Directionality and the Role of Polarization in Electric Field Effects on Radical Stability

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Abstract

Accurate quantum-chemical calculations are used to analyse the effects of charges on the kinetics and thermodynamics of radical reactions, with specific attention given to the origin and directionality of the effects. Conventionally, large effects of the charges are expected to occur in systems with pronounced charge-separated resonance contributors. The sign (stabilisation or destabilisation) and magnitude of these effects thus depends on the orientation of the interacting multipoles. However, we show that a significant component of the stabilising effects of the external electric field is largely independent of the orientation of external electric field (be it a charged functional group, a point charge or an electrode) and occurs even in the absence of any pre-existent charge separation. This effect arises from polarisation of the electron density of the molecule, induced by the electric field. This polarisation effect is greater for highly delocalised species, such as resonance-stabilised radicals and transition states of radical reactions. We show that this effect on the stability of such species is preserved in chemical reaction energies, leading to lower bond dissociation energies and barrier heights. Finally, our simplified modelling of the diol dehydratase-catalysed 1,2-hydroxyl shift indicates that such stabilising polarisation is likely to contribute to the enzyme catalysis.

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Introduction

Traditionally, polar effects on radical reactions are explained in the context of standard physical organic chemistry concepts and can be broadly split in the following distinct categories. The first is where direct orbital interactions between a charged functional group and radical lead to resonance stabilization that (i) would not occur in the absence of the charged group and (ii) could not occur if the charged functional group was replaced with an equivalent point charge. Intervalance charge transfer (IVCT) is a classic example of this effect. The second is where, in the absence of the charge, the radical itself is already stabilized by valence bond (VB) contributors with pronounced charge separation due to the electronegativity differences of the participating atoms/functional groups. In that case, this resonance stabilization can be enhanced or disrupted by protonation (or deprotonation) of the neighboring functionalities. For example, the stability of C-centered peptide radicals is greatly affected by the protonation or hydrogen bonding at the proximal nitrogen atom by destabilizing resonance contributor II (Scheme 1) by both competing for the nitrogen lone pair and destabilizing this contributor electrostatically.

![Scheme 1](image)

A third type of polar effect, and the subject of this work, is where the resonance stabilization of the radical is enhanced or disrupted not via direct orbital interactions (as in Scheme 1) but via through-space electric field effects. For example, deprotonation of the remote carboxylic acid group in 4-carboxy-TEMPO leads to significant stabilization of the nitroxide radical due to the electrostatic stabilization of the charge-transfer resonance contributor II (Scheme 2). What distinguishes these polar effects from the other two classes is that they do not require orbital overlap and indeed can be replicated by replacing the charged functional group with an equivalent electric field. The extreme case illustrating this concept is the reported catalytic effects of the external electric fields (EEFs) on, for example, radical biomimetic and Diels-Alder reactions, rationalized in the framework of standard directional polar interactions between the field and molecular dipole(s) on the basis of the VB contributors. Indeed, the ability of EEFs to catalyse Diels-Alder reactions was recently demonstrated experimentally.
Scheme 2. Effect of deprotonation on the resonance stabilization of a nitroxide radical.\textsuperscript{5}

Polar effects of this type can affect the kinetics as well as thermodynamics of radical reactions,\textsuperscript{10} as the pre-existing charge-separated VB contributors of the corresponding transition states can also be (de)stabilized by the charges.\textsuperscript{11} In particular, transition states of many hydrogen transfer reactions possess a greater ionic character compared with their reactants/products.\textsuperscript{12} Although it is debated in the literature as to which of the various TS contributors dominate the kinetics (in particular, short-range \textit{vs.} long-range triplet repulsion, \textit{i.e.} contributors \textit{C1-3}, see Scheme 3),\textsuperscript{13} it is clear that all of them will be affected by the charge.

\[ A - H + ^{1}B \leftrightarrow \left[ A \cdot H \cdot B \right]^{\ddagger} \leftrightarrow A^{\ddagger} + H - B \]

Scheme 3. Various valence-bond contributors (\textit{C1-9}), proposed for the transition state of a typical H• transfer reaction.\textsuperscript{13}

The involvement of the charge-separated TS contributors (mainly \textit{C4}↔\textit{C6} and \textit{C5}↔\textit{C7} in the case of identity reactions, Scheme 3) can reach significant magnitudes, as has been beautifully demonstrated by Hiberty, Shaik and co-workers \textit{via} comparison of the [H–Hal + H•] \textit{vs.} [Hal–H + Hal•] identity reactions.\textsuperscript{14} Specifically, they found that the barrier of [H–F + H•] reaction is higher than the barrier of [F–H + F•] reaction by \textit{ca.} 80 kJ mol\textsuperscript{−1} almost exclusively due to the difference in the stabilities of the ionic VB contributors of the corresponding transition states. While descriptors \textit{C4}↔\textit{C6} of [F--H--F]\textsuperscript{•} are relatively stable and afford significant resonance with the covalent structures, descriptors \textit{C5}↔\textit{C7} of [H--F--H]\textsuperscript{•} experience
destabilizing 3-electron repulsion that leads to the observed higher barrier. This notion is reflected in visibly divergent charge distribution in the two transition states\textsuperscript{15} that is seemingly counter-intuitive considering both reactions involve breaking and forming the same H–F bonds.

The key characteristics of the electric field effects on these radical reactions are that (i) they presume the existence of charge-separated contributors in the reaction participants and (ii) they are strongly directional. However, very recently we have discovered that remote charges can significantly stabilize even seemingly non-polar radicals such CH\textsubscript{2}=CH–C(CH\textsubscript{3})•–CH=CH\textsubscript{2}.\textsuperscript{7} More generally, even for polar radicals, such as the nitroxides, there appears to be a significant non-directional component to the electric field effects on radical stability.\textsuperscript{7} In the present work, we examine this non-directionality, and analyse the role of polarization and resonance in determining its magnitude.

**Computational Methods**

All computations were performed using the Gaussian\textsuperscript{16} and QChem\textsuperscript{17} software packages. Geometries of all species were optimised at the M06-2X/6-31+G(d) level (and kept frozen in the presence of the point charge), their energies in isolation and in the presence of remote charge(s) were computed at the same level (and selectively refined at the M06-2X/aug-cc-pVTZ level). Energy decomposition analyses involved computations at the Hartree-Fock level with the basis set, corresponding to that used in M06-2X computations. These methodologies have been previously extensively benchmarked and shown to be appropriate for the radical thermochemistry and electric field effects;\textsuperscript{6,7,9} additional benchmarking of the kinetics calculations against G3(MP2,CC)(+) is given in the Supplementary Material.

**Results and Discussion**

**Lessons from Energy Decomposition Analysis**

To understand the origin of these non-directional electrostatic effects on radical stability, it is helpful to isolate the contributions to them arising from the Hartree-Fock exchange energy, the electron correlation, and the remaining energy, which is known as the Hartree energy. To a first approximation, the degree of electron delocalization, and hence the stabilization due to resonance, is largely quantified at the Hartree-Fock level by the exchange energy.\textsuperscript{18} The exchange energy thus provides a simple estimate of the energetic effect due to increased (or decreased) resonance stabilization of the radical in the presence of the charge. The Hartree energy contains,
among other things, the Coulomb integrals, and thus provides a direct measure of any favourable (or unfavourable) electrostatic interactions. These include the interactions between the permanent multipoles on the interacting fragments (conventional electrostatic interaction) and interactions between permanent electrostatic moments on one fragment with induced electrostatic moments on the other (induction, or polarization). The physical interpretation of the correlation energy in the context of electrostatic stabilization of radicals is more complex, but it is worth noting that the correlation contribution to the effect of charge on the stability of the radical is relatively small in the cases studied here (vide infra).

Figure 1 shows the effect of the positive and negative charges on the stabilities of several radical species. For all species, the negative charge stabilizes the radical and this effect arises from the Hartree energy component. The positive charge has a more diverse effect on the radical stabilities, but noticeably the Hartree energy component is smaller in absolute terms compared to that from the negative charge. In dimethylnitroxide Me$_2$NO•, the charge-separated resonance contributor II (Scheme 2) is stabilized by the negative and destabilized by the positive charge. However, the non-equality of the Hartree components suggest that in addition to this electrostatic contribution there occurs polarization of the electron density. This polarization interaction is stabilizing for positive and negative charges, but is larger in absolute terms for the negative charge. For this reason, the Hartree component in the stabilization of the diallyl (CH$_2$=CH)$_2$C•CH$_3$, which lacks appreciable charge-separated contributors, by the negative charge is greater than by the positive charge. In most cases, charge appears to distort the resonance stabilization (negative exchange component), most likely because the energy difference between the contributors gets amplified.
Figure 1. Effect a remote point charge on the relative radical energy (M06-2X/6-31+G(d) electronic energies, kJ mol\(^{-1}\)). Positive values correspond to radical stabilisation in the presence of the charge compared to no charge. In all cases the negative (A) or positive (B) point charge is at a fixed distance from the formal radical centre (5-6 Å, for more details see Supplementary Material). These so-called total “switches” on radical stabilities (numbers in black above the columns) are split into HF/6-31+G(d) exchange energy (blue), the correlation energy (calculated as the M06-2X/6-31+G(d) – HF/6-31+G(d) difference, grey), and the remaining Hartree energy (red).

Importantly, this polarization is non-directional, as it corresponds to the induced redistribution of electron density within available delocalization domain. Figure 2 shows the relative stability of a effectively non-polar diallyl radical in the presence of variously positioned positive and negative point charges. In all cases, the Hartree component of the relative energy is positive as it comprises stabilizing induction, as well as electrostatics, stabilizing or destabilizing depending on the local bond dipoles of the molecule.
Figure 2. Effect of negative (A) and positive (B) point charge position on the relative stability of a diallyl radical (M06-2X/6-31+G(d) electronic energies, kJ mol\(^{-1}\)). Positive values correspond to radical stabilisation in the presence of the charge compared to no charge. In all cases the negative or positive point charge is at a 5 Å distance from the closest carbon atom, designated with a radical dot (for more details see Supplementary Material). These so-called total “switches” on radical stabilities (numbers in black above the columns) are split into HF/6-31+G(d) exchange energy (blue), the correlation energy (calculated as the M06-2X/6-31+G(d) – HF/6-31+G(d) difference, grey), and the remaining Hartree energy (red). 1 column

Whilst polarization might naturally be expected to lower the energy of any molecule in the presence of a charge, it is important to note that the effects reported here are clearly evident in reaction energies, such as the bond dissociation energies and associated radical stabilization energies. That is, delocalized radicals are more polarizable than their closed-shell precursors or analogous but fully saturated (localized) radicals (Scheme 4). Delocalised diallyl radical I has a noticeably higher polarizability along the molecular conjugation space than the corresponding R–H precursor III or a structurally similar saturated radical IV. Respectively, the lowering of the R–H BDE by a remote negative charge in III is more pronounced (~6 kJ mol\(^{-1}\)) than in V (~2 kJ mol\(^{-1}\)). Obviously, the polarisability of I is enhanced through conjugation with the adjacent double bonds. Indeed, if the system is distorted by rotating both \(\pi\) bonds so that they are
orthogonal to the unpaired electron (species II in Scheme 4), the polarizability (and stabilization by remote negative charge) drops to that of a localized radical IV. More generally, we have observed previously that in a series of otherwise structurally analogous radicals, there is a good correlation between the strength of the “pH-switch” on radical stability and the Mulliken spin density on the formal radical centre, in turn a simplified measure of the extent of delocalization of the radical (Figure 3).

It would thus appear that resonance leads to enhanced polarizability and hence enhanced inductive stabilization.

![Scheme 4](image)

Figure 3. Effect of deprotonation of the carboxylic acid on the R–X homolytic bond dissociation as a function of the spin density on the resulting X-centred radical.

**Effects on Kinetics**

The observation that polarization is enhanced by resonance stabilization is encouraging for the use of such electric field effects in catalysis. This is because transition states tend to be more delocalized (and thus more polarizable) than the reactants or products. Indeed, under the curve-
crossing model, the transition state can be thought of as the point at which the reactant and product electronic configurations are degenerate and hence undergo maximum resonance with each other. Of course, as noted above, transition states can also comprise charge-separated resonance contributors, and in such cases the sign and placement of the charge (and hence the orientation of the electric field) would either enhance or mute the stabilization from induction. To explore the net effect of charge on radical reactions, we considered a series of simple identity hydrogen transfer reactions, and investigated the effect of placing a charge down the transition state axis of symmetry. To avoid problems with associating the charge with one or other of the isolated reactants, we considered only the effects on the charges on the reaction pre-complexes and reaction barriers (see Figure 4).

Figure 4. Calculated energy profiles of the identity hydrogen transfer reactions in the absence (black) and presence (red) of a remote (–1) point charge at 5 Å (for X• = •CH3, •NH2, •PH2 and •PH4) or 7 Å (for X• = •OH and •SH) distance from the transferred H•, as well as the corresponding switches on the pre-complexes (bottom row) and transition states (top row), decomposed into the Hartree, correlation and Hartree-Fock exchange energy components (negative contributions are placed below the ‘zero’ lines). All energies are M06-2X/aug-cc-pVTZ electronic energies in kJ mol⁻¹. Also shown are the optimized geometries of the transition states in the presence of an anion (at distance r, shown in italics) and NBO charges on the transferred H• in the absence (black) and presence (red, in brackets) of a (–1) point charge, calculated using M06-2X/aug-cc-pVTZ method.
From Figure 4, it is seen that there is a significant stabilizing Hartree contribution to the transition states of all reactions, countered to varying extents by exchange. Again, as in the radical stabilities, there is a trade-off whereby electron redistribution enhances the induced Coulombic stabilization of the transition state (Hartree), but this can come at a cost to the resonance stabilization (exchange), because the relative stabilities of the various resonance contributors are affected. As expected, the effects on the pre-complexes are generally much smaller, and the net result on the reaction barrier is largely governed by the trade-off between polarization and resonance, with some barriers lowered significantly and others only marginally. Clearly, polarization raises the possibility of genuinely non-directional effects on kinetics and thermodynamics. Yet, this is rarely, if ever, achieved because of the accompanying directional effects due to charges stabilizing or destabilizing the pre-existing charge-separated resonance contributors.

A good example of this trade-off is illustrated in Figure 5, which shows the effects of charge on the barrier height for a simplified model of the 1,2-hydroxyl shift in the coenzyme-B12 mediated diol dehydratase. Previous work by Smith et al.\textsuperscript{21} has shown that a push-pull mechanism involving partial protonation and partial deprotonation of the respective hydroxyl groups can help to account for catalysis in this remarkable reaction. Depending on the acids and bases considered, barrier lowering of more than 100 kJ mol\textsuperscript{–1} was reported. Here we explore the extent, to which electric fields alone can help account for these catalytic effects. Initially, we placed various charges along the axis of symmetry of the transition state and discovered that significant inductive stabilization is largely countered by a destabilizing exchange component. Clearly, in this position, the charges are non-optimal for stabilizing the charge-separated resonance contributors to the transition state. However, when the same charges are placed in the locations, relative to the substrate, in which they appear in the substrate-bound crystal structure,\textsuperscript{22} the effects reinforce each other and significant catalysis is observed. That is, the enzyme appears to have evolved to place the charged residues so as to make the best catalytic use of the oriented electric field, experienced by the substrate. Admittedly, this is an over-simplified representation of the field within the active site, as it ignores the polarizing and shielding effects of the various residues and counter-ions. It is also clear that polarization cannot explain all of the catalytic action, which, no doubt, also involves specific orbital interactions between the various species involved. However, it is clear that significant induced electrostatic effects are important and that they are optimized by nature to make use of both resonance and polarization effects. Indeed, the role of electrostatics in enzyme catalysis is now widely accepted.\textsuperscript{23}
Figure 5. Practical example of kinetics switching. (A) Mechanism of 1,2-hydroxyl shift, (B) reactant diol inside the enzyme, optimized geometry of the transition state with the arrangements of the charged species as in the enzyme (C) or model calculations (D). (E) Energy decomposition of the forward barrier switches by the point charges, calculated using M06-2X/aug-cc-pVTZ method, all in kJ mol\(^{-1}\). (F) Energy profile of the switching by point charges at the M06-2X/aug-cc-pVTZ level (in each case, reactant is taken as a reference zero). 2 column

Conclusions and Outlook

There is growing evidence that electric field effects on the kinetics and thermodynamics of chemical reactions are a potentially useful tool for manipulating chemical processes, one that is widely harnessed by nature. Our analysis of radical reactions suggests that induced polar effects have a non-directional component due to the enhanced polarizability of resonance-stabilized species. However, the largest effects are observed when the species are appropriately oriented in the electric field so that charge-separated resonance contributors can also be stabilized. This raises the practical question of how to harness such effects in real systems. Clearly, nature achieves this in enzymes by binding the substrate in an optimal manner, relative to the charged residues in the active site. In solution-phase chemistry, we can mimic this by including charged functional groups on the substrate, auxiliary or catalyst, thus controlling the orientation of the electric field, associated with such groups, relative to the reaction centre. The drawback of this approach is that the fields, associated with charged functional groups, are progressively quenched by polar solvents, and hence low polarity solvents are required for maximum effect. Successful practical catalysis have been achieved by balancing the charged species solubility and solvent
polarity. Nonetheless, the use of heterogeneous catalysts and/or oriented external electric fields may be necessary to harness the full extent of electrostatic catalysis.

**Supplementary Material**

Details of the quantum-chemical computations, complete set of computed data and Cartesian coordinates of the investigated species.

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**References**


15 The following charges in these transition states are calculated using Natural Bond Orbital analysis at the M06-2X/aug-cc-pVTZ level: H(0.299)--F(-0.598)--H(0.299) and F(-0.242)--H(0.484)--F(-0.242).


