

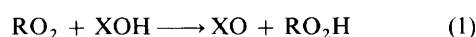
Entropic and Enthalpic Effects of 4-Methoxy Substitution in Phenoxy Radicals

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Values of $\Delta H_3 = (-12.4 \pm 1.6)$ kJ mol⁻¹, $\Delta S_3 = (-18.5 \pm 5.6)$ J K⁻¹ mol⁻¹ for reaction (3) (see text), corresponding to an O–H bond energy of 322.2 kJ mol⁻¹ in **1**, and to a 14.5 J K⁻¹ mol⁻¹ entropy loss for the CH₃O–Ar (Ar = aromatic) libration in **2** relative to **1**, are derived from the temperature dependence of the equilibrium constant K_3 , determined by EPR spectrometry in benzene–toluene media, between 251 and 304 K. These results allow, for the first time, discrimination between enthalpic and entropic effects on the rates of (O)H-atom abstraction by peroxy radicals from 4-methoxyphenols and related species.

It is generally acknowledged that phenolic antioxidants operate by scavenging peroxy radicals RO₂ to form stabilized phenoxy radicals XO, *via* relatively fast H-atom transfer reactions.¹ The effect of various aromatic ring substituents on the rate of reaction (1), presumably correlating with the thermochemical



stability of the resulting XO radicals, has been explored systematically.^{1–4} Thus, it has been found that alkyl groups, which provide hyperconjugative stability, and a 4-methoxy group, which mixes the SOMO (singly-occupied molecular orbital) with a p-type O-atom lone pair orbital, increase the value of k_1 . However, these effects are not strictly additive. As previously noted, the naïve application of these rules of thumb leads, for example, to the prediction that α -tocopherol (α -T), the most efficient natural antioxidant, *in vivo* as well as *in vitro*, should be as reactive as 4-methoxy-2,3,5,6-tetramethylphenol (MTAP), and only 50% more reactive than 4-methoxy-2,3,6-trimethylphenol (MTIP) at 300 K, at wide variance with experimental data.³

It was argued that stereoelectronic effects and the freezing of the *p*-alkoxy internal rotation, with the concomitant loss of internal entropy along the reaction coordinate during H-atom abstraction, impeded both in α -T and MTAP, but not in MTIP, could account for the observed discrepancies.^{2b}

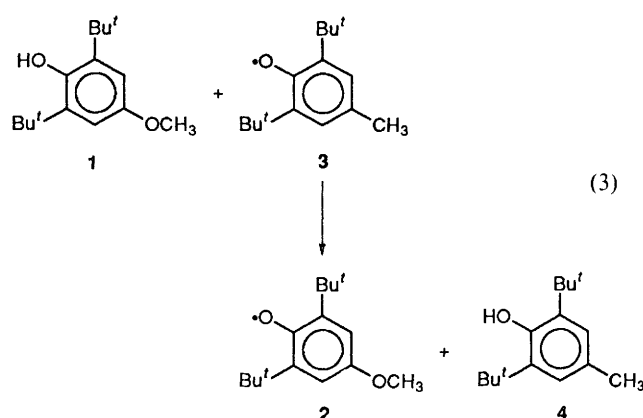
We have recently carried out EPR equilibrium measurements in radical buffers by a method that provided a direct value of $E_d(\text{O–H}) = 318$ kJ mol⁻¹ in α -T (E_d = bond dissociation enthalpy),⁵ only 8.4 kJ mol⁻¹ smaller than the similarly substituted MTAP.⁶ Based on these data, the well established linear free energy correlation (2), which assumes entropies of

$$[E_d(\text{XO–H})/\text{kJ mol}^{-1}] = 420.1 - 12.85 \log(k_1/\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}) \quad (2)$$

reaction and activation independent of the nature of X substituents in reaction (1),^{2b,4} yields $k_1(\alpha\text{-T})/k_1(\text{MTAP}) = 4.5$, instead of the experimental value of 8.2 at 300 K. Thus, this correlation performs poorly even for α -T and MTAP, although the *p*-substituents remain locked in both cases (albeit in parallel and perpendicular configurations, respectively). It appears that different factors, perhaps more subtle than those considered so far, control the thermochemistry and reactivity of phenolic antioxidants.

Since one of the goals of physical organic chemistry is to investigate the effect of substituents on stability and reactivity, and considering the availability of well established kinetic data for reaction (1), we decided to focus our attention on the

thermochemical aspects of this problem. In this paper, we report direct measurements of the equilibrium constant for reaction (3) as a function of temperature, that allow us to resolve the enthalpic and entropic effects associated with *p*-alkoxy substitution in phenoxy radicals.



Experimental

The EPR spectra of the different reaction mixtures were recorded on a Bruker ER 220 X-band spectrometer, at variable temperatures controlled by a B-VT 1000 unit, and measured with a calibrated Pt-resistance thermometer. Radicals were generated *in situ* by adding a known concentration of galvinoxyl radical G† (2×10^{-4} mol dm⁻³, Aldrich) to solutions of the parent phenols (*ca.* 0.1 mol dm⁻³) in benzene–toluene (1:1 v/v). This solvent mixture yields stable solutions over the solute concentration and temperature ranges employed in this study. Samples (120 mm³) thus prepared were frozen, degassed, sealed under nitrogen, and swiftly inserted into the previously thermostatted microwave cavity. Spectra were recorded after fixed periods, following thawing. Spectral line heights of **3** [a quartet of triplets, $a_{\text{mH}} = 0.231$ mT, $a_{\text{H}}(4\text{-CH}_3) = 1.121$ mT, Fig. 1(a)] in blank samples, *i.e.* in the absence of **1**, and in the different mixtures [Fig. 1(b)] were used to evaluate its equilibrium concentrations.⁵

Phenols (**1** and **4**, Aldrich) were recrystallized twice before use, and their purity checked by TLC. Analytical grade benzene and toluene solvents (Erba) were dried (potassium carbonate) and distilled.

† Galvinoxyl = 2,6-di-*tert*-butyl- α -(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)-*p*-tolylxy.



Fig. 1 (a) The X-band EPR spectrum of **3** in a benzene-toluene (1:1 v/v) solution of **4** (1.37 mol dm⁻³) and galvinoxyl (0.2 mmol dm⁻³); (b) the EPR spectrum of the solution resulting from the addition of **1** (9.35 mol dm⁻³) to the mixture used in Fig. 1(a)

Table 1 Equilibrium constants and free enthalpy for reaction (3) as a function of temperature

<i>T</i> /K	ln <i>K</i> ₃ ^a	Δ <i>G</i> ₃ /kJ mol ⁻¹
251.0	3.80 ± 0.47 (13)	-7.95 ± 0.96
261.5	3.33 ± 0.40 (13)	-7.20 ± 0.84
272.0	3.37 ± 0.44 (15)	-7.62 ± 1.00
283.5	2.99 ± 0.33 (10)	-7.03 ± 0.80
293.5	2.88 ± 0.81 (16)	-7.08 ± 2.14
304.0	2.71 ± 0.20 (7)	-6.70 ± 0.38

^a The figure between parentheses is the number of replicate determinations.

Results and Discussion

The 2,6-di-*tert*-butyl hindered phenoxy radicals generated as described earlier are so persistent that they do not decay appreciably on the timescale of present experiments, *i.e.* [2] + [3] = [G]₀, the initial galvinoxyl concentration. Hence, measurement of [3] in the presence and in the absence of **1** yields the information needed to evaluate *K*₃ at each temperature [eqn. (4)].

$$K_3 = \frac{[2][4]}{[1][3]} \quad (4)$$

Notice that the quantitative scavenging of galvinoxyl, a free radical isolable in pure form, allows the initial concentration of free radicals in this system to be easily determined, by eliminating the need for absolute calibrations with external standards. Equilibrium constants and the corresponding Δ*G*₃ values are presented in Table 1; ln *K*₃ is plotted *vs.* 1000/*T* in Fig. 2. A weighted least-squares linear fit leads to eqn. (5) and

$$\ln K_3 = (1496.8 \pm 187.4)T^{-1} - (2.23 \pm 0.68) \quad (5)$$

to Δ*H*₃ = (-12.40 ± 1.55) kJ mol⁻¹, Δ*S*₃ = (-18.47 ± 5.63) J K⁻¹ mol⁻¹. Observe that the logarithmic dependence of thermochemical parameters on radical concentration measurements greatly attenuates error propagation.⁵

From the value Δ*H* = 334.31 kJ mol⁻¹ for the reaction **4** = **3** + H, determined previously by the same technique against the absolute calorimetric value of *E*_d(2,4,6-tri-*tert*-butylphenoxy-H) = 399.92 kJ mol⁻¹,⁴ we obtain *E*_d(2,6-di-*tert*-butyl-4-methoxyphenoxy-H) = (321.9 ± 2.0) kJ mol⁻¹, intermediate between the O-H bond energies in MTAP (326.4) and α-T (318 kJ mol⁻¹).^{5,6}

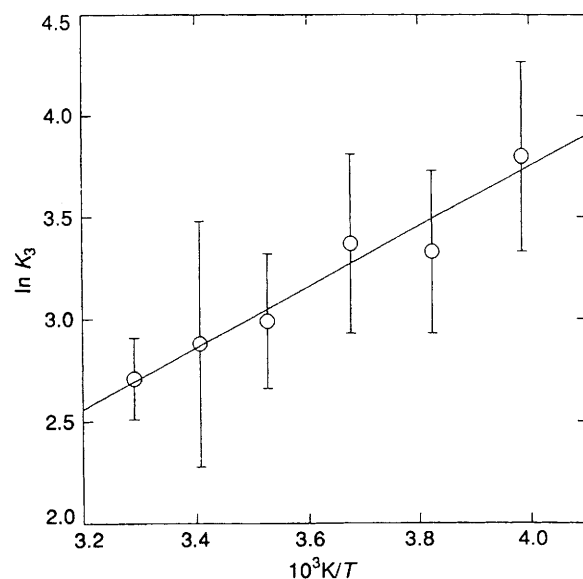


Fig. 2 Van't Hoff plot of ln *K* *vs.* 1000/*T*

The large negative entropy change in reaction (3) is at variance with the common assumption of Δ*S* ≈ 0 in metathetical reactions involving H-atom exchange between polyatomic species. The decrease in entropic content of the products can be justifiably ascribed to the freezing of the internal rotation of the *p*-methoxy group in **2** arising from conjugative delocalization of the odd electron with the lone pair on the *p*-methoxy oxygen atom. By this mechanism, the CH₃-O-Ar (Ar = aromatic ring) bond acquires partial double bond character, increasing the hindrance to the internal rotation of the methoxy group. The environment of the rotation of the methyl group about the CH₃-OAr bond also changes in reaction (3), and this effect must be accounted for to adequately quantify the intrinsic entropic loss due to conjugation.

We analysed the motion of the methyl moiety in the *p*-methoxy group in **1** in terms of the recently reported internal rotation potential function for anisole in solution [eqn. (6)]⁷

$$V(\theta, \varphi \text{ kJ mol}^{-1}) = 6.61 (1 - \cos 2\varphi) + 13.51 \cos^2 \varphi [1 - \cos (3\theta + 2\varphi)] \quad (6)$$

where φ is the angle formed by the O-CH₃ bond and the plane of the aromatic ring ($\varphi = 0$ when the methyl carbon lies on the plane) and θ is the angle about the O-CH₃ bond ($\theta = 0$ when one of the methyl C-H bonds is in the Ar-O-C plane, *trans* to Ar-O bond). The absolute minimum, $V(\theta, \varphi) = 0$, obviously occurs at $\theta = \varphi = 0$. However, since both motions are correlated, the minimum energy pathway for the rotation of the methyl group does not coincide with $V(\theta, 0)$. We located such a path by joining the minimum elements of a $V(\theta, \varphi)$ matrix, calculated at 0.3° intervals about (0, 0), using θ as a parameter and φ as the variable. The results are shown in Fig. 3.

These parabolas define the potential energy curves for θ -motions in **1**, and in the stabilized radical **2**, *i.e.* when $\varphi = 0$, respectively. From the derived force constants $k = (\partial^2 V / \partial \theta^2)_{\theta, \varphi}$, librational frequencies for the methyl group $\nu = (1/2\pi)(k/I_r)^{1/2}$ (where $I_r = 3.0 \text{ u \AA}^2$,* the reduced moment of inertia of a CH₃ rotor) and harmonic entropies $S_\theta = R [n/(e^n - 1) - \ln(1 - e^{-n})]$ ($n = h\nu/kT$) can be obtained.⁸ In this manner we obtain S_θ values of 9.12 and 5.15 J K⁻¹ mol⁻¹ for the methyl librations

* $1 \text{ u} = 1.66056 \times 10^{-27} \text{ kg}$.

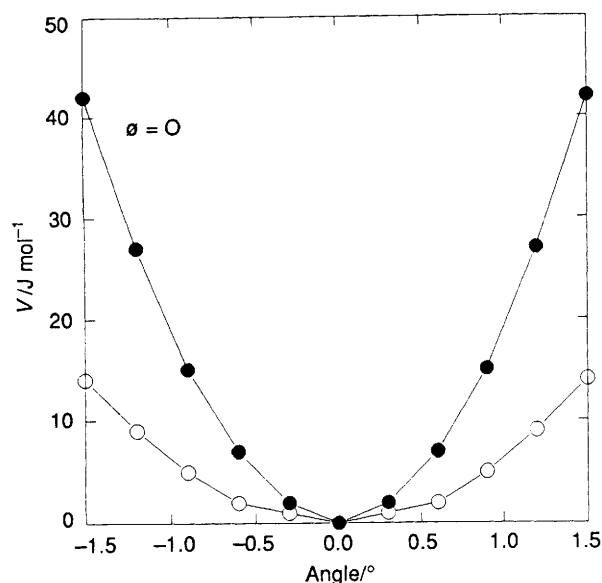


Fig. 3 Potential energy $V(\theta)$ for the $\text{CH}_3\text{-OAr}$ libration about $\theta = \varphi = 0$ [see eqn. (6) in the text];⁷ ○, the minimum energy path in **1**; ●, $V(\theta, \varphi = 0)$ corresponds to this motion in the radical **2**

in **1** and **2**, respectively. From $\Delta S_3 = \Delta S_\theta(\mathbf{2}) - \Delta S(\mathbf{1}) + \Delta S_{\text{CH}_3\text{-O-Ar}}(\mathbf{2}) - \Delta S_{\text{CH}_3\text{-O-Ar}}(\mathbf{1})$, we find that the Ar-OCH_3 rotor actually loses about $14.5 \text{ J K}^{-1} \text{ mol}^{-1}$ during H-atom abstraction.

Present results provide a direct measurement of the comparative effect of a 4-methoxy over a 4-methyl substituent on the thermochemical stability of phenoxy radicals. Interestingly enough, eqn. (2) correctly predicts, for the 12 kJ

mol^{-1} difference in the O-H bond dissociation energies of **1** and **4**, a ratio of $k_1(\mathbf{1})/k_1(\mathbf{4}) = 8.7$, in excellent agreement with the experimental value of 7.9, despite the fact that about 18 entropy units are lost in reaction (3). In other words, for similarly hindered phenols, enthalpic factors appear to dominate reactivity, regardless of entropic changes. This conclusion can only be rationalized if the barriers to the $\text{CH}_3\text{O-Ar}$ internal rotation are not fully developed at the transition states of reaction (1).

Conversely, as noted above, the relative reactivities of $\alpha\text{-T}$ and MTAP in reaction (1) only provide a coarse indication (within $\pm 3.3 \text{ kJ mol}^{-1}$) of the relative stabilities of their O-H bonds, even in the absence of entropic effects.

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