

SOMO–HOMO Conversion in Distonic Radical Anions: An Experimental Test in Solution by EPR Radical Equilibration Technique

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S Supporting Information

ABSTRACT: Bond dissociation energies (BDEs) of O–H bond in the hydroxylamines deriving from neutral and deprotonated forms of 4-carboxy-TEMPO have been measured in solution (acetonitrile and dimethylsulfoxide) by using the EPR radical equilibration technique. The experimental results confirm that stabilizing interaction between a remote negative charge and stable radicals, occurring in gas phase, is completely lost in polar solvents as predicted by theoretical computations.

Knowledge of the energy required to break bonds and energy released on making bonds is basic to our understanding of chemical reactivity. This is definitely true for reactions involving free radical intermediates. For these reactions, knowledge of the dissociation energies (BDEs) of the bonds that are being broken and made is generally sufficient to predict their thermochemistry and thus their feasibility.¹ Only in very selected examples, free radical reactivity can be significantly modulated by changing the nature of the medium^{2–4} or by noncovalent interactions.⁵

In this context, the recent report of Coote et al., who reported the significant stabilizing interaction occurring between a truly remote negative charge (such as carboxylate, sulfate or phosphate) and stable radicals (aminoxyl, peroxy or aminyl) in the absence of any π - or σ -conjugation or hyperconjugation and at a long-range separations of over 5 Å, is of great relevance.^{6–8}

This effect was ascribed to an inversion of SOMO and HOMO energy levels. While in most radicals the SOMO represents the highest energy occupied molecular orbital, in the presence of non- π -conjugated negative charge this is not the case, and the SOMO orbital is no longer energetically the highest occupied molecular orbital. The stabilization upon deprotonation is largest when a highly delocalized radical is combined with a less stable anion (i.e., the conjugate base of a weak acid) and is negligible for highly localized radicals and/or stable anions.

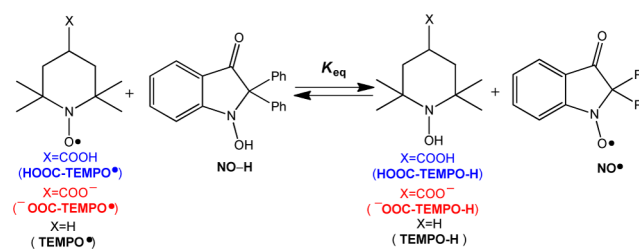
As a relevant case, it was shown by performing both theoretical calculations and CID negative-ion mass experiments that in the gas-phase 4-carboxy-2,2,6,6-tetramethylpiperidin-N-oxyl (HOOC-TEMPO•) is stabilized by ~ 5 kcal mol⁻¹ when switching from the neutral to the deprotonated form (•OOC-TEMPO•). This effect is responsible for a comparable decrease in dissociation energy of its bonds with carbon-centered radicals or hydrogen atoms, when passing from the protonated to the unprotonated form of carboxy-TEMPO (BDE-switch).

Provided BDE-switch is preserved in solution, this suggested a range of important applications, both in materials and biological sciences.⁶

In a very recent paper by the same authors, however, the applicability of BDE-switch in solutions was questioned.⁸ Actually, calculations of Gibbs free energies performed by using polarizable continuum model (PCM) indicated that increasing solvent polarity leads to loss in the switching effect. Specifically, in polar solvents such as acetonitrile (ACN), dimethylsulfoxide (DMSO), and especially water, the switches on the BDEs drop below 1.5 kcal mol⁻¹ and are no longer related to the gas-phase values.⁸ The loss of switching effect was related to the stabilization of the anion in polar solvents.

Because of the important applications of such effect, both in materials and biological fields, we decided to verify under real conditions (i.e., in solution) Coote’s computational predictions. To do this, we measured in ACN solutions the BDEs of O–H bond in the hydroxylamines (X-TEMPO-H) deriving from neutral and deprotonated forms of 4-carboxy-TEMPO (see Scheme 1).

Scheme 1



These determinations were done by using the EPR radical equilibration technique that has been largely used in our laboratory to measure BDE values of X–H bonds in many antioxidants.⁹ This consists in measuring the equilibrium constant for the hydrogen atom-transfer reaction (eq 1) between TEMPO derivatives and an appropriate reference hydroxylamine, (NO–H), that in the present case was represented by 2,2-diphenyl-3-oxo-N-hydroxyindoline (see Scheme 1).¹⁰



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$$K_{\text{eq}} = \frac{[\text{NO}\bullet]([\text{X-TEMPO}\bullet]_0 - [\text{X-TEMPO}\bullet])}{[\text{X-TEMPO}\bullet]([\text{NOH}]_0 - [\text{NO}\bullet])} \quad (2)$$

The reference hydroxylamine was chosen because: (i) the corresponding radical does not decay in the time interval required for EPR measurements, this allowing the determination of the radical concentrations to be made directly; (ii) the BDE (70.6 kcal mol⁻¹) is close to that of the hydroxylamine deriving from unsubstituted TEMPO• (69.6 kcal mol⁻¹);¹¹ (iii) the corresponding nitroxide radical shows an EPR spectrum relatively easy to be analyzed ($a_{\text{N}} = 9.48$ G, $a_{\text{H}} = 3.10$ G, $a_{\text{H}} = 2.91$ G, $a_{2\text{H}} = 1.00$ G); and (iv) it is soluble in ACN or DMSO.

EPR spectra were initially recorded at 298 K in ACN. According to the hydrogen atom-exchange equilibrium, diluted ACN solutions of NO-H (1.7–3.5 mM) and HOOC-TEMPO• (0.5–0.6 mM) were mixed at different ratios in order to obtain EPR spectra containing superimposed lines from both HOOC-TEMPO• and the nitroxide (NO•) derived from NO-H. Integration of the overall spectrum, showed that the total radical concentration after mixing was practically coincident with that of the starting HOOC-TEMPO• radicals and remained constant in time.

The relative amounts of the two radicals were obtained by computer simulation (see Figure 1), while the concentrations

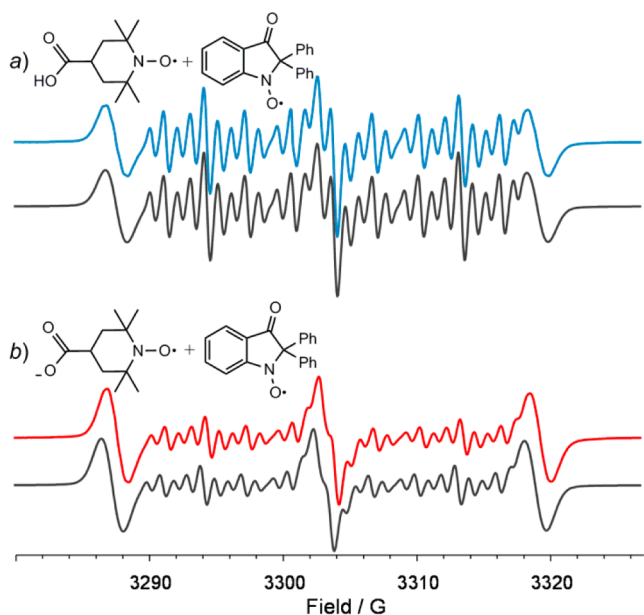


Figure 1. Experimental EPR spectra of ACN solutions containing HOOC-TEMPO• (0.50 mM) and NO-H (1.70 mM) recorded at 298 K in the absence (a, blue) and in the presence (b, red) of TEA (3.5 mM). In gray are the corresponding theoretical simulations obtained with $[\text{NO}\bullet]/[\text{X-TEMPO}\bullet]$ values of 0.47 (a) and 0.33 (b).

of the corresponding hydroxylamines were calculated by difference as shown in eq 2, where $[\text{X-TEMPO}\bullet]_0$ and $[\text{NO-H}]_0$ are the initial concentrations of the two species. The analysis of EPR spectra afforded a value for $K_{\text{eq}} = 0.049 \pm 0.002$ at 298 K corresponding to a $\Delta G^\circ = 1.78$ kcal mol⁻¹.

We repeated the same experiments in the presence of an excess of triethylamine (TEA) (TEA/nitroxide, 7/1). Under this condition, a quantitative deprotonation of the carboxylic acid to give ⁻OOC-TEMPO• radical is expected to occur. This was checked by recording ¹H NMR spectra of 4-oxocyclohex-

anecarboxylic acid 2 mM (which represents a suitable diamagnetic analogue of HOOC-TEMPO•) in the presence of 7 equiv of TEA both in ACN and DMSO. For example, in DMSO after the addition of the amine, the carboxylic hydrogen at 12.3 ppm is completely replaced by a signal at 6.3 ppm due to the triethylammonium proton (see Supporting Information, SI).

The formation of anionic species was further confirmed by measuring the nitrogen hyperfine splitting constants, a_{N} in the EPR spectra of X-TEMPO• before and after the addition of TEA.¹² This value changed from 15.74 to 15.82 G, respectively. Although this variation is not pronounced ($\Delta a_{\text{N}} = 0.08$ G), it is in line with the value $\Delta a_{\text{N}} = 0.07$ G observed in water with the same radical when changing the pH from 2 to 7 and predicted by theoretical computation.¹³

Analysis of EPR spectra obtained from ACN solutions at 298 K containing NO-H (1.7–4.4 mM) and ⁻OOC-TEMPO• (0.5–0.6 mM, TEA/nitroxide, 7/1) showed a small shift of the equilibrium toward nitroxide radical corresponding to a value of $K_{\text{eq}} = 0.025 \pm 0.002$ and $\Delta G^\circ = 2.18$ kcal mol⁻¹. By safely assuming that Gibbs free energy for NO-H is not influenced by the addition of TEA (*vide infra*), a ΔG° switch¹⁴ of only -0.40 kcal mol⁻¹ was thus obtained. This value is even less than that predicted by computations (-1.40 kcal mol⁻¹)⁸ and strongly supports the predicted loss of ΔG° switch in polar solution.

We repeated the same experiment in a more polar solvent like DMSO (see SI). In this case analysis of EPR spectra of ⁻OOC-TEMPO•/NO-H mixtures in the presence of TEA gave rise to an equilibrium constant ($K_{\text{eq}} = 0.044$) practically coincident to that measured with HOOC-TEMPO• ($K_{\text{eq}} = 0.045$), this corresponding to a negligible ΔG° switch.

We then determined the enthalpy and entropy changes for the hydrogen atom-transfer reaction by measuring K_{eq} over the range of temperatures from 293 to 358 K in ACN. According to the integrated van't Hoff equation, plotting of $\ln(K_{\text{eq}})$ vs $1/T$ (see Figure 2) resulted in a good straight line in both cases, from which $\Delta H^\circ = 0.40 \pm 0.2$ kcal mol⁻¹, $\Delta S^\circ = -4.66 \pm 1.4$ cal mol⁻¹ T⁻¹ and $\Delta H^\circ = 3.50 \pm 0.3$ kcal mol⁻¹, $\Delta S^\circ = 4.47 \pm 1.2$ cal mol⁻¹ T⁻¹ were derived for the neutral and anionic forms, respectively.

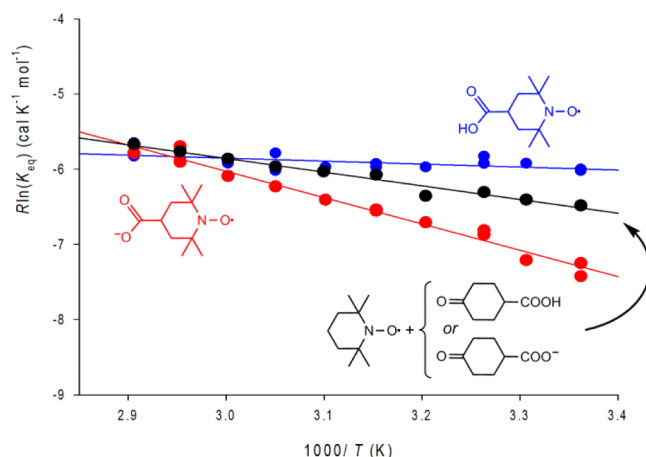


Figure 2. Plots of $\ln(K_{\text{eq}})$ versus T^{-1} for the hydrogen atom-exchange equilibrium in ACN between X-TEMPO• and NO-H. Blue X = COOH; red X = COO⁻; black X = H in the presence of the neutral and anionic form of 4-oxocyclohexanecarboxylic acid.

These results led to the following conclusions: (i) ΔG° switch¹⁴ shows an appreciable dependence on temperature, changing its sign at 338 K. Actually, it passes from -0.40 kcal mol⁻¹ at 298 K to 0 kcal mol⁻¹ at 338 K and to $+0.30$ kcal mol⁻¹ at 373 K.¹⁵ This result disagrees with calculations that indicated a substantial independency of ΔG° switch on temperature.⁸ (ii) A bond dissociation enthalpy (ΔH°) switch of -3.1 kcal mol⁻¹ is preserved in ACN solution. (iii) The ΔH° switch is counterbalanced by a ΔS° switch of $+9.13$ cal mol⁻¹ K⁻¹. This relevant effect should be related to SOMO–HOMO conversion and not to the hydrogen atom-transfer equilibrium. This was checked by obtaining a van't Hoff plot for the equilibrium between NO–H and the unsubstituted TEMPO radical in the presence of the neutral and anionic form of 4-oxocyclohexanecarboxylic acid (see Figure 2). In both cases we obtained the same values, within the experimental errors, as $\Delta H^\circ = 1.82 \pm 0.3$ kcal mol⁻¹ and $\Delta S^\circ = -0.41 \pm 1.6$ cal mol⁻¹ T⁻¹. The very small entropy variation observed in the present case is in line with the values generally observed in analogous hydrogen atom-transfer equilibria when solvation effects are not important.¹⁶

In conclusion, EPR experiments confirmed Coote's prediction that in polar¹⁷ solvents like ACN or DMSO at room temperature, ΔG° switch in the hydroxylamine HOOC-TEMPO–H is not relevant after conversion into distonic radical anion ⁻OOC-TEMPO•. We showed in ACN that this is the result of opposite enthalpic and entropic contributions. Because of significant unfavorable entropy change, also the temperature reduces the magnitude of ΔG° switch. Thus, polar reaction medium and temperature must be considered (and avoided) when modeling SOMO–HOMO energy-level conversion for applications like nitroxide-mediated polymerizations or enzyme catalysis.

■ ASSOCIATED CONTENT

📄 Supporting Information

Description of EPR measurements; detailed equilibria data obtained by EPR spectra; H NMR spectra of 4-oxocyclohexanecarboxylic acid; EPR spectra in DMSO. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(12) Integration of the spectrum due to X-TEMPO• before and after the addition of TEA showed that the total radical concentration after mixing does not change; this being an indication that the anionic species is completely soluble in ACN at the concentration employed in the experiments (0.5–0.6 mM).

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(14) ΔG° switch = $\Delta G^\circ(\text{HOOC-TEMPO}\bullet) - \Delta G^\circ(\text{OOC-TEMPO}\bullet)$.

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