

Kinetic and thermodynamic parameters for the equilibrium reactions of phenols with the **dpph**[•] radical

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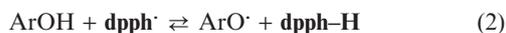
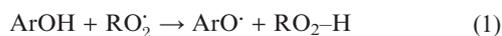
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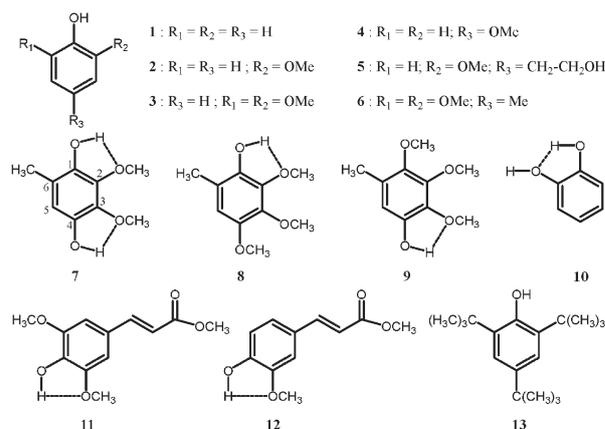
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The kinetics and energetics of the reversible reaction of phenols with the **dpph**[•] radical have been studied; steric shielding of the divalent N by the *o*-NO₂ in **dpph**[•] seems to be the main cause of the entropic barriers of this reaction.

Reactions of phenols (ArOH) with the **dpph**[•] (2,2-diphenyl-1-picrylhydrazyl) radical continue to be the focus of intense investigation¹ because they serve as a prototypical model for the reactions of peroxy radicals, RO₂[•], with ArOH which are extremely important, both in biology and chemistry, for their inhibitory effect on the autoxidation processes of organic materials.²



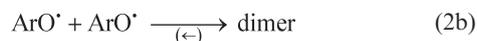
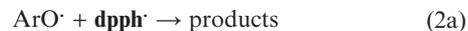
The analysis of a large number of experimental rate constants determined at 303 K with non-hindered phenols reveals, in fact, that the rate constants of reaction 1, k_1 , for polystyrylperoxy radicals correlate almost linearly with the rate constants relative to reaction 2, k_2 , being $k_1 \approx 4000 \times k_2^{3/4}$.³ This equation also shows that the RO₂[•] radicals are about 3 orders of magnitude more reactive than **dpph**[•] in the abstraction of the hydrogen atom from ArOH. In fact, reaction 1 is exothermic and essentially irreversible ($\Delta S_1 \approx 0$), since the O–H bond enthalpy (DH_{298}) of hydroperoxides varies in the range 86–88⁴ kcal mol⁻¹, whereas the $DH_{298}(\text{O-H})$ of ArOH with antioxidant activity are confined in the range 78–86³ kcal mol⁻¹. In contrast, reaction 2 is endothermic for most phenols since the $DH_{298}(\text{N-H})$ in **dpph-H** is comparatively low, being 78.9 kcal mol⁻¹ (*vide infra*). Reaction 2 is therefore expected to be reversible ($\Delta S_2 \approx 0$, *vide infra*) with a rate constant for the forward reaction slower than that of the reverse step, *i.e.* $k_2 \ll k_{-2}$. In this paper, we report on the kinetics and energetics of ArOH/**dpph**[•] reactions which may help in clarifying the intimate mechanism of the formal H-atom transfer from ArOH to **dpph**[•]. We chose for this study almost exclusively methoxyphenols (see Scheme 1) because for a few of them, reaction 2 is manifestly an equilibrium process. To avoid the undesirable complications of the so-called “sequential proton loss electron transfer”⁵ and the kinetic solvent effects,⁶ all reactions were exclusively studied in cyclohexane or *n*-hexane which are not hydrogen-bond acceptor solvents and inhibit phenol deprotonation. The course of the reaction was followed by



Scheme 1 Phenols investigated in the present study.

monitoring spectrophotometrically at 512 nm the loss of **dpph**[•] over time. Despite all reactions being almost exclusively studied in pseudo-first order conditions, *i.e.* with $[\text{ArOH}] \gg [\text{dpph}^{\bullet}] \approx 0.02\text{--}0.1$ mM, the **dpph**[•] loss very rarely followed first-order kinetics over the entire reaction time. In many cases the k_2 values, shown in Table 1, were therefore calculated from the initial rates at 298 K. We observed a substantial reduction of the rate of **dpph**[•] loss when the reactions were carried out in the presence of 0.1–1 mM **dpph-H**, and this confirmed the reversibility of reactions 2. However, with the exception of the phenols **3**, **8** and **13**, these reactions, either in the absence or in the presence of **dpph-H**, proceeded to completion, *i.e.*, to a total consumption of **dpph**[•].

This is because the aryloxy radicals produced in reaction 2 were in turn quenched by irreversible processes such as reactions 2a and 2b.



In a few instances, these two radical–radical processes are, however, equilibrium reactions themselves. The aryloxy radicals of **3**, for instance, dimerize reversibly with rate constants $2k_{2b}$ and k_{-2b} of $8.6 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ and 11 s^{-1} , respectively, in *n*-hexane at ambient temperature.⁷ Actually, the reaction of **dpph**[•] with **3** did not proceed to complete consumption of **dpph**[•] even with a concentration ratio $[\text{3}]:[\text{dpph}^{\bullet}]$ of 52:1 but reached an equilibrium position. Kinetic simulations† of the decay traces of **dpph**[•] + **3** showed that reaction 2a had no role in the overall process, *i.e.* the 2,6-(MeO)₂C₆H₃O[•] radicals are quenched by the **dpph**[•] radical too slowly for this reaction to compete with the dimerization 2b. The

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Table 1 Values of $DH_{298}(\text{ArO-H})$ (benzene solution) and rate constants in cyclohexane or *n*-hexane at 298 K for **1–13**

ArOH	$DH_{298}(\text{O-H})/\text{kcal mol}^{-1}$	Ref.	$k_2/\text{M}^{-1}\text{s}^{-1}$	$k_{-2}/10^4 \text{ M}^{-1}\text{s}^{-1}$	$k_{2a}/10^5 \text{ M}^{-1}\text{s}^{-1}$	$k_{2b}/10^8 \text{ M}^{-1}\text{s}^{-1}$	k_{-2b}/s^{-1}
1	87.2	8a	0.10				
2	85.3 ± 0.9	^a	0.92	4 ^e	0.01–1 ^e	17 ^g	
	88.6	8d					
3	82.1	8b	50	1.1 ^e		4.3 ^g	11 ^g
	81.7	8d					
4	81.7	8b	238				
	83.3	8d					
5	84.6	8c	3	3.0 ^f			
6	81.3	8c	90 ^c	0.73 ^f			
7	80.5	8d	990 ^d	0.52 ^e	2 ^e	0.8–4 ^e	50–100 ^e
		^a			≤ 1.5 ^a	2 ^h	
8	82.1 ± 0.6	^a	68	1.0 ^f			
9	83.4 ± 0.6	^a	11	1.8 ^f			
10	81.8 ^b	8e	1900			10 ^g	
11	81.2 ± 0.6	^a	226	0.70 ^f			
12	83.5 ± 0.6	^a	10	1.9 ^f			
13	80.1	8a	0.91				

^a Present work. ^b In isooctane solution. ^c The rate constant from the initial rates was divided by 2 (stoichiometric factor). ^d See the text. ^e Obtained from kinetic simulations. ^f See the text. ^g From ref. 7. ^h From ref. 12.

simulations also yielded for the reverse step of reaction 2 a rate constant k_{-2} of $(1.2 \pm 0.1) \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ at 298 K. The equilibrium constant K_2 can therefore be calculated to be $(50 \pm 5)/(1.2 \pm 0.1) \times 10^4 = (4.2 \pm 0.5) \times 10^{-3}$ at 298 K, in satisfactory agreement with the value of $(6 \pm 2) \times 10^{-3}$ obtained from the infinity-time absorbances and initial concentrations of reactants. The average value of 5.1×10^{-3} allows us to calculate ($\Delta S_2 \approx 0$) that the $DH_{298}(\text{O-H})$ in **3** is 82.0 kcal, in excellent agreement with the data reported in the literature, see Table 1.

Most of the $DH_{298}(\text{ArO-H})$ reported in Table 1 are taken from the literature.⁸ The values determined by EPR techniques in benzene solution, based on **13** as a reference compound, were adjusted downward by 1.1 kcal because of a recent revision of the $DH_{298}(\text{O-H})$ in **13**.^{8a} We also revised the O–H bond enthalpy of **2** reported in the literature^{8d} as 88.6 kcal mol⁻¹ to a value of ca. 85.3 ± 0.9 kcal mol⁻¹.[‡] The O–H bond enthalpies of **5** and **6** were instead estimated by using the group additivity rule^{8c} and subtracting 1.1^{8a} kcal from the final values. The $DH_{298}(\text{O-H})$ in *o*-methoxyphenols **2, 3, 5–7** correlate linearly with the corresponding log k_2 (see Fig. 1). The equation obtained was used to estimate the $DH_{298}(\text{O-H})$ in the *o*-methoxyphenols **8, 9, 11** and **12** on the basis of their k_2 values measured at 298 K. The $DH_{298}(\text{O-H})$ in **11** (81.2 kcal mol⁻¹) and **12** (83.5 kcal mol⁻¹) so obtained allow us to calculate that the *para* –CH=CH–COOMe group, according to our data, reduces the $DH_{298}(\text{O-H})$ in phenols by only ca. 1.4 kcal,

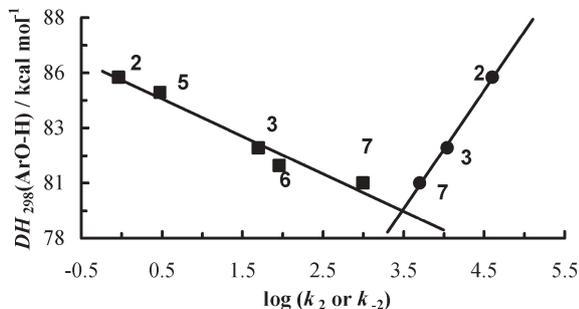


Fig. 1 Linear free-energy relationships between k_2 (■) or k_{-2} (●) and $DH_{298}(\text{O-H})$ for *o*-methoxyphenols **2, 3, 5–7**. The linear equations are: $DH_{298}(\text{O-H}) = 85.172 - (1.701 \times \log k_2)$ ($R = 0.98$) and $DH_{298}(\text{O-H}) = 60.608 + (5.354 \times \log k_{-2})$ ($R = 0.999$) in kcal mol⁻¹.

in fairly good agreement with an additive contribution of –2 kcal recently reported for –CH=CH–COOH.⁹ Kinetic simulations† of the **dpph**· decay in the presence of phenols **2, 3** and **7** allowed us to estimate the corresponding k_{-2} for reaction –2, see Table 1. These three values correlate linearly with the $DH_{298}(\text{O-H})$, as shown in Fig. 1, and the corresponding equation was used to estimate the values of k_{-2} at ambient temperature for the remaining *o*-methoxyphenols reported in Table 1. We also determined the N–H bond enthalpy $DH_{298}(\text{N-H})$ in **dpph-H** by monitoring the position of the equilibria **dpph**·/2,4,6-tri-*tert*-butylphenol **13** and **GO**·/**dpph-H** (**GO**· denotes the galvinoxyl radical) in the absence of O₂ at various temperatures (range 283–348 K) by UV-vis spectroscopy. The equilibrium constant at 295 K with **13** was determined to be 0.1378 ± 0.0013 whereas the van't Hoff plot yielded $\Delta H_2 = 1.4 \pm 0.5 \text{ kcal mol}^{-1}$ and $\Delta S_2 = 0.6 \pm 2 \text{ cal mol}^{-1}\text{K}^{-1}$. Therefore, according to these data we can calculate that $DH_{298}(\text{N-H}) = 80.1 - 1.4 = 78.7 \pm 0.5 \text{ kcal mol}^{-1}$ where 80.1 is the $DH_{298}(\text{O-H})$ in **13**. In the case of the **GO**· radical, the equilibrium constant at 295 K was determined to be 0.094 ± 0.019 whereas the van't Hoff plot provided the values of $\Delta S_{-2} = 1 \pm 2 \text{ cal mol}^{-1}\text{K}^{-1}$ and $\Delta H_{-2} = 1.4 \pm 0.4 \text{ kcal mol}^{-1}$. Given that the correct $DH_{298}(\text{O-H})$ in **GOH** is 77.7 ± 0.3 ^{10,8a} kcal mol⁻¹ we can calculate that the $DH_{298}(\text{N-H})$ in **dpph-H** is $77.7 + 1.4 = 79.1 \pm 0.5 \text{ kcal mol}^{-1}$. In conclusion, our measurements indicate that the $DH_{298}(\text{N-H})$ in **dpph-H** is $78.9 \pm 0.5 \text{ kcal mol}^{-1}$, in quite remarkable agreement with the value of 78.5 kcal mol⁻¹ obtained from Mahoney *et al.*'s data¹¹ after correcting by 1.1^{8a} kcal.

Ubiquinol-0, QH₂, reacts with **dpph**· with an observed rate constant of ca. $990 \text{ M}^{-1}\text{s}^{-1}$ (see Table 1). The interpretation of this value depends upon the quenching reactions of the semiquinone radical QH· which follow reaction 2. We can envisage two possible quenching processes for QH· (Q represents ubiquinone-0):



If reaction 2c is faster than reaction 2d then $k_2 = k_{\text{obs}}/2 = 495 \text{ M}^{-1}\text{s}^{-1}$; in the opposite case, *i.e.* $2d \gg 2c$, $k_2 \approx k_{\text{obs}} = 990 \text{ M}^{-1}\text{s}^{-1}$ whereas in the intermediate case, *i.e.* $2c \approx 2d$, $495 < k_2 < 990 \text{ M}^{-1}\text{s}^{-1}$. The temperature dependence of k_2 followed the

Table 2 Activation parameters of phenols for their reactions with the **dpph**[†] and RO₂ radicals

ArOH	dpph [†]		RO ₂ ^a	
	<i>A</i> ^b /M ⁻¹ s ⁻¹	<i>E</i> _a ^b /kcal mol ⁻¹	<i>A</i> /M ⁻¹ s ⁻¹	<i>E</i> _a /kcal mol ⁻¹
1	1.6 × 10 ⁶	9.8	1.59 × 10 ⁷	5.2
2	1.7 × 10 ⁵	7.2		
3	2.9 × 10 ⁵	4.9		
4	2.1 × 10 ⁶	5.4		
7	1.5 × 10 ⁵	3.3		
8	1.3 × 10 ⁵	4.5		
10	7.3 × 10 ⁵	3.5		
13	4.5 × 10 ³	5.0	1.6 × 10 ⁴	0.5

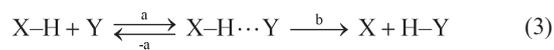
^a From ref. 15. ^b Experimental error *ca.* ±10%.

Arrhenius law with an *A*-factor of 1.5 × 10⁵ M⁻¹s⁻¹ and an activation energy of 3.3 kcal mol⁻¹ (see Table 2). Our results indicate that the *A*-factors of all phenols **1–13** are confined in the range, log(*A*/M⁻¹s⁻¹) = 3.6–6.3. QH[†] being still a “phenol”, its *A*-factor in reaction 2c may be similar or even identical to that of QH₂ in reaction 2, *i.e.* 1.5 × 10⁵ M⁻¹s⁻¹ while the activation energy is expected to be small. We can therefore conclude that *k*_{2c} may be ≤ 1.5 × 10⁵ M⁻¹s⁻¹. In contrast, the process of disproportionation of two semiquinone radicals derived from ubiquinol-2 has been reported to occur rapidly, the reported rate constant being 2.2 × 10⁸ M⁻¹s⁻¹ in acetonitrile solution at ambient temperature.¹² Kinetic simulations[†] of reactions 2, 2c and 2d using the above-mentioned rate constants and [dpph] ~ 2 × 10⁻⁴ M showed that *ca.* 90% of the QH[†] radical disappears by self-reacting, *i.e.* reaction 2d is largely predominant over reaction 2c and thus *k*₂ ≈ *k*_{obs} = 990 M⁻¹s⁻¹. Finally, this rate constant can be split into a contribution of *ca.* 764 and 226 M⁻¹s⁻¹ for the O–H groups at the 1- and 4-positions, respectively, of ubiquinol-0 on the basis of the difference in their bond enthalpies (*ca.* 0.9 kcal),^{8d} see Fig. 1.

The temperature-dependence of *k*₂ in cyclohexane in the range 280–348 K yielded the Arrhenius parameters given in Table 2. The pre-exponential factors show that reaction 2 is strongly affected by the steric effects of the substituents *ortho* to the reactive OH. The *A*-factors span, in fact, a comparatively large range, log(*A*/M⁻¹s⁻¹) = 3.65–6.32, with **13** and phenols **1** and **4** located, respectively, at the lower and higher limit of this range. However, no detectable difference seems to emerge from the *A*-factors of mono- and disubstituted phenols with methyl/methoxy groups at the *ortho*-positions.

The H-atom abstraction from **1–13** by the **dpph**[†] radical appears to be characterized by unusually low *A*-factors¹³ when compared with the “normal” value for an H-atom transfer reaction of *ca.* 3 × 10⁸ M⁻¹s⁻¹ or even when compared with the available data for the RO₂ radicals,¹⁵ see Table 2. This dramatic decrease of the *A*-factors with **dpph**[†] may have various origins. Steric shielding of the divalent N in **dpph**[†] by the *o*-NO₂ of the picryl ring is likely the most important of them. In fact, the stability of this radical had been suggested to be closely connected to the shielding effects more than the electronic effects of the nitro groups since removal of *p*-NO₂ had little effect while removal of one *o*-NO₂ group greatly increased its reactivity.¹⁶ Another possible and generally accepted explanation for low *A*-factors in H-atom transfer reactions between two heteroatoms X–H and ·Y (X, Y = N, O) is that such transfer reactions occur after a prior-equilibrium between a

hydrogen-bonded complex and the hydrogen-bond donor X–H and the hydrogen-bond acceptor (HBA) Y:^{4a}



With a large excess of the XH reactant, the first step follows first-order kinetics and, if its time scale is much shorter than the second, *i.e.* *k*_a[XH] + *k*_{-a} ≫ *k*_b, then it can be regarded as being at equilibrium. The observed rate constant for the overall process will therefore be equal to *k*_{obs} = *K*_{eq,a} × *k*_b/(1 + *K*_{eq,a} [XH]) ~ *K*_{eq,a} × *k*_b for comparatively low [XH]. We can therefore calculate that, log(*A*_{obs}/M⁻¹s⁻¹) ~ log(*A*_b/s⁻¹) + Δ*S*_a/2.303*R*, that is, the observed *A*-factor will be smaller than the value^{4a} of *A*_b because of the loss of freedom caused by formation of the HB-complex (Δ*S*_a < 0). Furthermore, it is important to realize that the **dpph**[†] radical has several HBA centres but a few of them, *e.g.* the *p*-NO₂, hold the H-atom of ArOH molecules in a non-productive neighbourhood because they are far apart from the divalent N. These HB-complexes must therefore re-dissociate and associate to an HBA centre suitable for product formation, a process that may require a long time scale.

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- [†] We used the “Chemical Kinetics Simulator” by IBM, version 1.01 (1995).
[‡] Table 2 shows that the *E*_a for phenol **2** in reaction 2 is 7.2 ± 0.7 kcal. Since for most phenols the activation energy for the reverse step of reaction 2 is on average *ca.* 1 ± 0.5 kcal we can calculate that the *DH*₂₉₈(O–H) in **2** is 78.9 + 7.2 – 1 = 85.1 ± 0.9 kcal, that in benzene solution becomes *ca.* 85.3 ± 0.9 kcal because of the enthalpy of hydrogen-bonding between benzene and **2** (see ref. 8a).
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