Radical Reactions

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Intermolecular Hydrogen Bonding Modulates the Hydrogen-Atom-Donating Ability of Hydroquinones**

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Hydrogen bonds and redox processes are highly connected in nature: redox enzymes use specific noncovalent interactions to control the redox behavior of organic cofactors such as quinones, flavins, nicotinamides, and pterins.[1] Among these cofactors, quinone and hydroquinone species play a central role in energy transduction, by shuttling electrons between the various components of electron-transport chains.[2] The role of hydrogen bonding in modifying the reduction potential and the reactivity of quinones has been extensively studied by using hydrogen-bond-donating solvents[3] and biomimetic receptors.[4] The impact of hydrogen bonding on the oxidation of hydroquinones to give hydrogen-bonded neutral semiquinones has received somewhat less attention, despite this reaction having been reported to be crucial for the cytochrome bc_1 complex,[5] a component of respiratory electron-transfer chains, and despite it being the basis of the antioxidant action of hydroquinones in apolar solvents.[6] The presence of a neutral semiquinone intermediate has also been proposed to be formed in the high affinity site (Q_H) of cytochrome bo_3 from *Escherichia coli*.[7] To better understand the mechanism of the enzymatically catalyzed oxidation of ubiquinol, and to inspire the synthesis of new antioxidants, the relationship between the hydrogen-atom-donating ability of hydroquinones and the hydrogen-bonding behavior of the reduced (hydroquinone) and partially oxidized (semiquinone) species should be rationalized quantitatively.

We report herein that the increase observed in the reactivity of a model hydroquinone toward free radicals upon addition of small amounts of hydrogen-bond-acceptor (HBA) solvents can be explained quantitatively in terms of the different strengths of the hydrogen bonds formed in the parent phenol and in the phenoxyl radical.

The reaction of 2,5-di-*tert*-amylhydroquinone (**1**) with the 2,2-diphenyl-1-picrylidrazyl radical (DPPH·) was studied by following the pseudo-first-order decay of the absorbance of DPPH· in the presence of **1** in a nitrogen-saturated CCl_4 solution containing small amounts of each of two HBA solvents, that is, acetonitrile (CH_3CN) and dimethylsulfoxide (DMSO).[8] The experimental k_{DPPH} values (Figure 1) show an initial increase at low concentrations of the cosolvent, then reach a maximum ($1.1 \times 10^4\,M^{-1}s^{-1}$ at DMSO = 0.02 M and $4 \times 10^3\,M^{-1}s^{-1}$ at CH_3CN = 0.2 M), and decrease on further addition of the cosolvent. This behavior, which can be interpreted on the basis of Scheme 1 and Equation (1),[9] which is derived

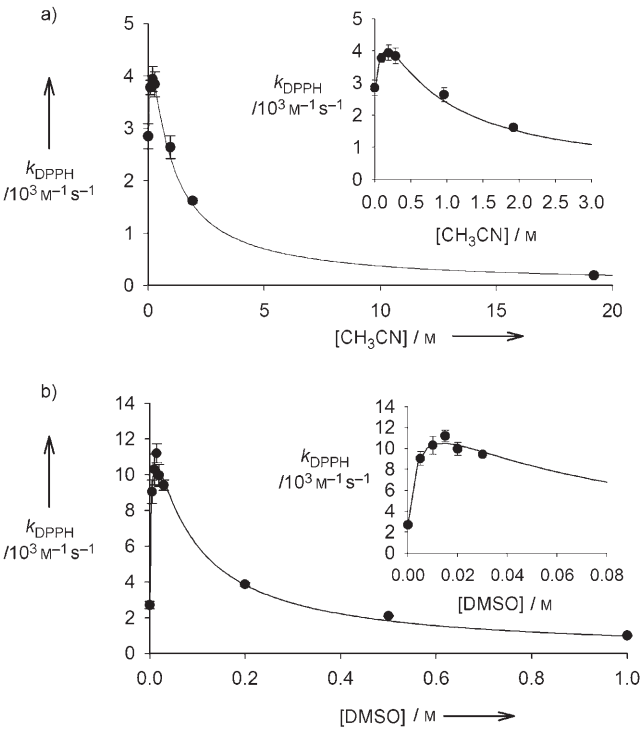

Figure 1. Rate constants, measured at RT in N_2-saturated CCl_4, for the decay of DPPH· in the presence of **1** as a function of CH_3CN (a) and DMSO (b) concentration. The insets show a magnified view of the initial parts of the plots.

$$k_{DPPH} = \frac{2k_1 + k_2 K_1 [S]}{K_1 K_2 [S]^2 + K_1 [S] + 1} \quad (1)$$

under the assumption that a phenolic OH group bound to a solvent molecule is not reactive toward free radicals,[10] implies that the free OH group of the partially solvated species **1S** reacts with DPPH· much faster than those of the uncomplexed hydroquinone **1** (that is, $k_2 > k_1$).

The values obtained by this procedure are reported in Table 1; in the case of CH_3CN, the equilibrium constants for the sequential complexation of the two hydroxy groups of **1** (K_1 and K_2) were also determined by IR spectroscopy by measuring the variation in the integration of the free OH signal at 3610 cm^{-1} with variation of the cosolvent concen-

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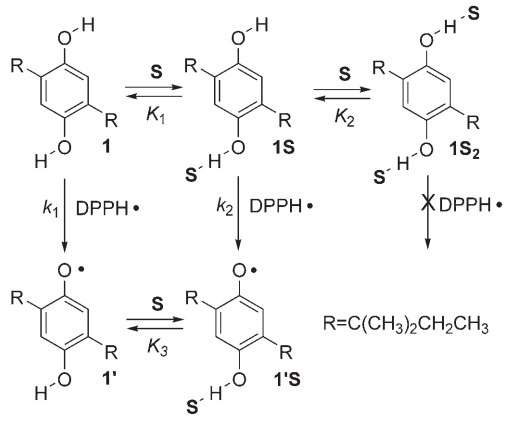
Table 1: Kinetic rate constants for the reaction of **1** and **1S** with DPPH• and equilibrium constants of complexation.

S	k_1[a] [10^3 M^{-1} s^{-1}]	k_2 [10^3 M^{-1} s^{-1}]	K_1^*[b] [M^{-1}]	K_2^*[b] [M^{-1}]	K_3[b] [M^{-1}]
CH_3CN	1.3 ± 0.2	5.9 ± 0.3	4.3 ± 0.5 3.2 ± 0.3[c]	3.0 ± 0.5 2.7 ± 0.2[c]	31 ± 4
DMSO	1.3 ± 0.2	14 ± 1	137 ± 43	28 ± 5	(1.0 ± 0.2) × 10^4

[a] For each OH group. [b] Microscopic equilibrium constants ($K_1^* = K_1/2$, $K_2^* = 2K_2$) correspond to each OH group and are obtained from the K_1 and K_2 values (Scheme 1) as shown in the Supporting Information and Ref. [9]. [c] Measured by IR spectroscopy.



Scheme 1. Reaction between 2,5-di-*tert*-amylhydroquinone and DPPH• in the presence of a hydrogen-bond-accepting solvent (**S**).

tration (see the Supporting Information). The difference between the results obtained in the two solvents indicates that DMSO forms stronger interactions than CH_3CN, which is in agreement with their Abraham β_2^H values of 0.78 and 0.44, respectively.[11] The anticooperativity of the hydrogen-bond interactions in hydroquinones[12] is the reason for $K_1 > K_2$.

The rate constant for the reaction of **1** with peroxyl radicals (k_{inh}) was also determined by means of inhibited autoxidation studies,[6,13] because of the importance of ROO• radicals in causing oxidative damage in natural and synthetic materials. The data reported in Figure 2 show that **1S** (**S** = DMSO) is five times more reactive than **1**, with k_{inh} values of $(3.0 \pm 0.6) \times 10^6$ for the complexed and $(5.8 \pm 0.8) \times 10^5$ M^{-1} s^{-1} for the free hydroquinone (for each OH group).

The kinetic data were rationalized on the basis of the well-established[15] dependence of the rate constant for hydrogen-atom transfer on the ArO–H bond dissociation enthalpy (BDE) values, which holds for phenols bearing the same *ortho* substituents [Eqs. (2) and (3)].[16]

$$\mathrm{Log}\, k_{\mathrm{DPPH}\cdot} = -0.51\,\mathrm{BDE(ArO{-}H)} + p \qquad (2)$$

$$\mathrm{Log}\, k_{\mathrm{ROO}\cdot} = -0.34\,\mathrm{BDE(ArO{-}H)} + q \qquad (3)$$

In the case of DPPH• [Eq. (2)], the BDE(O–H) value of the singularly solvated species **1S** was found, from the ratio of k_1 and k_2, to be smaller by −1.2 and −2.0 kcal mol^{-1}, for CH_3CN and DMSO, respectively, than that of **1**. In the case of peroxyl radicals [Eq. (3)], a BDE(O–H) difference of −2.1 kcal mol^{-1} was found with DMSO.

The decrease in the BDE(O–H) value, which depends upon the differential stabilization of the final (phenoxyl radical, **1′**) and initial (phenol, **1**) states of the hydrogen atom transfer reaction,[17] can also be estimated from the stabilization energies of these two species induced by the solvent. The

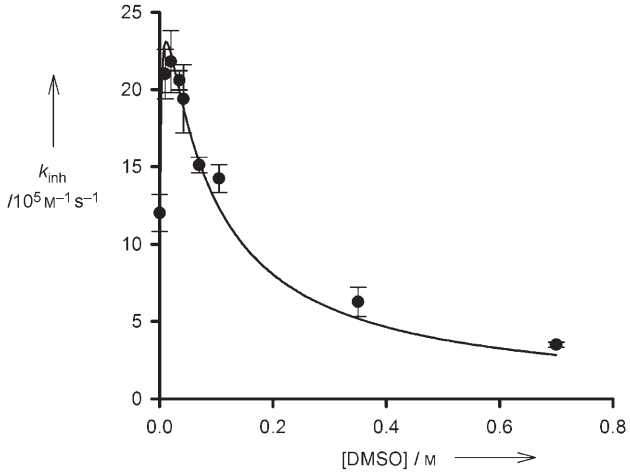


Figure 2. Dependence of the rate constant k_{inh} on the concentration of DMSO for the reaction of **1** with peroxyl radicals, obtained by inhibited autoxidation studies of styrene at 30 °C. Data were fitted using the equilibrium constants given in Table 1.

free energy of stabilization of phenol **1** at RT was determined from the K_1^* value (Table 1) to be −0.9 kcal mol^{-1} for CH_3CN and −2.9 kcal mol^{-1} for DMSO. The strength of the hydrogen bond in the phenoxyl radical **1′** was obtained by EPR spectroscopy by measuring the variations in the proton hyperfine splittings (a_H) of **1′** in benzene upon addition of increasing amounts of either CH_3CN or DMSO (Figure 3 and

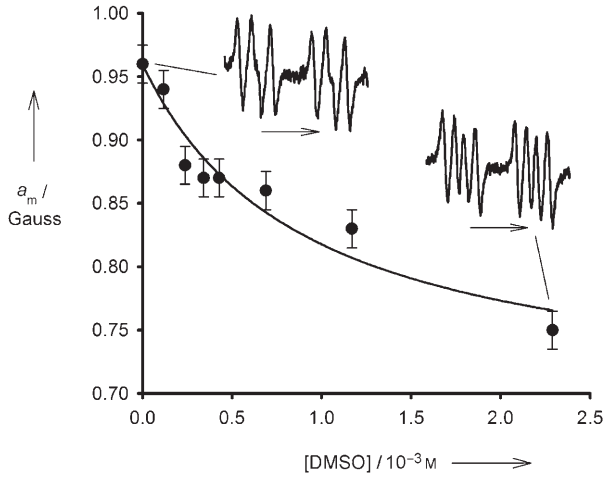


Figure 3. Coupling constant of the *meta*-hydrogen atom measured by simulation of the EPR spectra obtained by photolyzing **1** (7.7×10^{-2} M) in benzene in the presence of DMSO. Arrows correspond to 4 Gauss.

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Supporting Information).[17] The variations in the free energy of stabilization of **1** are essentially due to hydrogen-bonding interactions, since the macroscopic electrostatic contribution to a_H is negligible at the very low concentration of the cosolvent employed.[18] Thus, the equilibrium constant K_3 for the formation of **1S** could be determined from the EPR data by using Equation (4), where a_{free} and a_{bonded} are the values of the hyperfine splittings for the free and hydrogen-bonded radical species, and X corresponds to the molar fractions.[19]

$$a_H = a_{free} X_{free} + a_{bonded} X_{bonded} \quad (4)$$

Fitting the experimental proton splittings afforded the optimized values of a_{bonded} and of K_3 (Table 1), from which the free energy of stabilization of the **1′S** radical was determined to be -2.0 and -5.5 kcal mol^{-1} when **S** is CH_3CN and DMSO, respectively. From the K_3 values, the Abraham hydrogen bond donor parameter[11] α_2^H for the semiquinone radical **1′** was calculated to be 0.85 ± 0.06, which is in excellent agreement with the value estimated for its simple analogue HOO$^\bullet$ ($\alpha_2^H = 0.87$).[20] This value also indicates that the phenoxyl oxygen atom behaves as a strong electron-withdrawing group[21] (for comparison, α_2^H for *p*-NO_2PhOH is 0.82).[11]

The free energies of solvation for the semiquinone radical and the hydroquinone could be used to calculate the BDE(O–H) difference between **1** and **1S**, under the assumption that the entropic term $\Delta\Delta S$ is negligible.[17] Values of -1.1 and -2.6 kcal mol^{-1} with CH_3CN and DMSO, respectively, were found, which is in good agreement with the kinetic results.

In conclusion, the increase in the reactivity of a model hydroquinone toward free radicals, observed upon addition of small amounts of CH_3CN or DMSO, has been explained quantitatively by considering the different strengths of the hydrogen bonds formed in the parent phenol and in the semiquinone. These observations may help to better understand the enzymatic oxidation of ubiquinol, and may represent the first step toward the discovery of radical scavengers which take advantage of noncovalent interactions.

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