Calculation of the relative acidities and oxidation potentials of *para*-substituted phenols. A model for α-tocopherol in solution

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Relative acidities (ΔpK_a) of phenols and oxidation potentials (ΔE_{ox}) of the phenoxide anions have been calculated for nine *para*-substituted phenols using density functional theory. Solvent effects were incorporated using the conductor-like polarisable continuum method. Using the calculated ΔpK_a and ΔE_{ox} values in a thermodynamic cycle, the ΔBDE (bond dissociation enthalpy) of the phenols were also determined with all values calculated to within 1.5 kcal mol^{-1} of experiment. The ΔpK_a and ΔE_{ox} values were calculated for 6-hydroxy-2,2,5,7,8-pentamethylchroman (HPMC), a model for α-tocopherol for which there are no known experimental values. The acidity of this compound is raised by 2.4 pK_a units and lowered by −0.79 V relative to phenol with a calculated ΔBDE of −14.9 kcal mol^{-1}. There is a negative correlation ($r^2 = 0.86$) between the ΔpK_a and the ΔBDE values. A stronger and positive correlation is found between the ΔE_{ox} ($r^2 = 0.98$) and the ΔBDE values. Using these correlations it is uncovered that hydrogen abstraction of phenols, as measured by the ΔBDE, is driven by electron transfer rather than by proton transfer.

Introduction

It is becoming increasingly clear that certain antioxidants, a substantial number of which are phenols, are able to cross the blood–brain barrier and attenuate neurological dementia diseases.[1] At physiological pH, a change in protonation state can influence the rate at which a molecule will diffuse across membranes and other barriers such as the blood–brain barrier. Researchers studying the antioxidant capabilities of substituted phenols are therefore very interested in predictions of pK_a as one part of an integrated approach to lead identification for new therapeutic drugs.[2] Vitamin E (α-tocopherol) for example can donate a hydrogen in order to scavenge peroxyl radicals and thereby prevents the build-up of oxidative metabolites induced by amyloid β protein. Since vitamin E protects against the toxicity of amyloid β protein, it has been used in clinical trials for the treatment of Alzheimer's disease.[1]

In some cases, certain phenolic compounds act as radical trapping antioxidants through a sequential proton loss electron transfer (SPLET) mechanism.[3] Consequently, an understanding of substituent effects on, not only the pK_a of phenols, but also the oxidation potentials of the phenoxide anions becomes pertinent to the discussion of the SPLET mechanism. Determination of both ΔpK_a and ΔE_{ox} can lead to ΔBDE using a thermodynamic cycle proposed by Bordwell and Cheng,[4] given by eqn (1).

$$\Delta\mathrm{BDE} = 1.37\Delta pK_a + 23.06\Delta E_{ox} \qquad (1)$$

Currently, there are numerous studies that implicate the BDE or ΔBDE as a reliable measure of phenolic antioxidant activity, with ΔBDE being the difference between substituted phenols and phenol, *i.e.* BDE(X) − BDE(H). Both the BDE and ΔBDE can be obtained experimentally and computationally. Theoretical calculations appear to be gaining popularity in this field of research[5–9] largely owing to an increase in computational power, opening up the use of high-level electronic structure methods, particularly those rooted in density functional theory.[10–12]

There is one particular study devoted to the calculation of ΔpK_a of *ortho*-substituted phenols.[13] The authors of this study showed that calculation of the ΔpK_a values led to significant errors when compared to experiment. They concluded that although the correct trends were observed, *i.e.* substituent effects of the ΔpK_a are shifted in the right direction, the values of the ΔpK_a are somewhat exaggerated. Furthermore, they also found that there was no significant relationship between the ΔpK_a of phenols and the ΔBDEs of phenols. This observation can be explained by the fact that the ΔBDE is also dependent on the ΔE_{ox} of the phenoxide anion, with summation of the two leading to the overall ΔBDE as shown in eqn (1). We are not aware of any theoretical calculations that have been undertaken in order to determine the ΔE_{ox} values of phenoxide anions. There are, however, a number of studies devoted to determination of substituent effects on the BDE of phenols.[14,15]

Theoretical calculations of pK_a values require determination of both gas phase and solution phase free energies, with the former widely accepted to produce results matching experiment.[16] Continuum methods are popular in the determination of ΔpK_a values in solution. On one hand some researchers indicate that continuum methods are very reliable for the determination of absolute pK_a values of phenols, which would also translate into accurate ΔpK_a calculations.[17] On the other hand some investigators have noted that determination of ΔpK_a through theoretical calculations, in conjunction with continuum methods, is somewhat unreliable when compared to experiment.[18]

Our objective in this study is to re-evaluate the nature of substituent effects on the relative acidity of *para*-substituted phenols. To the best of our knowledge, not many computational studies have addressed the determination of the oxidation potentials of the phenoxide anion, as we do here. With these two

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properties evaluated we can then explore the way in which proton and electron transfers influence the relative bond dissociation enthalpies of phenols. Finally we calculate the ΔpK_a and ΔE_{ox} for 6-hydroxy-2,2,5,7,8-pentamethylchroman (HPMC), a model for α-tocopherol where the long phytol ($C_{16}H_{33}$) tail is replaced by a methyl group.

Computational methods

We use an isodesmic approach shown in Fig. 1 to calculate the relative acidities (ΔpK_a) and oxidation potentials (ΔE_{ox}),[19] given by eqn (2)–(5)

$$\Delta\Delta G_{pt} = (E[\text{X-PhOH}] - E[\text{X-PhO}^-]) - (E[\text{PhOH}] - E[\text{PhO}^-]) \quad (2)$$

$$\Delta\Delta G_{et} = (E[\text{X-PhO}^-] - E[\text{X-PhO}^\bullet]) - (E[\text{PhO}^-] - E[\text{PhO}^\bullet]) \quad (3)$$

where pt refers to proton transfer and et to electron transfer. The ΔpK_a (log units) and ΔE_{ox} (V) are calculated using eqn (4) and (5).

$$\Delta pK_a = -0.73\Delta\Delta G_{pt} \quad (4)$$

$$\Delta E_{ox} = -0.0434\Delta\Delta G_{et} \quad (5)$$

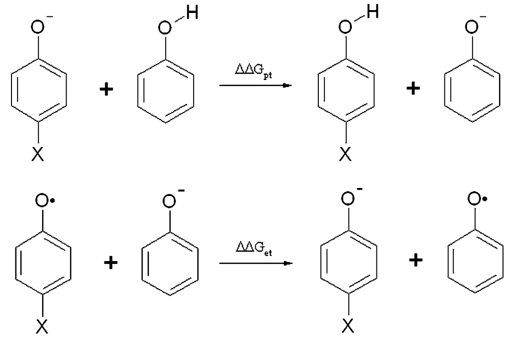

Fig. 1 Isodesmic reaction scheme for the determination of relative acidity (ΔpK_a) oxidation potential (ΔE_{ox}).

Bordwell and Cheng have determined pK_a values for many organic compounds including many phenols, from which we have selected nine *para*-substituted phenols[4] as shown in Table 1.

Table 1 All computed relative acidities (ΔpK_a/log unit), oxidation potentials (ΔE_{ox}/V) and bond dissociation enthalpies (ΔBDE/kcal mol^{-1}) of the phenols in this study

Substituent (X)	ΔpK_a Calc	ΔpK_a Expt	ΔE_{ox} Calc	ΔE_{ox} Expt	ΔBDE Calc	ΔBDE Expt
H	0.0	0.0	0.0	0.0	0.0	0.0
CH_3	1.38	0.90	−0.16	−0.10	−1.8	−1.1
$(CH_3)_3$	1.49	1.05	−0.15	−0.11	−1.4	−1.1
OCH_3	1.46	1.10	−0.37	−0.29	−6.5	−5.3
OH	1.76	1.76	−0.41	−0.47	−7.1	−8.3
NH_2	4.44	2.75	−0.81	−0.71	−12.5	−12.6
Cl	−1.16	−1.25	0.09	0.09	0.5	0.4
CN	−5.14	−4.80	0.56	0.48	5.9	4.4
CF_3	−3.48	−2.80	0.41	0.40	4.6	5.5
HPMC	2.40	—	−0.79	—	−14.9	−10.1[a]

[a] Experimental value taken from Lucarini *et al.*[22]

Geometry optimisation of the parent phenols and the corresponding phenoxide anions was carried out using the hybrid density functional theory, B3LYP, with the aug-cc-pVTZ basis set. For the closed-shell parent phenol and the phenoxide anions we used the restricted form of the B3LYP functional to perform the calculations. For the radical species we employed the unrestricted B3LYP form of the functional. In the isodesmic approach used here, zero-point energies, enthalpy corrections and entropy differences approximately cancel out between un-substituted and substituted phenols. Hence no explicit corrections are made in this study.

The solution phase calculations were done using the conductor-like polarised continuum model (C-PCM) method[20] with single-point calculations carried out on the gas phase geometry optimised phenols. The whole calculation in standard notation is denoted as C-PCM-B3LYP/aug-cc-pVTZ//B3LYP/aug-cc-pVTZ. All calculations were performed in the solvent dimethylsulfoxide (DMSO) (dielectric constant ε = 46.7), consistent with experiment. All calculations were carried out using the GAUSSIAN03 suite of programs.[21]

Results and discussion

It is important to clarify the interpretation of the sign of the reported values. A negative ΔpK_a indicates an increase in acidity relative to (parent) phenol since $\Delta pK_a = pK_a(X) - pK_a(H) < 0$ infers that the substituted phenol has a lower pK_a value than the parent. Secondly, a negative ΔE_{ox} indicates a lowering of the oxidation potential relative to phenol since $\Delta E_{ox} = E_{ox}(X) - E_{ox}(H)$. Conversely, a positive ΔE_{ox} value means that it is more difficult (*i.e.* it requires more energy) to remove an electron from the substituted phenol compared to the parent phenol. Finally, a negative ΔBDE also means a lowering of the BDE relative to phenol. In other words, in that case, abstraction of a hydrogen from the substituted phenol is facilitated compared to the parent phenol.

For the relative acidities, the results in Table 1 can be discussed in terms of two effects, namely the stabilisation of the parent phenol and destabilisation of the corresponding anion. For electron withdrawing groups, X = Cl, CN and CF_3, the anion is strongly stabilised through resonance with the net overall effect being an increase in acidity of phenols. In contrast, the electron donating groups, X = CH_3, $C(CH_3)_3$, OCH_3, OH, and NH_2 destabilise the anion and cause a decrease in acidity. Overall, the calculated relative acidities show good agreement with experiment, the mean absolute deviation being 0.5 pK_a log units, corresponding to an accuracy of 0.7 kcal mol^{-1} (using eqn (4)). The most significant deviation is registered at 1.69 log units for the NH_2 substituent. For the electron withdrawing groups, the values for X = Cl, CN and CF_3 show a deviation from experiment of 0.09, 0.34 and 0.68 log units, respectively. These compounds benefited most of the addition of diffuse functions, which are essential in the modelling of anions. Overall, discrepancies may be attributed in part to solvation energies being obtained for gas phase geometries. Optimisation in solvent would probably lead to more accurate results, particularly for the anion but such calculations are time consuming especially when considering larger compounds.

The relative oxidation, ΔE_{ox}, is also dependent on the stabilisation or destabilisation of both the anion and the radical. It is clear from both experimental and calculated values that the destabilisation of the anion combined with the ability of electron donors to stabilise the spin density facilitates electron transfer. The electron withdrawing groups are not able to stabilise the spin density in the radical and the ΔE_{ox} have positive values indicating electron transfer is not favoured. Our calculations show very good agreement with experiment, with a maximum discrepancy of 0.10 V.

As an example of how to interpret the values in Table 1 we quote *para*-CN phenol. Compared to phenol, the calculated ΔpK_a value of −5.14 log units for this substituted phenol indicates that removing a proton is easy. The oxidation potential, however, is raised by 0.56 V compared to phenol, which means that electron abstraction is difficult. Using eqn (1) one can assess how these two opposing effects weigh up against each other. From $\Delta BDE = 1.37 \times (-5.14) + 23.06 \times (0.56) = -7.0 + 12.9 = 5.9$ kcal mol^{-1} it is clear that the difficult electron abstraction (*i.e.* oxidation) dominates the proton removal in terms of energy contributions. The calculated ΔBDE has the largest positive value in Table 1 and expresses that hydrogen abstraction is difficult.

For all the phenols in this study, the errors in the ΔpK_a and the ΔE_{ox} calculations cancel out in the calculation of ΔBDE. All calculated values agree with experiment to within 1.5 kcal mol^{-1}, the mean absolute deviation being 0.7 kcal mol^{-1}. In terms of energy, the mean absolute deviation of E_{ox} is almost twice as large or 1.2 kcal mol^{-1}, and also 0.7 kcal mol^{-1} for pK_a. Therefore, we must conclude that the errors that are seen for the calculation of the pK_a and E_{ox} values must lie within the energy calculations of the anion. The reason for this is simply that the overall determination of the overall ΔBDE can be calculated by summing eqn (2) and (3) which lead to the cancellation of the anionic species (see also Fig. 1).

Fig. 2 shows the correlation between the relative acidities and the relative bond dissociation enthalpies. The three electron-withdrawing substituents appear in the upper left quadrant and the five electron-donating ones in the bottom right quadrant. The correlation coefficient, r^2, for experimental values is 0.75, somewhat worse than the coefficient ($r^2 = 0.86$) for the computed values. One would expect that if it is easy to remove a proton it will also be easy to remove a hydrogen atom. However, the negative gradient of Fig. 2 signifies exactly the opposite trend. An increase in acidity corresponds to a proportional decrease in ΔBDE. In terms of antioxidant activity the most active antioxidant as measured here is the *para*-NH_2 phenol with a ΔBDE of −12.5 kcal mol^{-1}. This compound is the least acidic phenol with a ΔpK_a of 4.44 log units.

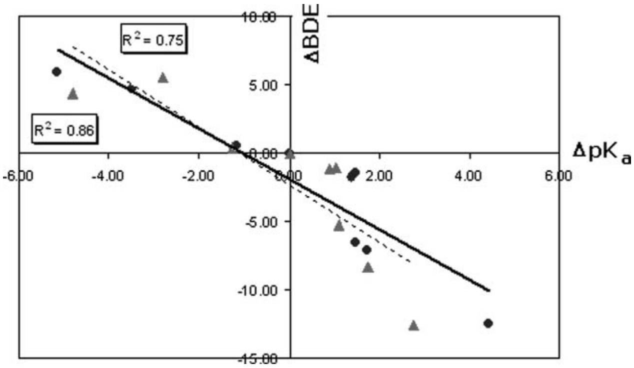

Fig. 2 Correlation of ΔBDE (kcal mol^{-1}) *versus* ΔpK_a for calculated values (solid line) and experimental values (dotted line).

Fig. 3 shows a strong linear correlation for both experiment and computed values ($r^2 = 0.97/0.98$) between ΔE_{ox} and ΔBDE. The positive gradient means that an increase in the oxidation potential results in a proportional increase in the BDE. Combining the evidence offered by Fig. 2 and 3 suggests that hydrogen abstraction is driven by the propensity of electron transfer rather than proton transfer.

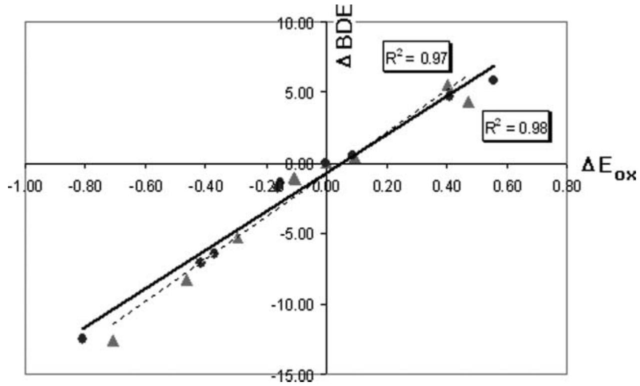

Fig. 3 Correlation of ΔBDE (kcal mol^{-1}) *versus* ΔE_{ox} (V) for calculated values (solid line) and experimental values (dotted line).

α-Tocopherol

We have calculated the relative acidity of the HPMC compound to be 2.4 log units lower than phenol. Also the computed ΔE_{ox} is −0.79 V lower than that of phenol. These two values combined yield a ΔBDE of −14.9 kcal mol^{-1}, which overestimates the experimental value (in non-polar medium) of −10.05 kcal mol^{-1}.[22] We point out that the ΔpK_a and ΔE_{ox} of HPMC have not yet been determined experimentally.

There may be some conformational issues regarding the calculation of the BDE of HPMC, as pointed out by Wright *et al.*,[11] which may serve to influence ΔBDE. These authors pointed out that the Ar–OH dihedral angle in HPMC is rotated 23° out of the aromatic plane when in fact it should be planar. Here we find that this angle is very close to planar, namely 7°. However, closer inspection of the literature surfaced X-ray data to show that this Ar–OH angle has two conformers with values of 47° and 59°.[23] It is clear from this discussion that conformational issues regarding the Ar–OH dihedral angle will influence the BDE of HPMC. The oxidation potential of the anion will not suffer from this kind of conformational effect since the proton is abstracted from the hydroxyl group. In order to check to see if there were any other conformers, we re-optimised HPMC, slightly perturbing the geometry starting with an Ar–OH dihedral angle of 50°. The result of this geometry optimisation yielded the same geometry and energy as before, indicating that we may have found the lowest energy conformer with the methods described here.

We have also investigated the proton hyperfine coupling constants for the HPMC radical in order to investigate the nature of solvent effects on the calculated hyperfine coupling constants. Previous work has shown that good results for proton hyperfine

Table 2 Calculated proton hyperfine coupling constants (in *G*) for the HPMC radical in DMSO

	a^H			
	4(CH_2)	5(CH_3)	7(CH_3)	8(CH_3)
CPCM-B3LYP/aug-cc-pVTZ//B3LYP/aug-cc-pVTZ	0.83	4.94	3.88	0.56
CPCM-B3LYP/aug-cc-pVDZ//B3LYP/aug-cc-pVDZ	1.49	5.03	3.95	0.97
CPCM-B3LYP/6–311G+(2d,p)//B3LYP/6–311G+(2d,p)	1.2	5.3	3.8	0.71
CPCM-B3LYP/6–31G(d)//B3LYP/6–31G(d)	1.77	5.7	4.23	1.14
CPCM-B3LYP/EPR-II//B3LYP/aug-cc-pVTZ	1.23	5.7	4.49	0.91
CPCM-B3LYP/EPR-II//B3LYP/aug-cc-pVDZ	1.46	5.74	4.55	0.95
CPCM-B3LYP/EPR-II//B3LYP/6–311G+(2d,p)	1.42	5.77	4.16	0.86
CPCM-B3LYP/EPR-II//B3LYP/6–31G(d)	1.44	5.74	4.16	0.86
CPCM-B3LYP/EPR-III//B3LYP/aug-cc-pVTZ	1.13	5.5	4.04	0.74
CPCM-B3LYP/EPR-III//B3LYP/aug-cc-pVDZ	1.2	5.52	4.38	0.77
CPCM-B3LYP/EPR-III//B3LYP/6–311G+(2d,p)	1.32	5.68	4.07	0.78
CPCM-B3LYP/EPR-III//B3LYP/6–31G(d)	1.34	5.66	4.08	0.79
[a]Experiment	1.48	6.04	4.55	0.96

[a] Experimental values taken from Burton *et al.*[29]

coupling constants can be obtained for phenolic antioxidants using both gas phase and continuum methods in combination with DFT calculations.[24–26] We also investigated the proton hyperfine coupling constants for the HPMC radical with the B3LYP method with different basis sets. The calculated proton hyperfine coupling constant for the HPMC radical is listed in Table 2.

The results listed in Table 2 indicate that the effects of solvation modelling on the proton hyperfine coupling constant are negligible with all values close to experiment in a non-polar solvent. It was also observed that the proton hyperfine coupling constants obtained using EPR-II basis sets developed by Barone[27,28] gave the closest agreement with experimental values.

Conclusions

We carried out calculations in order to determine the relative acidities, ΔpK_a, and relative oxidation potentials, ΔE_{ox}, of several *para*-substituted phenols with a view to modelling tocopherol in solution. We have demonstrated that

(i) calculated and experimental ΔpK_a values show good overall agreement (less than 0.7 log units) except for NH_2. The computed ΔE_{ox} values differ less than 0.1 V from experiment.

(ii) There is a fairly strong *negative* correlation between ΔpK_a and ΔBDE. An increase in acidity corresponds to a decrease in bond dissociation enthalpy. Strong electron-withdrawing substituents are the most acidic but have the highest ΔBDE, indicating that ΔpK_a cannot be used as a measure of antioxidant activity.

(iii) In contrast to the acidities, the relative oxidation potentials of the anions show a *positive* linear correlation with the relative bond dissociation enthalpies. This strong correlation shows that electron transfer is the main driving force for hydrogen abstraction.

(iv) Calculated proton hyperfine coupling constants in DMSO show good agreement with the experimental values determined in a non-polar solution. Solvation has little influence on the proton hyperfine coupling constants when used in conjunction with continuum methods.

(v) The proton hyperfine coupling constants obtained using EPR-II are closer to experiment than those by alternative basis sets (shown in Table 2).

(vi) The computed ΔpK_a value for HPMC is 2.4 and the ΔE_{ox} value of the corresponding anion is −0.79 V. This leads to a ΔBDE of -14.9 kcal mol^{-1}.

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