PERKIN 2

Entropy and enthalpy effects of 4-(phenylthio)-substituted phenols

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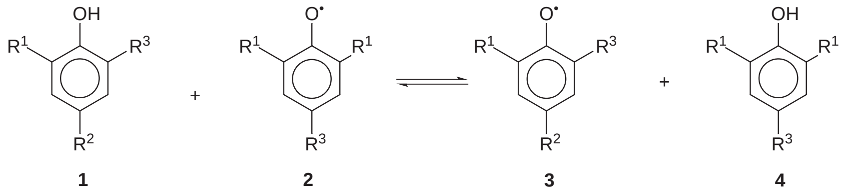
Electron paramagnetic monitoring of free phenoxyl radicals in benzene–toluene (1 : 1) solution has been used to study the temperature dependence of the equilibrium (*a*), for which the equilibrium constant, K_1 is



(*a*)

R^1 = Bu^t; R^2 = S-(3-methyl-4-hydroxy-5-*tert*-butylphenyl), R^3 = CH_3

given by eqn. (*b*).

$$K_1 = \frac{[3][4]}{[1][2]} \qquad (b)$$

The fit of experimental data to eqn. (*c*) yields ΔH_1 = 28.80 ± 3.39 kJ mol^{-1} and ΔS_1 = 116.9 ± 12.7 J K^{-1}

$$\ln K_1 = (-\Delta H/RT) + (\Delta S/R) \qquad (c)$$

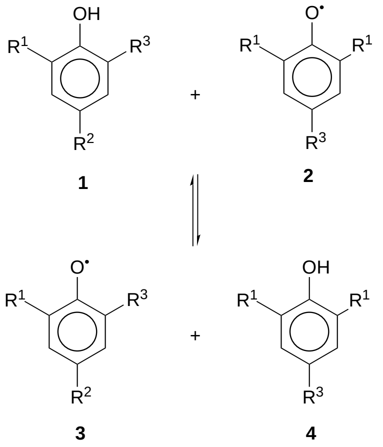
mol^{-1}. The entropy change value is about 30 J K^{-1} mol^{-1} in excess of the absolute entropy of the molecular rotor evolving about each of the C–S bonds in the thiobis(phenol) 1, thus denoting the enhancement by solute–solvent interactions. As well as using the enthalpy change to account for the stability of the generated phenoxyls, and/or the ability of hydrogen cession by phenols, the entropy change must also be measured when evaluating the antioxidant behaviour of this type of molecule, as its influence on the Gibbs free energy change is shown to be relevant.

Introduction

The antioxidant strength of phenols has been largely correlated with phenoxyl radical stability and evaluated by the phenolic O–H bond dissociation enthalpy [$D_{(O-H)}$].[1] The resonance stabilization of the unpaired electron is mainly determined by the type and location of the substituents on the aromatic ring. The presence of an oxygen atom connecting a *para*-alkyl group brings maximal antioxidant character when the whole molecule is a chromane ring system, as in the tocopherols.[1–8] However, in non-rigid phenolic molecules having internal rotation about the C_4–O bond, an entropy effect should be expected. This feature has been the subject of a previous work from our laboratory, where the cost of the entropy loss was estimated for a sterically hindered 4-methoxyphenoxyl radical.[7] Those results indicated that the origin of the entropic effect can be, not only the loss of degrees of freedom for that motion, but also solvent ordering surrounding the radical.

The present study has been to investigate the influence of a sulfur containing substituent, because of the availability of a class of such antioxidants, of which phenol **1** (synonyms Thioalkofen BM, Antioxidant 736) is a good example. The presence of a 4-(phenylthio) substituent (4-PTS) allows us additional insight into the molecular factors that can control the thermochemistry of the hydrogen transfer to phenoxyl radicals.

For that purpose, equilibrium (1) was monitored by means of electron paramagnetic resonance (EPR) in its equilibrium state and K_1 values were determined at varying temperature.



(1)

R^1 = Bu^t; R^2 = S-(3-methyl-4-hydroxy-5-*tert*-butylphenyl), R^3 = CH_3

Experimental

Reaction (1) was carried out in benzene–toluene (1 : 1) solvent mixtures in order to obtain stable solutions along the temperature range of K_1 measurements. Radicals were generated in the EPR sampling tubes by adding a known concentration of galvinoxyl radical [G; 2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxohexa-2,5-dien-1-ylidene)-*p*-tolyloxy free radical: Aldrich;

Table 1 Variation in equilibrium constant and Gibbs' free energy values with change in temperature for equilibrium (1)

T/K	ln K_1 [a]	σ^2 [b]	ΔG/kJ mol^{-1} [c]
243.5	0.075(6)	0.04	-0.15 ± 0.12
253.5	0.175(6)	0.14	-0.37 ± 0.13
263.5	0.864(8)	0.26	-1.89 ± 0.14
273.5	1.39(13)	0.28	-3.16 ± 0.09
283.5	1.62(6)	0.06	-3.82 ± 0.10
293.5	2.52(5)	0.01	-6.16 ± 0.04

[a] Number of measurements given in parentheses. [b] Variance of ln K_1. [c] Mean ± standard error.

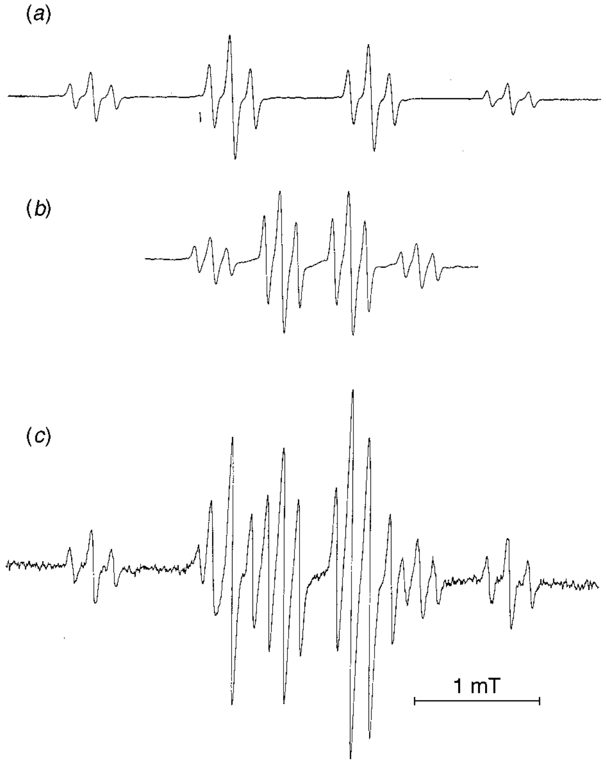


Fig. 1 X-band first derivative EPR spectrum of: (*a*) **2** in a benzene–toluene (1 : 1) solution of **4** (0.137 mol dm^{-3}) and galvinoxyl (0.2 mmol dm^{-3}); (*b*) similar condition EPR spectrum for **3**; (*c*) EPR spectrum of the solution resulting from the addition of **1** (0.85 mol dm^{-3}) to the mixture described in (*a*)

2×10^{-4} M] to solutions of the parent phenols. Samples, 120 µl in volume, were frozen and degassed by vacuum pumping up to 5 kPa to ensure constant pressure in the experiments. EPR spectra were recorded at fixed periods of time after thawing in the thermostatted cavity of a Bruker ER-200 X-band spectrometer equipped with a B-VT 1000 variable temperature unit. Peak-to-peak amplitudes of the first derivative spectral lines in the lowest field triplet of **2** [Fig. 1(*a*)] were measured in the absence of **1** (blank samples) and in the presence of **1** (reaction mixtures) to evaluate every radical concentration.

Proton NMR (200 MHz, in deuterochloroform) and FTIR (in nujol dispersion) were recorded on a Bruker AC-200 NMR and on a Nicolet Magna FTIR spectrometer, respectively, at the spectroscopy service unit UMYMFOR (CONICET-FCEN, University of Buenos Aires).

Phenols **1** (Antioxidant Kit, Chem Service, Illinois, USA) and **4** (Aldrich) were crystallized from hexane and their purity checked by TLC. Benzene and toluene (Merck, Analytical Grade) were dried on potassium carbonate and distilled before use.

Results and discussion

The persistence of radicals **2** and **3** makes it possible to monitor them by EPR. Their slow decay in the equilibria follows the kinetics reported for **2**[8] which means that the hydrogen transfer is very fast with respect to the lifetime of the radicals. Hence, [**2**] + [**3**] = [G$_0$], the concentration of galvinoxyl radical added to the parent phenols in generating the reaction system. [**2**] was measured in the presence and in the absence of **1** to find its concentration in the equilibria, and this value was subtracted from [G$_0$] to give [**3**]. [G$_0$] was obtained by direct weighing of highly pure G. This device avoids absolute calibrations with external standards.

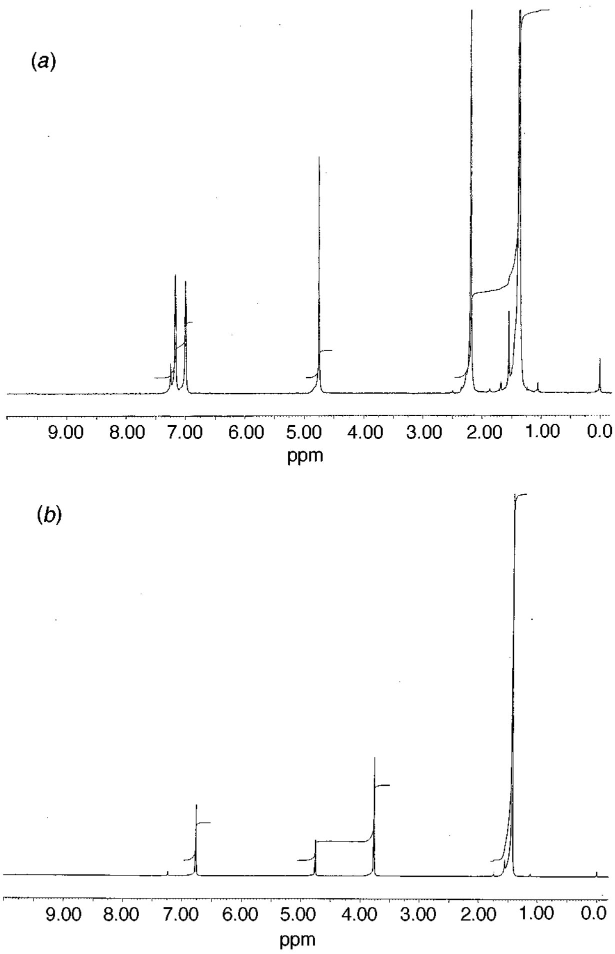


Fig. 2 ^{1}H NMR spectrum of: (*a*) **1**, δ_H 1.3675 (s, 9 H, *o*-Bu^t), 2.1845 (s, 3 H, *o*-Me), 4.7460 (s, 1 H, aryl-OH), 6.9886 and 6.9975 (poorly resolved d, 1 H, *m*-aryl-H), 7.1621 and 7.1720 (poorly resolved d, 1 H, *m*-aryl-H), 7.2466 (s, Cl_3CH impurity in Cl_3CD); (*b*) MOPH, δ 1.4323 (s, 18 H, 2,6-di-Bu^t), 3.7637 (s, 3 H, *p*-OMe), 4.7488 (s, 1 H, aryl-OH), 6.7592 (s, 2 H, two *m*-aryl-H), 7.2467 (s, Cl_3CH impurity in Cl_3CD)

Fig. 1(*a*), (*b*) and (*c*) shows the EPR records of **2**, **3** and their combined radical equilibrium, respectively. The values of ln K_1 and ΔG_1 at different temperatures are gathered in Table 1.

The fit of experimental data to eqn. (2) yielded $a = -3464 \pm 4.08$ and $b = 14.06 \pm 1.53$ (mean ± standard error) from which

$$\ln K_1 = aT^{-1} + b \qquad (2)$$

we can derive $\Delta H_1 = 28.80 \pm 3.39$ kJ mol^{-1} and $\Delta S_1 = 116.9 \pm 12.7$ J K^{-1} mol^{-1}. By knowing $\Delta H = 334.1$ kJ mol^{-1} for the reaction **4** = **2** + H, previously obtained against the absolute calorimetric value $D_{(O-H)} = 340.1$ kJ mol^{-1} in 2,4,6-tri-*tert*-butylphenol,[6,9] we obtain $D_{(O-H)} = 362.9 \pm 3.2$ kJ mol^{-1} for phenol **1**.

The present results indicate that an enthalpic stabilization has been introduced into the O–H of phenol **1** by the 4-PTS with respect to the 4-methyl analog, although the entropy change has made reaction (1) spontaneous.

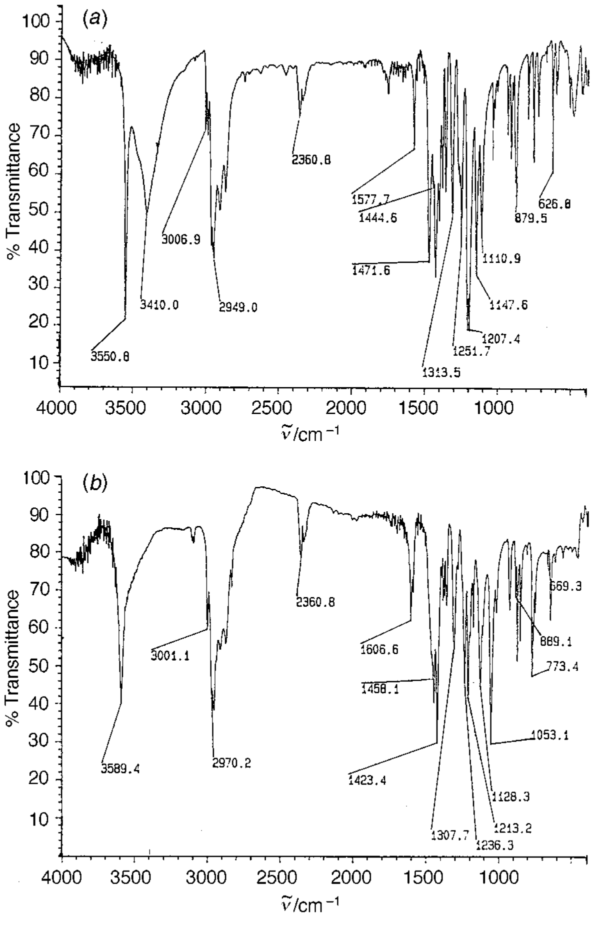
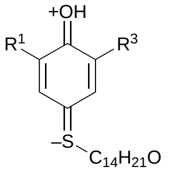


Fig. 3 Infrared (FTIR) spectrum of (*a*): **1**; (*b*): MOPH

Proton NMR [Fig. 2(*a*) and (*b*)] and IR [Fig. 3(*a*) and (*b*)] spectra were recorded for phenol **1** and 2,6-di-*tert*-butyl-4-methoxyphenol (MOPH) for comparative purposes.

The NMR spectrum of compound **1** shows two signals for the *meta*-aryl protons as is expected for the different alkyl substituents on the aromatic ring, both protons having chemical shifts above δ 7, while the singlet due to the same protons in MOPH is located at δ 6.759 [see captions to Fig. 2(*a*) and (*b*)]. Those data clearly indicate that the *para*-methoxy exerts a greater diamagnetic screening over the neighbouring sites of the molecule, a fact that correlates well with a stronger electron release ability towards the aromatic ring.

On the other hand, the infrared spectrum of MOPH exhibits a band at 3589.4 cm^{-1} for the O–H stretching, whereas that of **1** shows two distinct absorptions which can be assigned to the same vibration, 3550.8 and 3410.0 cm^{-1}; the latter is fairly broad and indicates hydrogen bonding to some extent, but the former shows a shift to a lower frequency, which suggests electron release towards the 4-PTS group,[10] a feature attributable to the low lying 3d orbitals of the sulfur atom.[11] As is often suggested, the sulfur atom can use its low energy unoccupied 3d orbitals to partially form double bonds, while maintaining a low bond angle value, and contribute to delocalizing the negative charge. This fact, combined with the electron donor character of the phenolic moiety, enhances the contribution of canonical structures such as **5**.



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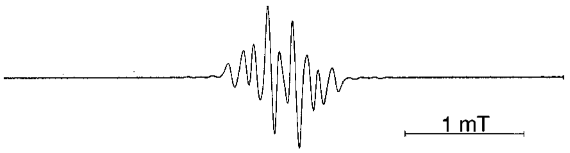

Fig. 4 X-band first derivative EPR spectrum of MOP: an overlapped quartet of triplets (see the text for hyperfine interactions)

This explanation agrees well with the difference in pK_a values of *para*-anisidine (5.34) and 4-methylthioaniline (4.35);[12] those values mean an easier heterolytic cleavage of the phenolic O–H bond, as opposed to a more difficult homolytic dissociation, with sulfur, rather than oxygen, at C_4. In other words, this is a good picture of the change in stability of the anions compared with the corresponding radicals. Those differences can be ascribed to the electron-acceptor character of the sulfur-containing substituent when facing a stronger electron donor such as the phenolic O–H group.

Hence, the high entropy gain in reaction (1) becomes understandable on the basis of the molecular polarization borne by **1** that is lost in its daughter radical. As a matter of fact, radical **3** can account for as much as 84 J K^{-1} mol^{-1} (the absolute entropy of the free rotation about each of the C–S bonds[13]) plus a little more than 30 J K^{-1} mol^{-1} in excess. As long as we are dealing with reactions in liquids that excess of entropy gain involves the loss or the decrease of the solvent ordering built up by the parent phenol.

It is likely that the dipole strength of MOPH is not comparable to compound **1**, mainly because of the better balanced electron affinity of the groups located on the opposite sides of the aromatic ring. Actually we had previously found the enthalpy and entropy change values for reaction (3)[7] as follows:

$$\text{MOPH} + \mathbf{2} \rightleftharpoons \text{MOP} + 4 \qquad (3)$$

$\Delta H_3 = -12.40$ kJ mol^{-1} and $\Delta S_3 = -18.47$ J K^{-1} mol^{-1}.

As a comment, we dare say that the quantities of the enthalpy and entropy change for reaction (1) fall into the correlation found for Frank and Evans for the vaporization of inert gases from water: $\Delta S = 14 + 0.0019\ \Delta H$,[14] a fact that told us about entropy driven equilibria. Since antioxidants are sometimes added to food or pharmaceuticals to preserve them from oxidation, it should be emphasized that only the tocopherols (in their natural sources and amounts) could be safe enough for avoiding undesirable effects on hydrogen transfer equilibria.

At this point, it seems appropriate to mention that the presence of steric hindrance due to the *ortho*-substituents in phenols of reaction (1) cancels only partially the repulsion cooperating with the thermochemical stabilization of the phenoxyl radicals.[15]

The EPR spectra of the phenoxyl radicals **2** [Fig. 1(*a*)], **3** [Fig. 1(*b*)] and MOP (Fig. 4) have the basis structure of a quartet of triplets, although this is only evident for **2** and **3** due to the relationship between the values of the *meta*-ring proton hyperfine interactions and those of the hydrogen nuclei in the *para*- or *ortho*-methyl substituents on the phenoxyl: $a_{(m\text{-H})} = 0.169$, $a_{(p\text{-Me})} = 1.125$ mT for **2**;[16] $a_{(m\text{-H})} = 0.124$, $a_{(o\text{-Me})} = 0.571$ mT for **3**;[17] $a_{(m\text{-H})} = 0.086$, $a_{(p\text{-OMe})} = 0.162$ mT for MOP.[18] All the EPR spectra show equivalence for both the methyl and the two *meta*-ring protons. As we can see in the NMR spectrum of **1**, its *meta*-ring hydrogen atoms have different chemical shifts. It may be that such a difference is lost in **3**, its daughter phenoxyl, but it is also possible that this small gap in magnetic moments is not enough to be displayed as distinct hyperfine interactions and only contributes to the line width in its radical EPR spectrum.

We still can derive some additional ideas from our previous[6,7] and present studies with these reaction systems. Hydrogen transfer reactions have been extensively studied as a model for the correlation of reactivity, selectivity and structure in free radicals.[1–5,19] Though absolute rate constants are actual estimations of phenol reactivity, small changes in selectivity between substrates may be made more apparent by evaluating the competitive hydrogen abstraction equilibria with a couple of radicals offering rather similar attachment and environment to the exchangeable hydrogen atom. The hindered phenoxyls used as substrates in our studies come from simple molecules and, besides allowing easy recognition and measurement, have their main structure differences confined to the *para*-substituent, whose influence on thermochemical parameters becomes straightforward. In addition, if the transition state may be regarded as a hydrogen bonded complex, then the O–H stretching vibration can be taken as the reaction coordinate.[19] Several studies about the deuterium effect have been performed, among which we should quote those by K. U. Ingold and coworkers, who found a good deal of isotope effect for the hydrogen transfer from α-tocopherol.[5]

In such a case fast, diffusion controlled, hydrogen transfers are expected[20] between phenolic substrates whose $D_{(O-H)}$ values range within 42.5 kJ mol^{-1}, the energy gap from the ground to the first excited vibrational level to a typical wavenumber about 3500 cm^{-1}. For those systems hydrogen transfer rate constants should be inherently independent of the equilibrium constant values.

We may conclude that although potential antioxidant reactivities of phenols can be well correlated with the stability of the phenoxyls generated, and both entities judged by means of the enthalpy change of the hydrogen transfer, entropy effects should not be neglected. They are indicative of polar influences which, together with resonance stabilization, are the origin of unexpected changes in selectivity, for reactions taking place in liquids. Moreover, the amount of the entropy change might be correlated with the average polarity of solvent mixtures, an aspect that we think deserves further study.

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