4 Recent advances in designed local electric fields

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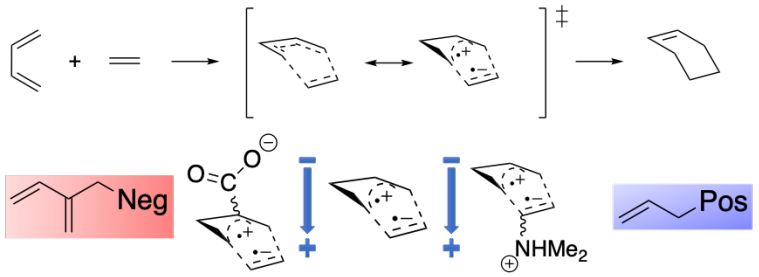
ABSTRACT

Remote designed local electric fields (D-LEFs) are emerging as a practical strategy for the manipulation of chemical reactivity. This chapter surveys the historical use of D-LEFs, and explores the theory and practical use of Brønsted acids and bases, metal ions, and ion-pairs as novel effectors of D-LEFs, with key concepts such as polarization illustrated using recent theoretical and experimental case studies. Particular attention is paid to the use of D-LEFs in concert with existing catalysts and catalytic strategies, within photochemistry and excited states, and in the manipulation of regio- and diastereoselectivity. Prospective advances in the efficient use of D-LEFs are also surveyed, and the need for further experimental validation of D-LEF effects is emphasised.

5.1 Introduction

Designed local electric fields (D-LEFs) are those fields arising from precisely-oriented charged species attached to substrates, catalysts, or auxiliaries to effect desired changes in chemical reactivity. These charged species are typically remote from the reaction centre and attached in such a way that their desired effect is realised predominately through-space, and not as an inductive or resonance effect. Practically, this means ensuring that the relevant charged species are not directly conjugated to a reaction centre, or otherwise indirectly associated with one via additional non-bonded interactions.

The D-LEFs generated by charged species can affect chemical reactions in a manner analogous to external electric fields (see, Chapter 2 by Shaik et al.), albeit with several practical considerations. The sign and orientation of D-LEFs relative to the reaction centre are controlled by the identity and careful placement of the charged species, respectively. The magnitude of the electrostatic effect depends upon how susceptible the reaction is to electrostatic effects, the distance and orientation of the charged group with respect to the reaction-axis, and also the reaction medium. Moreover, when that charged species is a Brønsted acid or base, the electric field can be controlled by changes in pH. Taking the prototypical Diels-Alder reaction between 1,3-butadiene and ethylene in Figure 2.11 of Chapter 2 by Shaik et al. as an example,[1] Figure 4.1 shows how this reaction could be catalysed either through placement of an anionic functional group on the diene or a cationic functional group on the dienophile. More generally, the charged species can also take the form of metal ions or charged additives (i.e. in Lewis acids or organometallic complexes).



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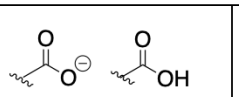
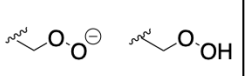
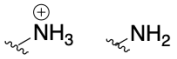
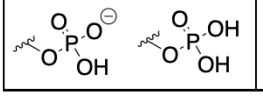
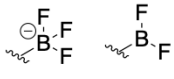
		 & other amines
		 permanent charge

Figure 4.1. Catalysis of a Diels-Alder reaction with a D-LEF. As explained in Chapter 3 by Shaik et al., an external field can lower the reaction barrier by stabilizing the (minor) charge-separated delocalisation contributor to the transition state.[1] *Here we show this external field can be mimicked either by placing a non-conjugated carboxylate on the diene or a non-conjugated ammonium on the dienophile. The table also lists some other possible charged groups that may be used in this way.*

Electrostatic interactions between charged groups and other species are necessarily ubiquitous in chemistry, being one of the fundamental interactions that define the discipline. More generally, electrostatic interactions between any species rarely occur in isolation from sigma inductive effects, conjugation and cross-conjugation, non-bonded interactions, and so forth. Thus, it is frequently convenient to classify electrostatically-dominated phenomena by the context in which it is found to be significant. For example, although the active sites of enzymes present perhaps the finest example of the catalytic power of D-LEFs in Nature,[2] the role of electrostatic fields within enzymes have been reviewed extensively and are not covered here.[3] Likewise, this chapter does not attempt to survey the broader role of molecular

electrostatics within ordinary chemical transformations, as such an undertaking would be necessarily expansive, but rather focuses on the *deliberate* introduction of remote charged species to catalyse or otherwise alter chemical reactions in a predictable manner.

This chapter first briefly surveys the historical application of D-LEFs (up to 2010) in Section 4.2, with an aim towards illustrating key advances which guide their present study. The specific theoretical considerations that underlie the effective use of charged species in D-LEFs are then explored in Section 4.3, with pertinent examples of each from the recent literature and a particular focus towards charge-dipole interactions and the role of electric polarizability. Section 4.4 outlines the synthetic utility and unique advantages of Brønsted acid/base D-LEFs, with case studies in the manipulation of the regio- and diastereoselectivity of simple Diels-Alder and S_N2 reactions, and in catalytic cycles and photochemical reactions. Some experimental validation studies are presented. Section 4.5 outlines the recent application of redox-inactive metal ions as effectors of D-LEFs, with particular focus on their use in polymer chemistry and their ability to modify the redox properties of adjacent species. Finally, the need for ongoing experimental validation of D-LEF effects is outlined, and possible applications of D-LEFs as effectors of chemical change are proposed and explored.

4.2 Historical Application of D-LEFs

The importance of through-space electrostatic interactions upon chemical reactivity was first recognised in the 19th Century by Ostwald,[4] and later by Bjerrum in 1923,[5] who showed that the difference between the dissociation constants of a diacid is always greater than its statistical value, but tends towards this latter value when the distance between the proton-donors is increased. That is, the anionic charge produced

from the first deprotonation of a dicarboxylic acid impedes the second such that the anion is a weaker acid than the corresponding monocarboxylic acid, and the magnitude of this effect is related to the distance between the two functional groups. Bjerrum and Ingold[6–9] separately used this observation to calculate the average distance between the two interacting charges using a simple solvation model which was later quantitatively extended by Kirkwood, Westheimer, and Shookhoff.[10–13]

Research into the role of local electrostatic fields upon the outcomes of reactions between small molecules began in earnest in the late 1950s, with the growing realisation that such fields could impede or catalyse simple reactions *via* direct (de)stabilization of transition states. For example, several groups reported the unusually high reactivity of molecules containing charged species (relative to their uncharged counterparts) in nucleophilic additions[14–17] and substitutions,[18] hydrolysis reactions,[19–26] proton transfers,[27,28] and enolizations,[29,30] with each group attributing the observed outcomes to the electrostatic stabilisation of their respective transition states by neighbouring functional groups. However, further analysis of these results suggested that electrostatic effects are in fact insignificant in some of these examples,[16] and most are complicated by the possibility of competing inductive effects and/or the existence of kinetically-indistinguishable general-acid catalysis pathways. Around the same time, Morawetz and co-workers found that the electrostatic environment afforded by cationic residues in synthetic polymers catalysed the reaction between bromoacetate and poly(4-vinylpyridine),[31] in a manner reminiscent of enzyme active sites.

Another method of delivering D-LEFs involves the use of oriented metal ions. Winstein and co-workers reported in 1959 that the addition of concentrated lithium perchlorate salts could massively increase the rate of ionisation of *p*-methoxyphenyl tosylate in

non-polar solvents.[32] While not a purely electrostatic phenomena, a similar strategy was successfully employed in the 1970s in a series of papers by Pocker and various co-workers and explained through an electrostatic perspective that invoked the dissimilar supramolecular properties of the lithium and perchlorate ions.[33–39] In the same period, Sousa and Larson synthesised crown ether model systems (Figure 4.2) which were designed to study the effect of deliberately-oriented alkali metals upon the photoexcitation of naphthalene derivatives; this appears to be among the first examples of remote D-LEFs from metal ions in the chemical literature.[40] Metal-ion-based D-LEFs are further explored in Section 4.5.

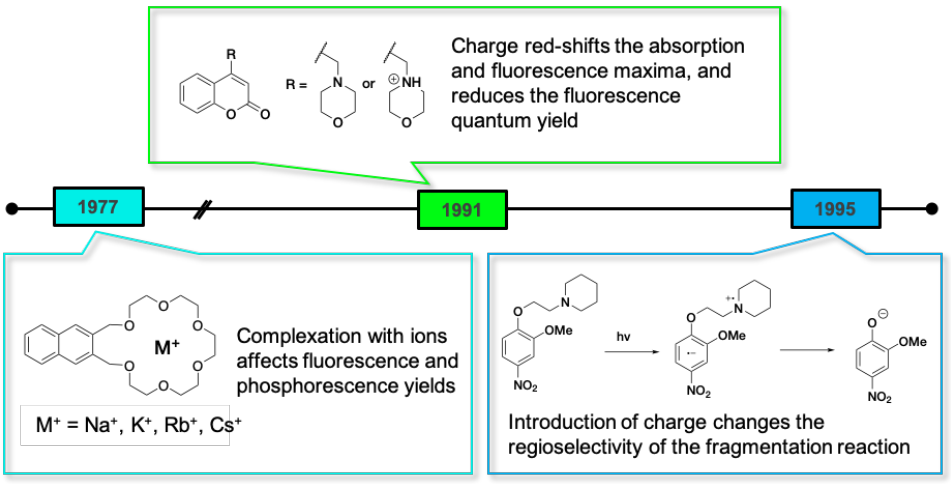


Figure 4.2. Selected examples of key advances in the use of D-LEFs over the past several decades; Sousa and Larson[40] (1977) showed that electrostatic fields from alkali metals, oriented within crown ether model systems, could modify the photochemical reactivity of aromatic systems. Uzhinov and co-workers[41] (1991) demonstrated that fields from a remote morpholinium could affect the photochemistry of organic luminophors, without the use of metal ions or ion-pairs. Likewise, Marquet and co-workers[42,43] (1995) demonstrated that a photo-generated piperidinium radical cation could act as an "on-demand" D-LEF, to alter the cleavage patterns of alkyl aryl ethers, much in the same way as Brønsted acids are used in Section 4.4.

Finally, in a series of contemporary papers, Marquet and co-workers found that photo-induced "topologically controlled coulombic interactions" could change the regioselectivity and kinetics of the reductive cleavage of alkyl aryl ethers.[42–44], while Uzhinov and co-workers found that remote morpholinium functional groups could shift the absorption and fluorescence spectra of organic luminophors, such that the sign and magnitude of the "intramolecular electrochromic effect" exhibited a strong orientation and distance dependence.[41]

In summary, numerous groups over the past century have suggested that electrostatic effects play a significant role in chemical reactivity. Moreover, many of the practical considerations which affect the magnitude of electrostatic interactions are evident from these studies, including the role of solvent polarity, the identity of the charge-carrying species, and the dependence of these effects on the distance and relative orientation of the electrostatic field and the reaction centre. These factors are now placed in a more formal theoretical framework in the following Section.

4.3 Theoretical background

4.3.1 Charge-Dipole Interactions

The theoretical basis of electrostatic catalysis is discussed in detail previously (see, Chapter 2 by Shaik et al.) however, the use of charged species to introduce D-LEFs raises some additional considerations. If we consider the effect of a remote charged group upon some transition state with dipolar character (i.e. in the case of charge-transfer, Figure 4.1), the potential that describes this interaction is, to a first approximation, simply an extension of Coulomb's law for a point charge-dipole interaction.

$$V(r,\theta) = -\frac{Q\mu\cos\theta}{4\pi\varepsilon_0 R^2} = -\frac{k_e Q\mu\cos\theta}{R^2} \qquad (4.1)$$

The form of equation 4.1 suggests that the extent to which a transition state dipole is stabilised by a remote charge is proportional to the magnitude of the applied charge (Q) and dipole (μ), the angle between the dipole axis and the charge (θ), and inversely related to the distance between them (R) squared and to the dielectric permittivity of the medium through which the interaction occurs. Implicit in this construction is that the distance between the point charge and the dipole, must be much larger than the length of the dipole itself. In other words, it is important to position the charged group carefully, in a manner analogous to aligning an external electric field along a reaction axis (Chapter 2), while also minimising the distance between the charged group and reaction centre without introducing undesirable non-electrostatic interactions. While the decay rate of electrostatic effects with distance is formally $1/R^2$ per Equation 4.1, the observed distance decay varies in practical systems because interactions between molecules and charges rarely obey idealised conditions. Additionally, Equation 4.1 is a simplification that neglects higher order interactions and electric polarization (*vide infra*). Figure 4.3 illustrates the effects of (a) orientation and (b) distance on D-LEF effects on acetophenone photochemistry[45] and alkoxyamine bond dissociation energies (BDEs)[46,47], respectively.

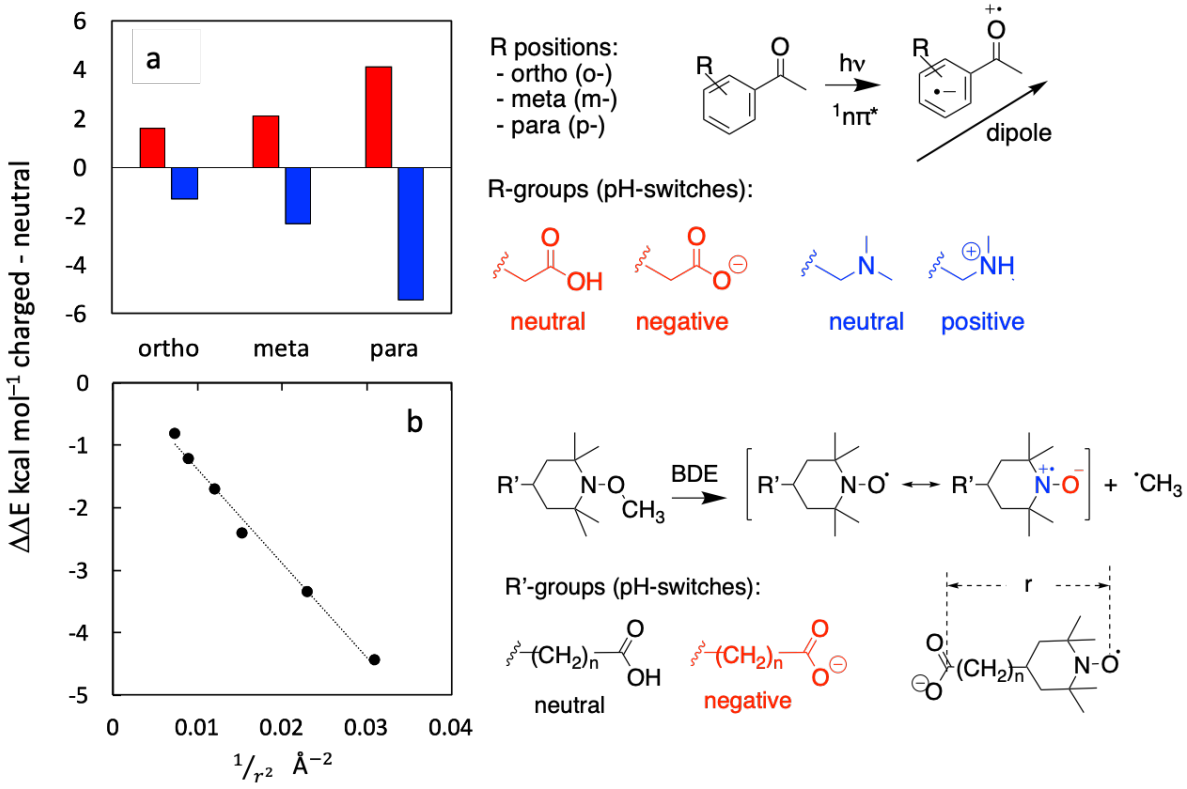


Figure 4.3. (a) The change in the $^1n\pi^*$ excitation energy (kcal mol^{-1}) upon charge formation for excitation of substituted acetophenone. The change is measured as the difference in excitation energy for the anionic or cationic species, versus the corresponding neutral species, and is defined such that a negative value is stabilizing. The directionality dependence is seen clearly in the sign differences of the effect of cationic and anionic charges, and the large effects of D-LEFs in the para-position (which maximises alignment of the D-LEF with the dipole of the excited state) and the diminishing effects for the maligned meta- and ortho- positions. Data taken from Ref. 45 (b) The change in the methyl bond dissociation energy (kcal mol^{-1}) of an alkoxyamine upon formation of charge. The change is measured as the difference in excitation energy for the anionic species versus the corresponding neutral species, and is defined such that a negative value is stabilizing. The distance r (Å) is measured from the nitroxide oxygen to the carbonyl carbon, and all species are treated as

extended conformers. The best fit to the decay rate versus distance for this reaction is 1/r. Data taken from Ref. 46,47. Part (a) was reproduced/adapted from Ref 45 with permission from the American Chemical Society, Copyright 2018.

The interaction potential between a point charge and dipole also depends upon Coulomb's constant k_e, which in a vacuum is equal to $1/(4\pi\varepsilon_0)$, where ε_0 is the dielectric permittivity of free space ($8.85418782 \times 10^{-12}$ m^{-3} kg^{-1} s^4 A^2). In solution, ε_0 is replaced by the relative dielectric permittivity or dielectric constant ε, the ratio of the permittivity in that solvent and ε_0. As the value of ε increases with increasing solvent polarity, the ability of a remote charged group to stabilize or destabilize a reaction centre diminishes rapidly. This is illustrated in Figure 4.4, which shows the change in the bond dissociation Gibbs free energy (BDFE) upon formation of a remote charge as a function of the increasingly polar solvent environment.[46] Three compounds were considered: a peroxide, an alkoxyamine and an unsaturated hydrocarbon. All form delocalized radicals upon dissociation, but in the case of the hydrocarbon they are not especially polar. In all cases, there is a significant decrease in the BDFE of each species going from the gas phase, to toluene, and to 1,2-dichloroethane (DCE), and then smaller decreases thereafter. In the case of the hydrocarbon, solvent effects from DCE are variable with respect to dielectric constant and likely a sign of the competition between solvent attenuation of electrostatic effects on the one hand, and stabilization of induced dipoles by the solvent on the other. As discussed in the next section, this competition is seen more generally when dipole effects are small and electric polarizability dominates the electrostatic interaction.

Nonetheless, the general decrease in stabilization with solvent polarity raises one of the paradoxes of effectively harnessing D-LEFs: to maximise classical electrostatic

interactions, a low-polarity solvent is typically required; however, to maximise the solubility of charged species, a polar solvent is typically required. As a result, while some charged species retain sufficient solubility in low-polarity solvents such as toluene, compromises are required in other scenarios, and moderately low-polarity solvents such as dichloro(m)ethane are used. While significant catalysis can still be experimentally realised (see, e.g.[48]), strategies for avoiding such compromises (e.g. through heterogeneous catalysis) are attractive.

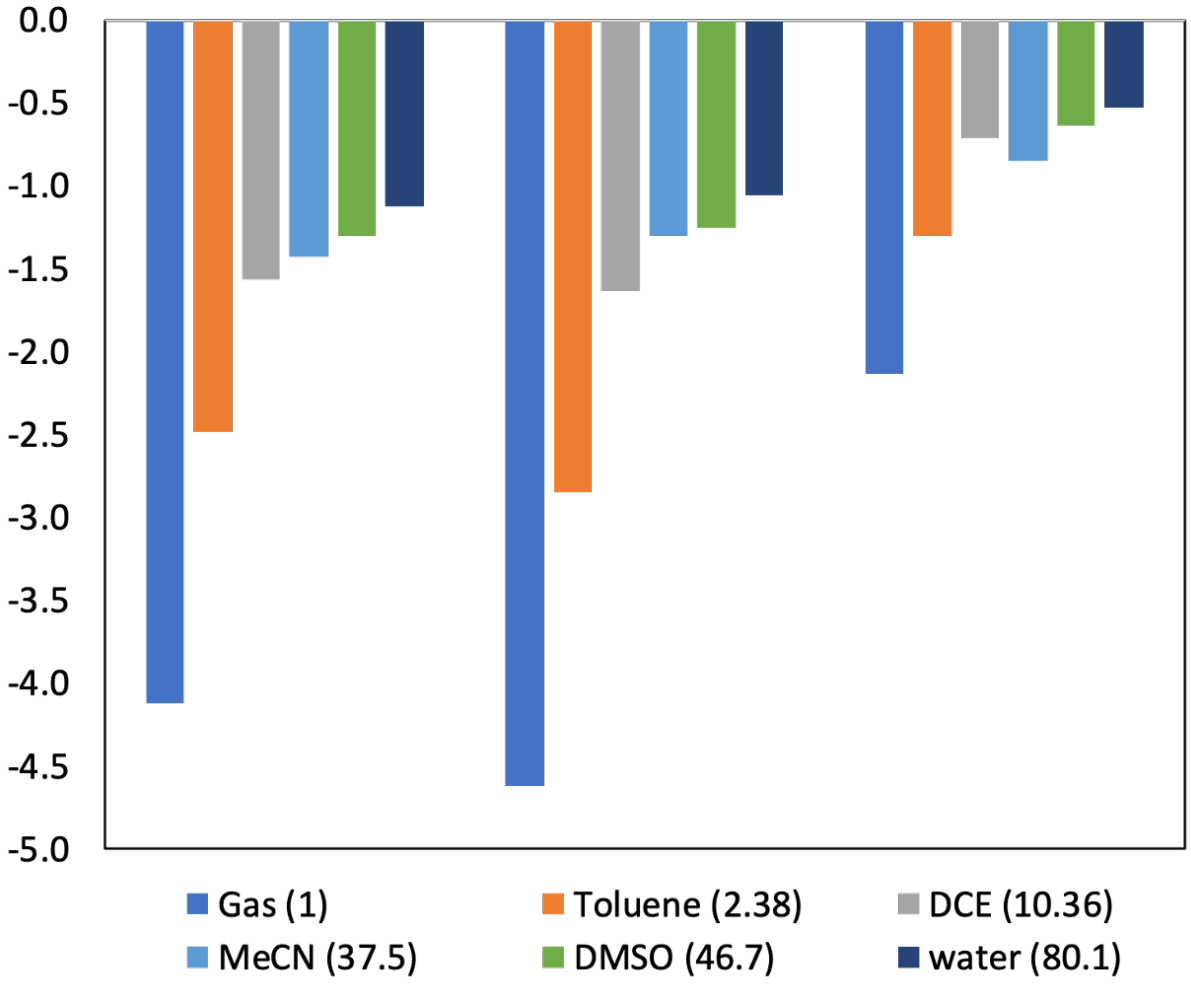
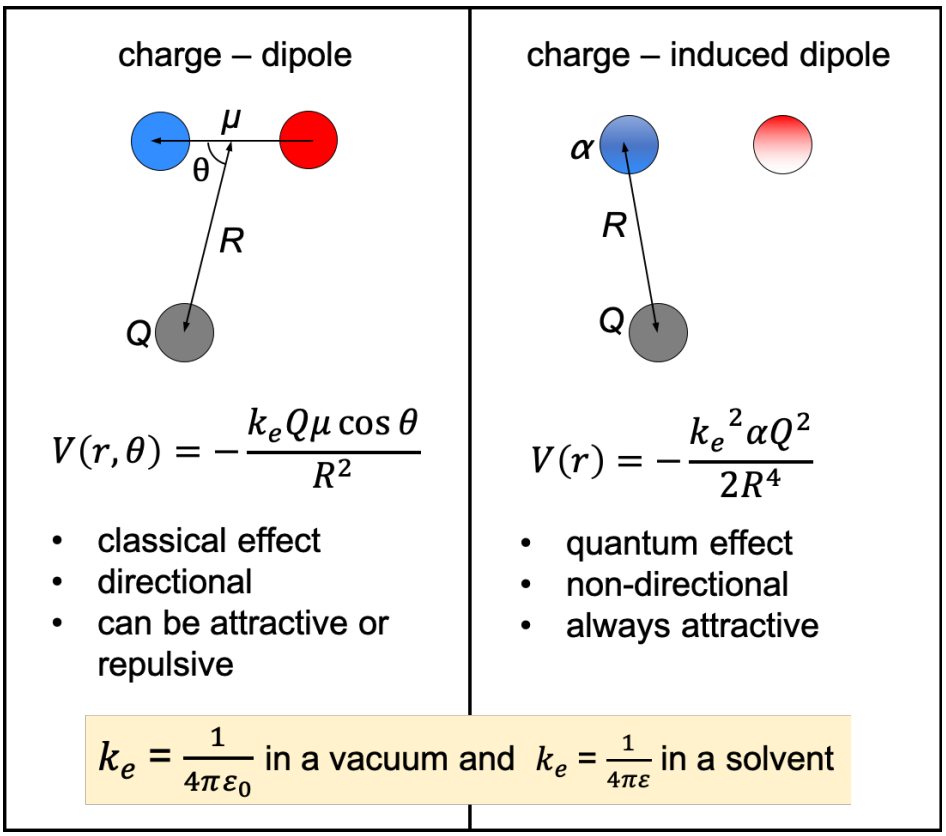


Figure 4.4. The change in bond dissociation Gibbs free energy (kcal mol^{-1}) upon charge formation for three different species as a function of solvent. Solvents are organised by increasing polarity (left-right, dielectric constant shown in brackets) and

DMSO = dimethyl sulfoxide, DCE = 1,2-dichloroethane, MeCN = acetonitrile. Data taken from Ref. 46.

4. 3. 2. Polarization

The use of Coulomb's law is instructive for identifying the key factors influencing the magnitude of stabilization by D-LEFs, but it is an over-simplification of a chemical system. Charged functional groups, such as a carboxylate or ammonium, are not strictly point charges, but rather are diffuse; likewise, reaction centres are rarely pure dipoles but contain higher-order elements such as quadrupoles that decay at different rates with distance. Most importantly, molecules and their functional groups are polarizable. That is, the presence of a charged group can alter the electron distribution in the molecule as electrons are able to distribute themselves closer to a positive charge and further from a negative charge. As nuclei are much less mobile, polarization serves to enhance stabilizing effects from electric fields and diminish destabilizing effects. A comparison of a charge-dipole interaction with a charge-induced dipole interaction is shown in Box 4.1.



Box 4.1. Comparison of a charge-dipole interaction with a charge-induced dipole (polarization) interaction.

The impact of polarization is seen clearly in Figure 4.5.[49] O-alkylphenyl ketones such as those presented are polar molecules, with a non-zero net dipole moment; because they possess an aromatic ground-state (S_0), these molecules can absorb particular wavelengths of light to undergo transitions from the S_0 to an excited singlet state, in this case the second excited singlet state (S_2, which is a $^1\pi\pi^*$ state). In the S_2 state, immediately after absorbing light and before geometry relaxation, the alkylphenyl ketone has a new dipole moment, larger in magnitude and oriented in a slightly different direction. One can stabilize the changing dipole in the transition from the S_0 to the S_2 state with a D-LEF from a remote charged functional group, such as an ammonium or trifluoroborane group. In Figure 4.5, an anionic D-LEF is positioned to stabilize the changing dipole and red-shift the transition, to an extent that one might

imagine (from the discussion of charge-dipole interactions in the previous Section 4.3.1) is attenuated in increasingly polar solvent. While the anionic D-LEF does red-shift the transition, the effect does not diminish with solvent polarity and in fact increases in acetone and DMSO. This is because the polar solvents stabilize the induced dipole thus in turn allowing greater electrostatic stabilization, despite competing solvent attentuation. Similar effects were observed but not noted in the earlier work of Hill and Coote.[50] Moreover, reversing the charge does not destabilize the transition. Polarizability thus dominates this system (though charge-dipole interactions are still important, compare the effects of a cationic and anionic charge in toluene or DCM, for example), with the consequence that stabilization can occur independently of the relative direction of the charge and dipole, and polar solvents can enhance rather than screen the stabilization due to D-LEFs.

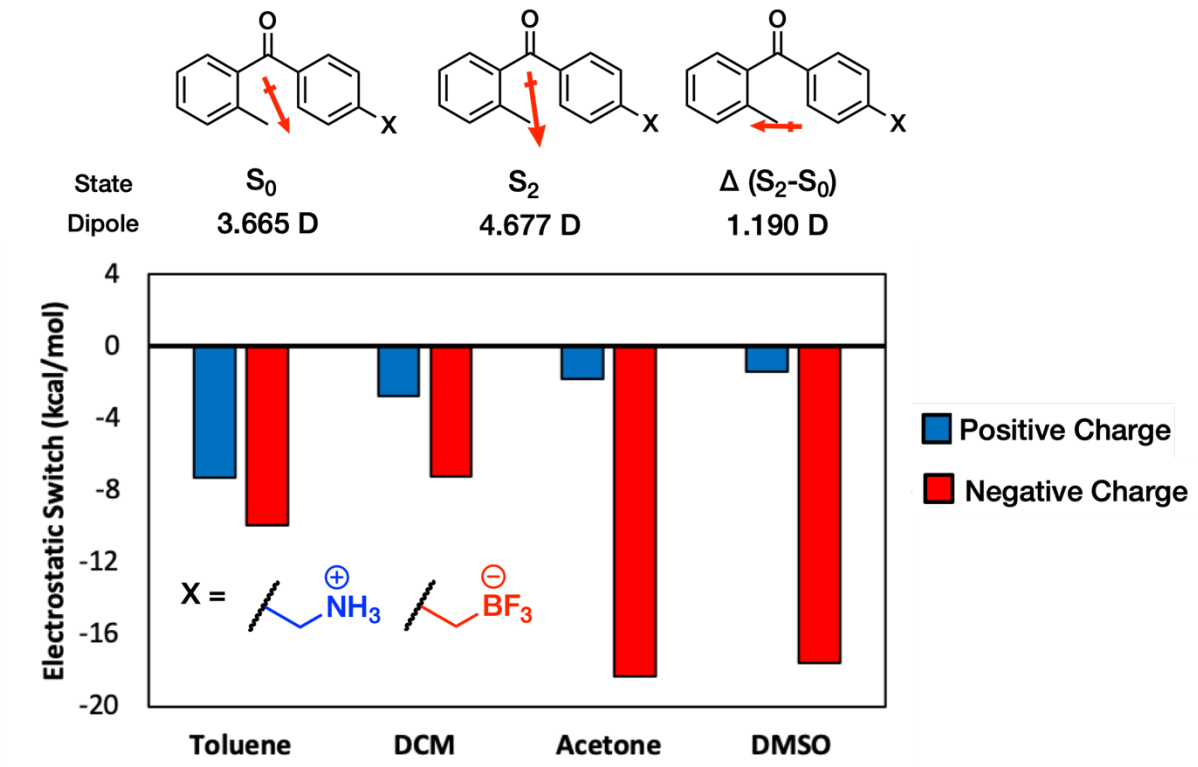


Figure 4.5. The effect of remote cationic (CFG = NH_3^+ / NH_2, blue) and anionic (CFG = BF_3^- / BF_2, red) D-LEFs upon the $^1\pi\pi^*$ transition of the o-alkylphenyl ketone motif in increasingly polar solvents. Switches are defined as the difference between the charged and neutral systems; a negative value indicates stabilization of the transition due to charge. Dipole moments are drawn in the Gaussian convention (from negative towards positive) in the absence of the Brønsted acid/base. Reproduced/adapted from Ref. 49 with permission from the American Chemical Society, Copyright 2020.

Polarizability, therefore, is an additional factor influencing the stabilization of molecules in D-LEFs (and indeed EEFs). Polarizability is enhanced in systems capable of undergoing resonance, and hence electrostatic effects are likewise enhanced in these systems. This is seen already in the contrast between Figure 4.3(a) and Figure 4.5 above. In 4.3(a), electrostatic effects on a $^1n\pi^*$ transition were shown to be highly directional and nearly equal and opposite when the signs of the charged groups are reversed.[45] In contrast, in Figure 4.5, the electrostatic effects on the $^1\pi\pi^*$ transition were shown to be universally stabilizing.[49] The difference between these two cases is the $^1n\pi^*$ state of acetophenone has a significant dipole but does not undergo resonance, whereas the $^1\pi\pi^*$ state of the benzophenone derivative (and indeed acetophenone also[45]) has a smaller dipole but undergoes significant resonance.

The relationship between resonance and susceptibility to electrostatic effects is further seen in Figure 4.6.[46,51] D-LEFs can significantly lower homolytic bond dissociation energies (BDEs) if one of the products is a delocalised radical and the charged group is attached to it. Figure 4.6(a) shows the decrease in BDE upon formation of a remote negative charge in two geometrically similar homologous series designed so that the distance of the charge from the formal radical centre upon fragmentation is relatively

constant. Despite being more than 6 Å from the radical centre, and having no conjugation with it, significant BDE lowering is observed in both series with the magnitude showing a good inverse correlation with the spin density on the formal radical centre. That is, the more delocalised the radical, the greater the BDE lowering.

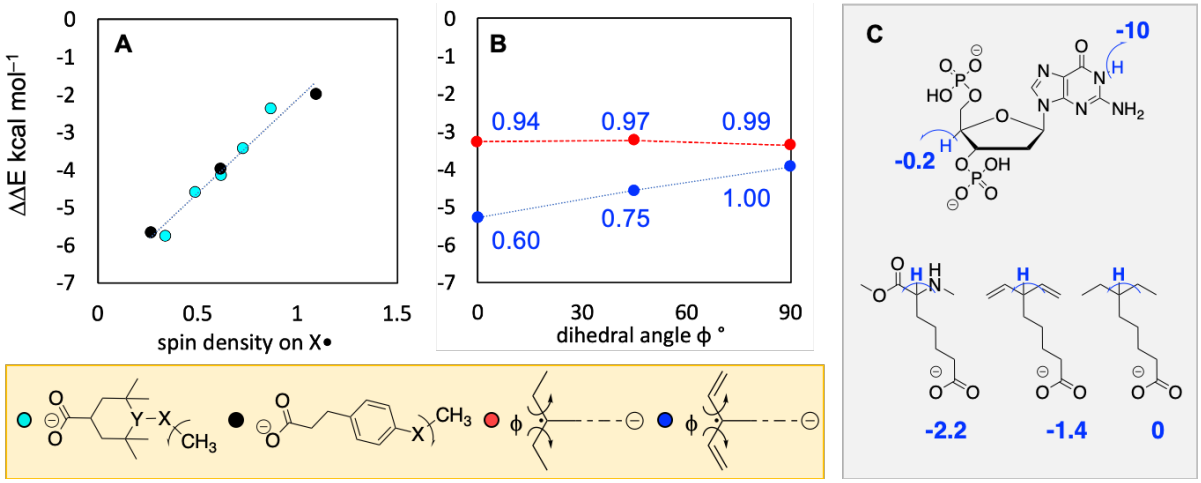


Figure 4.6. (A) The effect of an anionic (COO^- / COOH) electrostatic switch upon two series of X-CH_3 BDEs as a function of (Mulliken) spin density on the formal radical centre (X•). The more delocalized the radical, the greater the electrostatic stabilization. (B) The effect on the total energy of a diallyl and corresponding dialkyl radical when a point charge is placed at 5 Å separation from the radical centre. This stabilization is studied as a function of the dihedral angle of π (or pseudo-π) bonds as they are rotated to 90°, at which point they are orthogonal to the radical centre and unable to undergo resonance. As the resonance is switched off, the stabilization due to the point charge decays. (C) The differential effect of an anionic electrostatic switch (kJ mol^{-1}) upon the X-H BDEs of localised and delocalised radicals, including the sugar and base radicals in a model DNA fragment, and comparison of series in which radical delocalisation is systematically decreased from the captodatively stabilized "peptide-like" radical, the

diallyl and corresponding dialkyl radical. In all cases, a negative value indicates stabilization of the radical due to charge. Data taken from Refs. 46,51.

To show that this trend is due to resonance rather than merely dipole interactions, Figure 4.6(b) compares diallyl radicals stabilized by remote point charges or charged groups with corresponding dialkyl radicals. The diallyl radicals have no dipoles at all and yet are significantly stabilized (relative to their closed shell counterparts) by a remote negative charge; the corresponding dialkyls lack this resonance stabilization and show little or no susceptibility to the same D-LEF. Moreover, when the resonance is artificially inhibited in the diallyl radical through rotation of the π-bonds the extra stabilization is diminished. This is also seen in the model DNA fragment in Figure 4.6(c) which shows the impact of deprotonation of the phosphates on the stability of sugar and base radicals.[47] While deprotonation has little or no effect on the nearby sugar radicals, which are not delocalized, massive effects are observed upon the delocalised base radicals. This is also seen in the systematic decrease in electrostatic stabilization as the radical changes from a captodatively stabilized species, with the most resonance structures, to the diallyl system and to the dialkyl system, with only hyperconjugation. In other words, there is a strong relationship between the resonance stabilization of a radical and its electrostatic stabilization by D-LEFs, which in turn reflects the enhanced polarizability of resonance stabilized species.

D-LEFs Summary	Dipoles versus Polarizability
• Charged group is used to generate a local electric field. • Charge can be a Brønsted acid or base, a permanent charge such as a quaternary amine, or a metal ion • Control of orientation and distance is by careful placement of the charge on the substrate, auxiliary or catalyst • If charge is attached to the substrate a linker is necessary to ensure no conjugation with the reaction centre	Strong Dipoles / Low Polarizability Catalysis: • Decreases with distance • Decreases with solvent polarity • Increases with magnitude of dipole • Depends heavily on alignment Weak Dipoles / Strong Polarizability Catalysis: • Decreases with distance • Increases with solvent polarity • Does not require pre-existing dipole • Largely independent of alignment • Increases with polarizability, in turn with resonance capability

Box 4.2. Construction of and factors affecting D-LEFs.

4.4 D-LEFs from Remote Brønsted Acids or Bases

One approach to generate D-LEFs is to include remote Brønsted acids or bases nearby some reaction centre, and alter their protonation state by virtue of simple pH changes; in this way, electric fields can be introduced and manipulated at will. Recently, theoretical calculations have been used to demonstrate significant D-LEF effects on radical reactions,[46,47,51,52] Diels-Alder reactions,[53,54] nucleophilic substitution,[55] and a variety of photochemical reactions.[45,49,50] Here we select a few case studies highlighting the use of Brønsted acid and/or base D-LEFs to outline pertinent features of their use and design, before presenting experimental studies that reinforce these results.

4. 4. 1. Manipulating Regio- and Diastereoselectivity

One of the big advantages of D-LEFs is the ability to selectively activate alternative reaction pathways, thereby allowing one to, for example, enhance yields, favour minor products, and/or improve diastereoselectivity. As an example, Figure 4.7 shows the

reaction between 2-pyrone and 3-R-cyclopentene, where R is either a carboxylic acid or amine.[53] In the neutral form of either, the preferred transition state is the exo unhindered transition state (C). However, when the amine is protonated the exo hindered form (D) is preferred, while when the carboxylic acid is deprotonated the endo unhindered form is favoured (A). Thus, the anionic functional group causes a change in regioselectivity and the cationic group a change in diastereoselectivity. In all cases the presence of the charged group lowers the barrier for the preferred reaction, compared with the lowest barrier of the neutral system, by 6.7 kcal mol^{-1} in the gas phase for the negatively-charged system, and 8.9 kcal mol^{-1} for the positively charged system. While effects diminish with solvent, they remain significant in low-moderately polar solvents.[53]

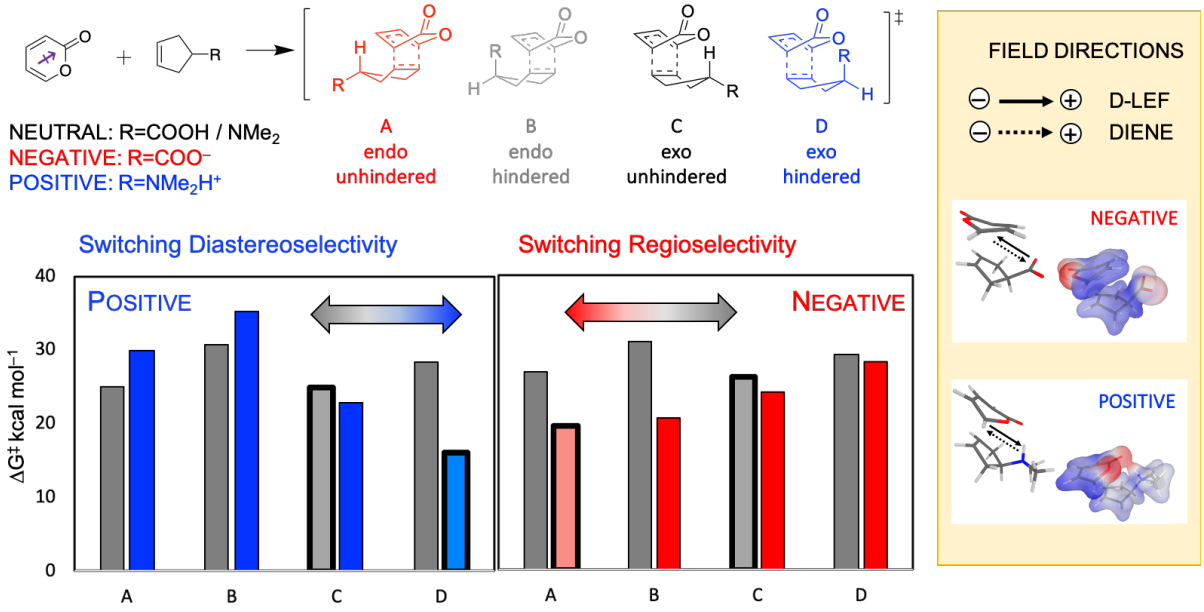


Figure 4.7. Switching regio- and diastereoselectivity in a Diels-Alder reaction with 2-pyrone.[53] Shown here are the four possible transition states for the reaction and their corresponding barrier heights for their neutral and charged forms. The electron density distribution in the preferred transition states for preferred negatively charged and

positively charged systems are also shown. Reproduced/adapted from Ref. 53 with permission from the PCCP Owner Societies, Copyright 2016.

Figure 4.7 shows why there is a change in regioselectivity between the cationic and anionic charges. The 2-pyrone has a pre-existing dipole of 4.93 D, pointing toward the carbonyl (shown in dotted lines in the transition structures of Figure 4.7, right). The dipole of the dieneophile is essentially reversed between the anionic and cationic versions, hence the optimal alignment of the diene with respect to the dienophile is also reversed. The change in diastereoselectivity upon deprotonation is due to competition between steric and electrostatic effects. The hindered exo transition state has the D-LEF better aligned to the dipole, and so when the D-LEF is positively charged this favourable interaction dominates the observed outcome. In contrast, in the neutral form, the dipole effects are small and steric effects dominate. In the negatively charged form, the hindered endo transition state is also better aligned with the dipole than the unhindered one, and the preferred enthalpic barrier actually reflects this, but the preference is smaller and entropic effects cause the preferred Gibbs free energy barrier to favour the unhindered transition state.

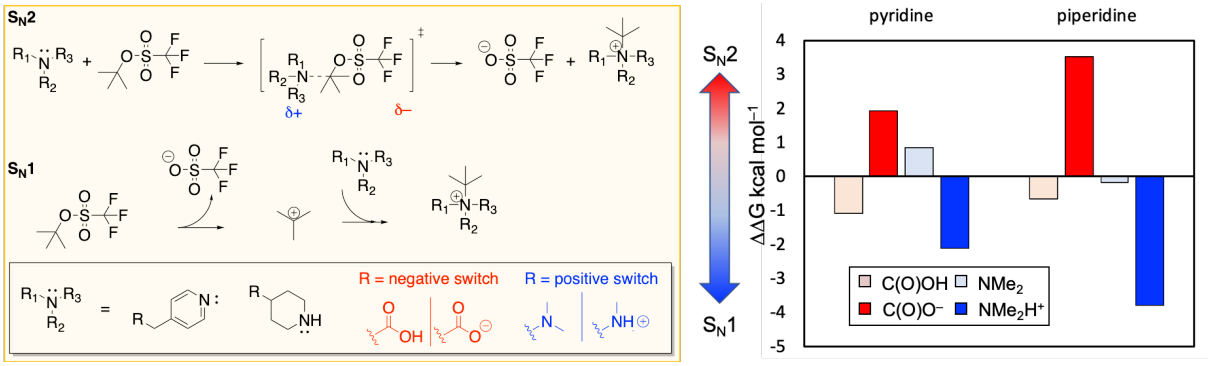


Figure 4.8. The effect of charged functional groups on nucleophilic substitution for methyl triflate with a substituted pyridine and a substituted piperidine. Plotted is the difference in the energy bottlenecks for S_N1 versus S_N2, calculated as a Gibbs free

energy difference (kcal mol^{-1}) at 298.15 K for the neutral and charged functional groups in dichloromethane. A positive number indicates that S_N2 is preferred; a negative indicates S_N1 is preferred.[55]

Another interesting example of D-LEFs manipulating regioselectivity is nucleophilic substitution involving a neutral nucleophile to yield charge-separated products (Figure 4.8).[55] When both reagents are neutral, the rate determining step in the S_N1 reaction is the dissociation of the substrate into a carbocation and a leaving group, as it involves a neutral species undergoing charge separation. This is true even for stabilized leaving groups such as triflate and stabilized carbocations such as *t*-Bu. The S_N2 process also involves this charge separation of course, albeit through formation of the product carbocation and the leaving group. The S_N2 transition state has a dipole with a δ-positive charge on the nucleophile side and a δ-negative on the leaving group side. As a result, introduction of a negative charge on the nucleophile stabilizes the S_N2 transition state, while a positive charge destabilizes it. In the corresponding S_N1 reaction, these charges will affect the second step of the reaction, the association of the carbocation with the nucleophile but cannot affect the first, rate-determining step as the nucleophile is not involved. As a result, negative charges on the nucleophile preferentially stabilize S_N2 over S_N1 in this situation, and vice versa for positive charges. In the latter case, this is not to say that the positive charges catalyse S_N1; rather they have a detrimental impact on S_N2. In the example shown in Figure 4.8, these switches are enough to transform a preference for S_N2 into a preference for S_N1 and vice versa.[55]

4. 4. 2. Catalytic Cycles

Thus far, the effect of D-LEFs has typically been discussed in the context of only simple, one-step reactions or processes, wherein the D-LEF is likely attached to the reacting molecule; a real test of their utility is in the context of multistep catalytic cycles, wherein the D-LEF could be incorporated onto the catalyst itself, forgoing the requirement to modify the molecule of interest. The key advantage to this approach is that it can often be used alongside existing catalytic strategies and complement them. In particular, if the D-LEF is a Brønsted acid or base, one could for example attach the D-LEF onto some existing catalyst and alter the reaction outcome as a function of pH, affording an orthogonal mechanism of control. This is particularly useful in the case of D-LEFs given that many catalysts already require their substrates to adopt a precise orientation, and the substrate will therefore have a known orientation with respect to the designed electrostatic field at key transition states. However, the use of D-LEFs in catalytic cycles brings added complexity, as one must now consider the impact of electrostatic fields on all stages of the cycle.

Figure 4.9 presents a computational study by Blyth and Coote,[54] which explored the simplest example of an ammonium D-LEF incorporated onto a catalyst, bis(3-(3-phenylureido)benzyl)ammonium, for the Diels-Alder reaction between *p*-quinone and various dienes; the use of D-LEFs in this catalytic cycle must consider the effect of electrostatic fields upon the association of substrates to the catalyst, the Diels-Alder reaction itself, the release of the product, the potential re-association of the product to the catalyst (product inhibition), and even the effect of the D-LEF upon the catalyst conformation (Figure 4.9(b)). If the D-LEF works as intended for the Diels-Alder reaction (by stabilising the partial charge transfer in the transition state), this will not necessarily result in an effective catalyst if the presence of the D-LEF also favours the

product-bound state, or prevents substrate association, for example. Additionally, in more complex catalytic cycles, the D-LEF might be oriented so as to promote one step of a cycle, but then be deleterious to the next step. However, in complex catalytic cycles, understanding whether these deleterious processes will occur in the presence of a remote charged functional group (or overcome the advantages of the D-LEF) is difficult to discern on the basis of free energy diagrams alone, especially when the D-LEF group could exist in either its charged or neutral form at any point along the reaction trajectory. Blyth and Coote used simple mathematical models based upon theoretical rate constants from *ab initio* data to demonstrate that, overall, their electrostatically-modified catalyst performed better when charged than uncharged, and catalysed selected Diels-Alder reactions without suffering from the previously-outlined concerns.[54] Similar concerns in the catalytic cycle of a P450 enzyme have been highlighted elsewhere (see, Chapter 3 by Shaik et al.).

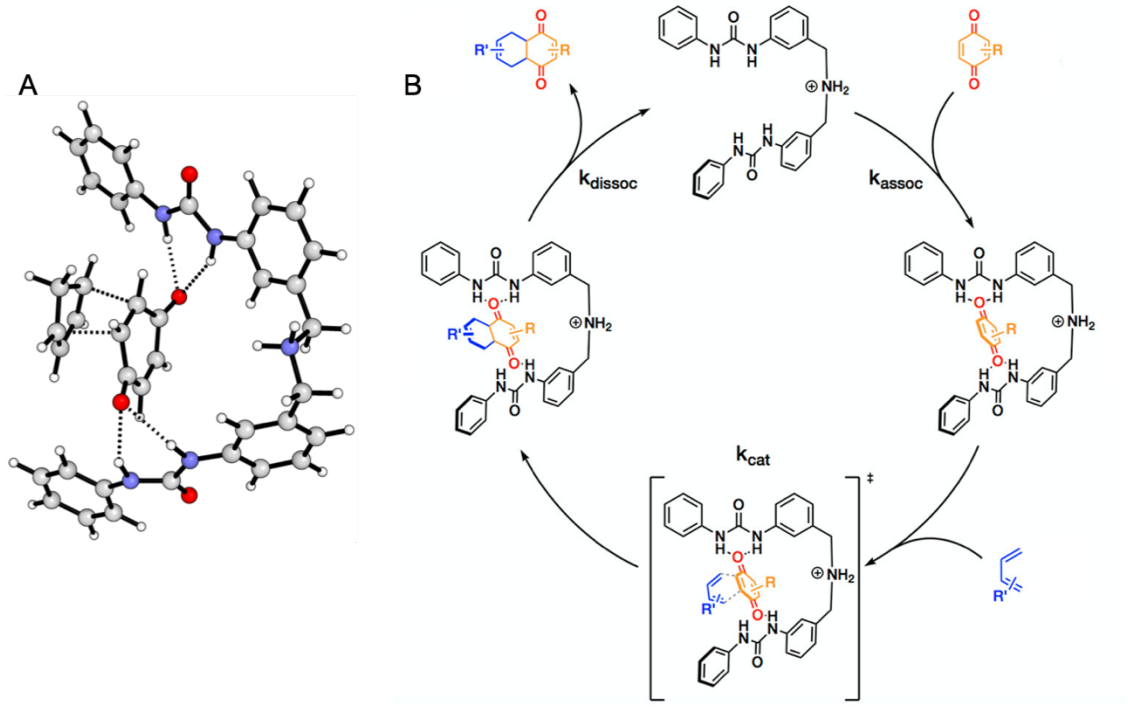


Figure 4.9. (A) An ammonium group D-LEF incorporated onto a hydrogen-bonding catalyst for the Diels-Alder reaction between p*-quinone and cyclopentadiene.*[54] *The*

catalyst utilises C_{2v} symmetry and relatively rigid N,N-diphenylurea moieties to promote productive configurations of the Diels-Alder transition state with respect to the D-LEF. *(B) The effect of the D-LEF on catalysis must be considered for every part of the catalytic cycle, including substrate association, catalysis, substrate dissociation, and the potential for product inhibition. If the D-LEF is a Brønsted acid, the cycle should be considered as a function of changing pH. Reproduced/adapted from Ref. 54 with permission from the American Chemical Society, Copyright 2019.*

The possibility of enhancing catalytic activity through the inclusion of charged groups on catalysts has been extensively explored by some groups (in fact, it is highly possible that many catalysts have an as-yet underappreciated electrostatic component to their activity). With some notable exceptions (*vide infra*), many of these "electrostatically-enhanced" or "charge-activated"[56–59] catalysts use charged functional groups as strong electron-withdrawing substituents or to promote key conformations; they differ from D-LEFs in that they typically do not operate primarily *via* through-space field effects. Others have proposed a "directed electrostatic activation"[60] mechanism that operates through-space in enantioselective organocatalytic cyclopropanations, but various aspects of this work have been disputed.[61,62] As such, these examples are outside the scope of this chapter. The related synergistic use of ion-pairs in electrostatic catalysis is discussed in Section 4.6.

An interesting example of the practical use of D-LEFs in catalysis has recently been published by Shaik and co-workers,[63] who convincingly demonstrated that the remarkable catalytic activity exhibited by two synthetic metallozyme complexes was effectively electrostatic in nature. These complexes, first reported experimentally by

Groves as efficient H-abstraction catalysts,[64] feature cationic substituents on the outer circumference of their ligands. Although these substituents are π-conjugated to the metal centre, the results of Shaik and co-workers demonstrated that the catalytic ability of the selected complexes was proportional to the field strength delivered by the charges, and provides quantitative insights into the use of D-LEFs in synthetic metallozymes. Similarly, contemporary work by Savéant and co-workers found that through-space electrostatic interactions dominated the electrochemical CO_2-to-CO conversion by iron(0) tetraphenylporphyrins, evidenced in part by the inhibition of catalysis when terminal *p*-trimethylanilinium groups were replaced by anionic sulfonates in the same position.[65] In addition, Houk and co-workers[66] briefly explored the mechanism of the aza-Diels-Alder reaction catalysed by tetraalkylammonium or trialkylsulfonium salts, which was reported as hydrogen-bonding catalysis by Maruoka and co-workers,[67,68] and suggested that the observed catalysis likely had an electrostatic field component. The observed catalysis that could be reproduced by external electric fields aligned along the reaction axis of the Diels-Alder reaction, supporting previous theoretical work by Shaik and co-workers.[1] Taken together, the examples in this section demonstrate that D-LEFs incorporated onto catalysts can be practically realised and effective tools in catalysis, despite the added complexity introduced by the catalyst.

4. 4. 3. D-LEFs in Photochemistry and Excited States

An interesting area of ongoing research involving D-LEFs surrounds their use in photochemistry and excited-states. The rationale behind this fact is simple; it is now well-understood that the effects of D-LEFs can be significant in the ground-state, and known that the sign and magnitude of these effects is related to the factors that dictate

charge-dipole interactions and electric polarizability. However, orbitals in excited-states are typically more diffuse than the corresponding orbitals in the ground-state. In other words, they are more polarizable, and thus are expected to be more strongly affected under the influence of an electrostatic field. In fact, much of the early literature studying electrostatic effects in chemistry revolved around photochemical reactions,[40,42] (see Section 4.2 and Section 4.5). Moreover, the ability of electric fields to lead to the shifting and splitting of spectral lines has been known for over a century,[69] and is the basis of Stark spectroscopy, wherein this splitting is used to detect and measure background electric fields in different molecular contexts.[70]

Despite this early interest and clear reasons for studying photochemical reactions under the presence of electrostatic fields, contemporary research in which D-LEFs are introduced so as to manipulate photochemistry is surprisingly sparse and relatively new. Hill and Coote reported in 2018 that D-LEFs arising from Brønsted acids and bases could have a significant effect on the stability of the ππ* transitions of acetophenone, a classic Type I photoinitiator, and a smaller and opposite effect upon the nπ* transitions.[45] They further noted that the effect of electric fields on the nπ* states was sign- and position-dependent (see Figure 4.3(a) above).

From the discussion in Section 4.3.1 and Section 4.3.2, it is clear that the effect of D-LEFs on nπ* transitions in this system arises primarily from charge-dipole interactions. However, in this same work, the influence upon ππ* transitions was shown to be largely due to polarization, with the stabilization effects being extremely large while opposite destabilization effects were almost negligible. Taken together, the effects on the relative energies of the nπ* and ππ* states could be tuned almost at will and,

although the effects were attenuated in increasingly polar solvents, they remained synthetically-relevant even in moderately-polar solvents.

In a follow-up study, Hill and Coote compared the effects of D-LEFs, Lewis acids, and increased conjugation upon the photochemistry of another Type I photoinitiator, the water-soluble Irgacure 2959,[50] with a view to red-shifting it to avoid damage in bioprinting while still maintaining its photoactivity. They found that the electric fields arising from Brønsted acid/base D-LEFs provided the greatest control over the relative energies of different excited states. In other words, because the sign and magnitude of electric field effects could be controlled by the relative position of the attached D-LEFs and the solvent environment, specific excited states could be targeted, while this was not true for the added Lewis acids and increased conjugation strategies. Nonetheless, inclusion of Lewis acids is a very simple approach to modifying photoinitiator behaviour, and photochemistry in general, and hence a lot of experimental studies to date have demonstrated very large effects on both UV-Vis and fluorescence spectra, though often accompanied by detrimental effects on the associated photochemical behaviour.[41,43,71,72]

Returning to D-LEFs, a very dramatic demonstration of polarizability and its implications for solvent attenuation was recently reported by Blyth and Coote in a study of D-LEFs upon the photochemical carboxylation of *o*-alkylphenyl ketones.[49] This is a complex photoenolization/Diels-Alder sequence that features both triplet and singlet reactivity.[73] A key finding of this work was that the effect of D-LEFs was in some circumstances not attenuated in increasingly polar solvents, and did not exhibit a strong direction-dependence. These results are due to the electric polarizability of the system, and are explained on a theoretical basis in Section 4.3.2.

Taken as a whole, the work outlined in this Section illustrates a key point: the study of D-LEFs in photochemical reactivity is an underappreciated and complex area of ongoing interest, and the results obtained in this area will likely contribute greatly to the understanding of D-LEF effects in practical synthetic chemistry, beyond simple ground-state reactions.

4. 4. 4. Selected Experimental Studies

While most of the case studies described above are based on benchmarked theoretical calculations, there are a growing number of experimental studies also demonstrating the impact of remote charged groups on reaction enthalpies and barriers. Figure 4.10 shows gas-phase experimental studies of the effect of deprotonation on the stability of a nitroxide radical. As shown previously in Figure 4.3(b) a negative charge in the 4-position of a TEMPO radical is predicted to stabilize it due to the dipole across the N–O• bond. In the gas-phase, these predictions were validated using Cooks' kinetic method[74] to measure the relative gas-phase proton acidity (GPA) of a nitroxide radical and its corresponding alkoxyamine (Figure 4.10).[47] In this method, the fragmentation patterns of proton bound dimer complexes are studied to assess the relative gas-phase acidities of the two fragments. The more acidic fragment gives up the proton and remains charged and visible in the mass-spectrometer, the less acidic species captures the proton and is invisible. Hence, the relative acidities can be related to the relative peak heights of the two fragments. Using a simple thermodynamic cycle, it is seen that the difference in GPA values is equivalent to the difference in bond dissociation energies of the neutral and deprotonated alkoxyamines — that is, the pH switch on the stability of the product nitroxide radical. As seen in Figure 4.10(a), pH switches of 6 kcal mol^{-1} (over 4 orders

of magnitude in equilibrium constant) were measured. What was particularly surprising about this work was the sheer magnitude of the electrostatic effects at such a relatively long range (6.4 Å between the charge and radical centre). In mass spectrometry so-called inert charge labels are often introduced at distances such as this so as to confer a charge-mass ratio on molecules and allow them to be studied. This work highlighted that such charge labels may not be as inert as previously thought.

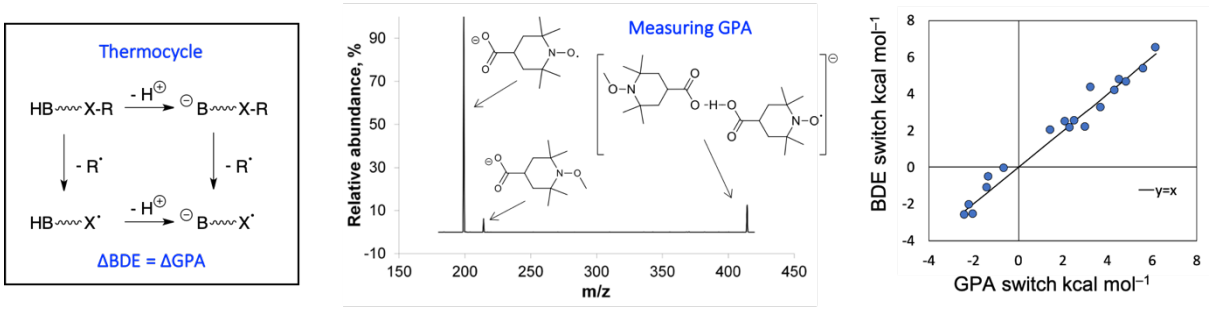
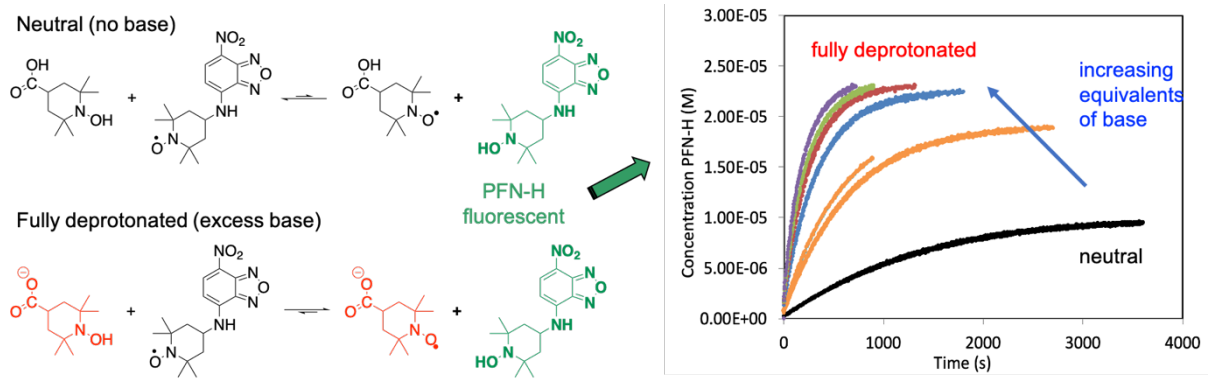


Figure 4.10 Experimental validation of pH-switches (kcal mol^{-1}) on the stability of nitroxide radicals in the gas-phase[47] *Mass spectrometry was used to study the fragmentation preferences of proton-bound dimer complexes of a nitroxide and its alkoxyamine so as to assess their relative gas-phase acidity (GPA). A thermocycle was used to demonstrate the equivalence of pH switches on GPA and bond dissociation energies, and theoretical (G3(MP2,CC)(+)//M06-2X/6-31+G(d,p)) BDE switches and experimental GPA switches were shown to agree to within a mean absolute deviation of < 0.3 kcal mol^{-1}. Reproduced/adapted from Ref. 47 with permission from Springer Nature, Copyright 2013.*

For synthetic chemistry, results in solution are more relevant. Figure 4.11 shows solution-phase experiments on the same 4-carboxy-TEMPO but in dichloromethane.[48] The effects of charge formation on radical stability were assessed using time-dependent fluorescence spectroscopy to follow the hydrogen atom transfer reaction of the hydroxyl amine of 4-carboxy-TEMPO was mixed with a pro-fluorescent nitroxide.

The pro-fluorescent nitroxide contains a fluorophore but due to the interaction with unpaired electron does not undergo fluorescence. Upon hydrogen atom transfer, the pro-fluorescent nitroxide is converted to a non-radical and can fluoresce and it is this fluorescence that allows the progress of the reaction to be studied. By carrying out the reaction in the presence and absence of base, the effects of deprotonation on the rate and equilibrium constant can be followed. The results showed that full deprotonation led to an increase in the forward rate coefficient by a factor ca. 20 and an increase in the equilibrium constant by a factor of ca. 30, both indicating the enhanced stability of the product nitroxide radical when the charge was present. While ca. 75 equivalents of triethyl amine was needed to fully deprotonate the 4-carboxy-TEMPO in dichloromethane, follow-up experiments showed that one equivalent of the stronger base dibutyl lithium was sufficient.[52] These same follow up experiments also showed that the charged group promoted thermal dissociation of alkoxyamines for nitroxide mediated polymerization at lower temperatures than the corresponding neutral species.[52]



Forward Rate Constant L mol^{-1} s^{-1}			Equilibrium Constant		
Neutral	Charged	Switch	Neutral	Charged	Switch
6.4	133.8	20.9	0.16	4.7	28.7

Figure 4.11 Experimental validation of pH-switches on the stability of nitroxide radicals in solution.[48] *Time-dependent fluorescence spectroscopy is used to measure the rate*

and final equilibrium position in the reaction of the hydroxyl amine of 4-carboxy-TEMPO and a profluorescent nitroxide (PFN) in the presence and absence of base (triethyl amine, TEA) in dichloromethane solution at 298 K. The results show that adding base to deprotonate the 4-carboxy-TEMPO both increases the forward reaction rate and the final equilibrium constant. Control experiments (not shown) were used to confirm that this was due to the electrostatic stabilization of the 4-carboxy-TEMPO. Part B is reproduced/adapted from Ref . 48 with permission from Royal Society of Chemistry, Copyright 2015,

4.5 Metal Ions as D-LEFs

Another way of creating a D-LEF is through inclusion of metal ions in a reaction, which has been noted briefly throughout Section 4.1 and Section 4.4.3. For example, through the 1980s and early 1990s, Clark et al. reported a series of pioneering theoretical studies showing that Li^+ cations significantly catalysed radical reactions such as radical addition,[75] methane oxidation,[76] and olefin epoxidation.[77,78] In the case of radical addition, it was postulated that metal ions should catalyse radical addition to 1-alkyl olefins to such an extent that propagation could outcompete degenerative chain transfer to monomer, making radical polymerization of these monomers possible. This was subsequently proven experimentally in 2006 by Michl et al.,[79] using carborane salts to deliver "naked" Li^+ cations capable of binding to the π-system of the monomers. While kinetics was not studied, a follow-up theoretical study of Clark[80] demonstrated that the Li^+ cations lowered the radical addition barrier both overall and with respect to the hydrogen transfer barrier. While the ions are effectively coordinated to the reaction centre through cation-π bonding, an electrostatic argument for catalysis was made on the basis of the decay rate with distance. Similar electrostatic arguments

were made for the Li^+-catalyzed propagation rate in the radical polymerization of methyl methacrylate (Figure 4.12), wherein the metal ion was also coordinated to the reaction centre, albeit through the carbonyl and not the C=C bond.[81,82] In this instance, an appreciation for the electrostatic origin of the catalytic allowed for catalysis to be optimized through increases to the charge on the metal centre.[81] Other classic examples of the electrostatic effects of metal ions are the early works of Jiao and Schleyer, who reported the electrostatic acceleration of electrolytic reactions[83] and 1,5-hydrogen atom shifts[84] by metal cation complexation, and the work of Shaik and co-workers, who showed that metal cations lower the barrier for C-X heterolysis.[85]

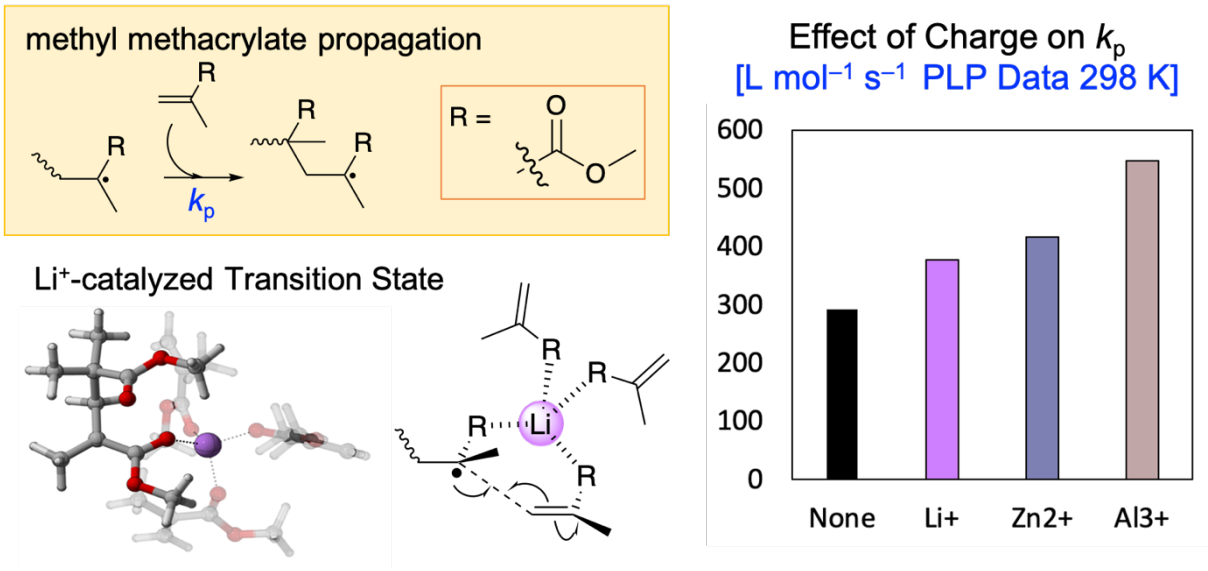


Figure 4.12. Metal ion catalysis of the propagation step of methyl methacrylate (MMA) polymerization. Shown here are the experimentally determined propagation rate coefficients in bulk MMA without metal ions, and with the addition of 5 mol% $LiNTf_2$, $ZnCl_2$ and $AlCl_3$. The SMD/M06-2X/6-31+G(d,p) optimized transition state for the propagation reaction of an MMA dimer radical in the presence of Li^+ is also shown. Reproduced/Adapted from Refs. 81,82 with permission from the Royal Society of Chemistry, Copyright 2014, 2017.

Unsurprisingly, non-redox active metal ions can, by virtue of their ability to electrostatically stabilize charged species, also predictably shift oxidation and reduction potentials, and modify the outcomes of transition metal-catalysed reactions.[86–89] Yang and co-workers used proximal metal cations to install D-LEFs in transition metal complexes, demonstrating in one case that the electric field generated from the metal ion was able to promote iron-catalyzed aerobic C-H oxidation at mild potentials ($E_{1/2}$ Fe^{III}/Fe^{II} vs. $[FeCp2]^{+/0}$ = -0.71 V). This was significant because, without the inclusion of the metal ion, only Fe salen complex derivatives that had been modified to include four nitro groups and Fe^{III}/Fe^{II} potentials greater than -0.27 V had been found to be sufficiently oxidising in the model reaction studied, and the inclusion of the metal ion inhibited deactivation pathways.[87] Significant effects upon redox potentials upon incorporation of non-redox active metal ions has been observed in many other systems.[87]

An important consequence of these electrostatic effects is that the electrolyte in electrochemical reactions should not necessarily be considered “innocent”. For example, Figure 4.13 shows the change in oxidation potential of a nitroxide radical as a function of the electrolyte anion.[90] The change in the oxidation potential follows the Lewis basicity of the anion, with the exception of HSO_4^- which is additionally stabilized by a hydrogen bond with the azole ring. The stronger Lewis bases are better able to electrostatically stabilize the oxidised species and thus lower the oxidation potential. Similar effects have been reported for nitroxide radicals in ionic liquids, where the ionic liquid is able to stabilize the oxidised and reduced species, in the latter case preventing protonation of the reduced form and allowing reduction to become reversible.[91]

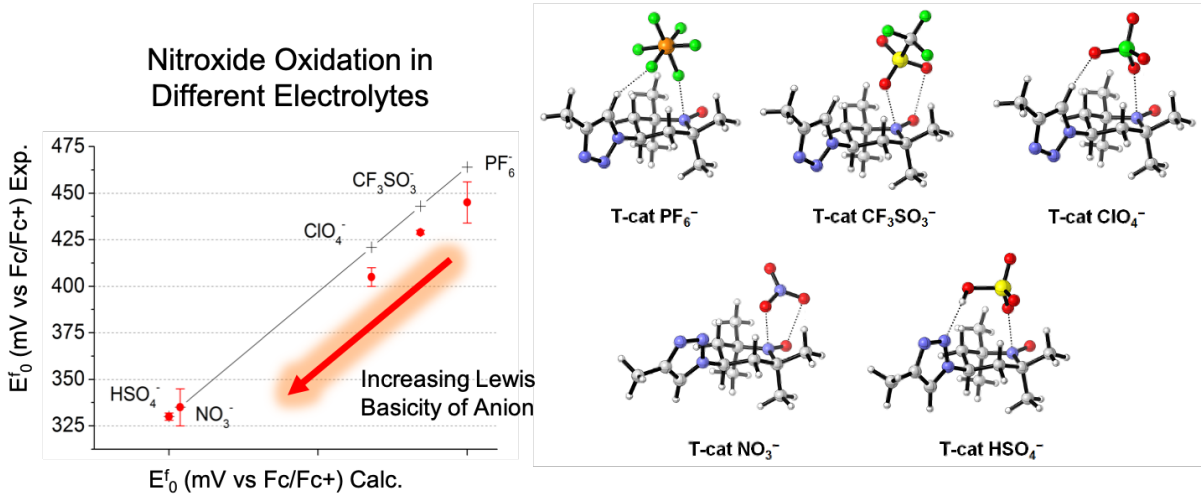


Figure 4.13. Theoretical and experimental oxidation potentials (mV versus Fc/Fc+) of a nitroxide radical in acetonitrile containing 1.0 × 10^{-1} M $Bu_4N^+X^-$ where X^- are the different anions shown. The computed complexes between the oxoammonium and anion are also shown.[90] *Reproduced/Adapted from Ref. 90 with permission from the American Chemical Society, Copyright 2016.*

Higher-order metal clusters can also be used as D-LEFs. Schwarz and co-workers experimentally showed that thermal gas-phase activation of methane toggles between methanol generation and hydrogen abstraction according to whether the catalyst, diatomic $[ZnO]C^+$, is ligated with acetonitrile.[92] Accompanying theoretical calculations showed that this ligand effect was electrostatic in origin. Similarly, the contrasting behaviour of $[Cu\text{-}C]^+/CH_4$, which activates 2 C-H bonds simultaneously, and $[Au\text{-}C]^+/CH_4$, where stepwise bond activation occurs, was also explained in terms of the electrostatic differences of the catalysts.[93]

4.6 Ion-Pairs as D-LEFs

Since the 1980's, ion-pairing catalysis has emerged as an important strategy in synthesis, wherein an anion and cation are spatially associated with a potential energy exceeding the thermal energy available to separate them, and this association is exploited in concert with secondary noncovalent interactions to achieve reaction control.[94] However, a full discussion of ion-pairing effects here is outside the scope of this chapter, although it is likely (by definition) that many instances of ion-pairing catalysis are driven by electrostatic interactions.[95–98] In fact, ion-pair D-LEFs have already been noted in Section 4.1 with the historical work of Marquet and co-workers,[44] where it was found that the presence of ion-pairs afforded increased regioselectivity in the cleavage of alkyl aryl ethers. Nonetheless, for the purposes of this Section, several recent examples of ion-pairing catalysis are selected with particular reference to those in which the directional electrostatic properties of ion-pairs dominate the observed reaction outcomes.

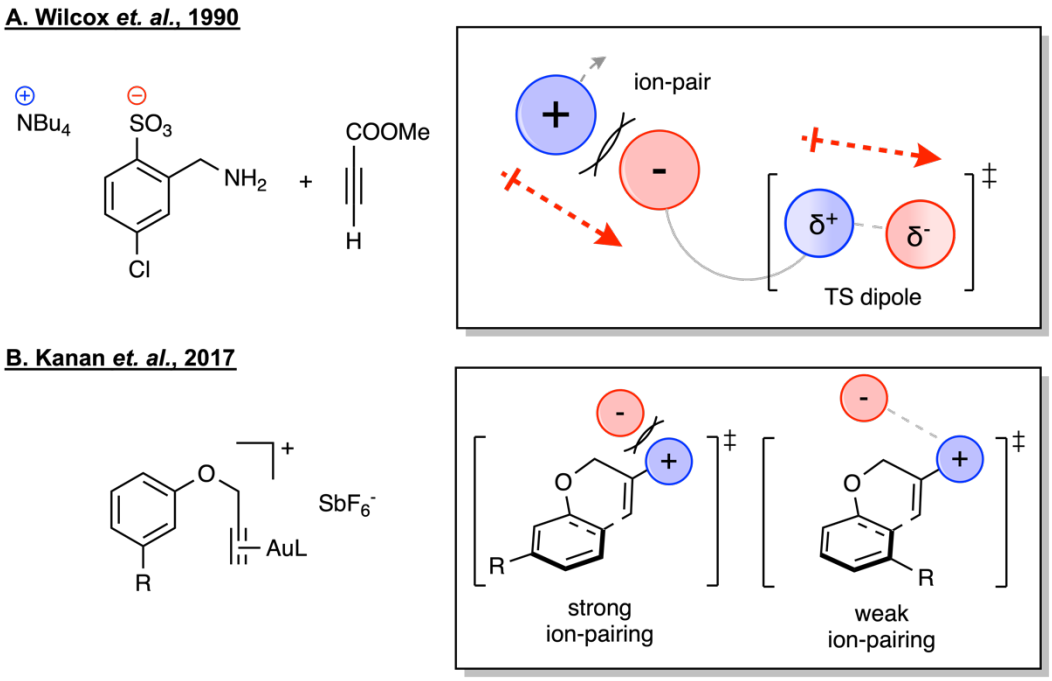


Figure 4.14. (A) Wilcox and co-workers[99,100] developed modified benzylic primary amines that incorporated the sulfonate of a tetrabutylammonium tosylate ion-pair to

create a dynamic dipole-dipole interaction in the transition state for the nucleophilic addition of methyl propynoate. (B) Kanan and co-workers[101] *demonstrated that differential transition-state stabilization by ion-pair interactions with a cationic gold catalyst could afford regioselectivity in the hydroarylation of phenyl propargyl ethers. Part B is adapted from Ref. 101 with permission from the American Chemical Society, Copyright 2017.*

In the 1990s, notable examples of ion-pair D-LEFs were published by Wilcox and co-workers. Over three particularly interesting papers (two reporting the same experiments), Wilcox and co-workers studied the rate of (a) the addition between benzylic primary amines with methyl propynoate[99,100] (Figure 4.14), and (b) a nitrile oxide cycloaddition,[102] each in the presence of the tetrabutylammonium tosylate ion-pair and subject to the so-called "intramolecular salt effect" in solvents of varying polarity. In the case of the former, Smith and Wilcox found that nucleophilic addition was catalysed by covalent attachment of one partner of the ion-pair to the reacting amine (though the possibility of competing hydrogen-bonding effects cannot be discounted); in the latter, Raposo and Wilcox showed *via* convincing experiments that a chiral phenylmaleimide derivative bearing an ionic group and associated counterion could control the diastereoselectivity of nitrile oxide cycloadditions by changing the most-favoured position and orientation of the ion-pair dipole relative to the transition state dipole.

More recently, Kanan and co-workers demonstrated that ion-pairing of a cationic Au(I) catalyst to a spectator counterion can markedly improve the regioselectivity of the hydroarylation of 3-substituted phenyl propargyl ethers.[101] These examples are particularly noteworthy because the observed effect is the result of electrostatic

interactions between the ion-pair and key transition states, as evidenced by changes in regioselectivity as a function of solvent polarity. In other words, the strength of ion-pairing is tuned to differentiate between competing transition states. In the work of Kanan, one of these competing transition states exhibits greater charge separation than the other and thus is expected to be more strongly affected by an electrostatic field, while in the work of Wilcox, selectivity was achieved *via* the ability of ion-pairs to dynamically adjust to stabilise the incipient transition dipole. From these brief examples, it is clear that further research into the use of ion-pair-based D-LEFs could prove to be an exciting avenue for electrostatic catalysis.

4.7 Prospects

Summing up, D-LEFs are a practical method for harnessing and scaling electrostatic catalysis. By placing a charged functional group, or non-redox active metal ion, on a substrate, catalyst or auxiliary one has the opportunity to both catalyse a reaction and alter its regio- and stereo- selectivity. This chapter has outlined the main principles governing these effects and illustrated some leading examples. While many of the examples to date are based on computational chemistry alone, experiment has validated these effects in practical systems. Nonetheless further experiments are important to grow this field and harness the full potential of electrostatic catalysis. Moreover, while the effect of D-LEFs upon simple ground-state reactivity of one-step reactions is relatively well-understood and has been investigated through many angles (metal ions, Brønsted acids/bases, EEFs, ion-pairs), more work is needed to explore complex, multi-step reactions.

As highlighted herein, to harness D-LEFs in most systems, there is a necessary compromise between maintaining a low polarity environment so as to maximise

electrostatic effects, and the need to solubilise charge species, which usually requires higher polarity solvents. One way to address is through better catalyst platforms, such as metal organic frameworks polymer supported catalysts[103], ion-pairs, zeolites, metal-binding motifs, pH-cycling of Brønsted acid/base D-LEFs, and higher-order aggregates (anti-electrostatic dimers, metal clusters, nanoparticles), etc. This is almost certainly the future of D-LEFs, although as work reviewed here has shown, even simple organic systems exhibit electrostatic effects that are sufficient to alter reaction pathways and facilitate otherwise unfeasible reactions.

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