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PAPER

Hydrogen bond donating ability of *meta* and *para* hydroxy phenoxyl radicals†

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H-bond complexes between 3- or 4-OH phenoxyl radicals and various H-bond accepting molecules were investigated by experimental and computational methods. The H-bond donating ability (α_2^H) of 2,6-di-*tert*-butyl-4-hydroxyphenoxyl radical (**1**) was determined as 0.79 ± 0.05 by measuring, using EPR spectroscopy, the variations of the hyperfine splitting constants of **1** as a function of the acceptor concentrations. A computational approach, based on DFT calculations, was employed to estimate the α_2^H values for OH-substituted phenoxyl radicals that were not persistent enough to be studied by EPR spectroscopy. The α_2^H value calculated for the 2,6-di-methyl analogue of **1** was 0.76, in good agreement with EPR experiments. The α_2^H values for 2-methoxy-4-hydroxy (**3**), 4-hydroxy (**4**), 4,6-di-methyl-3-hydroxy (**5**) and 3-hydroxy (**6**) phenoxyl radicals were computed as 0.77, 0.84, 0.66 and 0.71, respectively, indicating that α_2^H values were dependent on the presence of electron donating substituents and on the relative positions of the –OH and –O$^•$ groups. By correlating the α_2^H values for **4** and **6** with their water and gas-phase acidities, an unexpected role of water in promoting proton dissociation from these radicals was evidenced.

Introduction

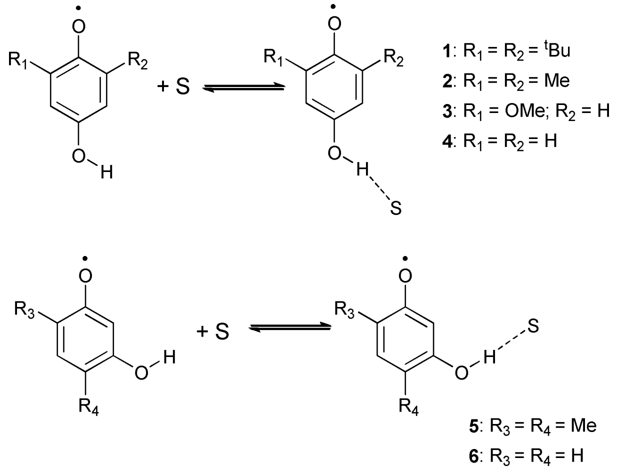
Formation of hydrogen bonds is an important issue in the chemistry of phenoxyl radicals. In enzymes and in photosynthetic systems, hydrogen bonds control the redox potential of tyrosine-based radicals and allow the performance of complex reactions.[1] Inter- and intramolecular H-bonds not involving the reactive OH groups are able to modulate the rates of H-atom abstraction from phenols by selectively stabilizing or destabilizing the incipient phenoxyl radicals.[2,3] Also, in organic chemistry protocols, it has recently been reported that phenoxyls can be used as intermediates for the green synthesis of biaryls provided that they are stabilized by the addition of strong hydrogen bond donors.[4]

Hydrogen bond donating and accepting abilities can be quantified by using Abraham's parameters α_2^H and β_2^H,[5] respectively, which have been successfully used, for instance, to explain solvent effects in radical reactions[6] and recognition events.[7] These parameters allow the prediction of the H-bond equilibrium constants (K_{HB}) in CCl_4 between any pair of molecules, if the α_2^H and β_2^H values of the interacting functional groups are known, as shown by eqn (1).[5]

$$\log K_{HB} = 7.354\ \alpha_2^H \times \beta_2^H - 1.094 \qquad (1)$$

Disappointingly, while hundreds of α_2^H and β_2^H values are known for molecules containing the most common functional groups, there are almost no data available for free radicals, with the exception of stable nitroxides (β_2^H of TEMPO is 0.46),[8] the hydroperoxyl radical (α_2^H of HOO$^•$ is 0.87),[9] and our previous measurement of α_2^H of the 2,5-di-*tert*-amyl-4-hydroxyphenoxyl radical (*vide infra*).[2]

Herein, we determined the H-bond donating ability of some phenoxyl radicals having an OH group in the 3 or 4 position (see Scheme 1), thus significantly expanding our previous communication.[2] Joint experimental and theoretical studies allowed us to determine the α_2^H value for differently substituted radicals, so that the effect of the substituents on α_2^H in phenoxyl radicals could be explored for the first time.



Scheme 1 Radicals investigated in the present study and their interaction with H-bond accepting solvents (S).

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The radicals investigated herein represent a simplified model for more complex biologically relevant phenoxyl radicals, such as the semiquinones formed from ubiquinol or plastoquinol in apolar environments,[10] or 3-OH phenoxyls that can be formed by oxidation of flavonoids and natural polyphenolic antioxidants.[11]

Results

EPR experiments

The addition of small amounts of H-bond accepting (HBA) co-solvents to a benzene solution of **1** caused remarkable variations of its spectrum (Fig. 1). In neat benzene, the spectrum was a distorted quartet, as the coupling constants with the two H_{meta} and the H_{OH} are about the same, while on addition of little amounts of a strong HBA solvent, such as hexamethylphosphoramide (HMPA), the spectrum steadily changed to a doublet of triplets. These changes, that were observed also on addition of small amounts of the other HBA co-solvents listed in Table 1, were attributed to the formation of the H-bond complex **1**···**S** shown in Scheme 1.[‡] Since H-bonding events are usually fast on the time scale of EPR spectroscopy, the spectrum observed at the various HBA solvent concentrations is the weighted average of the "free" **1** and of the solvated **1**···**S** species.[8,12] The observed hyperfine splitting constants (a) can be therefore described by eqn (2), where a_{free}, X_{free}, a_{HB} and X_{HB} are the constants and the molar fractions of the free radical **1** and of the **1**···**S** species, respectively.

$$a = a_{free}\, X_{free} + a_{HB}\, X_{HB} \qquad (2)$$

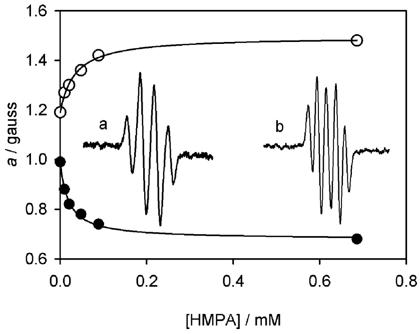

Fig. 1 Hyperfine splitting constants for **1** in benzene as a function of HMPA concentration. (●): $a(2H_{meta})$; (○): $a(H_{OH})$. The EPR spectra of **1** in neat benzene (a) and in HMPA 1.4×10^{-2} M (b) are shown.

By fitting the hyperfine splitting constant values as a function of [S] (see for instance Fig. 1), the equilibrium constants for H-bond formation K_{HB} and the hyperfine constants for the H-bonded species **1**···**S** (a_{HB}) could be determined.[§] These results are summarized in Table 1, together with the variation of free energy ($\Delta G°$) for the H-bond formation.

Table 1 Results obtained from the EPR study of the H-bond equilibrium between **1** and some H-bond accepting solvents in benzene

S	$\beta_2^{H\,a}$	$a_{HB}(2H_{meta})^b$	$a_{HB}(OH_{para})^b$	K_{HB}/M^{-1}	$-\Delta G°$/kcal mol^{-1}
EtCN	0.44	0.89	1.26	5.1 ± 0.5	0.96 ± 0.04
EtOAc	0.45	0.87	1.38	5.6 ± 0.5	1.02 ± 0.05
Py	0.62	0.72	1.19	140 ± 10	2.93 ± 0.04
DMF	0.66	0.77	1.38	230 ± 10	3.22 ± 0.04
Et_3N	0.67	0.45	0.88	292 ± 30	3.36 ± 0.06
DMSO	0.78	0.76	1.40	810 ± 50	3.97 ± 0.05
HMPA	1.00	0.68	1.50	$(4 \pm 1) \times 10^4$	6.3 ± 0.1

[a] H-bond accepting ability of **S**, from ref. 5 [b] Hyperfine splitting constants for the **1**···**S** species, in gauss.

Table 2 Strength of the H-bonds between phenoxyl radicals **2–6** and some acceptors (in kcal mol^{-1}), computed at the B3LYP/6-31+g(d,p) level

	$-\Delta H_{calc}$			
Radical	DMF	DMSO	Me_3PO^a	$\alpha_2^{H\,b}$
2	9.55	11.24	12.55	0.76
3	9.74	11.20	12.72	0.77
4	10.49	12.08	13.65	0.84
5	8.56	9.76	11.32	0.66
6	9.06	10.33	11.88	0.71

[a] The β_2^H of trimethyl phosphine oxide is 0.90 from ref. 7 [b] Estimated error: ±0.02.

By substituting K_{HB} and the β_2^H values of the co-solvents (see Table 1) into eqn (1), modified as suggested by Hunter to keep into account that the main solvent is benzene instead of CCl_4 (see the ESI†),[7] the mean α_2^H for **1** was obtained as 0.79 ± 0.05. This value is in agreement with that previously reported by us for 2,5-di-*tert*-amyl-4-hydroxylphenoxyl radical ($\alpha_2^H = 0.85 \pm 0.06$).[2]

Theoretical calculations

The interactions between **2–6** and three good H-bond acceptors with known β_2^H (DMF, DMSO and Me_3PO)[5,7] were investigated by means of DFT calculations at the B3LYP/6-31+g(d,p) level in the gas phase.[13] The enthalpy variations for the formation of H-bonds from the isolated reactants are reported in Table 2.

As expected, with the donor being the same, the $-\Delta H_{calc}$ values increased with the β_2^H of the acceptor, in the order DMF < DMSO < Me_3PO. Besides, the interaction energies with the same acceptor were proportional to the H-bond donating ability of the various radicals.

Gas phase enthalpy variations were related to solution phase α_2^H parameters by constructing an empirical relationship between these two values, as previously proposed by Mulder *et al.*[14] For this purpose, the strength of the H-bonds with DMSO, DMF and Me_3PO for some *meta* and *para* substituted phenols, whose α_2^H were available in the literature, were computed at the B3LYP/6-31+g(d,p) level. When plotting their α_2^H values against

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[‡] Splittings are also changed similarly by non-specific solvent effects, depending on the modification of the dielectric characteristic of the medium rather than on the formation of H-bonds.[8] These effects were evaluated by measuring the spectrum of a phenoxyl radical very similar to **1**, but lacking the OH moiety, *i.e.* the 2,6-di-*tert*-butyl-4-methoxyphenoxyl radical, in the same solvent mixtures used for studying H-bonding to **1**. In most cases, the spectrum of the methylated analogue of **1** did not change significantly, therefore showing that, at the concentrations used, dielectric effects of the solvents are negligible. A small effect was instead observed in the cases of EtCN and EtOAc at concentrations larger than 1 M (see ESI†).

[§] The concentration of **S** has been corrected for H-bond formation with the parent phenol of **1** (*i.e.* 2,6-di-*tert*-butyl-4-hydroxyphenol) which is able to act as an H-bond donor through its OH groups.

the computed ΔH_{calc}, good linear relationships were obtained (see for instance Fig. 2), and eqn (3)–(5) could be derived.

$$\alpha_2^{\mathrm{H}} = -0.0775\ \Delta H_{\mathrm{calc(DMF)}} + 0.0216;\ R^2 = 0.991 \quad (3)$$

$$\alpha_2^{\mathrm{H}} = -0.0923\ \Delta H_{\mathrm{calc(DMSO)}} - 0.272;\ R^2 = 0.993 \quad (4)$$

$$\alpha_2^{\mathrm{H}} = -0.0640\ \Delta H_{\mathrm{calc(Me_3PO)}} - 0.0422;\ R^2 = 0.988 \quad (5)$$

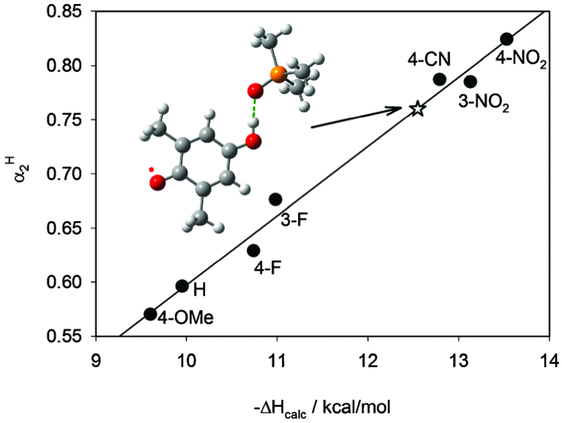


Fig. 2 Relationship between the literature α_2^{H} values for seven *meta* and *para* substituted phenols and the strength of their H-bonds with Me_3PO, calculated at the B3LYP/6-31+g(d,p) level in the gas phase. The equilibrium geometry for **2**···Me_3PO and the α_2^{H} for **2** is shown.

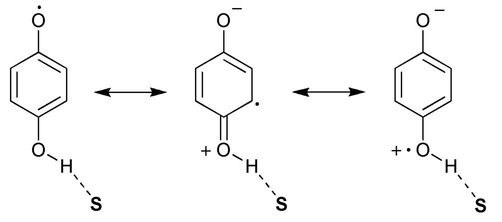
By substituting ΔH_{calc} for radicals **2–6** into eqn (3)–(5), the mean α_2^{H} values reported in Table 2 were then obtained.

Since replacing *tert*-butyl groups by methyl groups does not alter significantly the spin distribution[13] and so the ability of the *para*-OH group to interact with H-bond acceptors, we could compare the experimental α_2^{H} value for **1** to the calculated one for **2**.¶ These two values are equal within the experimental error, indicating that this computational approach is a reliable technique to gain quantitative estimates of H-bond equilibria in solution for transient species.

Discussion

Effects of H-bonds on hyperfine splittings of 1

Changes in hyperfine splittings measured by EPR for **1** are known to derive from the effects of H-bonding on the electronic distribution inside the radical. As shown in Scheme 2, H-bonding stabilizes the resonance structures with charge separation, as in these cases the O–H group is more polarized and hence it donates stronger H-bonds. In these structures, the unpaired electron is on the *meta* positions and on the 4-OH oxygen atom.[12] The coupling constant to the H_{OH} is therefore expected to increase, while in the *meta* positions, bearing negative spin density, delocalization of small positive spin density leads to an overall spin density decrease.[12]



Scheme 2 Resonance structures with charge separation in 4-OH phenoxyl radicals.

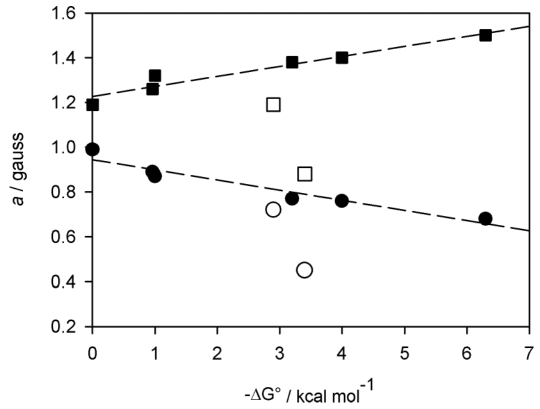


Fig. 3 Dependence of the splitting constants of **1**···**S** on the H-bond strength. Squares: $a(\mathrm{OH}_{para})$; circles: $a(2\mathrm{H}_{meta})$. Filled symbols are relative to non-basic solvents, empty symbols to pyridine and Et_3N.

The good linearity between hyperfine splittings and ΔG_{HB}, reported in Fig. 3, clearly indicated that the weight of polar resonance structures depicted in Scheme 2 is directly proportional to H-bond strength. The exception represented by pyridine and NEt_3 can be explained by considering that semiquinones are relatively acidic (*vide infra*) so **1** may transfer to some extent the hydroxylic proton to the HBA co-solvent, even in benzene solution, forming contact ion pairs.[15] Since in the radical anion the H-atom is no longer attached to the oxygen atom in the 4-position, and there is a positive spin density at the *meta* positions, both $a(\mathrm{H}_{\mathrm{OH}})$ and $a(\mathrm{H}_{meta})$ are lowered. As expected, these effects are proportional to the base strength, as the $\mathrm{p}K_{\mathrm{a}}$(MeCN) values of the conjugate acids of pyridine and NEt_3 are 12.5 and 18.8, respectively.[16]

Structural effects on α_2^{H}. The α_2^{H} values for **2–6** were all larger than that of phenol ($\alpha_2^{\mathrm{H}} = 0.60$),[5] thus indicating that phenoxyls are strong H-bond donors and that the "oxyl" substituent, either in the *meta* or *para* position, behaves as an electron-withdrawing (EW) group.[2,3,17,18]

The difference between **4** and **6** ($\Delta\alpha_2^{\mathrm{H}} = 0.13$) was unusually large if compared to phenols bearing strong electron-withdrawing groups. For instance, the α_2^{H} values for 3- and 4-NO_2 phenols are 0.79 and 0.82, ($\Delta\alpha_2^{\mathrm{H}} = 0.03$) and those for 3-CN and 4-CN phenols are 0.77 and 0.79 ($\Delta\alpha_2^{\mathrm{H}} = 0.02$).[5] We suggest that the EW character of the –O$^•$ group is mainly determined by the resonance structures reported in Scheme 2, while electron-withdrawing inductive effects, which should be effective also on the *meta* position, play a minor role.

Another point to note is that two alkyl or one methoxyl substituent in the *ortho* position to the –O$^•$ group lowered the α_2^{H} value by about 0.05–0.08 units. Reasonably, electron donation

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¶ To check this assumption, we calculated ΔH_{calc} for **1**···**DMF**, obtaining a value of –9.55 kcal mol^{-1}.

to the –O$^{\bullet}$ group slightly reduced its EW character, thus decreasing the α_2^H value of the *para* OH group.

Relationship between α_2^H and Brønsted acidity

It has been reported by Abraham and co-workers that, inside families of structurally related H-bond donors (such as unhindered phenols), a linear relationship between α_2^H and pK_a values may occur.[5] When plotting α_2^H values against pK_a in water for some unhindered *meta* and *para* substituted phenols, a linear dependence is obtained only at pK_a > 8, while the most acidic phenols have α_2^H values somewhat lower than expected from their pK_a (see Fig. 4a). When plotting the α_2^H values, calculated in the present work for **4** and **6** against their pK_a in H_2O, that are 4.1 and 7.0 respectively,[19] the investigated radicals were largely outside the curve of the reference phenols, even if considering the non-linearity of the α_2^H and pK_a relationship.

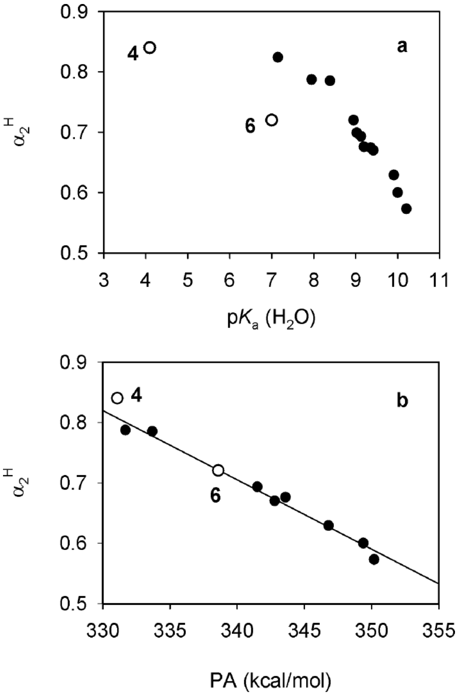

Fig. 4 Correlation between the α_2^H values for reference *meta* and *para* substituted phenols (●) and for **4** and **6** radicals (○), and their pK_a in water (panel a) or the proton affinity of the corresponding anions in the gas phase (panel b).

To clarify the role of water, the dependence of the α_2^H values on gas phase proton affinity (PA) was also investigated, as reported in Fig. 4b.[20,21] In this case, the α_2^H/PA plot of the reference phenols was linear. The proton affinities of the radical anions of **4** and **6**, recently reported by Fattahi *et al.* as (331 ± 1.7) kcal mol^{-1} and (338.6 ± 2.8) kcal mol^{-1}, respectively,[21] were in excellent agreement with their α_2^H values, as shown in Fig. 4b.

This anomalous behaviour may indicate an unexpected role of water in promoting the deprotonation of 3-OH and 4-OH phenoxyl radicals, with respect to phenols with EW substituents. We tentatively suggest that the –O$^{\bullet}$ substituent may experience a particularly strong solvation by H_2O molecules, which increases dramatically its EW character with respect to other "ordinary" EW groups such as –NO_2 or –CN.

Conclusions

In this work we evaluated on a quantitative basis the ability of an important class of radicals to donate hydrogen bonds to various acceptors having functional groups of biological relevance. Hydroxy-substituted phenoxyl radicals are important intermediates in the respiratory and photosynthetic chains, and in the radical chemistry of polyphenolic compounds, such as flavonoids or resveratrol. The ability to form hydrogen bonds has been quantified by using well known descriptors, usually applied to closed-shell molecules, which confer to our results important predictive power. As hydrogen bond formation is a crucial aspect of natural and artificial supramolecular systems, we believe that these results may be useful to rationalize the redox behavior of hydroxy phenoxyl radicals and of their parent phenols.

Experimental section

Reagents

Solvents were of the highest purity grade commercially available and were used as received. 2,6-Di-*tert*-butyl-4-hydroxyphenol was prepared according to the literature by reducing the corresponding 2,6-di-*tert*-butylquinone.[12]

EPR experiments

The 2,6-di-*tert*-butyl-4-hydroxyphenoxyl radical (**1**) was generated inside the cavity of an EPR spectrometer by continuous photolysis of an oxygen-free 0.03 M solution of 2,6-di-*tert*-butyl-4-hydroxyphenol in benzene,[12] in the presence of increasing amounts of H-bond accepting (HBA) co-solvents: propionitrile (EtCN), ethyl acetate (EtOAc), pyridine (Py), dimethylformamide (DMF), triethylamine (Et_3N), dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA). Samples were photolyzed with the unfiltered light from a 500 W high-pressure mercury lamp and the temperature was controlled with a standard variable temperature accessory. Intense spectra characterized by *g*-factors typical of aryloxyl radicals were observed (g = 2.0046), showing in all cases the interaction of the unpaired electron with two equivalent H-atoms (a = 0.99 G, in benzene) and one H-atom (a = 1.19 G, in benzene). The coupling constants are consistent with the loss of the H-atom from the OH group adjacent to both *tert*-butyl groups. If a small amount of MeONa dissolved in methanol was added to the sample, the spectrum simplified to a triplet (a = 0.83 G), indicating that in the presence of a strong base **1** loses the hydroxylic proton to give the corresponding radical anion. Similar experiments on the 4,6-di-*tert*-butyl-3-hydroxyphenoxyl radical were unsuccessful because of its low persistency (see the ESI†). Hyperfine splitting constants were determined by numerical fitting of experimental spectra[12] and the error is within ±0.02 G.

Computational details

DFT calculations were carried out using the Gaussian03 system of programs.[22] Geometries and energies were computed in the gas phase at the B3LYP/6-31+G(d,p) level as it has been demonstrated to yield sufficiently accurate structures for phenoxyl radicals and for H-bond complexes.[13,23] For molecules or H-bond complexes having multiple conformational minima, only the most stable ones were considered. In the case of **3**, the conformation having the –OMe group pointing away from the phenoxyl oxygen was considered.[24] Enthalpies at 298 K were computed using a scaling factor of 0.9806 to account for anharmonicity[25] and the nature of the ground states were verified by frequency calculations (zero imaginary frequency). The enthalpy difference for H-bond formation was not corrected for basis set superimposition errors, as they are usually low[23] and are expected to be cancelled out by the regression approach used in the present work. Calculations considering benzene as solvent (using the PCM method) gave results identical to those in the gas phase (see the ESI†).

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