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Origin and Scope of Long-Range Stabilizing Interactions and Associated SOMO–HOMO Conversion in Distonic Radical Anions

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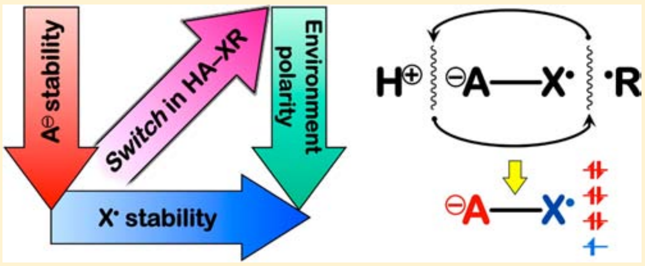
Ⓢ *Supporting Information*



ABSTRACT: High-level quantum-chemical methods have been used to study the scope and physical origin of the significant long-range stabilizing interactions between non-mutually conjugated anion and radical moieties in SOMO–HOMO converted distonic radical anions. In such species, deprotonation of the acid fragment can stabilize the remote radical by tens of kilojoules, or, analogously, formation of a stable radical (by abstraction or homolytic cleavage reactions) increases the acidity of a remote acid by several pK_a units. This stabilization can be broadly classified as a new type of polar effect that originates in Coloumbic interactions but, in contrast to standard polar effects, persists in radicals with no charge-separated (i.e., dipole) resonance contributors, is nondirectional, and hence of extremely broad scope. The stabilization upon deprotonation is largest when a highly delocalized radical is combined with an initially less stable anion (i.e., the conjugate base of a weaker acid), and is negligible for highly localized radicals and/or stable anions. The effect is largest in the gas phase and low-polarity solvents but is quenched in water, where the anion is sufficiently stabilized. These simple rules can be employed to design various switchable compounds able to reversibly release radicals in response to pH for use in, for example, organic synthesis or nitroxide-mediated polymerization. Moreover, given its wide chemical scope, this effect is likely to influence the protonation state of many biological substrates under radical attack and may contribute to enzyme catalysis.

INTRODUCTION

Radical ions are fascinating species that possess dual reactivity, and both modes—radical and ionic—can greatly affect one another. They are involved in many crucial biological processes and play an increasingly important role in a range of practical applications.[1,2] Radical ions can be broadly divided into two families: classic (conventional) in which the charge and unpaired spin are located on the same atom or conjugated fragment (e.g., as formed by electron addition to or removal from a neutral closed-shell species) and distonic, in which charge and spin are spatially separated and which are formed by ionization of zwitterions or diradicals.[3] The former are interesting in their own right and have been extensively studied in relation to their role in the radiation-induced damage of nucleic acids[4] and as a convenient tool for measuring gas- and solution-phase thermochemistry.[5] Seemingly exotic, distonic radical ions are actually quite common, often more stable than their conventional isomers and highly relevant to various research fields ranging from mass spectroscopy[6] to the decomposition of drinking water pollutants, and the photochemical damage of amino acids and peptides.[7]

There is a growing appreciation of the often dramatic differences in the stability and reactivity of distonic radical ions and their conventional radical ion, neutral radical, or charged closed-shell counterparts.[8] These differences can be employed, for example, to preferentially stabilize the classic or distonic form, as illustrated by Pius and Chandrasekhar[9] for the persistent organometallic radical anions $\bullet CH_2{-}XH^-$. More generally, standard through-bond and through-space polar effects can alter not only the stability of the radical but also, by extension, the strength of its bonds or the kinetics of its reactions.[10] Kenttämaa et al.[11] showed that reactivity of a phenyl radical is significantly altered in its distonic cation and anion derivatives. Boyd et al.[12] and later Radom and co-workers[13] found that, in general, protonation of X in $CH_3{-}X$ (where X = OH, NH_2, Hal, CN, NO_2, etc.) shortens and strengthens the bond (against homolytic cleavage) and destabilizes the resulting carbon-centered radical, while deprotonation of X has an opposite effect, typically smaller in magnitude. These properties have been explained in terms of orbital interactions, resonance stabilization and competing heterolytic dissociation. Similarly, N-protonation and N-deprotonation influences N–H bond dissociation energy (BDE) in carbamates.[14] Finally, interactions between charge and spin act both ways, i.e. an unpaired electron can affect the properties of the charged moiety, such as the strength of its conjugated acid. Indeed, abnormally low pK_a values were predicted for the carbon acidity of formic and acetic acid radicals $RCOO\bullet$.[15]

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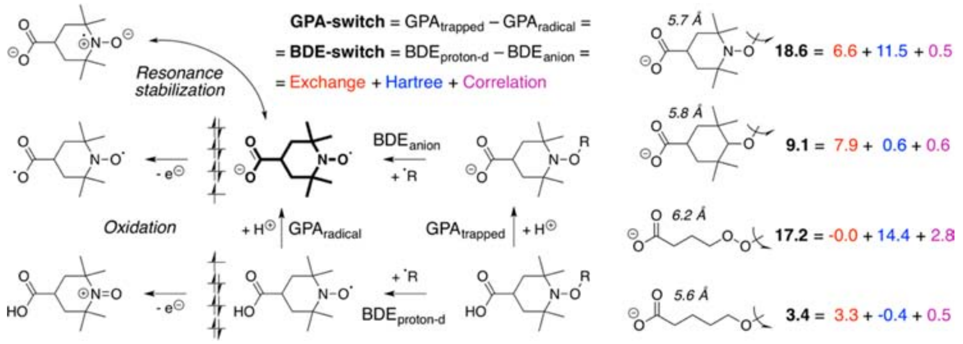


Figure 1. Properties of the 4-carboxylate-2,2′,6,6′-tetramethylpiperidine-*N*-oxyl (4-COO$^-$-TEMPO, in bold) distonic radical anion, a thermocycle relating switches on the radical BDE and the anion's conjugate acid gas-phase acidity (GPA) switch, as well as energy breakdown of the switches in different compounds with similar separation between formal charge and formal radical (in italics). Curly arrows indicate investigated breaking bonds. All BDE-switches (kJ mol^{-1}) were calculated using the G3(MP2,CC)(+)[16] method.

However, such effects of a charge on a radical (and of a radical on a charge) are not unexpected, considering that in the above studies the two moieties are in ultimate close proximity, i.e. separated by only one or two chemical bonds. Such interactions can also exist at larger separations—as much as 10 Å and above—provided, however, that the radical and charge are directly π-conjugated, i.e. polar effects utilizing resonance (orbital overlap). For example, stability of peptide C-centered radicals can be affected noticeably by the protonation at the distal amide nitrogen.[17] Another striking example is the weakening (by over 60 kJ mol^{-1}) of one $RC\equiv C{-}H$ bond in 2,6-diethynylnaphtalene toward the homolytic cleavage due to the deprotonation of the other acetylene group.[18] Furthermore, Ingold et al. discovered surprisingly large effects (~10 kJ mol^{-1} in thermodynamics and over 20 times speed-up in kinetics) of remote hydrogen bonds on the stability and reactivity of benzyl cations and phenoxyl radicals, arising in their charge-separated resonance contributors.[19]

In the absence of π-conjugation and, even more generally, any direct chemical bonding between the charge and radical, through-space polar effects can occur,[10a] albeit they typically remain significant within only a short-range of ~4−5 Å. Such effects are thought to arise in the Coloumbic interactions between the anion or cation and a permanent dipole, associated with the radical moiety, and hence are directional. For instance, C−H bonds can be selectively activated or deactivated toward homolytic cleavage by a remote amine radical cation in *n*-butylamine.[20] Furthermore, polar and inductive field effects in transition states of H-abstraction from the peptide backbone and adjacent side-chain carbons by Cl• contribute to the resistance of these units against radical damage.[21] Finally, the destabilizing effect of a positive charge on a polar resonance contributor $R^1R^2N^{\bullet +}{-}O^-$ of an aminoxyl radical $R^1R^2N{-}O\bullet$ (more commonly referred to as 'nitroxide')[22] was employed to design a pH-switchable agent for nitroxide mediated polymerization (NMP).[23]

However, very recently we have discovered a significant stabilizing interaction occurring between a truly remote negative charge and stable radical (in the absence of any π- or σ-conjugation or hyperconjugation and at long-range separations of over 5 Å, Figure 1),[24] which are not straightforward to rationalize in terms of conventional physical organic chemistry concepts.[25] Specifically, we found that deprotonation of an acid−base group (carboxylate, alkoxide, sulfate) results in an unprecedented stabilization of a remote radical, manifested in ~20 kJ mol^{-1} decrease in dissociation energy (or 4 orders of magnitude in the corresponding $\log K_{eq}$) of its bonds with carbon-centered radicals, as compared with the protonated or nonsubstituted forms. These computational results were verified by comparison with gas-phase thermochemistry measurements, as obtained via mass spectrometry, and the mean absolute deviation between the computationally derived BDE-switches and their experimental counterparts was just 1.7 kJ mol^{-1}.[24]

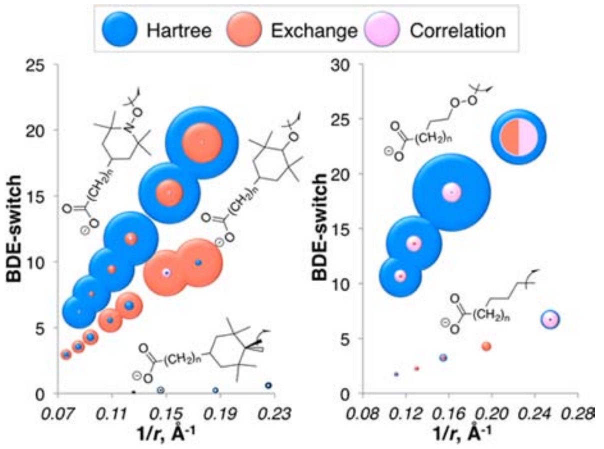


Figure 2. Energy breakdowns of the BDE-switches (*y*-axis, in kJ mol^{-1}) plotted vs inverse separation *r* between formal charge and formal radical (*x*-axis, in Å^{-1}); diameters of the 'bubbles' are proportional to the contributions of different components to the net BDE-switch. Negative contributions in the cyclic alkyl series are shown in white.

We also showed that this unexpected stabilization decays linearly with $1/r$ (where r is the distance between formal charge and formal radical, see Figure 2), does not appear to require chemical bonding between the two moieties (i.e., is a through-space rather than a through-bond effect) and is not associated with orbital overlap or net electron transfer.[26] At the same time, we found that this long-range pH effect on radical stabilization is only significant if the corresponding neutral radical is relatively stable (delocalized) initially (aminoxyl $R^1R^2NO\bullet$, aminyl $R^1R^2N\bullet$, peroxyl $ROO\bullet$). In less stable (more localized) radicals, such as alkoxyl $RO\bullet$, the magnitude of such pH-switches on radical stability, which we define as the BDE-switch = BDE[HA−X−R] − BDE[$^-$A−X−R], is much smaller (less than 10 kJ mol^{-1}). Admittedly, all of these species have dipole contributors to their resonance stabilization, as shown for aminoxyl in Figure 1, and an appropriately placed charge of the correct sign would stabilize such a contributor and thus the radical overall. In addition, polar effects can in principle act on the breaking bonds in the parent closed-shell compounds as well; e.g. a negative charge in the TEMPO ring is likely to destabilize a polar resonance contributor $R^1R^2NO^-\cdots{}^+R$ of an alkoxyamine R^1R^2NO-R, hence further decreasing the corresponding BDE.[27] However, when we decomposed the net BDE-switches into 'Correlation' (difference between net and Hartree−Fock (HF) energy), 'Exchange' (sum of exact α and β exchange contributions to HF) and 'Hartree' (difference between HF and Exchange) components, we found that these traditional directional polar effects arise mainly in the Exchange component of the pH switch. As seen in Figure 2, this component constitutes almost the entire switch in localized RO• radicals and contributes to the ROO• and R^1R^2NO• series. However, these latter[24] systems additionally involve an even greater Hartree contribution.[28] Furthermore, the corresponding alkyl series R•, which lack both the resonance stabilization and the dipole contributors in either form (open- or closed-shell), display negligible pH switching (Figure 2).

Intriguingly, we also showed that this unparalleled effect on stability and reactivity of distonic radical anions is associated with an electronic structure phenomenon known as orbital conversion, in which the singly occupied molecular orbital (SOMO, corresponds to the unpaired electron) is not the highest one (HOMO) because one or more doubly occupied orbitals corresponding to anion have greater energies (see Figure S1 in the Supporting Information [SI]).[24] This is surprising because normally in radicals the SOMO is the HOMO according to the aufbau principle, and such regular orbital occupation is indeed restored upon protonation of the anion. Yet, this behavior is not unprecedented, and has been observed in a very limited number of stable neutral radicals and developed into fascinating molecular electronics applications utilizing oxidation of such 'converted' radicals into high-spin states.[29] Indeed, our orbital-converted distonic radical anions were shown to oxidize preferentially to triplets, whereas the corresponding protonated species yield even-electron products.[24] Hence, stable distonic radical anions represent a new class of orbital converted compounds, and have the added advantage that the orbital conversion can be switched via pH.

This existence of long-range stabilizing interactions between certain radicals and anions is likely to be useful in a broad range of practical applications, from reversibly pH-switchable radical protecting groups in organic synthesis, controlled radical polymerization and polymer end-group modification, that can release or trap radicals in response to pH changes, to reversible pH-switchable orbital conversion and associated oxidation to high-spin states for use in molecular electronics and sensing applications. At the same time, our original report of this unusual and useful effect admittedly raises more questions than it answers.[24]

- *What is the cause of the effect?* Is orbital energy-level conversion the primary cause of the unexpected radical stabilization (and increased strength of anion's conjugated acid), or is it an accompanying feature of the unusually stable distonic radical anions? And if so, can the radical stabilization occur even in the absence of orbital conversion, i.e. caused by a negative point charge or electric field? If the stabilizing effect is polar in nature, can positive charges as well as the negative ones generate it, and can it appear in species without charge-separated (dipole) contributors and hence act nondirectionally?
- *What is the scope of the effect?* Is it limited to combinations of only those few anions and radicals that we have already considered,[24] or is it more common and can occur in, for example, carbon-centered radicals? Does it require radicals with dipoles in their resonance contributors? Can the magnitude of the stabilizing interaction be manipulated by the stabilities of radical and anion?
- *Is this new effect influenced by the external conditions*, such as temperature or binding of anion to cations other than a proton, and is it preserved in the condensed phase?

Answers to these and associated questions are crucial for better understanding of the origin of this new type of long-range interaction between a charge and an unpaired spin, and the dramatic effect it has on both the chemical stability and reactivity of the two moieties and the orbital configuration of the molecule comprising them. Moreover, they shape the practical applications of this discovery and its implications for various biological processes. In this work we use theory to address these important questions and explore the origin and the broad scope of the switching effect on radical and anion stability and the associated orbital reordering.

■ COMPUTATIONAL METHODOLOGY

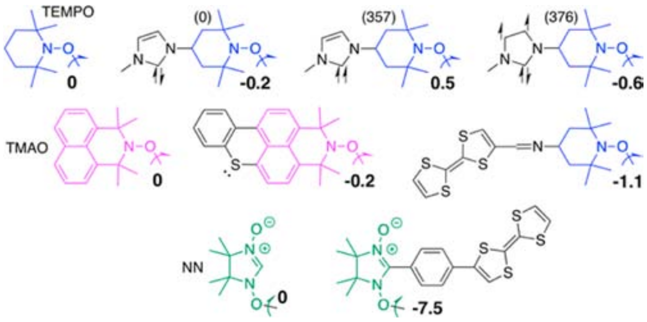
In order to explore the origin and scope of the long-range stabilizing interaction between the negative charge and the unpaired spin in distonic radical anions, and their associated SOMO−HOMO energy-level conversion, we have employed quantum-chemical methods of varying computational cost and accuracy, including *ab initio*, density functional theory (DFT) and several high-level composite G*n* methods. Our benchmark computational methodologies have been extensively tested against experimental data and shown to deliver results to within the chemical accuracy (~5 kJ mol^{-1} for bond dissociation energies and gas-phase acidities, and 0.050 V for redox potentials).[24,30−32] Moreover, both our previous results[24] and benchmarking for a representative test set in this work also reveal generally good agreement between the *switch* values calculated using our benchmark methods and various lower-cost procedures. In many cases this is due to fortuitous cancellation of errors, which is reflected in less cohesive results for the calculated absolute BDEs and GPAs. Nonetheless, of the lower-cost methods examined, M06-2X[33]/6-31+G(d) consistently exhibited excellent performance against the available experimental data and high-level G*n* results for the switches (mean absolute deviation from G3 is only 0.4 kJ mol^{-1}). For consistency all switch values shown and discussed below are calculated with this method, however representative results obtained using more sophisticated methodologies are provided in the SI. Where the absolute BDE and GPA values are involved, we either confirm M06-2X accuracy via benchmarking against high-level composite theoretical methods and, where available, experimental values, or employ the high-level G3(MP2,CC)(+) method[16] instead. Our earlier[24] and present results indicate that there is no appreciable difference between the switch values, calculated from electronic energies and corrected for thermal and entropic effects; thus, throughout this study we present the electronic energy switches, with the exception of the sections in which the thermochemical factors and solvation are discussed. All calculations were performed using *Gaussian* 09,[34] *QChem* 3.2[35] and *Molpro* 2009.1[36] software packages. A complete set of the obtained results and details of all the theoretical procedures, including extensive benchmarking, can be found in the SI.

■ RESULTS AND DISCUSSION

We have employed rigorously benchmarked theoretical methodology to clarify the origin and outline the broad scope of the mutually stabilizing effect of remote anion and radical, accompanied by an orbital energy-level conversion in the corresponding distonic radical anions. Specifically, we have calculated absolute bond dissociation energies (BDEs) and gas-phase acidities (GPAs) of a large array of molecules and molecular complexes comprising chemically diverse acid and radical moieties (coupled with different leaving groups) under various conditions, and ascertained the pH 'switches' on BDEs (from the differences between their protonated and deprotonated forms) and GPAs (odd- and even-electron forms). We have also studied the effects of detached positive and negative point charges on these different radicals. Using these results, which are outlined below, we first determine the contributions of orbital conversion and polar interactions to the stabilizing effect, and then quantify and analyze the roles of radical stability, anion stability, and external conditions on its magnitude.

Role of SOMO−HOMO Orbital Conversion. To date, using quantum-chemical methods ranging from single-determinant DFT to multireference MRPT2 and CASSCF we have shown that deprotonation of a remote acidic group in certain stabilized radicals leads to unprecedented radical stabilization and SOMO−HOMO conversion; in cases where much more muted stabilization is observed, there is no associated orbital conversion.[24] To assess whether SOMO−HOMO orbital conversion is the primary cause of the stabilization or merely associated with it, we have now considered a series of neutral aminoxyls containing nonconjugated aromatic heterocyclic fragments that also display SOMO−HOMO orbital conversion (as shown by quantum-chemical calculations in Figure S3 and Table S3 of the SI and, for selected compounds, evident from their experimentally observed oxidation to biradicals[29a,b,e]) but lack the remote negative charge. Additionally, we considered carbenes, both singlet and triplet, as an alternative neutral source of high-energy HOMO(s). For all of these neutral compounds, BDE-switches were assessed by comparison with the structurally similar but non-SOMO−HOMO converted NN (nitronyl nitroxide), TEMPO (2,2′,6,6′-tetramethylpiperidine-*N*-oxyl), or TMAO (1,1′,3,3′-tetramethyl-azaphenalene-*N*-oxyl) radicals (see Chart 1).

Chart 1. Calculated BDE-Switches (bold, in kJ mol^{-1}) for Various Neutral SOMO−HOMO Converted Aminoxyl Radicals, Containing Either a Heteroatomic or a Carbene Moiety As a Possible Source of High-Energy HOMO(s)[a]



[a]Switches are calculated relative to the structurally similar non-converted radicals NN (green), TEMPO (blue), and TMAO (purple), for which zero values are shown. Relative M06-2X/6-31+G(d) energies for triplet vs singlet carbenes are given in brackets (in kJ mol^{-1}).

Our results in Chart 1 unequivocally indicate that the experimentally[29a,b,e] and/or theoretically detected orbital conversion in such species does not translate to the stabilization of their radical moiety, as reflected in the calculated switches on their methyl BDEs. Thus, it appears that orbital conversion is not a primary physical cause of radical stabilization, quite understandably so, given that molecular orbitals are only constructs, albeit indispensable in explaining and predicting chemical reactivity.[37] At the same time we have shown[24] that orbital reordering does accompany unusually large switching of radical stability in our distonic radical anions, which leads us to conclude that SOMO−HOMO conversion is closely associated with this effect, i.e. both are likely to occur in species combining a stable radical and a relatively destabilized anion. This insight provides a strategy for designing a new class of pH-switchable SOMO−HOMO converted radicals for use in molecular electronics applications.

Nature of the Polar Interaction. The new stabilizing effect appears to require a charge and thus can be formally classified as a polar effect. As discussed in the Introduction, polar effects can act in a number of ways, yet none appears to apply to the observations in the present work. First, there is no *π*-conjugation (or orbital overlap of any other kind) between the charge and radical moieties in our test species; moreover, the BDE-switching is observed even in the absence of any chemical bonding, i.e. in the molecular complexes made of TEMPO radical and simple nonbonded anions, Cl^- and HO^- (Figure 3A). Second, we do not detect any appreciable net electron transfer between the two moieties (see Table S9 of the SI). Third, we have now shown that switches of a similar or even larger magnitude are achieved when molecular anions are replaced with the negative point charges (Figure 3A), which clearly have no formal orbitals associated with them.[38]

Nonetheless, the one possibility that we have not fully ruled out so far is that the observed stabilization is associated with the Coulombic interactions between the charges and permanent dipoles in the radical species. However, there are indications that the effects are not arising in dipole interactions alone. In particular, we have already demonstrated[24] that the switches in the delocalized, aminoxyl radicals are significantly larger than in the analogous (in terms of the dipole contributors) non-SOMO−HOMO converted, more localized, alkoxyl radicals, and originate in the Hartree energy component compared to RO• whose pH-switches arise almost exclusively in Exchange (Figure 2). Moreover, for the traditional directional polar effects involving dipoles, one would expect the effect of the positive charge to be of identical magnitude but opposite in sign to that of the negative charge. However, we find here that, while the net effects of the (+) and (−) charges on the methyl BDE of $R^1R^2NO-CH_3$ are somewhat similar in magnitude (Figure 3B), the switches on the energies of individual species (relative to the infinitely separated point charge and molecule, Figure 3C) reveal that stabilization of the radical by the negative charge is substantially larger for aminoxyl compared to that for alkoxyl and is evidently greater than just an opposite to the effect of a positive charge on it.

Finally, and most importantly, we can now demonstrate that the stabilization persists even in the absence of any permanent dipoles. Specifically, we have found two systems lacking charge-separated resonance contributors in which this stabilization

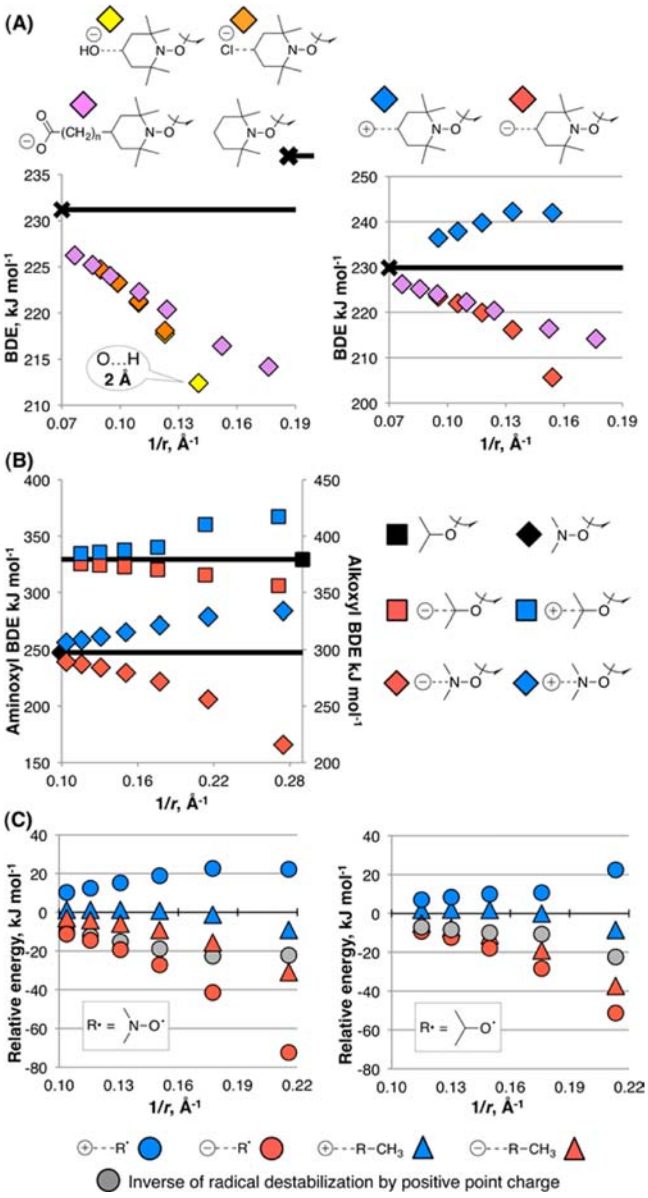


Figure 3. Effect of small anions and detached point charges on aminoxyl and alkoxyl stabilities: calculated absolute BDEs (A,B) and relative energies (C) plotted vs inverse separation between formal charge and formal radical.[39]

nonetheless persists. The first system is an aminyl radical of TEMPO, i.e. TEMP•, in which the BDE-switch is almost 10 kJ mol^{-1} compared with a virtually zero switch for an analogous carbon-centered radical (Figure 4A). Next, we have considered an essentially nonpolar bond, C−C, formed by a stable radical with no dipole character to its resonance contributors—diallyl—and compared it with an analogous fully saturated species, i.e., alkyl (Figure 4A). We find that, while there are slight differences in both the absolute BDEs and the BDE-switches for different conformations of $(CH_2)_n$ chains (Figure 4A, for details see SI), in general there is noticeably larger switching on the methyl BDEs of the resonance stabilized, unsaturated C-centered radicals compared to effectively no switching in correspondingly less stable alkyl radicals. And similarly to aminoxyls and peroxyls (Figure 2), both aminyl and diallyls contain substantial Hartree and moderate correlation contributions to their switches. Furthermore, we find that the stabilizing effect of a negative charge on the energy of a delocalized diallyl radical is also unexpectedly large compared to an alkyl or to an effect of the positive charge (Figure 4B).

All our observations so far suggest that there is a strong relationship between the strength of the pH switching and the degree of radical delocalization. Indeed, when we disrupt the resonance stabilization of a diallyl radical by rotating its π-bonds by 90°, the lost stabilization by a remote negative charge (compared to an infinitely separated −1 charge and radical in a given conformation, Figure 4C), ~6 kJ mol^{-1}, is approximately equal to the overall pH-switch on its methyl BDE at a similar separation (Figure 4A). At the same time, no change in stabilization is observed in the alkyl radical. Finally, in a field of two charges of different signs each arranged linearly at 7 Å from the opposite sides of the radical center (Figure 4D) switching in alkyl is still miniscule. In diallyl two positive charges predictably increase the BDE by ~8 kJ mol^{-1}, but the zwitterion and the pair of negative charges both have an opposite effect that is nearly double (~14 kJ mol^{-1}).

Physical Origin Uncovered. By now we know that the extra stabilizing effect arises primarily in the Hartree energy, suggesting that it originates in the Coulombic interactions. This is also consistent with our observation that our radical stabilization effect is reproduced (and even enhanced) when negatively charged groups are replaced by point charges. In other words, it is an electrostatic effect.

Our initial results[24] demonstrated that the BDE-lowering effect of deprotonation depended linearly on the inverse separation between the charge and the radical ($1/r$). However, those original systems comprise permanent dipoles in both the radical and closed-shell forms, and hence, the overall BDE-switch includes a combination of these standard polar effects as well as the additional electrostatic stabilization of the delocalized aminoxyl radical. In this work we find that in the absence of permanent polar contributors, as in the diallyl system, the linear distance-dependence is observed for $1/r^3$, which is the functional form expected for the energy of a charge−quadrupole interaction. These observations point to the origin of this stabilization effect in Coulombic interactions between the negative charge and the induced quadrupole, caused by repulsion of the electron density to the extremities of the molecule.

It is well-known that, in the absence of charge transfer or permanent dipoles, a remote charge will still stabilize a neutral molecule because the electrons, as delocalized quantum particles, are able to more effectively move away from the negative charge and thus experience less (in absolute terms) repulsion than the attraction experienced by the nuclei. This change in the distribution of the electron density is then reflected in induced dipole and quadrupole moments. However, such effects are generally expected to cancel in a chemical reaction. What we observe in the present work is that they *do not* in cases where the delocalization of an unpaired electron is drastically different between the reactants and products. What our results show is that these induced effects are greater if the radical is strongly resonance stabilized because of its consequently greater polarizability. Indeed, when a negative point charge is placed in the vicinity of the planar diallyl radical, local dipole moments of the carbon−carbon bonds increase by 0.10 and 0.14 electrons. In contrast, this change is only −0.04 and 0.02 for the diallyl radical conformer, in which the resonance is eliminated by 90° C−C bond rotations (see Figure S8 of the SI).

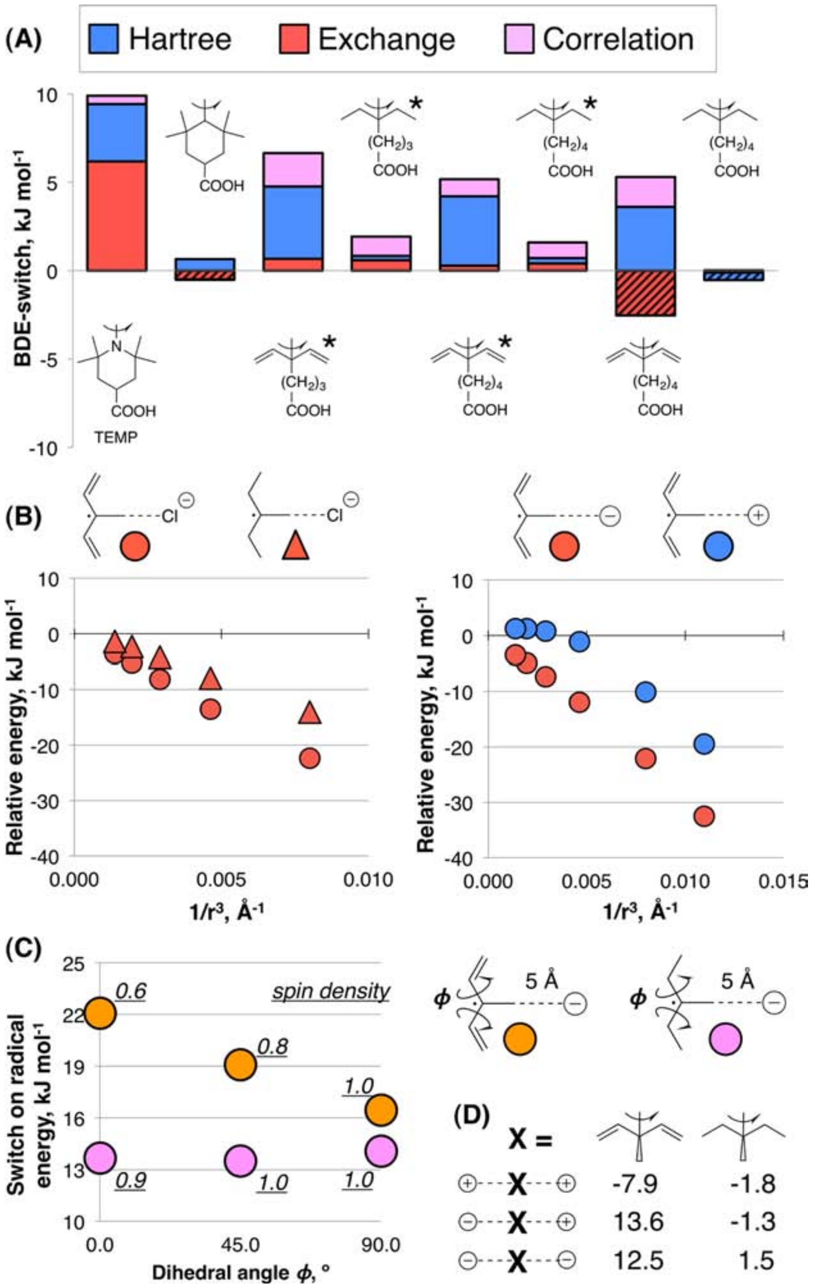
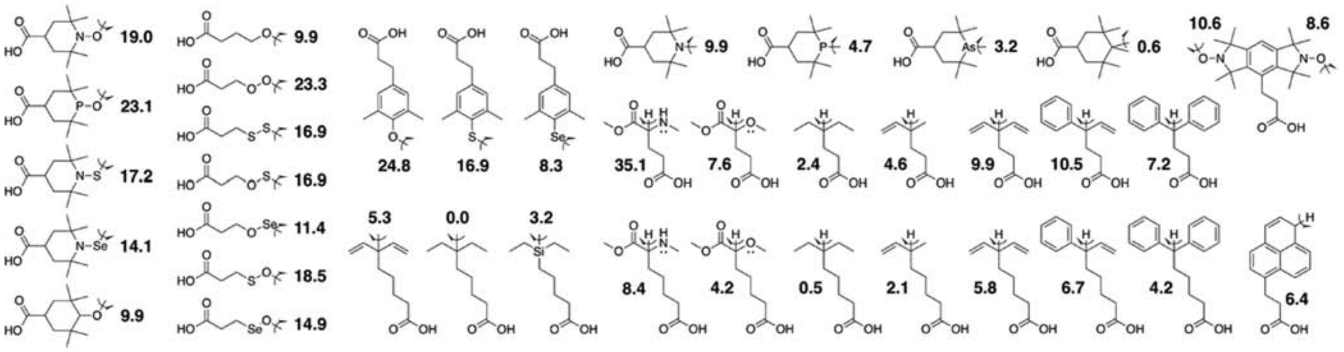


Figure 4. Switching in nonpolar aminyl, diallyl, and alkyl radicals by carboxylate and point charges. Calculated BDE-switches (A: * denotes different conformations of $(CH_2)_n$ chains, striped area refers to cancellation of the negative exchange contribution by the positive Hartree) and relative radical energies (B) at varying distance between formal charge and formal radical, as well as switches on radical energies for different conformers (C) and BDEs (D) of diallyl and alkyl in a field of one- and two-point charges.[39] See also Figure S6 of the SI.

Therefore, over and above conventional polar effects employing orbital interactions or permanent polar contributors, there is another, largely unappreciated yet extremely general and (counterintuitively) nondirectional stabilizing background polar effect of remote negative charge(s) on the delocalized radicals. It is important to note that this additional stabilization can be enhanced or diminished by traditional polar interactions between remote charges and polar resonance contributors to radical stability, to the extent that some radicals can even be destabilized by an appropriately placed negative charge, while others can benefit from surprisingly large stabilization effects of over 30 kJ mol^{-1} at 5 Å separation.

Effect of the Radical. Having shown that the surprising long-range nondirectional interaction between the charge and radical in distonic radical anions is fundamentally different from a conventional polar effect on the dipole resonance contributors and persists in their absence, we proceeded to utilize its correlation with the degree of electron delocalization, i.e. stability of the radical moiety. On the basis of this understanding in the present work we significantly expand the set of switching radicals to the various C, N, P, O, S, Se-centered radicals, and even diradicals (Chart 2). While there is no fully universal measure of the radical stability, for radicals of a similar chemical nature (especially carbon-centered radicals), the BDEs of their C−H bonds tend to be closely related to their intrinsic stabilities.[40] Our results reveal that the switches in a set of C-centered radicals are correlated with the absolute C−H BDEs for a given anion (Figure 5A); more stable radicals

Chart 2. Calculated Switches on Hydrogen and Methyl BDEs (bold, in kJ mol^{-1}) Achieved by Deprotonation of a Remote Carboxylic Group in Different Radicals



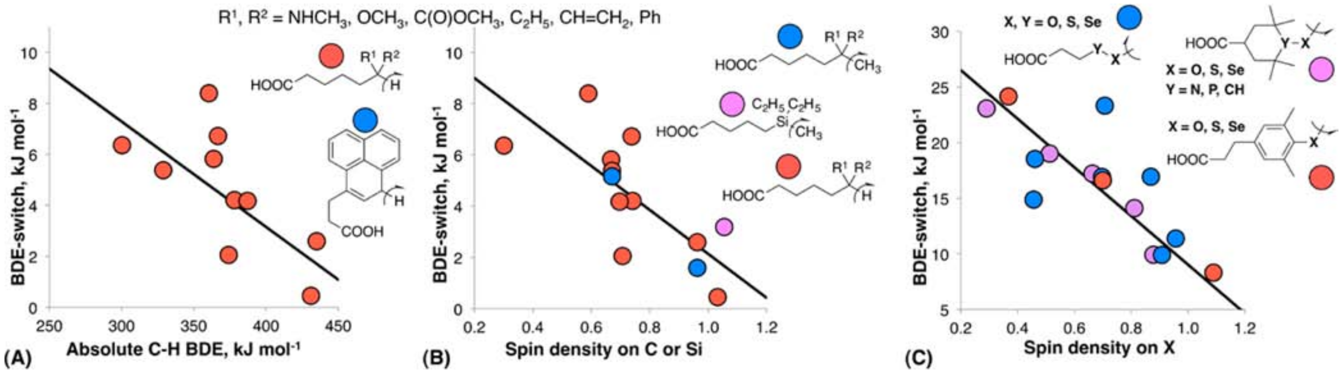


Figure 5. Radicals, more stable initially, are influenced more strongly by remote charges: calculated BDE-switches plotted vs absolute BDEs in protonated form calculated using the G3(MP2,CC)(+) method (A) and M06-2X/6-31+G(d) spin densities on the formal radical center in the protonated form (B,C). Solid black lines are obtained via best-fit regression of the plotted data points.

normally form weaker bonds (lower BDE) and have greater switches from carboxylate deprotonation. Radical stability can also be approximated by spin density; radicals, stabilized by delocalization (e.g., resonance) have less spin density on a formal radical center.[40] Indeed, an inverse correlation 'lower spin density—higher switch' holds for various families of both carbon- and heteroatom-centered radicals (Figure 5A and B). We should emphasize that plots in Figure 5 are not expected to be strictly linear as they encompass radicals of different chemical natures with slightly varying separation between spin and charge.

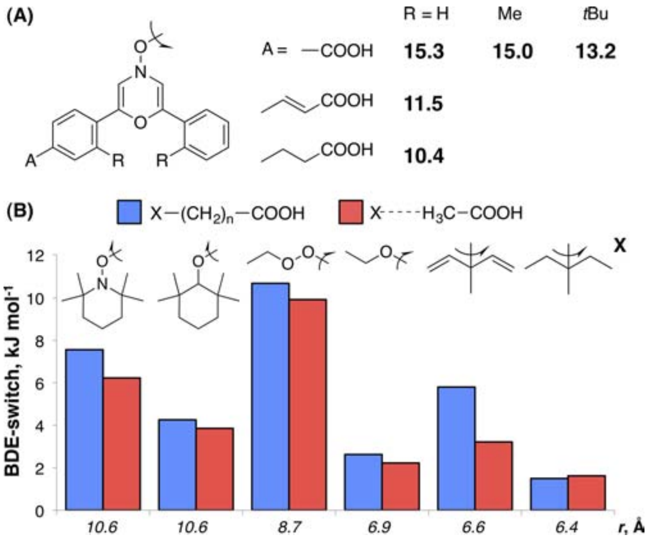
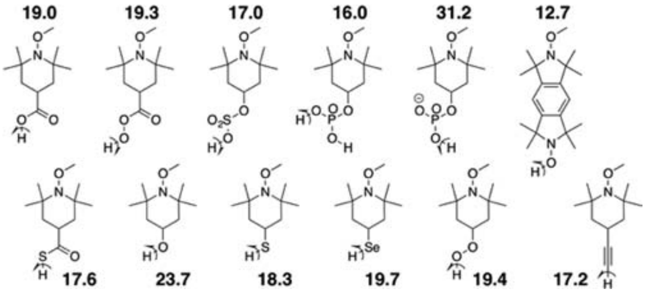


Figure 6. Calculated BDE-switches (kJ mol^{-1}) in oxazine-based aminoxyls (A), carboxylated radicals X•, and molecular complexes consisting of X• and acetic acid arranged geometrically to resemble the bonded analogues (B, separation distances r are shown below the horizontal axis).

The dependence of the switch on the radical stability is most pronounced in a series of chalcophenols (red circles in Figure 5C). The switch is the largest for phenol where radical stabilization via delocalization by an aromatic ring is the greatest. In thiophenol effective overlap between ring π-density (formed from carbon 2p$_z$ orbitals) and sulfur 3p$_z$ orbital bearing an unpaired spin is smaller, as is the switch. Finally, the mismatch in orbital sizes and energies prevents stabilization in selenophenol that accordingly displays the smallest switch (see also spin density plots in Figure S9 of the SI). Furthermore, the steric effects disrupting or enhancing radical stabilization can manipulate the magnitude of the switch. This is shown in Figure 6A for a series of oxazine-based aminoxyls in which direct conjugation between charge and radical is interrupted by steric repulsion between bulky substituents. Even more remarkable is the fact that eliminating π-conjugation between COOH and NO• has little effect on the magnitude of the BDE-switch—a standard polar effect between the conjugated moieties is substituted by an almost equally large new effect between a remote charge and a 'converted' radical (for details see Figure S10 and Table S14 of the SI). Finally, we have confirmed that the discovered interaction does not require chemical bonding between the two moieties because the switches from deprotonation of acetic acid placed in the vicinity of different radicals on their methyl BDEs are only marginally lower than the corresponding BDE-switches in the bonded analogues with identical mutual arrangement of spin and charge (Figure 6B). This minor difference is attributed to the σ-assistance (through-bond transmission) of a standard polar effect.[24,41]

Effect of the Anion. A stabilized radical is necessary but insufficient to trigger orbital conversion and associated stability switching. It needs to be partnered with a negative charge, and now that we understand the physical underpinnings of the switching, we predict that greater effects are to be observed for more localized anions. While radical stability is generally reflected in the strength of the bonds it forms, the thermodynamic stability of an anion A^- (a base) is quantified by the acidity of its conjugate acid HA: more acidic acids (release protons more readily, i.e. have lower GPAs and pK_as) produce more stable anions. Thus, for a given radical a larger BDE-switch is expected when it is coupled to acids with higher GPAs and pK_as (less acidic). To test whether there is indeed a quantitative correlation between GPA-switches and absolute acidities we studied a large set of aminoxyl radicals bonded to a variety of different acidic fragments, including carboxylate, sulfate, phosphate, alcohols, peroxide, and acetylide (Chart 3).

Chart 3. Calculated Switches on GPAs (bold, in kJ mol^{-1}) Achieved by Radical Release via Homolytic Cleavage of a Remote NO−CH_3 Bond in Alkoxyamines with Different Acidic Substituents



From Chart 3 we see that the nature of the acidic group has a strong effect on the strength of the BDE switch, and, when other factors (i.e., radical type, separation between the charge and radical) are controlled for, there is a visible correlation between acidities and GPA-switches (Figure 7A). Thus, the less acidic −OH group affords consistently larger switch for different radicals compared to a more acidic carboxylate (Figure 7B).

Furthermore, the switch for a given radical increases significantly with a larger negative charge; e.g. the BDE-switch can be almost doubled by full deprotonation of a diprotic acid such as phosphate (Chart 3) or if multiple acidic fragments are introduced to the molecule, which is demonstrated for mono- and dicarboxylated TEMPO, PROXYL (2,2′,5,5′-tetramethyl-pyrrolidine-*N*-oxyl), and TMIO (1,1′,3,3′-tetramethyl-isoindoline-*N*-oxyl) radicals in Figure 7C. At the same time, switching is quenched not only by anion protonation, but also by its binding to metal cations, although the magnitude of this quenching depends on the strength of binding in a formed salt,[42] as shown for carboxyTEMPO in Figure 7D.

By analogy, for a given metal cation, moving it away from the carboxylate gradually restores the switch (Figure S12 of the SI). Finally, we have established that orientation of the charged group, relative to the spin, does not affect the switching to any appreciable extent consistent with the through-space nature of the new effect (Table S22 of the SI).

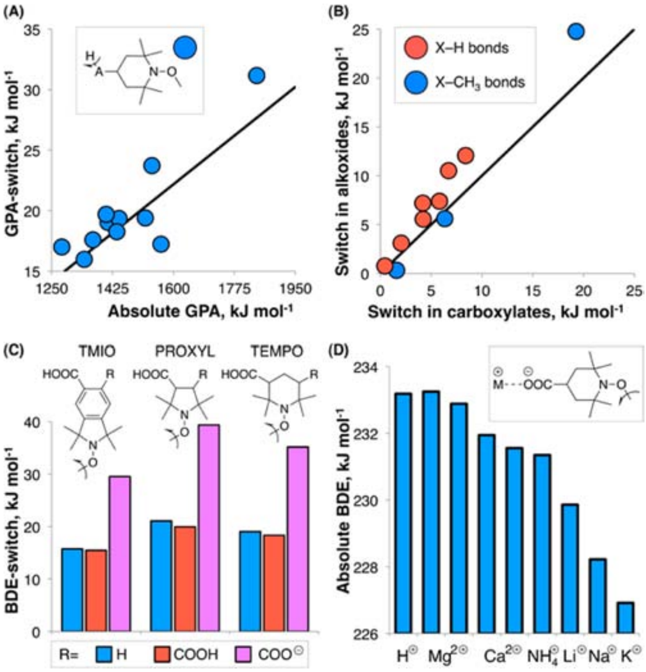


Figure 7. Acidities of initially less acidic groups are influenced more strongly by remote radicals. (A) Calculated GPA-switches plotted vs absolute GPAs in the closed-shell form of species in Chart 3. (B) GPA-switches of COOH and OH groups (X• = aminoxyl, diallyl, alkyl, etc.). (C) BDE-switches of various mono- and dicarboxy aminoxyls. (D) Absolute BDEs of carboxyTEMPO salts (for calcium and magnesium dimer salts (X^-−M^{2+}−X^-) were modeled; thus, BDEs of the two aminoxyls are given for each cation). Solid black lines in (A−C) are obtained via best-fit regression of the plotted data points.[39]

Effect of the Homolytically Cleaved Bond. Polar effects can act not only on the radical species formed by homolytic bond cleavage but also on the bonds themselves if they comprise polar descriptor(s).[43] As shown above, the R^1R^2NO−R bond in the alkoxyamine is stabilized by the resonance with a dipole descriptor $R^1R^2NO^-\cdots{}^+R$ that is further enhanced by a negative charge on an aminoxyl fragment (Figure 3C, left). Similar effects occur in ethers R^1R^2CHO−R (Figure 3C, right). To further investigate how the nature of the breaking bond influences the BDE-switch we studied the effect of the leaving group on the BDE-switches in a series of otherwise identical alkoxyamines and ether analogues (Figure 8). Not surprisingly, the effect of deprotonation is significantly larger on alkoxyamine BDEs compared with ethers, independent of the leaving group, and the energy breakdown again demonstrates a significant Hartree contribution in aminoxyl series complementary to exchange in both sets. However, the switch is not constant in either series—specifically, it is slightly diminished for benzyl and 1-ethoxy-1-oxoprop-2-yl (i.e., radical derived from H• addition to ethyl acrylate) and is noticeably lowered for ester and fluoromethyl leaving groups. We believe that additional effects stabilize these alkoxyamines and therefore decrease their switches.[40] In particular, for R = CH_2Ph resonance form $R^1R^2NO^-\cdots{}^+R$ is enhanced via extra stabilization of the positive charge by the aromatic ring (in addition to intramolecular H-bonding), while for R = fluoromethyl and ester R^1R^2NO−R bond is strengthened via anomeric stabilization.[27,31] In the case of 1-ethoxy-1-oxoprop-2-yl the

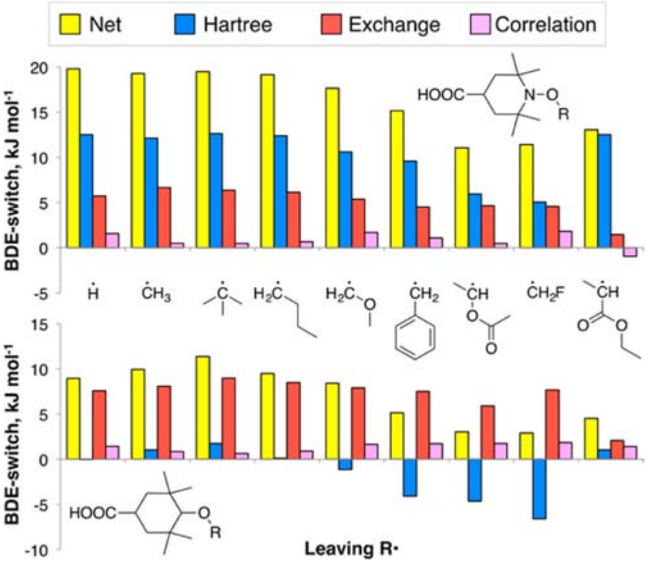


Figure 8. Effect of the leaving group on the switching: calculated BDE-switches of carboxyalkoxyamines R^1R^2NO-R and ethers R^1R^2CHO-R for different R groups.

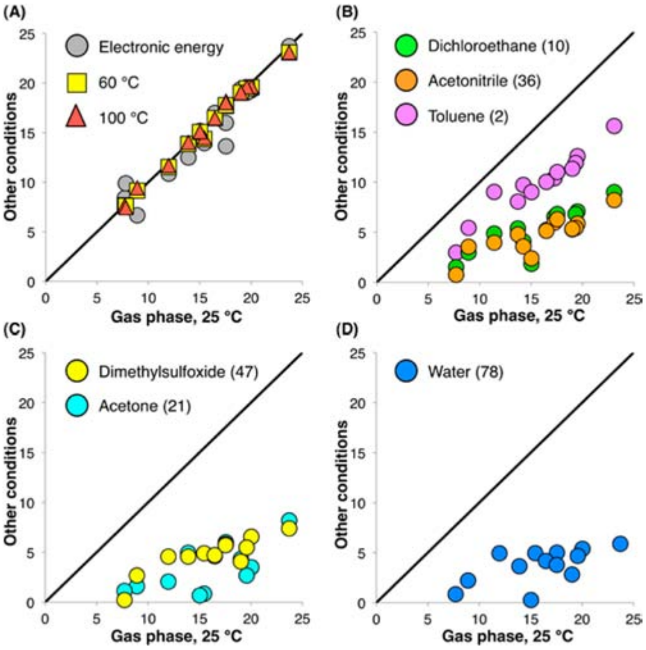


Figure 9. BDE-switches (kJ mol^{-1}) for a set of distonic radical anions calculated from electronic energies and gas-phase free energies at 60 and 100 °C (A) and in various solvents at 25 °C (B−D) plotted vs Gibbs free energy switches in the gas phase at 25 °C (kJ mol^{-1}). Solvent dielectric constants are given in brackets. Free energies of solvation were calculated using the polarizable continuum model (PCM).[44]

intramolecular hydrogen bonding contributes to the switch decrease. All of these interactions are shown explicitly in Figure S13 of the SI. While these additional effects should be taken into account when designing practical applications, the consistently large switches observed in their absence further confirm that there is an underlying stabilization of the radical independent of traditional polar interactions.

Effect of External Conditions. Thus far we have been considering the absolute BDEs and their switches in terms of electronic energies only. However, to be practically valuable the new switching effect has to be preserved, at least partially, under real service conditions. To evaluate the effect of various conditions on the magnitude of the switch we have constructed a test set of the species in Charts 2 and 3 and Figure 8 and calculated their BDE-switches (Figure 9). First, there is very little variation between the BDE-switches calculated from electronic energies and from the gas-phase Gibbs free energies at 25 °C and even less difference between switches at different temperatures (Figure 9A). Yet BDE-switches diminish in solution, although the extent of this attenuation varies. Specifically, in nonpolar organic solvents, such as toluene, the switch is largely preserved and correlates linearly with the gas-phase values (Figure 9B). Increasing solvent polarity leads to further loss in the switching effect (Figure 9B and C), and in highly polar solvents such as dimethylsulfoxide and especially water (Figure 9D) the switches on the BDEs drop below 5 kJ mol^{-1} and are no longer related to the gas-phase values. This is unfortunate but is nonetheless physically intuitive and in line with our understanding of the new effect. Specifically, we have shown that the discovered pH switching requires a relatively destabilized anion, whose stabilization via, for example, bonding to a cation reduces or even turns the effect off (Figure 7). While interactions between anions and nonpolar solvents are typically very weak, more polar solvents afford better solvation of an anion and thus stabilize it. Therefore, in the extreme case of aqueous solvation, no switching is observed, and the residual difference in the BDEs between the protonated and deprotonated forms can be attributed to a combination of (also attenuated) standard polar effects, complicated by other factors, such as an effect of the polarity of the leaving R-group on the change in its solvation energy upon bond dissociation. Moreover, these solvent effects manifest themselves in the orbital configurations of the distonic radical anions involved; in toluene, radicals that afford large BDE-switches still generally display SOMO−HOMO energy-level conversion, although the corresponding orbital energy gap is smaller compared to that in the vacuum, whereas in water they mostly restore an aufbau configuration (see Figure S14 of the SI).

These solvation effects on radical stabilization and orbital switching are likely to limit the general practical applications to low-polarity environments, such as low-polarity organic solvents in synthesis and polymerization, certain enzyme active sites and lipid bilayers in biological systems, and various solid-state environments (including soft materials) for molecular electronics applications. At the same time, depending on the leaving group involved, sizable traditional BDE-switches may be useable under polar environments for specific applications. At a more fundamental level, the results in the low-polarity environments further reinforce the close association between orbital conversion and BDE-switching.

■ CONCLUSIONS

In the present work we have determined the physical origin and the factors triggering and influencing an unprecedented long-range interaction between remote unpaired spins and negative charges in distonic radical anions, associated with the dramatically improved stability of the two moieties and an unusual SOMO−HOMO energy level converted configuration. It is commonly appreciated that individual chemical bonds are affected by an electric field and this effect can even translate to their reactions' energetics, especially if these bonds have a pronounced ionic character or a polar descriptor to their

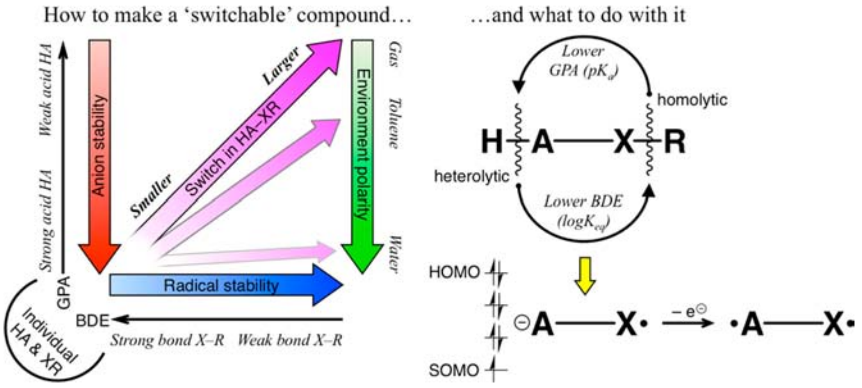


Figure 10. Design and properties of switchable molecules.

resonance.[45] It is also apparent that negative charges can influence radicals via orbital overlap if the two moieties are π- or hyperconjugated, via σ-inductive donation if they are not, or interact through space with the dipoles in the radical resonance descriptors. Combined, these factors form what is traditionally defined in physical organic chemistry as a standard polar effect. Our surprising finding, however, lies outside of this standard notion in that we observe a long-range interaction between a non mutually conjugated anion and radical, which nonetheless greatly affects the stability and reactivity of the two moieties. For many of the species considered in this work this new type of polar effect—electrostatic stabilization of a delocalized radical via deprotonation of a remote acid group forming an anion (i.e., a pH-switch)—complements the standard polar effects acting on the radical itself and/or the bonds it forms via the corresponding dipole resonance descriptors, which allows it to affect the energetics of such radical's reactions by tens of kilojoules per mole. However, the new effect is nondirectional and persists in the background even in radicals that have no charge-separated contributors to their resonance stabilization and thus are not influenced by the standard polar effects.

While we find that the orbital energy conversion in the various distonic radical anions is not the primary physical cause of their enhanced stability because (i) neutral SOMO−HOMO converted radicals exhibit ordinary stability and (ii) the stabilization effect is also afforded by the orbital-less negative point charges, such irregular electronic configurations do appear to closely accompany the extra stabilization. We also show that this stabilization depends on the relative localization of the anion and radical and originates in the charge-induced quadrupole and/or dipole Coulombic interactions, which give rise to the predominant Hartree energy contributions to the switches. Typically, the energy of a molecule decreases in the presence of a negative charge due to charge-nuclei attraction that is, however, partially compensated by the electron repulsion from it. Our results reveal that the latter destabilizing contribution is minimized when the unpaired electron is delocalized (and thus has greater polarizability, i.e. ability to 'move away' from the negative charge) compared with when it is localized either on an atom or in a chemical bond.

This electrostatic effect is influenced by the properties of the radical and anion and the external conditions in a well-understood manner, thus allowing us to frame simple guidelines for designing the 'switchable' compounds (Figure 10). Namely, the combination of an initially stable radical X● (forms weak X−R bonds) and a relatively destabilized anion A^- (conjugated base of a weak acid HA), reasonably proximate (5−10 Å) but nonconjugated with each other, would result in a substantial switch in their compound (or molecular complex) HA−XR. Implementing more than one radical or acid moiety is expected to further increase the switch, and it is likely to be the largest in the gas phase followed by low-polarity organic solvents. X and A in the resulting switchable species, HA−XR, can be radicals and anions of very different chemical natures and physical properties (a vast, albeit not exhaustive, set is given in Charts 2 and 3).

Most importantly, these switchable compounds can provide a great range of useful practical applications as well as have significant implications for biological chemistry (Figure 10). The ability to dramatically lower the homolytic dissociation energy of a remote bond though deprotonation of an acid, i.e. via pH, can be employed to manipulate radical release (and trapping) in synthetic applications. Among other applications, such reagents could be used in the living radical polymerization technique, NMP, and the related polymer end-group modification method, nitroxide radical coupling. Not only would these reagents contain a convenient pH switch, but in contrast to the current pH-switchable NMP agents,[23] their switched form would also be potentially a lot more stabilized than existing control agents, thereby affording better control for a broader range of monomers and at lower temperatures. By releasing radicals under mild, nonreducing conditions, such pH-switchable reagents might even find applications in natural product synthesis and in various analytical and medicinal imaging techniques that involve probing radical concentration, or pH.

The ability of a remote negative charge to stabilize a radical and thus lower the BDEs of corresponding closed-shell compounds can also be thought of as the ability of a remote radical to stabilize a negative charge and lower the pK_a values of acids (compared with those of corresponding closed-shell compounds).[24] Hence, pK_a values measured for closed-shell species or predicted by the contemporary quantitative structure−reactivity relationships that do not account for this newly discovered effect should not be straightforwardly extended to the persistent radicals and radical intermediates, which may become more acidic under radical attack than previously thought. This is particularly pertinent for biological chemistry, given that a number of the species reported to undergo switching in this study are representative of the types of radical intermediates that might be observed when biological substrates, such as peptides and lipids, undergo radical attack in the course of autooxidation. Moreover, certain enzymes appear to entail combinations of charges and radicals in their catalyzing action, and these long-range stabilizing interactions may be important to enzyme catalysis.

Finally, when a switchable compound is both deprotonated at the acid fragment and debonded at the radical fragment, it yields a distonic radical anion with a converted orbital configuration that can thus be oxidized to produce high-spin states with potential applications in the molecular electronics field. Incorporation of a pH switch on orbital conversion offers the extension of such compounds to other applications, including pH sensing. Admittedly, the orbital conversion and radical/anion stabilization effects diminish in high-polarity environments and generally disappear in water; however, many of the aforementioned applications and implications involve non- or low-polarity media, e.g. bulk monomer in polymerization, lipid bilayers and the active sites of enzymes, or solid state (including soft materials).

■ ASSOCIATED CONTENT

Supporting Information

Detailed description and extensive benchmarking of the theoretical procedures, full sets of obtained results, additional charts and figures, energy components, and optimized geometries in the form of Gaussian archive entries for all species in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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in the current study, appears to consistently overestimate the total switch for aminoxyl series but compares well for the alkoxyl series against nonapproximated higher-level composite methods. Therefore, UMP2 method systematically predicts an exaggerated correlation contribution for our converted $R^1R^2NO\bullet$ distonic radical ions but not for their $RO\bullet$ analogues, and in the current work we have used instead M06-2X.

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