A Study of the Substituent Effects on the O−H Bond Dissociation Enthalpies of Phenol Derivatives Using the ONIOM Method

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Abstract   The O–H bond dissociation enthalpies (BDE) of various substituted phenol derivatives were determined using the ONIOM(ROB3LYP/6-311++G(2df,2p):PM6) approach. Computed BDE(O–H)s of all phenol derivatives were in good agreement with available experimental values, and also well correlated with the Hammett constants, σ_p. It is found that the strong electron-donating NH_2 and $N(CH_3)_2$ substituents induce a significant decrease in the BDE(O–H)s. On the contrary, the strong electron withdrawing NO_2 and CF_3 groups result in an increase in BDE(O–H)s.

Keywords   Bond dissociation enthalpies, Antioxidant, Phenol derivatives, ONIOM method

1. Introduction

Phenolic antioxidants (ArOH) play an important role in the prevention of several chemical and biological processes including the biological ageing, foodstuff deterioration, synthetic polymer degradation [1-3], etc. The function of phenolic antioxidants is a scavenger active against reactive oxygen species (ROS) such as superoxide anion radical, singlet molecular oxygen and hydroxyl radical. There are several mechanisms of phenolic antioxidant action, and the net result of all mechanisms is similar to each other: transferring hydrogen atom radical to the free radicals [4-8]. A high rate of hydrogen atom transfer is expected to be related to a low O–H bond dissociation enthalpy (BDE). Therefore, the BDE parameter (capacity to donate an H atom) is a key feature for evaluating the antioxidant activity of a natural compound. Sterically hindered phenols (Figure 1b) represent a large group of synthetic antioxidants widely used in synthetic polymers stabilization [9]. It is well-known that phenolic compounds act as chain-breaking antioxidants.

Numerous attempts have already been investigated to measure or predict the accurate BDEs of organic compounds in both experimental [10-14] and quantum chemical [15-19] techniques. Although quantum chemical study is already well established for accurately predicting BDEs, there are still many challenges in treatment of large compounds.

The ONIOM approach, which is an integrated method proposed by Morokuma and co-workers [20-22], is an efficient computational tool for the study of large molecular systems. In our previous studies, we performed an integration of the ROB3LYP/6-311++G(2df,2p) level with the semi-empirical PM6 method into a two-layer ONIOM to reasonably produce accurate BDE(O–H)'s of phenolic compounds. Deviation of calculated values from experiment is ± (1–2) kcal/mol [23, 24].
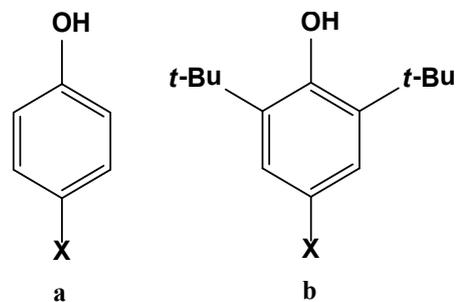
X = H; *t*-Bu; CH_3; CH_3O; CH_3CO; C_6H_5; CF_3; CN; F; NH_2; $N(CH_3)_2$; NO_2; OH

Figure 1.   Structure of mono-substituted phenols (a) and sterically hindered phenols (b)

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In the present paper, we thus apply the ONIOM(ROB3LYP/6-311++G(2df,2p):PM6) approach to determine the BDEs of the O–H bonds of various substituents of sterically hindered phenols and mono-substituted phenols (as shown in Figure 1) in the gas-phase, and to assess the effect of various electron-donating or electron-withdrawing groups at the para-position on the change of the BDE. The obtained results for mono-substituted phenols will then be compared with identical group of substituents in *para*-position, in order to describe the effect of the two *tert*-butyl (t-Bu) groups on studied enthalpies. In addition, our observation will also be compared to the available experimental data. The relationship between the calculated BDEs and Hammett constants will be also correlated.

2. Theoretical and Computational Methods

All computations were performed using the Gaussian 09 suite of program [25]. Geometry optimizations and vibrational frequency calculations were conducted using the semi-empirical PM6 method. Vibrational frequencies obtained at the PM6 level were subsequently scaled by a factor of 1.078 [26] for estimating the zero-point vibrational energies (ZPE). The BDE value was determined from total enthalpies of the individual species in the gas-phase, as follows:

$$BDE(ArO−H) = H(ArO^{\bullet}) + H(H^{\bullet}) − H(ArOH)$$

Where H's are the enthalpies of different species at 298.15 K and 1.00 atm. The enthalpies were estimated from the given expression: $H(T) = E_0 + ZPE + H_{trans} + H_{rot} + H_{vib} + RT$. The H_{trans}, H_{rot}, and H_{vib} are the translational, rotational, and vibrational contributions to the enthalpy, respectively. E_0 is the total energy at 0 K and ZPE is the zero-point vibrational energy. The enthalpy value for the hydrogen atom in the gas phase was taken at its exact energy of −0.5 hartree at 0 K and thermal correction at the given temperature is added the value of 2.5RT.
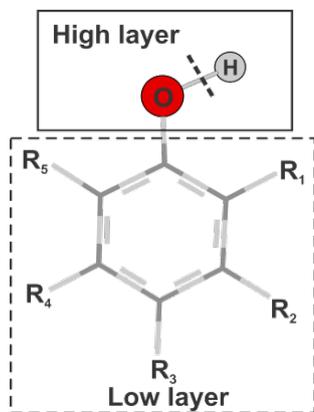

Figure 2.   Schematic description of two-layer proposed ONIOM model

By improving the results of the previous paper [24], we

choose a partitioning scheme for the two-layer ONIOM (as described in Figure. 2) that generates an accurate estimation of BDE(O−H) within 1–2 kcal/mol deviation. According to this, each molecule is divided into two layers, the atoms at the breaking bond is treated as a high layer while the leftover atoms of the molecule belong to the second layer, which is treated as a lower layer. The ROB3LYP/6-311++G(2df,2p) method is thus applied for the atoms in the high layer, whereas the PM6 procedure is applied for the low one. In this model (Figure. 2), the core layer which has only one oxygen atom and one hydrogen atom, relates to the target bond for estimating BDE at the high level. The rest are defined as the low layer.

3. Results and Discussion

3.1. Agreement between Calculated and Experimental BDE(O–H)s

In this part, the ONIOM(ROB3LYP/6-311++G(2df,2p): PM6) approach were used to determine the BDEs of the O–H bonds of 26 para-substituted sterically hindered phenols and phenols. The calculated BDE(O–H) values are summarized in Table 1.

In order to evaluate the reliability of employed computational approach for substituent effect description, it is necessary to compare the calculated and the experimental values. From the calculated results for a series of substituted phenols (as shown in Table 1), the largest deviation (ΔBDE) between the calculated and the experimental BDE(O–H) values is 2.5 kcal/mol which is found in the case of p-CH$_3$CO-C$_6$H$_2$(t-Bu)$_2$OH. For the other substituted compounds, the deviation are smaller and in the range from −1.8 to 0.7 kcal/mol. The results also show that the BDE(O–H) values obtained from the ONIOM method are reasonably accurate and in agreement with the best experimental data with the deviation of only ±1.0 kcal/mol.

3.2. Effect of Substituents on BDE(O–H)s

The substitution of a functional group in the molecule generally causes considerable changes in physico-chemical properties. Therefore, the understanding of substituent effect on O–H bond cleavage as well as on various molecular properties is important. The substituent effects were described in terms of Δ'BDEs, where Δ'BDE is the difference between the bond dissociation enthalpies of the substituted and the parent phenol, Δ'BDE = BDE(substituted phenols) − BDE(phenol). Relationship between Δ'BDE values and substituents was shown in Table 1 and Figure 3.

In the case of mono-substituted phenol, among the electron-withdrawing group, NO$_2$ has the strongest effect to the BDE(O–H). The BDE value is 5.4 kcal/mol higher than the ones of phenol. The other electron-withdrawing groups like CH$_3$CO, CF$_3$, and CN induce an increase in BDEs in the range from 2.1 to 3.7 kcal/mol compared with the BDE of phenol. In the case of electron-donating groups including

t-Bu, CH$_3$, CH$_3$O, C$_6$H$_5$, F, NH$_2$ and N(CH$_3$)$_2$, OH, the BDE(O−H) values tend to be lower than the BDE(O–H) of phenol. The largest decreases in BDE which are -6.3 and -6.9 kcal/mol, are found for the strongest electron-donating NH$_2$ and N(CH$_3$)$_2$ groups, respectively. The obtained results can be interpreted knowing that electron-donating groups induce the positive inductive effect (+I). This factor causes the strong polarization of the O–H bond, thus, decreases the BDEs, while the presence of electron-withdrawing ones in molecule results in the increase of BDEs.

Table 1. Experimental and theoretical BDEs (kcal/mol) related to para-substituted molecules and Hammett constants σ$_p$

Substituent	Mono-substituted phenols				Sterically hindered phenols				σ$_p$[d]
	Calc.	Expt.[a]	ΔBDE[b]	Δ' BDE[c]	Calc.	Expt.[a]	ΔBDE[b]	Δ' BDE[c]	
p-H	87.3	88.0	-0.7	0	83.1	82.8	0.3	-4.2	
p-*t*-Bu	85.5	85.3	0.2	-1.8	81.8	81.2	0.6	-5.5	-0.20
p-CH$_3$	85.1	86.1	-1.0	-2.2	81.4	81.0	0.4	-5.9	-0.17
p-CH$_3$O	81.8	82.6	-0.8	-5.5	79.8	79.7	0.1	-7.5	-0.27
p-CH$_3$CO	90.0	90.3	-0.3	2.7	85.6	83.1	2.5	-1.7	0.50
p-C$_6$H$_5$	85.7	85.0	0.7	-1.6	82.0	81.2	0.8	-5.3	-0.01
p-CF$_3$	91.0	91.4	-0.4	3.7	86.4	N/A	N/A	-0.9	0.54
p-CN	89.4	90.1	-0.7	2.1	85.1	84.2	0.9	-2.2	0.66
p-F	86.5	87.2	-0.7	-0.8	82.6	N/A	N/A	-4.7	0.06
p-NH$_2$	81.0	80.8	0.2	-6.3	78.2	80.0	-1.8	-9.1	-0.66
p-N(CH$_3$)$_2$	80.4	80.3	0.1	-6.9	78.1	N/A	N/A	-9.2	-0.83
p-NO$_2$	92.7	93.8	-1.1	5.4	87.3	86.7	0.6	0	0.78
p-OH	82.5	82.2	0.3	-4.8	80.4	N/A	N/A	-6.9	-0.37

[a] Ref. [27]

[b] ΔBDE = ΔBDE$_{calc.}$ − ΔBDE$_{expt.}$

[c] Δ'BDE = BDE(C$_6$H$_{5-n}$X$_n$OH) − BDE(C$_6$H$_5$OH)
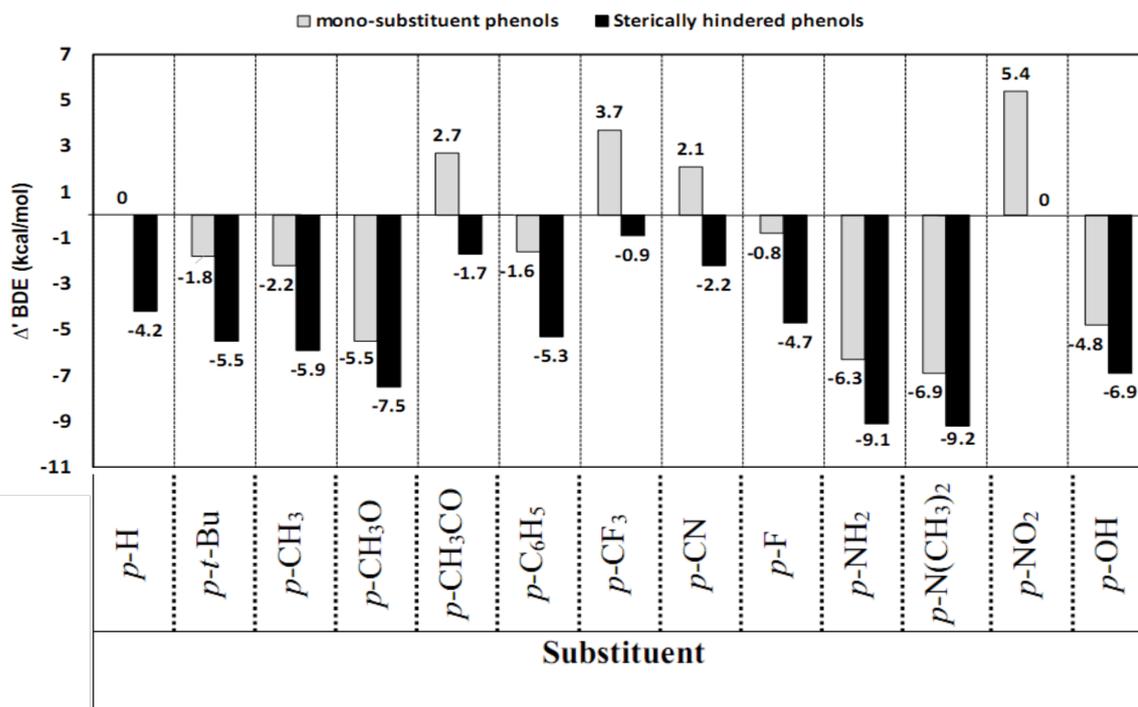
[d] Ref. [28]

Figure 3. Effect of substituents on BDE(O–H)s of mono-substituent phenols and sterically hindered phenols

A similar tendency is observed in the case of sterically hindered phenols, but the differences in BDE values are considerably larger than those of mono-substituted phenols. In fact, BDEs of sterically hindered phenols with electron-withdrawing and electron-donating groups are all lower than the ones of phenol. The decrease in BDEs is caused by the presence of two electron-donating *tert*-butyl groups in *ortho*-positions to the phenolic O–H bond. BDE of sterically hindered phenols with the strongest electron-withdrawing NO_2 group is the same to that of phenol. On the other hand, the largest BDE(O–H) decrease which are –9.1 and –9.2 kcal/mol, are achieved by the strong electron-donating NH_2 and $N(CH_3)_2$ groups, respectively.

3.3. Relationship between the Calculated BDEs and Hammett Constants

The Hammett equation (and its extended forms) has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms. Hammett constants σ_m (for substituent in *meta* position) and σ_p (for substituent in *para* position) obtained from the ionization of organic acids in solutions can successfully predict equilibrium and rate constants for a variety of families of reactions [28].

Hammett constants correlate very well with the changes in BDE(O−H) in the case of phenols [15]. The correlation between calculated BDE values and Hammett constants, σ_p, for mono-substituent phenols and sterically hindered phenols is presented in Figure 4. The equations obtained from the linear regression are as follows:

BDE (kcal/mol) = $7.63\sigma_p$ + 86.01 (R^2 = 0.9329)
(mono-substituent phenol)

BDE (kcal/mol) = $5.83\sigma_p$ + 82.43 (R^2 = 0.9561)
(sterically hindered phenol)

The correlation coefficients in mono-substituent phenols and sterically hindered phenols reached 0.93 and 0.96, respectively. Linear regressions show that the ONIOM method satisfactorily describes the dependence of the expected linear BDE versus Hammett constant. The BDE(O−H) value increases with the increase in the electron-withdrawing ability of the substituent. This is a very important conclusion because this can be utilized in the synthesis of novel phenolic derivatives with enhanced antioxidant properties.

4. Conclusions

In this paper, the bond dissociation enthalpies of *para*-substituted phenols and sterically hindered phenols in the gas-phase were investigated using ONIOM(ROB3LYP/ 6-311++G(2df,2p):PM6) approach. The calculated results are in very good accordance with available experimental data. In addition to the character of substituents, the influence of number of substituents was also evaluated. The largest decrease in BDE(O–H)s results from the strong electron-donating NH_2 and $N(CH_3)_2$ groups. On the contrary, the strong electron withdrawing NO_2 and CF_3 groups result in an increase in BDE(O–H)s. Therefore, the improvement of the phenolic antioxidant effectiveness, i.e. the decrease of the BDE(O–H), can be accomplished by the substitution of electron-donating groups at the *para* position.
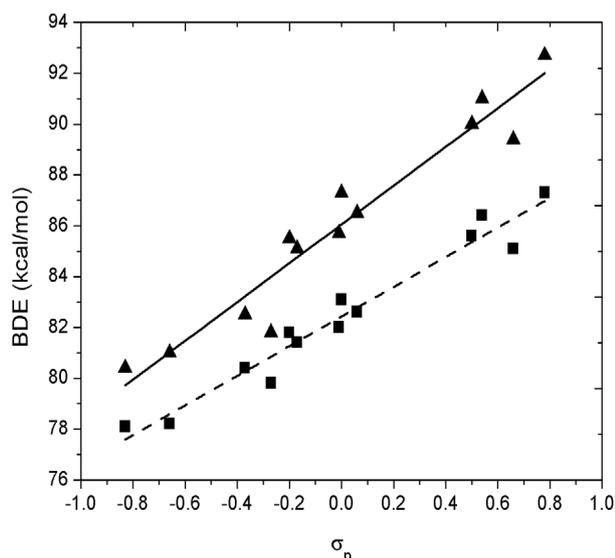
Figure 4. Dependence of BDE on σ_p for mono-substituted phenols (solid triangles, solid line) and sterically hindered phenol (solid squares, dashed line) in gas phase

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