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Switching radical stability by pH-induced orbital conversion

Abstract

In most radicals the singly occupied molecular orbital (SOMO) is the highest-energy occupied molecular orbital (HOMO); however, in a small number of reported compounds this is not the case. In the present work we expand significantly the scope of this phenomenon, known as SOMO–HOMO energy-level conversion, by showing that it occurs in virtually any distonic radical anion that contains a sufficiently stabilized radical (aminoxyl, peroxy, aminyl) non- π -conjugated with a negative charge (carboxylate, phosphate, sulfate). Moreover, regular orbital order is restored on protonation of the anionic fragment, and hence the orbital configuration can be switched by pH. Most importantly, our theoretical and experimental results reveal a dramatically higher radical stability and proton acidity of such distonic radical anions. Changing radical stability by 3–4 orders of magnitude using pH-induced orbital conversion opens a variety of attractive industrial applications, including pH-switchable nitroxide-mediated polymerization, and it might be exploited in nature.

Keywords

ph, induced, orbital, stability, conversion, radical, switching

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Switching Radical Stability By pH-Induced Orbital Conversion

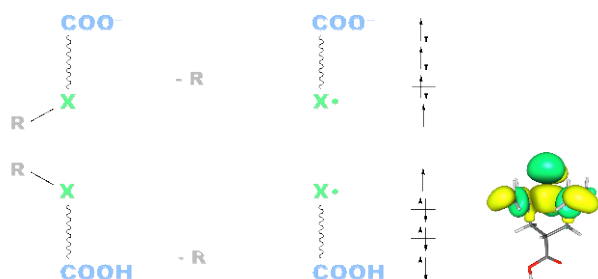
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Abstract

In most radicals the singly-occupied molecular orbital (SOMO) is the highest-energy occupied one (HOMO); however, in a small number of reported compounds this is not the case. In the present work we significantly expand the scope of this phenomenon, known as SOMO-HOMO energy-level conversion, by showing that it occurs in virtually any distonic radical anion containing a sufficiently stabilized radical (aminoxyl, peroxy, aminyl) non- π -conjugated with a negative charge (carboxylate, phosphate, sulfate). Moreover, regular orbital order is restored upon protonation of the anionic fragment, and hence the orbital configuration can be switched by pH. Most importantly, our theoretical and experimental results reveal a dramatically higher radical stability and proton acidity of such distonic radical anions. Changing radical stability by 3-4 orders of magnitude using pH-induced orbital conversion opens a variety of attractive industrial applications including pH-switchable nitroxide mediated polymerization, and might be employed in nature.

The electronic configuration of an atom or a molecule is generally defined according to the aufbau principle: ‘a maximum of two electrons are put into orbitals in the order of increasing orbital energy’¹. Yet, there is growing theoretical and experimental evidence for its violation in quantum dots², transition metal complexes^{3,4} and even fully organic molecules⁵. Moreover, a limited number of recent publications report non-aufbau occupation of molecular orbitals in open-shell molecules (i.e., radicals), where the molecular orbital accommodating the unpaired electron (the singly-occupied molecular orbital, or SOMO) is no longer energetically the highest occupied one (HOMO). Sugawara and colleagues found that molecules combining the stable radical nitronyl nitroxide (NN•) non- π -conjugated with an aromatic heterocycle such as tetrathiafulvalene (TTF) produce triplet biradicals upon one-electron oxidation, suggesting that the HOMO from which the electron is removed is doubly occupied (**1**, Fig. 1a). Consistent with this observation, the measured oxidation potential of NN•-TTF is similar to that of TTF and not NN•. The salts of such “spin-polarized donors” were the first fully organic materials displaying coexistence of conductivity and ferromagnetism, and possess giant magnetoresistance. Their peculiar electronic structure was confirmed by cyclic voltammetry, electron spin resonance, UV-Vis spectroscopy and quantum-chemical calculations.⁶ So-called SOMO-HOMO energy-level conversion has also been observed in nitroxyl metalladithiolates (**2**, Fig. 1b)⁷ and carboxy-TTF crystals (**3**, Fig. 1c)⁸, the latter representing the first fully organic self-doped molecular conductor.

Figure 1 | Reported examples of organic and organometallic systems with SOMO-HOMO conversion. a, Structure and proposed mechanism of “spin-polarization”⁹ of the donor’s HOMO in nitronyl nitroxide – tetrathiafulvalene compounds⁶. **b,** Structure, energy diagram of the density functional theory (DFT) molecular orbitals and scheme of two-electron oxidation of SOMO-HOMO converted TEMPO (2,2’,6,6’-tetramethylpiperidine-*N*-oxyl) bound dithiolate (2-thioxo-1,3-dithiole-4,5-dithiolate) complex of Ni²⁺, accompanied by intramolecular cyclization of an initially formed triplet biradical^{7,10}. **c,** Schematic structure and energy diagram of the CASSCF molecular orbitals of a tetramer of the carboxy-TTF ammonium salt⁸.

All of the known fully organic systems displaying SOMO-HOMO energy-level conversion combine a stable radical moiety that is non- π -conjugated with a donor unit, which provides higher-energy doubly-occupied orbitals. However, the nature of this donor unit (typically, a S- or Se-containing unsaturated heterocycle) does not allow one to control the energetic ordering of the molecular orbitals by external stimuli, and limits the detection (and practical applications) of the orbital conversion almost exclusively to the formation of high-spin states upon oxidation, without providing an insight into the properties of the parent open-shell compound. In the present work we focus on designing new SOMO-HOMO converted compounds with an alternative source of high-energy HOMO(s) that would enable us to switch between the ‘regular’ and ‘converted’ orbital configurations. Using quantum chemistry and gas-phase thermochemical measurements, we significantly expand the scope of SOMO-HOMO conversion to various distonic radical anions that combine a stable radical (aminoxyl, peroxy, aminyl) moiety providing the SOMO and a negative charge, localized on an acid-base fragment (carboxylate, phosphate, sulfate, alkoxide), which provides high energy HOMO(s). These drop below the SOMO upon protonation to the conjugate acid form. Moreover, we show that the manifestation of SOMO-HOMO conversion is not limited to the redox behaviour and that an unprecedented long-range interaction between the unpaired electron and negative charge leads to a dramatic increase in the stability of the radical and acidity of the conjugate acid. The acid-base motif provides an exceptional instrument for switching the orbital configuration and the radical stability, by pH. The fact that SOMO-HOMO conversion can be achieved and switched in a simple manner suggests it might be exploited in nature and incorporated into various industrial applications.

Results and Discussion

Orbital conversion. To test whether distonic radical anions containing a stabilized radical, non- π -conjugated with a negatively charged functional group, display pH-switchable SOMO-HOMO conversion, we considered two distinct types of stable radical species – cyclic sterically-hindered aminoxyls (commonly referred to as ‘nitroxides’,¹ $R_1R_2NO\bullet$) and acyclic primary peroxy radicals ($RCH_2OO\bullet$). To each species we introduced a remote carboxylic acid group that was sufficiently separated from the radical centre to eliminate any possibility of π -conjugation, thereby securing only long-range interactions between the investigated radical and donor moieties. We found that, according to our single- and multireference ab initio and DFT calculations, the carboxylate anion provides higher-energy doubly-occupied MOs, and upon its protonation the regular orbital configuration is restored (e.g., SOMO is HOMO, see Fig. 2a,b and Supplementary Figs S1-S4).

To further confirm their unusual electronic structure, we investigated the gas-phase oxidation of our distonic radical anions (Fig. 2c,d). While COOH-TEMPO (4-carboxy-2,2',6,6'-tetramethylpiperidine-*N*-oxyl radical) **5** is easily and reversibly oxidized into a stable closed-shell oxoammonium cation¹¹, its SOMO-HOMO converted analogue COO⁻-TEMPO **4** favours removal of an electron from its doubly-occupied HOMO resulting in a neutral biradical (triplet ground state, see also Supplementary Fig. S6), rather than a closed-shell zwitterion (Fig. 2c). We should emphasize that comparison of the ionization energies (IEs) of the electrons in the SOMO and HOMO is not rigorously representative of the intrinsic energies of these orbitals. If we consider the reverse process – reduction of the neutral triplet – in which an electron is put in the lower of the two singly-occupied orbitals, Coulombic repulsion between the electrons in the resulting doubly-occupied MO would result in these electrons having a lower IE than the unpaired electron. In fact, we were unable to compare the biradical oxidation product of **6** (Fig. 2d) with a corresponding closed-shell zwitterion, because localization of the positive charge on oxygen

leads to a strongly disfavoured electronic structure, which upon geometry relaxation undergoes rapid decomposition (see Supplementary Fig. S6).

Figure 2 | Distonic radical anions – a new class of species with the SOMO-HOMO conversion. Preferential formation of biradical oxidation products confirms orbital switching in the deprotonated carboxy-aminoxyl and -peroxyl radicals. Shown are M06-2X/6-31+G(d) optimized geometries, spin density plots (for open-shell species only) and dipole moments (μ , in Debye), along with the MCSCF(9,5)/6-31+G(d) molecular orbital configurations of the investigated carboxy-aminoxyl (**a**) and -peroxyl (**b**) radicals in the switched (deprotonated) and non-switched (protonated) forms, as well as the closed-shell (blue) and triplet biradical (red) products of their one-electron oxidation (**c** and **d**). Calculated relative energies (E_r , in kJ mol^{-1}) are given for the oxidation products of distonic radical anions only. See Supplementary Figs S1-S4 for the orbital plots and configurations, and Fig. S6 for the detailed description of the oxidation products.

Radical stability. Having designed free radicals with pH-controlled SOMO-HOMO energy-level conversion, we explored their stability in the switched and non-switched forms. A representative practical measure of radical stability is its bond dissociation free energy (BDFE) with simple carbon-centred radicals such as methyl, $\bullet\text{CH}_3$. We calculated the methyl BDFEs of our carboxy-aminoxyl and -peroxyl radicals in their neutral and deprotonated forms in the gas phase at 25°C and found that deprotonation of the carboxylic group (and thus switching from regular to the converted orbital configuration) weakens their bonds with $\bullet\text{CH}_3$. The magnitude of this BDFE-switch, which we define for a radical $\text{COOH-X}\bullet$ as $[\text{BDFE}(\text{COOH-X-R}) - \text{BDFE}(\text{COO}^-\text{-X-R})]$, is ca. 20 kJ mol^{-1} for the aminoxyl and 15 kJ mol^{-1} for the peroxyl (or approx. 3.5 and 2.0 orders of magnitude in K_{eq} , see also Supplementary Table S1). Thus, deprotonation and associated SOMO-HOMO conversion in these radicals boosts their stability – an unexpected finding considering the spatial separation and the absence

of any obvious π -conjugative interaction between the anionic and radical moieties. In this regard, our calculations confirm that there is no spin density on the remote anion (Fig. 2a,b).

Radical stability is influenced by polar effects^{12,13}, which, at long range, act primarily through-space rather than through-bond¹⁴. For example, the stability of the aminoxyl radical is affected by resonance between its two forms, **I** and **II** (Fig. 3a)¹⁵. The recently proposed pH-switchable nitroxide mediated polymerization (NMP) agent **8**¹⁶ employs polar effects by introducing several basic groups (Fig. 3b)¹⁷, which upon protonation destabilize **II** and thus the radical overall. This results in slower decomposition of the corresponding alkoxyamines, indicating an increased strength of their NO-R bonds. However, the magnitude of this pH-switch (< 15 fold) is significantly smaller than the pH effects observed in our SOMO-HOMO converted species (> 2000 fold), despite the fact that the charge in **4** is more distant from the radical centre than in **8** (Fig. 3b).

Nevertheless, deprotonation of COOH group resulting in an electron-donating carboxylate anion is expected to stabilize **II** in our trial aminoxyl, and possibly act in a similar way in the peroxy radical. Therefore, to determine whether this standard polar effect could account for the observed BDFE-switching, we employed the elegant procedure of Grob et al., who studied the effect of amino group protonation on the COOH pK_a in the homologue series $^+NR_3(CH_2)_nCOOH$ via comparison to a reference system $CR_3(CH_2)_nCOOH$ that is structurally very similar but lacks a polar contribution¹⁸. In our case we chose reference compounds that were structurally similar but lacked orbital conversion. Thus we have chosen an alkoxy radical as our reference system for both the aminoxyl ($R_1R_2NO\bullet$ is substituted by $R_1R_2CHO\bullet$, **9**) and the peroxy ($RCH_2O\bullet$, **11**, instead of $RCH_2OO\bullet$) distonic radical anions and confirmed the absence of the orbital conversion in either COOH protonation state using the same multireference methodology as above (Fig. 3c, see also Supplementary Fig. S5). We then calculated the gas-phase BDE-switches (in electronic energy terms to avoid complications from thermal or entropic contributions) for these four homologue series (see Fig. 3d,e and Supplementary

Tables S2-S3). Although our chosen theoretical methods include implicit dispersion, we have additionally evaluated its contribution to the BDE-switches using standard dispersion corrections for DFT¹⁹. In all cases conformations of the (CH₂)_n chains were kept anti to eliminate the effects of hyperconjugation and hydrogen bonding, except where such conformations were not local minimum energy structures (see Supplementary Figs S7-S8).

We find that all of our radicals exhibit some degree of pH switching, reflecting a modest polar effect on radical stability, however the switch is significantly larger in the corresponding SOMO-HOMO converted systems (by 10-15 kJ mol⁻¹ at 5 Å separation). Interestingly, in these latter species the BDE-switch at 5 Å separation between the radical and the carboxylate group exceeds 20 kJ mol⁻¹, and linearly decays with 1/*r*, as could indeed be expected for a polar effect¹⁸. However, the energy breakdown reveals significant contributions of correlation and Hartree components to the magnitude of the BDE-switch, which also depend linearly on 1/*r*, non-surprisingly considering that the molecular Hamiltonian operator contains 1/*r* two-electron terms²⁰. In the reference non-SOMO-HOMO converted alkoxyl analogues of the aminoxyl radicals, correlation and Hartree components are virtually zero, and the pH-switch arises almost exclusively from the Hartree-Fock exchange, which is similar in magnitude to that in the switched series and also decays as 1/*r*, thus providing a measure of the standard polar effect contribution (Fig. 3e, right). The situation is somewhat complicated in the case of acyclic alkoxyl series (Fig. 3d, right) due to the conformational changes around R₁CH₂–CH₂O• bonds and the related hyperconjugation of the radical centre with the C–H bonds (see Supplementary Fig. S7), but it is clear that past 5 Å separation the BDE-switch does not exceed 5 kJ mol⁻¹. We also note that the dispersion contribution is negligible in all series (see Supplementary Table S4).

Figure 3 | pH-switching of radical stability. Comparison between the BDE-switches in converted (carboxy-aminoxyl and -peroxyl) and non-converted (carboxy-alkoxyl) systems reveals that both decay with the

separation distance but originate in different energy components. **a**, Two resonance forms of an aminoxyl radical. **b**, Switching of aminoxyl stability by pH-induced standard polar effects¹⁸ (blue numbers are the distances between the two coloured atoms in the M06-2X/6-31+G(d) optimized geometries, Å) acting on the resonance forms in **a**. **c**, Structures, M06-2X/6-31+G(d) spin density plots (for open-shell species only) and dipole moments (μ , in Debye), as well as MCSCF(9,5)/6-31+G(d) molecular orbital configurations of the reference radicals in protonated and deprotonated forms. **d-e**, Energy decomposition of the calculated BDE-switches (G4(MP2)-6X for acyclic series and ONIOM approximation for the cyclic series, gas phase, kJ mol^{-1}) in the pairs of homologue series of trial and reference radicals, plotted against the number of methylene units n and inverse of distance r between the radical centre and the carboxylic carbon; “Correlation” is the difference between total and Hartree-Fock energies, “Hartree” is the sum of Coulomb, kinetic and potential energy contributions to the HF energy, “Exchange” is the sum of alpha and beta exchange contributions to the HF energy, for details see Methods and Supplementary Information.

Finally, σ -assistance represents another possible type of through-bond interaction between the remote negative charge and radical centre²¹⁻²³. To assess its contribution to the pH switching, we compared carboxy-TEMPO $n=4$ homologue **15** in the extended-chain conformation to its lowest gas-phase energy conformer **14**, in which the anion is closer to the radical moiety (Fig. 4a). The calculated absolute methyl BDEs of the deprotonated alkoxyamines follow the $1/r$ dependence (Fig. 4b). We also constructed a complex of TEMPO and acetic acid **16**, structurally resembling the $n=4$ extended chain conformer **15**, but clearly free of any through-bond interaction. Its calculated absolute BDE also sits on the $1/r$ line (Fig. 4b), and the BDE-switch is only 1.4 kJ mol^{-1} lower than that of the corresponding chemically bonded system. These observations confirm the primarily through-space nature of the pH effect on the radical stability associated with the orbital conversion and reveal only a minor contribution from σ -assistance. However, σ -assistance might be contributing to the observed

oscillations of the BDE-switch (and in particular its exchange component) in Fig. 3d²⁴ and affecting the electronic configuration of the biradical oxidation products (Fig. S6)^{21,25}.

Figure 4 | Assessing the σ -assistance effect. The through-space rather than through-bond nature of the pH-switching effect on radical stability is illustrated by the similarity of the BDE-switches in the two systems with and without direct chemical bonding between radical and anion. **a**, M06-2X/6-31+G(d) optimized geometries and BDE-switches (in electronic energy terms, kJ mol^{-1}) of non-substituted TEMPO (top left), carboxy-TEMPO $n=4$ homologues in extended chain (top right) and lowest energy (bottom left) conformations, and the corresponding non-bonded TEMPO...CH₃COO⁻ complex (bottom right). **b**, Calculated methyl BDEs (kJ mol^{-1}) of the species in **a** and full carboxy-TEMPO homologue series (extended chain conformers with $n=0-10$); for details see Methods and Supplementary Information.

Experimental verification. It is important to appreciate that our pH-induced orbital switching is associated with both the stability of the radical moiety and the acidity of the carboxylic acid group. This is clearly demonstrated by a simple thermocycle that relates the difference in the gas-phase enthalpy of deprotonation (i.e., the gas phase acidities, or GPAs) of carboxy-aminoxyl and its alkoxyamine to the difference in the gas-phase BDEs of the same alkoxyamine in its protonated and deprotonated forms (Fig. 5a, see also Supplementary Fig. S9). Hence we can use the values of the GPA-switches, determined using the kinetic method, as direct measures of our theoretically predicted BDE-switches. To measure the GPA difference, we synthesize a dimer complex $[A^-H^+B^-]$ using negative ion electrospray ionization and subject it to collision-induced dissociation (CID) in a tandem mass spectrometer. If AH is more acidic than BH, the dissociation equilibrium favours the $A^- + BH$ product channel, and thus by comparing the abundances of the A^- and B^- product ions we can determine the GPA-switch for this pair (for details see Supplementary Information). To assess the

BDE-switch in the carboxy-aminoxyl, we prepare a proton-bound dimer where A is that aminoxyl and B is its alkoxyamine. This is illustrated for the carboxy-TEMPO **4** and its methyl alkoxyamine **17** in Fig. 5b, from which it is immediately obvious that **4** is more acidic than **17** (positive GPA-switch), in agreement with our calculations (positive BDE-switch).

We repeated these experiments for the benzyl and fluoromethyl alkoxyamines of carboxy-TEMPO and carboxy-PROXYL (3-carboxy-2,2',5,5'-tetramethylpyrrolidine-*N*-oxyl radical), and in all cases the aminoxyl radical is more acidic than the analogous alkoxyamine, which confirms that the BDE-switch is due to an effect acting on the radical and is relatively independent on the nature of the leaving R-group. Further, according to our results carboxy-PROXYL is more acidic than carboxy-TEMPO, in agreement with their experimental pK_a values¹⁵. We additionally studied various combinations of alkoxyamines primarily for benchmarking purposes (Supplementary Fig. S10 and Table S7). There is an excellent agreement between experimental and theoretical results for the full set of dimers (Fig. 5c,d), with a mean absolute deviation of only 1.7 kJ mol⁻¹. In order to obtain the absolute GPAs, we performed similar experiments on the dimers containing the aminoxyl or alkoxyamine of interest and a reference acid with known GPA, benzoic acid. In this manner we obtained GPAs of 1411 kJ mol⁻¹ for carboxy-TEMPO **4** and 1430 kJ mol⁻¹ for its methyl alkoxyamine **17**, which are (i) in exceptional agreement with our theoretical calculations (1414 kJ mol⁻¹ and 1432 kJ mol⁻¹ respectively at 25°C) and (ii) consistent with the GPA-switch of 13.7 kJ mol⁻¹ determined from direct examination of a dimer formed from this pair (Fig. 5c).

Due to the transient nature of peroxy radicals these experiments cannot be applied to verify our calculations on the carboxy-peroxy radicals, because their absolute BDEs are significantly higher and competitive dissociation processes are expected to contaminate the results. Nevertheless, we were able to confirm their increased stability in the deprotonated form indirectly, by considering their formation *via* oxygen addition to the corresponding carbon-centred radicals (that are not stable enough to sustain

orbital conversion themselves). According to our calculations, addition of oxygen to the $^{\ominus}\text{OOC}-(\text{CH}_2)_3\text{CH}_2\bullet$ radical is more exoergic (by 20 kJ mol^{-1} in the gas phase at 25°C) than to $\text{HOOC}-(\text{CH}_2)_3\text{CH}_2\bullet$, because, as shown above, distonic peroxy radical anion is stabilized and displays SOMO-HOMO conversion. Experimental rate constants of oxygen addition to substrates of a similar chemical nature are equal to $1.8 \times 10^{-10} \text{ cm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (representing a reaction efficiency of 30% at 34°C)²⁶ for 4-carboxycyclohexyl and $1.3 \times 10^{-11} \text{ cm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (or 3% at 25°C)²⁷ for regular cyclohexyl radicals (see Supplementary Information). Considering that oxygen addition is a fast process with an early transition state, this *ca.* 15-fold difference in reactivity indicates substantial stabilization of the anionic (versus neutral) radical product.

Figure 5 | Experimental proof of the BDE-switching by pH-induced orbital conversion. **a**, Thermocycle relating the difference in the BDEs of the switched and non-switched aminoxyl radicals with the difference between their GPAs and the GPAs of the corresponding alkoxyamines; all reported quantities are in enthalpic terms. **b**, M06-2X/6-31+G(d) optimized geometry and spin density plot, as well as the CID negative-ion mass spectrum of the $[\text{A-H-B}]^-$ dimer (A = carboxy-TEMPO **4** and B = carboxy-TEMPO-methyl **17**) at the collision energy of 10 units. Optimized COO-H bond lengths in the dimer are equal to 1.33 \AA for A and 1.11 \AA for B. **c** and **d**, Calculated BDE-switches (gas-phase, 25°C) plotted against experimentally measured GPA-switches for carboxy-TEMPO *vs.* its alkoxyamines, carboxy-PROXYL *vs.* its alkoxyamines, carboxy-PROXYL *vs.* carboxy-TEMPO and different combinations of alkoxyamines (only one example is shown), for details see Supplementary Information.

Scope. SOMO-HOMO energy-level conversion can thus be achieved by combining a stable radical moiety (aminoxyl and peroxy) with a remote negative charge (carboxylate) and is directly related to an increased radical stability, as illustrated by the lower X–R BDEs (where X is the switched radical). Our

GPA experiments indicate that the effect of the R-group on this BDE-switch is mild (Fig. 5c), further confirming that it originates primarily as an effect on the stability of $X\bullet$ (rather than $X-R$). We also explored the effect of other anionic groups, such as thiocarboxylate, phosphate, sulfate and alkoxide, using TEMPO **13** as a substrate (**18-21** in Fig. 6a). In all cases there is a significant BDE-switch, and hence pH-switching and associated orbital conversion is not limited only to the carboxylate donor unit.

These results prompted us to investigate the possibility of SOMO-HOMO conversion in the deprotonated nucleic acid radicals, formed as a result of oxidative damage *via* hydrogen atom abstraction by, for example, hydroxyl radical. While abstraction from the sugar moiety yields relatively unstable carbon-centred radicals, not expected to undergo orbital rearrangement, abstraction from the base leads to highly stable delocalized radicals with potential for SOMO-HOMO conversion (Fig. 6b). According to the calculated BDEs, this is exactly the case with both the model DNA **22** and RNA **23** radicals – abstraction from the 4th position of the sugar ring is not affected by the protonation state of the phosphate groups, whereas deprotonation increases the vulnerability of the base moiety by over 35 kJ mol⁻¹. Furthermore, we find that upon vertical ionization regular sugar-derived radicals form closed-shell zwitterions, whereas converted base-derived radicals favour biradical species, similarly to the carboxy-aminoxyl radicals (see Supplementary Fig. S12). Indeed, the radicals formed by H-abstraction from the base nitrogen atoms are among the major detected products in model experimental and computational studies²⁸. This provides a peculiar insight into nature's way of protecting these damage-susceptible moieties by locking them inside the double helix.

Figure 6 | SOMO-HOMO conversion in various substrates. pH-switching of orbital stability is observed in anions other than carboxylate and not only aminoxyl or peroxy, but also aminyl radicals, as demonstrated by the calculated BDE-switches (*italics*, in electronic energy terms, kJ mol⁻¹) in TEMPO-CH₃ substituted with different anionic groups (**a**, using G3(MP2,CC)(+) method) and in model DNA **22** and RNA **23** sugar and base (guanine)

moieties (**b**, using ONIOM approximation to the G3(MP2)RAD energies at the MP2/6-311+G(3df,2p) level of theory); see Supplementary Tables S9-S10 for details.

Conclusions

SOMO-HOMO conversion appears to be more common than previously thought, occurring whenever a molecule contains a sufficiently stabilized radical (such as aminoxyl, aminyl or peroxy), non- π -conjugated with a negative charge, localized on an acid-base fragment (carboxylate, phosphate, sulfate, alkoxide). Protonation of the anionic fragment restores the regular orbital configuration, and hence SOMO-HOMO conversion is easily manipulated by pH. Moreover, the orbital conversion is associated with a dramatic increase in the stability of the radical species, significantly weakening its bonds with hydrogen and carbon-centred radicals. This implies that mass-spectrometry studies of distonic radical anions should be interpreted with caution. Provided the effect is preserved in solution, it also suggests a range of tempting industrial applications, such as pH-switchable agents for nitroxide-mediated polymerization¹⁶, or, more generally, a convenient protecting group for carbon-centred free radicals. Furthermore, our preliminary findings suggest that SOMO-HOMO conversion also occurs in nucleic acid radicals, and given its through-space nature, it may be relevant in enzyme catalysis. These findings reinforce the notion that ‘the chemistry of radical ions is perhaps more complex than is generally appreciated’²⁹.

Methods

Theoretical Procedures. All ab initio and density functional theory calculations were performed using Gaussian 09³⁰, QChem 3.2³¹, Molpro 2009.1³² and GAMESS 2010³³ software packages. Geometries of all species, with the exception of the products of vertical oxidation, were fully optimized using M06-2X/6-31+G(d) and, selectively, BMK/6-31+G(2df,p) methods, and the frequencies were calculated at the same levels and scaled by recommended scale factors³⁴. For the homologue series, (CH₂)_n chains were kept in the extended conformations, while full conformational searches at a resolution of 60° were performed for all other species in the present work. Accurate electronic energies were calculated using a variety of methods ranging from DFT and MP2 to high-level composite G3(MP2)RAD,³⁵ G3(MP2,CC)³⁶ and G4(MP2)-6X³⁷ procedures. Calculations on radicals were performed with an unrestricted wave function except in cases designated with an “R” prefix where a restricted open-shell wave function was used. For large systems (over 15-20 heavy atoms), where high-level composite calculations were not feasible computationally, a double-layer ONIOM-type procedure was applied instead and the MP2/6-311+G(3df,2p) method was used for the full system. Reported thermochemical values (gas-phase bond dissociation energies, acidities and relative ionisation energies) were calculated in conjunction with the gas-phase entropies and thermal corrections at 25°C, obtained using standard textbook formulas for the statistical thermodynamics of an ideal gas under the harmonic oscillator approximation³⁸ in conjunction with the optimized geometries and scaled frequencies. These methods have been extensively tested against experimental data and shown to deliver results to within the chemical accuracy (*ca.* 5 kJ mol⁻¹ for bond dissociation energies and 0.050 V for redox potentials)^{11,39,40}. We should emphasize that in the majority of cases studied here both the absolute values of the aforementioned thermochemical parameters and, more importantly, their relative differences (e.g., BDE- and GPA-switches) vary within only a small range of 7 kJ mol⁻¹ depending on the theoretical method without affecting the reactivity trends and our conclusions.

Ordering and occupation of molecular orbitals of the various radical species were evaluated at a range of theoretical levels, including inexpensive single-reference HF, DFT and MP2 calculations with different basis sets, as well as more sophisticated multireference MCSCF and MRPT2 simulations (as implemented in GAMESS)³³ using 6-31+G(d) basis on a (9,5) active space constructed of occupied orbitals only, and CASSCF/STO-3G method (as implemented in Gaussian 09)³⁰ on a (7,8) active space containing both occupied and virtual molecular orbitals. The adopted approaches were found to accurately describe the orbital configuration in several earlier studies of different SOMO-HOMO converted radicals⁶⁻⁸. We find that orbital arrangements obtained using single-reference methods are strongly dependent on the method, basis set, type of wave function and even software code⁴¹. Nonetheless, the two conceptually different multireference approaches that we have used both confirm the predicted SOMO-HOMO energy-level conversion in our trial carboxy-aminoxyl and -peroxyl radicals, as well as its absence in their protonated forms and in the reference alkoxy species. A detailed description of the theoretical procedures and expanded set of results are given in the Supplementary Information.

Experimental Procedures. Alkoxyamines were synthesized from aminoxyl radical precursors by a standard literature procedure⁴². Equimolar mixtures of aminoxyl radical and alkoxyamine were prepared pairwise in methanol to a final concentration of *ca.* 10 μM . Proton-bound dimers were generated by negative ion electrospray ionization upon infusion of these methanolic solutions at a rate of 5 $\mu\text{L min}^{-1}$ into the ion source of a Waters QuattroMicro (Manchester, UK) triple quadrupole mass spectrometer. The mass spectrometer was operated in the negative ion mode, and controlled by Micromass MassLynx software (Version 4.1). The capillary voltage was set to -3.0 kV, cone voltage - 20 V, source temperature 80°C and desolvation temperature 110°C, to optimize the production of desired proton-bound cluster ions. Nitrogen was used as the drying gas, at a flow rate of 300 L h^{-1} while collision-induced dissociation experiments used laboratory frame energies of 5-25 V as required

and argon as the collision gas (3.0 ± 0.1 mTorr). All mass spectra and ion abundance ratios reported here are the averages of at least 200 cumulative scans. The kinetic method⁴³⁻⁴⁶ was used for the determination of relative and absolute gas phase deprotonation enthalpies based on the relative ion abundances resulting from competitive dissociation of a mass-selected cluster ion. The application of this method to data from this instrument has previously been described⁴⁷ and further details of this analysis are provided in the Supplementary Information.

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Author Contributions

GG and MLC designed the project and co-wrote the manuscript, with assistance from the other authors. GG carried out the computational studies, and GG and MLC analysed the computational results. SJB and DLM designed and analysed the experimental studies, which were carried out by DLM.

Additional Information

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