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Electronic Effects on O−H Proton Dissociation Energies of Phenolic Cation Radicals: A DFT Study[†]

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Abstract: The electronic effects on O−H proton dissociation energies (PDEs) of para- and meta-substituted phenolic cation radicals have been investigated by density functional theory (DFT) using B3LYP function on a 6-31G(d, p) basis set. The calculation results indicate that electron-donating groups raise the O−H PDE and electron-withdrawing groups reduce the parameter, which are opposite to the electronic effects on O−H bond dissociation energies (BDEs). In addition, the electronic effects on O−H PDE are much stronger than those on O−H BDE. The differences result from the distinct electronic effects on stabilities of phenolic cation radicals and parent phenols. The finding also implies the proton-transfer process is unlikely a rate-controlling step for phenolic antioxidants to scavenge free radicals. Moreover, like O−H BDE, O−H PDE correlate better with the resonance parameter R^+ than with field/inductive parameter F. Therefore, O−H PDEs of para-substituted phenolic cation radicals are mainly governed by the resonance effect.

Introduction

Phenolic antioxidants (ArOH) have attracted much attention in recent years, due to their great potential to be used in pharmacy and chemical industry.[1] It is well-known that there are two pathways for ArOH to scavenge free radicals, e.g., peroxyl radical (ROO$^\bullet$), the hydrogen-transfer mechanism (1),[2] and the proton concerted electron-transfer mechanism (2).[3]

$$\mathrm{ROO^\bullet + ArOH \rightarrow ROOH + ArO^\bullet} \qquad (1)$$

$$\mathrm{ROO^\bullet + ArOH \rightarrow ROO^- + ArOH^{\bullet +} \rightarrow ROOH + ArO^\bullet} \qquad (2)$$

For the first mechanism, the reaction rate is determined to a certain extent by the O−H bond dissociation energies (BDEs) of ArOH.[4] Hence, the parameter has been thoroughly studied[5,6] and has been successfully used in elucidating the structure−activity relationships (SAR) of ArOH[7] and in rational design of novel antioxidants.[8] However, the second mechanism was given much less attention, especially for the proton dissociation process. There only exist several experiments devoted to determine the pK_a values[9] or the lifetimes of phenolic cation radicals (ArOH$^{\bullet +}$).[10] To gain the whole knowledge of the radical scavenging mechanisms of ArOH, it is necessary to theoretically investigate the electronic effects on O−H proton dissociation energies (PDEs) of ArOH$^{\bullet +}$ by the way similar to the study on O−H BDE,[6] which is the aim of this paper.

Methods

Density functional theory (DFT) has been successfully used in studying the electronic effects on O−H BDE,[6] so

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[†] Abbreviations: ArOH, phenolic antioxidant; ArOH$^{\bullet +}$, phenolic cation radical; DFT, density functional theory; O−H BDE, O−H bond dissociation energies; O−H PDE, O−H proton dissociation energies; ROO$^\bullet$, peroxyl radical; SAR, structure−activity relationships; SPC, stability of phenolic cation radical; SPP, stability of parent phenol; SPR, stability of phenoxyl radical.

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Table 1. Theoretical Relative O−H PDE, SPC, SPR, and O−H BDE (kcal/mol) for Para-Substituted Phenolic Cation Radicals and Phenols, Brown Parameters σ_p^+, F, and R^+, and Experimental Parameters $\log(1/\tau_{exp})$ and pK_a Values

X	O−H PDE	SPC	SPR	O−H BDE[a]	$\sigma_p^{+\ b}$	F^b	$R^{+\ b}$	pK_a[c]	log (1/τ_{exp})[d]
H	0	0	0	0	0	0	0	−8.1	6.57
Me	−6.30	7.69	1.39	1.84	−0.31	0.01	−0.32	−7.1	6.38
F	0.57	0.10	0.67	2.01	−0.07	0.45	−0.52		
Cl	−0.36	0.49	0.13	0.67	0.11	0.42	−0.31	−9.9	6.5
OH	−10.01	13.56	3.55	5.40	−0.92	0.33	−1.25	−5.5	
OMe	−14.28	18.01	3.73	5.46	−0.78	0.29	−1.07	−4.7	6.47
SH	−11.21	14.06	2.85	3.70	−0.03	0.3	−0.33		
SMe	−17.36	21.16	3.80	4.69	−0.6	0.23	−0.83		
NH_2	−21.83	29.30	7.47	8.56	−1.3	0.08	−1.38	4.5	6.17
NMe_2	−28.90	36.39	7.49	9.50	−1.7	0.15	−1.85	6.2	5.94
CHO	6.16	−7.07	−0.91	−2.47	0.73	0.33	0.4		
CN	8.70	−10.05	−1.35	−2.36	0.66	0.51	0.15	−13	6.96
NO_2	14.57	−17.59	−3.02	−4.42	0.79	0.65	0.14	−15	6.64
CF_3	7.19	−9.16	−1.97	−2.48	0.61	0.38	0.23	−13	

[a] Data from ref 6g. [b] Data from ref 12. [c] Data from ref 9. [d] Data from ref 10a.

Table 2. Theoretical Relative O−H PDE, SPC, SPR, and O−H BDE (kcal/mol) for Meta-Substituted Phenolic Cation Radicals and Phenols, Hammett Parameters σ_m, and pK_a Values

X	O−H PDE	SPC	SPR	O−H BDE[a]	σ_m[b]	pK_a[c]
H	0	0	0	0	0	−8.1
Me	−4.72	5.20	0.48	0.43	−0.07	−7.9
F	3.72	−4.84	−1.12	−1.14	0.34	
Cl	3.70	−5.06	−1.36	−1.15	0.37	−10.5
OMe	−11.57	10.60	−0.97	−1.21	0.12	−6.2
NH_2	−20.36	22.12	1.76	0.36	−0.16	3.0
NMe_2	−29.19	30.23	1.04	0.95	−0.16	5.9
CN	11.21	−14.24	−3.03	−2.68	0.56	−14
NO_2	13.35	−16.83	−3.48	−2.92	0.71	−14
CF_3	6.98	−8.80	−1.82	−1.63	0.43	−14

[a] Data from ref 6g. [b] Data from ref 12. [c] Data from ref 9.

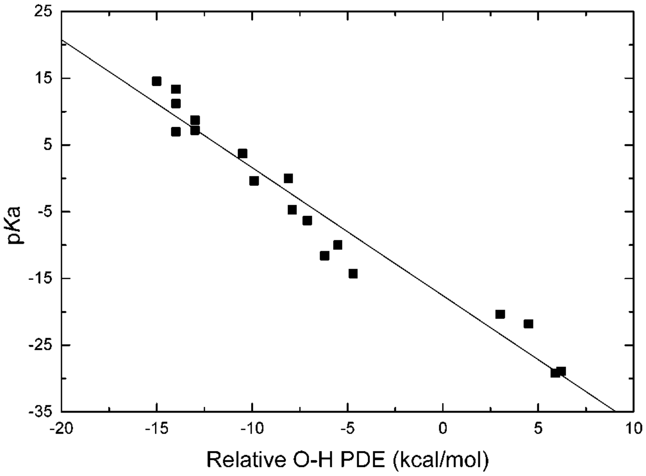
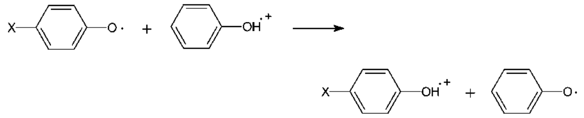


Figure 1. Correlationship between pK_a values and relative O−H PDE of para- and meta-substituted phenolic cation radicals. The correlation coefficient is −0.97537.

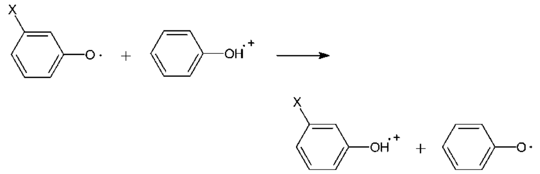
in this work the B3LYP function on the 6-31G(d, p) basis set was employed to optimize the structures and calculate the O−H PDE of para- and meta-substituted $ArOH^{•+}$ in gas phase. The detailed procedure can refer to ref 6g. The quantum chemical calculations were accomplished by the Gaussian 94 program.[11]

According to the implication of O−H PDE, the parameter is determined by the stability of the phenoxyl radical (SPR) and the stability of the phenolic cation radical (SPC): O−H PDE = SPR − SPC. Hence, six isodesmic reactions (3−8) were constructed to characterize the three parameters. Equations 3 and 4 give the relative O−H PDEs of para- or meta-substituted phenolic cation radicals with respect to unsubstituted species. Equations 5 and 6 indicate the substituent effects on the SPR. Equations 7 and 8 give the interaction between the substituents and the $OH^{•+}$ group. The effectiveness of the isodesmic method has been demonstrated by the studies of electronic effects on O−H BDE.[6c,g]

Characterization of relative O-H PDE:

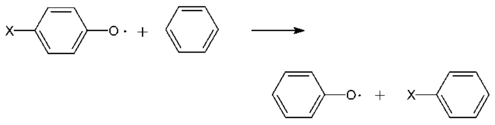


(3)



(4)

Characterization of SPR:



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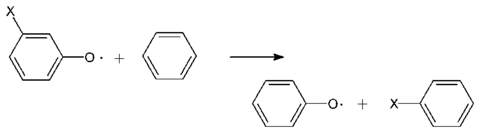
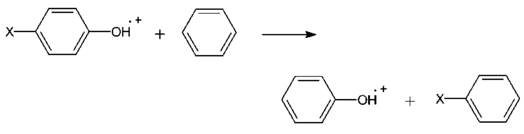


(6)

Characterization of SPC:



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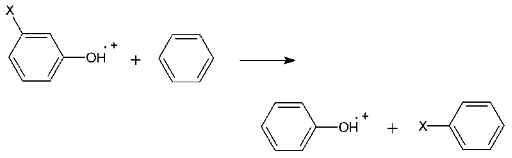

(8)

Results and Discussion

The total electronic energies for para- and meta-substituted molecules indicated in isodesmic reactions were calculated and contained in the Supporting Information. Accordingly, relative O−H PDEs, SPC, and SPR for para- or meta-substituted $ArOH^{•+}$ and O−H BDEs

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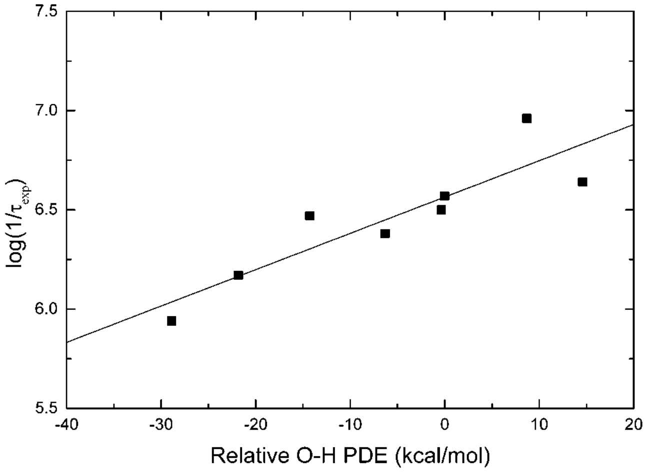

Figure 2. Correlationship between $\log(1/\tau_{exp})$ and relative O−H PDE of para-substituted phenolic cation radicals. The correlation coefficient is 0.88915.

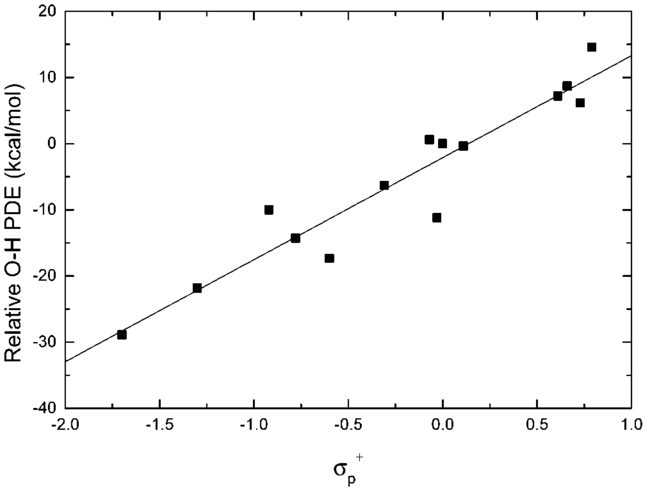

Figure 3. Correlationship between relative O−H PDE of para-substituted phenolic cation radicals and σ_p^+. The correlation coefficient is 0.95093.

Table 3. Correlation Coefficients between Relative O−H PDE, SPR, SPC, and Brown Parameters σ_p^+, R^+, and F

	relative O−H PDE	SPC	SPR
σ_p^+	0.95093	−0.95616	−0.96115
R^+	0.90953	−0.91735	−0.93302
F	0.62589	−0.61905	−0.58266

for para- or meta-substituted phenols were obtained and are listed in Tables 1 and 2.

Evaluation of the Calculated Results. To our knowledge, this is the first time the O−H PDE of $ArOH^{\bullet+}$ has been obtained by theoretical calculations, so we have to evaluate the calculated results at first. Obviously, the pK_a values of $ArOH^{\bullet+}$ depend on the O−H PDE. The higher the O−H PDE, the more difficult the proton is to dissociate and the higher the pK_a. There exists a good correlation between experimental pK_a values and calculated relative O−H PDEs (Tables 1 and 2, Figure 1, $r = -0.97537$). In addition, the lifetimes (τ_{exp}) for $ArOH^{\bullet+}$ also relate to the O−H PDE; i.e., high O−H PDE corresponds to long τ_{exp}. The correlation coefficient between $\log(1/\tau_{exp})$ and calculated relative O−H PDE is 0.88915 (Figure 2), better than that between $\log(1/\tau_{exp})$ and other calculated parameters, such as spin density on the oxygen and change in charge distribution on OH.[13] Therefore, we think the calculated results are acceptable and applicable in the following discussion. However, Bordwell and Cheng proposed that the relative O−H PDE of p-NMe_2-phenolic cation radical was ∼−20 kcal/mol,[9] which is smaller than the calculated value of −28.90 kcal/mol. It seems the difference between them will not be elucidated until further experiments are done.

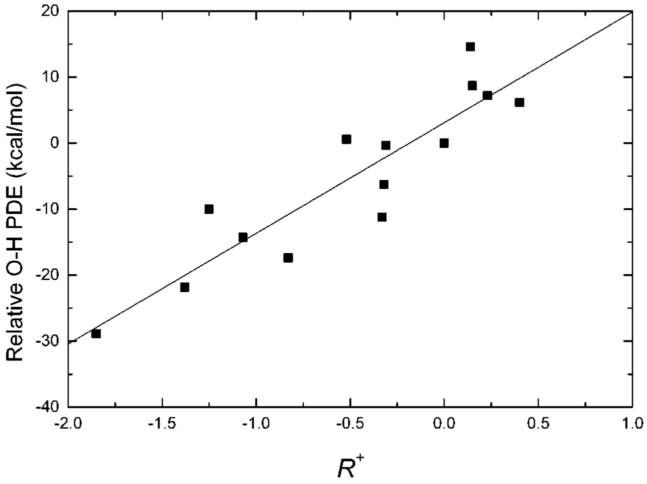

Figure 4. Correlationship between relative O−H PDE of para-substituted phenolic cation radicals and R^+. The correlation coefficient is 0.90953.

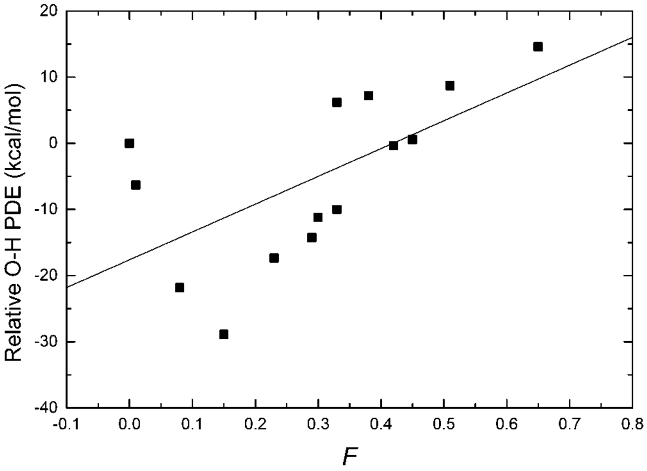

Figure 5. Correlationship between relative O−H PDE of para-substituted phenolic cation radicals and F. The correlation coefficient is 0.62589.

Electronic Effects on O−H PDE of Para-Substituted $ArOH^{\bullet+}$. As shown in Figure 3, the correlation between relative O−H PDE and Brown parameter σ_p^+ is fairly good ($r = 0.950\,93$). The positive coefficient suggests that electron-donating groups raise the O−H PDE and electron-withdrawing groups have an opposite effect, which is different from the electronic effects on O−H BDE that electron-donating groups reduce and electron-withdrawing groups enhance the parameter.[6] Another character of O−H PDE is that the electronic effects on

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[12] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

[13] Employing the data for para-substituted phenols in ref 10a, the correlation coefficients between $\log(1/\tau_{exp})$ and spin density on oxygen and change in charge distribution on OH were calculated to be 0.73795 and 0.72263, respectively.

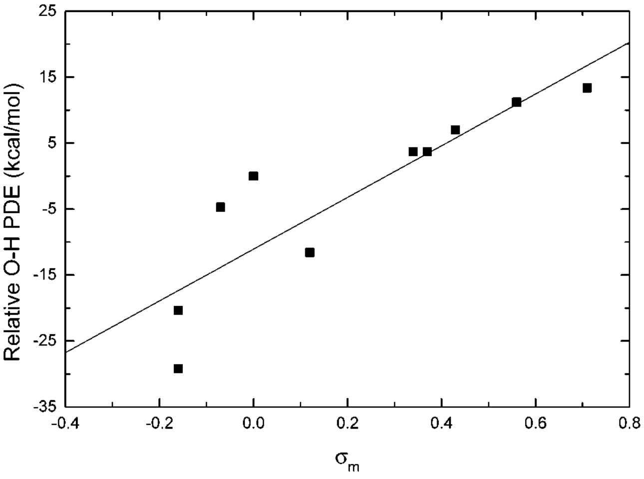

Figure 6. Correlationship between relative O−H PDE of meta-substituted phenolic cation radicals and σ_m. The correlation coefficient is 0.87778.

O−H PDE are much stronger than those on O−H BDE (Table 1), which is in accordance with the experimental results.[9] Taking into account that O−H BDE is determined by stability of the phenoxyl radical (SPR) and stability of the parent phenol (SPP), O−H BDE = SPR − SPP, the difference between O−H PDE and O−H BDE must stem from the distinct electronic effects on SPC and SPP. It is known that a charged molecule or radical is more sensitive to the electronic effects than its neutral counterpart; thus, O−H PDE are mainly determined by SPC (Table 1), in contrast with O−H BDE, which are mainly determined by SPR.[6] Furthermore, electron-donating groups are favorable to stabilize $ArOH^{\bullet +}$ but destabilize the parent phenol, and electron-withdrawing groups have an opposite effect. Therefore, the electronic effects on O−H PDE are opposite to those on O−H BDE. This also implies that electron-donating groups are not beneficial to accelerate the proton-transfer process. Taking into account that the radical-scavenging activity of ArOH is efficiently enhanced by substitution of electron-donating groups,[7,8] it is reasonable to conclude that the proton-transfer process is not a rate-controlling step for ArOH to scavenge free radicals, e.g., $ROO^{\bullet}$.

Since the para electronic effects of substituents are composed of two main parts, a field/inductive component, represented by parameter *F*, and a resonance component, characterized by parameter R^+, i.e., $\sigma_p^+ = F + R^+$,[12] we attempted to investigate whether the O−H PDE are mainly determined by field/inductive or resonance effect. It has been found that O−H BDE are mainly governed by resonance effects, which are of great importance in elucidating the SAR for flavonoid antioxidants.[6g] From Table 3, it can be seen that the correlations between SPR, SPC, and R^+ are much better than those between SPR, SPC, and *F*, indicating the SPR and SPC are mainly governed by the resonance effect. Accordingly, the resonance effect should play a key role in determining the O−H PDE. In fact, the correlation between the relative O−H PDE and R^+ (Figure 4, $r = 0.909\ 53$) is much better than that between relative O−H PDE and *F* (Figure 5, $r = 0.625\ 89$).

Electronic Effects on O−H PDE of Meta-Substituted $ArOH^{\bullet +}$. It is interesting to note that although the electronic effects on O−H BDE of meta-substituted phenols are much lower than those on O−H BDE of para-substituted phenols, the electronic effects on O−H PDE of para- or meta-substituted phenolic cation radicals are similar to each other (Tables 1 and 2). In addition, a correlation between relative O−H PDE and Hammett parameter σ_m was also observed (Figure 6), indicating electron-donating groups enhance and electron-withdrawing groups reduce the O−H PDE (Table 2). These characters also result from the fact that SPC is a dominant factor in determining O−H PDE and the cation radical is much more sensitive to electronic effects at the meta position than the phenoxyl radical or parent phenol.

In summary, owing to the distinct electronic effects on stabilities of $ArOH^{\bullet +}$ and parent phenols, the electronic effects on O−H PDEs are much different from those on O−H BDEs. First, electron-donating groups raise the O−H PDE and electron-withdrawing groups reduce the parameter. Second, the electronic effects on O−H PDE are much stronger than those on O−H BDE. Third, para or meta electronic effects on O−H PDE are similar to each other, in contrast with those on O−H BDE where the latter effect is much lower than the former. Accordingly, the proton-transfer process is unlikely a rate-controlling step for ArOH to scavenge free radicals.

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Supporting Information Available: Optimized structures and total energies for all calculated molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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