Chapter 28

An Ab Initio Guide to Structure–Reactivity Trends in Reversible Addition Fragmentation Chain Transfer Polymerization

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The effects of substituents on the addition–fragmentation reaction, $P_n\cdot + S=C(Z)SR \rightarrow P_nSC\cdot(Z)SR \rightarrow P_nSC(Z)=S + R\cdot$, of the reversible addition fragmentation chain transfer (RAFT) process have been studied via high-level ab initio calculations. A number of simple isodesmic quantities are introduced in order to rank the stabilities of the RAFT agents and the RAFT-adduct radicals, together with the efficiency of addition–fragmentation and of the overall chain transfer process. The stabilities of the RAFT agents and RAFT-adduct radicals are mainly affected by the Z group, while the chain transfer efficiency depends mainly on the R group. The rankings can be used as a first-reference guide for selecting an R and Z group for a given polymerization.

Introduction

The reversible addition fragmentation chain transfer (RAFT) process is an important new method for controlling molecular weight and architecture in free-radical polymerization (1). RAFT can be used to generate complex macromolecular architectures such as comb, star and block copolymers, for use in bioengineering and nanotechnology applications (2). Control is achieved by protecting the majority of the growing polymer chains from bimolecular termination processes, through their reversible trapping into a dormant thiocarbonyl compound (known as the polyRAFT agent), as follows:

A delicate balance of the rates of these various reactions is required, so as to ensure that the dormant species is orders of magnitude greater in concentration than the active species but that the exchange between the two forms is rapid. The reactivity of the RAFT agent must thus be tailored to the reactivity and stability of the polymeric propagating radical; information on the mechanism, kinetics and thermodynamics of these individual steps can greatly assist in the design and selection of optimal RAFT agents.

Although many experimental groups have examined the effects of substituents on the RAFT process (2, 3), these experimental studies have necessarily focussed on measurable quantities such as the polydispersity of the resulting polymer or the apparent chain transfer constant (4) – parameters that are a complicated function of several individual rate coefficients. Hence, although experimental studies have provided extremely useful quantitative information on the performance of specific RAFT agents, and provided a number of important qualitative insights, the tasks of interpreting the more subtle structure-reactivity trends and predicting the behavior of as-yet-untested RAFT agents are not straightforward. Computational quantum chemistry offers an attractive complementary approach to studying the effects of substituents on this complicated process. Using high-level *ab initio* molecular orbital calculations, it is possible to obtain the rate and equilibrium constants for each individual reaction and the stabilization energies of the individual species *directly*, without recourse to kinetic model-based assumptions. Moreover, the calculations yield additional mechanistic information (such as the geometries of the reactants, products and transition structures, and the charge and spin density distributions within these species) that can assist in the interpretation of results. Computational chemistry also offers the possibility of considering a much wider range of substituents, including RAFT agents that have not as yet been synthesized.

Recently, we have used high-level *ab initio* calculations to study the kinetics and thermodynamics of the addition-fragmentation reaction in the RAFT process (5). Based on these results we have been able to design a new class of

multi-purpose RAFT agent that has subsequently been demonstrated to control free-radical polymerization (6). Others have used lower-level semi-empirical or density functional theory calculations to study the overall chain transfer reaction, and have shown that the results have practical value in choosing appropriate leaving groups (3b, 7). However, although there is now a reasonable qualitative understanding of structure-reactivity trends in the RAFT process, the current data is not in a generally useful form. In particular, results from the low-level and high-level computational studies are not directly comparable, and a number of the more important RAFT agent substituents (especially belonging to the xanthate and dithiocarbamate sub-classes) are not represented. The aim of the present work is to provide a more comprehensive account of the effects of substituents on the RAFT process, and build a practical database of reagent stabilities that should assist in the design and selection of optimal RAFT agents for controlling the various classes of monomers.

In the present work we study the effects of the R, R' and Z substituents on the addition-fragmentation reaction, $R^{\bullet} + S=C(Z)SR \rightarrow R'SC^{\bullet}(Z)SR \rightarrow R'SC(Z)=S + R^{\bullet}$, for a wide range of practical R, R' and Z-substituents. The substituents considered embrace the various classes of compounds currently in use as RAFT agents (including dithioesters, xanthates, dithiocarbamates, and trithiocarbonates) with leaving groups that represent a wide range of monomeric radicals and their tertiary methyl-substituted derivatives. We also study the effects of R, R' and Z on the stabilization energies of the various radical and thiocarbonyl species, via a series of isodesmic reactions.

Computational Procedures

Standard ab initio molecular orbital theory and density functional theory calculations have been performed using the GAUSSIAN 03 (8) and Molpro 2000.6 (9) software. Calculations were performed at a high level of theory that was chosen on the basis of recent assessment studies covering both the specific case of addition-fragmentation (10) and a range of related radical reactions (11). Geometries were optimized at the B3-LYP/6-31G(d) level of theory, and zero-point vibrational energy corrections were calculated using B3-LYP/6-31G(d) frequencies, and scaled by the appropriate scale factors (12). Improved energies were then calculated using the G3(MP2)-RAD level of theory, a high-level composite procedure designed to reproduce coupled cluster energies [CCSD(T)] with a large triple zeta basis set via additivity corrections (13). For the reactions of the largest xanthate ($Z = OCH(CF_3)PO(OMe)_2$), G3(MP2)-RAD calculations were approximated using an ONIOM-based approach as follows (10). The "core", corresponding to $Z = OCH_2CF_3$, was studied at G3(MP2)-RAD, and then corrected for the substituent effect of the full system, as calculated at the RMP2/6-311+G(3df,2p) level. We have recently shown that this approach is capable of reproducing the G3(MP2)-RAD calculations of the full system to within 1 kcal mol⁻¹ at a fraction of the computational cost (10).

Although direct comparison with experimental data for addition-fragmentation reactions is problematic, studies of related systems indicate that the computational approach is capable of achieving chemical accuracy. For instance, Scaiano and Ingold (14) have reported an experimental equilibrium constant (based on laser flash photolysis studies) of $1.2 \times 10^6 \text{ L mol}^{-1}$ for the addition of *tert*-butyl radicals to di-*tert*-butyl thioketone at 25°C, whereas we have calculated a value of $7.9 \times 10^5 \text{ L mol}^{-1}$ using this ab initio approach (15). Likewise, our calculated propagation rate coefficients for the radical polymerization of vinyl chloride and acrylonitrile are within a factor of 2 of the experimental values (16).

Results and Discussion

The key to controlling free-radical polymerization via the RAFT process is to choose RAFT agent substituents (R and Z) and reaction conditions such that the equilibrium between the propagating radical and dormant thiocarbonyl species is rapidly established during the early stages of the process, and that this dormant species is orders of magnitude greater in concentration than the propagating species, and that the exchange between the two forms is rapid. These requirements entail that (a) the RAFT agent is sufficiently reactive relative to the propagation step, but not so reactive that the propagating radical becomes irreversibly trapped as the RAFT-adduct radical; and (b) the initial leaving group (R•) fragments from the RAFT-adduct radical in preference to the propagating species, but is still capable of reinitiating polymerization. To assist in RAFT agent design, we present here a database of substituent effects on (a) the addition-fragmentation equilibrium and (b) the chain transfer reaction.

For a complete treatment of substituent effects, one must consider the combined effects of R and Z on each individual addition-fragmentation reaction, from both kinetic and thermodynamic viewpoints. However, given the broad range of R and Z combinations possible, such a study would be very cumbersome, and it would be difficult to identify chemical trends and to predict the behavior of as-yet untested combinations of substituents. Instead, we define some simple thermodynamic measures for the isolated effects of the R and Z substituents on the addition-fragmentation and chain transfer reactions, and on the stabilities of the component species.

- We define the fragmentation efficiency (ΔH_{frag}) for a specific Z-group as the enthalpy (0 K) of the following isodesmic reaction: $\text{CH}_3\text{SC}(\text{Z})\text{SCH}_3 + \text{S}=\text{C}(\text{H})\text{SCH}_3 \rightarrow \text{CH}_3\text{SC}(\text{H})\text{SCH}_3 + \text{S}=\text{C}(\text{Z})\text{SCH}_3$. This measures the susceptibility of the RAFT-adduct radical to β -scission (i.e., the reaction $\text{CH}_3\text{SC}(\text{Z})\text{SCH}_3 \rightarrow \text{S}=\text{C}(\text{Z})\text{SCH}_3 + \text{CH}_3\cdot$), relative to the reference case where $\text{Z} = \text{H}$; the more exothermic the reaction, the more susceptible the radical is to β -scission.

- We define the chain transfer efficiency for a specific R-group as the enthalpy (0 K) of the overall chain transfer reaction $\text{CH}_3\cdot + \text{S}=\text{C}(\text{CH}_3)\text{SR} \rightarrow \text{R}\cdot + \text{S}=\text{C}(\text{CH}_3)\text{SCH}_3$. This measures the leaving group ability of R $\cdot$ relative to the reference $\text{CH}_3\cdot$ radical; the more exothermic the reaction, the better the leaving group. A related approach based on bond dissociation energies has recently been used by Matyjaszewski and Poli (7b) to study chain transfer in RAFT.
- We measure the stabilities of the RAFT-adduct radicals and leaving group radicals as their radical stabilization energies (RSE), in the usual manner (5e, 17). That is, the RSE of a radical R $\cdot$ is measured as the enthalpy (0 K) of the isodesmic reaction $\text{R}\cdot + \text{CH}_4 \rightarrow \text{R-H} + \text{CH}_3\cdot$.
- We measure the stabilities of the RAFT-agents using analogous isodesmic reactions. When the interest is in the effect of Z, stability is estimated by the enthalpy change for the reaction $\text{S}=\text{C}(\text{Z})\text{SCH}_3 + \text{CH}_3\text{-H} \rightarrow \text{S}=\text{C}(\text{H})\text{SCH}_3 + \text{CH}_3\text{-Z}$. When the interest is in the effect of R, the relevant reaction is $\text{S}=\text{C}(\text{CH}_3)\text{SR} + \text{CH}_3\text{-SH} \rightarrow \text{S}=\text{C}(\text{CH}_3)\text{SCH}_3 + \text{R-SH}$.

Analyzing the chain transfer efficiency in these simple terms allows the effects of R and Z to be conveniently separated and ordered. Below, we describe these effects, and demonstrate how the rankings of R and Z can be used to select a RAFT agent to control a given monomer. Occasionally, special situations arise in which subtle stereoelectronic effects transpire to override the general trends. We will also give some examples of this below. Despite these exceptions, the tables of data serve as a useful starting point from which one can identify a range of candidate RAFT agents for detailed testing.

Choice of Z group. In the overall chain transfer reaction $\text{P}_n\cdot + \text{S}=\text{C}(\text{Z})\text{SR} \rightarrow \text{P}_n\text{SC}(\text{Z})\text{S} + \text{R}\cdot$, the group Z is contained within a thiocarbonyl compound on both sides of the equation. On this basis, one might expect Z to contribute minimally to chain transfer efficiency. However, such an assumption is inadequate, as one must also take into account the intermediate RAFT-adduct radical $\text{P}_n\text{SC}(\text{Z})\text{SR}$. For efficient chain transfer, it is necessary to use a Z group that promotes both the addition of $\text{P}_n\cdot$ to the RAFT agent (step 1), and the fragmentation of R $\cdot$ (or $\text{P}_n\cdot$ in the case of the polymeric equilibrium) from the RAFT-adduct radical (step 2). There are two possible scenarios. If the propagating radical $\text{P}_n\cdot$ is relatively unstable (i.e. reactive), step 1 poses little problem. The main concern in this case is to promote step 2 so that the propagating radical does not become irreversibly trapped as the RAFT-adduct radical. In contrast, if the propagating radical is relatively stable (unreactive), then step 2 is favoured and the priority is instead to promote step 1. In the first of these two scenarios, a Z group must be chosen that either destabilizes the RAFT-adduct radical or stabilizes the thiocarbonyl product. In the second scenario, the Z group must destabilize the RAFT agent or stabilize the RAFT-adduct radical.

Table I. Effect of Z group on stabilities and fragmentation enthalpies.^a

Z	Stability of RAFT Agent $\text{S}=\text{C}(\text{Z})\text{S}-\text{CH}_3$	RSE of RAFT-adduct radical $\text{CH}_3-\text{S}-\dot{\text{C}}(\text{Z})-\text{S}-\text{CH}_3$	ΔH_{frag}
CN	-5.9	99.2	48.8
Ph	41.3	96.3	21.0
CF ₃	-17.1	62.6	17.8
H	0.0	61.1	0.0
Cl	29.9	63.9	-1.3
imidazole-N	44.8	74.5	-1.5
CH ₂ Ph	39.2	65.0	-1.9
SCH ₂ CH ₃	59.4	81.5	-4.4
pyrrole-N	54.5	76.0	-5.4
CH ₃	35.1	59.9	-10.0
SC ₂ H ₅	59.3	76.5	-11.1
F	43.5	46.9	-24.0
OCH(CF ₃)P(O)(OCH ₃) ₂	80.0	61.3	-29.3
OCH ₂ CF ₃	80.2	63.7	-35.4
OC(CH ₃) ₃	81.0	59.0	-37.1
OCH(CH ₃)P(O)(OCH ₃) ₂	89.3	65.2	-37.9
NH ₂	92.8	73.5	-38.5
OCH(CH ₃) ₂	90.7	63.2	-40.8
OCH ₂ CH ₃	86.8	59.0	-44.3
OCH ₃	85.9	58.5	-45.0
N(CH ₃) ₂	94.2	76.9	-46.9
N(CH ₂ CH ₃) ₂	105.6	95.5	-50.2

^aRSEs and enthalpies (0 K, kJ mol⁻¹) were calculated at the G3(MP2)-RAD level of theory using B3-LYP/6-31G(d) optimized geometries and include scaled B3-LYP/6-31G(d) zero-point energy corrections.

In Table I are shown the effects of Z on the stabilities of RAFT agents and RAFT-adduct radicals (for R = R' = CH₃). The Z groups are listed in order of increasing fragmentation efficiency of the RAFT-adduct radicals. Considering first the RAFT agents, it can be seen that the Z groups fall into three main classes. The first class comprises those Z groups that strongly stabilize RAFT agents. Alkoxy and amino groups fall into this class, and typically give stabilities in excess of 80 kJ mol⁻¹. The high stability of RAFT agents with Z = OR or NR₂ arises from lone-pair donation onto the C=S bond, as shown in eq 1. At the other end of the spectrum are the σ -withdrawing Z groups CN and CF₃, which destabilize the RAFT agents relative to Z = H. The remaining Z groups

fall into an intermediate range. Thus, typical dithioesters, such as those with $Z = \text{CH}_3$, Ph, or CH_2Ph , have stabilities of approximately 40 kJ mol^{-1} . The fluorinated RAFT agent $\text{S}=\text{C}(\text{F})\text{SCH}_3$ also comes within this range, at 43.5 kJ mol^{-1} . In this case, the effects of lone-pair donation and σ -withdrawal counteract each other.

Within these three classes, the positions of certain RAFT agents are worthy of note. One example is the trithiocarbonate RAFT agents. Although the SR group is potentially a good lone-pair donor, it is not as effective as oxygen or nitrogen, and the trithiocarbonates' stabilities fall short of the xanthates and dithiocarbamates by approximately $20\text{--}35 \text{ kJ mol}^{-1}$. A second noteworthy case is the dithiocarbamates that have $Z = \text{pyrrole}$ or imidazole. These agents have stabilities much lower than those of typical dithiocarbamates. Such an observation supports the principle upon which these agents were designed (18), namely that the donor ability of Z should be restricted if the nitrogen lone pair is delocalized over the aromatic ring. As a third example, note can be made of the special xanthate agents having $Z = \text{OCH}_2\text{CF}_3$, $\text{OCH}(\text{CH}_3)\text{P}(\text{O})(\text{OCH}_2)_2$, or $\text{OCH}(\text{CF}_3)\text{P}(\text{O})(\text{OCH}_2)_2$. These agents were designed (3d) on the basis that the σ - and π -withdrawing characteristics of the trifluoromethyl and phosphonate substituents would reduce the lone pair donor ability of Z . It appears, however, that the destabilizing characteristics of such α -substituents are minor, because these agents' stabilities fall only slightly below those of the corresponding regular xanthates.

Considering next the RAFT-adduct radicals, it must first be pointed out that the stability of these radicals is generally high, regardless of the Z group – the RSEs for these radicals are typically in excess of 60 kJ mol^{-1} . Stability arises because lone-pair donation by the two SR groups provides an effective means for delocalization of the unpaired electron. Nevertheless, the Z groups can be divided into several distinct categories based on whether Z enhances or diminishes this stabilizing feature.

In one category lie the π -acceptor Z groups CN, Ph, pyrrole, and imidazole. These give highly stable RAFT-adduct radicals. In isolation these substituents are typically strong radical stabilizers because the unpaired electron is able to be delocalized into their vacant π^* orbitals (5e). In combination with the lone pair donor SR groups, the stabilizing effect of small π -acceptor groups such as CN is enhanced by captodative interactions as shown in eq 2. For larger aromatic π -acceptor groups such as Ph, the captodative effect can be outweighed by steric effects, as a compromise must be reached between the optimum geometry of a benzylic radical (planar carbon centre) and that of a simple alkylthio-substituted

radical (puckered). Nonetheless, they remain strong radical stabilizers, and give rise to relatively long-lived intermediate radicals (19).

In another category lie the lone-pair donor Z groups, NR_2 , OR, SR, Cl and F. Their effects on the stability of the RAFT-adduct radical are not straightforward. To start with, the stabilization associated with the presence of a single SCH_3 group on a carbon-centered radical (i.e., $\text{CH}_3\text{S}-\text{CH}_2\cdot$) is 40.7 kJ mol^{-1} , but if a second SCH_3 group is present (i.e., $\text{CH}_3\text{SC}(\text{H})\text{SCH}_3$) the RSE is only 61.1 kJ mol^{-1} (5e). The diminished capacity for extra stabilization by the second SCH_3 group arises because the interaction between carbon and the lone pair of the first sulfur atom places the unpaired electron into a higher-energy molecular orbital, reducing the ability of the second sulfur atom to interact with it. The capacity for stabilization by a third lone pair donor substituent (i.e., Z) is similarly reduced unless Z is a stronger lone-pair donor than SCH_3 . Moreover, the stabilizing effect of these lone pair groups is countered to varying extents by σ -withdrawal. Thus, the Z groups NH_2 , $\text{N}(\text{CH}_3)_2$, $\text{N}(\text{CH}_2\text{CH}_3)_2$, SCH_3 , and SCH_2CH_3 provide net stabilization to the RAFT-adduct radical (RSE's $> 70 \text{ kJ mol}^{-1}$), but the alkoxy groups OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, and $\text{O}(\text{CH}_3)_2$ provide no additional stabilization relative to $\text{Z} = \text{CH}_3$. In the latter radicals, the σ -withdrawing character of Z outweighs the lone-pair donor ability. The importance of σ -withdrawal in the RAFT-adduct radicals is further demonstrated by the similarity between the RSEs of the NR_2 and SR_2 groups, despite the stronger lone-pair donor character of the former (17). In the RAFT agents, also, the relative stabilities of the alkoxy-, amino-, and alkylthio-substituted agents reveal similar trends in σ -withdrawing character, but in these species the lone-pair donor character of Z is more important.

By considering all of these trends, a Z group can be chosen to suit the reactivity of a desired propagating radical. For example, in the polymerization of vinyl acetate (VA), the propagating radical is relatively unstable. Therefore, the fragmentation of the propagating radical from the RAFT-adduct radical is a major concern, and the traditional solution has been to employ Z groups that stabilize the thiocarbonyl product of fragmentation. Thus, xanthates and dithiocarbamates are the agents of choice for VA polymerization (2, 3d, 20). This solution comes at a cost, however. Because the lone-pair donor OR and NR_2 groups render a thiocarbonyl species less reactive, xanthates and dithiocarbamates are not as useful for more stable propagating radicals – for instance when preparing copolymers of VA with more stable monomers. We have recently noted (6a) that a better solution would be to promote fragmentation by destabilizing the RAFT-adduct radical, rather than stabilizing the RAFT agent. From Table I, it is clear that a fluorine Z-group is capable of

achieving this. Thus, when $Z = F$, the strong σ -withdrawing character destabilizes both the RAFT-adduct radical and the RAFT agent, relative to a xanthate or dithiocarbamate. The net result is that fragmentation is only ~ 13 – 26 kJ mol^{-1} less thermodynamically favourable than that for the xanthates and dithiocarbamates, yet the addition of a propagating radical to the $S=C$ bond is not inhibited. The compounds $S=C(F)SR$ are currently under testing as dual-purpose RAFT agents for controlling both stable and unstable monomers.

Choice of R group. It is only in exceptional cases that the effect of R on the overall chain transfer efficiency depends on the intermediate RAFT-adduct radical. Thus, for an analysis of the effects of R, one can consider two species: the RAFT agent $S=C(Z)SR$ and the leaving-group radical $R\cdot$. In Table II are shown the effects of typical R groups on the stabilities of RAFT agents and the corresponding leaving-group radicals $R\cdot$. The R groups are ranked in order of increasing efficiency of the chain transfer reaction $S=C(CH_3)SR + CH_3\cdot \rightarrow S=C(CH_3)SCH_3 + R\cdot$. Considering the relative magnitudes of the RAFT agent stabilities and of the $R\cdot$ RSEs, one may conclude that the major influence on chain transfer enthalpy is the stability of $R\cdot$. In a practical RAFT agent, the release of $R\cdot$ from the RAFT-adduct radical $P_nSC\cdot(Z)SR$ should be competitive with the release of $P_n\cdot$, and the radical whose release is favoured is normally the one whose stability is greater.

The leaving-group radicals listed in Table II are subject to the typical stabilizing influences that affect carbon-centered radicals. For example, the $R\cdot$ radicals $\cdot C(CH_3)_2CN$ and $\cdot C(CH_3)_2Ph$ are relatively stable due to delocalization of the unpaired electron onto the π -acceptor substituent. Hyperconjugative stabilization also comes into play, as evidenced by the trend toward increased stability as the number of CH_3 groups attached to the radical centre is increased.

In the RAFT agents, the electronic and steric properties of R influence stability in the opposite sense. R groups containing electron-withdrawing substituents destabilize RAFT agents, by restricting the capacity for the electron delocalization shown in eq 3. Increasing methylation causes destabilization by inducing nonbonded interactions over the rigid $S=C(Z)-SR$ framework.

Since, in the overall chain transfer process, the RAFT agent is consumed and the radical $R\cdot$ is produced, the steric and electronic effects of R are exerted in two complementary ways. This result agrees well with the recent interesting work of Matyjaszewski and Poli (7b), who used density functional calculations to show that chain transfer is favoured by bulky R groups and is subject to polar effects. One might thus conclude that in order to promote chain transfer, an R group should be chosen such that the RSE of $R\cdot$ is greater than the RSE of $P_n\cdot$. However, the need to promote the release of $R\cdot$ must be balanced against the need for $R\cdot$ to initiate further polymerization. If $R\cdot$ is too stable, then the re-

initiation step $R\cdot + M \rightarrow R-M\cdot$ will be inhibited. It is therefore not easy to predict how well a given R group will perform on the basis of its chain transfer exothermicity alone.

Table II. Effect of R group on stabilities and chain transfer enthalpies.^a

R	Stability of RAFT Agent	RSE of R $\cdot$	ΔH_{CT}
CH(CH ₃) ₂	-1.2	24.0	2.0
CH ₂ CH ₃	-0.8	14.1	1.8
CH ₃	0.0	0.0	0.0
CH ₂ OCOCH ₃	-11.8	17.9	-4.8
CH ₂ CONH ₂	-0.8	21.2	-6.5
CH(CH ₃)OCOCH ₃	-15.9	24.4	-8.6
C(CH ₃) ₃	-14.1	29.7	-10.1
CH(CH ₃)Cl	-7.1	27.0	-14.3
CH(CH ₃)CONH ₂	2.9	41.1	-14.3
CH ₂ Cl	-7.3	21.1	-15.9
CH ₂ COOCH ₃	-5.1	21.5	-20.0
C(CH ₃) ₂ OCOCH ₃	-29.6	18.0	-22.0
CH ₂ COOH	-5.5	21.2	-22.3
C(CH ₃) ₂ Cl	-16.3	31.1	-24.3
CH(CH ₃)COOCH ₃	-7.5	41.3	-29.4
CH(CH ₃)COOH	-8.4	41.3	-33.2
C(CH ₃) ₂ COOCH ₃	-8.3	54.9	-35.9
C(CH ₃) ₂ CONH ₂	-18.7	54.7	-36.9
CH ₂ CN	-5.5	31.9	-41.4
CH ₂ Ph	0.4	58.9	-41.7
C(CH ₃) ₂ COOH	-11.3	56.1	-41.8
CH(CH ₃)Ph	-0.8	68.0	-42.2
CH(CH ₃)CN	-4.6	47.3	-42.6
C(CH ₃) ₂ CN	-15.8	59.0	-56.6
C(CH ₃) ₂ Ph	-14.9	70.3	-57.5

^aRSEs and enthalpies (0 K, kJ mol⁻¹) were calculated at the G3(MP2)-RAD level of theory using B3-LYP/6-31G(d) optimized geometries and include scaled B3-LYP/6-31G(d) zero-point energy corrections.

A practical example of this difficulty is provided by the polymerization of methyl methacrylate (MMA). It has been found experimentally (3b) that, when using dithiobenzoate RAFT agents having different R groups (Z = Ph) in MMA polymerization, control is good when R is C(CH₃)₂Ph or C(CH₃)₂CN, but not when R is CH₂Ph, C(CH₃)₃, CH(CH₃)Ph, C(CH₃)₂CONH(alkyl), or

$C(CH_3)_2COO(alkyl)$. The poor performance of the $C(CH_3)_3$ group could be readily understood on the sole basis of an unfavourable ΔH_{CT} relative to the model propagating radical $\cdot C(CH_3)_2COOCH_3$. The remaining findings, however, cannot. It must be recognized that the use of the monomer radical as a model for the propagating radical is at best a rough approximation, since penultimate unit effects can be significant. In the case of the initial "unimeric" propagating radical, the penultimate unit will be the initiator-derived end-group (typically $C(CH_3)_2CN$). Once this substituent is incorporated, the calculated ΔH_{CT} value for the propagating radical decreases substantially (to $-50.5 \text{ kJ mol}^{-1}$). For this corrected species, only the $C(CH_3)_2Ph$ or $C(CH_3)_2CN$ radicals in Table II have favorable ΔH_{CT} values, which is then in accord with the experimental observations.

Incorporating penultimate unit effects is an important but computationally laborious task that needs to be considered for a proper analysis of a given polymerization. However, with the simple monomer radicals at hand, Table II provides a method for allowing unsuitable R groups to be disregarded without investing in a rigorous theoretical or experimental study. Groups for which the chain transfer enthalpy is much more or much less exothermic than that of the monomeric radical are unlikely to be worthy of pursuit, and the best R group candidates would be those for which ΔH_{CT} is only slightly more or slightly less exothermic than that for $M\cdot$.

Exceptions to the trends. Tables I and II can be used as a first-reference guide for selecting an R and Z group for a given polymerization. The use of these tables should, however, be made with due regard to their implicit assumptions. Firstly, the rankings are based on the assumption that the thermodynamics of chain transfer are a predictor of the kinetics. This simplification was drawn from the earlier finding (21) that radical additions to C=S bonds typically have very low activation barriers – that is, that $\Delta H^\ddagger_B$ is equivalent to ΔH_B . A second approximation implicit in the rankings is that any effects of the R group on the stability of the RAFT-adduct radical can be ignored. Furthermore, the possibility of synergistic interactions between the R, Z, and P_n groups has also been ignored.

An important situation in which thermodynamics are not a good predictor of kinetics is the fragmentation step of the xanthate-mediated polymerization of vinyl acetate. As depicted in Figure 1, the activation barrier for fragmentation of the radical $CH_3SC\cdot(OCH_3)SCH_2OCOCH_3$ is nearly 23 kJ mol^{-1} lower than that of the radical $CH_3SC\cdot(O^tBu)SCH_2OCOCH_3$ (5b). The barrier lowering cannot be due to steric effects alone, however, as the barriers for the corresponding methyl-substituted radicals $CH_3SC\cdot(OCH_3)SCH_3$ and $CH_3SC\cdot(O^tBu)SCH_3$ are almost identical to that for the $Z = ^tBuO$ and $R = VA$ case. Instead, the difference stems from a hydrogen-bonding interaction in the transition state for the $Z = CH_3O$ and $R = VA$ adduct. A close contact between the carbonyl oxygen and one of the OCH_3 protons takes place in the transition state for the $Z = CH_3O$

and R = VA adduct, but is absent in the Z = ^tBuO and R = VA analogue. This feature corresponds to a rate enhancement of three orders of magnitude, and could only be identified by conformational screening of the transition states and direct calculation of the fragmentation rates.

Figure 1. Acceleration of fragmentation in a xanthate-derived RAFT-adduct radical due to hydrogen-bonding in the transition state.

More generally, isodesmic quantities provide no information on the absolute thermodynamics (let alone kinetics) of the individual addition-fragmentation steps and this can be very important for the understanding of the overall process. In particular, when radical addition to the RAFT agent is highly exothermic (typically, if $K > 10^6 \text{ L mol}^{-1}$), the intermediate RAFT-adduct radical can function as a radical sink and contribute to the overall control mechanism (22). This in turn can lead to rate retardation or even, in the extreme case, inhibition of the polymerization process. The kinetics and thermodynamics for a range of individual addition-fragmentation reactions have been reported elsewhere (5, 19). For most common combinations of R and Z substitutions, addition of $\text{R}^\bullet$ to the RAFT agent $\text{S}=\text{C}(\text{Z})\text{SCH}_3$ is indeed exothermic, as can be inferred from the fact that the enthalpy of the reference reaction $\text{CH}_3^\bullet + \text{S}=\text{C}(\text{H})\text{SCH}_3 \rightarrow \text{CH}_3\text{SC}(\text{H})\text{SCH}_3$ is $-74.2 \text{ kJ mol}^{-1}$ (5e). Despite this, in most cases the exothermicity is not sufficiently large to impair the overall polymerization kinetics except when RAFT-agent is substituted with strongly stabilizing Z-groups such as phenyl (19) and/or when the propagating radical is a poor radical leaving group, as in vinyl acetate polymerization. In these cases, the overall polymerization kinetics can only be understood through a detailed examination of the kinetics and thermodynamics of the individual addition-fragmentation reactions. Nonetheless, the isodesmic quantities in Tables I and II can allow one to anticipate when rate retardation is likely to be important: namely, when Z-

groups having high values of ΔH_{frag} (Table I) are combined with leaving groups or propagating radicals that have high values of ΔH_{CT} (Table II).

The possibility of synergistic interactions between substituents is another important consideration. In particular, attention has been drawn to the importance of homoanomeric interactions in certain RAFT-adduct radicals (5e). In the simple RAFT-adduct radical $\text{CH}_3\text{SC}(\text{CH}_3)\text{SCH}_3$, the preferred geometry allows maximum orbital overlap between the unpaired electron and the sulfur lone pairs. However, when the R-group of the RAFT-adduct radical is substituted with a strong π -acceptor group, it reduces the lone-pair donor ability of its attached sulfur atom and instead the unpaired electron is delocalized into the antibonding orbital of the S-R bond. This stabilizes the radical overall but weakens the S-R bond and promotes fragmentation of $\text{R}^\bullet$, often in opposition to considerations of steric and radical stabilization effects. Thus for example, $\text{C}(\text{CH}_3)_2\text{CN}$ is a considerably better leaving group than $\text{C}(\text{CH}_3)_2\text{Ph}$, despite their near identical RSEs and steric bulk, because the CN substituent is a much stronger π -acceptor and is thus subject to stronger homoanomeric interaction (5e). As a further complicating factor, we have noted that the homoanomeric effect is further modulated by Z; for example, a fluorine substituent has been shown to inhibit the homoanomeric effect and alter leaving group abilities (6b). Hence, it is possible for all three groups R, P_n , and Z to interact within a RAFT-adduct radical, leading to complicated structure-reactivity trends.

Conclusions

Ab initio calculations can assist in the rationalization of substituent effects in the chain transfer reaction of RAFT polymerization. Broadly speaking, Z groups can be categorized according to whether they are suited to relatively unstable propagating radicals ($\text{Z} = \text{OR}, \text{NR}_2$) or to relatively stable propagating radicals ($\text{Z} = \text{alkyl}, \text{aryl}, \text{SR}, \text{aromatic amines}$). The ordering of the R groups shows that the stability of $\text{R}^\bullet$ is most important; one must choose an R group that is a sufficiently good leaving group compared with $\text{P}_n^\bullet$ but that is still capable of re-initiating polymerization. Although some more complicated situations arise in which the predictions of these rankings break down due to more subtle stereoelectronic effects, the rankings are useful for selecting a range of candidate RAFT agents that are appropriate for detailed theoretical or experimental testing.

Acknowledgement. Financial support from the Australian Research Council, useful discussions with Dr David Henry and Professor Leo Radom, and a generous allocation of computing time on the National Facility of the Australian Partnership for Advanced Computing are gratefully acknowledged.

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