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Why Static O-H Bond Parameters Cannot Characterize the Free Radical Scavenging Activity of Phenolic Antioxidants: *ab initio* Study

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Abstract: The static O-H bond parameters including O-H bond length, O-H charge difference, O-H Mulliken population and O-H bond stretching force constant (*k*) for 17 phenols were calculated by *ab initio* method HF/6-31G**. In combination with the O-H bond dissociation enthalpies (BDE) of the phenols determined by experiment, it was found that there were poor correlationships between the static O-H bond parameters and O-H BDE. Considering the good correlationship between O-H BDE and logarithm of free radical scavenging rate constant for phenolic antioxidant, it is reasonable to believe that the ineffectiveness of static O-H bond parameters in characterizing antioxidant activity arises from the fact that they cannot measure the O-H BDE.

Keywords: Antioxidants, free radical scavenging effect, O-H bond dissociation enthalpy, O-H bond length, O-H bond stretching force constant, O-H charge difference, O-H Mulliken population, QSAR.

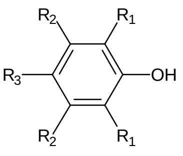
Recently, selecting high efficient phenolic antioxidants with low toxicity was paid much attention[1-4]. Moreover, quantitative structure-activity relationships (QSAR) for phenolic antioxidants have been investigated to accelerate the selection process[5-7]. Hence, how to theoretically characterize the free radical scavenging activity of phenolic antioxidants is important and significant. Although the parameters characterizing O-H bond dissociation energy or enthalpy (BDE) correlate well with the logarithm of the free radical scavenging rate constants (lg*ks*)[8-11], it is a time-consuming process to calculate the O-H BDE accurately, because we will have to calculate the phenoxy free radical generated after H-abstraction reaction. Therefore, it is interesting to investigate whether there exist static O-H bond parameters, such as O-H bond length, O-H charge difference, O-H Mulliken population and O-H bond stretching force constant (*k*), that can measure the free radical scavenging activity. Apparently, calculating these parameters is rather time-saving, as only parent molecule has to be calculated. In fact, some of them have been used in practice to predict phenolic antioxidant activity[12,13]. But unfortunately, other studies showed that there were poor correlationships between the static O-H bond parameters and lg*ks*[9,14]. Furthermore, the prediction made by O-H charge difference that hydroxyls in ring A are catechin's active center to scavenge free radicals is opposite to the experiment[12], as most experiments indicate that hydroxyls in ring B are the active center for flavonoid antioxidants[15-18]. Thus, it is significant and interesting to explain why these static parameters are ineffective. Considering the good correlationship between O-H BDE and lg*ks*, it is reasonable to hypothesize that the ineffectiveness of the static O-H bond parameters arises from that the parameters cannot characterize the O-H BDE at all. But, this is difficult to understand, as these static parameters are commonly believed to be the measure of BDE. Although Brinck and co-workers recently suggested that the trends in the O-H BDE cannot be linked to the changes in the properties of the bond itself[19], there still lacks a comprehensive correlation study to demonstrate whether the static indexes can measure the O-H BDE. In this paper, static parameters for 17 phenols were calculated by high level quantum chemical method. In combination with the experimentally determined O-H BDE, a thorough correlation investigation has been performed.

Methods

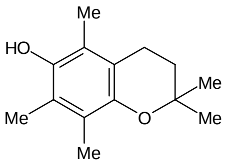
The calculation procedure is as follows. Molecular mechanic method MMX[20] in program PCMODEL was used to optimize the molecular structures preliminarily. Then complete geometry optimizations were performed progressively by semiempirical method (AM1[21] in MOPAC7) and *ab initio* method (STO-3G, HF/3-21G, and HF/6-31G**) in GAUSSIAN 94.

Results and Discussion

Table 1 Experimentally determined O-H BDE and theoretically calculated parameters.



Phenol



HPMC

Phenol	R$_1$	R$_2$	R$_3$	BDE$_{exp}$ [a]	O-H BL [b]	O-H CD [c]	O-H MP [d]	*k* [e]
1	H	H	H	88.30	0.9427	1.0037	0.3272	11.0669
2	H	H	Me	86.20	0.9425	1.0055	0.3273	11.0745
3	H	H	CMe$_3$	85.30	0.9425	1.0060	0.3275	11.0749
4	H	H	OMe	82.81	0.9423	1.0089	0.3276	11.0910
5	Me	H	H	84.50	0.9412	1.0256	0.3282	11.1979
6	CMe$_3$	H	H	82.80	0.9367	1.0341	0.3237	11.5947
7	OMe	H	H	83.16	0.9446	1.0243	0.3284	10.9270
8	H	CMe$_3$	H	86.62	0.9426	1.0053	0.3276	11.0659
9	H	OMe	H	86.70	0.9424	1.0014	0.3285	11.0854
10	Me	H	Me	82.73	0.9412	1.0271	0.3282	11.2003
11	CMe$_3$	H	CMe$_3$	81.24	0.9367	1.0364	0.3239	11.5935
12	OMe	H	OMe	80.00	0.9442	1.0275	0.3285	10.9619
13	CMe$_3$	H	Me	81.02	0.9366	1.0358	0.3239	11.6067
14	CMe$_3$	H	OMe	78.31	0.9425	1.0428	0.3133	10.9930
15	Me	H, Me	OMe	79.20	0.9415	1.0307	0.3244	11.1440
16	Me	Me	OMe	81.88	0.9405	1.0340	0.3290	11.2526
17	HPMC			78.25	0.9420	1.0354	0.3222	11.0810
r [f]					0.2008	-0.8637	0.5966	-0.1462

[a] O-H bond dissociation enthalpies (in kcal/mol) determined by experiment[22].

[b] O-H bond length (in angstrom) calculated by HF/6-31G**.

[c] O-H charge difference calculated by HF/6-31G**.

[d] O-H Mulliken population calculated by HF/6-31G**.

[e] O-H bond stretching force constant (in mDyne/angstrom) calculated by HF/6-31G**.

[f] Correlation Coefficient between O-H BDE and static O-H bond parameters.

Figure 1 orrelationship between O-H BDE and O-H bond length, *r* = 0.2008.

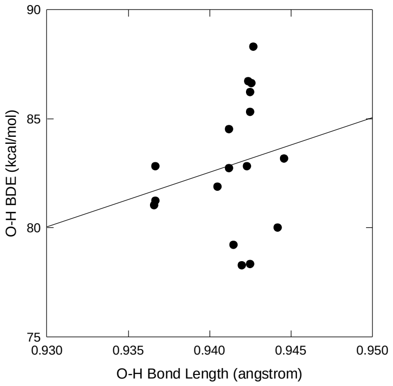


Figure 2 Correlationship between O-H BDE and O-H charge difference, *r* = -0.8637.

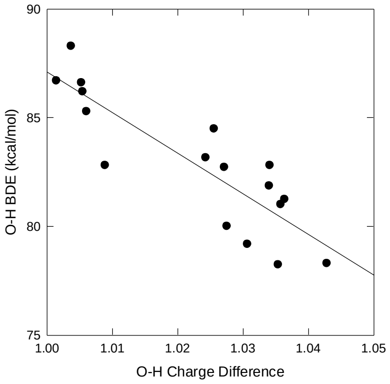


Figure 3 Correlationship between O-H BDE and O-H Mulliken population, *r* = 0.5966.

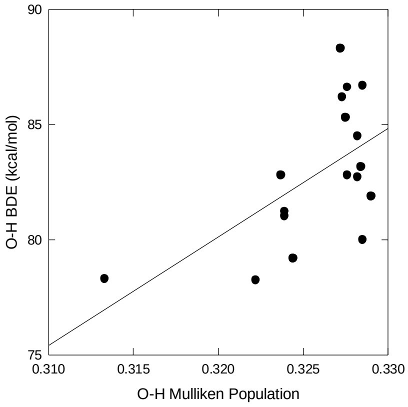
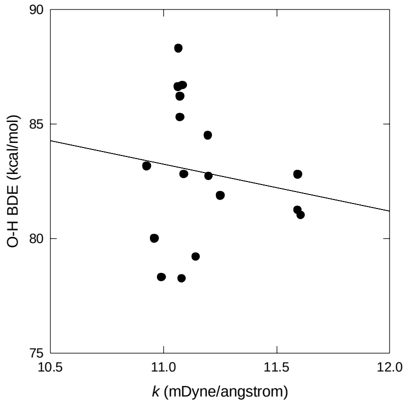


Figure 4 Correlationship between O-H BDE and O-H bond stretching force constant (*k*), ***r*** = -0.1462.



The static O-H bond parameters including O-H bond length , O-H charge difference, O-H Mulliken population and *k*, calculated by HF/6-31G**, are listed in **Table 1**. And the correlationships between O-H BDE and the static parameters are illustrated in **Figures 1-4**. It can be seen that the correlationships between O-H BDE and O-H bond length, O-H Mulliken population or *k* are very poor ($r < 0.6$). Hence, these static parameters cannot measure the O-H BDE. For O-H charge difference, the correlationship is a little better (r = -0.8637). However, the correlationship is not good enough to measure the O-H BDE. And it is interesting to note that the slope of the regression line is negative, implying that the higher the O-H charge difference, the lower the O-H BDE. This is opposite to the general consideration that high O-H charge difference corresponds to strong O-H bond[12]. In the previous study on catechin, it was pointed out that the O-H charge differences for the resorcinol in ring A were lower than that for the catechol in ring B[12]. Thus, it was conjectured that the hydroxyls in ring A were more active than that in ring B to scavenge free radicals. But this was not in agreement with the experimental phenomenon that ring B was the active center for flavonoid antioxidants[15-18]. In fact, the free radical of catechol generated after H-abstraction reaction can be stabilized by forming an intramolecular hydrogen bond and by resonance effect[23]. So, catecholic hydroxyls in ring B are more active than the resorcinolic hydroxyls in ring A. From the negative correlationship between O-H charge difference and O-H BDE, it is easy to understand why O-H charge difference gave a opposite prediction on the catechin' active center.

In summary, O-H bond length, O-H charge difference, O-H Mulliken population and k cannot measure the O-H BDE, so they cannot characterize the free radical scavenging activity of phenolic antioxidants. Thus, to predict natural phenolic antioxidant activity, we will have to calculate O-H BDE, despite it is a time-consuming process.

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