JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
*J. Phys. Org. Chem.* **12**, 144–150 (1999)

# Quantum mechanical evaluation of the anodic oxidation of phenolic compounds

**I. Vedernikova,[1] J. P. Tollenaere[2] and A. Haemers[1]***

[1]Department of Pharmaceutical Chemistry, Universitaire Instelling Antwerpen, Universiteitsplein 1, 2610 Antwerp, Belgium
[2]Janssen Research Foundation, Turnhoutseweg 30, 2340 Beerse, Belgium

*Received 16 February 1998; revised 26 May 1998; accepted 28 May 1998*

ABSTRACT: The electronic structures of a series of phenols, phenoxyl cation radicals and phenoxyl radicals were calculated by the AM1 method. On the basis of the presumed electrochemical reaction, the electronic structure criteria determining the antioxidant activity are discussed. Ionization potentials, absolute electronegativity, activation energy, difference in the heat of formation between the compounds and their radicals and spin distribution were found to be important criteria. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: phenols; anodic oxidation; electronic structure; quantum mechanics; AM1 method

## INTRODUCTION

Redox processes are very important in biochemistry and medicine. Phenolic compounds can interfere with these redox reactions and are interesting as tools in biochemical studies and as antioxidants in medicine. The low O—H bond energy and, hence, the easy formation of a free radical, acting as an effective alkylperoxyl radical trap, favour the inhibition of the free radical process taking place in biochemical oxidation reactions.

The antioxidant properties of phenolic compounds as active oxygen scavengers have been investigated in great detail: superoxide anions,[1–3] hydroxyl radicals,[2,4] lipid peroxidation[2,5,6] and nitric oxide radicals.[7] Pro-oxidant activity of phenolic compounds has also been reported and can be linked to their ability to autoxidize in the presence of dissolved oxygen. Superoxide anion radicals, hydroxyl radicals[8,9] or peroxides[10] can be produced in a one-electron redox reaction, with or without transition metal ions. The pro-oxidant activity of phenolic compounds may also be linked to their direct reduction of Fe(III) to Fe(II), resulting in the production of a hydroxyl radical through a Fenton reaction. During metabolic autoxidation of polyphenolic compounds in aqueous buffer, semiquinone radicals and quinones, the effective oxidants, are formed.[11] Moreover, the contribution of oxygen radicals to DNA cleavage by quinone compounds derived from phenolic antioxidants has been examined.[12]

The antioxidant properties can be tested with physicochemical methods such as electron paramagnetic resonance,[13,14] electrochemical oxidation[15,16] and reduction.[17] The half-wave oxidation potential of phenols ($Ep/2$) is considered to be a good parameter for describing antioxidant activity. Indeed, from a chemical point of view, the antioxidant activity of phenols is based on an electron transfer followed by phenolic hydrogen abstraction and on the stability of the free radical formed:

$$\mathrm{ArOH} \rightarrow \mathrm{e}^- + \mathrm{ArOH}^{+\cdot} \rightarrow \mathrm{H}^+ + \mathrm{ArO}^{\cdot}$$

This reaction can be measured in an anodic oxidation as a simplified model for biological antioxidant activity where the electron, released from the phenolic group, can combine with radical species such as hydroxyl- and peroxyl radicals. The radical transformation products also participate in the oxidation inhibition.

We looked for a correlation of this half-wave oxidation potential and different calculated parameters in a series of phenols in order to find a relationship between molecular properties and redox activities. If successful, this relationship may then be used to predict the antioxidative capacities of these compounds.

Physico-chemical properties and antioxidant activity have already been correlated with several theoretical parameters: Hammett constants,[16,17] the degree of overlap between the *p*-type lone pair electrons of oxygen with the aromatic ring[16,18] and with quantum chemical semi-empirically calculated differences of the heat of formation between the compound and its radical.[19]

In an electrochemical context, however, we have to keep in mind that phenols are oxidized to pyrocatechol and hydroquinone, the latter being oxidized to quinone. Hydroxylated aromatic compounds typically form dimeric products. The mechanism of dimer formation

---

**Correspondence to:* A. Haemers, Department of Pharmaceutical Chemistry, Universitaire Instelling Antwerpen, Universiteitsplein 1, 2610 Antwerp, Belgium. E-mail: haemers@uia.ua.ac.be

CCC 0894–3230/99/020144–07 $17.50

by anodic processes has not yet been studied, but probably involves a free radical stage. Tar formation of phenol radicals is an important drawback and is irreversible. Its influence on the reaction as a whole will depend on the amount of phenol converted into a tar-like oxidation product: the smaller this amount, the lower is the probability of electrode deactivation and of interference with the diffusion-controlled kinetics. The complexity of the anode process may affect the *E*p/2 values.

## EXPERIMENTAL

### Oxidation potentials

Half-wave redox potentials (*E*p/2) were determined from the first sweep of the oxidation wave in solutions (methanol in 0.1 M sodium phosphate buffer, pH 6.5) containing 0.1 mM of compound. Voltammograms were recorded with a glassy carbon electrode (Metrohm 6.1204.040). An ECO Autolab polarograph was used, controlled by GPES software.

### Calculations

All calculations were performed with the semiempirical AM1 method[20] employing MOPAC 6.0 software[21] in Insight II (MSI/BIOSYM, San Diego, CA, USA, 1995). Geometry optimizations were performed with the PRECISE keyword. The geometries of the parent compounds, their cation radicals and radicals were optimized using UHF followed by RHF calculation. Our AM1 geometry optimization for phenol corresponds with B3LYP/6-31G('p') obtained geometries and with experimental data.[22]

The unpaired spin density arising from an odd-electron system can be calculated with either RHF and UHF. In an UHF calculation the $\alpha$ and $\beta$ MOs have different spatial forms. Hence spin density is calculated as the difference between $\alpha$ and $\beta$ MOs. In the RHF formalism the multi-electron configuration interaction calculation (MECI) was performed with the ESR keyword.

A MECI calculation involves the interaction of microstates (microstates, also known as Slater determinants, represent configuration or patterns of occupancy of MOs) representing specific permutations of electrons in a set of MOs. Starting with a set electronic configuration, either closed-shell or open-shell, but UHF, the first step in a MECI calculation is the removal of the electrons to be used in the CI from the MOs. The total energy of the configuration is evaluated as the energy of the interactions of all previously defined configurations. Diagonalization then results in state functions and the spin states of the state functions.

The following parameters were selected: ionization potential (*IP*) and absolute electronegativity ($\chi$) of the free phenol, energy of activation ($\Delta\Delta H^{\ddagger}$), ionization potential (*IP*) and spin delocalization ($D_s$) of intermediate cation radicals and free radicals and finally the heat of formation of the radical ($\Delta\Delta H_R$). The experimentally obtained *E*p/2 values and the calculated parameters are summarized in Table 1.

It should be kept in mind that these calculations pertain to the *in vacuo* situation. Owing to the structural similarity of the compounds studied here, one may argue that solvation effects may be very similar throughout the series of compounds.

Linear regression analyses were computed using Microcal Origin 4.0 for Windows (Microcal Software, Northampton, PA, USA). All compounds tested (Table 1) were used in the regression analysis.

## RESULTS AND DISCUSSION

### Correlation of *E*p/2 with the ionization potential

The energy of the HOMO, determining the ionization potential (*IP*) (Koopman's theorem), can be correlated with the ability of the phenol to donate electrons. This correlation is presented in the following equation and in Fig. 1.

$$E\mathrm{p}/2 = 0.446 IP_{\mathrm{ArOH}} - 3.359$$

This equation holds for closed-shell molecules. In an open shell case the energy of the singly occupied MO cannot be directly related to the corresponding ionization potential. Making the usual assumption that the MOs remain unchanged during the ionization process, the ionization potential of the radical is given by

$$IP = -E^{\circ} + 1/2J^{\circ\circ}$$

where $E^{\circ}$ is the orbital energy of the singly occupied MO and $J^{\circ\circ}$ is the corresponding Coulomb integral.[24]

A good relationship was found between the ionization potential of the corresponding radical species and the oxidation potential (Fig. 1). It may be described by the following equation:

$$E\mathrm{p}/2 = 0.343 IP_{\mathrm{ArOH}^{+\cdot}} - 4.282$$

and

$$E\mathrm{p}/2 = 0.405 IP_{\mathrm{ArO}\cdot} - 2.893$$

Figure 2 shows the ionization potential of phenols in more detail.

Calculation for nitrogen-containing compounds met with some difficulties. In contrast with experiments, almost all $sp^3$ nitrogen systems are predicted to be pyramidal and the charge on nitrogen atoms is most likely of incorrect sign and unrealistic magnitude. In this case, the ionization potentials need to be corrected using the outer valence Green's function (OVGF) technique. The OVGF technique is used with the self-energy extended to

**Table 1.** Experimentally obtained *E*p/2 values and the calculated parameters

| No. | Compound | *E*p/2 | $IP_{ArOH}$ | $\chi$ | $\Delta\Delta H^{\ddagger}$ | $IP_{ArOH^{+\cdot}}$ | $D_{sArOH^{+\cdot}}$ | $\Delta\Delta H_R$ | $IP_{ArO\cdot}$ | $D_{sArO\cdot}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4-Aminophenol | 0.148 | 8.27 | 3.92 | 174.19 | 13.24 | 0.125 | 30.51 | 7.68 | 0.125 |
| 1a | 4-Acetaminophenol | 0.28[a] | 8.46 | 4.09 | 180.38 | 13.51 | 0.077 | 32.85 | 8.06 | 0.077 |
| 1b | 3,5-Dimethyl-4-acetaminophenol | 0.21[a] | 8.34 | 4.00 | 176.80 | 12.99 | 0.053 | 31.00 | 7.82 | 0.053 |
| 1c | 3,5-Dimethoxy-4-acetaminophenol | 0.12[a] | 8.32 | 4.02 | 175.50 | 12.97 | 0.048 | 30.74 | 7.60 | 0.050 |
| 1d | 3,5-Dithiomethyl-4-acetaminophenol | 0.12[a] | 7.83 | 3.88 | 169.40 | 11.98 | 0.048 | 26.56 | 7.35 | 0.048 |
| 1e | 3,5-Difluoro-4-acetaminophenol | 0.32[a] | 8.87 | 4.58 | 190.24 | 13.63 | 0.067 | 31.52 | 7.81 | 0.067 |
| 1f | 3,5-Dichloro-4-acetaminophenol | 0.34[a] | 8.78 | 4.51 | 186.91 | 13.36 | 0.067 | 32.03 | 8.24 | 0.067 |
| 1g | 3,5-Dibromo-4-acetaminophenol | 0.32[a] | 8.83 | 4.60 | 187.79 | 13.34 | 0.067 | 32.86 | 8.37 | 0.067 |
| 2 | 5-Hydroxyindole | 0.370 | 8.30 | 4.07 | 180.63 | 13.37 | 0.091 | 34.12 | 7.91 | 0.100 |
| 3 | 2,4,6-tri(*tert*-butyl)phenol | 0.399 | 8.64 | 4.04 | 182.68 | 13.49 | 0.029 | 31.27 | 8.18 | 0.037 |
| 4 | 2,6-Di(*tert*-butyl)-4-methylphenol | 0.409 | 8.62 | 4.05 | 183.57 | 13.54 | 0.029 | 29.29 | 8.19 | 0.037 |
| 5 | 2,6-Di(*tert*-butyl)phenol | 0.424 | 8.80 | 4.17 | 193.55 | 13.95 | 0.032 | 36.04 | 8.39 | 0.043 |
| 6 | 3-Dimethylaminophenol | 0.487 | 8.31 | 3.86 | 177.48 | 13.74 | 0.060 | 38.85 | 8.65 | 0.071 |
| 7 | 4-Methoxyphenol | 0.509 | 8.65 | 4.17 | 177.19 | 13.76 | 0.090 | 30.64 | 8.26 | 0.100 |
| 8 | 2,4-Di(*tert*-butyl)phenol | 0.519 | 8.78 | 4.11 | 187.97 | 13.79 | 0.036 | 34.74 | 8.36 | 0.051 |
| 9 | 4-(*tert*-Butyl)phenol | 0.602 | 8.89 | 4.22 | 192.50 | 14.13 | 0.059 | 36.41 | 8.54 | 0.077 |
| 10 | 2,6-Dimethylphenol | 0.602 | 8.88 | 4.24 | 192.76 | 14.32 | 0.077 | 34.17 | 8.42 | 0.077 |
| 11 | Acetovanillone | 0.621 | 9.08 | 4.33 | 194.82 | 14.18 | 0.062 | 36.62 | 8.59 | 0.067 |
| 12 | 3-Methylphenol | 0.651 | 9.02 | 4.31 | 196.81 | 14.61 | 0.090 | 37.78 | 8.74 | 0.100 |
| 13 | 2-(*tert*-Butyl)phenol | 0.653 | 8.93 | 4.24 | 193.75 | 14.33 | 0.056 | 37.45 | 8.57 | 0.067 |
| 14 | 3-Aminophenol | 0.655 | 8.53 | 4.00 | 183.31 | 13.99 | 0.111 | 38.43 | 8.77 | 0.100 |
| 15 | 3-(*tert*-Butyl)phenol | 0.663 | 8.99 | 4.28 | 194.76 | 14.47 | 0.053 | 37.44 | 8.68 | 0.067 |
| 16 | 2-Methylphenol | 0.675 | 8.96 | 4.22 | 195.23 | 14.48 | 0.100 | 36.09 | 8.59 | 0.100 |
| 17 | 4-Methylphenol | 0.680 | 8.88 | 4.22 | 193.63 | 14.22 | 0.091 | 36.32 | 8.53 | 0.091 |
| 18 | 2,6-Difluorophenol | 0.704 | 9.46 | 4.89 | 207.24 | 15.10 | 0.111 | 35.17 | 8.92 | 0.111 |
| 19 | 3-Chlorophenol | 0.707 | 9.34 | 4.66 | 204.08 | 14.87 | 0.125 | 38.62 | 9.05 | 0.125 |
| 20 | 3-Methoxyphenol | 0.714 | 8.88 | 4.26 | 192.83 | 14.31 | 0.091 | 37.60 | 8.87 | 0.091 |
| 21 | 4-Chlorophenol | 0.721 | 9.12 | 4.51 | 199.15 | 14.38 | 0.125 | 36.85 | 8.83 | 0.125 |
| 22 | 3-Fluorophenol | 0.736 | 9.37 | 4.67 | 205.98 | 15.09 | 0.125 | 39.08 | 9.14 | 0.125 |
| 23 | 3,5-Dimethoxyphenol | 0.739 | 8.96 | 4.27 | 193.02 | 14.28 | 0.067 | 39.25 | 8.97 | 0.072 |
| 24 | 3-Hydroxybenzaldehyde | 0.844 | 9.44 | 4.99 | 205.18 | 14.98 | 0.125 | 38.68 | 9.07 | 0.111 |
| 25 | Phenol | 0.846 | 9.11 | 4.36 | 199.48 | 14.85 | 0.143 | 37.66 | 8.80 | 0.143 |
| 26 | 4-Hydroxybenzaldehyde | 0.858 | 9.49 | 4.97 | 207.41 | 14.89 | 0.111 | 39.91 | 9.16 | 0.111 |
| 27 | 4-Hydroxyacetophenone | 0.858 | 9.42 | 4.90 | 205.27 | 14.79 | 0.083 | 39.53 | 9.09 | 0.100 |
| 28 | 3-Nitrophenol | 0.881 | 9.95 | 5.56 | 216.76 | 15.45 | 0.111 | 40.71 | 9.56 | 0.100 |
| 29 | $\alpha,\alpha,\alpha$-Trifluoro-*p*-cresol | 0.890 | 9.79 | 5.07 | 213.70 | 15.34 | 0.100 | 40.57 | 9.51 | 0.100 |
| 30 | 3-Hydroxyacetophenone | 0.927 | 9.39 | 4.93 | 203.80 | 14.91 | 0.125 | 38.33 | 9.01 | 0.100 |
| 31 | $\alpha,\alpha,\alpha$-Trifluoro-*m*-cresol | 0.936 | 9.68 | 5.05 | 212.67 | 15.34 | 0.091 | 39.57 | 9.51 | 0.111 |
| 32 | 4-Nitrophenol | 0.985 | 10.07 | 5.57 | 219.80 | 15.50 | 0.111 | 41.55 | 9.80 | 0.100 |

[a] Data from Ref. 23.

include a third-order perturbation correction.[25] This correction was performed with the GREENF(NOCC) keyword where the total number of occupied orbitals is included in the Green's function calculation.

## Correlation with absolute electronegativity ($\chi$)

Any chemical system is characterized by its electronic chemical potential, its absolute electronegativity and its absolute hardness.[26] A high $\chi$ value is an indication of strong Lewis acid properties.

A correlation could be established between the absolute electronegativity and *E*p/2 (Fig. 3). When $\chi$ decreases, *E*p/2 also decreases. If $\chi$ is, however, sufficiently small (compounds with weak Lewis acid properties), *E*p/2 decreases more rapidly. This relationship can be described by a Boltzmann function and gives rise to a sigmoidal curve:

$$Ep/2 = -1.01/(1 + e^{25.79\chi - 25.799}) + 0.866$$

This implies that only for phenolic compounds with low electronegativity (<4.3 eV) does *E*p/2 change significantly with the absolute electronegativity.

## Correlation with the propensity for radical formation

A simplified reaction profile of phenolic oxidation is shown in Fig. 4. The propensity for radical formation of phenols can be estimated by $\Delta\Delta H_R$ and $\Delta\Delta H^{\ddagger}$.

We calculated $\Delta\Delta H_R$ as the difference in the heat of

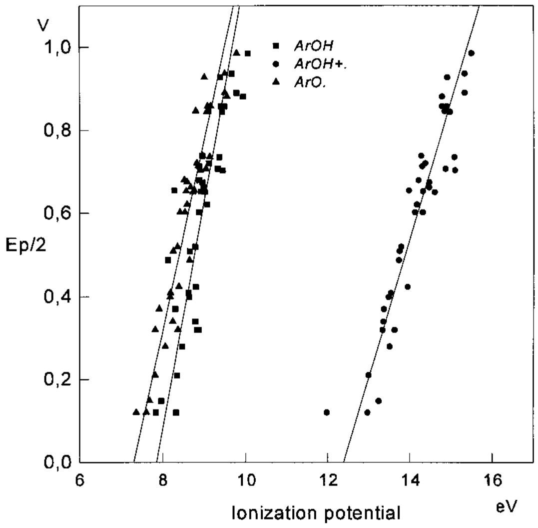

**Figure 1.** Correlation of *E*p/2 with ionization potential. The correlation coefficients are 0.9446 (ArOH), 0.8581 ($ArOH^{+\bullet}$) and 0.9404 ($ArO^\bullet$)

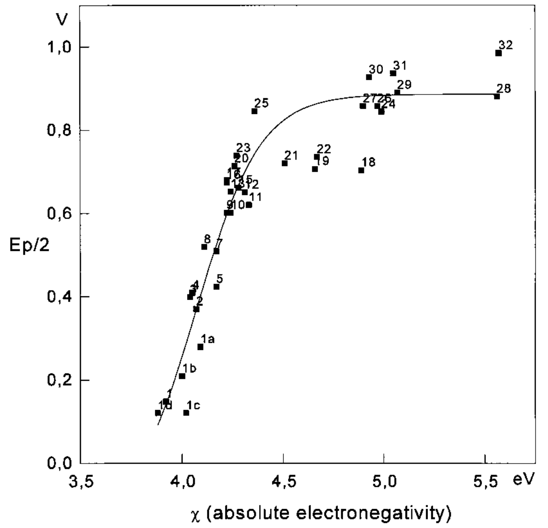

**Figure 3.** Correlation of *E*p/2 with absolute electronegativity

formation between neutral phenol (ArOH) and phenolic radical ($ArO^\bullet$). According to Burton *et al.*,[27] this difference is a measure of the strength of the O—H bond. The data show free radical formation to be endothermically facilitated by donor and hindered by acceptor substituents (Fig. 5). We found an improved relationship between *E*p/2 and $\Delta\Delta H_R$ when the latter is corrected by the ionization potential, demonstrating that electron-donating properties of phenolic compounds can be better explained by combining the propensity of radical formation and the relative HOMO (Fig. 6). $IP_{min}$ is the lowest *IP* value found among the compounds in Table 1.

A very similar relationship was found when the

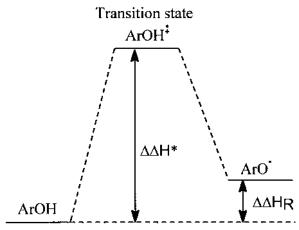

**Figure 4.** Simplified reaction profile of phenolic oxidation

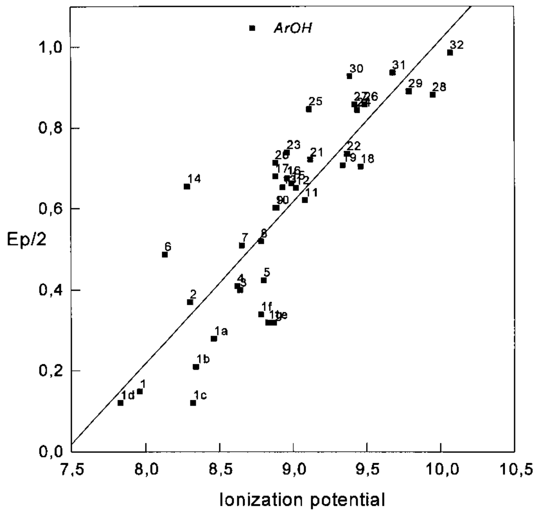

**Figure 2.** Correlation of *E*p/2 with ionization potential. *E*p/2 = (0.399 ± 0.39) *IP* - (2.974 ± 0.351); *n* = 32, *r* = 0.858, SD = 0.126

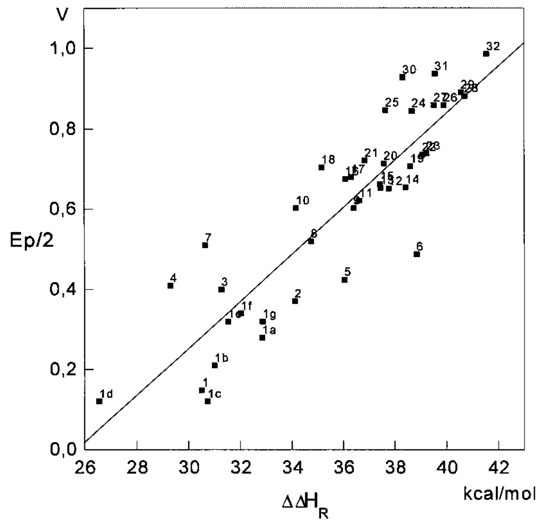

**Figure 5.** Correlation of *E*p/2 with propensity for radical formation. *E*p/2 = (0.058 ± 0.005) $\Delta\Delta H_R$ − (1.503 ± 0.179); *n* = 32, *r* = 0.889, SD = 0.113

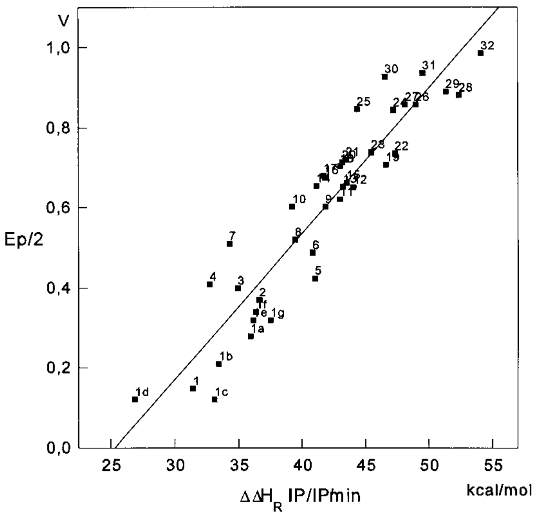

**Figure 6.** Correlation of *E*p/2 with corrected propensity for radical formation. $Ep/2 = (0.036 \pm 0.002)\ \Delta\Delta H_R IP/IP_{min} - (0.920 \pm 0.097)$; $n = 32$, $r = 0.934$, SD = 0.088

parameters were taken in a linear correlation:

$$Ep/2 = 0.118(0.22\Delta\Delta H_R + 0.103IP) - 2.849$$

where *IP* is in kcal mol$^{-1}$ (1 eV = 23.060 kcal mol$^{-1}$) (Fig. 7).

The transfer of the phenolic hydrogen is indeed the rate-limiting step in the reaction between a phenol and a peroxyl radical. This is in agreement with a large deuterium kinetic isotope effect in the phenol-mediated peroxidation.[10] The intermediate cation radical transition state may be very important in the reaction. We calculated the corresponding energy of activation ($\Delta\Delta H^{\ddagger}$) of the cation radical transition state as the difference in heat of formation between cation radical and phenol. The correlation is shown in Fig. 8.

In addition, we observed a linear relationship between

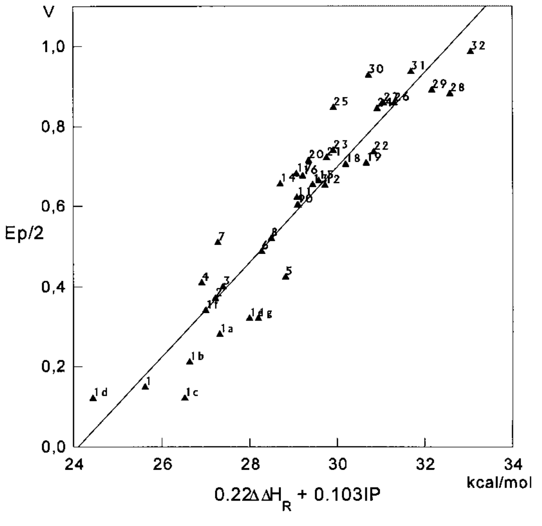

**Figure 7.** Correlation of *E*p/2 with propensity for radical formation and ionization potential. $Ep/2 = (0.118 \pm 0.007)$ $(0.22\ \Delta\Delta H_R + 0.103\ IP) - (2.894 \pm 0.209)$; $n = 32$, $r = 0.938$, SD = 0.085

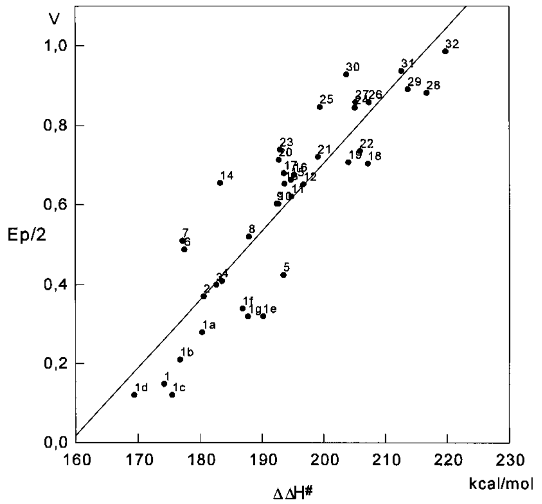

**Figure 8.** Correlation of *E*p/2 with energy of activation of the cation radical transition state. $Ep/2 = (0.017 \pm 0.001)\Delta\Delta H^{\ddagger} - (2.727 \pm 0.282)$; $n = 32$, $r = 0.889$, SD = 0.112

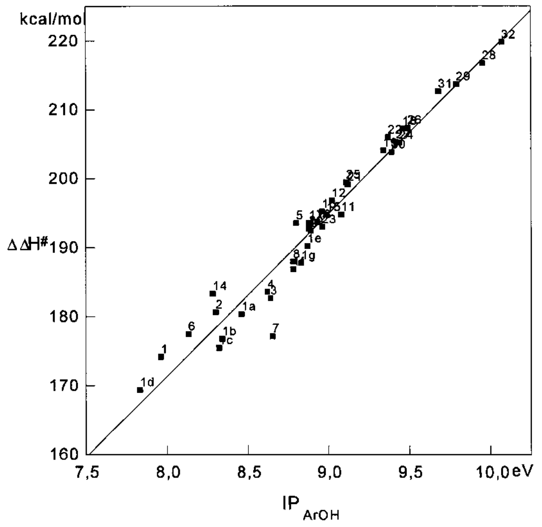

**Figure 9.** Correlation of energy of activation with ionization potential. $\Delta\Delta H^{\ddagger} = (23.563 \pm 0.824)IP - (17.130 \pm 7.377)$; $n = 39$, $r = 0.987$, $SD = 2.644$

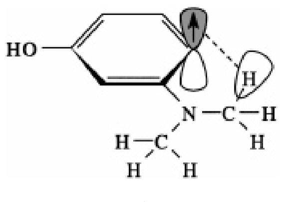

**Figure 10.** Spin polarization of the *p*-electron of carbon with the orthogonal hydrogen of 3-dimethylaminophenol

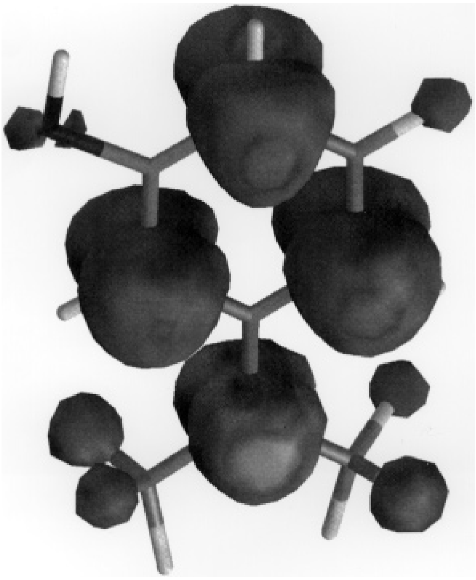

**Figure 11.** Spin delocalization of 3-dimethylaminophenol (obtained with SPARTAN, from Wavefunction, Irvine CA, USA)

the energy of activation ($\Delta\Delta H^{\ddagger}$) and the ionization potential (Fig. 9), showing consistency in our calculations.

## Importance of hyperconjugative interaction for radical stability

The free radical is stabilized by electron delocalization in a conjugated system. The stability of the radical species depends on the part of the molecule involved. Two series of molecules can be distinguished. One series contains strong electron-donating substituents such as amino and methoxy groups while substituents in the other series such as *tert*-butyl-substituted phenols are able to provide appreciable hyperconjugative interaction between an unpaired electron in a *p*-orbital on carbon, oxygen or nitrogen with hydrogen.

This is explained as follows: MO calculations place the odd electron in a $\pi^*$-antibonding orbital having its largest *p*-orbital coefficients at C-$\alpha$. The $\alpha$-position is assumed to have the highest $\pi$-electron spin population. Coupling is transmitted through the bonding electrons, but the unpaired electron is located in an orbital orthogonal to the sp$^2$-orbitals where the hydrogen atoms are attached. The pair of electrons in the *p*-atom bond are spin-polarized in such a way that one, having its spin parallel to that of the unpaired electron, spends more time at the carbon end of the bond (a manifestation of Hund's rule); the electron which spends more time associated with hydrogen is therefore of opposite spin to the odd electron. This is illustrated for *m*-dimethylaminophenol in Figs 10 and 11. Figure 11 shows a higher spin density on the H-atoms near the aromatic ring.

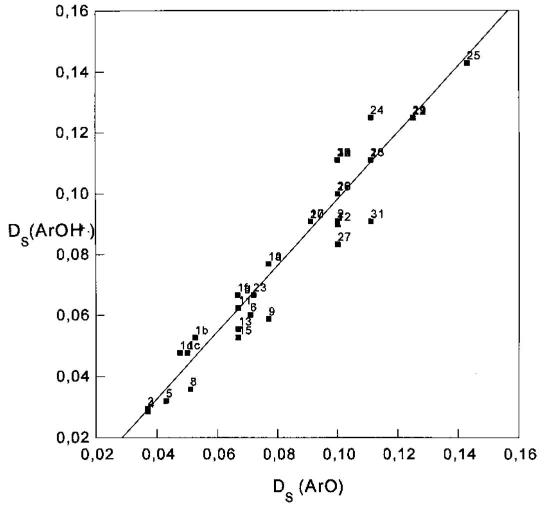

**Figure 12.** Correlation of spin distribution of free radicals with spin distribution of cation radicals. $D_S$ (ArOH$^{+\cdot}$) = (1.095 ± 0.047) $D_S$ (ArO$^{\cdot}$) − (0.011 ± 0.001); $n = 32$, $r = 0.967$, $SD = 0.008$

We calculated the spin distribution of free radicals and the corresponding cation radicals as a sum of the square of coefficients of SOMO divided by the number of atoms bearing the unpaired electron ($D_S$). This parameter can be used for quantitative estimation of radical stabilization. Figure 12 shows $D_S$ of the free radicals and their corresponding cation radicals and the linear relationship between them. Compounds with the lowest $D_S$ values show the best stabilization capacity (Fig. 12).

## CONCLUSION

We evaluated the anodic half-wave oxidation potential (*E*p/2) as a potential parameter for the determination of the antioxidant activity of phenolic compounds by comparing these experimental values with computed molecular properties.

The corresponding ionization potential (*IP*), absolute electronegativity ($\chi$), propensity for radical formation calculated as the difference in heat of formation between phenol and its radical ($\Delta\Delta H_R$), corrected by *IP* and the energy of activation of the cation radical transition state, calculated as the difference in heat of formation between this radical cation and the phenol ($\Delta\Delta H^{\ddagger}$), correlate very well with the measured oxidation potential, indicating that the model employed (ArOH$^{+\cdot}$) allows one to estimate the redox properties of phenolic compounds.

The correlation between $\chi$ and *E*p/2, however, follows a Boltzmann function and the electronegativity of strong Lewis acids ($\chi > 4.5$ eV) does not correlate with their *E*p/2 values. A correlation of *E*p/2 with a function combining *IP* and $\Delta\Delta H_R$ gives the best results.

We have to keep in mind that potential antioxidant activity is due to electron-releasing properties and to radical stabilization. Radical stabilization can be induced by electron-attracting functions and by hyperconjugation. It is a matter of course that the latter is far more important in antioxidant compounds. The hyperconjugation possibility should be considered as an important property of substituted phenolic compounds and can be shown by using spin distribution ($D_s$). Hence, $E$p/2 can be used to evaluate the antioxidant activity of a phenol. Compounds with high antioxidant activity will combine low $E$p/2 values with a pronounced spin distribution in the corresponding free radical.

## REFERENCES

1. J. Robak and R. J. Gryglewski, *Biochem, Pharmacol.* **37**, 837–841 (1988).
2. Y. Hanasaki, S. Ogawa and S. Fukui, *Free Rad. Biol. Med.* **16**, 845–850 (1994).
3. G. Rastelli, L. Constantino and A. Albasini, *Eur. J. Med. Chem.* **30**, 141–146 (1995).
4. S. Rafat Husain, J. Cillard and P. Cillard, *Phytochemistry* **26**, 2489–2491 (1981).
5. J. Torel, J. Cillard and P. Cillard, *Phytochemistry* **25**, 383–385 (1986).
6. A. K. Ratty and N. P. Das, *Biochem. Med. Metab. Biol.* **39**, 69–79 (1988).
7. S. A. B. E. Van Acker, M. N. J. L. Tromp, G. R. M. M. Haenen, J. F. Wim van der Vijgh and A. Bast, *Biochem. Biophys. Res. Commun.* **214**, 755–759 (1995).
8. M. J. Burkitt and L. Milne, *FEBS Lett.* **379**, 51–54 (1996).
9. G. Cao, E. Sofic and R. L. Prior, *Free Rad. Biol. Med.* **22**, 749–760 (1997).
10. P. K. Witting, V. W. Bowry and R. Stocker, *FEBS Lett.* **375**, 45–49 (1995).
11. P. Wardman, *J. Phys. Chem. Ref. Data* **18**, 1637–1755 (1989).
12. T. Okubo, F. Nagai, K. Ushiyama and I. Kano, *Toxicol. Lett.* **90**, 11–18 (1997).
13. P. Rapta, V. Misik, A. Stasko and I. Vrabel, *Free Rad. Biol. Med.* **18**, 901–908 (1995).
14. K. Nakagawa, S. Tero-Kubota, Y. Ikegami and N. Tsuchihashi, *Photochem. Photobiol.* **60**, 199–204 (1994).
15. K. Mukai, K. Fukuda, K. Tajima and K. Ishizu, *J. Org. Chem.* **53**, 430–432 (1988).
16. S. A. B. E. van Acker, L. M. H. Koymans and A. Bast, *Free Rad. Biol. Med.* **15**, 311–328 (1993).
17. S. V. Jovanovic, M. Tosic and M. G. Simic, *J. Phys. Chem.* **95**, 10824–10827 (1991).
18. T. Doba, G. W. Burton and K. U. Ingold, *J. Am. Chem. Soc.* **105**, 6506–6508 (1983).
19. F. G. Bordwell and X.-M. Zhang, *J. Phys. Org. Chem.* **8**, 529–535 (1995).
20. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.* **107**, 3902–3909 (1985).
21. J. J. P. Stewart, *J. Comput. Aided Mol. Des.* **4**, 1–105 (1990).
22. J. S. Wright, D. J. Carpenter, D. J. McKay and K. U. Ingold, *J. Am. Chem. Soc.* **119**, 4245–4252 (1997).
23. J. G. M. Bessems, H.-D. Gaisser, J. M. Te Koppele, W. P. Van Bennekom, J. N. M. Commandeur and N. P. E. Vermeulen, *Chem–Biol. Interact.* **98**, 237–250 (1995).
24. M. J. S. Dewar, H. W. Kollmar and S. H. Suck, *Theor. Chim. Acta* **36**, 237–239 (1975).
25. L. S. Cederbaum and W. Domcke, *Adv. Chem. Phys.* **36**, 206–210 (1977).
26. R. G. Pearson, *J. Mol. Struct. (THEOCHEM)* **87**, 261–265 (1992).
27. G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad and K. U. Ingold, *J. Am. Chem. Soc.* **107**, 7053–7056, (1985).