewis acids employed to date, the rare earth metal triflates, are known for their large ionic radii and high coordination numbers, properties that would probably favour a multiple chelation mechanism.

Conclusions

In the present work, we have accurately quantified the rate-enhancing effect of LiNTf_2 on the free radical polymerization of polar monomer (MMA) by PLP. Significant increases in the propagation rate coefficient, k_p , were observed across varying LiNTf_2 initial concentrations. In addition, we determined that LiNTf_2 is essentially ineffective, across the broad range of

concentrations examined, for isotactic control in the radical polymerization of MMA ($mm < 4\%$ under all conditions investigated). Whilst this result is disappointing from the perspective of improving stereocontrol in free-radical polymerization, the propagation catalysis is likely to be useful in its own right to enhance other aspects of structural control. In particular, enhancing propagation relative to termination should improve controlled radical polymerization, at least with non-coordinating control agents, while enhancing propagation relative to transfer could help to suppress chain branching.

We have also examined this system in detail using *ab initio* molecular orbital theory. We find that there is significant thermodynamic preference for Li^+ binding to the terminal-penultimate groups of the growing MMA chain end, compared to the main polymer chain and monomer. Furthermore this terminal-penultimate complexation of Li^+ selectively orientates these groups into the *pro-meso* configuration required for isotactic propagation, with chelated *pro-racemo* arrangements significantly higher in energy. Crucially however this significant thermodynamic preference for the “correct” binding mode for isotactic propagation fails to result in stereocontrol because of its strong thermodynamic preference. That is, this binding mode is anti-catalytic: it stabilizes the growing radical to an extent that its subsequent propagation rate coefficient is significantly reduced. Instead, propagation predominantly occurs *via* (pseudo)cyclization of a Li^+ bridged terminal-monomer complex. As this mode does not simultaneously bind the terminal and penultimate side-chains, no significant stereocontrol is anticipated. While this binding mode is less thermodynamically favoured than terminal-penultimate

complexation, it activates the monomer toward propagation to such an extent that the overall propagation step is actually catalyzed relative to the other binding modes. On the basis of this work we suggest that strategies for effective stereocontrol need to be re-considered and reagents that simultaneously active monomer while binding to the terminal and penultimate groups offer more promise.

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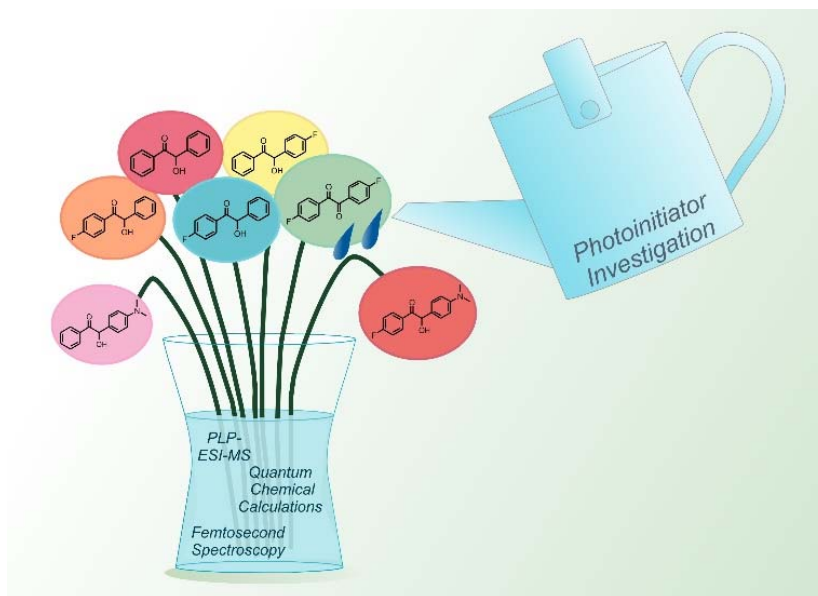
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4.3 Publication 4

Towards a Quantitative Description of Radical Photoinitiator Structure-Reactivity Correlations

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This manuscript is a peer-reviewed regular original research article that was published in *Macromolecules*. The computational results that are used to quantitatively determine the reactivity of the radical fragments are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.

Toward a Quantitative Description of Radical Photoinitiator Structure–Reactivity Correlations

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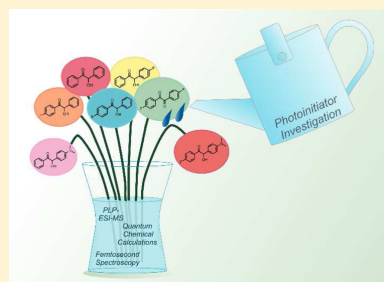
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Supporting Information

ABSTRACT: The fundamental influence of the structure and substitution of radical photoinitiators was investigated via a trifold combination of pulsed-laser polymerization with subsequent electrospray-ionization mass spectrometry (PLP-ESI-MS), femtosecond transient absorption (fs-TA) spectroscopy, and quantum chemistry. For the first time, a library of benzoin-derived photoinitiators with varied substitution patterns was synthesized. In the PLP-ESI-MS study, different photoinitiators were compared pairwise in so-called cocktail experiments, enabling the direct comparison of their initiation efficiency. In the fs-TA experiments, the transient response was observed after UV excitation in the visible spectral region, allowing for a description of excited state dynamics, which was analyzed with the aid of TD-DFT calculations. *Ab initio* calculations were undertaken to determine the reactivity of the radical fragments generated from these photoinitiators and to quantify the influence of various substituents on the rate of addition to monomer. In summary, the influence of the substituent on the initiation efficiency, intersystem crossing (ISC) behavior, excited state dynamics, and the extinction coefficients were analyzed. Hence, relaxation pathways and reaction mechanisms were optimized to explain disparate initiation efficiencies of a wide range of newly designed photoinitiators with varying substitution patterns. The strongly divergent absorptivities of the different photoinitiators and their corresponding initiation efficiencies underline that the absorptivity of a molecule is by no means an unequivocal measure for its reactivity when excited at a specific wavelength. In fact, the most efficient initiators are governed by one $n\pi^*$ singlet state with a very low extinction coefficient at the excitation wavelength and one or two triplet states with $n\pi^*$ character.



INTRODUCTION

Radical photoinitiators play a fundamental role in key polymer applications in academia as well as in industrial research, spanning from coatings, adhesives, varnishes, to dental and cosmetic applications.^{1,2} Thus, the initiation process of the photoinduced polymerization reaction is of crucial importance for the chemical nature of the final product as well as for the rate at which the polymerization is initiated. Although light usually plays a role solely in the very first step of a polymerization, a closer look into the fate of an initiator molecule upon irradiation gives valuable information on how and with which propensity an initiating fragment is incorporated into a polymer chain, i.e., how it is actually able to initiate a polymerization.³ A tremendous number of different photoinitiator systems for light-induced free radical polymer-

ization (FRP) have been reported over the past decades. However, to the best of our knowledge, no fundamental studies addressing the specific structure–reactivity correlation of a photoinitiator have been reported to date. Thus, the design of new photoinitiators has been based on trial and error experimentation. The differentiation into type I (radical formation after α -cleavage of the excited molecule) and type II photoinitiators (radical formation after H-abstraction from a second molecule) categorizes the radical formation pathway. For type I photoinitiators, such as acetophenones,^{3,4} hydroxyalkyl phenones,^{5,6} acylgermanes,^{7,8} acylphosphines,⁹ or benzoin^{3,10} and its derivatives, radical formation is based on a

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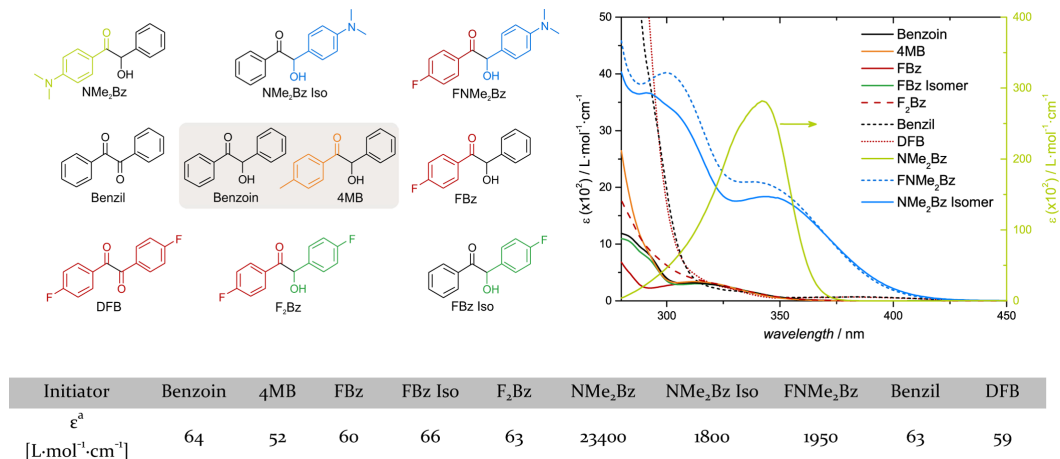
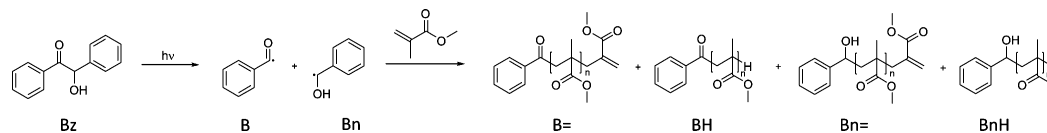


Figure 1. Overview of the analyzed photoinitiators with varied substitution (left side) and their corresponding extinction coefficients in the UV–vis region (right side). For clarity reasons the axis for the extinction coefficient of the photoinitiator NMe₂Bz is situated on the right side. Bottom: table with the extinction coefficients for the analyzed photoinitiators at 351 nm. ^aAt 351 nm excitation wavelength.

unimolecular process. They usually exhibit an ultrafast intersystem crossing (ISC) upon irradiation with UV light from a singlet to a triplet state and subsequently undergo α -cleavage, forming two radical fragments, at least one of which is capable of initiating a polymerization reaction. The performance of photoinitiators strongly depends on the employed system and the targeted product properties. The important factors in their efficiency are their absorption behavior, their radical cleavage, and the reactivity of the formed radicals. Thus, the comparison of photoinitiators is possible in manifold ways, for instance based on their UV–vis absorbance,^{11–13} their dissociation and initiation quantum yield,^{14,15} their polymerization rate,^{11–13,16,17} or their final monomer conversion in particular applications. Therefore, a series of techniques have been employed in order to evaluate the photochemical properties of photoinitiator systems, such as the steady-state photolysis,^{12,13} fluorescence probe technique,¹⁴ IR spectroscopic evaluation in real time,^{11–13,16} or photodifferential scanning calorimetry (photo-DSC).¹⁸ A focus not only on the photochemical behavior of photoinitiators but also on the mechanistic aspects of radical formation has been provided by time-resolved laser flash spectroscopy with detection via UV–vis, IR, and EPR for the investigation of the photochemistry and photophysics of a series of photoinitiators, carried out by Turro and co-workers.⁵ The initiating species can thereby be pursued by EPR spectrometry,^{11–13} and possible side products can be detected by photochemically induced dynamic nuclear polarization (CIDNP).⁷ As pointed out in our previous studies^{3,19} electrospray-ionization mass spectrometry coupled with pulsed-laser polymerization (PLP-ESI-MS) combined with femtosecond pump–probe spectroscopy serves as a powerful tool for quantitative photoinitiator comparison. In this way, specific photoinitiator fragments can be compared in their initiation ability, resulting in so-called initiation efficiency ratios that can be determined for different photoinitiator couples, for instance, for benzoin and 2-methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP), two widely used photoinitiators, or benzoin and 4-methylbenzoin (4MB).³

Typically, chemists—without having the background knowledge about photoinitiation processes—tend to refer solely to the absorptivity of a photoreactive molecule at a certain wavelength in order to predict its reactivity and/or efficiency. In simple terms, a molecule with a high extinction coefficient absorbs more photons than a molecule with a lower extinction coefficient. Consequently, the molecule with the higher extinction coefficient should be excited with a higher probability and, for instance, perform a bond cleavage at higher yield compared to molecules with lower extinction coefficients. Therefore, a frequent conclusion is that a good photoinitiator is characterized by a high absorptivity at the employed wavelength. However, as we show in our study, this approach is at best questionable. The main reasons are that the absorption of a photon can entail a multitude of different processes, whereof the bond cleavage is only one of several possible pathways. After the absorption of a photon the photoinitiator molecule is promoted into an electronically excited state. From this state the molecule can perform a series of deactivation processes that can be chemical in nature or involve energy loss via radiative (luminescence) or nonradiative pathways (internal conversion, IC, and ISC). Hence, a competition among several processes exists. Finally, the reactivity of the photoinitiator radical itself is still of high importance. A multitude of formed radicals cannot be efficient if they are not sufficiently reactive to add to a monomer double bond. Thus, for the comparison of photoinitiators it is of high importance to keep in mind that disparate initiator performances can be due to different rates of radical production as well as different radical reactivities.^{3,20} In the present study a route toward a quantitative analysis is suggested when searching for efficient photoinitiators. Aiming at an instruction for a “tailor-made” photoinitiator fulfilling specific requirements and demands, the influence of substitution is investigated in the light of the Hammett relation.²¹ It will be shown that this aspect requires detailed knowledge of the nature of the molecules’ electronic states. On the basis of the commonly employed photoinitiator benzoin, we synthesized a library of

Scheme 1. Pathway of Radical Formation and the Main Disproportionation Products for Both Radical Fragments Using the Example of Benzoin (Bz) as a Typical Photoinitiator^a



^aThe combination products are omitted for clarity reasons.

benzoin-like photoinitiators with varied substitution patterns. The photoinitiators of the library were, among others, chosen due to their red-shift in the absorption behavior compared to benzoin. As will be demonstrated, a stronger red-shift does not necessarily result in a better initiation efficiency in comparison to benzoin. Indeed, the opposite is often the case. For a quantitative comparison of the selected photoinitiators, pulsed-laser polymerization combined with electrospray-ionization mass spectrometry (PLP-ESI-MS) served as the comparative tool, investigating two photoinitiators in a so-called cocktail experiment. Additionally, femtosecond-transient absorption (fs-TA) experiments were applied to monitor the transient response of the photoinitiators after UV excitation in the visible spectral region, allowing for an elucidation of the excited state dynamics. Quantum chemical calculations were used to determine (i) the location and character of excited electronic states and (ii) the rate coefficients for the addition of photoinitiator radical fragments to methyl methacrylate (MMA). Finally, results from the three different viewpoints are summarized to provide insight into the structure–reactivity relationships of photoinitiators.

RESULTS

Building on our previous investigation of benzoin and its characteristic excitation behavior,⁹ one of the aims of the present work was to enhance its efficiency. To this end, we selected substituents designed to increase the absorptivity in the UV–vis region and thus enhance the initiation efficiency of the benzoin derivative. For the prediction of the absorptivity, Hammett parameters can be taken into account. They enable the gradual increase of the extinction coefficient for the desired excitation wavelength (i.e., at 351 nm), as shown in the further course of this study. Thus, a library of photoinitiators (see Figure 1, left side) was synthesized, based on the molecular structure of benzoin, but with varying substitution patterns. Electron donating groups, such as methyl and dimethylamine, and electron withdrawing groups, such as fluorine, were incorporated into the benzoin structure. Substitutions were made at the aromatic ring: alongside the carbonyl group and alongside the hydroxyl group. In addition to benzoin derivatives, the photoinitiator library contains benzil and its substituted derivative difluorobenzil (DFB). Every substitution in a molecule causes a change in its electronic structure, associated with a change in its reactivity. The actual effect of the substitution on the photoinitiator reactivity and excited state dynamics is analyzed and interpreted.

UV–Vis Spectroscopic Evaluation of Photoinitiators.

As noted in the Introduction, the initiation efficiency of a photoinitiator is frequently linked to its absorptivity. In general, a high extinction coefficient at the employed wavelength can be beneficial for the reactivity of a photoinitiator. However, our experiments show that a strong absorptivity is not mandatory

for an efficient photoinitiator. The photoinitiators of the library depicted in Figure 1 were, among others, chosen due to their red-shifted absorption compared to benzoin. We demonstrate that photoinitiators with a stronger red-shift showed a poorer performance and a lower initiation efficiency in comparison to benzoin. UV–vis spectrometry of the employed photoinitiators shows large differences between the benzoin derivatives. Benzoin itself, a well-known photoinitiator, shows a very low extinction coefficient ($64 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ at 351 nm excitation wavelength) compared to its derivatives, most of which are not known to act as photoinitiators (see Figure 1). The fluorine-substituted benzoin derivatives FBz, FBz Iso, and F₂Bz show similar extinction coefficients (60, 66, and $63 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ at 351 nm). The extinction coefficients of benzil and DFB are comparable to those of FBz and F₂Bz. The dimethylamine-substituted derivative NMe₂Bz Iso and the corresponding fluorine-carrying FNMe₂Bz show a similar absorption behavior, regarding the extinction coefficient ($1812 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ at 351 nm for NMe₂Bz Iso and $1950 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ for FNMe₂Bz) as well as the absorption pattern. The dimethylamine-substituted derivative NMe₂Bz shows a particularly increased extinction coefficient ($23400 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ at 351 nm) and a different absorption pattern compared to all other analyzed photoinitiators.

Initiation Efficiencies Seen from PLP-ESI-MS. In the PLP-ESI-MS study, the various photoinitiators were compared pairwise in so-called cocktail experiments, enabling the direct comparison of their initiation efficiency. In a PLP experiment, the laser beam hits the sample containing photoinitiators in various ratios and monomer. Excitation of the photoinitiator leads to the generation of radicals that can initiate a free radical polymerization (FRP) of the monomer. The termination processes of an FRP are disproportionation and combination, as illustrated in Scheme 1. The nature of the monomer determines the ratio of disproportionation to combination products. In the case of methacrylates, the disproportionation products are superior in number; however, combination products can still be found. Since the occurrence of two initiator fragments that act as chain ends provides no information on which fragment initiated the propagation, a mass spectrometric analysis of combination products gives no insight into the initiation process. The information on which fragment of the employed photoinitiator served as the initiating radical, i.e., how the propagation of a polymer chain was initiated, is retained in the disproportionation products. Additionally, when at least two photoinitiators are employed, the disproportionation products provide information on which specific radical fragment performs better. In a mass spectrum, disproportionation peaks appear in pairs with a mass difference of 2 amu. In this study the disproportionation peaks are labeled “X=” or “XH”—where “X” defines the chemical nature of the α -position of the polymer chain, i.e., the fragment that initiated

the propagation (for instance B, FB, or MB)—while “=” and “H” imply the nature of the ω -end of the chain, depending on the role of the end group in the H-abstraction during the disproportionation process. The quantitative comparison of the initiation efficiency of several photoinitiators toward MMA in PLP was carried out employing a method evaluating the peak heights Δh of the polymer signals in each repeating unit (illustrated in Figure 2). The two disproportionation

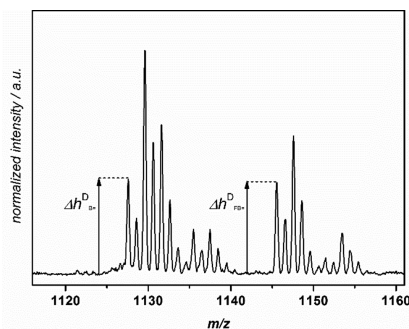


Figure 2. ESI-MS spectrum of pMMA initiated by a mixture of benzoin/FBz in the ratio 1/1, showing the disproportionation peaks B= and FB=. The peak heights $\Delta h^D_{B=}$ and $\Delta h^D_{FB=}$, employed for the determination of the initiation efficiencies, are exemplarily shown.

structures—bearing a double bond or no double bond at the chain end (for instance, B= or BH)—form a peak cluster (see Figure 2). The first peak of such a cluster shows no isobaric overlap with the other product peaks and is thus selected for the comparison. As already described in our earlier publications, the relative peak heights are employed for the determination of a mole fraction $F^X(i)$ of a disproportionation product with the end group X, originating from the initiating fragment.^{3,10,19,22–24} Thus, the relative number of macromolecular chains initiated by the aforementioned fragment X is directly correlated with $F^X(i)$. If the assumption is valid that the propagation of the monomer radical is not affected by the initiating fragment (at least not for $DP_n > 2$), the end group X is equally distributed over all chain lengths. The $F^X(i)$ values for a certain fragment X can be plotted versus the degree of polymerization, DP_n (refer to Figure S1), in order to illustrate the distribution of X over all chains detected in the ESI-MS. A chain-length-independent ionization process can be assumed if the aforementioned plot exhibits a constant gradient close to zero (as seen in Figure S1). In this case the polymer chain length has no influence on its ionization ability. However, in order to compensate a potentially mass-biased ESI process, the mass-bias-free ratio $G_{m/z,0}$ of two disproportionation products is obtained, employing an established method described in our earlier mass spectrometric studies.^{3,10,19,22,23} The approach utilized here is equivalent to our previous studies, for instance in the case of the quantitative comparison of MMMP, benzoin, and 4MB³ or the mesitoyl and benzoyl fragment.¹⁰ For the quantitative comparison of the initiation efficiency of photoinitiators, PLP experiments with different molar ratios of the respective species have to be carried out. Subsequently, $G_{m/z,0}$ of each repeating unit is plotted against the varied molar photoinitiator ratios in the initial polymerization mixture, exhibiting a linear trend (see Figure S2). The ratio at which

$G_{m/z,0} = 1$ is the initiator ratio that is necessary to achieve an equal initiation ability of the compared fragments and that is consequently the quantitative initiation efficiency ratio between these fragments. The resulting initiator efficiency ratios are provided in Table 1 alongside the same values normalized against the extinction coefficients at 351 nm, and the results are discussed below.

Table 1. Overview of the Initiators Compared via PLP-ESI-MS, Their Corresponding Initiation Efficiency Ratios, and the Initiation Efficiency Ratios Normalized with Respect to the Extinction Coefficients at 351 nm

Compared fragments (initiators)		Initiation efficiencies PLP-ESI-MS	Initiation efficiencies normalized to ϵ^b
B (benzoin)	MB (4MB)	1:0.86 ^c	1:1.06
B (benzoin)	FB (FBz)	1:0.75	1:0.80
MB (4MB)	B (FBz Iso)	1:2.44	1:2.92
FB (FBz)	B (FBz Iso)	1:1.10	1:1.00
B (benzoin)	FB (F ₂ Bz)	1:1.09	1:1.11
BNMe ₂ (NMe ₂ Bz)	B (benzoin)	n.d. ^a	
B (NMe ₂ Bz Iso)	MB (4MB)	n.d. ^a	
B (benzoin)	FB (FNMe ₂ Bz)	n.d. ^a	
B (benzil)	FB (DFB)	1:1.67	1:1.78

^aNot determined due to substantial polymer yield differences of the compared photoinitiators. ^bAt 351 nm. ^cDetermined in a previous study.³

Femtosecond Pump-Probe Spectroscopy. In order to gain deeper insight into the relevant processes within the excited states of a photoinitiator, pump-probe experiments were performed. Transient absorption (TA) profiles of the photoinitiators shown in Figure 1 were recorded using MIB as the solvent that is structurally similar to the monomer MMA. All initiators were excited at 351 nm, the same wavelength as employed in the PLP experiments. The photoinitiator is excited into a specific electronic state by the pump pulse and the evolution of the excited states' population of the samples was probed at several wavelengths in the range of 500–600 nm. Because of the low extinction coefficients for some of the initiators and the resulting low amplitudes (<1 mOD) under excitation at 351 nm, no transient absorption spectra were recorded with a white-light continuum.

In the further course of this study, the results of the pump-probe experiments are presented in separated groups consisting of structurally similar photoinitiators. The transients of all samples probed at 500 nm are shown in Figures 3–5 and discussed below. Some of the photoinitiators possess a manifold of higher singlet and triplet states leading to a superposition of different processes after UV excitation, whereby entanglement of the dynamics to specific electronic states is somewhat difficult. As in our previous study,¹⁹ we found out that a useful comparison was nevertheless possible by probing at 500 nm, where the number of superimposed excited states seems to be at a minimum. The results for further probe wavelengths can be found in the Supporting Information. All pump-probe experiments were evaluated by fitting with triexponential functions in order to obtain time constants τ_i and their related amplitudes A_i (see Tables S2–S4).¹⁹ Furthermore, it is important to note that the obtained transients for the different photoinitiators vary remarkably in their behavior on a short time scale. Usually, the time constant

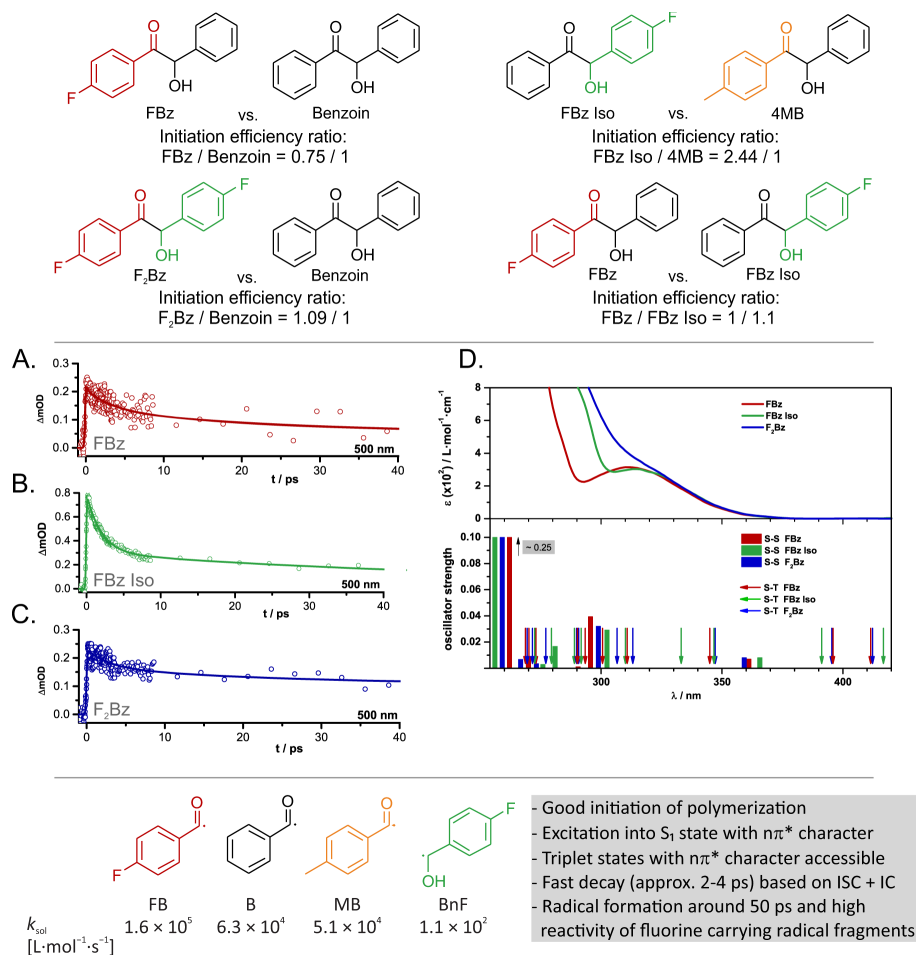


Figure 3. Combined analytical results for the investigation of FBz, FBz Iso, and F₂Bz. Upper part: initiation efficiency ratios of FBz vs benzoin, FBz Iso vs 4MB, F₂Bz vs benzoin, and FBz vs FBz Iso determined by PLP-ESI-MS. Middle part: transients of FBz (A), FBz Iso (B), and F₂Bz (C) from femtosecond pump-probe experiments with probe pulses at 500 nm. UV-vis extinction and results from TD-DFT calculations with electronic states and transitions (D). Bottom part: radical fragments of FBz, FBz Iso, F₂Bz, benzoin, and 4MB and their corresponding rate coefficients for the addition to MMA, k_{sol} .

τ_1 represents a combination of IC and ISC. The time constant τ_2 reflects different triplet dynamics including radical formation, depending on the present relative position and number of states as well as their characters. At this state of analysis, a more detailed assignment is not possible, yet also not necessary for the interpretation within the scope of the current work; this also includes τ_3 .

Initiation Efficiencies Seen from Theoretical Calculations. In order to assess the transient data and gain a better understanding of the dynamical processes taking place, it is necessary to have a general idea of the electronic state properties of all investigated photoinitiators. Since photoinitiators of type I are evaluated in this study, radical formation obviously arises from triplet states, and therefore the preceding step of relaxation via ISC from an excited singlet state is the

initial and determining process for efficient initiation. In this context it can be helpful to consider the magnitude of the energy gap between originating singlet state and underlying triplet states. As is already known from earlier studies of benzoin and 4MB¹⁹ and predicted by the El-Sayed selection rules,²⁵ the character of singlet states and maybe also of the triplet states is important in determining the efficiency of a photoinitiator. Therefore, a closer look into the involved orbitals is essential and useful. Another important factor that influences photoinitiator efficiency is the reactivity of the radical fragments generated from bond scission. If these radical fragments are not sufficiently reactive, then the photoinitiator will be unable to effectively initiate FRP. Photoinduced homolysis of benzoin and its derivatives produces two characteristically different radical fragments that have quite

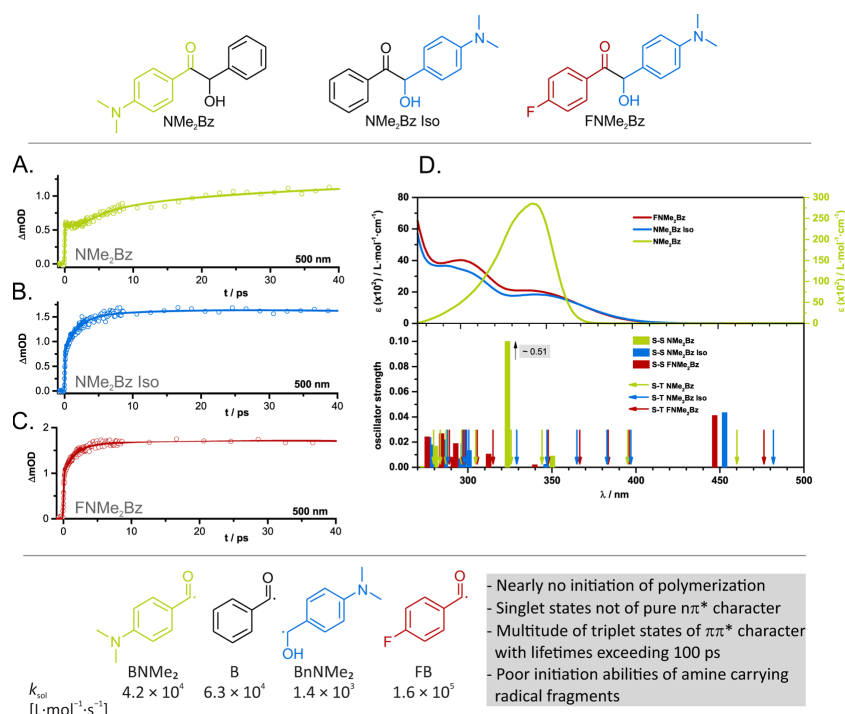


Figure 4. Combined analytical results for the investigation of NMe₂Bz, NMe₂Bz Iso, and FNMe₂Bz. Transients of NMe₂Bz (A), NMe₂Bz Iso (B), and FNMe₂Bz (C) from femtosecond pump-probe experiments with probe pulses at 500 nm. UV-vis extinction and results from TD-DFT calculations with electronic states and transitions (D). Bottom part: radical fragments of NMe₂Bz, NMe₂Bz Iso, and FNMe₂Bz and their corresponding rate coefficients for the addition to MMA.

distinct reactivities. Acyl radicals, like most other sp^2 -type radicals, are unstable and highly reactive species. Because of their electronic structure, acyl radicals are not as effectively stabilized by adjacent substituents as sp^3 -type radicals. Benzoin-derived acyl radicals are relatively localized, and so varying the para substituent of the adjacent phenyl would alter their reactivity mainly through inductive effects. In contrast, hydroxybenzyl radicals are significantly more stable and much less reactive sp^3 -type radicals. These radicals are stabilized by conjugative interactions with the adjacent phenyl and hydroxyl groups and are thus significantly less reactive. The reactivity of these radicals should also be more sensitive to variations in the para substituent, as this substituent forms part of the aromatic π system that stabilizes the radical (mesomerically).

To assess the reactivity of the initiator-derived radicals toward MMA, rate coefficients were calculated using high-level *ab initio* molecular orbital theory calculations (Table 2). For the radical fragments investigated in this study, the following order of reactivity for addition to MMA was obtained: FB > B > MB > BNMe₂ >> Bn > BnF. Interestingly, incorporating an electron-donating para substituent (NMe₂) slightly lowers the reactivity of acyl type radicals to monomer while it significantly increases the reactivity of hydroxybenzyl radicals. Likewise, incorporating an electron-withdrawing para substituent (F) increases the reactivity of acyl radicals, but it significantly decreases the reactivity of hydroxybenzyl radicals. If it is assumed that polar effects favor the addition of radicals

with well-defined electrophilic or nucleophilic character, these divergent substituent effects can be rationalized by considering the polar characteristics of the corresponding radical species. The hydroxybenzyl radical is relatively nucleophilic, and incorporating an electron-donating substituent in the para position will further increase this nucleophilic character. In contrast, acyl radicals, because of their sp^2 structure, are very electrophilic, and incorporating an electron-withdrawing para substituent will further increase this electrophilic character through inductive effects. As anticipated, a greater effect is observed moving from R = F to R = NMe₂ in hydroxybenzyl-type radicals (factor of 10 increase in k_{add}) compared with acyl systems (factor of 5 decrease in k_{add}). For further details refer to the Supporting Information.

DISCUSSION

Analysis of the Photoinitiators. In the following, a detailed discussion of the behavior of the photoinitiators is provided. The initiators are simultaneously examined from the three previously described perspectives: via PLP-ESI-MS, femtosecond spectroscopy, and theoretical calculations.

FBz, FBz Iso, and F₂Bz. Halogen substituents in organic compounds generally exert inductive (−I) as well as mesomeric effects (+M), based on their electronegativity and free electrons. This dual effect makes them an interesting group of substituents for photoinitiators. Fluorine, as the most electronegative element, takes on a special position. Three

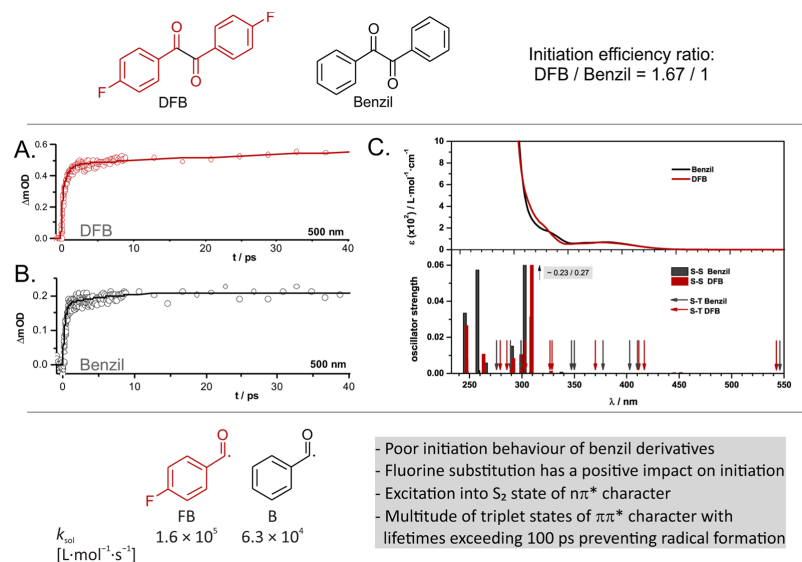


Figure 5. Combined analytical results for the investigation of DFB and benzil. Upper part: initiation efficiency ratios of DFB and benzil determined by PLP-ESI-MS. Middle part: transients of DFB (A) and benzil (B) from femtosecond pump-probe experiments with probe pulses at 500 nm. UV-vis extinction and results from TD-DFT calculations with electronic states and transitions (C). Bottom part: radical fragments of DFB and benzil and their corresponding rate coefficients for the addition to MMA.

Table 2. Theoretically Calculated Barriers ($\text{kJ}\cdot\text{mol}^{-1}$) and Rate Coefficients ($\times 10^4 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$) for the Addition of Photoinitiator Radical Fragments to MMA, in Bulk at -5°C^a

Radical fragment	$\Delta G_{\text{gas}}^\ddagger$	k_{gas}	$\Delta G_{\text{sol}}^\ddagger$	k_{sol}
FB	48.8	7.7	40.3	16
B	51.6	2.2	42.4	6.3
MB	51.8	2.0	42.8	5.1
BNMe ₂	51.7	2.1	43.2	4.2
BnNMe ₂	46.7	20.0	50.8	0.14
Bn	49.9	4.8	55.0	0.02
BnF	49.5	5.6	56.5	0.01

^aNote: rate coefficients have been corrected (by a factor of 2) for reaction path degeneracy.

fluorine-substituted benzoin derivatives—once in para position of the benzoyl group (FBz), once in para position of the hydroxyl-carrying aromatic ring (FBz Iso), and once at both para positions (F₂Bz)—were investigated. FBz was compared to benzoin via PLP-ESI-MS. Thereby, the comparable polymer output of both initiators in PLP is beneficial. In a direct comparison an initiation efficiency ratio of 0.75/1 for the fragments FB/B was determined, related to the fluorine-substituted benzoyl fragment (FB) compared to the benzoyl fragment (B). Thus, FBz shows a lower initiation efficiency than benzoin. FBz Iso, the regioisomer of FBz, was compared to 4MB. A mass spectrometric comparison of FBz Iso to benzoin cannot be performed due to their identical benzoyl fragments. However, since the initiation efficiency ratio between benzoin and 4MB (B/MB = 1/0.86) has been determined in a previous study,³ the para-methyl-substituted 4MB can be employed for the comparative investigation of

benzoyl fragments from various photoinitiator structures. Thus, FBz Iso proved to be an excellent photoinitiator with an initiation efficiency ratio of B/MB = 2.44/1 for the benzoyl fragment (B) derived from FBz Iso compared to the methylbenzoyl (MB) of 4MB. Interestingly, no polymer initiated by the para-fluorine-substituted fragment of FBz Iso (BnF) was found in the ESI-MS (this can be explained by the particularly low rate coefficient of BnF for the addition to MMA). The comparison of FBz to FBz Iso resulted in an initiation efficiency ratio of FB/B = 1/1.1, assigning a better initiator performance for FBz Iso. F₂Bz, the benzoin derivative with fluorine substitution at both para positions, showed a higher initiation efficiency compared to benzoin: FB/B = 1.1/1. Thus, fluorine substitution at the noninitiating hydroxy fragment shows a positive impact on the initiation efficiency. However, the fluorine substitution at the initiating benzoyl fragment, next to the noninitiating fragment, additionally enhances the overall initiator performance.

The TAs of FBz, FBz Iso, and F₂Bz attract particular attention due to their very low optical densities and—in contrast to all other investigated photoinitiators in this study—their purely triexponential decay. All corresponding time constants retrieved at a probe wavelength of 500 nm are similar. For τ_1 a decay of 2–4 ps is obtained (see Table S2) and for τ_2 20–50 ps with a third time constant exceeding the experimental maximum delay range of 2 ns. The time constants are in very good agreement with previous work on benzoin and 4MB.¹⁹

TDDFT calculations showed that FBz, FBz Iso, and F₂Bz have an S_1 singlet state around 350 nm with a dominant share of $n\pi^*$ character. For FBz, FBz Iso, and F₂Bz two triplet states are located below the excited singlet state S_1 , as already observed for the efficient photoinitiators benzoin and 4MB:

first, a T_1 triplet state with a prevailing $n\pi^*$ character for FBz, FBz Iso, and F_2Bz and, second, a T_2 triplet state with $\pi\pi^*$ character for FBz, with $\pi\pi^*/n\pi^*$ character for FBz Iso and a mixed $\pi\pi^*/n\pi^*$ character for F_2Bz . Thereby, FBz Iso exhibits a smaller energy gap $S_1 \rightarrow T_2$ compared to FBz and F_2Bz . However, the energy gap $T_2 \rightarrow T_1$ is smaller for FBz and F_2Bz compared to FBz Iso.

A combination of ISC and IC, enabled by the energetic positioning of T_1 and T_2 , presumably contributes to the fast decay in the dynamics of the transients of FBz ($\tau_1 \sim 2.7$ ps), FBz Iso ($\tau_1 \sim 2.0$ ps), and F_2Bz ($\tau_1 \sim 2.7$ ps). Theoretical calculations also confirm an increased reactivity of the FB radical fragment (rate coefficient of $6.3 \times 10^4 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ for the addition to MMA) compared to the B fragment. However, FBz presumably forms less radicals than benzoin. Thus, the positive effect of radical reactivity of FB is compensated.

NMe₂Bz, NMe₂Bz Iso, and FNMe₂Bz. Benzoin derivatives carrying an amine group have been previously reported in the literature.^{26–28} Because of the strongly electron-releasing effect of the dimethylamine group, this substituent was chosen for our study. The strongly elevated extinction coefficients as well as the red-shifted absorption bands compared to benzoin and 4MB raised our expectations for creating highly reactive photoinitiators. However, after the first PLP-ESI-MS experiments we found that our dimethylamine-substituted benzoin derivatives showed very poor polymer yields ($\leq 0.5\%$) compared to benzoin ($\sim 4.5\%$), under identical PLP conditions. In order to improve the polymer yield, FNMe₂Bz was synthesized: While maintaining the amine substitution at the hydroxy-carrying side of the benzoin structure, the para-position of the benzoyl moiety was simultaneously substituted with a fluorine group. However, in contrast to the results for FBz and FBz Iso described above, the fluorine substitution in FNMe₂Bz did not increase the polymer yield. Because of this very low polymer output of the amine-carrying benzoin derivatives, a quantitative comparison of the initiation efficiencies via PLP-ESI-MS could not be performed.

On the other hand, due to the high extinction coefficients of the amine-carrying molecules, their investigation via transient absorption spectroscopy was well-accessible. Upon absorption of UV light at 351 nm NMe₂Bz is excited into the S_1 state with $n\pi^*$ character, whereas NMe₂Bz Iso and FNMe₂Bz are excited into the S_2 state. The S_1 states of the latter can be described by a $\pi\pi^*$ character and are therefore not suitable for photoinitiator purposes. Their S_1 states, however, offer an $n\pi^*$ (FNMe₂Bz) and a mixed character (NMe₂Bz Iso). All three amine-carrying benzoin derivatives possess a multitude of triplet states, offering a $\pi\pi^*$ or a mixed character. The ISC from $n\pi^*$ singlet states into $\pi\pi^*$ triplet states can be easily performed due to the change of the molecular orbital configuration, as predicted by the El-Sayed selection rule.²⁵ However, the multitude of triplet states can lead to an overlay of several processes, explaining the long delay times for the transients, exhibiting the formation of a plateau that is reached after a few picoseconds. Thus, the amine-carrying species show completely different TA traces compared to those of FBz, FBz Iso, and F_2Bz . The strongly differing extinction coefficients of NMe₂Bz compared to NMe₂Bz Iso and FNMe₂Bz are striking. At the same time the calculated transition of the three benzoin derivatives show a corresponding trend. Transitions of FNMe₂Bz and NMe₂Bz Iso are comparable, whereas those of NMe₂Bz differ. At the same time NMe₂Bz Iso and FNMe₂Bz exhibit similar transients. This similar trend for NMe₂Bz Iso and FNMe₂Bz can presumably be

explained by the identical positioning of the dimethylamine substituent. An additional factor that could explain the poor polymerization ability of the amine-carrying photoinitiators are the theoretically calculated rate coefficients of the addition of the radical fragments to MMA. The dimethylamine para-substituted benzoyl fragment (BNMe₂, $4.2 \times 10^4 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$) shows a 33% lower rate coefficient compared to the benzoyl fragment (B, $6.3 \times 10^4 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$). However, the fluorine-substituted benzoyl fragment (FB, $1.6 \times 10^5 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$) shows a considerably higher rate coefficient than the benzoyl fragment. Yet, the polymer yields of FNMe₂Bz and NMe₂Bz are similar. Thus, we assume that the numerous triplet states of the dimethylamine-substituted benzoin derivatives—and their overlay—are the main cause for the very low polymer yield, preventing the excited molecules from performing radical scission. Thus, the radicals that can initiate a polymerization cannot be formed in a sufficient number.

DFB and Benzil. The positive influence of fluorine substitution, as observed for FBz Iso and F_2Bz , was further investigated for the photoinitiator system of benzil. Since benzil is known to be a poor photoinitiator for low irradiation energies, the influence of fluorine substitution is of particular interest. The direct comparison of para-substituted difluorobenzil (DFB) with benzil showed indeed a clearly higher initiation efficiency for DFB. An initiation efficiency ratio of 1.67/1 for the initiator fragments FB/B of DFB and benzil was determined via PLP-ESI-MS. In their transients, both benzil and DFB show low absorptivities for all probe wavelengths. Thereby, for different probe wavelengths, a shift in the development of the TA can be observed. In particular, the absorption at 500 nm probe (see Figure 5) results in a positive increase of some hundreds of femtoseconds for DFB whereas for benzil the signal rises much slower (some picoseconds). This increase is further illustrated by the positive sign of the amplitudes and by the decay on a picosecond time scale for both systems. Femtosecond experiments showed that both DFB and benzil are excited into the S_2 singlet state upon irradiation with UV light at 350 nm.

The transition into the first singlet state could comprise a dark state possessing a particularly low oscillator strength. Singlet singlet transitions ($S \rightarrow S$) via conical intersection—as is the case for mesitol¹⁹—could be possible. The required singlet states S_1 and S_2 of benzil and DFB both have $n\pi^*$ character. Below the S_1 state six triplet states can be found. Thereby, only T_1 and T_4 exhibit an $n\pi^*$ character, whereas T_1 is presumably not accessible. The remaining triplet states, offering $\pi\pi^*$ or mixed characters, are unsuitable for radical formation. Thus, the small amount of formed radicals could cause the poor initiation ability of benzil derivatives in general. The higher rate coefficient for addition to MMA for the fragment FB compared to B explains the better initiation efficiency of DFB compared to benzil. Both DFB and benzil form a small amount of radicals. However, the higher reactivity of fluorine-substituted benzoyl radicals promotes the initiation efficiency of DFB.

In summary, seen from the PLP-ESI-MS experiments, the substitution with electron-withdrawing groups has a negative influence on the initiation efficiency of a benzoin-like photoinitiator. Regardless of its position in the aromatic system—alongside the carbonyl group (NMe₂Bz) or hydroxy group (NMe₂Bz Iso)—the dimethylamine-substituted derivatives show lower initiation efficiencies compared to benzoin. Additionally, the dimethylamine substituent has a deteriorating effect on fluorine-substituted benzoin derivatives, as seen for

FNMe₂Bz. For FBz, the benzoin derivative with fluorine substitution on the aromatic system alongside the carbonyl group shows a slightly negative influence on the initiation efficiency. However, for its regioisomer FBz Iso, the initiation efficiency is increased compared to FBz and strongly increased compared to 4MB. For F₂Bz the initiation efficiency is increased compared to benzoin.

As noted above, for the prediction of the initiation efficiencies of a photoinitiator, Hammett parameters are sometimes taken into account. They enable the gradual increase of the extinction coefficient for the desired excitation wavelength (i.e., at 351 nm), shown above in the discussion of the UV-vis absorption of the photoinitiator library. However, as discussed in the further course of this study, Hammett parameters do not allow for a qualitative, let alone a quantitative prediction of the initiation efficiency. Instead, a set of characteristic properties and structural requirements for an ideal photoinitiator can be derived from our results.

A significant factor for the efficiency of a photoinitiator is the character of its electronic states that are involved during the process of excitation and ISC. Good photoinitiators exhibit only few (≤ 2) triplet transitions located below the excited singlet states. Besides the character of the triplet state,²⁹ further characteristics are crucial for the initiation efficiency of a photoinitiator. A good initiator exhibits an excitation into a singlet state with $n\pi^*$ character and performs a subsequent transition into a triplet state offering an equal character ($n\pi^*$). However, a poor initiator offers a multitude of triplet states below the S₁ state (partly with $\pi\pi^*$ character). A great number of triplet states presumably results in an overlay of different electronic processes that can be traced due to their residual absorption for long delay times (triplet dynamics). Therefore, intense transient absorptions are an indication for a relatively poor initiation behavior of a photoinitiator, caused by its long-term abidance in triplet states prior to the radical fragmentation process. On the basis of our results, we conclude that a good benzoin-like photoinitiator should fulfill the following criteria:

(i) The extinction coefficient should be close to 60 L·mol⁻¹·cm⁻¹. Smaller values may represent dark singlet states that can result in conical overlap, as observed for mesitol.¹⁹ However, higher values are no inevitable sign for a good photoinitiator but can, on the contrary, imply transitions from $n\pi^*$ to $\pi\pi^*$ excited states, having an inappropriate character for radical formation (refer to Figure 4).

(ii) After the excitation into a singlet state a fast ISC process in the time range of 2–4 ps ensures the sufficient formation of photoinitiator species in triplet states.

(iii) As a further selective criterion for a good photoinitiator, we observed a time frame of maximum 100 ps for the formation of radicals which derive from the initiators' triplet state. At this stage, radicals are formed and could initiate a polymerization, yet the selective criteria for a good photoinitiator are not exhausted.

(iv) Radicals can vary immensely in their reactivity toward monomer double bonds, as illustrated by the rate coefficient k_{sol} for the addition of a radical fragment to MMA in Figures 3–5 and Table 2. Thus, a photoinitiator that fulfills all the above criteria, yet generates a high amount of unreactive radicals, will most likely not possess a high initiation efficiency. On the other hand, a photoinitiator that generates highly reactive radical fragments, but in only very low numbers, will presumably not perform with a high initiation efficiency, as observed for the

amine-substituted benzoin NMe₂Bz, NMe₂Bz Iso, and FNMe₂Bz in Figure 4.

CONCLUSIONS

Our study of benzoin-type photoinitiators demonstrates that a set of parameters are required in order to quantify their efficiencies. Among these are low ground state absorption at the excitation wavelength—usually characterized by an $n\pi^*$ singlet state. In agreement with recent results,³ the subsequent ISC should occur on a time scale of 2 ps. Ideally, the resulting triplet state is of $n\pi^*$ character as well, which is in line with previous findings.²⁹ The number of triplet states below the lowest singlet states should not exceed two with at least one of them being of $n\pi^*$ character. The time constant for the α -cleavage should be within 100 ps (typically 25–50 ps). Further, the number of singlet states below the lowest singlet state, so-called dark states (one-photon forbidden states), should be zero since otherwise the internal conversion is too fast with respect to ISC—presumably due to the occurrence of conical intersections. This has been shown previously for mesitol.¹⁹ Finally, using molecules with two highly reactive radical species such as DFB is not beneficial owing to the existence of too many triplet states below the lowest excited singlet state. Note that these rules do not necessarily make those molecules useless in case they do not fulfill all of these requirements perfectly. However, they will certainly lack a considerable amount of conversion efficiency as observed for benzil and difluorobenzil, for instance.

As implied by the preceding conclusions, an *a priori* identification of good photoinitiators is not possible by simply inspecting one of the aforementioned properties. It is the interplay between different characteristics that needs to be addressed. It remains for future investigations to examine this approach for other types of photoinitiators.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b02336.

Results of quantum chemical calculations, evaluation of transient data, amplitude calculations, normalized TA traces, and singlet absorption bands (PDF)

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Notes

The authors declare no competing financial interest.

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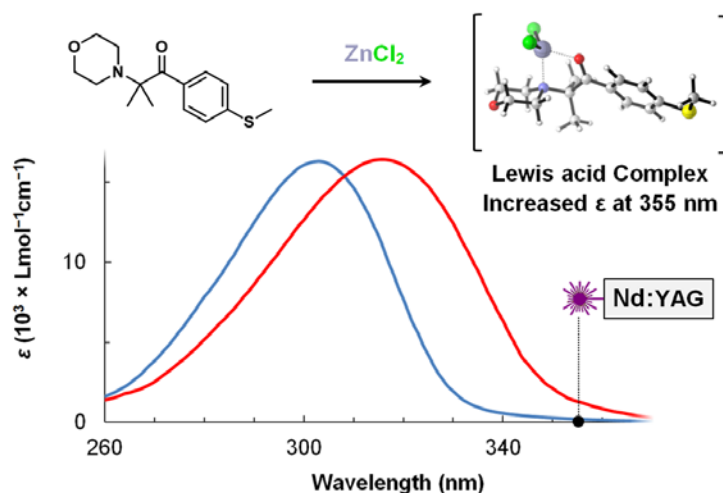
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4.4 Publication 5

The Effects of Lewis Acid Complexation on Type I Radical Photoinitiators and Implications for Pulsed Laser Polymerization

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This manuscript is a peer-reviewed regular original research article that was published in *Polymer Chemistry*. A majority of the computational results presented in this manuscript are my own work. Mr. Adam Mater performed several exploratory calculations on some of the complexes in this study. I obtained the experimental results for this manuscript jointly, with the assistance of Dr. Leesa Smith. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.



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The effects of Lewis acid complexation on type I radical photoinitiators and implications for pulsed laser polymerization†

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In the present work, we examine the effects of zinc chloride (ZnCl_2) and aluminium chloride (AlCl_3) complexation on the photochemistry of two well-known type I photoinitiators, methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA). High-level *ab initio* calculations and experimental results demonstrate that Lewis acid complexation has a significant effect on the individual processes that comprise radical photoinitiation. Theoretical calculations predict that ZnCl_2 coordinates to MMMP and DMPA to form thermodynamically stable bidentate ketone–amine and ketone–ether chelates, respectively. Meanwhile, the AlCl_2^+ cation coordinates to MMMP and DMPA to form a tridentate ether–amine–ketone chelate and a bidentate ketone–ether chelate, respectively. We found that addition of ZnCl_2 and AlCl_3 to solutions containing MMMP significantly increase its molar extinction coefficient (ϵ) between 350–360 nm. In contrast, the complexation of either ZnCl_2 or AlCl_3 to DMPA slightly reduces the value of ϵ in the 350–360 nm range. Time dependent density functional theory (TD-DFT) calculations demonstrate that Lewis acid complexation blue shifts the $n\pi^*$ excitations of both DMPA and MMMP, while concurrently red shifting the $\pi\pi^*$ transitions. Complexation also significantly alters the stability and reactivity of the photoinitiator fragment radicals. Lewis acid complexation localizes and destabilizes acyl radicals, resulting in significantly increased reactivity towards methyl methacrylate (MMA). In contrast, complexation of Lewis acids dramatically reduces the reactivity of the morpholine substituted isopropyl radical and the dimethoxyphenyl radical towards MMA. Alternative complexation at the methyl ester side-chain of MMA has a beneficial effect on the reactivity of all fragments, increasing addition rate coefficients by 2–4 orders of magnitude. We discuss some of the important implications of these findings for pulsed laser polymerization (PLP), and acetophenone photochemistry more generally.

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Introduction

Pulsed laser polymerization (PLP) is an elegant kinetic technique that allows propagation rate coefficients (k_p) to be determined with very high accuracy and precision.^{1–3} In a PLP experiment, consecutive laser pulses are used to generate radicals at regular intervals *via* the photolysis of a photoinitiator. These fragment radicals rapidly initiate polymer chain-growth, which continues until they are terminated by analogous fragments generated from subsequent laser pulses. Some of the growing polymer chains will not be terminated by the immedi-

ately following laser pulse but will continue to propagate until subsequent pulses. This leads to a characteristic multimodal molecular weight distribution (MWD), which can be analysed by size-exclusion chromatography (SEC) to determine k_p in a relatively model-free manner.

While PLP is a reasonably robust method for k_p determination, it requires fairly specific radical fluxes; otherwise the resultant MWD will be devoid of the features necessary for accurate k_p determination.⁴ If the radical flux generated by each laser pulse is too small, the termination of propagating polymer chains will not be properly controlled by the laser pulses; the so called “*low-termination limit*”. Under low-termination limit conditions, the MWD can contain artefacts caused by irregular (non-laser controlled) termination and erroneous dependencies of k_p on laser pulsing-rate can be observed.⁵ Moreover, MWDs obtained under low-termination limit conditions often have several poorly resolved inflection points that may not be integer multiples of the apparent primary peak; with the true primary peak being obscured. Conversely, if the

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radical flux generated on each laser pulse is too large, then almost all the propagating polymer chains will be terminated after every pulse and the so called “high-termination limit” is reached. Under high-termination limit conditions, formation of the secondary (and any higher order) molecular weight peaks (or ‘overtones’) will be suppressed and a featureless MWD that is composed entirely of the primary peak material will be obtained.

The radical flux in a given PLP experiment will be determined by several factors, including the laser pulse energy, as well as the photoinitiator identity and concentration. However, because of photoinitiator consumption, a broad range of radical concentrations may be sampled in a single experiment.⁶ Thus, obtaining a MWD with PLP characteristics depends on the appropriate selection of total irradiation time, laser power, pulse-rate and the photoinitiator identity as well as its initial concentration. The conditions necessary for PLP are well established for most common monomers, notably: acrylates,^{7,8} methacrylates,^{9–11} styrene¹² and acrylamide.¹³

As illustrated schematically in Fig. 1, acetophenone photoinitiation is itself a highly complex phenomenon that is comprised of various individual processes. First, the photoinitiator absorbs incident light; with a given molar extinction coefficient (ϵ) describing the portion of photons that are absorbed at a particular wavelength. Depending on the wavelength(s) emitted by the light source and the energy of the singlet excited states, excitations to several excited states may occur (for instance S_1 and S_2 in Fig. 1). Internal conversions (IC) can then lead to very rapid de-excitation between excited states of similar energies, without photon emission (with compensating vibrational and rotational excitations). A given singlet excited state (S_1 in Fig. 1) will then undergo an ultra-fast inter-system crossing (ISC) to a triplet state of comparable energy (with an efficiency given by ϕ_{isc}). From a triplet state (T_1 in Fig. 1) the photoinitiator can fragment *via* α -cleavage to form two radical

species (with a rate coefficient k_c and lifetime τ_{T_1}). These radical fragments react with monomer to initiate (radical) polymerization with a particular rate coefficient (k_{add}).

Several competing processes (marked in grey in Fig. 1) can reduce the efficiency of photoinitiation, although most of these side-processes simply reform ground-state photoinitiator. For instance, following the absorption of incident light, fluorescence can lead to de-excitation with a compensating radiative emission. Hence, the efficiency of photoinitiation will partly depend on the relative rates of ISC and fluorescence. Similarly, following an ISC to the triplet manifold, radical generation will be in competition with phosphorescence and de-excitation *via* photoquenching (rate coefficient, k_q). Even after bond scission, the fragment radicals can recouple inside their solvent cage to regenerate the ground state photoinitiator, instead of initiating polymer chain growth.

For a type I photoinitiator, the initiation quantum yield (ϕ_i) will depend on the relative efficiency of initiation compared with these side-processes.¹⁴ Initiation quantum yield can be expressed mathematically as follows:¹⁴

$$\phi_i = \phi_{isc} \left(\frac{k_c}{\frac{1}{\tau_{T_1}} + k_q[M]} \right) \left(\frac{k_{add}[M]}{k_t^0 + k_{add}[M]} \right)$$

where k_t^0 is the sum of pseudo first-order rate coefficients for the decay of the formed radical and $[M]$ is the monomer concentration. Meanwhile, under steady state conditions, initiation quantum yield is related to the overall polymerization rate (R_p) as follows:¹⁴

$$R_p = \frac{k_p[M]}{\sqrt{k_t}} \sqrt{\phi_i I_0 (1 - \exp(-2.3\epsilon l [I]))}$$

where k_t is the termination rate coefficient, I_0 is the energy of the incident light, l is the path-length and $[I]$ is the photoinitiator concentration.

Our interest in photoinitiation was prompted by our attempts to use PLP to quantify the catalytic effects of Lewis acids on propagation kinetics. We recently successfully employed PLP to show that the weak Lewis acid lithium bis(trifluoromethane)sulfonamide ($LiNTf_2$) catalyses the propagation of methyl methacrylate (MMA).¹⁵ Earlier work by Pedron and co-workers also used PLP to explore the effect of lithium triflate ($LiOTf$) on the propagation kinetics of ethoxy methacrylates, noting similar catalytic effects.¹⁶ However, $LiNTf_2$ and $LiOTf$ are relatively weak Lewis acids and our attempts to examine the effects of stronger Lewis acids were hampered by the loss of PLP characteristics, especially at higher flashing rates. This was despite the fact that the same reaction conditions produced excellent PLP characteristics in the absence of these Lewis acids. More generally we note that PLP kinetic studies of Lewis acid-mediated radical polymerization are rare, although encouraging k_p enhancement has been observed in ionic liquids.^{17–23}

While the deterioration of PLP characteristics suggests that Lewis acids may adversely affect radical photoinitiation, the

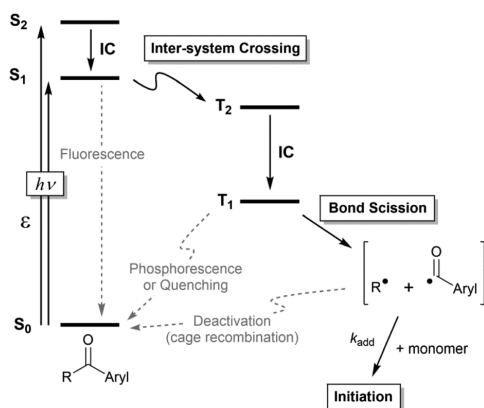


Fig. 1 A Jablonski diagram illustrating the photoinitiation of a type I acetophenone initiator. Note that vibrational relaxation is omitted for clarity.

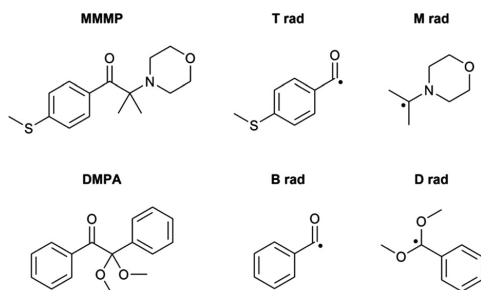


Fig. 2 Chemical structures of MMMP and DMPA and the fragment radicals that result from photolysis.

precise impacts of complexation are poorly understood. Without proper understanding of these effects, it is difficult to determine which photoinitiator/Lewis acid combinations might be particularly susceptible. Given its complexity, properly predicting (or rationalizing) initiator efficiency requires the simultaneous evaluation of multiple factors.²⁴ Assessments to correlate efficiency to a single property, such as ϵ values, will generally lead to erroneous conclusions. An array of different experimental techniques (often employed in tandem) can be used to study photoinitiation, including IR-based techniques, fluorescence probes,²⁵ steady-state photolysis,^{26,27} photodifferential scanning calorimetry,²⁸ EPR-based methods,^{26,27,29} laser flash photolysis^{30,31} and electrospray ionization mass spectrometry.^{24,32,33} While various experimental approaches can be used to study the performance of different photoinitiators, it is likely that the presence of Lewis acids would also affect k_p and k_t . Hence, initiator efficiencies may not be straightforwardly related to conversions, molecular weights or transient radical concentrations.

In this context, we have carried out a combined experimental and theoretical study to assess the impacts of Lewis acid coordination on the individual factors that collectively determine photoinitiator efficiency. In this work, we examine the effects of two important Lewis acids, zinc chloride (ZnCl_2) and aluminium chloride (AlCl_3), on two popular type I acetophenone photoinitiators; methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) (see Fig. 2). We then examine the behaviour of these systems, highlighting the diverse, and at times divergent, effects Lewis acids can have on photolysis and fragment reactivity. The implications of these results for successful PLP in the presence of Lewis acids are then discussed.

Materials

Ethyl acetate (EA) (Emsure, >99.5%) was first dried over anhydrous magnesium sulfate (Emsure, >98%) and then on activated 3 Å molecular sieves (Aldrich). 2-Methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) (Aldrich, 98%) was purified by

recrystallization in ethanol prior to use. 2,2-Dimethoxy-2-phenylacetophenone (DMPA) (Aldrich, 99%) was purified by recrystallization in ethanol/water and dried under vacuum at room temperature. Zinc chloride (Aldrich, >99.995%) and aluminium chloride (Aldrich, >99.99%) were used as received.

Experimental

UV spectra were measured on a Cary-Bio 50 spectrophotometer in quartz cells with 1 cm path length. We verified that neat ethyl acetate (EA) has no significant absorptions in the 260–380 nm range (see Fig. S1 in ESI†). Moreover, we confirmed that in the absence of MMMP and DMPA, solutions of ZnCl_2 and AlCl_3 in EA are similarly transparent in this range (see Fig. S1 ESI†). Thus, we note that the observed changes in UV spectra following Lewis acid addition cannot be attributed to charge transfer absorbance between the Lewis acids and EA solvent, or to trace impurities that may be present in either Lewis acid. Manipulations involving ZnCl_2 and AlCl_3 (and their respective EA solutions) were performed under an N_2 atmosphere using standard dry box techniques. Spectra were taken immediately in sealed quartz cells to prevent contamination from atmospheric moisture that could potentially react with the Lewis acids.

Theoretical methodology

All geometry optimizations were performed using the M06-2X functional,³⁴ in combination with a modified 6-31+G(d,p) basis set. This modified basis set utilizes the standard 6-31+G(d,p) basis set for atoms first and second row atoms,^{35–39} in conjunction with the all electron 6-31G(d) basis set for Zn.⁴⁰ Entropies, thermal corrections and zero-point vibrational energies were scaled by recommend scale factors.⁴¹ Improved single-point energies were calculated using the high-level composite *ab initio* G3(MP2)-RAD method,⁴² in conjunction with the ONIOM approximation^{43,44} for larger systems. The SMD solvent model⁴⁵ was used to correct for implicit solvent effects. The methodology used in this work has been extensively benchmarked, including for radical addition kinetics and bond homolysis.^{46–48} Moreover, in the present work, we benchmarked this methodology against experimentally available Lewis acid/base binding enthalpies and rate coefficients for similar radical addition reactions (see Tables S2 and S3 as well as Fig. S3 and S4 of ESI†).

Adiabatic ionization energies (IE) of the radical fragments and electron affinities (EA) of monomer species were calculated using G3(MP2)-RAD(+); a modified version of G3(MP2)-RAD where single point energy calculations are performed with the 6-31+G(d) basis set instead of 6-31G(d) for better treatment of anionic species. Time dependent density functional theory (TD-DFT) was performed with M06-2X and the modified 6-31+G(d,p) basis set, in conjunction with the SMD solvent model.⁴⁵ Electrostatic potential surfaces (ESPs) are based on

Gasteiger point charges calculated using the UM06-2X/6-31+G (d,p) SCF density. All standard *ab initio* molecular orbital theory, density functional theory (DFT) and time dependent-density functional theory (TD-DFT) calculations were carried out using Gaussian 09⁴⁹ as well as Molpro 2012⁵⁰ and 2015⁵⁰ software packages. A more detailed description of all the computational procedures, conformational searching, benchmarking and a full set of obtained results can be found in the ESI.†

Results and discussion

As overall initiator efficiency is dependent on several different factors, we have utilized a combination of experimental and theoretical techniques to better understand the effects of Lewis acid complexation on each aspect of photoinitiation. Results of this comprehensive investigation are now presented and discussed in turn.

Lewis acid binding modes to MMMP and DMPA

Prior to assessing the impact of AlCl_3 and ZnCl_2 on the photoexcitation behaviour of MMMP and DMPA, the precise coordination structure of all relevant complexes and their stability must be determined. MMMP and DMPA contain multiple Lewis base-donor sites and so can coordinate AlCl_3 and ZnCl_2 in several different binding arrangements, many of which have multiple conformational isomers. We rigorously examined each of these possible binding modes to determine the most energetically favourable complex for each Lewis acid/photo-

initiator combination. In addition to evaluating the mode of complexation, we also determined the thermodynamic selectivity for photoinitiator complexation in the presence of competing solvation of the Lewis acid by MMA monomer. To ensure that the theoretical methodology used could accurately describe Lewis acid/base interactions, we benchmarked it using experimentally obtained binding enthalpies for an array of boron trifluoride (BF_3) complexes with common ligands,⁵¹ including esters, ketones, amines and ethers. Excellent quantitative agreement was noted between theoretically predicted values and reliable calorimetric data; with a mean absolute deviation and maximum deviation of 2.6 and 5.2 kJ mol^{-1} , respectively (see Table S2 and Fig. S3 of ESI†).

As a Lewis base, MMMP possesses 4 potential donor sites: the O atoms of the ketone and ether, the N atom of the amine and the S atom of the thioether. In addition to examining monodentate coordination of AlCl_3 and ZnCl_2 at each of these donor sites, we also exhaustively considered various possible bi- and tri-dentate coordination modes. Meanwhile, DMPA possesses 3 potential ligation sites: a ketone and two methoxy ether moieties. For both AlCl_3 and ZnCl_2 , we investigated monodentate coordination at each donor site and also bidentate ketone-ether coordination. As AlCl_3 has a known tendency to form $[\text{AlCl}_2(\text{ligand})_n][\text{AlCl}_4]$ type complexes in solution,^{52,53} coordination of the $[\text{AlCl}_2]^+$ cation to both photoinitiators was also considered. The geometries of the most thermodynamically favourable Lewis acid/photoinitiator complexes and their relative binding free-energies in MMA solution are given in Fig. 3.

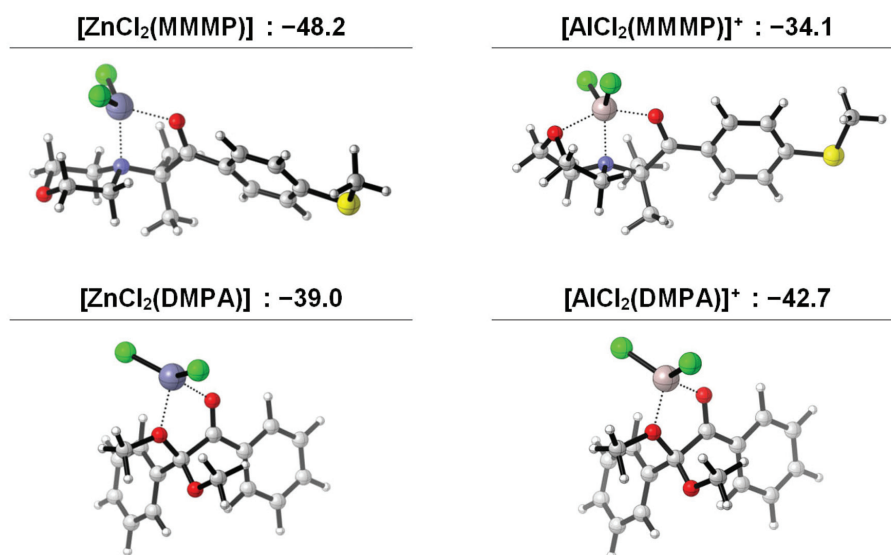


Fig. 3 Predicted coordination structures of the $[\text{ZnCl}_2(\text{MMMP})]$, $[\text{AlCl}_2(\text{MMMP})]^+$, $[\text{ZnCl}_2(\text{DMPA})]$ and $[\text{AlCl}_2(\text{DMPA})]^+$ complexes. Note that an additional solvating MMA ligand was omitted from the $[\text{AlCl}_2(\text{DMPA})]^+$ complex for clarity. The Gibbs free binding energy of each photoinitiator complex, relative to competing solvation by MMA monomer, is indicated in kJ mol^{-1} .

As Fig. 3 illustrates, the most favourable mode of ZnCl_2 complexation to MMMP and DMPA is *via* a 5-membered ketone–amine and ketone–ether chelate, respectively. Assuming neutral complex speciation, the bulkier AlCl_3 coordinates to the ether of MMMP in a monodentate arrangement, with complexation at the ketone moiety also reasonably favourable (see Fig. S5 of ESI†). Meanwhile calculations predict that AlCl_3 preferentially coordinates to the ketone of DMPA to form a neutral monodentate ketone complex (see Fig. S5 of ESI†). However, reaction of the neutral $[\text{AlCl}_3(\text{MMMP})]$ and $[\text{AlCl}_3(\text{MMA})]$ complexes to form the $[\text{AlCl}_2(\text{MMMP})][\text{AlCl}_4]$ contact ion-pair was found to be quite energetically feasible ($-11.7 \text{ kJ mol}^{-1}$). Indeed, Levason and co-workers found that many AlCl_3 complexes adopt analogous ion-pair type structures with bidentate diphosphine ligands.⁵⁴ Moreover, even in relatively low polarity solvents, such as tetrahydrofuran (THF), the formation of $[\text{AlCl}_4]^-$ has been detected.⁵² As illustrated in Fig. 3, the cationic $[\text{AlCl}_2(\text{MMMP})]^+$ complex adopts a tridentate ketone–amine–ether chelate, while the $[\text{AlCl}_2(\text{DMPA})]^+$ complex forms a bidentate keto–ether chelate coordination structure.

We should note that the exact conditions used in PLP experiments, in particular the Lewis acid/monomer identity and concentration, may affect the Lewis acid/photoinitiator complex stability. Furthermore, in the case of AlCl_3 , the precise speciation is almost certainly quite complicated (and condition dependent). At high AlCl_3 loadings, significant amounts of Cl^- abstraction and ion-pairing of the resultant species would be anticipated. Under these conditions the complexes shown in Fig. 3 would predominate, due to their high binding selectivity over the comparably solvated monomer complexes. At very low AlCl_3 loadings, the dominate species present would be neutral $[\text{AlCl}_3(\text{MMA})]$, in which case the speciation predicted in Fig. S5† may be observed. We should note that the very low binding selectivity for the neutral $[\text{AlCl}_3(\text{MMMP})]$ complex is inconsistent with the observed changes in the respective UV-Vis spectra (see Fig. 4). Thus, we conclude that under the conditions used in a typical PLP experiment ($>1 \text{ mol\% AlCl}_3$ loading), sufficient AlCl_2^+ is available to form $[\text{AlCl}_2(\text{MMMP})][\text{AlCl}_4]$ and $[\text{AlCl}_2(\text{DMPA})][\text{AlCl}_4]$ type photoinitiator complexes.

Effects of complexation on UV-Vis spectra

The molar extinction coefficient (ϵ) of a given photoinitiator describes the portion of incident light of a particular wavelength that is absorbed by the solution. While photoinitiators must have reasonable ϵ values at the wavelength of the light source to be effective, very large ϵ values are not necessarily indicative of more efficient photoinitiation.²⁴ Nevertheless, UV-Vis spectroscopy can be employed to examine the effect of complexation on the energies of the singlet excited states. The UV-Vis spectra of MMMP from 260–380 nm, in the presence and absence of ZnCl_2 and AlCl_3 are illustrated in Fig. 4. Spectra for the visible region are provided in Fig. S2 of the ESI† and show clear absorption tails for both MMMP/ AlCl_3 and MMMP/ ZnCl_2 .

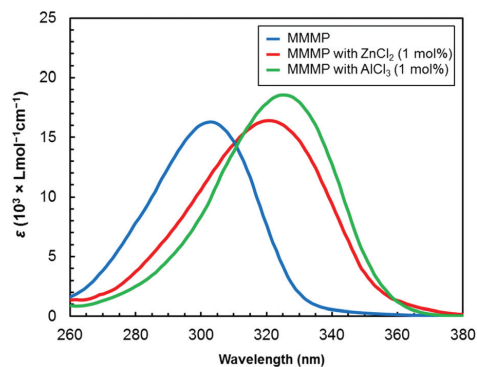


Fig. 4 Molar extinction coefficients (ϵ) for MMMP in the EA, EA with added ZnCl_2 ($[\text{ZnCl}_2]_0/[\text{EA}]_0 = 1\%$) and EA with added AlCl_3 ($[\text{AlCl}_3]_0/[\text{EA}]_0 = 1\%$).

As depicted in Fig. 4, MMMP possesses an intense $\pi\pi^*$ transition at around 305 nm, with an ϵ value of approximately $1.6 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$. As illustrated by Fig. 3, ZnCl_2 and AlCl_3 significantly change the UV spectrum of MMMP; inducing red shifts in its absorbance maximum of 19 and 23 nm, respectively. At 355 nm, the wavelength of a typical PLP experiment, these changes result in an increase in ϵ by around an order of magnitude (see Table S1 of ESI†).

The UV-Vis spectra of DMPA in the presence and absence of ZnCl_2 and AlCl_3 are presented in Fig. 5. Spectra for the visible region are provided in Fig. S2 of the ESI† and show a clear absorption tail for DMPA/ AlCl_3 but not DMPA/ ZnCl_2 . DMPA has a fairly weak but observable mixed $n\pi^*$ transition that occurs at 342 nm ($\epsilon = 2.6 \times 10^2 \text{ L mol}^{-1} \text{ cm}^{-1}$). In addition, an intense $\pi\pi^*$ transition is observed, with a maximum below 260 nm ($\epsilon \sim 7 \times 10^3 \text{ L mol}^{-1} \text{ cm}^{-1}$ at 260 nm). Complexation of ZnCl_2 or AlCl_3 dramatically changes the absorbance profile of

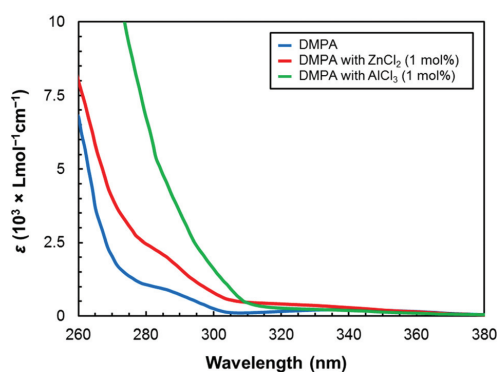


Fig. 5 Molar extinction coefficients (ϵ) for DMPA in the EA, EA with added ZnCl_2 ($[\text{ZnCl}_2]_0/[\text{EA}]_0 = 1\%$) and EA with added AlCl_3 ($[\text{AlCl}_3]_0/[\text{EA}]_0 = 1\%$).

DMPA; particularly in the 260–320 nm range. However, addition of ZnCl_2 or AlCl_3 only slightly affects the ϵ value of DMPA at 355 nm (see Table S1 of ESI†).

Excited-state energetics and dynamics

As prototypical radical photoinitiators, acetophenone derivatives have relatively well understood excitation behaviour. In particular, MMMP and DMPA have had their photophysical and photochemical properties characterized in many pioneering studies over the last few decades.^{55–59} The $^1(\text{n}\pi^*)$, $^3(\pi\pi^*)$, and $^3(\text{n}\pi^*)$ excited states of these species usually intersect in a similar structural region, which leads to short singlet lifetimes, rapid ISC and minimal fluorescence.⁶⁰ Type I photoinitiators rapidly fragment *via* α -cleavage from their $^3(\text{n}\pi^*)$ state, while type II initiators abstract a hydrogen atom from a coinitiating group (usually an alcohol or amine). As the excited states of acetophenone derivatives normally intersect in a similar structural region, time dependent-density functional theory (TD-DFT) calculations were used to investigate the impacts of complexation on photoexcitation behaviour.

The vertical excitations energies to the singlet and triplet states of MMMP as well as the $[\text{ZnCl}_2(\text{MMMP})]$ and $[\text{AlCl}_2(\text{MMMP})]^+$ complexes, are contrasted in Fig. 6. MMMP is a highly efficient photoinitiator and has relatively straightforward and predictable photoexcitation behaviour (see Fig. 6a). MMMP has a weak S_1 excited state of $\text{n}\pi^*$ character that lies below an intense S_2 $\pi\pi^*$ transition. Two essentially degenerate triplet states lie below S_1 , T_1 and T_2 , which have $\pi\pi^*$ and $\text{n}\pi^*$ character, respectively. Following excitation to S_1 , a rapid ISC to the triplet manifold would occur, due to the favourable energetic position and matched character of S_1 and T_1 (such $^1(\text{n}\pi^*)$ to $^3(\pi\pi^*)$ crossings are allowed by the El-Sayed rules⁶¹). The near degeneracy of T_1 and T_2 would then enable crossing between these states and subsequent α -cleavage from the essentially degenerate $\text{n}\pi^*$ T_2 state. Gas-phase DFT calculations were used to estimate the barrier for α -cleavage on the triplet surface.

From the optimized T_1 geometry, α -cleavage of MMMP is predicted to be highly kinetically and thermodynamically favourable; proceeding with a small barrier and favourable reaction energy of 20.3 and $-33.4 \text{ kJ mol}^{-1}$, respectively (see Fig. S6 of ESI†). The calculated excited state and fragmentation behaviour is completely consistent with the short excited singlet and triplet lifetimes of MMMP determined from time resolved laser spectroscopy ($\tau_{\text{S}_1} = 700 \text{ ps}$ and $\tau_{\text{T}_1} = 10 \text{ ns}$ in benzene).⁵⁷

ZnCl_2 complexation to MMMP significantly destabilizes the $^1(\text{n}\pi^*)$ excited state, while concurrently red shifting the $^1(\pi\pi^*)$ excitation (see Fig. 6b). While this red shift leads to a significantly higher ϵ value at *ca.* 355 nm, it is also accompanied by much more complicated photoexcitation behaviour. Aside from the reordering of the S_1 and S_2 states, the lowest energy $^3(\pi\pi^*)$ state (T_1) is almost 1 eV more stable than the $^3(\text{n}\pi^*)$ state (T_2) (at the S_0 geometry). Unsurprisingly, an even more dramatic effect is observed following complexation of the more Lewis acidic AlCl_2^+ cation (see Fig. 6c). The effects of ZnCl_2 and AlCl_2^+ complexation on the excited states of MMMP can be rationalized by considering their underlying character. As an $\text{n}\pi^*$ excitation promotes an electron from a localized non-bonding ketone oxygen orbital to a fairly delocalized aromatic π^* orbital, these excited states would have reduced Lewis basicity at the ketone oxygen atom. Conversely, $\pi\pi^*$ type excitations promote an electron from a π orbital predominantly associated with the aromatic ring to a reasonably delocalized π^* orbital that has some ketone oxygen character. Thus, the $\pi\pi^*$ type excited states have increased Lewis basicity at the ketone oxygen atom. To illustrate the differences in the basicities of each type of excited state, the electrostatic potential (ESP) surfaces of the T_1 ($\pi\pi^*$) and T_2 ($\text{n}\pi^*$) states of MMMP are provided in Fig. 7. The natural atomic charges (from a Natural Bond Orbital analysis) of the respective ketone and ether oxygen atoms are also indicated.

As shown in Fig. 7, the $^3(\pi\pi^*)$ state of MMMP is significantly more basic on the ketone oxygen atom compared to the $^3(\text{n}\pi^*)$ state. This difference in basicity explains the stabilizing/

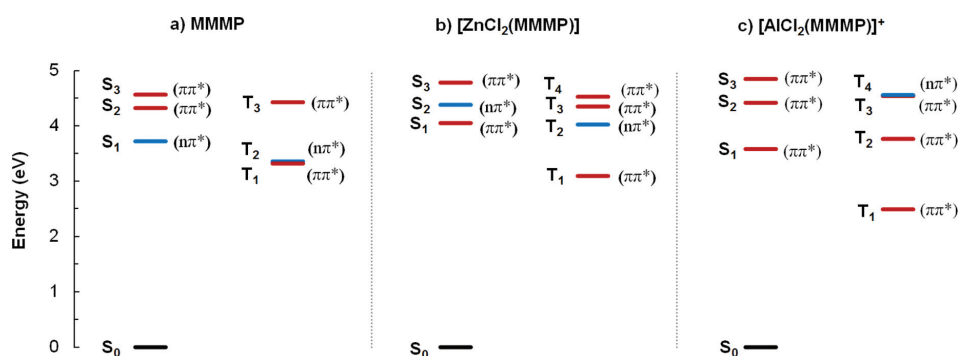


Fig. 6 The vertical singlet and triplet excitations states of: (a) MMMP, (b) $[\text{ZnCl}_2(\text{MMMP})]$ and (c) $[\text{AlCl}_2(\text{MMMP})]^+$. The predominant character of each excited state is indicated in parenthesis.

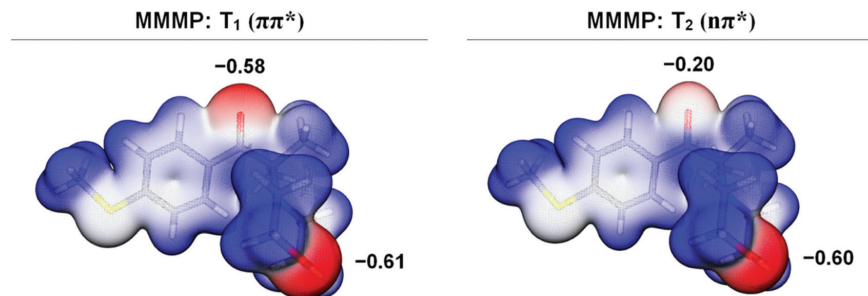


Fig. 7 The contrasting electrostatic potential (ESP) surfaces of MMMP's $\pi\pi^*$ and $n\pi^*$ triplet excited states. For reference, the natural atomic charges (from a Natural Bond Orbital analysis) of the ketone oxygen atoms are also given.

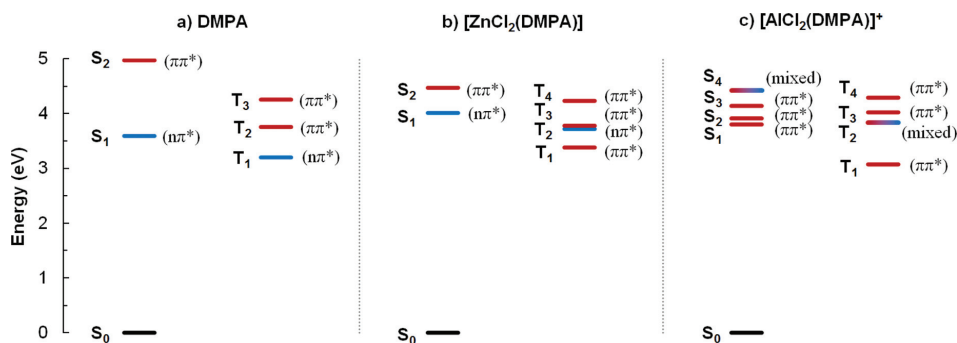


Fig. 8 The vertical singlet and triplet excitations of: (a) DMPA, (b) $[\text{ZnCl}_2(\text{DMPA})]$ and (c) $[\text{AlCl}_2(\text{DMPA})]^+$. The predominant character of each excited state is indicated in parenthesis.

destabilizing effects observed in the excited states of both complexes. Similarly, previous work by Fang and co-workers found that water complexation (H-bonding) to the ketone oxygen atom induces a red shift in the $\pi\pi^*$ type excitations of valerophenone, while concurrently blue shifting the $n\pi^*$ excitations.⁶⁰

Analogous excitation profiles of DMPA as well as the $[\text{ZnCl}_2(\text{DMPA})]$ and $[\text{AlCl}_2(\text{DMPA})]^+$ complexes are illustrated in Fig. 8. TD-DFT calculations indicate that, like MMMP, unbound DMPA has relatively straightforward photoexcitation behaviour (see Fig. 8a). It possesses an S_1 state of predominantly $n\pi^*$ character, with two triplet states located in the vicinity of S_1 . These T_1 and T_2 states have predominantly $n\pi^*$ and $\pi\pi^*$ character, respectively. The low lying $^3(\pi\pi^*)$ state of DMPA likely relays the S_1 state to T_1 , as the $^1(n\pi^*)$ to $^3(\pi\pi^*)$ transition is allowed by the El-Sayed rules. Gas-phase DFT calculations confirm that the T_1 state of DMPA is of $n\pi^*$ character (see Fig. S7 of ESI†) and indicate that α -cleavage from this state is highly kinetically and thermodynamically favourable. Indeed, bond scission proceeds with a negligible barrier of 26.3 kJ mol^{-1} and highly favourable reaction energy of $-52.4 \text{ kJ mol}^{-1}$ (see Fig. S7 of ESI†). The calculated excited state

energies and fragmentation barriers are consistent with the short excited singlet and triplet lifetime of DMPA determined from time resolved laser spectroscopy ($\tau_{S_1} < 15 \text{ ps}$ and $\tau_{T_1} = 0.25 \text{ ns}$ in benzene).⁵⁸

Both DMPA complexes have much less predictable excitation behaviour due to analogous destabilization of the $n\pi^*$ states and stabilization of $\pi\pi^*$ states (see Fig. 8b and c). While complexation of ZnCl_2 does not lead to a reordering of the $^1(n\pi^*)$ and $^1(\pi\pi^*)$ states, it extensively reorders the corresponding triplet excited states. The lowest energy triplet state (T_1) of $[\text{ZnCl}_2(\text{DMPA})]$, which has predominantly $\pi\pi^*$ character, is *ca.* 0.3 eV more stable than the nearest $n\pi^*$ type state (T_2). Unsurprisingly, AlCl_2^+ coordination has an even larger effect. The S_1 , S_2 and S_3 excited states of the $[\text{AlCl}_2(\text{DMPA})]^+$ all possess predominantly $\pi\pi^*$ character, while the intense S_4 state was found to have mixed character. On the triplet surface, T_1 was found to be *ca.* 0.7 eV more stable than the nearest state T_2 (which has mixed character). Two other triplet states, T_3 and T_4 , of $\pi\pi^*$ character are located in the vicinity of T_2 . Clearly both complexes have much more complicated photoexcitation behaviour than unbound DMPA.

Effects of complexation on photoinitiator photolysis

Complexation of Lewis acids to the ketone moiety of MMMP and DMPA clearly affects the energetics of the excited states. However, as noted in the introduction, quantum initiation yield depends on the rates of various competing photo-physical and -chemical processes. This makes it difficult to quantitatively determine initiator efficiency using theoretical techniques alone. Nonetheless, we can draw some more qualitative conclusions by considering some of the effects of complexation, drawing from previous literature where relevant.

For efficient photoinitiation, the ISC must outcompete both fluorescence and internal conversion. The $[\text{ZnCl}_2(\text{DMPA})]$ complex retains a $^1(\text{n}\pi^*)$ state as the lowest energy singlet excited state. It is probable that ISCs in these complexes would proceed to the nearest $^3(\pi\pi^*)$ state (T_3). The $[\text{ZnCl}_2(\text{MMMP})]$, $[\text{AlCl}_3(\text{MMMP})]^+$ and the $[\text{AlCl}_3(\text{DMPA})]^+$ complexes have their $^1(\text{n}\pi^*)$ and $^1(\pi\pi^*)$ inverted. Although it is not clear what effect this inversion may have on the rate of ISC, we note that $^1(\pi\pi^*)$ to $^3(\text{n}\pi^*)$ crossings are also El-Sayed allowed.⁶¹ Moreover, as Marian noted in an excellent review,⁶² vibronic interactions can also significantly increase the rates of El-Sayed-forbidden inter-system crossings.^{63–66} Additionally, Al, Cl and Zn would be expected to exert a modest heavy atom effect,⁶¹ which may also increase the rate of ISCs.

The differences in the triplet surfaces of the complexes compared with their parent photoinitiators is striking. The lowest energy triplet state of these complexes have $\pi\pi^*$ character and the nearest $\text{n}\pi^*$ states lie significantly above T_1 (ca. 0.3–2.0 eV). This reordering could potentially lead to much slower rates of photolysis and longer triplet lifetimes, as $^3(\pi\pi^*)$ states do not readily undergo fragmentation.⁶⁰ Recent work has demonstrated that various amine-substituted benzoin derivatives, which also possess a multitude of low lying ($\pi\pi^*$) type triplet states, have very long triplet lifetimes and are uncharacteristically poor photoinitiators.²⁴ Moreover, as Fang and co-workers outlined, analogous reordering of $^3(\pi\pi^*)$ and $^3(\text{n}\pi^*)$ states in valerophenone significantly lengthens triplet lifetimes in aqueous solution.⁶⁰ In this regard, our TD-DFT calculations predict that Lewis acids exert much more significant energetic effects on the triplet $\text{n}\pi^*$ and $\pi\pi^*$ states.

It is perhaps tempting to conclude, unequivocally, that Lewis acid complexation would lead to longer triplet lifetimes and poorer photoinitiation behaviour. However, Fang and co-workers also noted that the barriers for both 1,5-H atom transfer and α -cleavage in valerophenone were significantly lowered by H-bonding in aqueous solvation.⁶⁰ Moreover, an elegant study by Fouassier and co-workers found that the triplet lifetime of MMMP decreases significantly with increasing solvent polarity and is notably shorter in protic solvents, such as ethanol and isopropanol.⁵⁷

While it is not possible here to determine the barrier to α -cleavage of the DMPA or MMMP complexes quantitatively, we note that fragmentation increases the ketone oxygen basicity of unbound MMMP and DMPA. According to natural atomic charges, the transition state for α -cleavage and the

product acyl radicals are both significantly more Lewis basic than the respective $^3(\text{n}\pi^*)$ state (see Fig. S6 and S7 of ESI†). Hence, Lewis acid complexation at the ketone moiety would stabilize the α -cleavage transition states and product acyl radicals more significantly than the reactant $^3(\text{n}\pi^*)$ states. Depending on the extent of this stabilization, the $^3(\text{n}\pi^*)$ states of these complexes may even become dissociative and could potentially intersect the T_1 $^3(\pi\pi^*)$ state as the C–C bond undergoes normal vibrational stretching.

In summary, while Lewis acid complexation can red-shift the intense $\pi\pi^*$ absorption of acetophenone photoinitiators and dramatically increase their UV-absorbance at particular wavelengths, these changes are not necessarily reflective of more effective homolysis. Our calculations demonstrate that these changes are accompanied by significant destabilization of the crucially important $\text{n}\pi^*$ excited states. While photolysis is still expected, and could potentially even occur into the visible region, it is accompanied by more complex photo-dynamics and possibly longer triplet lifetimes. These effects could help to explain our observed loss of PLP characteristics (particularly at high pulse rates), under conditions that are effective in the absence of Lewis acid.

Effect of Lewis acids on fragment stability and reactivity

For a photoinitiator to be effective, at least one of the fragments generated from homolysis must rapidly react with monomer to initiate polymer chain growth. Indeed, a fundamental assumption of PLP kinetic experiments is that the rate coefficient for the addition of photoinitiator fragments to monomer (k_{add}) is significantly faster than propagation (k_{p}) and so initiation is not rate limiting. Photolysis of MMMP forms two highly reactive radical fragments; a thio-substituted benzoyl acyl radical (T rad) and a morpholine-substituted isopropyl radical (M rad) (see Fig. 2). In contrast, photolysis of DMPA results in fragments that are more differentiated in reactivity; a highly reactive benzoyl acyl radical (B rad) and a relatively unreactive dimethoxy substituted benzyl type radical (D rad) (see Fig. 2).⁵⁹ Experimental estimates of k_{add} for the B rad reacting with MMA are of the order of $10^5 \text{ L mol}^{-1} \text{ s}^{-1}$.⁶⁷

As the reactivity of the radical fragments towards monomer underpins the success or failure of photoinitiation, we sought to quantify and rationalize the effect of Lewis acid coordination on fragment reactivity. As such, we used high-level *ab initio* quantum chemistry to calculate rate coefficients for addition of these fragment radicals to MMA monomer (k_{add}). Prior to performing these calculations, we verified that our methodology could accurately predict experimentally determined rate coefficients for similar addition reactions (see Table S3 and Fig. S4 in ESI†). We noted excellent agreement (to within a factor of 3) between theoretically predicted and experimentally determined rate coefficients for these benchmarking reactions. We should also emphasize that very similar methodology has been extensively benchmarked in numerous studies over the last decade and its accuracy is well established.^{46–48}

Table 1 The effect of AlCl_3 -complexation on the calculated^a rate coefficient for initiator fragment addition to MMA (k_{add}). To assist the rationalization, radical stabilization energies (RSEs), gas-phase reaction enthalpies (ΔH_{gas}) and sum of the radical ionization energy and monomer electron affinity ($\text{IE}_R + \text{EA}_M$) were also calculated^a

Initiator fragment/Lewis acid	Monomer/Lewis acid	RSE (kJ mol^{-1})	ΔH_{gas} (kJ mol^{-1})	$\text{IE}_R + \text{EA}_M$ (eV)	$\Delta G_{\text{sol}}^\ddagger$ (kJ mol^{-1})	k_{add} ($\text{L mol}^{-1} \text{s}^{-1}$)
B rad	MMA	53.3	−109.7	6.65	45.6	1.26×10^5
B rad/ AlCl_3	MMA	3.9	−179.9	7.25	39.4	1.55×10^6
B rad	MMA/ AlCl_3	53.3	−125.5	4.51	34.1	1.29×10^7
T rad	MMA	53.4	−110.7	6.30	44.3	2.14×10^5
T rad/ AlCl_3	MMA	3.8	−178.7	7.01	40.1	1.18×10^6
T rad	MMA/ AlCl_3	53.4	−127.6	4.17	30.5	5.64×10^7
D rad	MMA	65.9	−99.9	5.88	52.1	9.14×10^3
D rad/ AlCl_3	MMA	46.9	−91.8	6.80	71.8	3.29
D rad	MMA/ AlCl_3	65.9	−130.8	3.75	24.4	6.74×10^8
M rad	MMA	48.3	−95.1	5.15	37.2	3.85×10^6
M rad/ AlCl_3 (O bound)	MMA	43.3	−103.3	5.68	37.5	3.33×10^6
M rad/ AlCl_3 (N bound)	MMA	39.0	−82.2	6.45	70.0	6.54
M rad	MMA/ AlCl_3	48.3	−121.3	3.02	<20	> 10^9

^a All values were calculated at 25 °C. The T and M radicals result from photodissociation of MMMP; the B and D radicals are from DMPA (see Fig. 2). All k_{add} values were corrected (by a factor of 2) for reaction path degeneracy.

The k_{add} values for various addition reactions were calculated from first principles to explore the effects of Lewis acid complexation on radical fragment reactivity. For these calculations we used AlCl_3 as a model Lewis acid and rigorously examined coordination to the radical fragment (in all positions where Lewis acid coordination was observed in Fig. 2) and also to ester group of adding MMA monomer. Table 1 details the reaction energetics for the addition of these various initiator fragments under these different binding scenarios. To assist efforts to rationalize these k_{add} values, gas-phase reaction enthalpies (ΔH_{gas}) and the sum of the radical fragment ionization energy and electron affinity of MMA ($\text{IE}_R + \text{EA}_M$) were also calculated. The effect of AlCl_3 complexation on the radical stabilization energies (RSEs) of the fragment radicals was also examined. The sum of the radical ionization energy and monomer electron affinity ($\text{IE}_R + \text{EA}_M$) is frequently used to assess the importance of polar-effects in radical addition reactions; non-negligible charge transfer is indicated by an $\text{IE}_R + \text{EA}_M$ value of <7–8 eV, with lower values signifying greater polar stabilization of the transition state.⁶⁸ Many radical-based transfer, addition and fragmentation reactions obey the Bell-Evans-Polanyi principle.^{69,70} Thus, RSE and ΔH_{gas} values can be used to infer changes in reactivity caused by general enthalpic effects.

As outlined in Table 1, the following order of reactivity with MMA is obtained for the unmediated addition reactions: M rad > T rad ~ B rad > D rad. This ordering can be rationalized by considering the enthalpic and polar characteristics of these reactions. As would be anticipated from their RSEs, addition of the B rad and T rad fragments is enthalpically highly favourable but relatively minor amounts of polar stabilization are observed. In contrast, the D rad fragment has more nucleophilic character but the corresponding addition reaction is less enthalpically favourable because this radical is both fairly hindered and extensively delocalized. The tertiary M rad has the least favourable reaction enthalpy (because of high steric

hindrance) but it is also highly nucleophilic and so the corresponding addition reaction is strongly favoured by polar effects.

As Table 1 illustrates, AlCl_3 coordination to the radical fragment has a highly variable effect on reactivity. The following order of reactivity was obtained for the AlCl_3 complexed radical fragments: M rad (O bound) > T rad ~ B rad > M rad (N bound) > D rad. The predicted k_{add} values for the addition of the AlCl_3 complexed B rad and T rad fragments to MMA are 1.15×10^6 and $1.18 \times 10^6 \text{ L mol}^{-1} \text{s}^{-1}$, respectively; approximately an order of magnitude faster than the corresponding unmediated reactions. In contrast, complexation of AlCl_3 to the M rad (at the amine N) and to the D rad significantly reduces the reactivity of these radicals, with k_{add} values of only 6.54 and $3.29 \text{ L mol}^{-1} \text{s}^{-1}$, respectively. Unsurprisingly, complexation of AlCl_3 at the remote ether moiety of the M rad had essentially no effect on its reactivity.

Pleasingly, this quite divergent reactivity behaviour can be rationalized by considering the differing importance of enthalpic and polar effects in the respective systems. The conjugate n-donor groups of the M rad and D rad do not delocalize their respective radicals as effectively as the equivalent acyl oxygen atoms of the B rad and T rad. Consequently, complexation of AlCl_3 to the D rad and M rad only modestly destabilizes the respective radicals and actually decreases the favourability of ΔH_{gas} . Moreover, AlCl_3 complexation significantly reduces the inherent nucleophilic character of these radicals, which results in significantly less charge-transfer stabilization of the respective transition states. In other words, for the M rad and D rad, AlCl_3 complexation has a very detrimental effect on charge-transfer stabilization, which is not countered by increased enthalpic favourability.

In contrast, AlCl_3 complexation greatly destabilizes both acyl radicals (*i.e.*, B rad and T rad) and consequently the ΔH_{gas} for the respective addition reactions is around 70 kJ mol^{-1} more favourable in the presence of Lewis acid. Thus, the enhanced reactivity of the B rad and T rad following complexa-

tion to the adjacent π donor (acyl O atom) can be assigned to significant localization of the respective radicals. These acyl radicals are inherently less nucleophilic and so the reduction in charge-transfer stabilization following AlCl_3 complexation is more than compensated by the increased enthalpic favourability of MMA addition.

Interestingly, significant radical destabilization is observed following AlCl_3 complexation to all photoinitiator fragment radicals (see the RSE values in Table 1). As a result of this destabilization, these photoinitiator fragment radicals are significantly weaker Lewis bases than their ground-state parent photoinitiators and, more significantly, MMA monomer. Consequently, thermodynamic speciation of the ZnCl_2 and AlCl_3 would result in Lewis acid coordination at the ester side-chain of MMA monomer, rather than to these fragment radicals. However, as it is unclear if ligand exchange kinetics would be sufficiently rapid to allow Lewis acid repositioning following photolysis, addition of uncomplexed photoinitiator fragment radicals to $[\text{AlCl}_3(\text{MMA})]$ was also investigated.

As indicated in Table 1, coordination of AlCl_3 at the conjugate ester side-chain of MMA also has a significant effect on k_{add} . For $[\text{AlCl}_3(\text{MMA})]$, the following order of radical reactivity is obtained: M rad > D rad > T rad > B rad. The predicted k_{add} values for the addition of the B rad and T rad fragments to complexed MMA are over two orders of magnitude faster than the corresponding unmediated reactions. More remarkably, the rate of addition of the D rad to complex MMA exceeds the diffusion limit $10^8 \text{ L mol}^{-1} \text{ s}^{-1}$, and is more than 4 orders of magnitude faster than the unmediated reaction. While no formal transition state for the addition of the M rad to AlCl_3 -complexed MMA could be identified, we believe this reaction proceeds *via* outer-sphere electron transfer (OSET) with a subsequent recombination of the formed cation and radical anion. For the purposes of the present work, we have assumed that this reaction is also diffusion limited.

The remarkable catalysis observed with AlCl_3 complexation to the methyl ester of MMA can be largely attributed to polar effects, although minor enthalpic increases are also observed. Complexation of AlCl_3 to MMA lowers its electron affinity by more than 2 eV, strongly enhancing the monomer's inherent electrophilic character. Consequently, charge transfer effects dominate these reactions, with the k_{add} values directly correlated with radical nucleophilicity (as measured by their ionization energies). In summary, complexation of the AlCl_3 to acyl initiator fragments greatly increases their reactivity toward monomer through radical destabilization effects. For the M rad and D rad complexes, this destabilization is more modest, and less favourable charge-transfer actually slows addition to MMA. If ligand exchange were to occur, complexation of AlCl_3 to MMA monomer would then significantly increase the reactivity of all initiator fragments *via* polar effects. As a weaker Lewis acid than AlCl_3 , ZnCl_2 would have less dramatic effects on fragment radical stability and the electrophilicity of MMA. Nonetheless, analogous (though more modest) changes to k_{add} would also be expected in the corresponding ZnCl_2 systems.

Conversely, as a stronger Lewis acid than AlCl_3 , AlCl_2^+ would likely exert an even larger kinetic effect. Unfortunately, high-level reactivity calculations using realistically solvated ZnCl_2 or AlCl_2^+ species are intractable.

Conclusions and implications

Several important conclusions regarding the effect of Lewis acid complexation on acetophenone photoinitiators can be made. Where reasonable, these conclusions have been generalized so as to be more broadly applicable to other photoinitiator/Lewis acid combinations.

Lewis acid complexation at the ketone moiety induces significant changes in the UV-Vis spectra of acetophenone derivatives. These changes will have a variable effect on absorbance, depending on the combination of photoinitiator and Lewis acid, and the wavelength of the incident light source. Lewis acids that possess multiple free coordination sites, or readily displaceable anionic ligands (particularly ^-OTf or $^-\text{NTf}_2$), are likely to form 5-membered chelates with any acetophenone derivatives that have either nitrogen or oxygen based functionality in the γ position. Such chelate complexes will probably be more stable than monomer solvated Lewis acid complexes and will have lower initiation efficiencies because of stronger solvent cage effects. Bulkier Lewis acids, such as trivalent halides, are less likely to form chelate complexes without displacement of anionic ligands and thus may interact less selectively with the photoinitiator at low Lewis acid concentrations. The use of bulkier photoinitiators, such as adamantane and norbornane substituted acetophenones,⁷¹ may aid future PLP experiments with strong Lewis acids.

While it is a bulky Lewis acid, the behaviour of AlCl_3 requires special comment. Theoretical calculations indicate that in its neutral form, AlCl_3 would not interact significantly with MMMP under competing solvation by MMA. Moreover, the predominant ether-bound $[\text{AlCl}_3(\text{MMMP})]$ complex would have similar photoexcitation behaviour to that of uncomplexed MMMP. However, MMMP could readily displace monomer from $[\text{AlCl}_2(\text{MMA})_3]^+$ cation, which forms from the self-ionization of $[\text{AlCl}_3(\text{MMA})]$. As this self-ionization process is itself concentration dependent, the effects of Lewis acids on initiation may vary depending on the reaction conditions.

In the present work, Lewis acid complexation to acetophenone derivatives was found to significantly red-shift their UV-Vis spectra, raising hope that these types of systems may be used in the visible region. Indeed, studies in this direction are now underway. However, the observed spectral changes result from significant stabilization and destabilization of underlying $\pi\pi^*$ and $n\pi^*$ excited states, resulting in more complicated excitation dynamics. Indeed, longer triplet lifetimes, slower photolysis and lower radical concentrations may be observed. As Lewis acids may adversely affect the triplet lifetimes of photoinitiators, high-flashing rate PLP experiments should be attempted with some caution.

In addition, Lewis acid complexation has a significant effect on the stability and reactivity of photoinitiator radicals. Coordination of Lewis acids to acyl fragments localizes and considerably destabilizes these radicals, significantly increasing reactivity towards monomer. Lewis acid coordination also localizes and destabilizes dimethoxy phenyl and morpholine substituted isopropyl radicals, although to a smaller extent, while making these radicals less reactive towards MMA. For all of the photoinitiator fragments examined, $[\text{AlCl}_3(\text{MMA})]$ was found to be considerably more reactive than uncomplexed monomer; with k_{add} increasing by 2–4 orders of magnitude, depending on the identity of the adding fragment radical.

Remarkably, Lewis acids have the potential to significantly affect all aspects of photoinitiation. Understanding these effects will greatly aid in the selection of appropriate photoinitiators for PLP kinetic studies of Lewis acid-mediated radical polymerization, and more generally with the design of novel visible light photoinitiating systems.

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4.6 Supporting information

A detailed description of the experimental and computational methodology, summary tables of PLP data and raw energies, example SEC traces, as well as optimized geometries for all the species in this chapter can be found on the CD-ROM attached at the back of this thesis. Supporting information for Publications 3, 4 and 5 can also be obtained free of charge from <http://www.rsc.org/suppdata/py/c4/c4py00190g/c4py00190g1.pdf> [Publication 3], http://pubs.acs.org/doi/suppl/10.1021/acs.macromol.5b02336/suppl_file/ma5b02336_si_001.pdf [Publication 4] and <http://www.rsc.org/suppdata/c6/py/c6py01445c/c6py01445c1.pdf> [Publication 5].

5. Stereoregulation in the Radical Polymerization of Methacrylate Salts

5.1 Overview

Inherent polymer stereochemistry in radical polymerization is characteristic of the monomer system but can be modified, at least some extent, by changes to the reaction conditions, such as solvent identity and polymerization temperature.¹¹² Nonetheless, the inherent stereoselectivity is usually very low for most common monomers, unless they have chiral and /or exceptionally bulky side-chains.¹¹³⁻¹¹⁸ Moreover, as we have seen in this thesis, despite 50 years of research, attempts to control the tacticity of important common monomers through the use of simple chemical additives have generally failed, especially when isotactic polymer is desired. Research in this thesis has suggested that a large part of this problem relates to binding selectivity of the Lewis acid, and particularly a kinetic preference for binding to the terminal and monomer side-chains, a mode that catalyses but does not control the stereospecificity of the polymerization.

In this context, methacrylic acid (MAA) and its salts are an intriguing for several reasons. Firstly, the MAA salts by design contain Lewis acids at every side-chain which may, to some extent, overcome binding selectivity problems. In most other polymerizations, solubility constraints preclude the use of stoichiometric Lewis acid concentrations. Secondly, controlling the tacticity of MAA is important in its own right as the polymer is useful in biomedical applications and this monomer cannot be polymerized directly via stereospecific ionic procedures. Thirdly, MAA has the capability to function as a relatively low-cost ionic auxiliary for MMA. Indeed, in this thesis an improved procedure for converting the polymer of calcium methacrylate (CaMA) to poly(MMA) has been developed and is outlined in **Appendix 8.1**. Fourthly, 50 years of research on this system has revealed that tacticity can range from values of $m = 3\%$ to 80% , depending on the temperature, solvent, counter-cation or pH in the case of MAA itself (see **Table 2**).¹¹⁹⁻¹²⁶ For instance, CaMA has one of the highest isotactic values reported for a simple monomer ($m = 78\%$ in DMF or $m = 80\%$ in DMF/toluene).¹²² However, if the counter-cation is changed to Mg^{2+} under the same conditions, isotactic content is lowered to $m = 44\%$.¹²² Alternatively, if the solvent is changed to water for CaMA, isotactic content is lowered to $m = 24\%$.¹²² Understanding this variation, and how the systems displaying high isotacticity overcome the catalytic effects of terminal-monomer binding, will help optimize control in this system. It may also provide insights

into how to defeat the catalysis versus stereocontrol dichotomy in other systems, such as MMA.

Table 2 Illustrative examples of the highly variable tacticity that can be obtained from the radical polymerization of methacrylic acid and methacrylate salts under different conditions.

Counteranion	Solvent	Temp (°C)	Tacticity (%)				Ref
			<i>mm</i>	<i>mr</i>	<i>rr</i>	<i>m</i>	
None ^a	bulk	60	9	46	45	32	119
None ^a	Toluene	60	8	41	51	28	120
None ^a	water	45	4	33	64	20	121
None ^a	DMF	60	5	30	65	20	122
None ^a	MCH ^b	0	>1	18	82	9	123
None ^a	<i>i</i> -PrOH	−78	>1	5	95	3	119
H ₃ N ⁺ <i>i</i> -Bu	water	60	>1	12	87	6	124, 125
NH ₄ ⁺	water	60	>1	17	83	9	124, 125
NMe ₄ ⁺	water	60	4	17	79	12	126
NEt ₄ ⁺	water	60	4	16	80	12	126
NEt ₄ ⁺	water	5	>1	8	92	4	126
Na ⁺	water	60	5	34	61	22	124, 125
Ca ²⁺	water	60	6	36	58	24	122
Ca ²⁺	DMF ^c	60	60	35	5	78	122
Ca ²⁺	DMF ^c /Toluene	60	65	30	5	80	122
Ca ²⁺	DMF ^c /water	60	30	47	23	54	122
Mg ²⁺	DMF ^c	60	20	48	32	44	122
Li ⁺	DMSO ^d	60	29	53	18	56	122

^aNon-ionized methacrylic acid. ^b2-methylcyclohexanol. ^c*N,N*-dimethylformamide. ^dDimethylsulfoxide.

To address these questions, two theoretical studies have been undertaken. The first part of this chapter [*Publication 6*], explores the effect of ionization (and hence pH) on the kinetics of MAA propagation. It is shown the propagation rate coefficient and tacticity of MAA can be accurately predicted by high-level quantum theory. Moreover, the work demonstrates that the *rapid interconversion* scheme (as outlined in **Chapter 3**) is the correct kinetic scheme for tacticity determination in MAA. This work also explains the effects of ionization on propagation kinetics and syndiotacticity, in terms of hydrogen bonding between the ionized monomer and non-ionized polymer terminus. Intriguingly, this study also suggested that the side-chain of the terminal radical had a notably higher Brønsted basicity than other carboxylate groups in the polymerization.

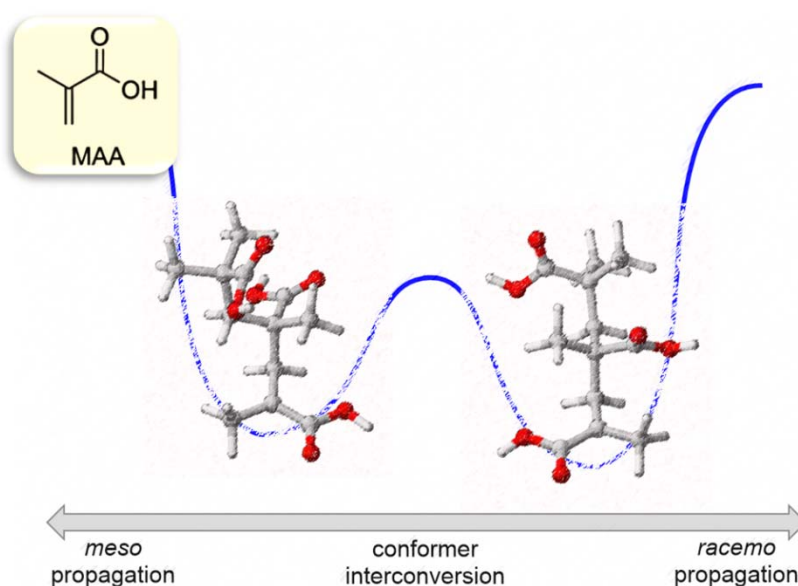
The second part of this chapter [*Publication 7*], presented in draft form, uses high-level theory to examine the origins of isotactic control in CaMA. High-level calculations indicate that the terminal carboxylate group of the propagating radical has a higher Lewis basicity (towards Mg^{2+} and Ca^{2+}) than other side-chains in the polymerization. Calculations suggest that isotactic control in CaMA results from the formation of Ca^{2+} /carboxylate bridging scaffolds, which have a tendency to form around the terminal radical because of this higher basicity. These scaffolds are likely disrupted by polar solvent and/or the use of smaller counter-cations (such as Mg^{2+}), hence explaining the variability. On the basis of this work, we predict that further optimization of the conditions to maximize bridging scaffold formation (through temperature and solvent changes) may lead to enhanced isotacticity. More generally, the work indicates that the catalysis versus stereocontrol dichotomy can be defeated by multiple chelation. This principle could potentially be applied in other systems by using, for example, bridging ligands.

5.2 Publication 6

Effects of Ionization on Tacticity and Propagation Kinetics in Methacrylic Acid Polymerization

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In Controlled Radical Polymerization: Mechanisms, Matyjaszewski, K.; Sumerlin, B.S.; Tsarevsky, N.V.; Chiefari, J., Eds., American Chemical Society Publications, United States, **2015**, pp. 51-72.



This manuscript is a peer-reviewed original research book chapter that was published in the *ACS Symposium Series Book Controlled Radical Polymerization: Mechanisms*. The literature overview, computational results and discussion presented are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.

Chapter 3

Effects of Ionization on Tacticity and Propagation Kinetics in Methacrylic Acid Polymerization

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Theoretical calculations have been performed to model the propagation kinetics and ionization behavior of methacrylic acid (MAA) from first principles. The pK_a values of various COOH groups of chemical species with direct relevance to MAA polymerization have also been calculated. At a given temperature, syndiotacticity increases with solvent polarity and ionization, and herein we show that accurate quantum chemistry can correctly account for these effects and explain their origin in terms of the changing structure of the charged propagating species.

Introduction

The objective of synthetic polymer chemistry is to control the assembly of macromolecules to facilitate alterations to their microstructure and bulk properties. Over the last few decades, living radical polymerization has revolutionized polymer synthesis by allowing precise control of most aspects of polymer microstructure. Unfortunately, these approaches by themselves have no influence on polymer stereochemistry (tacticity), which is usually poorly regulated. Despite being the focus of many pioneering investigations over the last 60 years, the synthesis of stereoregular polymers via radical polymerization has remained enormously challenging (*1*). Since the first attempts to control stereochemistry in radical polymerization in the 1950s, a broad array of strategies

have been developed (Scheme 1), with notable success in some monomer systems (1). However, many of these approaches are difficult and expensive to implement, while others have a relatively narrow scope or are simply unable to replicate the high stereoselectivity that can be achieved in contemporary anionic and coordination polymerization. Some of the most effective (and elegant) strategies, such as stereoregular templating (2–4), are impractical and could not be readily applied to grams scale polymer synthesis. The strategy that is best able to balance the competing demands of effectiveness and practicality is monomer modification to incorporate bulky (5–8), chiral (9, 10) and ionic auxiliaries (11–20).

Confinement techniques	Monomer modification	Chemical additives
☐ Organic frameworks ☐ Inorganic frameworks ☐ Metal-organic frameworks ☐ Cyclodextrins ☐ Polymer templates	☐ Bulky auxiliaries ☐ Chiral auxiliaries ☐ Self-assembling auxiliaries ☐ Multiple H-bond auxiliaries ☐ Ionic auxiliaries	☐ Bulky polar solvents ☐ Lewis acids ☐ Ionic liquids ☐ π -stacking solvents

Scheme 1. Different strategies for stereocontrol in radical polymerization.

Methacrylic acid (MAA) is a particularly intriguing system for which a variety of polymer tacticities can be targeted depending on pH, counteranion identity and solvation conditions. The synthesis of poly(MAA) and its derivatives is of interest more broadly for applications as diverse as pH selective carriers for drug delivery (21) to radiological protection (22) and reinforcing agents for rubber (23). In this work we use quantum chemistry, in addition to drawing on previous experimental work, to explore the propagation kinetics in the radical polymerization of non-ionized and ionized methacrylic acid (MAA).

Previous Experimental Studies of MAA

The radical polymerisation of MAA in bulk and toluene at 60 °C affords polymer with a syndiotactic triad fraction (*rr*) of 45% and 51%, respectively (24, 25). Solvation in polar solvents increases this syndiotactic tendency. For instance, in water at 45 °C and DMF at 60 °C, polymer with an *rr* of 64% and 65%, respectively is formed (17, 20). Syndiotacticity can be further enhanced by performing polymerizations at reduced temperatures. For instance, the

polymerization of MAA in 2-methylcyclohexanol at 0 °C and isopropyl alcohol at -78 °C afforded polymer with an *rr* of 92% and 95%, respectively (24, 26). More than 60 years ago, it was erroneously reported that methacrylate anions cannot undergo radical polymerization (27). It was later clarified that the radical initiator used in this study, hydrogen peroxide, was ineffective at high pH and it was subsequently verified with appropriate initiators that ionized methacrylic acid can undergo radical polymerization; although both propagation and termination are significantly inhibited (28, 29). In addition, Bovey noted that the resultant polymer stereochemistry is pH dependent, with syndiotacticity increasing at high pH (12). Since these initial reports, the propagation kinetics of ionized acrylic and methacrylic acid in aqueous conditions has been the subject of a number of pioneering investigations. Kabanov and coworkers found that in addition to pH, the identity of the neutralizing agent also influenced resultant polymer stereochemistry (13, 14). More recently, Gramain found the radical polymerization of the tetramethyl and tetraethyl ammonium methacrylate in aqueous conditions also yielded highly syndiotactic polymer (16). Rizzardo et al. used methacrylate salts and water-soluble RAFT agents to synthesize syndiotactic-rich polymer with a low polydispersity and designer end-groups (17). The majority of these ionized MAA studies have been performed in aqueous conditions and have found that syndiotactic-rich polymer is formed. Results from these various studies are summarized in Table 1, where it is clear that the tacticity of poly(MAA) can vary significantly depending on the polymerization conditions and the ionization state of the COOH moieties; understanding and modeling these results, is the aim of the present work.

Theoretical Background

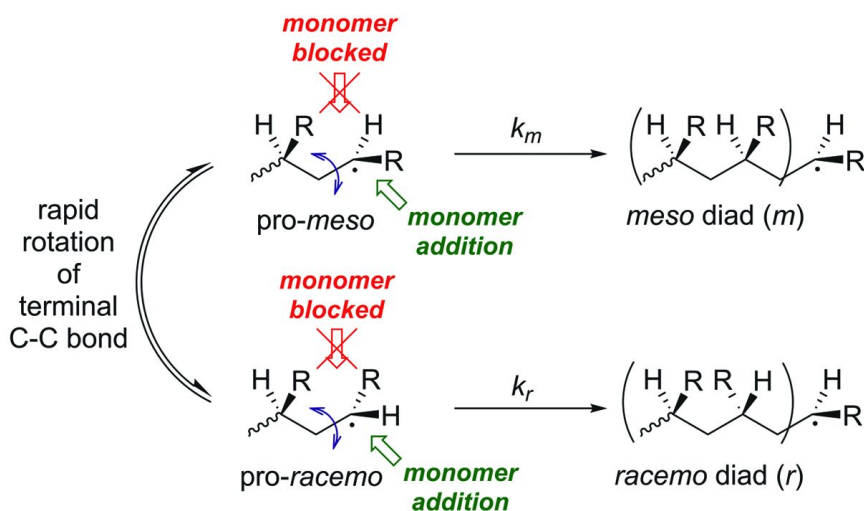
Stereochemistry in radical polymerization is determined by the relative orientation of the terminal and penultimate side-chains during monomer addition (Scheme 2). The steric bulk of the penultimate unit blocks monomer addition to the *cis*-face of the planar radical and thus addition occurs exclusively at the *trans*-face. Hence, the conformations of the polymer terminus can be classified as either *pro-meso* or *pro-racemo* based on the relative orientation of the terminal and penultimate side-chains with respect to the macromolecular backbone. These configurations can interconvert via rotation of the terminating main-chain C-C bond (indicated by the blue arrow in Scheme 2), without disrupting conjugation between the radical and the terminal side-chain. Thus, it would be reasonably anticipated that these conformers would rapidly equilibrate prior to propagation and hence their concentration would depend only on their thermodynamic stability rather than the rate of their formation. Provided this occurs, tacticity is determined by the relative concentrations of the *pro-meso* and *pro-racemo* conformations and their relative reactivity to monomer addition. Hence, predicting tacticity from first principles requires at least a tetrameric transition state model of the polymer system.

Table 1. Illustrative examples highlighting the effect of solvents and counteranions (or neutralizing agents) on the resultant poly(MAA) stereochemistry

Cation	Solvent	T (°C)	Tacticity (%)				Ref
			<i>mm</i>	<i>mr</i>	<i>rr</i>	<i>r</i>	
None ^a	bulk	60	9	46	45	68	(24)
None ^a	toluene	60	8	41	51	71	(25)
None ^a	water	45	4	33	64	81	(17)
None ^a	DMF ^b	60	5	30	65	80	(20)
None ^a	MCH ^c	0	>1	18	82	91	(26)
None ^a	<i>i</i> -PrOH	−78	>1	5	95	98	(24)
H ₃ N ⁺ <i>i</i> -Bu	water	60	>1	12	87	93	(13, 14)
NH ₄ ⁺	water	60	>1	17	83	92	(13, 14)
NMe ₄ ⁺	water	60	4	17	79	88	(16)
NEt ₄ ⁺	water	60	4	16	80	88	(16)
NEt ₄ ⁺	water	5	>1	8	92	96	(16)
Na ⁺	water	60	5	34	61	77	(13, 14)
Ca ²⁺	water	60	6	36	58	76	(20)

^a None denotes unionized methacrylic acid. ^b N,N-dimethylformamide.

^c 2-methylcyclohexanol.



Scheme 2. The mechanism of tacticity determination in free-radical polymerization of a mono-substituted alkene, H₂C=CHR. The blue arrow indicates the terminal chain bond.

The authors of earlier computational studies of acrylic and methacrylic acid (30), and methyl methacrylate (31), have failed to properly appreciate these mechanistic subtleties. Both studies erroneously modelled tacticity by calculating the rate of formation of (trimeric) *pro-meso* and *pro-racemo* conformations. However, as these conformations can interconvert, their concentration is not under kinetic control and thus the rate of their formation is completely irrelevant to the prediction of tacticity. Moreover, both of these studies attempted to predict tacticities, which are diastereoselectivities, using transition structures that only possessed a single stereogenic center.

To avoid such erroneous computational modeling of tacticity, and to properly explain the effect of stereocontrol agents, it is of critical importance that this mechanism is clarified and its subtleties are appreciated. The rational improvement of existing polymerization procedures relies on an adequate understanding of the structure and reactivity of the propagating species. Thus, improving existing stereocontrol is dependent on identifying the underlying mechanism of stereoselection and understanding both its complexities and limitations. In this work, we aim to clarify the propagation kinetics of non-ionized and ionized MAA, using accurate state-of-the-art quantum chemical calculations. First, we examine the propagation kinetics of non-ionized MAA, using quantum chemistry to predict propagation rate coefficients and tacticities from first principles. We utilize these calculations to demonstrate the correctness of the qualitative mechanism presented in Scheme 2 and so clarify the complexities surrounding tacticity determination in radical polymerization. Secondly, we examine the ionization behaviour of model systems relevant to MAA polymerizations and explore the effects of ionization on propagation kinetics.

Computational Procedures

We have used the high-level composite *ab initio* G3(MP2,CC) method (32) to calculate propagation barriers, rotational barriers and reaction energies for uncharged dimeric MAA systems. In cases where either the reactant, transition state or product was anionic, we have (consistently) applied the modified G3(MP2,CC)(+) method. For larger trimeric and tetrameric systems (where these methods are infeasible), we have employed an ONIOM inspired approximation (33, 34), with UMP2/GTMP2Large used to model remote substituent effects. For pK_a calculations on unimeric models (and isobutyric acid), we have used the highly accurate CCSD(T)-F12a approximation (35) in conjugation with the VTZ-F12 optimized F12 basis set (36). The highly efficient CCSD(T)-F12 approximations afford significantly more accurate results than normal CCSD(T) calculations with a comparable basis set. For instance, the CCSD(T)-F12a approximation in conjugation with a standard AVTZ basis set, has been shown to deliver mean absolute deviations of only 1 kJ mol⁻¹ from benchmark CCSD(T)/CBS data for a diverse test set of reaction energies; giving better performance than CCSD(T)/AV5Z (35). For pK_a calculations on the larger dimeric and trimeric models (where such high-level calculations are infeasible) we

have used the G3(MP2-CC) (+) and UMP2/GTMP2Large methods, respectively, in conjunction with an ONIOM inspired approximation (33, 34).

Throughout this work we have used M06-2X/6-31+G(d,p) geometries and appropriately scaled frequencies (37) to obtain accurate gas-phase free-energies (38). Rotational saddle points were identified by performing a relaxed scan around the dihedral of interest and further optimizing the identified approximate saddle point geometry without any constraints at M06-2X/6-31+G(d,p). Except where otherwise noted, solvation free energies were calculated using the COSMO-RS model (39–41). Additionally, a small number of calculations were performed on unimeric systems (see text) with the SMD model (42) for comparative purposes. The ADF package (43) was used to compute COSMO-RS solvation free energies on gas-phase structures at the BP/TZP level of theory (as it was parameterized for), and the remaining parameters were kept as default values (44). SMD calculations were performed using Gaussian 09 (45), at the M06-2X/6-31+G(d,p) level of theory, with all other parameters kept as their defaults. All standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were carried out using Gaussian 09 (45), with the exception of CCSD(T) and CCSD(T)-F12a calculations, which were performed using Molpro 2012 (46, 47). We note that similar methodology has been previously shown to predict accurate values for the kinetics and thermodynamics of a wide range of reactions, including propagation (48–50).

Propagation Kinetics of Non-Ionized Methacrylic Acid

Equilibration of Polymer Conformations

The first question we need to investigate is whether the concentrations of the *pro-meso* and *pro-racemo* radicals can rapidly interconvert on the timescale of a propagation step or not (see Figure 1). As noted above, if they can, then their concentrations depend only on their relative free energies, rather than the kinetics of their formation, and tacticity predictions can be simplified accordingly (see Scheme 2). To demonstrate that *pro-racemo* and *pro-meso* conformations can rapidly interconvert, the rotational Gibbs free energy barriers around the terminal chain bond (indicated θ in Figure 1) were calculated. For linear conformations, this barrier was found to be very modest; only 17 - 18 kJ mol⁻¹ (depending on the solvation conditions) relative to the global minimum conformation. Unsurprisingly, this barrier was larger in helical conformations; increasing to 27 - 28 kJ mol⁻¹. In addition, the barrier for the conversion of linear and helical conformations (indicated ϕ in Figure 1) was also examined. This barrier was found to range between 20 - 25 kJ mol⁻¹, depending on other conformational aspects of the polymer terminus. In contrast to these very modest rotational barriers, the Gibbs free energy barrier for propagation in typical radical polymerizations ranges from 45 - 60 kJ mol⁻¹ (depending on the monomer system, temperature, solvation conditions etc.). These results unequivocally demonstrate that both *pro-meso*/ *pro-racemo* and linear/ helical conformations can equilibrate prior to propagation; as such rotations would be several orders of magnitude faster than propagation.

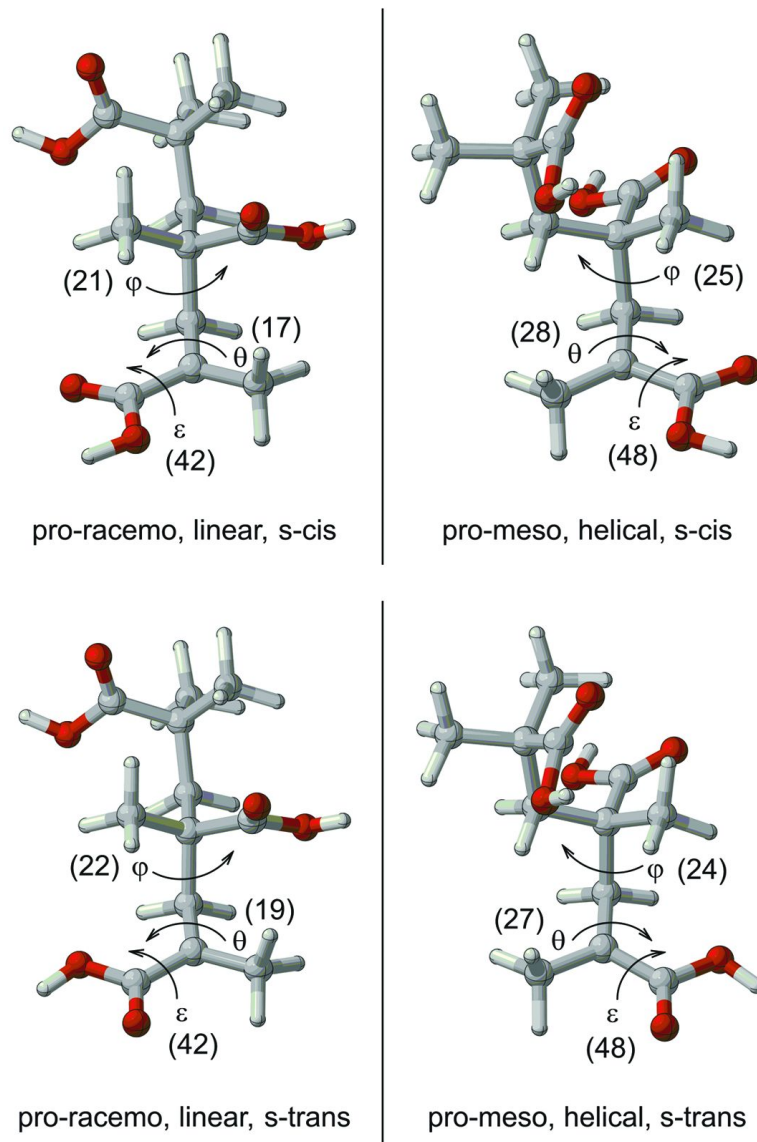


Figure 1. The geometries of the lowest energy pro-racemo and pro-meso conformations of s-cis and s-trans type radicals. Various rotations are indicated (θ , ϕ and ϵ), with their corresponding Gibbs free energy barrier (in kJ mol^{-1}) relative to the global minimum conformation stated in parentheses.

The only high energy rotation that would be expected in poly(MAA) systems is around the terminal COOH group (indicated ϵ in Figure 1). This rotation, which converts s-cis to s-trans radicals (and vice versa), disrupts conjugation between the COOH group and the C-centered radical. This rotational barrier was found to be more comparable to propagation, around 42 - 48 kJ mol^{-1} depending other conformational aspects of the polymer terminus. Collectively, these results indicate that the only aspect of polymer conformation that could be under some kinetic control is the population of s-cis/ s-trans radicals.

Importance of Explicit Solvent Interactions

COOH moieties have a well-known tendency to form 6 membered cyclic H-bonded dimers in non-polar solvents. To investigate the stability of these H-bonded dimers for MAA, the Gibbs free energy for their formation was calculated from first principles. In the gas phase the H-bonded dimer is (unsurprisingly) quite stable; by around 20 kJ mol⁻¹ compared to separated monomer units. In water the H-bonded dimer is unstable and solvation of the component MAA units is significantly more favorable; by around 15 kJ mol⁻¹. This suggests that COOH dimerization in aqueous conditions is negligible and so should not be considered for studies of propagation kinetics. In bulk MAA, COOH dimer formation is predicted to be slightly unfavorable (by 0.4 kJ mol⁻¹). However, we should note that applying continuum solvation corrections in bulk monomer may not accurately describe the tendency of COOH groups to form dimers. Indeed, as Deglmann noted, dimerization would decrease the effective polarity of the solvent mixture (51). This reduction in polarity would make the formation hydrogen bonded dimers more energetically favorable, causing further dimerization of COOH groups (and further reduction in solvent polarity) until an equilibrium point is reached. It is quite unclear if COSMO-RS (or indeed any other continuum solvent model) can properly account for the dynamic nature of these effects and to what extent these effects are implicitly accounted for by the solvent model. Thus, it is difficult to accurately determine the dimerization energy of COOH moieties in bulk MAA, although it seems likely that some portion of the solution would form dimers.

Propagation Kinetics and Tacticity

As the rotational barrier around the terminal COOH group is comparable to the range of typical barriers for propagation, it is somewhat unclear if s-cis and s-trans radicals can completely equilibrate or if their concentration might be under some kinetic control. Thus, the propagation of s-cis and s-trans type radicals was considered separately. While our prior calculations suggest that a significant portion of the COOH units of MAA exist as dimers in bulk solution, unfortunately we found that the computational cost associated with modelling these dimers in kinetic calculations was prohibitive. As such, we calculated the predicted kinetics without any explicit treatment of COOH dimers in the respective chemical models of propagation. A potential energy surface (PES) for propagation of s-trans type trimer radicals (in bulk and aqueous solution) is depicted in Figure 2. A very similar surface is observed for s-cis radicals, although both *meso* and *racemo* propagation barriers were slightly larger (by around 3 kJ mol⁻¹) on account of their slightly more stable reagent conformers and slightly less stable transition structures. However, the predicted stereoselectivities were found to be fairly independent of the conformation of the terminal COOH group, varying by less than 0.5 kJ mol⁻¹ between the s-cis and s-trans surfaces.

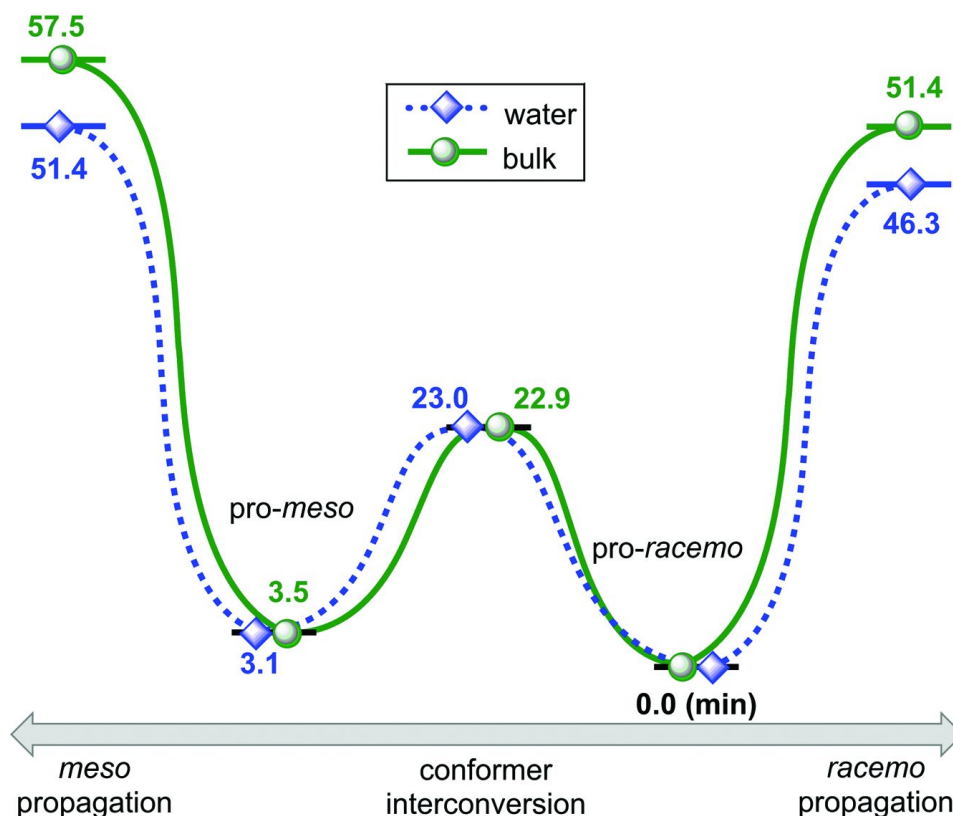


Figure 2. The potential energy surface (in kJ mol⁻¹) for the propagation of an *s*-trans MAA trimer in bulk (green line) and aqueous solution (blue line) at 25 °C. The rotational barriers for the interconversion of the lowest energy *s*-trans pro-racemo and pro-meso conformation are also indicated for comparison.

Given the barrier for *s*-cis to *s*-trans conversion is close to that for propagation, it is somewhat unclear if *s*-cis and *s*-trans type conformations would be able to fully equilibrate prior to propagation. However, these calculations suggest that *s*-cis/*s*-trans radicals possess nearly identical stereoselectivity, although their reactivity difference may have some effect on the absolute propagation rate. In any case, the *s*-cis/*s*-trans equilibration is still around 4-8 kJ mol⁻¹ more favorable than propagation at the present level of theory and so for the purposes of this work we have assumed that they do equilibrate on the timescale of a propagation step. Thus, we have calculated an effective barrier using the lowest energy reagent conformation and the lowest energy transition state conformations, regardless of the conformation of the radical. The theoretically calculated propagation rate coefficients and tacticities are given in Table 2, with corresponding experimental values shown for comparison (52, 53).

Table 2. A comparison of theoretical and experimentally derived propagation rate coefficients (k_p), Arrhenius parameters (E_a and A) and tacticity.^a

<i>Solvent</i>	<i>Bulk</i>		<i>Water</i>	
	<i>Theory</i>	<i>Exp</i>	<i>Theory</i>	<i>Exp</i>
$\log k_p$	3.68	4.76	4.55	3.73
E_a	15.0	16.1 ± 1.6	10.0	15.0 ± 0.3
$\log A$	6.31	5.58	6.30	6.44
tacticity (r)	91%	68%	87%	81%

^a $\log k_p$ and $\log A$ given in $\text{L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$, E_a is given in kJ mol^{-1} . Experimental values taken from references (17), (24), (52) and (53).

Comparing the theoretical predictions with experiment in Table 2, we note that there is reasonable agreement, to within an order of magnitude, in the k_p across both solvent systems. The theoretical results also correctly predict that k_p increases by roughly an order of magnitude in aqueous solution compared to in bulk MAA. The Arrhenius parameters show a somewhat larger deviation, but are still within the expected range for a first principles prediction of a rate coefficient, particularly in such a highly solvent sensitive system. The activation energy (E_a) in water was found to be around 5 kJ mol^{-1} below the experimental value, although the respective frequency factors (A) were in reasonable agreement. Conversely, for bulk MAA, E_a agreed well with experiment, while A was overestimated by around an order of magnitude. The calculated results correctly predict an increase in propagation rate coefficient of around an order of magnitude moving from bulk to water, but assign this increase to enthalpic rather than entropic effects. While this latter result is contrary to the experimental data, it is not surprising given the use of continuum solvent models for both systems. Continuum solvent models attempt to describe solvation, which is a very complex phenomenon, using a variety of physical approximations. Such models can recreate the average effect of solvation reasonably well; however they may not adequately describe more subtle explicit interactions, such as the dynamic hydrogen bonding effects, expected in these systems. The present results highlight that continuum models can predict variations in reactivity quite well, but need to be employed cautiously in systems where explicit solute solvent interactions are present.

The theoretical predictions of tacticity presented in Table 2 agree qualitatively with experiment; correctly predicting the modest syndiotactic preference of MAA. Quantitatively, tacticity is well predicted in aqueous solutions; with the 6% discrepancy from experiment corresponding to an error of only 1 kJ mol^{-1} in the stereoselectivity. In addition to the tacticities reported in Table 2, we predicted tacticities of $r = 95\%$ in methyl cyclohexanol at 0°C and $r = 99\%$ in isopropyl alcohol at -78°C . These tacticities were also in good agreement with experimental values of 91% and 98%, respectively. This level of agreement corresponds to a consistent overestimation of the syndiotactic selectivity (relative to experiment)

on the order of 1 kJ mol⁻¹, which is reasonably minor in the context of a quantum chemical calculation. However, the tacticity prediction in bulk deviated by 23% from the experimental value, which corresponds to an error of around 4 kJ mol⁻¹ in the stereoselectivity. As tacticity is dependent on the relative energy difference of quite similar reactions, large amounts of intrinsic error cancelation would be expected and so such a large deviation is quite surprising. It is likely that this deviation originates from a failure to consider explicit COOH dimers when modelling propagation in bulk. Such interactions would increase the effective steric bulk of the COOH groups. This increase in the steric bulk of the side-chains would be expected to alter the underlying stereoselectivity of propagation, thereby decreasing syndiospecificity in a manner analogous to bulky methacrylates (54). While explicitly modeling solvent interactions around the COOH groups would likely improve the agreement with the experimentally determined parameters, such considerations would be computationally prohibitive at the high levels of theory used here, and are beyond the scope of the present work.

In contrast to the present results, the previous theoretical study (30) that (incorrectly) equated the rate of formation of *pro-meso* and *pro-racemo* conformations to tacticity, would have concluded that poly(MAA) is slightly isotactic; as transition states leading to *pro-meso* conformations were found have lower electronic energies than the corresponding *pro-racemo* structures. This inference is completely contrary to experimental data, further demonstrating the importance of modelling stereoselectivity with an appropriate chemical model and a kinetically correct mechanistic scheme (in addition to choosing sufficiently accurate theoretical procedures).

Polymerization of Ionized Methacrylic Acid

Having examined the non-ionized MAA systems, we now consider the effects of deprotonation of the propagation kinetics. While the radical polymerization of ionized MAA has attracted significant interest, the exact structure of the propagating species under different conditions remains quite speculative. It is well known that for the monomeric species the degree of ionization is identical to degree of neutralization. However, this correlation is not valid for the polymeric species because of differing p*K*_a values (and thus differing degrees of ionization at a particular p*H*) and because of the accumulation of counteranions on surface of the polyanion (53). These differing p*K*_a values may lead to an exchange of protons and/or counteranions between the COO⁻ groups of the monomer and the polymer terminus (53). Thus, the precise structure of the polymer terminus, which is likely influenced by the identity of the counteranion, degree of ionization and ionic strength, may also vary with conversion. These complexities make the experimental analysis of ionized MAA polymerizations extremely difficult and hence it is not possible to unambiguously determine and validate different kinetic models of propagation.

Clearly it would be desirable to clarify the structure of the polymer terminus in ionized conditions and the mechanism of propagation. However, determining the acidity of all the relevant COOH groups in an MAA polymerization is

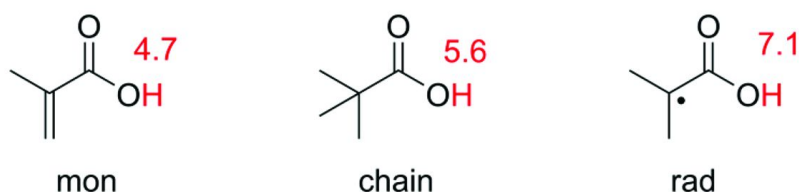
difficult or even impossible with experimental techniques. While measuring the pK_a values of isolated MAA monomer and poly(MAA) is straightforward, it is generally not possible to apply similar experimental methodology to the polymer terminus because of the very low concentration of radical chain-ends in the polymerising medium. As radicals are known to influence the stability of conjugated (55) and even remarkably non-conjugated anions (56), it cannot be assumed that the COOH moieties of the polymer terminus would be deprotonated in an analogous manner to the main chain. This is a situation where theoretical chemistry can provide meaningful insights into the underlying structure of the polymer terminus, which is inaccessible from direct experiments.

pK_a Values of Poly(MAA)

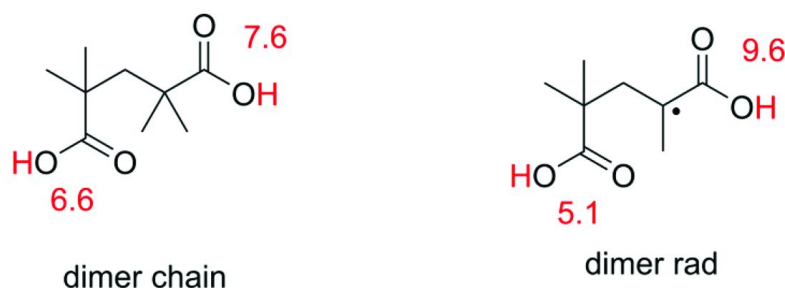
To clarify the protonation structure of the polymer terminus under different conditions, the pK_a values of various model systems were calculated from first principles using a proton exchange approach. Isobutyric (57), glutaric (22) and tricarballic acid (22) were selected as reference acids for monoprotic, diprotic and triprotic systems, respectively. Prior to discussing these pK_a values, the accuracy of the unimeric pK_a predictions was rigorously examined. We note the excellent agreement (to within 0.5 pK_a units) between the predicted pK_a values (see Figure 3) and the experimentally determined values of 4.65 for methacrylic acid (58) and 5.03 for chain (pivalic acid) (59). To assess the influence that the continuum solvation model has on these values, we tested the use of an alternative model, SMD. The absolute pK_a values predicted with SMD were found to be consistently below those predicted by COSMO-RS; Mon: 4.0, Chain: 5.0 and Rad: 6.9. These discrepancies are reasonably systematic and do not significantly affect the relative pK_a values of the unimeric models. These results suggest that the predicted pK_a values are fairly insensitive to choice of the continuum solvent model and so very high accuracy could be anticipated. Having confirmed the high accuracy of the predicted pK_a values, we will now discuss their origin and significance in more detail.

Interestingly, the calculated pK_a values in Figure 3 indicate that the COOH group conjugated to the carbon radical is significantly less acidic than the COOH groups of either the monomer or a model polymer chain segment. These differences were found to originate entirely from their respective gas-phase acidities and can be rationalized by considering the effect of cross-conjugation between the C-centred radical and the COOH/ COO⁻ group. When the COOH is protonated, the C-centred radical can be delocalized on the carbonyl O atom. However upon deprotonation, this resonance is inhibited by the competing delocalization of the O anion in the COO⁻ group. Hence, deprotonation disrupts the delocalization of the radical and is thus significantly more unfavourable than in the comparable non-radical systems. This qualitative rationale is supported by M06-2X/6-31+G(d,p) spin densities, which indicate that the C-centred radical is relatively delocalized in the protonated structure (0.84) and significantly more localized in the deprotonated structure (0.96).

Unimeric



Dimeric



Trimeric

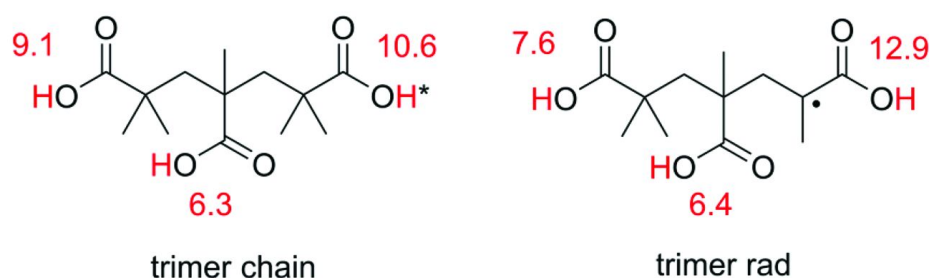


Figure 3. pK_a values of various unimeric, dimeric and trimeric models relevant to MAA polymerization. * Indicates that the respective proton is transferred to the adjacent COO^- group prior to deprotonation (see text).

Having established the influence of the conjugated substituent on $COOH$ acidity, larger and more realistic dimeric and trimeric models were considered. Recently, it was reported that some types of distonic radical anions show remarkable stability compared with analogous non-radical species (56). Thus, we sought to examine if such stabilization could increase the acidities of remote $COOH$ groups of the poly(MAA) terminus. Indeed, we found that the penultimate $COOH$ unit of the dimer radical model is more acidic than the comparable dimer chain system. However in contrast, the pK_{a1} value for the penultimate $COOH$ moiety in the trimer radical system was very similar to the corresponding dimer and trimer chain. Thus, it appears that long-range stabilizing interactions in these poly(MAA) distonic radical anions are negligible, which would be anticipated on the basis of the relatively high localization (and thus low polarizability) of

the C-centred radical and the high dielectric constant of the aqueous reaction medium (56). Instead, the relatively low pK_{a1} in the dimer radical compared to the chain systems probably results from the different stabilities of the intramolecular H-bonds that are formed upon ionization. A similar effect was observed in the trimeric systems, with pK_{a2} of the trimer radical being significantly below that of the corresponding trimer chain model.

Given the significant influence of the (conjugated) substituent on the unimeric pK_a values, it is interesting to contrast the successive ionization behaviour of the trimer chain and trimer radical systems. In the trimer chain system, the first ionization occurs at the central COOH moiety. As anticipated, the second ionization is accompanied by a proton transfer, which protonates the central COO^- at the expense of the remaining terminal COOH group. This proton transfer reduces electrostatic repulsion by maximising the separation between the two resultant COO^- groups. As expected, an analogous proton transfer also occurs in the respective triprotic reference acid, Tricarballic acid. However, in the trimer radical system no proton transfer occurs between the first and second ionization steps. Remarkably, deprotonating the COOH conjugated to the terminal radical is so unfavourable that ionization of the adjacent (penultimate and antepenultimate) COOH groups occurs instead.

Given that Deglmann and co-workers have performed similar calculations on acrylic acid (AA) (51), it is worth briefly comparing their results with the present MAA systems. In the AA systems, Deglmann noted no significant differences between the pK_a values of the COOH moieties of acrylic acid, with all solution-phase acidities differing by less than 1 pK_a unit. We confirmed this earlier computational result with our high level theory (CCSD(T)-F12a/VTZ-F12//M06-2X/6-31+G(d,p) and COSMO-RS solvation corrections), which affords predicted pK_a values of 3.6 for AA monomer, 4.6 for a unimeric AA radical and 4.8 for unimeric AA chain (which is also the reference acid). The results indicate that the cross-conjugation in AA systems is much weaker than in the corresponding MAA models reported in this work.

Ionization of Polymerizing Methacrylic Acid Solutions

These theoretical pK_a values provide a foundation on which to predict the ionization behaviour of polymerizing MAA solutions. However, we should note that these theoretically predicted pK_a values implicitly assume infinite dilution of solutes and hence zero ionic strength. Clearly, the ionic strength of actual polymerizing MAA solutions is non-zero and at high ionic strength Debye shielding would significantly influence these pK_a values. While the monovalent salts of MAA are strong electrolytes, the corresponding salts of poly(MAA) are weak polyelectrolytes and thus the ionic strength of a polymerizing solution decreases with an increase in monomer conversion. As such, the Debye length would depend on the initial monomer concentration and increase with conversion over the course of a polymerization. While incorporating the effects of ionic strength into first principles pK_a predictions is not straightforward, its influence

on speciation can be understood more qualitatively by comparing the Debye length (κ^{-1}) of different solutions to the separation between the COO^- moieties of the polymeric systems. We should emphasize that it is our aim to explore the polymerization of MAA under a diverse range of conditions and not simply the high ionic strength/ low conversion regimes relevant to PLP-SEC experiments.

At high ionic strengths, Debye shielding would likely screen repulsion between the adjacent COO^- groups on the polymer terminus and chain. Thus, direct conjugation effects would likely be the largest influence on the acidities of the different COOH moieties and hence the ionization behavior would probably be best described by the unimeric pK_a values. Even under the high ionic strength regime, the variable acidity of the COOH groups significantly affects speciation between $\text{pH} = 4$ to 8 (see Figure 4). For instance, at $\text{pH} = 6$, most of the COOH groups of the monomer (95%) and the polymer chain (71%) would be ionized, compared with only a small fraction of polymer terminus (7%). At lower ionic strength, Debye shielding would no longer screen repulsion between the adjacent COO^- groups on the polymer terminus and polymer chain. As such, the pK_a values of the polymer terminus and main-chain would be influenced by the ionization state of the nearest adjacent COOH/COO^- group(s). Thus, the tendency or the polymer terminus to ionize would be described by the pK_{a2} of the dimer radical model, while the ionization of the polymer chain would be described first by the pK_{a1} and then subsequently by the pK_{a3} value of the trimer chain model. The larger variation in the COOH acidities would lead to a more dramatic speciation difference with pH (see Figure 4).

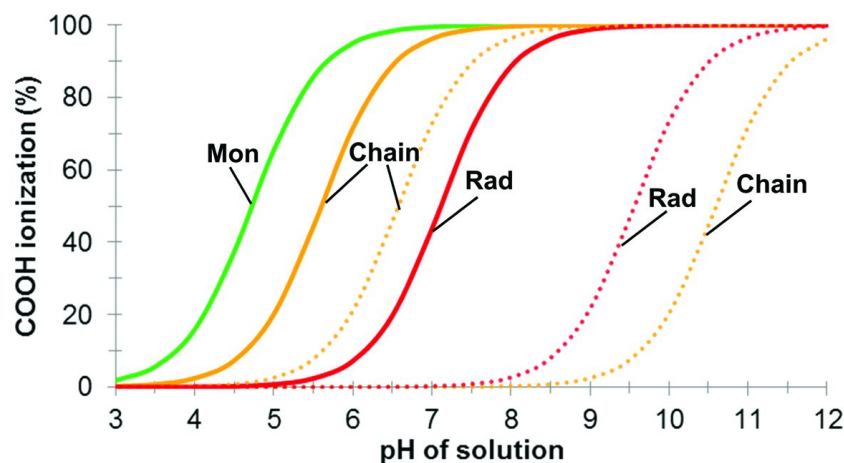


Figure 4. The effect of pH on the ionization of COOH moieties of the polymer radical (Red), main chain (yellow) and monomer (green). Solid lines indicate the predicted speciation using unimeric pK_a values, which is relevant at high ionic strength (I). Dashed lines indicate the speciation predicted by dimer radical (pK_{a2}) and trimer chain (pK_{a1} and pK_{a3}) values, which is relevant at lower I .

Effect of Ionization on the Propagation Kinetics

Having established the relative acidities of the COOH groups in a MAA polymerization, the effects of deprotonation on propagation were examined using progressively ionized models. These models neglect any explicit interactions between the polymer terminus and counteranions. Nevertheless, these calculations are expected to provide a reasonable, albeit imperfect model for systems with large diffuse counteranions, such as $^+\text{NMe}_4$ and $^+\text{NEt}_4$. In addition to neglecting explicit counteranion effects, we should again emphasize that such quantum chemical calculations implicitly assume solvation at infinite dilution and so completely neglect Debye shielding effects. To minimize inaccuracies incurred from the use of continuum solvent models, the barriers and reaction energies for the ionized systems were calculated via a Hess's law thermocycle using experimentally referenced solution-phase acidities and the fully protonated data as a reference. This approach implicitly corrects for errors arising from the treatment of intramolecular H-bonds and anionic systems with continuum solvation models.

Prior to considering larger oligomer systems, the kinetic effects of ionization of the COOH groups were examined using a relatively small dimer transition state model (See Figure 5). Upon ionization of the monomer, the barrier to propagation increases significantly (by around 7 kJ mol^{-1}) as the incoming methacrylate anion hydrogen bonds to the terminal COOH group. This H-bond was found to be very short ($\sim 1.4 \text{ \AA}$) and in the gas-phase C-C bond formation was followed by rapid hydrogen transfer to the new terminal COO^- group. Ionization of the monomer was found to have no significant effect on the thermodynamic favorability of addition. Remarkably, this hydrogen bonded transition structure can itself be used to qualitatively explain kinetic effects observed in experimental PLP-SEC studies. In these studies, a decrease in both E_a and A is observed with increasing monomer ionization. We speculate that these decreases could be caused by the formation of a strong hydrogen bond (upon ionization) between the radical chain-end and incoming monomer. Such a bond would likely stabilize the transition structure enthalpically and so lower E_a but would also significantly increase its rigidity and so also decrease A . Ionization of both COOH groups dramatically increases the barrier for propagation (by more than 20 kJ mol^{-1} compared to the fully protonated structure) and also significantly reduces its thermodynamic favorability. As argued quite intuitively in classic studies of ionized MAA propagation, these effects are readily attributable to the electrostatic repulsion between the adjacent COO^- groups of the monomer and radical. However, as discussed by Buback and co-workers, electrostatic repulsion between COO^- groups does not play a significant role in PLP-SEC experiments, which are performed at high ionic strength where repulsive interactions are adequately screened (53).

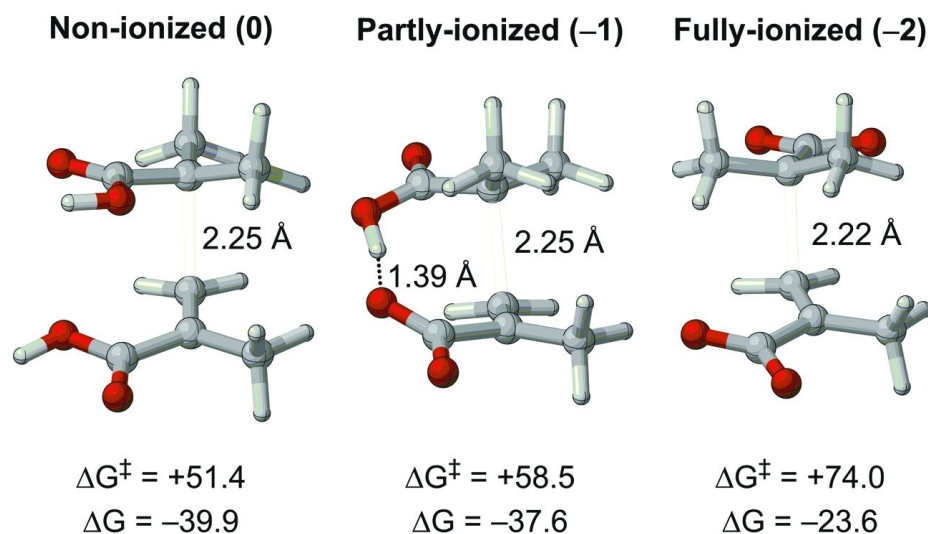


Figure 5. A comparison of progressively ionized dimeric transition structures (charge given in parenthesis), respective aqueous barriers and corresponding reaction energies (in kJ mol^{-1}) at 25 °C. Forming C-C bond and H-bond distances are indicated.

These calculations suggest that at high pH, under conditions where adjacent COO^- repulsion is not adequately screened (i.e., low ionic strength), addition of methacrylate anions to the ionized radical terminus would be very slow. This does not necessarily preclude propagation completely, as counteraction condensation may still facilitate some chain growth. While reports of propagation rates coefficients for ionized MAA at low ionic strength are rare, it is interesting to compare the results of Sontag and co-workers (60) to the present calculations and PLP-SEC studies. Using ESR, Sontag estimated the propagation rate for ionized MAA at high pH at very low ionic strengths, finding a k_p of $15 \text{ L mol}^{-1} \text{ s}^{-1}$ (60). Interestingly this value is around a factor of 30 smaller than a comparable value determined at high ionic strengths by Buback and co-workers, using PLP-SEC experiments (53). While this difference may simply reflect uncertainties in the ESR determined rate coefficient, it could also be indicative of ionic strength effects on propagation rate. Indeed, Sontag and co-workers also found that under such high pH low ionic strength conditions, poly(MAA) showed an enhanced tendency to depropagate and bimolecular termination was retarded, presumably because of electrostatic repulsion between the ionized polymer termini (60).

To allow rough predictions of stereoselectivity under ionized conditions, monomer addition via this hydrogen bonded transition state was examined for trimeric radicals. The geometries of the lowest energy syndiotactic and isotactic transition states for the addition of ionized monomer to trimeric poly(MAA) are shown in Figure 6. The predicted stereoselectivity for these additions is $r = 93\%$ at 25 °C, increasing from $r = 89\%$ for the corresponding non-ionized reaction. Interestingly, these results suggest that even ionizing the monomer notably increases the stereoselectivity of propagation. While further ionization of these propagating isotactic and syndiotactic polymer chains could also be investigated in a similar manner, we found the computational cost associated with these predictions was prohibitive. It is also unclear if such predictions of tacticity and propagation rate would be relevant to any practical systems and so correlating these predictions with experimental data would be very difficult. As such, we limit our focus to the present mono-anionic transition states, which are expected to provide reasonable chemical models, even at high ionic strength.

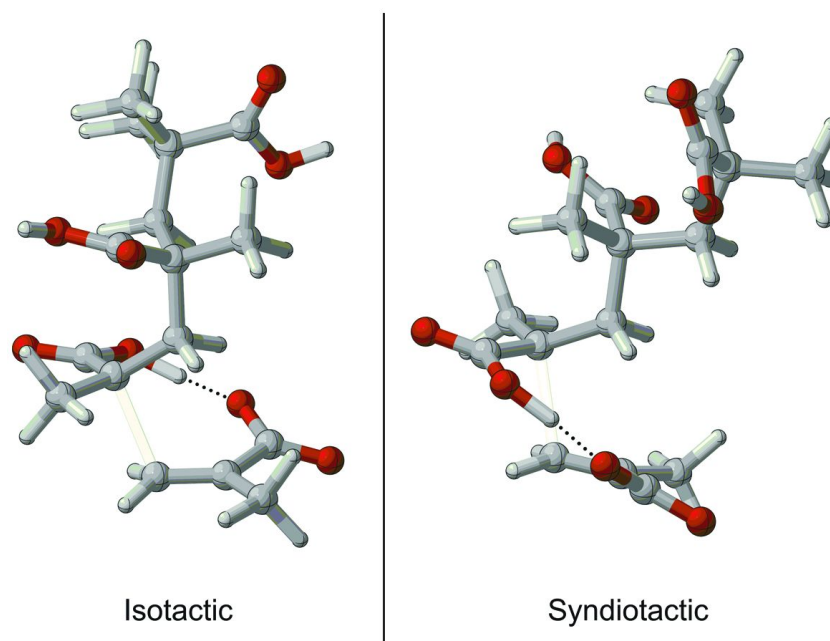


Figure 6. The geometries of the lowest energy transition states leading to isotactic (meso) and syndiotactic (racemo) addition of ionized monomer to a poly(MAA) trimer.

Conclusions

Returning now to the experimental data of Table 1, where it is clear that a given temperature, syndiotacticity increases with solvent polarity and ionization, we note that accurate quantum chemistry can correctly account for these effects and explain their origin (see Figure 7). In particular, in an ionized MAA

polymerization the formation of hydrogen bonds in the transition states between the incoming monomer and radical leads to an increased syndiotactic tendency. Ionization of the COOH groups of the polymer chain itself would likely increase this syndiotactic selectivity further, although under high ionic strength conditions the resultant electrostatic repulsion may be at least partly screened by Debye shielding. In bulk MAA polymerizations, the syndiotactic tendency is lowered because hydrogen bonding of the side chains with the monomer increases the effective bulk of the side chain creating helical structures in which steric repulsion favours an isotactic tendency in a manner analogous to bulky methacrylates. Moreover, on the basis of the transition structures of the ionized and partially ionized species, we can also tentatively attribute counteraction dependencies in the stereoselectivity of ionized MAA to the structure of the charged species. Large diffuse cations such as $^+\text{NMe}_4$ and $^+\text{NEt}_4$ would not be expected to interact strongly with the propagating polymer terminus and hence highly syndiotactic polymer would be formed. In contrast, smaller and more charged cations such as Ca^{2+} would likely chelate to COOH/COO $^-$ groups around the polymer terminus and such chelation would likely increase the isotacticity of the polymer.

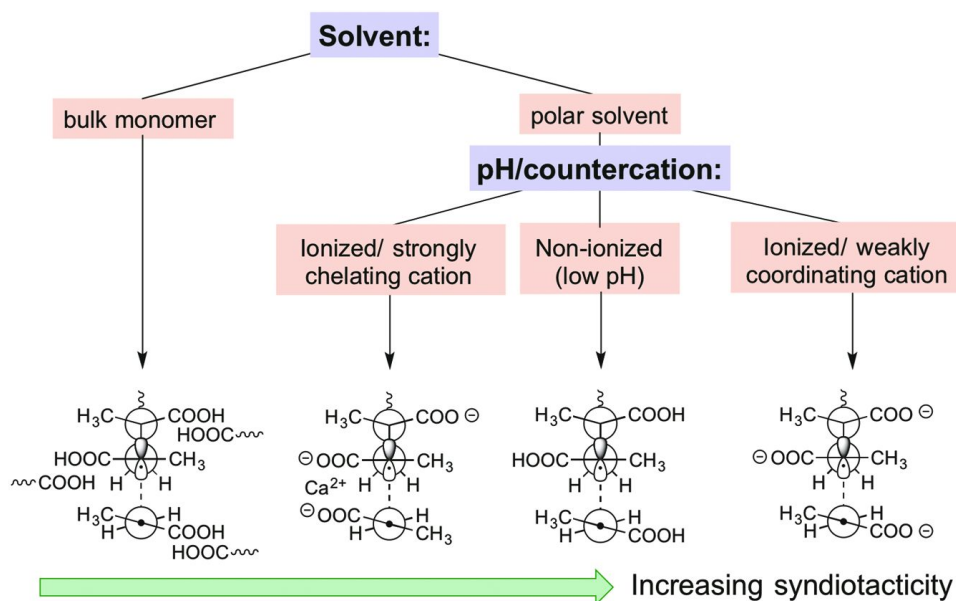


Figure 7. Mechanistic interpretation of stereocontrol in methacrylic acid polymerization.

Acknowledgments

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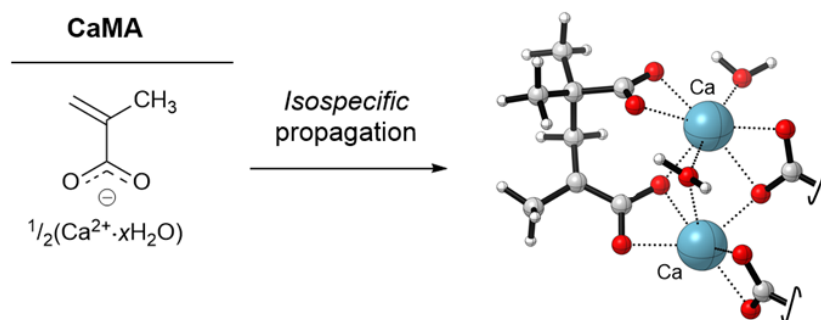
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5.3 Publication 7

Isotactic Regulation in the Radical Polymerization of Calcium Methacrylate: Is Multiple Chelation the Key to Stereocontrol?

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Draft Manuscript (In Prep)



The following is a draft manuscript for a regular original research article. The literature overview, computational and experimental results and discussion presented are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.

Isotactic regulation in the radical polymerization of calcium methacrylate: Is multiple chelation the key to stereocontrol?

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In the present work we use accurate quantum chemistry to explain the origins of isospecificity in radical polymerization of calcium methacrylate hydrate (CaMA). Distonic radical-cation interactions are shown to be crucial in determining the reactivity of different coordination structures. Cation coordination to the terminal and monomer side chains leads to shorter radical-cation distances and enhances the reactivity of these modes over the stereocontrolling terminal-penultimate binding modes. This is why Lewis acid mediated radical polymerization often fails to produce highly isotactic polymer for common monomers such as methyl methacrylate. In the case of CaMA, however, theoretical calculations suggest that the poly(CaMA) terminus forms a chelated bridging scaffold in DMF, and on this basis we propose that isotactic control in CaMA results from the multiple chelation of the terminal, penultimate and incoming monomer carboxylate groups within this bridging scaffold. The bridging scaffold is disrupted in more polar solvents and/or if alternative non-chelating counter-cations are employed, leading to loss of isotactic control. These results suggest that higher levels of isotactic control may be achievable if reaction conditions are optimized to favour bridging scaffold formation. The broader importance of these findings to stereocontrol in radical polymerization is also discussed.

Introduction

The aim of polymer synthesis is to construct macromolecules with well-defined and precisely controlled microstructures. Controlled radical polymerization has revolutionized synthetic polymer chemistry by providing a convenient radical-based route to polymers with narrow polydispersities and customizable chain-end functionalities.¹ Unfortunately, most radical-based polymerizations still result in polymer with poorly regulated stereochemistry (tacticity). Over the last 50 years, much pioneering research has explored strategies to synthesize stereoregular polymers via radical polymerization, although this endeavour has proved enormously challenging.² In an attempt to emulate the excellent stereoselectivity of anionic and coordination polymerizations, various studies have examined the incorporation of metal cations in radical polymerizations.² Such cations can coordinate to the pendent side-chains of the polymer terminus and influence the stereoselectivity of propagation. While arguably less practical than employing simple chemical additives (such as metallic Lewis acids), altering the inherent monomer structure to include ionic auxiliaries can afford reasonably stereoregular polymer.²

As the COOH groups of methacrylic acid (MAA) can be readily ionized by both organic and inorganic bases,

stereoselectivity in the radical polymerization of methacrylate salts has been investigated in numerous studies over last 5 decades (see Table 1).³⁻¹³ A majority of these studies have examined the stereochemical effect of various counter-cations in aqueous solutions,³⁻¹⁰ where ionic interactions are weakened by the high dielectric constant of water ($\epsilon \sim 78$).¹⁴ Under these conditions, polymers with syndiotactic triad fractions (*rr*) ranging from 39 to 92% are obtained, depending on the counter-cation identity and polymerization temperature.³⁻¹⁰ While there are a plethora of studies that investigate the stereoregulating effect of different counter-cations in aqueous conditions, there are comparatively few studies in other solvents.¹¹⁻¹³

Around 25 years ago, Okamoto and coworkers found that the radical polymerization of the dimethylacrylic salt of trans 1,2-diaminocyclohexane in CHCl_3 at 60 °C afforded polymer with a slightly lower syndiotactic content (*rr* = 35%),¹¹ compared with bulk MAA polymerisation (*rr* = 45%).¹⁵ Subsequently, Ishigaki found that the resultant polymer stereochemistry in the radical polymerization of zinc methacrylate in CHCl_3 could be influenced by various bidentate ligands, although the stereochemistry of the polymers obtained was not highly regulated.¹² More recently, Kadokawa et al. reported that the radical polymerization of the calcium methacrylate hydrate (CaMA) in *N,N*-dimethylformamide (DMF) afforded polymer with an isotactic triad fraction (*mm*) of 60%.¹³ Kadokawa noted that obtaining this high level of isotactic selectivity was dependent on a prudent choice of solvent and was significantly lowered as the

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polarity of the reaction mixture was increased by progressive addition

of

Table 1. Selected examples of the radical polymerizations of methacrylic acid salts^a

Counter-cation	Solvent	[M] ₀ (mol L ⁻¹)	Temp (°C)	Yield (%)	Triad tacticity (%)			Ref
					<i>mm</i>	<i>mr</i>	<i>rr</i>	
None ^b	bulk	11.79	60	–	9	46	45	15
None ^b	water	3.87	45	100	4	33	64	16
H ₃ N ⁺ i-Bu	water	0.92	60	–	>1	12	87	17, 18
NH ₄ ⁺	water	0.92	60	–	>1	17	83	17, 18
Na ⁺	water	0.92	60	–	5	34	61	17, 18
NMe ₄ ⁺	water	0.63	60	–	4	17	79	19
NEt ₄ ⁺	water	0.47	60	–	4	16	80	19
NEt ₄ ⁺	water	0.47	5	–	>1	8	92	19
None ^b	DMF ^c	1.00	60	97	5	30	65	20
Ca ²⁺	DMF ^c	0.33	60	54	60	35	5	20
Ca ²⁺	DMF ^c /toluene (1:2)	0.33	60	56	65	30	5	20
Ca ²⁺	DMF ^c /water (1:1)	0.33	60	98	22	45	33	20
Ca ²⁺	water	1.00	60	99	6	36	58	20
Mg ²⁺	DMF ^c	1.00	60	72	20	48	32	20
Li ⁺	DMSO ^d	1.00	60	98	29	53	18	20

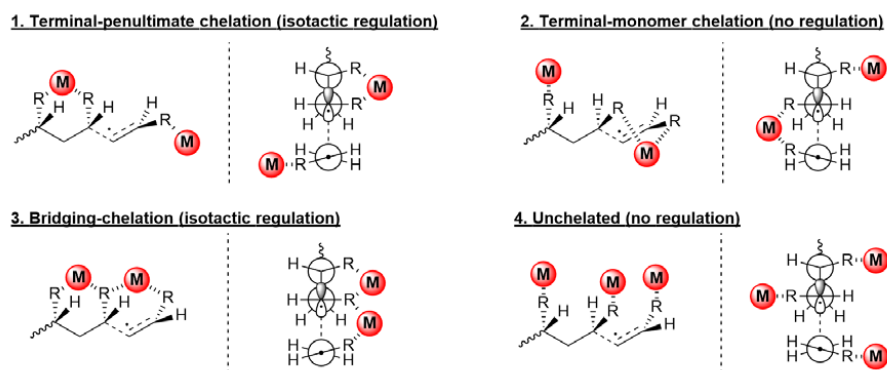
^a[M]₀ denotes the initial monomer concentration, mixed solvent volume ratio is given in parenthesis and “–” indicates quantity not reported. ^bNone denotes unionized methacrylic acid (MAA). ^cN,N-dimethylformamide. ^dDimethyl sulfoxide.

water.¹³ Conversely, lowering the polarity of the reaction mixture by the progressive addition of toluene improved the isotactic regulation (to *mm* = 65%).¹³ Interestingly, Kadokawa also noted that the radical polymerization of lithium and magnesium methacrylate hydrate (MgMA) under comparable conditions afforded predominantly atactic polymers, with an *mm* of 29 and 20%, respectively.¹³

Intriguingly, in addition to influencing polymer stereochemistry, metal cations can enhance the reactivity of radicals toward C=C and C≡C bonds.^{21–23} Pioneering theoretical work by Clark has uncovered the importance of odd-electron interactions with metal ions in the radical addition reactions of non-polar alkenes^{24, 25} and several radical ring closures (so called ‘radical-clock’ reactions).^{26, 27} More than 25 years ago, Clark predicted that radical addition to non-polar alkenes could be catalysed by coordination of Li⁺ to the C=C bond.²⁴ Michl et al. later experimentally verified this prediction, finding that the Li⁺ salts of a non-coordinating carboborane anion could facilitate the radical polymerization of 1-alkenes by catalysing propagation over the degenerative hydrogen transfer reactions that otherwise impede the formation of high polymer.^{21–23} Clark demonstrated that these rate accelerations are predominantly caused by electrostatic effects and suggested such catalysis does not require covalent interactions between the metal cation and the C=C bond.^{25, 26} Indeed, in a previous theoretical study, Clark found that the rate of a radical ring closure could be enhanced by roughly 18-fold via the complexation of the coordinatively saturated Li⁺(tetrahydrofuran)₄ species to the C=C bond. This catalysis was observed despite the relatively large 4.5 Å separation between the Li⁺ and the forming radical centre.²⁶ More recent theoretical and experimental studies, focussing on distonic radical anions rather than cations, suggest electrostatic stabilization of delocalised radicals may be a general phenomenon.^{28–31}

While Clark has thoroughly examined odd-electron catalysis in non-polar alkenes, the potential importance of these interactions in polar monomer systems is not widely appreciated and remains comparatively underexplored. Recently, we demonstrated that lithium bis(trifluoromethane) sulfonamide (LiNTf₂) significantly increased the propagation rate coefficient of methyl methacrylate (MMA) by using pulsed laser polymerization.³² Theoretical calculations also indicated that coordination of Li⁺ to the ester moiety of a unimeric MMA radical increased the radical stabilization energy (RSE) by between 5 to 8 kJ mol⁻¹, depending on the extent of cation solvation.³² Similar catalysis was also very recently reported in the LiNTf₂ mediated radical polymerization of N,N-dimethylacrylamide,³³ which suggests that such catalysis may be relevant to a wide-array of polar systems. The results suggest that distonic radical-cation interactions are significantly influencing both the stability of the polymer terminus and the reactivity of different propagation pathways.

The structure of polymer terminus would be expected to significantly influence stereoselectivity during polymerization. In principle, a bifunctional monomer, such as CaMA or MgMA, can propagate via 4 different pathways (see Scheme 1). Unfortunately, the precise solution-phase structure of the poly(CaMA) and poly(MgMA) termini is quite speculative and thus the mechanistic origins of isotactic regulation are poorly understood. These uncertainties make it difficult to rationally select counter-cations and reaction conditions that will improve existing stereocontrol. Consequently, optimising stereoselectivity is reliant on tedious trial and error experimentation. Clearly, it would be desirable to clarify both the coordination structure and the mechanism underlying isotactic regulation in these systems; unfortunately doing so is difficult or even impossible using experimental techniques. In this context, theoretical chemistry is a particularly valuable tool that can provide meaningful insight into the structure and reactivity of these novel systems.



Scheme 1 Idealised propagation pathways for bifunctional ionic monomers of the form $H_2C=CHR$, where $R = COO^-$. These scenarios illustrate the possible positions of metal ion (M^{2+}) coordination to the growing polymer terminus.

In our previous study of the radical polymerization of MMA mediated by $LiNTf_2$, we found that the expected stereocontrol afforded by terminal-penultimate chelation was undermined by the kinetic favourability of the terminal-monomer mode.³² This kinetic favourability can be rationalized by considering the underlying distonic radical-cation interactions in the respective transition structures. Specifically, the kinetic favourability of the terminal-monomer chelate pathway would be enhanced by the close proximity of Li^+ to the forming radical, while conversely the relatively large radical-cation separation in the terminal-penultimate mode would comparatively inhibit monomer addition. Given distonic radical-cation interactions are predominantly electrostatic in origin, one would reasonably anticipate that these selectivity issues could be relevant for polymerizations involving methacrylate (and acrylate) salts and most, if not all, Lewis acid-mediated polymerizations. In this light, the relatively high of isotacticity in certain CaMA polymerizations is intriguing.

In this work, we use accurate quantum chemistry to examine the origin and limitations of isotactic selectivity in CaMA. We also propose explanations for the variation in control observed using different counter-cations and solvents. In this way, we hope to identify strategies for further optimizing isotactic control in this particular system, which is important in its own right as an ionic auxiliary for MMA polymerization. Moreover, understanding how the catalysis versus stereocontrol dichotomy is resolved in CaMA may lead to better strategies for stereocontrol more generally.

Methodology

In this work, we employed the high-level composite *ab initio* G3(MP2)-RAD(+) method, which is a variant of normal G3(MP2)-RAD³⁴ where the calculations with the 6-31G(d) basis set are replaced with corresponding 6-31+G(d) calculations to allow for better treatment of the anionic species. In larger systems where this high-level method was infeasible, we used R(O)MP2/GTMP2L in conjunction with an ONIOM inspired

approximation.^{35, 36} Throughout this work, we used M06-2X/6-31+G(d,p) geometries³⁷ and appropriately scaled frequencies³⁸ to obtain accurate gas-phase free energies. For all calculations involving calcium, we adopted Rassolov's 6-31+G(d) and 6-31+G(d,p) basis sets³⁹ rather than the Gaussian default. Similar methodology has been previously shown to predict accurate values for the kinetics and thermodynamics of a wide range of radical reactions, including propagation.⁴⁰⁻⁴²

As the novel systems investigated in this work feature alkali metals, we also benchmarked R(O)MP2/GTMP2L against G3(MP2)-RAD(+) for a test set of 105 absolute binding enthalpies for some representative Ca^{2+} and Mg^{2+} species. This benchmarking confirmed the excellent intrinsic accuracy of R(O)MP2 for COO^- , DMF and H_2O binding enthalpies to various Ca^{2+} and Mg^{2+} complexes, with a mean absolute deviation (MAD) of only 3.6 kJ mol⁻¹ and a maximum deviation of 9.4 kJ mol⁻¹. Moreover, these deviations were found to be quite systematic, as indicated by the mean signed deviation (MSD) of -3.3 kJ mol⁻¹. Thus, when calculating relative binding enthalpies, such as ligand exchange enthalpies, large degrees of intrinsic error cancellation would be expected and even higher accuracy could be anticipated.

All standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were carried out using Gaussian 09⁴³ and Molpro 2012⁴⁴ software packages. A more detailed description of all the computational procedures, benchmarking, conformational searching, as well as full set of obtained results can be found in the Electronic Supplementary Information.[†]

Results and Discussion

From the previous experimental work, it is clear the isotactic selectivity of bifunctional methacrylate monomers is highly dependent not only on the identity of the counter-cation but also the polymerization conditions. Concurrently, previous theoretical work hints at the potential importance of distonic radical-cation interactions and casts doubt on the kinetic

feasibility of the terminal-penultimate propagation pathway, which is the most intuitively obviously mechanism for isotactic regulation. These studies raise several questions regarding the structure and reactivity of the poly(CaMA) and poly(MgMA) termini, namely: Are distonic radical-cation interaction significant in these ionic systems? Is the terminal-monomer or terminal-penultimate propagation pathway more reactive and could this be a general trend applicable to other monomer systems? What is structure of the respective polymer termini? Perhaps most critically, what is the mechanistic origin of the isotactic selectivity in CaMA, why is this selectivity not observed in MgMA and why is the stereocontrol condition dependent? To answer these questions, we have employed *ab initio* quantum chemistry. So that accurate calculations can be performed on these highly complex systems, the polymer termini have been truncated to relatively small oligomeric models. None of the oligomers examined in this study are large enough to allow for a quantitative prediction of tacticity, which requires at least tetrameric transition state models.⁴⁵ Instead, we aim to use theory more qualitatively to explore the interactions occurring at the polymer terminus and investigate the potential origins of stereoselectivity. Results of this computational investigation are now presented and discussed in turn.

Distonic Radical-Cation Interactions

In the radical polymerization of a methacrylate salt, such as CaMA or MgMA, there are 3 functionally distinct COO[−] moieties that differ in their primary substitution (see Fig. 1): those of the monomer (Mon), polymer terminus (Rad) and polymer mid-chain (Chain). Previous theoretical work that examined these models in aqueous solution found that the Rad unimer had a proton affinity that was around 1.5 - 2.5 pK_a units higher than the Mon or Chain; indicating a significant difference in the Brønsted basicities of the respective carboxylate groups.⁴⁵ To evaluate the potential importance of distonic radical-cation interactions, the relative binding enthalpies of these models to a variety of Ca²⁺ and Mg²⁺ species was calculated, as the cations were progressively solvated by both DMF and H₂O (see Table 2). The change in the radical stabilization energy (ΔRSE) of the Rad model upon metal-ion complexation was also calculated.

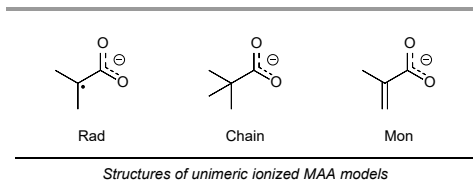


Fig. 1 Ionized unimeric models of the polymer terminus (Rad), polymer chain (Chain) and MAA[−] monomer (Mon).

Interestingly, these calculations indicate that the Rad unimer has significantly greater binding enthalpies to comparably solvated Ca²⁺ and Mg²⁺ species than the Chain or Mon models. In contrast, no significant variation was observed

in the binding enthalpies of the Mon and Chain models, which differed by < 3 kJ mol^{−1} in a majority of the systems examined. These calculations also indicate that the carbon-centred radical is stabilised by the coordination of Ca²⁺ or Mg²⁺ to the COO[−] moiety, with the radical stabilisation energy (RSE) increasing by 6 - 28 kJ mol^{−1} relative to the uncoordinated Rad species, depending on the identity of the coordinating cation and the extent of its solvation. To confirm that this stabilization originates from electrostatic effects, the change in RSE upon metal-ion coordination was compared to the separation between the carbon-centred radical and cation (see Fig. 2).

Table 2 Relative binding enthalpies^a of unimeric models to various Ca²⁺ and Mg²⁺ species.

Species	Chain	Mon	ΔRSE ^b
Ca ²⁺	27.3	27.9	24.0
Ca ²⁺ (H ₂ O)	24.5	25.2	20.8
Ca ²⁺ (DMF)	20.3	21.8	17.1
Ca ²⁺ (H ₂ O)(DMF)	13.7	14.5	9.9
Ca ⁺ (Mon)	14.9	15.7	10.6
Ca ⁺ (Mon)(H ₂ O)	14.0	14.5	10.0
Ca ⁺ (Mon)(DMF)	12.4	13.2	8.8
Ca ⁺ (Mon)(H ₂ O)(DMF)	12.3	13.5	9.0
Ca ⁺ (Mon)(H ₂ O)(DMF) ₂	3.8	10.1	5.9
Mg ²⁺	30.0	31.8	27.4
Mg ²⁺ (H ₂ O)	27.1	28.3	23.6
Mg ²⁺ (H ₂ O) ₂	24.1	25.0	20.4
Mg ²⁺ (DMF)	24.2	25.4	20.4
Mg ²⁺ (H ₂ O)(DMF)	21.0	22.5	17.3
Mg ⁺ (Mon)	15.9	17.8	12.0
Mg ⁺ (Mon)(H ₂ O) ₂	13.8	16.2	10.1
Mg ⁺ (Mon)(DMF)	12.4	12.1	8.9
Mg ⁺ (Mon)(H ₂ O) ₂ (DMF)	10.4	12.3	8.1
Mg ⁺ (Mon)(H ₂ O) ₂ (DMF) ₂	11.7	8.8	6.4

^a Relative binding enthalpies are referenced against the corresponding Rad species, calculated at 25 °C and are reported in kJ mol^{−1}. ^b The change in radical stabilization energy (RSE) relative to the uncoordinated Rad species.

As indicated in Fig. 2, the change in the RSE relative to the uncoordinated species is closely correlated to the distance between the radical and cation; increasing by as much as 8 - 10 kJ mol^{−1} for every 0.1 Å shortening of this separation. This relationship appears to be approximately reciprocal, as suggested by Coulomb's law. The horizontal displacement of the Ca²⁺ and Mg²⁺ curves in Fig. 2 probably reflects the different polarities of the cation/COO[−] bond. Consistent with their respective electronegativity's, the Ca²⁺ systems were found to have higher amounts of charge localized on the metal atom compared with the analogous Mg²⁺ species.

While noting the close correlation of ΔRSE to radical-cation separation, we caution against using Fig. 2 to infer absolute distance cut-offs for these interactions. RSEs arbitrarily define the stabilization of a radical species, R[•], as the relative C-H bond dissociation energy (BDE) of R-H referenced against the BDE of CH₃-H. If instead the strength of the distonic radical-cation interaction was gauged by the C-C BDE of R-CH₃ referenced against CH₃-CH₃, which is arguably also a valid

proxy for inherent radical stability,⁴⁶ an additional stabilization of 2–5 kJ mol^{−1} is observed in most systems. This would in turn suggest a longer distance cut-off before these interactions become negligible. For the purposes of the present work, we simply note that distonic radical-cation interactions have a significant stabilizing effect in model CaMA and MgMA systems, which is strongly dependent on the distance between the radical and cation.

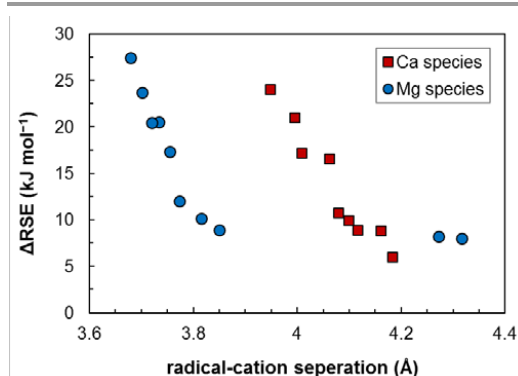


Fig. 2 The correlation between the increase in radical stabilization energy (ΔRSE) and the separation of the radical and metal cation.

Catalysis vs. Stereocontrol

Perhaps the most intuitive mechanism for isotactic regulation in CaMA is via the formation of a kinetically labile chelate complex between Ca²⁺ and the terminal and penultimate COO[−] groups of the poly(CaMA) terminus. Chelation in this position would presumably prearrange the poly(CaMA) terminus into linear *pro-meso* configurations and thus impart an energetic preference for isotactic propagation. This mechanism is also analogous to the mechanism of isotactic regulation that has been cited in Lewis acid-mediated radical polymerization.^{47–57} However, even if it can be assumed that the COO[−] groups are chelated in a pairwise manner, there is still a second propagation pathway available where Ca²⁺ coordinates between the terminal and incoming monomer side-chains instead. This alternative coordination mode would

not regulate the relative orientation of the terminal and penultimate COO[−] groups and thus it is unlikely to have high isotactic selectivity. Consequently, unless there is a significant kinetic preference for the terminal-penultimate propagation pathway, the terminal-monomer mode will counter any expected isotactic control. To examine if there is any kinetic selectivity between these two pathways, the propagation of dimeric models of CaMA and MgMA via the terminal-penultimate and terminal-monomer pathway was considered. The geometries relative energies of the terminal-penultimate and terminal-monomer transition structures of CaMA and MgMA are illustrated in Fig. 3. For these illustrative calculations we modelled CaMA and MgMA as mono- and dihydrates, respectively.

Remarkably, despite the structural similarities of the terminal-penultimate and terminal-monomer transition states, the latter mode is favoured by 11.3 and 11.8 kJ mol^{−1} in CaMA and MgMA, respectively. In both systems, this preference was found to originate entirely in the enthalpic component of the free-energies and is somewhat counteracted by the entropy. The terminal-monomer mode was favoured by 15.2 and 18.8 kJ mol^{−1} in CaMA and MgMA, respectively.

While the importance of distonic radical-cation interactions in these propagation pathways may not be immediately obvious, they provide a foundation for rationalizing the observed kinetic selectivity. Radical-cation stabilization would favour propagation pathways that maintain short radical-cation distances. Chelation moves the metal cation out of the COO[−] plane, which positions it closer to the intervening backbone segment. Consequently, the terminal-monomer pathway positions the Ca²⁺ cation much closer to the forming radical (3.89 Å) than the terminal-penultimate mode (4.09 Å), which accounts for the surprising difference in their stability. Analogous effects are observed with Mg²⁺, with the terminal-monomer pathway situating the cation 0.20 Å closer to the forming radical centre than the terminal penultimate pathway. We should emphasize that distonic radical-cation interactions are certainly not the only influence on structure and reactivity in these systems; but they are particularly pertinent when comparing propagation pathways that differ only in the position of cation chelation.

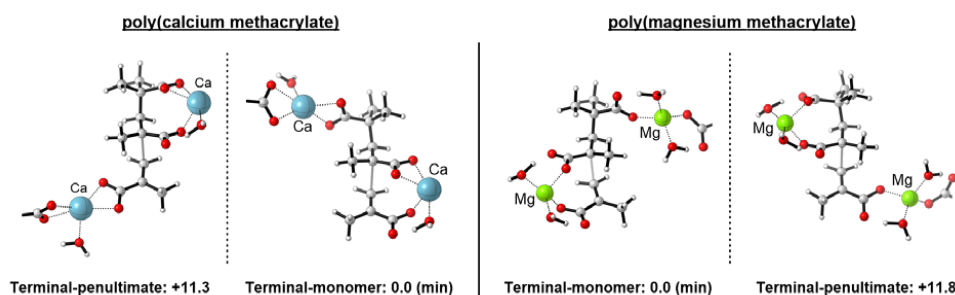


Fig. 3 The geometries and relative free-energies (at 25 °C, in kJ mol^{−1}) of trimeric terminal-penultimate and terminal-monomer transition structures for CaMA and MgMA. In these illustrations, solvating methacrylate anions (Mon) around the metal ions have been truncated for clarity.

While the favourability of terminal-monomer propagation can be rationalized satisfactorily on the basis of distonic radical-cation stabilization, it is completely contrary to the requirements of the previously proposed terminal-penultimate mechanism. To be a viable explanation for the origin of isotactic selectivity, the terminal-penultimate pathway would need to be not only competitive with the terminal-monomer mode but actually the dominant propagation pathway. In contrast, these calculations indicate that the non-stereocontrolling terminal-monomer pathway is actually significantly more favourable. Moreover, this selectivity can be fully rationalized by considering the radical-cation separation in the respective systems. These results indicate that the isotactic regulation reported for CaMA cannot be attributed to simple terminal-penultimate chelation as originally suggested.

Coordination Structure of the Polymer Termini

Having found that the terminal-penultimate chelate complex is relatively unreactive, we considered if an alternative structure could account for the isotactic selectivity. In coordination chemistry, COO[−] groups are known to adopt a diverse array of binding modes; dependant on the identity of the metal cation and its ligands. Simple carboxylates salts of Ca²⁺ have a strong tendency to form bridging scaffolds, which result in the formation coordination polymers during crystallization. In particular, the triply bridging $\mu\text{-}\eta^2\text{:}\eta^1$ motif is frequently encountered in calcium carboxylate salts due to the large ionic radii (1.00 Å)⁵⁸ and high coordination number of Ca²⁺ (typically 6-8).⁵⁹ In a comparative study of simple calcium carboxylate crystal structures, Srinivasan et al.⁵⁹ noted that bridging COO[−] coordination is normally observed in the solid-state when there are three or less water molecules coordinated to Ca²⁺. Intriguingly, bridging COO[−] coordination is also observed in the crystal structures of a structural isomer of CaMA, bis(*trans*-2-butenato) calcium⁶⁰ and in small model systems, such as calcium glutarate salts.⁶¹

While bridging carboxylate motifs are undoubtedly favourable in solid-state Ca²⁺ structures, it is perhaps more questionable if these scaffolds can persist in polar solutions.

Interestingly, Buló et al. noted the formation of very stable trimetallic clusters with bridging COO[−] groups and short Ca²⁺-Ca²⁺ distances (~ 4 Å) in molecular dynamics simulations of ionized poly(acrylic acid) in aqueous solution.⁶² Moreover, it has long been known that the addition of ethanol to concentrated aqueous solutions of calcium acetate results in gelation,⁶³ which can be attributed to formation Ca²⁺/COO[−] based coordination polymer networks. It is also worth noting that protic solvents, such as ethanol and water, can stabilize carboxylate groups via hydrogen bonding much more effectively than aprotic solvents, such as DMF.

To elucidate the structure of the poly(CaMA) terminus, the relative stabilities of bridged, chelated and non-chelated dimer models were calculated from first principles. The geometries and best estimates of the relative free-energies of these coordination structures are presented in Fig. 4. We should emphasize that these relative energies properly account for all of the required ligand exchange/ displacement reactions necessary for a fair comparison of these binding modes. Interestingly, the bridging coordination mode is around 40 kJ mol^{−1} more favourable than either the chelated or non-chelated coordination structures; implying that the additional Ca²⁺/COO[−] interactions formed in the bridged dimer are significantly stronger than the Ca²⁺/DMF interactions that would otherwise form from the (further) solvation of either non-bridging species.

These results should be interpreted with some caution, as the calculations were performed in the gas-phase and so may not precisely replicate the actual solution-phase energetics of these exchange reactions. It may seem sensible to apply continuum solvation corrections to these species in an attempt to capture implicit solvation effects (in addition to the explicit effects already included in our model). However, we note that other studies have indicated that using this dual approach does not necessarily yield more accurate results.⁶⁴ Applying an explicit/ implicit solvation approach not only leads to ambiguities with regard to how many explicit solvent molecules to include but can also lead to 'double counting' of some solute-solvent interactions.⁶⁴

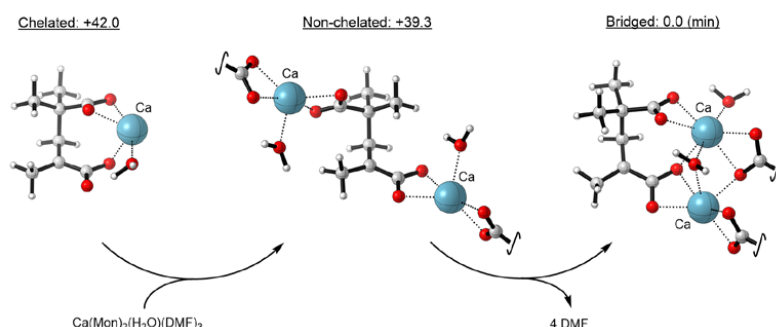


Fig. 4 The geometries and relative free energies (at 60 °C, in kJ mol^{−1}) of the chelated, non-chelated and bridged structures of the poly(CaMA) terminus. Methacrylate monomer (Mon) has been truncated and explicitly solvating DMF molecules have been omitted for clarity.

Notwithstanding this uncertainty, the preference for bridging modes is significant and we can conclude that there is a clear preference for formation of a bridging scaffold, even in the presence of competing ligation by DMF. While the favourability of this bridging mode is surprisingly large in energetic terms, the speciation of the poly(CaMA) terminus will depend on the equilibrium concentration of the various solute and solvent species. In a solution-phase CaMA polymerization, there is a relatively large excess of solvent with respect to other species; with over an order of magnitude more DMF molecules than monomer in a 1 mol L⁻¹ solution. The speciation of the poly(CaMA) terminus will be affected by the large excess of DMF, which would to some extent counter the inherent energetic preference for the bridging mode, and may explain why isotactic control is not perfect in this system.

To examine if the enhanced Lewis basicity of the terminal carboxylate group could favour selective formation of the bridging scaffold at the polymer terminus, dimerization energetics of Ca(Mon)₂(H₂O) to form an analogous monomer-based bridging motif was also investigated. While the carboxylate groups of the monomer are less Lewis basic than those of the polymer terminus, we speculated that perhaps the extra flexibility of these untethered groups might increase the favourability of bridging coordination. In contrast to these expectations, the formation of a bridging scaffold via monomer dimerization was found to be favourable by only 22.0 kJ mol⁻¹. In other words, these calculations suggest that the formation of a bridging scaffold at the poly(CaMA) terminus is over 15 kJ mol⁻¹ more favourable than formation of an analogous structure via monomer dimerization. This free-energy difference was found to result almost entirely from the enthalpic component and indicates that the bridging scaffold at the polymer terminus is over 2 orders of magnitude more stable (at 60 °C) than analogous monomeric structures. Given the significant excess of DMF solvent compared to monomer solute, these calculations suggest that the monomer would not significantly aggregate in DMF solutions and would predominantly exist as ion-pairs (rather than quartets or higher order aggregates).

Magnesium Methacrylate

In contrast to Ca²⁺, Mg²⁺ has a relatively small ionic radius (0.72 Å)⁵⁸ and so its ligands tend to adopt a more rigid octahedral coordination structure. Mg²⁺ normally coordinates to carboxylate groups in a monodentate arrangement, particularly in the presence of protic coligands such as water. Nevertheless, carboxylate salts of Mg²⁺ are also known to form ionic oligomers and polymers in the solid state, particularly in absence of strongly coordinating coligands and if the number of neutral O-donors is less than two.⁶⁵ The studies of Troyanov and Kemnitz, highlight the diverse range of solid-state structures that magnesium acetates can adopt in the presence of different ligands.⁶⁵ Unfortunately, Kadokawa and co-workers do not report the hydration state of the MgMA that they used in their study.¹³ Given their preparative procedure involved mixing magnesium hydroxide with MAA in water,¹³ it is probable that they obtained MgMA as the tetrahydrate.

However, this conclusion would depend on the exact drying procedures employed, as magnesium acetate tetrahydrate can form oligomeric Mg₅(OH)₂(acetate)₈ species on heating.⁶⁶

Because the hydration state of the MgMA used by Kadokawa is uncertain, we did not attempt to predict the solution-phase structure of the poly(MgMA) radical terminus using analogous calculations. Instead, we note more qualitatively, that if MgMA was obtained as a tetrahydrate, it is unlikely that carboxylate bridging structures would form in DMF. Even in the solid-state, magnesium acetate tetrahydrate adopts a non-bridging molecular structure.⁶⁷ It would be desirable to clarify the hydration state of the MgMA to ascertain the likelihood of bridging motif formation. However, even if the poly(MgMA) radical terminus is assumed to form a bridging scaffold, we note that the smaller ionic radius and coordination number of Mg²⁺ would make it much less flexible. It is likely that the more flexible Ca²⁺ structures would better accommodate the inherent rigidity of the growing polymer chains and thus propagate much more readily.

Revised Mechanism

Having confirmed the favourability of the bridging coordination mode for CaMA in DMF solution, it is worth briefly re-examining the mechanism of isotactic control. The bridging binding mode of CaMA provides a mechanistic rationale for this selectivity, as such modes would simultaneously chelate the terminal, penultimate and monomer COO⁻ groups during propagation. Moreover, this complex would effectively position Ca²⁺ in both the stereocontrolling (terminal-penultimate) and catalytic (terminal-monomer) positions. The previously observed solvent dependency can also be readily rationalized. The addition of water would likely disrupt the bridging scaffold at the poly(CaMA) terminus and thus lead to more propagation via the non-stereocontrolling pathways. Specifically, water would dramatically weaken the interaction between the Ca²⁺ and COO⁻ side-chains and could result in proton exchange to the terminal radical. Indeed, previous theoretical work has demonstrated that H-bonding between the protonated terminal radical and incoming methacrylate anions favours racemo propagation.⁴⁵ Conversely, the addition of toluene would likely increase the favourability of the bridging scaffold compared to the other coordination modes (by lowering the dielectric constant of the solution).

The relationship between temperature and isotactic selectivity is much more difficult to predict. Ionic aggregation is usually favoured by increasing temperature, because the accompanying reduction in the dielectric constant of the solvent enhances Coulombic interactions between the component ions. This suggests that the formation of bridging scaffolds should be favoured at higher temperatures. However, the isotactic selectivity of the bridging structures themselves may decrease as temperatures increase and counter the expected enhancements to the overall isotactic content. That is, while increasing temperatures may favour bridging coordination modes, they may also reduce their inherent isotactic selectivity. However, in a mixed solvent

system with a low dielectric constant, competition from non-bridging structures would likely be minimal and hence isotactic selectivity would be expected to decrease as the temperature increases. In other words, competition from non-bridging structures would be expected to be particularly significant at lower temperatures in high dielectric constant solvents, but addition of a non-polar solvent should enhance the control, particularly at lower temperatures.

Conclusions

The radical polymerization of methacrylic acid and its salts is known to give rise to a diverse array of tacticities depending on the counter-cation and reaction conditions. In particular, in DMF, CaMA can afford a surprisingly high degree of specificity, which is valuable in its own right and as an ionic auxiliary for methyl methacrylate. In the present work, we have used high-level quantum chemistry to explain this useful and intriguing behaviour. High-level calculations demonstrate the importance of distonic radical-cation interactions in polar systems. Moreover, calculations suggest that isotactic control results from bridging modes, which simultaneously catalyse and control the stereochemistry by binding the monomer, terminal and penultimate side-chains simultaneously.

Optimization of the energetic preference for bridging modes, through temperature, solvent and choice of counteraction, should lead to improved isotactic control in these systems. More generally, it highlights a potential control strategy for resolving the catalysis versus stereocontrol dichotomy previously identified for the LINTf₂-mediated polymerization of MMA. Difficulties that arise from the high reactivity of non-stereocontrolling terminal-monomer binding modes can be overcome by simultaneously coordinating cations in all three (terminal, penultimate and monomer) positions. While such bridging modes are more readily targeted in ionic monomers, they may be achievable in other systems through the use of suitably designed bridging ligands or large diameter high coordination number Lewis acids. Work in this direction is currently underway.

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6. Nitroxide-Mediated Polymerization of Vinyl Chloride and Electrostatic Effects on TEMPO Monolayers

6.1 Overview

Nitroxide-Mediated Polymerization (NMP) is one of the most popular and widely-employed living-radical polymerization methodologies. NMP utilizes stable nitroxide radicals to reversibly deactivate the propagating polymer radicals (see **Figure 9**). Over the last few decades, the successful NMP of a broad array of monomers has been reported and a variety of novel polymeric architectures (including block, graft and random copolymers, brushes, stars) have been synthesized.^{18, 127, 128} However, the polymerization of non-activated monomers, such as vinyl esters, vinyl amides and vinyl halides, has posed a significant challenge for NMP (and other living-radical procedures as well).³⁹ In these monomers systems, the high reactivity of the propagating radical facilitates various side-reactions that can interfere with the reversible deactivation reactions of various living-radical processes.¹²⁹ Vinyl chloride (VC) is one of the most industrially and commercially important monomers; globally, poly(VC) is the third most produced plastic polymer.¹³⁰ As is typical for non-activated monomer systems, synthesising poly(VC) with a narrow molecular weight distribution and well-defined chain-end functionality has proven to be very difficult. In the first part of this stand-alone chapter, the low temperature NMP of VC is investigated using a combination of experimental and theoretical techniques [*Publication 8*].

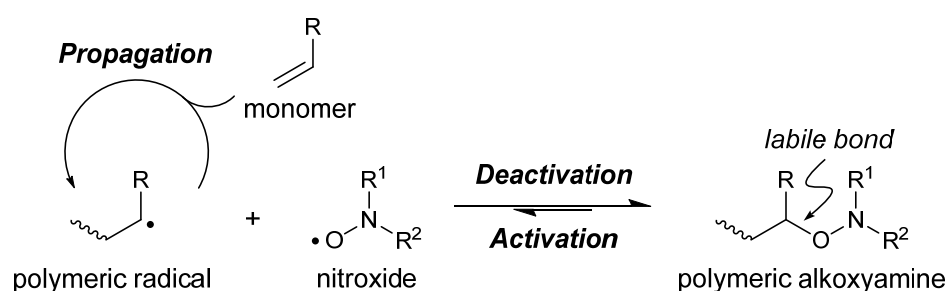


Figure 9 The governing activation-deactivation equilibrium of a normal NMP.

Remarkably, experimental work demonstrated that the NMP of VC mediated by BlocBuilder® was feasible at low temperatures (30 – 42 °C). The living nature of this polymerization was confirmed via various chain-extension experiments and poly(VC)-poly(MMA) based block copolymers were synthesized. This surprising experimental result is completely counter-intuitive from a mechanistic perspective, as other systems

with more stabilized (and hindered) radicals require higher temperatures ($> 90\text{ }^{\circ}\text{C}$) to maintain reasonable levels of polymeric alkoxyamine homolysis (and polymer chain growth).¹³¹ Consistent with this ‘chemically intuitive’ semi-quantitative argument, theoretical calculations reveal that the terminal C–O bond in the corresponding PVC alkoxyamine is too strong to facilitate a successful NMP by a classic activation-deactivation mechanism. Indeed, this bond was found to be at least 10 orders of magnitude too strong to mediate a successful NMP by this mechanism. However, theoretical calculations also demonstrated that the introduction of unsaturated defects (via dehydrochlorination) can significantly enhance the reactivity of these alkoxyamines. As such, a tentative mechanism based on chain-end dehydrochlorination is presented. It should be emphasized that this mechanism is based on very limited evidence and is considered to be fairly speculative. Future experimental and/or computational studies will hopefully be able to clarify the mechanism of this polymerization.

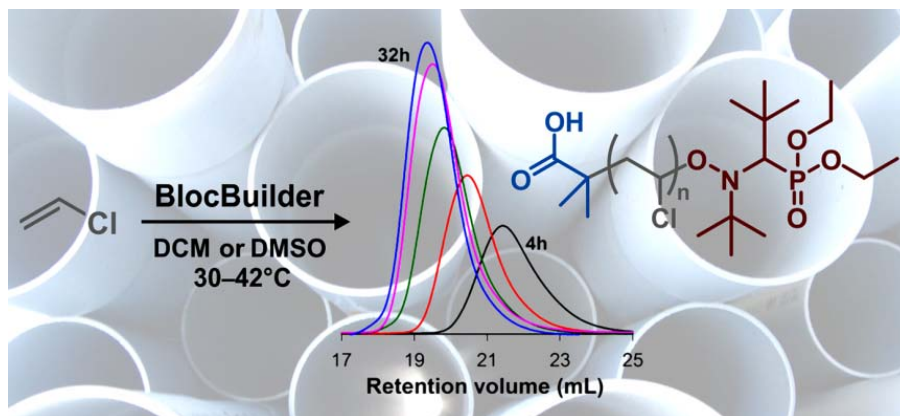
The second part of this chapter examines the remarkable effect of Lewis acid/base interactions on the redox behaviour of TEMPO monolayers [*Publication 9*]. Theoretical and experimental studies have demonstrated that remote anions can significantly stabilize nitroxide radicals in both the gas-phase and low polarity environments.¹³²⁻¹³⁴ While this stabilization is directly correlated with anion basicity and is quenched in moderate to high polarity solvents,¹³³⁻¹³⁵ the importance of electrostatic interactions in non-redox chemical processes has only recently been realized.¹³⁶ In the second part of this chapter, electrostatic interactions between electrolyte counter-anions (Lewis bases) and the oxidized TEMPO monolayer (Lewis acid) are found to significantly influence the electroactivity of these novel surfaces. That is, the electrolyte anion can affect the voltammetric responses of grafted nitroxide radicals in a way that is not quantifiable by adjusting the Frumkin “a” term but which is consistent with surface ion-pairing. This work demonstrates that the ratio of surface nitroxide radical to oxoammonium cation can be predictably manipulated by simply changing the electrolyte. Additionally, this provides a starting point for future studies on the effect of electric fields on NMP, and more generally, may aid the development of heterogeneous systems for catalysis.

6.2 Publication 8

Nitroxide-Mediated Polymerization of Vinyl Chloride at Low Temperature: Kinetic and Computational Studies

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Macromolecules, **2016**, 49, 490–498,



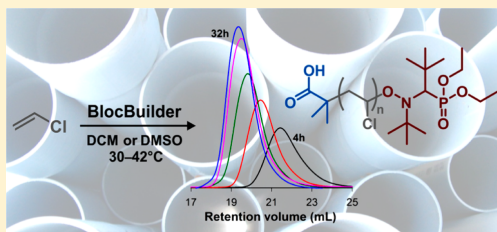
This manuscript is a peer-reviewed regular original research article that was published in *Macromolecules*. The computational results and the mechanistic discussion are my own work. My supervisor Michelle Coote assisted with the formulation of the key ideas and also provided valuable suggestions, extensions and corrections to my drafts.

Nitroxide-Mediated Polymerization of Vinyl Chloride at Low Temperature: Kinetic and Computational Studies

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Supporting Information

ABSTRACT: The synthesis of poly(vinyl chloride) (PVC) by nitroxide-mediated polymerization (NMP) using the SG1-based BlocBuilder alkoxyamine at low temperature (30 and 42 °C) is reported. The reaction system was studied regarding the nature of the solvent, the monomer-to-solvent ratio, the polymerization temperature, and the target molecular weight. First-order kinetics and linear evolutions of the molecular weight with vinyl chloride (VC) conversion were obtained in dichloromethane (DCM) and dimethyl sulfoxide (DMSO) together with decreasing dispersities ($\bar{D}$) down to 1.59–1.47. The resulting PVC was fully characterized by ¹H nuclear magnetic resonance spectroscopy (¹H NMR), ³¹P NMR, and size exclusion chromatography (SEC). The ¹H NMR and ³¹P NMR revealed the existence of very small content of structural defects and the presence of chain-end functional groups (~91% SG1 chain-end functionality). Chain extension experiments were performed with VC, methyl methacrylate (MMA), and a mixture of monomers (90% of MMA and 10% of styrene (S)) and confirmed the “livingness” of the PVC-SG1 macroinitiators, giving access to different PVC-based block copolymers. High level *ab initio* molecular orbital calculations suggested that the C–O bond in the PVC-SG1 alkoxyamine is too strong to mediate the NMP of VC by simple “classic” activation–deactivation equilibrium and is possibly being mediated by a SG1-mediated dehydrochlorination mechanism. The results presented in this study established a new route to afford a wide range of new complex macrostructures based on PVC segments.



1. INTRODUCTION

In the past two decades, reversible deactivation radical polymerization (RDRP) methods have revolutionized the field of polymer synthesis. These approaches enable the facile design of polymers with a stringent control over their structures, their functionalities, and their architectures using radical-based mechanisms.¹ Among the different RDRP methods, atom-transfer radical polymerization (ATRP),^{1e,f,2} reversible addition–fragmentation chain transfer (RAFT)^{1b–d,3} polymerization, and nitroxide-mediated polymerization (NMP)^{1a,4} remain the most popular. Nowadays, it is possible to control the polymerization of a very broad range of monomer families (e.g., styrenics, acrylates, methacrylates, 1,3-dienes, etc.) using RDRP methods with certain ease and under rather mild experimental conditions. An immense part of the research effort has been focused on the development of more efficient control agents,^{1a,b} more active catalysts,⁵ and more environmentally friendly polymerization reactions⁶ (e.g., green solvents,⁷ mild reaction temperatures,⁸ etc.). Despite all these

achievements, RDRP of nonactivated monomers (e.g., vinyl acetate, VC, *N*-vinylpyrrolidone) remains enormously challenging. Poly(vinyl chloride) (PVC) is one of the highest volume polymers (~39.3 million tons in 2013)⁹ and can only be prepared on an industrial scale by free-radical polymerization (FRP).¹⁰ Several features of VC make its control by RDRP methods particularly challenging, such as: (i) a very high reactivity ($k_{p,VC} = 11 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$ (at 50 °C); $k_{p,MMA} = 0.51 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$ (at 60 °C)),¹¹ (ii) an unusually high chain transfer constant to the monomer ($C_{M,VC} = (10.8–16) \times 10^{-4}$; $C_{M,MMA} = (0.07–0.25) \times 10^{-4}$, values at 60 °C),¹³ and (iii) the nonsolubility of PVC in its monomer as well as in most common organic solvents.¹⁴

Some attempts to produce PVC by RDRP methods have been reported, namely by single electron transfer living radical

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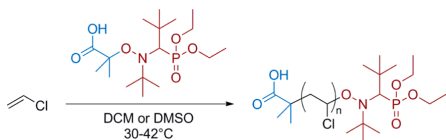
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polymerization (SET-LRP),¹⁵ single electron transfer degenerative chain transfer living radical polymerization (SET-DTLRP),^{14,16} cobalt-mediated radical polymerization (CMRP),¹⁷ supplemental activator and reducing agent (SARA) ATRP,^{7a,8a} and RAFT.¹⁰ However, the study of other RDRP techniques facilitates a deeper understanding of VC polymerization and broadening the number of PVC-based macromolecular structures could have valuable synthetic utility. NMP is particularly appealing for VC polymerization because of the simplicity of this protocol (an alkoxyamine, a 2-in-1 molecule, releases both the initiator and the control agent upon heating), the robustness of the process, the broad range of monomers that can be polymerized by this method, and the absence of residual catalysts, color, or toxic moieties.^{1a}

Braun and co-workers¹⁸ investigated the nitroxide-mediated suspension polymerization of VC at 70 °C using various nitroxides including 2,2,6,6-tetramethylpiperidin-1-ylxyl (TEMPO) and (di-*tert*-butyl nitroxide) DBN and reported low polymerization rates and high $\bar{D}$ values ~ 2 . Additionally, no information regarding the structural characteristics of the resulting PVC was provided. This information would be of particular relevance regarding the impact of temperature on the formation of structural defects that result from various unavoidable side reactions.^{14,19} Importantly, the presence of these unwanted structures has been shown to be the major cause for the low thermal stability of PVC.²⁰

In this context, we report for the first time the NMP of VC using the commercially available SG1-based alkoxyamine, BlocBuilder, earlier termed MAMA-SG1 (Scheme 1).^{1a,21}

Scheme 1. General Scheme and Conditions for the NMP of VC Initiated by the SG1-Based BlocBuilder Alkoxyamine



BlocBuilder has one of the highest dissociation rate constants ($k_d = 0.34 \text{ s}^{-1}$ at 120 °C)²² among commercially available alkoxyamines, making it attractive for the polymerization of monomers such as VC with less stabilized propagating radicals. Moreover, considering the high occurrence of side reactions (e.g., chain transfer to monomer) at elevated temperatures ($>60 \text{ °C}$) for the polymerization of VC, we have chosen to conduct NMP of VC at 42 °C, as a known standard temperature for VC RDRP.^{10,14} Another advantage of using the BlocBuilder alkoxyamine relies on the presence of a carboxylic acid group attached to the initiating moiety, which provides a convenient route for further PVC modifications to afford complex macrostructures using well-known coupling protocols.^{1a,23}

2. EXPERIMENTAL SECTION

2.1. Materials. VC (99.9%) was kindly supplied by CIRES Lda, Portugal. MMA (99% stabilized; Acros) and S (+99%; Sigma-Aldrich) were passed over a basic alumina column before use to remove the radical inhibitors. The BlocBuilder alkoxyamine (99%, recrystallized before use) and the SG1 nitroxide (85%) were kindly supplied by Arkema. Dichloromethane (DCM) (Fluka, HPLC grade), DMF (Sigma-Aldrich, +99.8%), DMSO (Acros, +99.8% extra pure), THF (Panreac, HPLC grade), and cyclohexanone (Sigma-Aldrich, 99.8%)

were distilled before use. Deuterated tetrahydrofuran (d_8 -THF) (Euriso-top, 99.5%), sulfolane (+99%; Acros), 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF₆, >98%; TCI (Tokyo Chemical Industry Co. LTD)), methanol (Labsolve, 99.5%), and polystyrene (PS) standards (Polymer Laboratories) were used as received.

2.2. Techniques. The 600 MHz ¹H NMR spectra of samples were recorded on a Varian VNMRs 600 MHz spectrometer, with a 3 mm PFG triple resonance indirect detection probe, in d_8 -THF with tetramethylsilane (TMS) as an internal standard. ³¹P NMR spectra of samples were recorded on a Bruker Avance III 400 MHz spectrometer, with a 5 mm TIX triple resonance detection probe, in d_8 -THF with diethyl phosphite (DEP) as an internal standard. The chromatographic parameters of the samples were determined using a size exclusion chromatography setup from Viscotek (Viscotek TDAmix) equipped with a differential viscometer (DV) and right-angle laser-light scattering (RALLS, Viscotek), low-angle laser-light scattering (LALLS, Viscotek), and refractive index (RI) detectors. The column set consisted of a PL 10 mm guard column (50 × 7.5 mm²) followed by one Viscotek T2000 column (6 μm), one MIXED-E PLgel column (3 μm), and one MIXED-C PLgel column (5 μm). A dual piston pump was set with a flow rate of 1 mL/min. The eluent (THF) was previously filtered through a 0.2 μm filter. The system was also equipped with an online degasser. The tests were done at 30 °C using an Elder CH-150 heater. Before the injection (100 μL), the samples were filtered through a polytetrafluoroethylene (PTFE) membrane with 0.2 μm pore. The system was calibrated with narrow PS standards. The dn/dc value was determined as 0.105 for PVC. Molecular weight (M_n^{SEC}) and dispersity ($\bar{D} = M_w/M_n$) of synthesized polymers were determined by triple detection calibration using the OmniSEC software version: 4.6.1.354.

2.3. Procedures. NMP of VC was carried out in a 50 mL glass high-pressure tube equipped with a magnetic stir bar. In the kinetic studies each point represents a single experiment.

Typical Procedure for the NMP of VC in DCM at 42 °C with [VC]₀/[BlocBuilder]₀ = 250/1. A 50 mL Ace Glass 8645#15 pressure tube, equipped with a bushing and a plunger valve, was charged with a mixture of BlocBuilder alkoxyamine (111 mg, 0.29 mmol) and DCM (5.0 mL) (previously bubbled with nitrogen for 5 min). The precondensed VC (5 mL, 73 mmol) was added to the tube. The exact amount of VC was determined gravimetrically. The tube was sealed, submerged in liquid nitrogen, and degassed through the plunger valve by applying reduced pressure and filling the tube with nitrogen about 20 times. The valve was closed, and the tube reactor was placed in a water bath at 42 ± 0.5 °C under stirring (700 rpm). After 24 h, the reaction was stopped by plunging the tube into ice water. The tube was slowly opened, the excess VC was evaporated inside a fume hood, and the mixture was precipitated into 250 mL of methanol. The polymer was separated by filtration and dried in a vacuum oven until constant weight, yielding 2.58 g (56.6%) of PVC ($M_n^{SEC} = 10\,800$, $\bar{D} = 1.49$).

Typical Procedure for the "One-Pot" Chain Extension Experiment from SG1-Terminated PVC. A 50 mL Ace Glass 8645#15 pressure tube, equipped with a bushing and a plunger valve, was charged with a mixture of BlocBuilder alkoxyamine (167 mg, 0.44 mmol) and DCM (3.0 mL) (previously bubbled with nitrogen for 5 min). The precondensed VC (3.0 mL, 43.7 mmol) was added to the tube. The exact amount of VC was determined gravimetrically. The tube was sealed, submerged in liquid nitrogen, and degassed through the plunger valve by applying reduced pressure and filling the tube with nitrogen about 20 times. The valve was closed, and the tube reactor was placed in a water bath at 42 °C under stirring (700 rpm). After 7 h, the reaction was stopped by plunging the tube into ice water. The tube was slowly opened, and the excess VC was evaporated inside a fume hood. The monomer conversion (conv) was determined gravimetrically (49.1%), and the $M_n^{SEC} = 6000$ and $\bar{D} = 1.60$ were determined by SEC. DCM (14.0 mL) (previously bubbled with nitrogen for 5 min) and the precondensed VC (14.0 mL, 204 mmol) were added in the medium without any purification of the previously obtained PVC-SG1 macroinitiator. The tube was sealed, submerged in

liquid nitrogen, and degassed through the plunger valve by applying reduced pressure and filling the tube with nitrogen about 20 times. The valve was closed, and the tube reactor was placed in a water bath at 42 °C under stirring (700 rpm). The reaction was stopped after 48 h by plunging the tube into ice water. The tube was slowly opened, and the excess VC was evaporated inside a fume hood. The monomer conversion were determined gravimetrically (44.1%), and the $M_n^{SEC} = 20\,600$ and $\bar{D} = 1.59$ of the resulting PVC-*b*-PVC diblock copolymer were determined by SEC.

Typical Procedure for the Synthesis of PVC-*b*-PMMA Diblock Copolymer by NMP. The PVC-SG1 macroinitiator (conv = 66%, $M_n^{th} = 5000$, $M_n^{SEC} = 6600$, $\bar{D} = 1.56$) was obtained following the previously described procedure. After precipitation in methanol, the polymer was dissolved in THF and reprecipitated in methanol. The polymer was dried under vacuum until constant weight. A mixture of MMA (5.0 mL, 46.9 mmol) and PVC-SG1 macroinitiator ($M_n^{SEC} = 6600$, $\bar{D} = 1.56$, 310 mg, 0.047 mmol), previously dissolved in DMSO (5.0 mL), was added to the Schlenk reactor. The reactor was deoxygenated by five freeze–pump–thaw cycles and filled with nitrogen. Then the reactor was placed in the oil bath at 100 °C under stirring (600 rpm). The reaction was stopped after 54 h, and the mixture was analyzed by ¹H NMR spectroscopy to determine the MMA conversion (45.5%) and by SEC to determine the macromolecular characteristics of the resulting PVC-*b*-PMMA diblock copolymer ($M_n^{SEC} = 44\,700$ and $\bar{D} = 1.89$).

Typical Procedure for the Synthesis of PVC-*b*-P(MMA-*co*-S) Copolymer by NMP. The PVC-SG1 macroinitiator (conv = 66%, $M_n^{th} = 5000$, $M_n^{SEC} = 6600$, $\bar{D} = 1.56$) was obtained following the previously described procedure. After precipitation in methanol, the polymer was dissolved in THF and reprecipitated in methanol. The polymer was dried under vacuum until constant weight. A mixture of MMA (5.0 mL, 46.9 mmol), S (0.52 mL, 4.5 mmol), and PVC-SG1 macroinitiator ($M_n^{SEC} = 6600$, $\bar{D} = 1.60$, 451 mg, 0.075 mmol), previously dissolved in DMF (5.52 mL), was added to the Schlenk reactor. The reactor was deoxygenated by five freeze–pump–thaw cycles and filled with nitrogen. Then the reactor was placed in the oil bath at 100 °C under stirring (600 rpm). The reaction was stopped after 44 h, and the mixture was analyzed by ¹H NMR spectroscopy to determine the MMA (34.5%) and S (36.8%) and by SEC to determine the macromolecular characteristics of the resulting PVC-*b*-P(MMA-*co*-S) copolymer ($M_n^{SEC} = 36\,400$ and $\bar{D} = 1.78$).

2.4. Computational Procedures. In this work we used the high-level composite *ab initio* G3(MP2)-RAD method²⁴ in conjunction with an ONIOM inspired approximation and M06-2X thermochemistry²⁵ to obtain accurate gas-phase energies. The SMD continuum solvation method²⁶ was used to model implicit solvent effects, with dichloromethane, toluene, and methyl propanoate used as solvents for the vinyl chloride, styrene, and methyl methacrylate systems, respectively. Similar methodology has been previously shown to predict accurate values for the thermodynamics (and kinetics) of a wide range of radical reactions, including alkoxyamine bond dissociation energies.²⁷ All standard *ab initio* molecular orbital theory and density functional theory calculations were performed using Gaussian 09²⁸ and Molpro 2012²⁹ software packages. A more detailed description of all the computational procedures can be found in the Supporting Information.

3. RESULTS AND DISCUSSION

3.1. Influence of the Solvent. In this work, the controlling ability of the BlocBuilder alkoxyamine was investigated for the polymerization of VC. Using an alkoxyamine avoids the use of an additional conventional radical initiator since both an initiating radical and a nitroxide are released at elevated temperature. Additionally, this alkoxyamine exhibits a high dissociation rate constant ($k_d = 0.34\text{ s}^{-1}$ at 120 °C),²² thus enabling NMP to proceed at low temperature, unlike many other alkoxyamines.

The first study was focused on the influence of the solvent over the polymerization. Different solvents and solvent mixtures were selected based on the solubility of PVC and further investigated for the NMP of VC initiated by BlocBuilder alkoxyamine at 42 °C (Table 1). Results showed that the

Table 1. Conversion and Macromolecular Characteristics Obtained for the NMP of VC Using Different Solvents at 42 °C after 24 h

entry ^a	solvent	conv (%)	$M_n^{th} \times 10^{-3}$ (g/mol)	$M_n^{SEC} \times 10^{-3}$ (g/mol)	$\bar{D}$
1	THF	30	5.5	5.9	1.72
2	DMF	22	5.3	5.9	1.73
3	sulfolane/DMSO = 80/20 (v/v)	29	5.8	6.1	1.78
4	cyclohexanone	39	7.4	7.7	1.59
5	DMSO	14	3.5	3.8	1.47
6 ^b	DMSO	22	5.3	5.8	1.58
7	BMIM-PF ₆ /DMSO = 50/50 (v/v)	32	7.0	8.8	1.59
8	DCM	57	10.7	10.8	1.49
9 ^c	DCM	29	5.3	9.7	1.56

^aReaction conditions: $[VC]_0/[BlocBuilder]_0 = 250$; $[VC]_0/[solvent] = 1/1$ (v/v). ^bPolymerization time (t_{rx}) = 48 h. ^cUsing additional SG1 free: $[SG1]_0/[BlocBuilder]_0 = 0.1$.

BlocBuilder alkoxyamine was able to significantly improve the NMP of VC compared to early attempts by producing PVC with dispersities far below 2. This was effective in a wide range of solvents which demonstrates the versatility of the NMP system used. In particular, best results were obtained in cyclohexanone (Table 1, entry 4), DMSO (Table 1, entries 5 and 6), and especially in DCM for which $\bar{D} = 1.49$ (Table 1, entry 8). In an attempt to accelerate the VC polymerization, the use of [BMIM-PF₆]/DMSO = 50/50 (v/v) was examined. This confirmed the synergetic effect observed in SARA ATRP, since the final conversion (conv) was much higher than in pure DMSO.³⁰ THF, DMF, and sulfolane/DMSO = 80/20 (v/v) (20% of DMSO was added to the sulfolane to allow the solubilization of BlocBuilder in the mixture) appeared less adequate solvents since $\bar{D}$ values ranged from 1.72 to 1.78 (Table 1, entries 1–3). Nevertheless, there was in all cases a good agreement between the theoretical and experimental molecular weights, which suggested good control over the PVC structure. The addition of 10% of free SG1 (Table 1, entry 9) significantly reduced the final conversion but had no beneficial effect on the $\bar{D}$.

Based on these results, DCM was chosen as the optimal solvent for a comprehensive kinetic study of the NMP of VC. After about 30 h, a rather high VC conversion was obtained (~60%). This resulted in first-order kinetics (Figure 1a), suggesting a constant concentration of growing radicals during the polymerization. This is in sharp contrast to the two linear dependencies of $\ln[M]_0/[M]$ vs time plots which were observed in the polymerization of VC by both SET-DTLRP^{16i–k} and RAFT¹⁰ but is in accordance with the SARA-ATRP method.^{8a} Additionally, the SG1-mediated NMP of VC initiated by the BlocBuilder alkoxyamine in DCM enabled higher final monomer conversion (60%) to be reached than that obtained with the RAFT system (50%) previously reported.¹⁰ NMP of VC was also rather well-controlled as shown by the decrease of the $\bar{D}$ values during the reaction as well as by the good agreement between experimental and

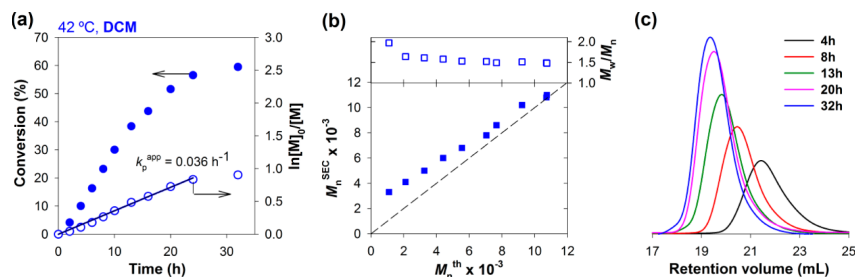


Figure 1. NMP of VC in DCM at 42 °C initiated by the SG1-based BlocBuilder alkoxyamine. (a) Conversion and $\ln[M]_0/[M]$ vs time. (b) Number-average molecular weight (M_n^{SEC}) and dispersity (M_w/M_n) vs theoretical number-average molecular weight (M_n^th). (c) Evolution of the SEC traces during the polymerization. Reaction conditions: $[VC]_0/[BlocBuilder]_0 = 250/1$; $[VC]_0/[solvent] = 1/1$ (v/v).

theoretical molecular weight values (Figure 1b). Finally, SEC chromatograms of PVC samples obtained at different times of reaction showed unimodal distributions with no visible sign of accumulation of dead polymer chains and significant shifts toward higher molecular weights (Figure 1c).

3.2. Influence of the Monomer Concentration. In solution NMP, the initial concentration of monomer (which also corresponds to the monomer-to-solvent ratio) may strongly influence the polymerization rate and may also sometimes impact the quality of control.^{7d,31} Three different monomer-to-solvent ratios (1/2, 1/1 and 2/1) were investigated for the NMP of VC in DCM at 42 °C initiated by the BlocBuilder alkoxyamine (Table 2, entries 1–3). Overall, the

Table 2. Conversion and Macromolecular Characteristics Obtained for the NMP of VC in DCM at 42 °C after 24 h

entry ^a	$[VC]_0/[DCM]$ (v/v)	conv (%)	$M_n^th \times 10^{-3}$ (g/mol)	$M_n^{SEC} \times 10^{-3}$ (g/mol)	$\bar{D}$
1	1/2	39	7.6	8.5	1.58
2	1/1	57	10.7	10.8	1.49
3	2/1	45	7.8	11.4	1.56

^aReaction conditions: $[VC]_0/[BlocBuilder]_0 = 250/1$.

results showed no general trend regarding the influence of the initial concentration of VC. As expected, the rate of reaction increased with the initial concentration of VC (Table 2, entries 1 and 2), as higher monomer conversion was achieved for the same reaction time (i.e., 24 h). However, for the highest monomer concentration studied (i.e., $[VC]_0/[DCM] = 2/1$) there was an apparent decrease in the rate of polymerization, as judged by the lower monomer conversion obtained for the more diluted reaction medium (Table 2, entries 2 and 3). This might be related to the poor solubility of the VC in the growing PVC, which can cause diffusional problems during the polymerization and limit monomer conversion.

3.3. Influence of Polymerization Temperature. The polymerization temperature is an important parameter to consider when optimizing RDRP systems. Temperature is particularly crucial for standard NMP, as the activation/deactivation equilibrium of the initiating and propagating species are solely governed by temperature. Also, in the case of PVC, high temperatures can contribute to the appearance of structural defects in the polymeric structure.^{14,16g} NMP of VC was evaluated in the range of 30–60 °C (Table 3). The results showed that NMP of VC can proceed successfully at near room temperature ($T = 30$ °C) with no detrimental effect on the

Table 3. Conversion and Macromolecular Characteristics Obtained for the NMP of VC in DCM at Different Temperatures after 24 h

entry ^a	T (°C)	conv (%)	$M_n^th \times 10^{-3}$ (g/mol)	$M_n^{SEC} \times 10^{-3}$ (g/mol)	$\bar{D}$
1	30	39.7	7.1	7.7	1.53
2	42	56.6	10.7	10.8	1.49
3	60	37.1	6.7	6.1	1.68

^aReaction conditions: $[VC]_0/[BlocBuilder]_0 = 250/1$.

control of PVC compared to the same experiment performed at 42 °C ($\bar{D} \approx 1.50$, Table 3, entries 1 and 2). However, when the temperature was increased up to 60 °C (Table 3, entry 3), a significant increase of the $\bar{D}$ was noticed, suggesting the occurrence of side and/or irreversible termination reactions during the polymerization. This loss of control was also accompanied by a decrease in the final monomer conversion, for the same reaction time. Considering both the control over the molecular weight and the polymerization rate, a temperature of 42 °C appears to be optimal.

3.4. Influence of the Degree of Polymerization. The robustness of a RDRP system can be evaluated by different criteria among which it is its ability to control the growth of polymer chains for different targeted molecular weights. Figure 2 shows the kinetics of the NMP of VC for a targeted number-average degree of polymerization (DP_n) of 100. The polymerization proceeded in a controlled manner, with a good agreement between the experimental and predicted values (and M_n^{SEC} increased linearly with VC conversion, Figure S1) as well as decreasing $\bar{D}$ values throughout the reaction reaching ~ 1.5 (Figure 2b). As with the earlier experiments performed with $DP_n = 250$ (Figure 1), the SEC chromatograms of PVC samples obtained at different times intervals showed unimodal distributions with no visible sign of accumulation of dead polymer chains and constant shifts toward higher molecular weights (Figure 2c).

Additional studies were performed targeting different DP_n values of VC. The results presented in Table 4 demonstrate that it is possible to prepare well-defined PVC with a range of molecular weights, suggesting that the NMP of VC using BlocBuilder alkoxyamine is quite robust.

3.5. Analysis of the PVC Structure. To gain a deeper insight into the structure of the PVC obtained by SG1-mediated NMP initiated by the BlocBuilder alkoxyamine, a sample (Table 4, entry 1) was analyzed by ¹H NMR spectroscopy (Figure 3). The characteristics signals of the

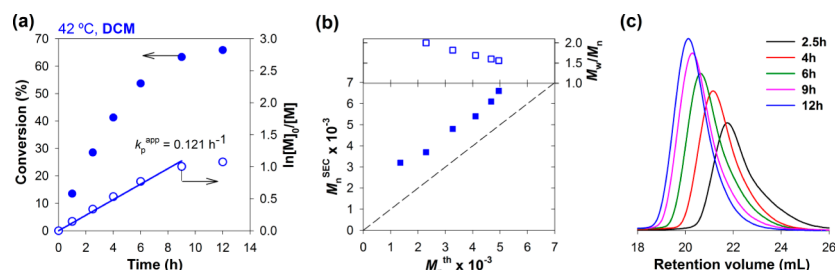


Figure 2. NMP of VC in DCM at 42 °C initiated by the SG1-based BlocBuilder alkoxyamine. (a) Conversion and $\ln[M]_0/[M]$ vs time. (b) M_n^{SEC} and M_w/M_n vs M_n^{th} . (c) Evolution of the SEC traces during the polymerization. Reaction conditions: $[VC]_0/[BlocBuilder]_0 = 100/1$; $[VC]_0/[solvent] = 1/1$ (v/v).

Table 4. Conversion and Macromolecular Characteristics Obtained for the NMP of VC in DCM at 42 °C for Different Targeted DP_n Values ($[VC]_0/[BlocBuilder]_0$)

entry	$[VC]_0/[BlocBuilder]_0$	time (h)	conv (%)	$M_n^{th} \times 10^{-3}$ (g/mol)	$M_n^{SEC} \times 10^{-3}$ (g/mol)	$\bar{D}$
1	100/1	7	49	4.3	6.0	1.60
2	100/1	12	66	5.0	6.6	1.56
3	250/1	24	57	10.7	10.8	1.49
4	500/1	24	47	15.9	16.9	1.54
5	1000/1	48	52	34.7	30.4	1.53

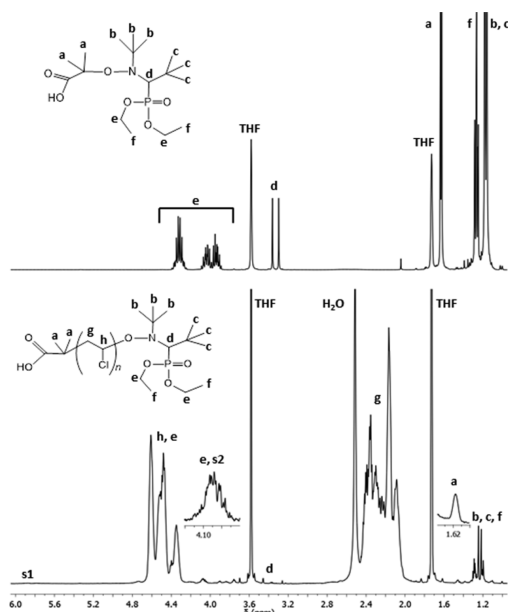


Figure 3. ¹H NMR spectra in *d*₈-THF of (a) the BlocBuilder alkoxyamine and (b) the purified PVC ($M_n^{SEC} = 6000$; $\bar{D} = 1.60$) obtained in Table 4, entry 1.

PVC assigned on the spectrum were in agreement with those reported in the literature.^{7a,8a,10} The ¹H NMR spectrum of the BlocBuilder alkoxyamine, also included in Figure 3, to confirm the retention of both chain-end functionalities on the polymer. The spectrum of the PVC reveals the resonances of the repeat unit $\text{CH}_2\text{--CHCl}$: g (1.9–2.7 ppm) and h (4.2–4.7 ppm),

respectively. The spectrum of the PVC also reveals the resonances of the initiating and mediating BlocBuilder alkoxyamine fragments: a at 1.62–1.64 ppm, b, c, and f at 1.10–1.40 ppm, d at 3.35–3.42 ppm, and e at 3.98–4.15 ppm.

To evaluate the impact of the BlocBuilder alkoxyamine on the formation of structural defects, a PVC ($M_n^{SEC} = 29.3 \times 10^3$; $\bar{D} = 1.76$) was synthesized by FRP using Trigonox 187 W40 as a conventional initiator under identical experimental conditions and compared to a PVC obtained by NMP (Table 4, entry 1). The most representative structural defects for transfer to monomer and easily detected is the $\text{--CH=CH--CH}_2\text{Cl}$. Comparing the signal intensities of hydrogen atoms of PVC backbone $\text{--CH}_2\text{CHCl--}$ (h, 4.2–4.7 ppm) and the hydrogen atoms of the $\text{--CH=CH--CH}_2\text{Cl}$ defect structure (5.8 ppm for CH=CH (s1, Figure 3 and Figure S2) allows quantifying the defect in PVC samples (it is not possible to do the comparison considering the signal at 4.1 ppm for CH_2 (s2, Figure 3 and Figure S2) because this signal is overlapped with e in the PVC-SG1). The $\text{--CH}_2\text{CHCl--}/\text{--CH=CH--CH}_2\text{Cl}$ molar ratio is 1000/0.86 for PVC-FRP while this ratio is 1000/0.42 for PVC-SG1. These results showed much less structural defects in the PVC obtained by SG1-mediated NMP, which is also in agreement with other RDRP techniques as SET-DTLRP¹⁴ and RAFT.¹⁰

To probe the end-group fidelity of the synthesized PVC, ³¹P NMR spectroscopy was performed. This is a convenient and accurate method, which relies on the determination of the living chain fraction (LF) by quantifying the presence of the phosphorus-containing SG1 nitroxide end group with diethyl phosphite (DEP) as an internal reference.^{12,32} The spectrum of PVC-SG1 is reported in Figure 4 and gave a LF of ~91%, which is similar to LF values reported for the NMP of styrenics and acrylates and clearly establishes the living nature of the PVC and retention of the SG1 fragment. This also opens the door to chain extensions to prepare PVC-based block copolymers by NMP.

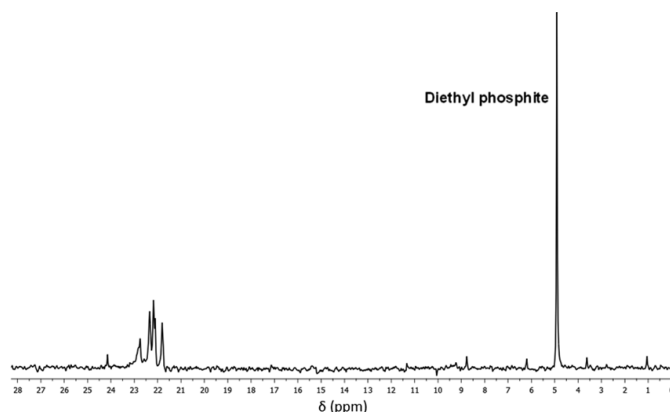


Figure 4. ^{31}P NMR spectrum in d_8 -THF of the purified PVC ($M_n^{\text{SEC}} = 6000$; $\bar{D} = 1.60$) obtained in Table 4, entry 1.

3.6. Evaluation of the PVC Livingness. The livingness of a polymer obtained by a RDRP technique is of paramount importance for block copolymer synthesis and macromolecular engineering purposes. The living character of the previously obtained PVC-SG1 (Table 4, entry 1) was further confirmed by a successful chain extension experiment by a “one-pot” chain extension experiment from SG1-terminated PVC of VC in DCM at 42 °C. The SEC traces presented in Figure 5 showed a

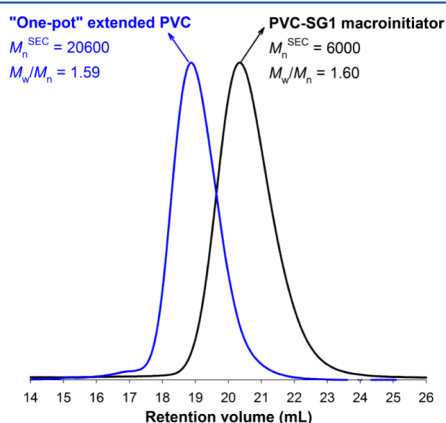


Figure 5. SEC chromatograms of the PVC-SG1 macroinitiator (conv = 49%, $M_n^{\text{th}} = 4300$, $M_n^{\text{SEC}} = 6000$, $\bar{D} = 1.60$) (black line), and the extended PVC-*b*-PVC (conv = 44%, $M_n^{\text{th}} = 26\,500$, $M_n^{\text{SEC}} = 20\,600$, $\bar{D} = 1.59$) (blue line) after “one-pot” chain extension in DCM.

complete shift of the low molecular weight SG1-terminated PVC macroinitiator (conv = 49%, $M_n^{\text{th}} = 4300$, $M_n^{\text{SEC}} = 6000$, $\bar{D} = 1.60$) toward high molecular weight polymer (conv = 44%, $M_n^{\text{th}} = 26\,500$, $M_n^{\text{SEC}} = 20\,600$, $\bar{D} = 1.59$), thus demonstrating the formation of an extended PVC-*b*-PVC.

Additionally, to diversify the range of PVC-based macromolecular architectures, a PVC-SG1 (Table 4, entry 2) macroinitiator ($M_n^{\text{SEC}} = 6600$, $\bar{D} = 1.56$) initiated the NMP of MMA to produce PVC-*b*-PMMA (conv_{MMA} = 45.5%, $M_n^{\text{th}} = 52\,100$, $M_n^{\text{SEC}} = 44\,700$, $\bar{D} = 1.89$) diblock copolymer and the

NMP of MMA with 10% of S to produce PVC-*b*-P(MMA-*co*-S) (conv_{MMA} = 34.5%, conv_S = 36.8%, $M_n^{\text{th}} = 44\,800$, $M_n^{\text{SEC}} = 36\,400$, $\bar{D} = 1.78$) diblock copolymer (Figure 6).

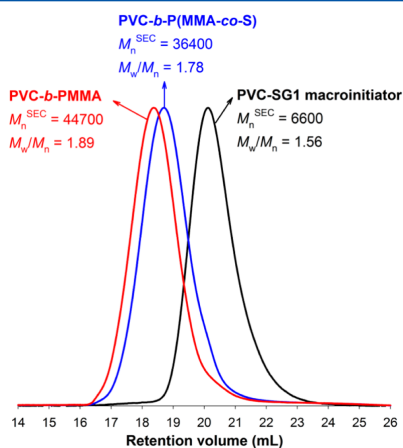


Figure 6. SEC chromatograms of the PVC-SG1 macroinitiator (conv = 66%, $M_n^{\text{th}} = 5000$, $M_n^{\text{SEC}} = 6600$, $\bar{D} = 1.56$) (black line), the PVC-*b*-PMMA diblock copolymer (conv_{MMA} = 45.5%, $M_n^{\text{th}} = 52\,100$, $M_n^{\text{SEC}} = 44\,700$, $\bar{D} = 1.89$) (red line) by NMP in DMSO, and PVC-*b*-P(MMA-*co*-S) (conv_{MMA} = 34.5%, conv_S = 36.8%, $M_n^{\text{th}} = 44\,800$, $M_n^{\text{SEC}} = 36\,400$, $\bar{D} = 1.78$) (blue line) block copolymer by NMP in DMF at 100 °C for 54 and 44 h, respectively.

The chemical structures of the block copolymers were confirmed by ^1H NMR spectroscopy (Figures S3 and S4). These results demonstrated the “living” character of the PVC-SG1 macroinitiator and the possibility of using the reported system in the synthesis of unique and novel PVC-based copolymers with unprecedented properties.

3.7. Computational Studies on the Mechanism of Low-Temperature NMP of VC. NMP is a reversible deactivation radical polymerization process that employs stable nitroxide radical as a mediating species. Achieving a NMP with “living” characteristics relies on the presence of a thermally

labile C–O bond in the corresponding polymeric alkoxyamine; otherwise, deactivation of the propagating radicals will be irreversible. The strength of this bond is dependent on the structure of the nitroxide and polymeric radical from which the alkoxyamine is composed. For a given nitroxide, the bond dissociation free energy (BDFE) of the C–O bond depends on both the stability of the polymeric radical and its substitution, with more stable and more bulky substituted polymeric radicals affording lower BDFEs.²³ For these reasons, one would intuitively expect that NMP polymerization of VC mediated by SG1 radicals would fail, especially at low temperatures (42 °C), because deactivation of the propagating radical should be irreversible. While SG1 radicals have mediated the successful NMPs of various monomers including, *n*-butyl acrylate (*n*-BA)^{21a} and S,^{21a} these polymerizations must be performed at elevated temperatures (90–120 °C) to maintain reasonable levels of alkoxyamine homolysis. Additionally, it should also be noted that the propagating radical species in these polymerizations are significantly more stable and sterically hindered than VC radicals (see radical stabilization energies (RSE) in Table S).^{27d} To properly quantify the governing activation–

diffusion limited $k_{\text{deactivation}}$ of $\sim 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$, $k_{\text{activation}}$ would be $4.5 \times 10^{-14} \text{ s}^{-1}$, which is approximately 10 orders of magnitude too slow to mediate a successful NMP. In other words, the C–O bond of the PVC-SG1 alkoxyamine is around 40–50 kJ mol⁻¹ too strong to facilitate a viable NMP activation–deactivation equilibrium. Even at the elevated temperatures (100 °C) used for the MMA and MMA/S chain-extension experiments, *K* is still over 5 orders of magnitude too low to facilitate sufficient levels of PVC-SG1 macroinitiator homolysis. Alternative O–N breakage of the PVC-SG1 alkoxyamine, which would decompose the SG1 nitroxide (irreversibly) into an aminyl radical, is also thermodynamically disfavored at both 40 and 100 °C.

In contrast to the unfavorable *K* value for the PVC-SG1 system, the C–O bond of the PS-SG1 alkoxyamine is predicted to be sufficiently labile at 100 °C (but not 40 °C) to facilitate a successful NMP. This theoretical prediction is consistent with previous experimental results, as it is well-known that the NMP of S must be performed at elevated temperatures (usually ≥ 90 °C) to yield polymeric products within practical time frames.³³ In contrast to the other two alkoxyamines, the *K* value for the PMMA-SG1 system is predicted to be too large and so irreversible combination/disproportionation of propagating chains would severely compromise this NMP.³⁴ Indeed, the addition of S monomer to MMA-SG1 polymerizations improves the livingness, as the intermediate styryl radicals are more susceptible deactivation by SG1 radicals.³⁴ In summary, the theoretically predicted *K* values are not only consistent with intuitive expectations based on a semiquantitative analysis of the size and stability of the corresponding radical species but also with previous experimental results in S-SG1 and MMA-SG1 systems.^{12,21a} Moreover, we should emphasize that the theoretical methodology used to estimate these BDFEs has been extensively benchmarked (including against experiment) in previous studies.²⁷

Could Dehydrochlorination Facilitate Reactivation? As high-level calculations suggest that the high BDFE of the C–O bond in the PVC-SG1 alkoxyamine should completely prohibit reactivation, the presently reported experimental success is both highly surprising and intriguing. Perhaps the most straightforward explanation for the experimental success of the NMP of VC is that the SG1 radical and/or PVC-SG1 alkoxyamine participate in side reactions, which form a more reactive intermediate alkoxyamine that is more susceptible to homolysis. If the PVC-SG1 alkoxyamine undergoes dehydrochlorination in the vicinity of the chain ends, then the resultant allylic defect could facilitate the decomposition of the parent alkoxyamine by allowing for the elimination of a stable allylic PVC radical. Indeed, theoretical calculations indicate that two possible dehydrochlorinated PVC-SG1 structures possess much lower

Table 5. Radical Stabilization Energies (RSE), Bond Dissociation Free-Energies (BDFE), and *K* for SG1-Mediated NMP of VC, S, and MMA

monomer system (bond homolysis)	RSE of unimeric radical ^a	40 °C		100 °C	
		BDFE ^a	<i>K</i>	BDFE ^a	<i>K</i>
VC (C–ON)	13.2	134.0	4.5×10^{-23}	121.5	9.7×10^{-18}
VC (CO–N)		140.0	4.4×10^{-24}	128.0	1.2×10^{-18}
S (C–ON)	54.8	95.6	1.1×10^{-16}	83.2	2.2×10^{-12}
MMA (C–ON)	41.1	65.1	1.4×10^{-11}	51.9	5.4×10^{-8}

^aRSE and BDFE values given in kJ mol⁻¹. Dichloromethane, toluene, and methyl propanoate were used as solvents for VC, S, and MMA, respectively. The VC, S, and MMA radicals were modeled as dimers. RSE values were taken from ref 27d.

deactivation equilibrium constant (*K*) of the PVC-SG1 system, high-level theory was used to calculate the BDFE of the C–O bond in corresponding alkoxyamine (see Table S). For comparative purposes, the BDFEs of the C–O bonds in both PS-SG1 and PMMA-SG1 alkoxyamines were also calculated using the same computational methodology. As electron-donating substituents can destabilize the O–N bond of the nitroxide,^{27c} O–N breakage was also examined for VC.

At 40 °C, the C–O bond BDFE of the PVC-SG1 alkoxyamine is calculated to be 134.0 kJ mol⁻¹, while the corresponding *K* value is 4.5×10^{-23} . Even assuming a very fast

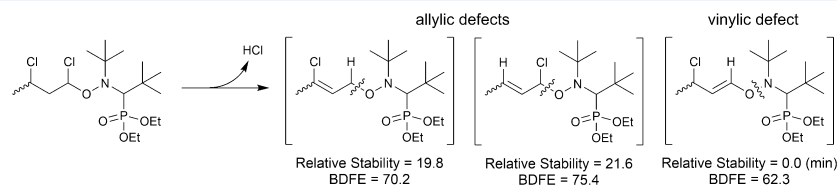


Figure 7. Possible dehydrochlorinated PVC-SG1 structures, with relative stabilities of the alkenes. BDFEs of the marked bond and relative alkene stability calculated at 40 °C are given in kJ mol⁻¹.

C–O bond BDFEs and would be able to effectively (re)activate chain growth (Figure 7), even at low temperatures (42 °C).

Unfortunately, the exact mechanistic details of any potential dehydrochlorination reactions are currently unclear. While dehydrochlorination of unstabilized PVC is well noted at high temperatures (>150 °C),²⁰ the conditions used in this polymerization are obviously much milder. However, it should be noted that amines can facilitate dehydrochlorination of PVC at lower temperatures (~80 °C),³⁵ and so it is possible that the SG1 is selectively mediating the dehydrochlorination mechanism in the vicinity of the chain-end. In its favor is the absence of competing reactions in the otherwise stable PVC-SG1. Once the unsaturated defect is formed, the alkoxyamine can undergo homolysis and, given the low radical concentration, undergo several propagation steps before being trapped again by the SG1.

However, a potential problem with the mechanism is the possibility of competitively generating a vinylic PVC-SG1 structure. The O–N bond in this vinylic structure is actually less stable than the C–O bond of either allylic structure. If both defects form competitively, O–N homolysis would irreversibly decompose SG1 radicals into aminyl radicals and the resulting polymerization would be poorly controlled. While the low polydispersity of the PVC obtained in the present work ($\bar{D}$ = 1.5) is unprecedented, it is significantly above that of an optimized NMP for a less reactive monomer ($\bar{D}$ < 1.2), and formation of vinylic groups may be a possible reason for this result. The low concentration of C=C defect structures detected by ¹H NMR in the resulting PVC may simply reflect the reversibility of the dehydrochlorination reaction under these conditions. However, we should also caution that there is limited evidence for this dehydrochlorination mechanism, and so this mechanism is quite tentative. Indeed, more detailed mechanistic studies of this remarkable and surprising polymerization are currently underway.

4. CONCLUSIONS

The SG1-mediated polymerization of VC initiated by the BlocBuilder alkoxyamine was successfully performed at low temperatures (e.g., 30 and 42 °C) and led to improved control on the resulting PVC compared to early results in the literature using other nitroxide structures. The structural characterizations (¹H NMR and ³¹P NMR) suggested the existence of very small content of structural defects and the high preservation of the chain-end functionalities. PVC-SG1 macro-initiators were successfully used in chain extension experiments to produce different PVC-based diblock copolymers. This work is of significant importance as it could open the door to various macromolecular architectures comprising PVC segments using NMP and all its benefits compared to other RDRP methods. Further experimental and computational studies are required for complete understanding of the mechanism of this remarkable low-temperature “NMP” of VC.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b02017.

¹H NMR spectra of PVC-*b*-PMMA and PVC-*b*-P(MMA-*co*-S) block copolymers and complete computational data (PDF)

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Notes

The authors declare no competing financial interest.

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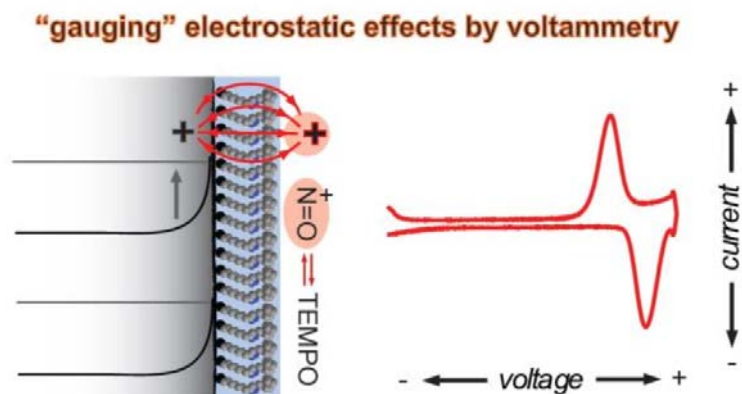
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6.3 Publication 9

TEMPO Monolayers on Si(100) Electrodes: Electrostatic Effects by the Electrolyte and Semiconductor Space-Charge on the Electroactivity of a Persistent Radical

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TEMPO Monolayers on Si(100) Electrodes: Electrostatic Effects by the Electrolyte and Semiconductor Space-Charge on the Electroactivity of a Persistent Radical

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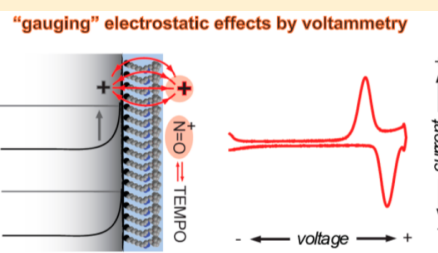
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Supporting Information

ABSTRACT: This work demonstrates the effect of electrostatic interactions on the electroactivity of a persistent organic free radical. This was achieved by chemisorption of molecules of 4-azido-2,2,6,6-tetramethyl-1-piperidinyloxy (4-azido-TEMPO) onto monolayer-modified Si(100) electrodes using a two-step chemical procedure to preserve the open-shell state and hence the electroactivity of the nitroxide radical. Kinetic and thermodynamic parameters for the surface electrochemical reaction are investigated experimentally and analyzed with the aid of electrochemical digital simulations and quantum-chemical calculations of a theoretical model of the tethered TEMPO system. Interactions between the electrolyte anions and the TEMPO grafted on highly doped, i.e., metallic, electrodes can be tuned to predictably manipulate the oxidizing power of surface nitroxide/oxoammonium redox couple, hence showing the practical importance of the electrostatics on the electrolyte side of the radical monolayer. Conversely, for monolayers prepared on the poorly doped electrodes, the electrostatic interactions between the tethered TEMPO units and the semiconductor-side, i.e., space-charge, become dominant and result in drastic kinetic changes to the electroactivity of the radical monolayer as well as electrochemical nonidealities that can be explained as an increase in the self-interaction "a" parameter that leads to the Frumkin isotherm.



1. INTRODUCTION

To realize the full technological potential that molecular and supramolecular systems hold, our ability to control molecular topology, and hence function, needs to be coupled to the sturdiness of a solid device.¹ Persistent organic free radicals have a key role in chemistry and biology,² and nitroxide radicals, such as the 2,2,6,6-tetramethyl-1-piperidinyloxy radical generally referred to as TEMPO, and its derivatives are very interesting both from a fundamental³ as well as from an applied⁴ point of view. Assembly of persistent radicals on solid surfaces by physisorption is often complicated by the competition between the thermodynamic assembly and unwanted kinetic traps;⁵ hence, chemical routes to tether TEMPO species onto a solid, such as gold- and carbon-based materials are starting to appear.⁶ Silicon, in particular the (100)

orientation, remains the technologically most relevant material of our age,⁷ and this material is still bringing fresh momentum to the fields of electrochemistry,⁸ spintronics,⁹ and molecular electronics.¹⁰ No reports are available for the tethering of nitroxide radicals on silicon electrodes. This is presumably because of the ease of binding between silicon surface bonds and the unpaired valence electron of the singly occupied molecular orbital of the TEMPO molecule, which would result in the loss of the free radical character.¹¹ Here we address this issue using a two-step chemical route to preserve the unpaired spin upon grafting. A Si(100)-H surface is first functionalized by the thermal hydrosilylation of α,ω -alkynes to yield a short

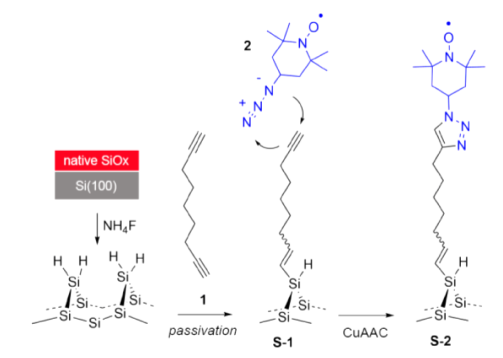
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functional monolayer where direct electrical communication between a grafted molecule and the substrate is still possible.¹² Thereafter, TEMPO is attached with the radical preserved.

The properties of a near-surface region are remarkably different to the properties of the bulk. For instance, issues of mass transport can be neglected. Similarly, the chemical interactions of a grafted molecule with either the solid, neighboring molecules or supporting electrolyte molecules may dramatically change the chemical,¹³ optical,¹⁴ or redox¹⁵ properties. The purpose of the current study is to investigate how the electrostatic interactions between surface-grafted TEMPO units and residual charges in the semiconductor space-charge, or electrolyte ions, can predictably tune the electroactivity of a common radical species. To achieve both the passivation of the substrate against anodic decomposition^{12a} as well as to circumvent the high reactivity of the Si–H surface toward the oxygen function in the TEMPO molecule, we have relied on an established wet chemistry protocol to prepare alkyne-terminated monolayers (S-1, Scheme 1).^{12b,16} The

Scheme 1. Thermal Hydrosilylation of 1,8-Nonadiyne 1 at a Si(100)-H Electrode (S-1) and Covalent Attachment of 4-Azido-TEMPO 2 via CuAAC “Click” Reactions to Yield the Redox-Active Radical Film (S-2)



chemical passivation of the Si(100) surface, as depicted in Scheme 1, is generally proven to be a difficult experimental task,¹⁷ and a definitive mechanism for the thermal hydrosilylation of 1-alkynes is still debated.¹⁸ The mainly dihydride phase (=SiH_2) of the chemically etched (100) surface¹⁹ does not allow for a complete reaction of Si–H sites,²⁰ but if the monolayer can retain a degree of π – π interactions, then anodic decomposition of the substrate can be greatly limited.^{12a} The 1-alkyne moiety that remains exposed at the monolayer distal end in S-1 samples can engage in highly selective copper-catalyzed alkyne–azide cycloaddition reactions (CuAAC²¹) to immobilize an azide-tagged version of TEMPO (S-2). This chemistry opens up access to an interface where (i) the Si/C contrast enables one to complement analytical electrochemical methods with surface-sensitive X-ray spectroscopic techniques^{12a} and (ii) the presence of a band gap in the semiconducting substrate allows one to shift redox reactions contra-thermodynamically if assisted by visible radiation, i.e., energetic gain in a catalytic application of the radical film.

2. EXPERIMENTAL METHODS

2.1. Chemicals and Materials. Unless otherwise noted, all chemicals were of analytical grade and used as received. Chemicals used in surface modification procedures and electrochemical experiments were of high purity (>99%). Hydrogen peroxide (30 wt % in water), ammonium fluoride (PuranalTM, 40 wt % in water), and sulfuric acid (PuranalTM, 95–97%) used in wafer cleaning and etching procedures were of semiconductor grade from Sigma-Aldrich. 1,8-Nonadiyne (1, Sigma-Aldrich, 98%) was redistilled from sodium borohydride (Sigma-Aldrich, 99+%) under reduced pressure (80 °C, 10–12 Torr) and stored under high-purity argon atmosphere prior to use. 4-Azido-2,2,6,6-tetramethyl-1-piperdinyloxy (2, 4-azido-TEMPO) was prepared in two steps from 4-hydroxy-2,2,6,6-tetramethyl-1-piperdinyloxy (4-hydroxy-TEMPO, Sigma-Aldrich, 97%) through published methods²² with minor modifications (Supporting Information). Thin-layer chromatography (TLC) was performed on silica gel using Merck aluminum sheets (60 F₂₅₄). Merck 60 Å silica gel (220–400 mesh particle size) was used for column chromatography. Gas chromatography–mass spectrometry (GC-MS) analyses were performed by means of an Agilent Technologies 7890A GC system equipped with a HP-5 capillary column (5% phenyl methyl siloxan, 30 m $\times$ 250 μm $\times$ 0.25 μm) interfaced with an Agilent 5975N MSD scheme operating in electron impact (EI) mode. The helium carrier gas flow rate was 14 mL/min, and the temperature was increased from 100 to 280 °C at a temperature ramp rate of 15 °C/min. The column was held at the initial and final temperatures for 5 min. Tetrabutylammonium perchlorate (Bu_4NClO_4 , Sigma-Aldrich, >99%), used as supporting electrolyte, was recrystallized twice from 2-propanol. Milli-Q water (>18 M Ω cm) was used to prepare solutions, chemical reactions, and surface cleaning procedures. Dichloromethane, 2-propanol, and ethanol for surface cleaning procedures were redistilled prior to use. Prime-grade, single-side-polished silicon wafers (100-oriented ($100 \pm 0.5^\circ$), p-type (boron-doped), $500 \pm 25 \mu\text{m}$ thick, with nominal resistivity of 0.001–0.003 Ω cm) were obtained from Siltronic, S.A.S. (Archamps, France) and are referred to as highly doped. Prime-grade, single-side-polished silicon wafers (100-oriented ($100 \pm 0.09^\circ$), n-type (phosphorus-doped), $500 \pm 25 \mu\text{m}$ thick, 1–10 Ω cm resistivity) were purchased from Virginia Semiconductors, Inc. (Fredericksburg, VA) and are referred to as lowly doped.

2.2. Surface Modification. **2.2.1. Acetylene-Functionalized Silicon(100) Electrodes (S-1).** Assembly of the acetylenylated Si(100) surface (S-1) by covalent attachment of the diyne 1 followed a previously reported procedure (Scheme 1).¹² In brief, silicon wafers were cut into pieces (approximately $10 \times 30 \text{ mm}^2$), cleaned for 20–30 min in hot Piranha solution (100 °C, a 3:1 (v/v) mixture of concentrated sulfuric acid to 30% hydrogen peroxide), rinsed with water and then etched with a deoxygenated 40% aqueous ammonium fluoride solution for 5 min. (**Caution:** Piranha solution is a strong oxidant and reacts violently with organic substances.) The samples were then transferred, taking extra care to exclude air completely from the reaction vessel (a custom-made Schlenk flask), to a degassed (through a minimum of 30 min of argon bubbling) sample of diyne 1. The samples were kept under a stream of argon while the reaction vessel was immersed in an oil bath set to 160 °C for 3 h. The flask was then opened to the atmosphere, and the functionalized surface samples (S-1) were rinsed several times with dichloromethane and rested for a 12 h period in a sealed vial at +4 °C under dichloromethane before being further reacted with the TEMPO molecule 2.

2.2.2. CuAAC Attachment of 4-Azido TEMPO onto the Acetylenyl Surface (S-2). CuAAC reactions were used to attach 4-azido-TEMPO (2) to the acetylenyl surface (S-1). To a reaction vial containing the alkyne-functionalized silicon surface (S-1) was added (i) the azide (2, 0.5 mM, 2-propanol/water, 1:1), (ii) copper(II) sulfate pentahydrate (20 mol % relative to the azide), and (iii) sodium ascorbate (100 mol % relative to the azide). Reactions were carried out in air at room temperature under ambient light, and unless noted otherwise, they were stopped by removal of the samples from the reaction vessel after a reaction time of 2 h. The surface-bound [1,2,3]-triazoles (S-2) were

rinsed consecutively with copious amounts ethanol, water, ethanol, and dichloromethane and blown dry in argon before being analyzed.

2.3. Surface Characterization. **2.3.1. X-ray Photoelectron Spectroscopy.** X-ray photoelectron spectra (XPS) were obtained on an ESCALAB 220iXL spectrometer fitted with a monochromatic Al K α source (1486.6 eV), a hemispherical analyzer and a 6 multichannel detector. Spectra of Si 2p (89–108 eV), C 1s (276–295 eV), N 1s (391–410 eV), and O 1s (523–542 eV) were recorded in normal emission ($\theta = 90^\circ$) with the analyzing chamber operating below 10^{-9} mbar. The resolution of the spectrometer is ca. 0.6 eV as measured from the Ag 3d $_{5/2}$ signal (full width at half-maximum, fwhm) with 20 eV pass energy. High-resolution scans were run with 0.1 eV step size, dwell time of 100 ms, and the analyzer pass energy set to 20 eV. After background subtraction, spectra were fitted with Voigt functions. All energies are binding energies expressed in electronvolts, obtained by applying to all samples a rigid shift to bring the energy of the C 1s peak to a value of 285.0 eV.

2.3.2. X-ray Reflectometry. X-ray reflectivity (XRR) profiles of S-2 samples (highly doped) were measured under ambient conditions on a Panalytical Ltd. X'Pert Pro Reflectometer using Cu K α X-ray radiation ($\lambda = 1.54056$ Å). The X-ray beam was focused using a Göbel mirror and collimated with 0.2 mm presample slit and a postsample parallel plate collimator. Reflectivity data were collected over the angular range $0.05^\circ \leq \theta \leq 5.00^\circ$, with a step size of 0.010° and counting time of 10 s per step. Prior to measurements, samples were stored under argon and exposed to air for approximately 10 min in order to be aligned on the reflectometer. From the experimental data, structural parameters of the self-assembled structures were refined using the MOTOFIT analysis software with reflectivity data presented as a function of the momentum transfer vector normal to the surface $Q = 4\pi(\sin \theta)/\lambda$.²³ The Levenberg–Marquardt method was used to minimize χ^2 values in the fitting routines.

2.3.3. Electrochemical Characterization. Electrochemical experiments of the silicon electrodes (S-2 samples) were performed in a PTFE three-electrode cell with the modified silicon surface as the working electrode, a platinum wire (ca. 30 mm²) as the counter electrode, and a plastic body silver/silver chloride “leakless” as the reference electrode (eDAQ, part ET072–1). The reference electrode was checked against the ferrocene/ferricenium couple (Fc⁺/Fc) at a glassy carbon electrode before and after each experiment. All potentials are reported versus the formal potential, E_f° , for the Fc⁺/Fc couple (1.0×10^{-3} M ferrocene solutions in acetonitrile containing either Bu₄NPF₆, Bu₄NClO₄, Bu₄NO₃, Bu₄HSO₄, or Bu₄NCF₃SO₃). All solutions for electrochemical measurements of contained 1.0×10^{-1} M of the Bu₄N salt as supporting electrolyte. The surface coverage, Γ , in mol cm⁻², was calculated from the faradaic charge taken as the background-subtracted integrated anodic current. All electrochemical experiments were performed at room temperature (23 ± 2 °C) in a grounded Faraday cage in air and either shielded from ambient light or deliberately illuminated (lowly doped samples, when stated) using a fiber-coupled high-power tungsten source from World Precision Instruments (model Novaflex optical illuminator) with an output of approximately 4500 lx. A rectilinear cross-sectional Viton gasket defined the geometric area of the working electrode to 28 mm². The back side of the silicon sample was exposed with emery paper and rubbed with gallium–indium eutectic. A planar copper electrode was pressed against the sample backside and served as ohmic contact. Electrochemical measurements were performed using a CH instruments 650D electrochemical analyzer (CH Instruments, Inc.). The 95% confidence limit of the mean of experimentally determined quantities, such as surface coverage Γ , and the voltage of the current peaks are calculated as $t_{n-1}s/n^{1/2}$, where t_{n-1} depends on the number of repeats and varied between 3.18 and 2.23,²⁴ s is the standard deviation, and n is the number of repeated measurements (n was between 3 and 10). The device flat-band potential (E_{fb}) was estimated for S-2 samples on lowly doped electrodes from measurements of the open-circuit voltage (OCV) under illumination (Figure S7).²⁵ Experimental cyclic voltammograms of S-2 samples were analyzed by a commercial digital simulation program (DigiElch 7, ElchSoft). Butler–Volmer kinetics was used to estimate charge transfer parameters. A semi-infinite 1D

diffusion at an electrode of planar geometry was assumed; all diffusion coefficients were set to 1×10^{-5} cm² s⁻¹. The number of equally spaced nodes in the spatial grid perpendicular to the electrode was set to 39. The adsorption process is simulated on the basis of the Frumkin isotherm using different values for the self-interaction parameter a . Simulations in DigiElch of the surface redox reaction require modeling a system made up by two redox couples, and charge-transfer is assumed to proceed only by direct reduction/oxidation of the adsorbed species. The first couple (sln), does not undergo a charge-transfer reaction (k was set to 0.0 s⁻¹), and it is entered for the sole purpose of mimicking a species adsorbed on the electrode surface. The independent variables that describe the adsorption, i.e., the forward rate constant k_f and the equilibrium constant $K = k_f/k_i$, describing the adsorption process, were set to 1×10^{10} and 1×10^{14} , respectively. Observed electrocatalytic curves were compared against those of simulations for a system comprising two redox couples. One of these redox couples is the TEMPO unit strongly adsorbed on the electrode surface and plays the role of a redox mediator for the heterogeneous oxidation of bromide to bromine (written in DigiElch as $Br^- \rightarrow Br^\bullet + e^-$). The anodic wave does not plateau because this process is not the more common diffusive EC' mechanism. The follow-up homogeneous chemical step for the formation of tribromide anion from bromide was not considered in the simulation.²⁶ The standard potential and rate constant of the adsorbed redox couple were set to the experimental values of S-2 samples on either illuminated lowly doped or dark highly doped electrodes, $D_{Br^-} = D_{Br^\bullet} = 1 \times 10^{-5}$ cm² s⁻¹, the $Br^-/Br^\bullet$ electrochemical process was neglected ($k_0 = 0$ cm s⁻¹), and the speed (k_F) of the heterogeneous reaction occurring between the adsorbed and not adsorbed redox couple is varied ($oxoammonium + Br^- \xrightarrow{k_f} TEMPO + Br^\bullet$).

2.4. Computational Methods. High-level *ab initio* calculations were used to predict the interaction energies between the Bu₄N counter-anions (HSO₄⁻, NO₃⁻, ClO₄⁻, CF₃SO₃⁻, and PF₆⁻) and oxidized S-2 film. For these calculations, we utilized a truncated model of the S-2 film containing the (oxidized) TEMPO ring substituted with the 4-methyl-1,2,3-triazole substituent (denoted T-cat for short). Calculations were performed at a high level of theory, chosen on the basis of our previous studies of the redox behavior of nitroxide radicals.²⁷ We utilized the high-level composite *ab initio* G3-(MP2,CC)(+) method, a variation of standard G3(MP2,CC) theory²⁸ where calculations with the 6-31G(d) basis set are replaced with the 6-31+G(d) basis set (for better treatment of anions). This high-level methodology was utilized in conjugation with an ONIOM inspired approximation,²⁹ with RMP2/GTMP2Large employed to model remote substituent effects. All geometry optimizations and frequencies calculations were performed at the M06-2X/6-31+G(d,p) level of theory³⁰ and frequencies were scaled by recommended factors.³¹ The SMD model was used to correct for implicit solvation effects.³² All standard *ab initio* calculations were performed using the Gaussian 09³³ and Molpro 2012 software packages.³⁴

To ensure maximum systematic error cancellation, we considered only the relative ΔG_{IP} values. These were converted to absolute values using the experimental redox potential for the HSO₄⁻ salt as the reference species. This approach is analogous the proton exchange method, which is able to provide accurate pK_a values even when absolute pK_a predictions (those that do not use a reference acid) are significantly less accurate.³⁵ The calculated absolute ΔG_{IP} values, along with the optimized geometries and all associated computational data and detailed theoretical procedures, are provided in the [Supporting Information](#).

3. RESULTS AND DISCUSSIONS

The grafting of the TEMPO moieties (S-2, Scheme 1) onto the acetylene-terminated Si(100) surfaces (S-1) was initially verified by XRR and XPS. XRR allows the thickness (d) of thin films to be measured with atomic resolution as a result of the high contrast in scattering length density (SLD)³⁶ of the organic molecules in the SAM ($SLD \approx 1 \times 10^{-5}$ Å⁻²)

compared to those of air ($SLD = 0$) and the silicon substrate ($SLD = 2.01 \times 10^{-5} \text{ \AA}^{-2}$). Figure 1 shows the measured

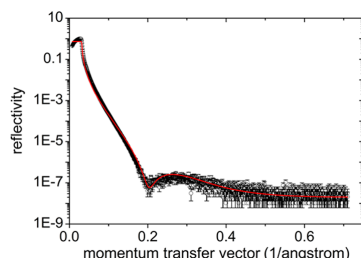


Figure 1. XRR profile of TEMPO monolayers (S-2) assembled on Si(100) electrodes by CuAAC reactions of 4-azido TEMPO on monolayers of 1,8-nonadiyne.

specular XRR curve for S-2 samples. The theoretical fit to the experimental data is shown as a solid line.²³ Unlike the Fresnel-like decay of the Si(100)–H surface,³⁷ XRR profiles for S-2 show clear interference thickness oscillations that could be simulated using a one-layer model of 16 Å thickness, which is close to the theoretical length of 14 Å. The refined value of scattering length density for the CuAAC-modified substrates (S-2) is $14.1 \times 10^{-6} \text{ \AA}^{-2}$ and as high as those achieved for SAMs on gold substrates in close-packed Langmuir–Blodgett films.³⁸ The surface roughness between the silicon surface and the monolayer, as determined by XRR refinement, was 2.9 Å, which is typical for high-quality silicon substrates.³⁹ XPS spectra acquired for S-2 samples are shown in Figure S1. This appearance of the N 1s electrons after the CuAAC reaction is in good agreement with the literature for analogous derivatization procedures on solid surfaces.^{12b} There was no evidence for the high binding energy N 1s signal (ca. 405 eV)⁴⁰ that corresponds to the electron-deficient nitrogen atom in the azido group, hence confirming negligible physisorption of the radical species in the film. A least-squares refinement of the N 1 emission gives three fitted peaks with binding energies of 400.4, 401.7, and 402.7 eV. The position of the main low binding energy line in the S-2 samples is in agreement with the 400.6 eV previously assigned to nitroxide nitrogen atoms in thin films of the *p*-nitrophenyl nitroxide radical.⁴¹ Electrons from the triazole heterocycle contributed to the 400.4 and 401.7 emissions only, with an expected ratio of the peak areas being ca. 2:1.^{12b,42} The weak shoulder observed on the high binding energy side (402.7 eV) is tentatively assigned to a shakeup satellite⁴³ of N–O electrons.

Figure 2a shows cyclic voltammograms for S-2 samples prepared on highly doped electrodes. The TEMPO films exhibited cyclic voltammetry waves of moderate stability (Figure S2) attributable to the chemically reversible nitroxide/oxoammonium ion oxidation/reduction process^{15b} and with a surface coverage $\Gamma = 2.21 \pm 0.09 \times 10^{-10} \text{ mol cm}^{-2}$ and the magnitude of the peak scales with the voltage scan rate (ν) and not with the square root of ν , which is indicative of an electroactive substrate-bound monolayer (Figure S3). With only few exceptions,⁴⁴ for most electrochemical experiments, a large excess of an inert electrolyte salt is necessary. This is done to restrict the potential gradient only within a distance of few nanometers from the surface and to compensate for charges created upon electron transfer, hence preventing an increase in

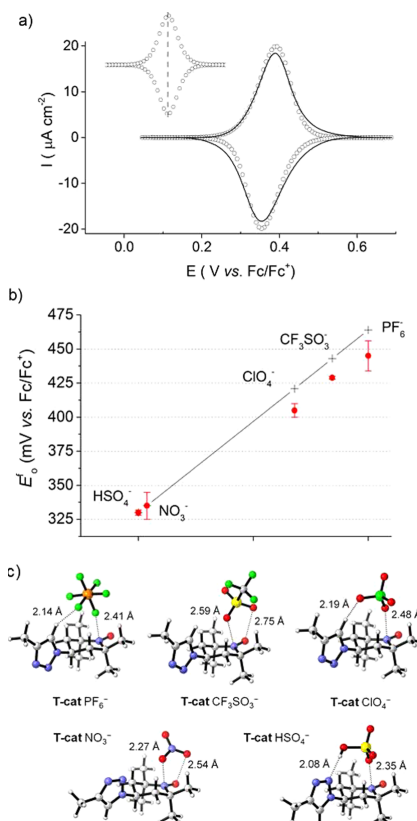


Figure 2. Cyclic voltammetry for S-2 samples prepared on Si(100) electrodes (highly doped, 0.001–0.003 Ω cm). (a) Background-subtracted observed (solid line) and simulated (symbols) voltammograms at 100 mV s^{−1} in MeCN containing 1.0 × 10^{−1} M Bu₄NClO₄. Inset shows the simulated voltammetry for a reversible and noninteracting electroactive monolayer system (*k* was set to 10⁴ s^{−1} and Frumkin “*a*” was set to zero). Ideal adsorptive-shaped waves are symmetric with respect to E_r^0 and show a 90.6/*n* fwhm. (b) Shifts of the experimental E_r^0 (red circles) and changes to the theoretical redox potential (+) as a function of the chemical composition of the electrolyte anion (Tables S1 and S2). (c) M06-2X/6-31+G(d,p) optimized geometries of the complexes between electrolyte anions and a truncated model of the S-2 film containing the oxidized TEMPO substituted with the 4-methyl-1,2,3-triazole substituent (denoted T-cat).

local resistivity during the experiment. In a high dielectric constant solvent such as acetonitrile, the electrochemical behavior of self-assembled monolayers depends strongly on the nature of the supporting electrolytes,⁴⁵ and ion pairing with the redox unit is known to affect both kinetics and thermodynamics.⁴⁶

Figures 2b and S4 display CV data of TEMPO monolayers in acetonitrile solutions containing different Bu₄N salts. Notably, the positions of the anodic and cathodic peaks appear to relate to the anion chemistry; the apparent formal potential (E_r^0) moves progressively anodically in the sequence HSO₄[−] < NO₃[−] < ClO₄[−] < CF₃SO₃[−] < PF₆[−] (Table S1). With the exception of

HSO_4^- , the magnitude of the displacement in E_i^0 tracks the empirical value of the anion Lewis basicity (Figure 2b and Table S2, *vide infra*). In the case of HSO_4^- , theoretical calculations (Tables S3–S5) indicate that the additional stabilization is due to formation of a hydrogen bond with azole ring (Figure 2c). The value of Γ was approximately 50% of that reported for close-packed TEMPO monolayers assembled on gold electrodes,⁴⁷ but even for this “diluted”, system the shape of the experimental redox waves is not ideal,^{15b} showing a minor asymmetry. The experimental fwhm is also independent of surface coverage in the range of Γ explored (Figure S5), yet is larger than the theoretical values of 90.6/n mV (Figure 2a inset). For instance, the observed fwhm is ca. 100 mV for ClO_4^- or NO_3^- -based electrolytes (102 ± 1 and 94 ± 6 mV, respectively) and upward to ca. 112 ± 1 and 119 ± 3 mV in CF_3SO_3^- and PF_6^- solutions, respectively (Table S1). A small peak asymmetry coupled to a small increase (ca. 5–10 mV) over the ideal fwhm's can be simulated and accounted for in terms of slow charge transfer kinetics (Figure 2a, simulated CV in symbols with refined electrochemical rate constant k and refined fwhm being 3.6 s^{-1} and 96 mV, respectively). At present, we are unsure as to what factors other than slow kinetics contribute to the nonideal fwhm's in the ClO_4^- and PF_6^- systems especially because these nonidealities persist when the rate is enhanced by up to 5-fold for illuminated lowly doped substrates (*vide infra*).

We note, however, that a large number of models have been proposed to explain such nonidealities,⁴⁸ and in the Nernstian case of an electrochemically reversible system ($k \rightarrow \infty$),⁴⁹ when the energy of interaction between like molecules is larger than that between unlike molecules, the observed fwhm will be larger than that for the ideal noninteracting case.

In reversible systems, the extent of these putative electrostatic interactions have often been parametrized simply by introducing changes to the Frumkin a factor that leads to the corresponding isotherm (Figure S6).⁵⁰ However as noted above, our highly doped S-2 systems have finite electron transfer kinetics; hence, using this approach would probably lead to an oversimplification and would fail to give a meaningful quantitative explanation on both peak broadening and shifts in E_i^0 values. In our discussion we therefore focus exclusively on the electrolyte-related shifts to E_i^0 and interpret the data by showing a correlation between the observed voltammograms and calculated quantities. Notably, the displacement in E_i^0 (Table S2) tracks the empirical value of the anion Lewis basicity with the exception of HSO_4^- for which, as noted above, a favorable hydrogen bond with the azole ring leads to additional stabilization. An electrostatic component can be separated for the Lewis acid–base interaction (oxoammonium–electrolyte anion interaction), and this electrostatic scheme brings about a reduction in the thermodynamic cost for the TEMPO oxidation. This is supported by the theoretical calculations of the oxoammonium–electrolyte anion interaction energies that are stabilizing overall (see Supporting Information) and predict a progressive anodic shift in the redox potential in the same order as in experiment: $\text{HSO}_4^- < \text{NO}_3^- < \text{ClO}_4^- < \text{CF}_3\text{SO}_3^- < \text{PF}_6^-$. In brief, the nature of the electrolyte anion appears to have a large effect on i – E curves in a way that is not quantifiable as a commonly reported adjustment of the Frumkin a term (Figure S6). The direction of the displacement in E_i^0 values is consistent with the chemistry involved, and this implies that for a given bias one is able to predictably alter the ratio of surface reductant to surface oxidant, i.e., surface

nitroxide to oxoammonium, by a simple change in the electrolyte; for instance, increasing the oxidizing power of a TEMPO film by increasing the Lewis base character of the electrolyte anion. This aspect is potentially of great significance when one considers applications of TEMPO films in heterogeneous catalysis.⁵¹ To illustrate this, we have coupled the homogeneous TEMPO charge transfer reaction to the heterogeneous oxidation of bromide ions and extracted the dependency of the apparent heterogeneous rate constant as a function of electrolyte, with the highest k_{cat} measured for PF_6^- systems (Figure S8).

As introduced above, our chemical strategy to immobilize the nitroxide radical on the highly doped substrate can be expanded to a Si(100) electrode of low doping where the internal electrical field of the semiconductor space-charge⁵² can be used to drive the redox reaction(s) contrathermodynamically (Figure 3). The same surface chemistry used for the S-2 samples on the

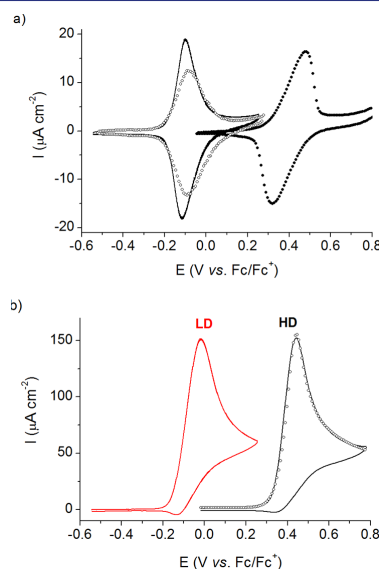


Figure 3. Cyclic voltammograms for S-2 samples prepared on n-Si electrodes (lowly doped, 1–10 $\Omega \text{ cm}$). (a) Dark oxidation and reduction waves (symbols) and their underpotential shift with supra band gap illumination (lines). CVs were obtained at a voltage sweep rate of 100 mV s^{-1} in MeCN containing $1.0 \times 10^{-1} \text{ M}$ of either Bu_4NClO_4 (solid line, fwhm = 91 mV) or Bu_4NPF_6 (empty symbols, fwhm = 120 mV). (b) Observed (lines) and simulated (symbols) CV of the electrocatalytic mechanism on illuminated lowly or highly doped S-2 samples (LD or HD, respectively) in the presence of $0.5 \times 10^{-3} \text{ M}$ Bu_4NBr in $1.0 \times 10^{-1} \text{ M}$ of Bu_4NPF_6 . The refined value of k_{cat} for the reaction between the adsorbed oxoammonium and nonadsorbed bromide was $3.2 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

highly doped electrodes (Figure 2) was applied to n-type Si(100) electrodes of low doping (ND, $\sim 4.5 \times 10^{14}$ to $5.0 \times 10^{15} \text{ cm}^{-3}$, resistivity = 1–10 $\Omega \text{ cm}$). The dark current–voltage characteristics of the S-2 electrode (Figure 3a, symbols) reveal the extent of the expected kinetic limitations for the tunneling across the semiconductor space-charge; both asymmetry in the peaks⁵³ and a sizable peak-to-peak separation are a manifestation of slow charge transfer kinetics ($k_{\text{et}} \approx 0.01 \text{ s}^{-1}$) in the

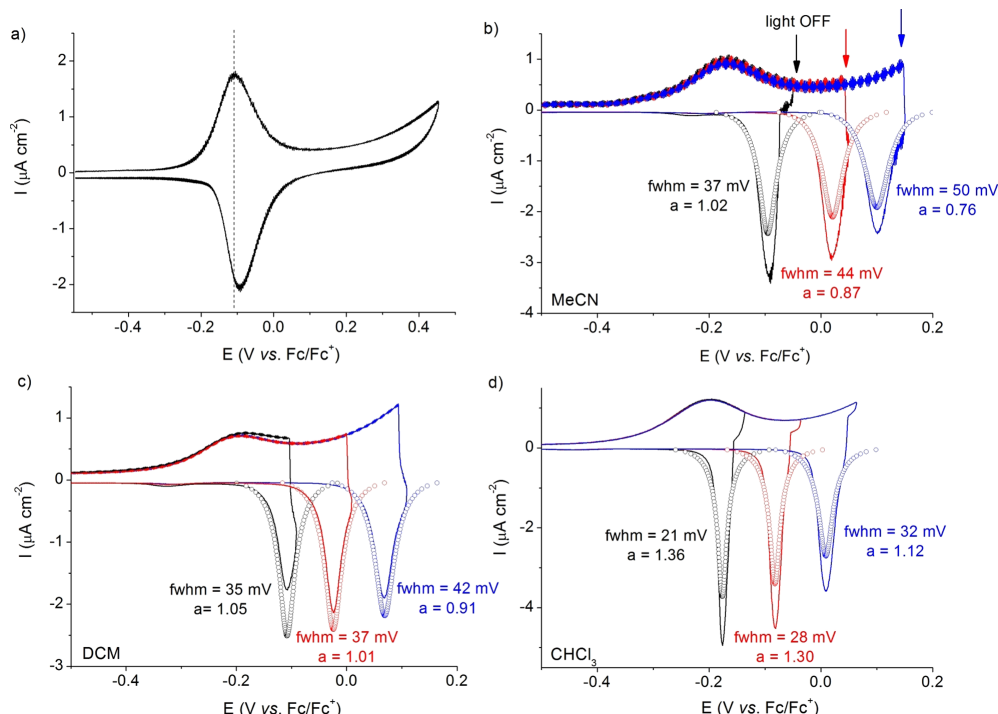


Figure 4. (a) Example of “peak inversion” in CVs of S-2 electrodes of low doping under illumination (Bu_4NClO_4 and $\nu = 100 \text{ mV s}^{-1}$). (b–d) “Peak inversion” can be deliberately induced in CVs of S-2 samples on lowly doped electrodes when illumination is switched off at the anodic vertex (0.4, 0.5, or 0.6 V) in Bu_4NClO_4 electrolytes using solvents of progressively lower dielectric constant (37.5 for acetonitrile, 8.9 for dichloromethane, and 4.8 for chloroform). Simulated voltammograms (symbols) and refined values of the self-interaction parameter “a” are indicated in figure.

dark lowly doped samples. In the light-activated faradaic response,^{8,54} this kinetic barrier is largely removed (Figure 3a, solid line, $k_{\text{et}} \approx 15 \text{ s}^{-1}$), and the values of E_f^0 are shifted approximately 500 mV more negative with respect to the low or high doping S-2 samples in the dark (Figure 2a). Peak shapes in the illuminated lowly doped samples are near-to-ideal (fwhm = $95 \pm 7 \text{ mV}$) in ClO_4^- electrolytes but remain significantly broader in PF_6^- (fwhm = $131 \pm 5 \text{ mV}$), hence reinforcing the notion that factors other than kinetics are causing this nonideality (*vide supra*). The uphill shift is consistent with the measured OCP under illumination (Figure S7a) and is a result of a process mediated by photogenerated valence band holes as previously reported for gallium and germanium photoanodes.^{52,55} As anticipated in the introduction, the shift in the E_f^0 of the homogeneous TEMPO reaction can translate into an energetic gain for a heterogeneous reaction, such as the oxidation of bromide ions in solution. The electrocatalytic process that is mediated by the surface TEMPO molecule on illuminated lowly doped samples (Figure 3b) is shifted uphill by about 500 mV compared to the same heterogeneous reaction on highly doped (metallic) samples (Figure S8).

The CV data for illuminated S-2 samples of low doping have been reproduced several times, with no major differences in peak-to-peak separations ($11.5 \pm 1.5 \text{ mV}$), fwhm ($95 \pm 7 \text{ mV}$), and Γ ($2.05 \pm 0.04 \times 10^{-10} \text{ mol cm}^{-1}$) values (ClO_4^- data); however, a remarkable phenomenon was observed in at least

four independently prepared and analyzed samples (Figures 4a and S7). In these four samples, the cathodic current peaked at a more anodic potential than that of the anodic peak. A current across an electrified interface is always indicative of an overall rate; hence, this “inversion” would immediately be disregarded as an artifact on a common metallic surface. However, a similar observation was reported in 1979 by Wrighton and co-workers for illuminated n-type gallium arsenide electrodes⁵² that were modified with surface-bound ferrocenes. As tentatively suggested by Wrighton, a reduction rate being higher than the oxidation rate at an anodic regime may result from the charges of the adsorbed oxidized species affecting the electrostatics of the semiconductor electrode.⁵⁶ In the cases at hand (S-2, n-type, low doping), the flat-band potential of the system, E_{fb} , may be forced to shift anodically when during the voltammetric sweep the relative amount of neutral nitroxide radical to positively charged oxoammonium ion changes in favor of the latter. The observed sudden dominance of the reduction rate at a bias that is anodic of the oxidation wave may result from an electrostatic effect on the semiconductor space-charge, such that the oxoammonium species force bands to flatten, removing the tunneling barrier for the electrons leaving the electrode. It is important to note that the light intensity used in our experiments appears not to be high enough to force the bands to flatten completely (Figure S7a) and that the high dielectric medium ($\epsilon_{\text{MeCN}} = 37.5$) is not completely masking

interactions between the ionized semiconductor space-charge and oxoammonium species. Because of this electrostatic “push” by the oxoammonium species on the space-charge, the onset of depletion requires a more positive bias, hence resulting in an oxoammonium-assisted smaller barrier to the flow of cathodic currents across the interface.

To support this electrostatic explanation for the “peak inversion” phenomenon, we performed voltammetry in solvents of different dielectric constants to minimize or amplify this putative electrostatic effect, and we deliberately switched off the illumination source precisely at the anodic vertex. Figure 4b–d shows a series of CVs for S-2 samples on lowly doped electrodes, with only the sweep toward the anodic region performed under illumination. The anodic “illuminated” wave in Figure 4 has nothing unusual; hence, the theoretical current–voltage characteristics can be simulated on the basis of the Frumkin isotherm using a “zero” value of the Laviron self-interaction parameters a , i.e., the Langmuir isotherm without interactions⁵⁷ involving TEMPO units (*vide infra*). From a different angle, the observed peak shape implies ideality in the sense that the surface concentrations of the reduced and oxidized species equal their activities.⁵³ The light is then switched off at the anodic vertex (set either as 0.4, 0.5, or 0.6 V) in order to deliberately introduce a space-charge barrier for electrons to enter the semiconductor (anodic reaction). The flux of photogenerated holes is brought to a sudden halt, and a very sharp reductive peak appears instantly. The net result is a sudden increase in the reduction rate when the light is switched off, i.e., under these conditions the reductive peaks occur at a potential that is more positive than the oxidative peak. By doing this, we have supported the above hypothesis of the “peak inversion” (Figure 4a) being the result of an electrostatic effect of the oxoammonium on the semiconductor space-charge. Furthermore, we can now assume that the reduction event is fast and behaves similar to a Nernstian process; hence, we can tentatively analyze our adsorbed system by using models that hold for reversible systems. As introduced above, a conventional approach to quantify the observed drop in experimental fwhm’s in terms of attractive forces is the parametrization developed by Laviron based on the Frumkin isotherm (Figures 4, S6, and S9 and section §S1). In this model, the voltammetry response is derived under Nernstian conditions by taking into account a simple isotherm, the so-called Frumkin isotherm, which introduces the a parameter. This is a dimensionless constant describing the extent of attractive and repulsive interactions between molecules,⁵⁸ and is directly related to the fwhm value (Supporting Information section §S1). When the light source is switched off at the anodic vertex, band-bending in the depleted semiconductor space-charge is rapidly restored, and the balance of attractive to repulsive forces experienced by the adsorbed oxoammonium species appears to tilt in favor of the attractions, with the refined a increasing above the zero value (Figure 4b–d). In line with this explanation, this putative electrostatic effect on the a self-interaction parameter, which we ascribe tentatively to a space-charge effect on the oxoammonium/anion attractions, becomes in fact more pronounced as the solvent dielectric is reduced by moving from acetonitrile to chloroform solutions (Figure 4b,d).

4. CONCLUSIONS

This article presented a two-step acetylenylation/click procedure as a wet chemistry approach to tether a nitroxide radical to a silicon surface and preserve its open-shell state. This

is the first example of the attachment of a redox-active stable free radical onto a semiconducting surface. From a fundamental standpoint, these surface systems can be used as a laboratory model to explore the recently reported electrostatic effects on chemical bonding and reactivity.^{5,59} Here we have explored to what extent electrostatic effects arising either from electrolyte species or ionized dopants in the semiconductor space-charge can influence the redox activity of the free radical. We have shown experimentally that it is possible to gauge these effects as changes to voltammetric responses. This knowledge may aid the development of electrocatalytic heterogeneous systems where the redox reaction of interest can be coupled to semiconductor effects and therefore driven contra-thermodynamically by up to 0.5 V.

All experimental results show good agreement with theoretical calculations and show that the redox properties of nitroxide radical monolayer can indeed be predictably manipulated by controlling the electrostatics between the tethered persistent radical and electrolytes or semiconductor.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04788.

Synthetic methods, XPS data, additional theoretical data, geometries and procedures, additional electrochemical data and simulations (PDF)

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Notes

The authors declare no competing financial interest.

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6.5 Supporting information

A detailed description of the computational methodology, summary tables of raw energies and optimized geometries for all the species in this chapter can be found on the CD-ROM attached at the back of this thesis. Supporting information for Publications 8 and 9 can also be obtained free of charge from http://pubs.acs.org/doi/suppl/10.1021/acs.macromol.5b02017/suppl_file/ma5b02017_si_001.pdf [Publication 8] and http://pubs.acs.org/doi/suppl/10.1021/jacs.6b04788/suppl_file/ja6b04788_si_001.pdf [Publication 9].

7. General conclusions

7.1 Summary of key findings

This thesis presents a broad array of discoveries and insights that are centred on the theme of stereocontrol in radical polymerization but that also extend into controlling other aspects of polymer chemistry (and related fields) more generally:

1. A detailed mechanistic comparison of Lewis acid-mediated stereocontrol in both radical polymerization and small-molecule radical synthesis is presented. Using existing literature from both fields, the fundamental difficulties in obtaining stereocontrol in radical polymerization are identified and (where possible) assessed. While some mechanistic aspects of stereocontrol in Lewis acid-mediated radical polymerization are currently unclear, indiscriminate Lewis acid binding and incorrect positioning are likely the most significant limitations on tacticity control.
2. The use of computational chemistry to study reactions of relevance to radical polymerization is reviewed and recommended methodology is established. This methodology is then applied to clarify the mechanism of tacticity determination in the unmediated free-radical polymerization of methyl methacrylate, styrene and methacrylic acid. The correctness of the rapid-exchange model is confirmed for these common monomers. The frequently used slow-exchange model is shown to be based on a dubious kinetic assumption and its use for tacticity prediction is discouraged.
3. The effect of lithium bis(trifluoromethanesulfonyl)imide on the tacticity and propagation kinetics of methyl methacrylate was examined via both experimental techniques and high-level *ab initio* calculations. While the effects on tacticity were very minor, pulsed laser polymerization (PLP) experiments revealed a modest catalytic effect on the propagation rate coefficient of methyl methacrylate. High-level calculations indicate that Li^+ selectively binds to the terminal and penultimate side-chains of the propagating radicals and imparts a pro-*meso* conformational preference. However, this binding mode deactivated the polymer radical towards propagation. A less thermodynamically favourable non-stereocontrolling binding mode (in which the terminal and incoming monomer

side-chains are bound) catalysed monomer addition to such an extent that this mode was the dominant propagation pathway. This finding explains the lack of stereocontrol in this system. Moreover, as this catalysis is electrostatic in origin, it is likely to be a significant limitation in other Lewis acid-mediated polymerizations. Propagation catalysis is extremely useful in its own right, particularly in improving molecular weight control in living-radical polymerization and for minimizing defect structure formation. Attempts to optimize the catalysis using Lewis acids with higher charges showed qualitatively promising results, but were omitted from the thesis because they were hampered by a loss of PLP characteristics in the resultant molecular weight distributions.

4. By employing a combination of high-level theory and experiment, the required criteria for high photoinitiation efficiencies in PLP experiments were identified. While it is apparent that initiator efficiency is significantly influenced by chemical substitution, photoinitiation is highly complex and efficiency is not straightforwardly related to a single property (e.g. extinction coefficient or fragment radical reactivity). Instead, photoinitiator efficiency depends on several factors, which are systematically evaluated for several benzoin derivatives. These insights facilitated subsequent studies on the effect of Lewis acids on Type I acetophenone initiators.
5. The presence of Lewis acids was found to significantly affect the photoinitiation behaviour of Type I acetophenone derivatives. Zinc chloride and aluminium chloride can significantly alter the absorption spectrum of methyl-4'-(methylthio)-2-morpholinopropiophenone (MMMP) and 2,2-dimethoxy-2-phenylacetophenone (DMPA). These changes are symptomatic of more complex photoexcitation behaviour and are also accompanied by significant changes in fragment radical reactivity. Theoretical calculations suggest that the photochemistry of these complexes is significantly more complicated than that of unbound MMMP or DMPA. However, as Lewis acids red shift the intense UV-Vis absorptions of both photoinitiators, it is possible that simple Lewis acids could be used in conjunction with acetophenone derivatives in visible light initiating systems. Moreover, the ability of common Lewis acids to alter the photoinitiation properties (such as the absorbance maxima, initiator efficiency and radical

reactivity) of acetophenone derivatives could be utilized in many other photochemical applications.

6. The effect of ionization on the propagation kinetics of methacrylic acid is explored with high-level theory, which can accurately predict the propagation rate coefficient and tacticity under different conditions. Experimentally observed effects of ionization on the Arrhenius parameters can be rationalized by the formation of a strong hydrogen bond between the ionized monomer and non-ionized polymer terminus. Moreover, this hydrogen bonding increases the syndiospecificity of propagation. These calculations also indicate that the terminal carboxylate group of methacrylic acid is significantly more basic than other side-chains in the polymerization.
7. The mechanism of isospecific propagation of calcium methacrylate is examined with high-level theory. These calculations indicate that the high isospecificity of calcium methacrylate (CaMA) propagation probably results from the formation of calcium/carboxylate bridging scaffolds. Additional literature evidence for this multiple-chelation mechanism is presented and discussed. Based on this new mechanism, further improvements to stereocontrol in MAA (and AA) should be possible by modifying reaction conditions (e.g. solvent, temperature) to favour these bridging modes. Moreover, an improved procedure for converting poly(CaMA) to poly(MMA) was developed (see **Appendix 8.1**) and thus, this offers one possible way of producing isotactic poly(MMA) via a cost-effective ionic auxiliary. More generally, the method by which CaMA overcomes the catalysis versus stereocontrol dichotomy highlights a possible strategy for stereocontrol more generally via the use of bridging ligands.
8. An unusual low-temperature nitroxide mediated polymerization (NMP) of vinyl chloride is examined. Theoretical results confirm that the normal NMP activation/deactivation equilibrium is infeasible and a tentative mechanism proceeding via dehydrochlorination of the alkoxyamine chain-ends is presented. This work highlights the invaluable contributions that theoretical chemistry can make to mechanistic studies of polymerization reactions.

9. The effect of Lewis acid/base complexation on the redox behaviour of TEMPO monolayers is examined. Theoretical and experimental results demonstrate that the oxidation potential of these monolayers is influenced by Lewis acid/base interactions between the resultant oxoammonium cation and the counter-anions of the electrolyte. High-level theory can quantitatively predict the magnitude of these effects with excellent accuracy. This work further highlights the importance of electrostatic effects in chemical reactions, and establishes the foundation for novel research in which electric fields will be used in an attempt to control NMP of polymers on an electrode.

7.2 Future work and outlook

While radical polymerization was traditionally perceived as the least controllable chain polymerization process, pioneering work over the last few decades has overcome supposed limitations on molecular weight and chain-end control, and so redefined the scope and utility of radical polymerization. While the possibility of controlling stereochemistry in radical polymerization remains of enormous interest, it is a highly challenging endeavour from a mechanistic perspective. As highlighted in this thesis, unlike small molecule synthesis, there is a multiplicity of binding modes between Lewis acids and the various polymer, radical and monomer side-chains, most of which are not stereocontrolling. Moreover, the work presented in **Chapter 4** demonstrates that even when Lewis acids bind in the ‘correct’ stereocontrolling terminal-penultimate position, this binding mode deactivates the polymer radical towards propagation. Indeed, non-stereocontrolling terminal-monomer binding electrostatically catalyses monomer addition and dominates overall propagation. This catalysis is significant and useful in its own right. Propagation catalysts can be used to produce polymer with fewer defect structures and hence enhanced thermal- and photo-stability. However, given these electrostatic effects are likely to be observed more generally, it indicates that other strategies are required for stereocontrol.

Fortunately, work in this thesis also has identified a possible solution to the catalysis versus stereocontrol dichotomy. Using theoretical calculations, it was shown that the high degree of isotactic control achieved in CaMA, results from bridging scaffolds that simultaneously bind the terminal, penultimate and monomer side-chains. Strategies that mimic this approach using bridging ligands or large tridentate binding Lewis acids, may offer a potential strategy for isotactic control in other monomers. Indeed, it is likely that the isotactic control observed in (meth)acrylamide polymerizations with rare earth metal triflates results from binding of the terminal, penultimate and monomer side-chains simultaneously. Moreover, (meth)acrylic acid salts themselves show great promise as low-cost ionic auxiliaries for the synthesis of poly(acrylates) and poly(methacrylates), and an improved conversion procedure for CaMA was developed to exploit this opportunity. We believe higher levels of isotactic control should be attainable by exploiting bridging interactions in calcium methacrylate and potentially other metal methacrylates.

We should also note that when performing pulsed laser polymerization in the presence of Lewis acids, photoinitiators should be selected with some caution. While the precise effects of Lewis acid complexation on photolysis are currently unclear, we note any adverse effects could probably be avoided by the use of bulky non-chelating acetophenone derivatives. These initiators should not interact significantly with most Lewis acids and complexation to monomer would actually enhance the reactivity of their fragment radicals. Obviously, it would be highly desirable to clarify the effect of Lewis acid complexation on the singlet and triplet lifetimes of more typical initiators, such as methyl-4'-(methylthio)-2-morpholinopropiophenone. The ability of Lewis acids to influence photoinitiation could potentially be exploited to develop novel visible light initiating systems.

Prior to the development of living-radical polymerization, many chemists were pessimistic and cynical of the prospects of molecular weight and chain-end control in radical-based polymerizations. In this context, similarly dismissive attitudes towards stereocontrol should certainly be discouraged. Indeed, the surprising low temperature nitroxide-mediated polymerization of vinyl chloride (presented in **Chapter 6**) highlights the need to continually question, extend and revise accepted mechanisms so that any limitations and/or deficiencies can be better understood. In this regard, theoretical modelling of relatively good examples of stereocontrol, such as Yb(OTf)₃ mediated polymerization of *N,N*-dimethylacrylamide (see **Table 1**), would be of great benefit to confirm or refute the proposed mechanism of isotactic control. Unfortunately, given the size of this control agent, sufficiently accurate calculations would almost be intractable with current software and hardware constraints.

Stereocontrol strategies in radical polymerization have utilized expertise in fields as diverse as synthetic inorganic and organic chemistry to biological and supramolecular chemistry. As such, a more comprehensive understanding of a broad range of topics, from non-covalent interactions to radical reactivity, is likely to assist the advancement of stereocontrol in radical polymerization. Undoubtedly, many further studies will contribute to this important area of research and hopefully more effective tacticity control strategies will be developed in the near future. We hope that this thesis will spur new advancements in this exciting area of research.

8. Appendices

8.1 Procedure for the conversion of poly(calcium methacrylate) to poly(methyl methacrylate)

In their original report, Kadokawa and co-workers converted poly(calcium methacrylate) to poly(methacrylic acid) by dissolving a small amount of the prepared polymeric gel (~20 mg) in a large amount of 1 M NaOH (40 mL) and passing the solution through an pre-acidified ion-exchange resin.¹²² The resulting poly(methacrylic acid) was then methylated with diazomethane, first using a methanol/ether mixed solvent, then a second time using benzene as a solvent.¹²² This procedure would be impractical for gram-scale synthesis because of the (apparent) poor solubility of poly(calcium methacrylate) in NaOH solution, the need to use an ion-exchange resin and the use of diazomethane (which is both highly toxic and potentially explosive). As such, we explored and developed an alternative isolation and conversion strategy (see **Figure A1**).

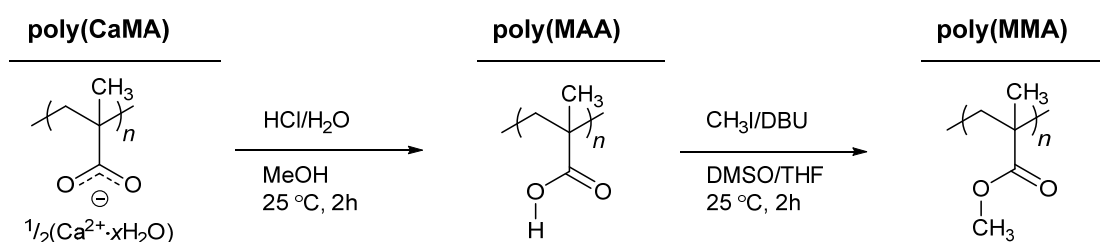


Figure A1 The procedure that we developed to convert poly(CaMA) into poly(MMA).

Poly(calcium methacrylate) was prepared as a gel via the radical polymerization of calcium methacrylate in *N,N*-dimethylformamide (Chem-Supply, > 99.8%), using azobisisobutyronitrile (Aldrich, 99%) as an initiator. Poly(calcium methacrylate) (~40 mg) was dissolved in a (~2 mL) mixture (20:1 by volume) of methanol (Merck, GC grade) and concentrated HCl (Emsure, 37%). After 2 hours, the resulting poly(methacrylic acid) was precipitated into a large excess of wet acetone (~20 mL) (Ajax, reagent grade), collected by filtration and washed with additional acetone. The obtained poly(methacrylic acid) was twice more purified by reprecipitation from a minimal amount of acidified methanol by addition into excess acetone. After being dissolved in a similar amount of acidified methanol (~2 mL), calcium chloride dihydrate (~100 mg) (Merck, > 99.5%) was found to be completely soluble in wet acetone (20 mL).

Thus, reasonable separation of the desired poly(methacrylic acid) from the byproduct (calcium chloride) was achieved by exploiting their divergent solubility in acetone.

After poly(methacrylic acid) was obtained, a methylation procedure inspired by Yamada and co-workers was employed.¹³⁷ Attempts to rigorously follow the original procedure of Yamada and co-workers lead to high but not quantitative esterification of the poly(methacrylic acid) samples (with methylations typically stalling at around 90% esterification). Doubling the specified methyl iodide and 1,8-Diazabicyclo[5.4.0]undec-7-ene concentration had little to no effect on the amount of esterification. As precipitate was observed after 90 minutes in all these esterification reactions, we attribute the suboptimal esterification to the poor solubility of the resultant polymer in dimethyl sulfoxide.

To address this problem, a revised procedure was developed as follows: Poly(methacrylic acid) (40 mg) was dissolved in dimethyl sulfoxide (1.5 mL) (Emsure, > 98.5%) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (90 μ L) (Aldrich, 98%) and methyl iodide (Aldrich, 99%) (74 μ L) was added. This solution was stirred at room temperature for 90 min (as per Yamada's procedure) and then tetrahydrofuran (Honeywell Burdick & Jackson, GC/GPC grade) (0.75 mL) and additional methyl iodide (74 μ L) was added. Precipitate that had formed following the first stage of the reaction was redissolved with the addition of tetrahydrofuran. This homogeneous solution was stirred for a further 30 min and then poured into a large excess of methanol (20 mL). The resulting white precipitate was filtered, washed with additional methanol and purified twice by reprecipitation from chloroform (Emsure, reagent grade) by addition into methanol. The product poly(methyl methacrylate) (36 mg, 78% yield) was then dried under vacuum and characterized by ¹H-NMR in deuterated chloroform (*D* = 99.8%, Cambridge Isotope Laboratories). The degree of esterification of the obtained polymer was found to exceed 99% (see **Figure A2**). Calcium methacrylate was prepared by addition of excess methacrylic acid (Aldrich, 99%) to calcium hydroxide (Aldrich, 95%) suspended in water. The clear solution was stirred for 3 hours and concentrated under rotary evaporation to afford a white powder. This solid was isolated by filtration, washed with acetone and then dried under vacuum at room temperature. All other reagents were obtained from the suppliers listed and used as received.

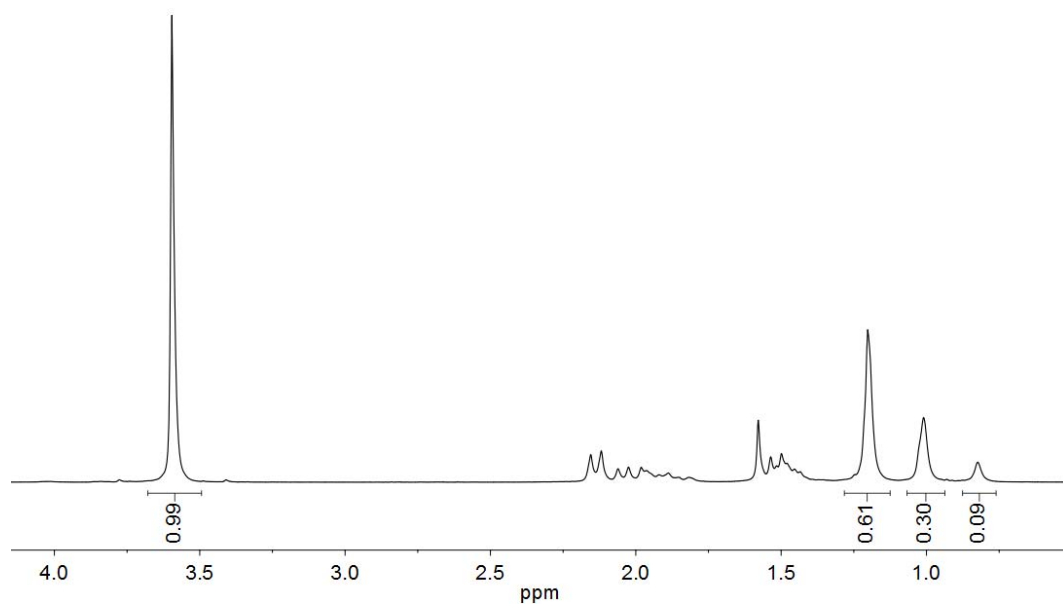


Figure A2 ^1H -NMR spectrum of poly(MMA) prepared from calcium methacrylate via radical polymerization in DMF at 60 °C, which was converted and methylated via the above procedure.

8.2 Computational chemistry

8.2.1 INTRODUCTION: WHAT IS COMPUTATIONAL CHEMISTRY?

Over the last few decades, rapid advancements in computer processing capacity and the development of efficient quantum chemical algorithms have redefined the capabilities of computational chemistry. In theory, computational chemistry can be used to predict any physical observable; including geometric structures, reaction and activation energies, vibrational and electronic transitions (corresponding to IR and UV-Vis spectra, respectively), atomic charges, electrostatic potentials, polarizabilities and hyperpolarizabilities, and NMR shielding and coupling constants. Moreover, computational chemistry can be used to simulate complex chemical processes, quantify and rationalize reactivity and revise fundamental reaction mechanisms. It can also provide information that is difficult, if not impossible, to access with experimental techniques. However, computational chemistry must also be employed cautiously, as the validity of the results obtained not only hinges on the reasonableness of the chemical model, but also the accuracy of electronic structure procedures used.

“Anyone can do calculations nowadays. Anyone can also operate a scalpel. That doesn't mean all our medical problems are solved.”
- Karl K. Irikura

8.2.2 THE SCHRÖDINGER EQUATION APPLIED TO ATOMIC AND MOLECULAR SYSTEMS

The theoretical basis for computational chemistry is one of the most important and fundamental formulations in quantum mechanics, the time-independent Schrödinger wave equation (TISWE):

$$\hat{H}\Psi = E\Psi \quad [A1]$$

In *Equation A1*, Ψ is the wave function that completely describes the quantum state of a system of fundamental particles, including probability amplitudes for the positions of all the particles in the system, $\hat{H}$ is the Hamiltonian operator that is associated with the total observable energy and E is the total (scalar) energy of the system. The TISWE is an eigenvalue equation that describes stationary states.

In quantum mechanics, there is an operator associated with each observable parameter of a given physical system. The Hamiltonian operator is defined as the sum of the kinetic ($\hat{T}$) and potential energy operators ($\hat{V}$):

$$\hat{H} = \hat{T} + \hat{V} \quad [\text{A2}]$$

In chemical systems (i.e. for atomic and molecular species), the total kinetic energy operator can be expressed as the sum of the kinetic energy operators for the electrons ($\hat{T}_e$) and nuclei ($\hat{T}_n$):

$$\hat{T} = \hat{T}_e + \hat{T}_n \quad [\text{A3}]$$

Similarly, the total potential energy operators can be written as a sum of component nuclear-nuclear repulsion ($\hat{V}_{nn}$), nuclear-electron attraction ($\hat{V}_{ne}$) and electron-electron repulsion ($\hat{V}_{ee}$) terms:

$$\hat{V} = \hat{V}_{nn} + \hat{V}_{ne} + \hat{V}_{ee} \quad [\text{A4}]$$

In quantum chemical calculations, operator expressions are simplified through the use of specialized units; bohr (distance), electron mass (mass), electron charge (charge) and hartree (energy). The following expressions assume use of these specialized units for an arbitrary (non-relativistic) chemical system. The kinetic energy operators for the electrons and nuclei can be written as:

$$\hat{T}_e = -\frac{1}{2} \sum_i \nabla_i^2 \quad [\text{A5}]$$

$$\hat{T}_n = -\frac{1}{2M_A} \sum_A \nabla_A^2 \quad [\text{A6}]$$

In *Equation 5* and 6, ∇^2 denotes the differential Laplace operator, while M_A denotes the mass of the A^{th} nuclei. The differential Laplace operator is defined as:

$$\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \quad [\text{A7}]$$

The nuclear-nuclear repulsion, nuclear-electron attraction and electron-electron repulsion operators are given by:

$$\hat{V}_{nn} = \sum_{A>B} \frac{Z_A Z_B}{|R_A - R_B|} \quad [\text{A8}]$$

$$\hat{V}_{ne} = - \sum_i \sum_A \frac{Z_A}{|R_A - r_i|} \quad [\text{A9}]$$

$$\hat{V}_{ee} = \sum_{i>j} \frac{1}{|r_i - r_j|} \quad [\text{A10}]$$

In *Equations A8 - A10*, R_A , R_B , r_i and r_j denote the position of the A^{th} nucleus, B^{th} nucleus, i^{th} electron and j^{th} electron, respectively (A and B are used to index nuclei, while i and j are used to index electrons). Similarly, Z_A and Z_B denote the charge of the A^{th} and B^{th} nuclei, respectively.

As nuclei are significantly more massive than electrons (a proton alone is nearly 2000 times more massive than an electron),¹³⁸ their motions are significantly slower. Under the *Born-Oppenheimer approximation*,^{139, 140} the motions of nuclei and electrons are decoupled and so electrons are assumed to react instantaneously to the motions of nuclei. This approximation makes $\hat{V}_{nn}$ a constant and $\hat{T}_{nn} = 0$. It also implies the total wave function can be separated into a product of nuclear (Ψ_n) and electronic (Ψ_e) terms:

$$\Psi(R_1, \dots, R_A, r_1, \dots, r_i) = \Psi_n(R_1, \dots, R_A) \Psi_e(r_1, \dots, r_i) \quad [\text{A11}]$$

Substitution and simplification of these expressions affords the electronic Schrödinger wave equation, which describes the electronic energy of an atomic or molecular system for a given set of (fixed) nuclear coordinates ($R_1, \dots, R_A$):

$$\left[-\frac{1}{2} \sum_i \nabla_i^2 - \sum_i \sum_A \frac{Z_A}{|R_A - r_i|} + \sum_{i>j} \frac{1}{|r_i - r_j|} \right] \Psi_e(r_1, \dots, r_i) = E_e \Psi_e(r_1, \dots, r_i) \quad [\text{A12}]$$

Note that in *Equation A12*, the nuclear-nuclear repulsion term has been omitted (this term shifts the eigenvalues by a constant amount but has no effect on the eigenfunctions – it can be calculated separately from *Equation 8* for a given set of nuclear coordinates).

Once solved, *Equation A12* affords the electronic energy for a given nuclear configuration (i.e., geometry); solving this equation as a function of geometry then provides a potential energy surface (PES). While *Equation A12* may appear deceptively simple, it is very difficult to solve exactly, except for 1-electron systems. Even now, decades after this electronic Schrödinger wave equation was first formulated, quantum chemists are refining the approximations and computational algorithms that are used to solve this equation.

8.2.3 HARTREE-FOCK THEORY

Ab initio (Latin: “From the beginning”) procedures attempt to describe chemical systems using only theoretical principles and fundamental constants; without recourse to experimental data.^{139, 140} Hartree-Fock (HF) theory is the simplest *ab initio* procedure and forms the foundation for most of the more complex and accurate wave-function based methods. Recall that, according to the *Born-Oppenheimer approximation*, the total wave function can be expressed as a product of nuclear and electronic terms:

$$\Psi(R_1, \dots, R_M, r_1, \dots, r_N) = \Psi_n(R_1, \dots, R_M) \Psi_e(r_1, \dots, r_N) \quad [\text{A11}]$$

Unfortunately, the electronic wave-function is dependent on the coordinates of every electron in system and the position of a given electron will depend on the positions of all other electrons. Under the *independent electron approximation*,^{139, 140} it is assumed that the electronic wave function can be expressed as the *Hartree* product of individual 1-electron wave functions ($\psi_1, \dots, \psi_N$), known as molecular orbitals (MOs):

$$\Psi_e(r_1, \dots, r_N) = \psi_1(r_1) \times \dots \times \psi_N(r_N) \quad [\text{A13}]$$

While this approximation greatly simplifies the electronic wave function and so reduces the computational cost of solving the electronic Schrödinger wave equation, it completely neglects the instantaneous Columbic interactions of the electrons. Instead, each electron only experiences an average field created by the other electrons in the system. As the *Hartree* product (Equation A13) is not antisymmetric with respect to interchange of electron coordinates, a *Hartree-Fock* wave-function is constructed using a *Slater determinant* to ensure that electrons are indistinguishable:

$$\Psi_e = \frac{1}{\sqrt{N!}} \begin{vmatrix} \psi_1(r_1) & \dots & \psi_N(r_1) \\ \vdots & \ddots & \vdots \\ \psi_1(r_N) & \dots & \psi_N(r_N) \end{vmatrix} \quad [\text{A14}]$$

If it is assumed that MOs can be expressed as a *linear combination of atomic orbitals* (the LCAO approximation),^{139, 140} then:

$$\psi_i(r_i) = \sum_{\mu} c_{\mu i} \chi_{\mu}(r_i) \quad [\text{A15}]$$

In Equation 15, $c_{\mu i}$ are the MO coefficients and χ_{μ} are the basis functions that describe the atomic orbitals.

HF theory has several variants based on how electron spin is treated. In so called *restricted HF* or simply “RHF”, each spatial orbital is assigned two spin orbitals:

$$\chi_i^\alpha(r_i, \omega) = \phi(r_i)\alpha(\omega) \text{ and } \chi_i^\beta(r_i, \omega) = \phi(r_i)\beta(\omega) \quad [\text{A16}]$$

In other words, each spatial orbital is used twice; once for the α spin electrons and once for the β spin electrons. While this approach is reasonable in *closed-shell systems* (that is for species with no net electron spin), it obviously cannot be applied to *open-shell systems* because the number of α and β spin electrons differs. In *open-shell systems*, two different variants of HF theory can be employed. *Unrestricted HF* (UHF) overcomes the problem of differing numbers of α and β spin electrons by allowing the spatial part of spin orbitals to vary. In other words, UHF uses completely separate spatial orbitals for α and β spin electrons. The other variant used in *open-shell systems* is *restricted open-shell HF* (ROHF). ROHF theory employs a *restricted* approach, assigning each spatial orbital two spin orbitals for all the paired electrons, but then uses singly occupied MOs to describe the remaining unpaired electrons.

According to the *variational theorem*, the energy determined from any approximate wave function will be larger than the energy of the exact wave function. Thus, the energy of the exact wave function acts as a lower bound on the calculated expectation value of the energy; allowing the MO coefficients to be optimized until a minimum energy is reached:

$$\langle E \rangle = \langle \Psi | \hat{H} | \Psi \rangle \geq E_{\text{exact}} \quad [\text{A17}]$$

In *Equation A17*, $\langle E \rangle$ is the expectation value of the energy obtained from a trial Ψ and E_{exact} is the exact energy of the system. Computation of the HF energy requires the MO coefficients to be specified, while these coefficients need to be optimized by minimizing the HF energy according to the *variational theorem*. Thus, a *self-consistent field* (SCF) process is used:

- 1) Initially, a trial set of MOs is adopted.
- 2) The trial (or inconsistent) MOs are used to compute a Hamiltonian (known as a Fock operator).
- 3) The electronic Schrödinger wave equation (under HF assumptions) is solved using this Fock operator and new MOs are obtained.

- 4) If these new MOs are inconsistent with the previous MOs then the process is repeated from step 2). If the new MOs are consistent with the previous MOs then the SCF has converged.

Applying an SCF approach, it is possible to solve the electronic Schrödinger wave equation (under HF assumptions) to obtain the RHF, UHF or ROHF energies.

8.2.4 BEYOND HF

The greatest drawback of HF theory is that it completely neglects *electron correlation*, that is, the instantaneous Columbic interactions of the electrons. While *correlation energy* is only a very small fraction of the total electronic energy, it is highly sensitive to changes in electronic structure (for instance those associated with chemical reactions) and usually cannot be neglected. Within computational chemistry there are a hierarchy of different *post-HF* approximations for the treatment of correlation energy, with varying levels of accuracy. There are three main ‘families’ of methodologies: Møller–Plesset perturbation (MPn) theory¹⁴¹⁻¹⁴⁷ (with the most popular variant being second-order Møller–Plesset corrections, or simply MP2), couple cluster (CC) theory¹⁴⁸⁻¹⁵⁰ (with the most widely used variant being single, double and perturbative triple excitations, or simply CCSD(T)) and finally configurational interaction (CI) theory¹⁵⁰⁻¹⁵² (with one of the most widely used variants being quadratic configurational interaction with single, double and perturbative triple excitations, or simply QCISD(T)). The CC and CI methodologies have the advantage that they provide an increasingly accurate description of electron correlation (as successively more terms are added) and so converge to the exact (non-relativistic) energy. Full Configurational Interaction (FCI) applied with an approximation of a complete basis set can yield the exact non-relativistic energy to a specified precision, although at enormous computational expense.

While both CC and CI methods provide a route to exactitude (at least in theory), poor cost scaling severely limits the practical application of some of the more accurate variants. Taking O as method determined pre-factor and N as relative measure of system size (roughly determined by the number basis functions); HF scales formally with $O(N^4)$, although most commercial software packages can achieve closer to $O(N^2)$ scaling. In contrast, even the more truncated CC and CI variants like CCSD and QCISD scale as $O(N^6)$, while CCSD(T) and QCISD(T) scale as $O(N^7)$, and CCSDT and QCISDT scale as $O(N^8)$. MPn procedures scale more modestly as $O(N^{n+3})$. QCI, CC and MPn methodologies have the disadvantage of being *non-variational*, but they are *size-*

consistent; that is, the calculated energy of two molecules at large separation (in a non-interacting complex) is equal to the sum of the energies of each molecular species. Mathematically, *size consistency* is defined as:

$$E(A + B) = E(A) + E(B) \quad [A18]$$

In *Equation A18*, $E(A + B)$ is the total energy of the molecular complex of A and B at sufficiently large separation so interactions between these species are negligible, while $E(A)$ and $E(B)$ are the individual energies of molecules A and B , respectively. *Size consistency* is particularly important when modelling molecular complexes, as well as addition and dissociation reactions.

8.2.5 BASIS SETS

The atom-centred functions (χ_μ) that are used to construct MOs (and thus used to describe the electronic wave function) are known as basis functions and collectively form the basis set. Generally, larger basis sets describe both the atomic orbitals and the overall wave function more accurately, although at increased computational cost. Intuitively, it would seem advantageous to construct basis sets from mathematical functions that closely describe the shape of the underlying atomic orbitals. 1s atomic orbitals are properly described by Slater functions (Slater-Type Orbitals, or simply STOs), which are of the basic form:

$$\begin{aligned} \chi_{abc}^{STO}(x, y, z) &= Nx^a y^b z^c \exp(-\alpha|x^2 + y^2 + z^2|) \\ &= Nx^a y^b z^c \exp(-\alpha r) \end{aligned} \quad [A19]$$

In *Equation A19*, N is a normalization constant, a , b and c define the angular momentum of the atomic orbital and α describes its width. While Slater functions can properly describe the short and long range behaviour of 1s atomic orbitals, their mathematical form results in complex integrals that are very difficult (and expensive) to solve.

To avoid these difficulties, most basis sets are constructed from Gaussian-Type Orbitals (GTOs), that is, atomic orbitals that are approximated using Gaussian functions of the form:

$$\begin{aligned} \chi_{abc}^{GTO}(x, y, z) &= Nx^a y^b z^c \exp(-\alpha(x^2 + y^2 + z^2)) \\ &= Nx^a y^b z^c \exp(-\alpha r^2) \end{aligned} \quad [A20]$$

In *Equation A20* (as before), N is a normalization constant, a , b and c define the angular momentum of the atomic orbital and α describes its width. While adopting GTOs yields

integrals that are much easier to solve, the correct $\exp(-ar)$ radial behaviour of atomic wave functions is not well modelled by the $\exp(-ar^2)$ behaviour of the Gaussians. In practice, a linear combination of several Gaussian primitives is required to adequately describe atomic orbitals. Gaussian functions cannot correctly model the short-range behaviour of atomic orbitals because of the nuclear-electron cusp.

In so called *minimal basis sets*, only one basis function is used to describe each orbital of the atom's occupied subshells (in its ground electronic state); thus only 1 basis function is used for H and He (occupied subshells: 1s), 5 basis functions for Li–Ne (occupied subshells: 1s, 2s, 2p_x, 2p_y and 2p_z) and 9 basis functions for Na–Ar, etc. The STO-3G basis¹⁵³ is an example of a *minimal basis set*, in which each of these atomic orbitals is approximated by a linear combination of 3 primitive Gaussians. Unfortunately, *minimal basis sets* are much too rigid to accurately describe molecular orbitals and cannot properly model the anisotropic nature of chemical bonding. To obtain accurate results, basis sets must describe each atomic orbital using multiple basis functions. Basis sets that use two, three, four or five basis functions to describe each atomic orbital are known as *double-*, *triple-*, *quadruple-* and *quintuple-zeta* basis sets (etc.), respectively.

As chemical changes usually only involve the valence electrons, most basis sets use a different number of functions to describe the core and valence atomic orbitals, so called *split-valence* basis sets. Perhaps the best known examples of *split-valence* basis sets are the X-YZG and X-YZWG Pople type¹⁵⁴⁻¹⁶¹ basis sets. In Pople basis sets, a single basis function composed of X primitive Gaussians is used to model each of the core atomic orbitals, while the valence orbitals are modelled with two (YZ) or three (YZW) basis functions; with Y, Z and W indicating the number of primitive Gaussians used for each of these basis functions. For instance, 6-31G is an example of a *split-valence double zeta* basis set; it models each of the core atomic orbitals with a single basis function comprised of 6 primitive Gaussians, while each of the valence orbitals is described by 2 basis functions, with one of these functions comprised of 3 primitive Gaussians and the other composed of a single primitive Gaussian.

Basis sets are often augmented with other types of functions; namely *polarization* and *diffuse functions*. *Polarization functions* are functions with higher angular momentum than the occupied valence atomic orbitals. Addition of these functions increases the flexibility of the basis set by allowing the orbitals to distort and become more asymmetric. For Pople basis sets, *polarization functions* are indicated by “*” or by “(d)” style notation. For instance, 6-31G(d) (or equivalently 6-31G*) indicates that d *polarization functions*

have been added to all heavy first and second row atoms; 6-31G(d,p) indicates that in addition to these d *polarization functions* on heavy atoms, p *polarization functions* have also been added to hydrogen atoms. *Diffuse functions* are Gaussians that have large spatial extents, that is, they decay much more gradually than normal basis functions. *Diffuse functions* are crucial for systems with dispersed electron density, such as anions and Rydberg states. For Pople basis sets, the augmentation of *diffuse functions* is indicated with “+” notation; indicating that an s and p type *diffuse function* has been added to each non-hydrogen atom.

Another important family of basis sets is the correlation consistent polarized (cc-p) Dunning basis sets¹⁶²⁻¹⁶⁵; cc-pVnZ and their augmented *diffuse function* containing counterparts aug-cc-pVnZ (where *n* is D, T, Q, 5, etc.). In Dunning type basis sets, *n* indicates the number of basis functions used to describe each of the valence orbitals; D, T, Q and 5 indicate *double*-, *triple*-, *quadruple* and *quintuple-zeta* quality (etc.). Dunning basis sets are carefully designed to converge smoothly to the complete basis set (CBS) limit; calculations with progressively larger basis sets (for instance with aug-cc-pVDZ, aug-cc-pVTZ and aug-cc-pVQZ) can be extrapolated to approximate the use of an infinite basis set. Notably, most wave function based electronic structure procedures, including MP2 and CCSD(T), are strongly basis set dependent. Employing *double-zeta* basis sets (for instance 6-31G(d)) with such methods will not normally yield accurate energies and use of at least *triple-zeta* basis sets is usually required.

8.2.6 MANAGING COMPUTATIONAL COST AND COMPLEXITY

As only finite computational resources are available, it is necessary to balance the accuracy of quantum chemical calculations with their feasibility. As indicated in Figure A3, both an appropriate treatment of correlation energy *and* a sufficiently large basis set are required for accurate results. It is worth emphasizing that neither FCI/STO-3G nor HF/CBS yield accurate electronic energies; the former theory treats correlation energy accurately but uses a very small rigid basis set to (very poorly) describe the underlying molecular orbitals, while the latter theory uses an extrapolation to an infinite basis set but completely neglects electron correlation.

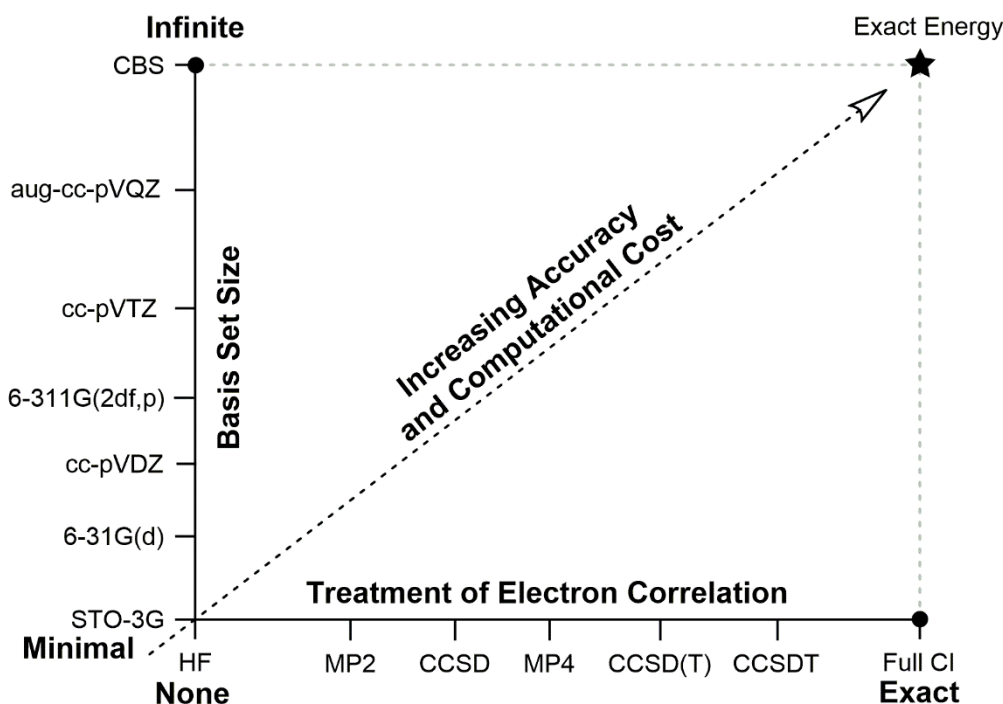


Figure A3 Pople Diagram illustrating the requirements for accurate quantum chemical calculations.

Most of the thermodynamic (pK_a values, redox potentials, equilibrium constants) and kinetic (rate coefficients) properties of interest to chemists are defined in terms of the relative energies of two (or more) different species. The errors that arise from the incomplete treatment of electron correlation and the use of finite basis sets are often fairly systematic. Consequently, relative energies are usually much less sensitive to choice of computation methodology than total absolute energies. That is, computation of accurate relative energies is usually much less demanding than computation of comparably accurate absolute energies.

While ‘acceptable’ accuracy will depend largely on context, a sufficiently accurate treatment of electron correlation is achieved in most chemical systems with CCSD(T) (or QCISD(T)). Provided appropriately large basis sets are employed (see below), CCSD(T) relative energies will (usually) only differ from corresponding exact values by $1\text{--}2\text{ kJ mol}^{-1}$.^{166, 167} Thus, CCSD(T) is frequently labelled the “gold-standard” of computational chemistry, as this level accuracy is sufficient to answer most chemical questions. However, CCSD(T) energies are notably less accurate in chemical systems where total correlation energy is dominated by *static* (rather than *dynamic*) correlation, that is, in systems that possess significant *multi-reference* character. In such systems, alternative theoretical approaches such as CASSCF,^{168–170} CASPT2¹⁷¹ or more accurate CC procedures (such as CCSDT, CCSDT(Q), CCSDTQ, etc.) may be required.

As geometric properties are normally less sensitive to electron correlation than single-point energies, structures can usually be optimized at lower levels of theory. In computational chemistry, it is fairly common to use a dual approach; optimizing structures using relatively low levels of theory, while performing high level single-point energy calculations. The notation used for this dual approach is energy-procedure/energy-basis set//geometry-procedure/geometry-basis set. For instance, CCSD(T)/cc-pVTZ//RMP2/6-31G(d) indicates that CCSD(T)/cc-pVTZ single point energies have been calculated on RMP2/6-31G(d) optimized structures. At a consistent level of theory, obtaining geometries is much more computationally expensive than obtaining single-point energies; as geometry optimizations require a local minima in the electronic energy with (respect to change in the nuclear coordinates) to be found. Thus, a dual approach is also pragmatic as it is normally feasible to obtain single-point energies at much higher levels of theory than could be used for geometry optimizations.

8.2.7 DENSITY FUNCTIONAL THEORY

Density functional theory (DFT) attempts to solve the TISWE (Equation 1.0) and calculate the energy of a molecule or atomic species using the one-electron density ($\rho(r)$) and an unknown energy functional. The Hohenberg-Kohn Theorems,¹⁷² which form part of the inspiration for DFT, state firstly, that *the ground state external potential (and thus total electronic energy of the ground state) is a unique functional of the electron density*, and secondly that *a density that minimizes the total energy of the ground-state is the exact ground-state density*. Using the electron density rather than a wave function to obtain the total energy has been touted as a way of circumventing the very poor size scaling of wave function based methods. Unfortunately, the first Hohenberg-Kohn Theorem is not constructive but rather an existence proof via a *reductio ad absurdum*. It establishes that the ground state external potential is a unique functional of the electron density but provides no insights into the actual mathematical form of this functional. Consequently, the exact DFT functional is unknown.

Modern DFT functionals are based on the Kohn-Sham equations,¹⁷³ which cleverly consider the Hamiltonian for a fictitious system of *non-interacting electrons* that have an overall ground-state density that is identical to the real atomic or molecular system (where the electrons are able interact). The energy functional ($E[\rho(r)]$) can then be expressed as the sum of the kinetic energy of the *non-interacting* electrons ($T_{ni}[\rho(r)]$), nuclear-electron attraction ($V_{ne}[\rho(r)]$), classical electron-electron repulsion ($V_{ee}[\rho(r)]$) and corrections to both the kinetic energy due the *interacting* nature of the electrons

($\Delta T[\rho(r)]$) and to the electron-electron repulsion due to non-classical behaviour ($\Delta V_{ee}[\rho(r)]$):

$$E[\rho(r)] = T_{ni}[\rho(r)] + V_{ne}[\rho(r)] + V_{ee}[\rho(r)] + \Delta T[\rho(r)] + \Delta V_{ee}[\rho(r)] \quad [\text{A21}]$$

The final two correction terms in *Equation 21* are frequently referred to as the *exchange-correlation* energy. As the Hamiltonian for a system of *non-interacting electrons* can be expressed as a sum of one-electron operators, they have eigenfunctions that are *Slater determinants* of individual one-electron eigenfunctions and so are readily calculated.

The formulation and implementation of many aspects of DFT is analogous to that of HF. However, HF is deliberately constructed to be approximate, while the construction of DFT is exact (at least in theory). Unfortunately, describing the *exchange-correlation* energy in terms of the one-electron density is very difficult and requires the use of several different approximations. Indeed, the development of better approximations for describing this term is the subject of active research in quantum chemistry. Once approximations are used to calculate the *exchange-correlation* energy, DFT is no longer *variational*, although both exact and approximate forms of DFT are *size-consistent*. While theoretically, DFT is exact and formulated from fundamental physical and mathematical arguments, in practice many popular DFT functionals are heavily parametrized using test sets of experimental and (wave-function derived) theoretical data. While current DFT functionals offer reasonable accuracy at low computational cost, they can also fail spectacularly and unexpectedly.¹⁷⁴ Moreover, there is no systematic way to improve DFT results and choice of functional is quite subjective. Many of the most popular functionals, such as B3LYP, have been found to fail dramatically (often to the extent that results are qualitatively incorrect).¹⁷⁴ Because of this often variable and unpredictable accuracy, DFT should always be employed cautiously.

8.2.8 COMPOSITE PROCEDURES

Over the last decade, so called “*composite*” *ab initio* procedures have become increasingly popular compared to traditional methodologies; mainly because of their improved cost-effectiveness. *Composite procedures* pragmatically combine the results of calculations performed at different levels of theory and/or perform extrapolations schemes by using calculations with progressively larger basis sets. Most *composite procedures* are based on the observation that *ab initio* methodologies generally have

quantitatively similar basis set dependencies. This simple observation can be formulated as follows:

$$E_{high/large\ basis} - E_{high/small\ basis} \cong E_{low/large\ basis} - E_{low/small\ basis} \quad [A22]$$

In Equation 22, *high*, *low*, *large basis* and *small basis* denotes high accuracy and low accuracy electronic structure procedures and large and small basis sets, respectively. While the choice of the high and low level electronic structure procedure is somewhat arbitrary, the approximation in Equation A22 is more accurate if both methods treat correlation energy in a similar manner. Equation A22 can then be rearranged to:

$$E_{high/large\ basis} \cong E_{high/small\ basis} - E_{low/small\ basis} + E_{low/large\ basis} \quad [A23]$$

Equation A23 indicates that high level large basis set electronic energies (which would be prohibitively costly) can be approximated using several much less computationally demanding calculations. Many *composite procedures* also employ extrapolation schemes to approximate the CBS limit at a given level of theory.

The Gaussian *composite procedures*¹⁷⁵⁻¹⁷⁹ (Gn), originally developed by Curtiss and co-workers are among the most popular. In G3 theory,¹⁷⁸ electronic energies are calculated as follows:

$$\begin{aligned} E_{G3} = & MP4/6-31G(d) + [MP4/6-31+G(d) - MP4/6-31G(d)] \\ & + [MP4/6-31G(2df,p) - MP4/6-31G(d)] \\ & + [QCISD(T)/6-31G(d) - MP4/6-31G(d)] \\ & + [MP2(full)/G3Large - MP2/6-31G(2df,p) \\ & - MP2/6-31 + G(d) + MP2/6-31G(d)] + SO + HLC \end{aligned} \quad [A24]$$

(based on HF/6-31G(d) optimized geometries and frequencies)

In Equation 24, *SO* is the spin-orbit corrections (applicable to atoms only) and *HLC* is the higher level correction (that is calculated from the number of α and β electrons).

Another popular variant of G3 theory is the less computationally intensive G3(MP2)-RAD procedure¹⁸⁰:

$$\begin{aligned} E_{G3(MP2)RAD} = & U(R)CCSD(T)/6-31G(d) + R(O)MP2/GTMP2Large \\ & - R(O)MP2/6-31G(d) + SO + HLC \end{aligned} \quad [A25]$$

(based on B3-LYP/6-31G(d) optimized geometries and frequencies)

Other well-known *composite procedures* include the CBS methods¹⁸¹⁻¹⁸⁸ developed by Petersson and co-workers, and the Wn methods^{167, 189-191} formulated by Martin and co-workers.

Composite procedures usually deliver the same level of accuracy as the corresponding large basis set CCSD(T) (or equivalent) calculation they are attempting to approximate at a fraction of the computational cost¹⁷⁵⁻¹⁷⁹ and as such they have been used extensively in this thesis. Other aspects of computational modelling, such as, partition function evaluation, conformational searching and solvation modelling are discussed extensively in **Chapter 3**.

8.2.9 REFERENCES FOR COMPUTATIONAL METHODOLOGY

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