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Substituent Effects on O–H Proton Dissociation Enthalpies of Catecholic Cation Radicals: A DFT Study

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Substituent Effects on O–H Proton Dissociation Enthalpies of Catecholic Cation Radicals: A DFT Study#

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Abstract

Density functional theory (DFT) at the B3LYP/6–31G(d,p) level was employed to investigate the substituent effects on O–H proton dissociation enthalpies (PDEs) of catecholic cation radicals. First, it was revealed that the *ortho* OH–group had little influence on the O–H PDE, because the electronic effect and the intramolecular hydrogen bond (IHB) effect arising from *ortho* OH–group counteract each other. Second, the 4–substituent effect upon O–H PDEs for catecholic cation radicals was comparable to that for monophenolic cation radicals, which meant that electronic contributions played a dominant role in the substituent effects. Third, there existed good correlations between O–H PDEs and other theoretical parameters, such as O–H bond length and bond stretching frequency, suggesting these parameters would be valid to characterize the proton dissociation process, in contrast to the characterization of homolysis of O–H bond that only bond dissociation enthalpy is an appropriate parameter.

Keywords. Density functional theory; O–H proton dissociation enthalpy; cation radical; electronic effect; intramolecular hydrogen bond; phenolic antioxidant.

Abbreviations and notations

ArOH, phenolic antioxidant
DFT, density functional theory
ED, electron–donating
EW, electron–withdrawing
IHB, intramolecular hydrogen bond
O–H BDE, O–H bond dissociation enthalpy
O–H PDE, O–H proton dissociation enthalpy
ZPVE, zero point vibrational energy

1 INTRODUCTION

Phenolic antioxidants (ArOH) have received much attention in recent years, due to their wide application in chemical industry, pharmaceutical industry and food industry [1–3]. As generally considered, at least two mechanisms are involved in the radical–scavenging processes for ArOH, the hydrogen–transfer mechanism, Eq. (1) [4–7], and the proton concerted electron–transfer

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[#] Dedicated to Professor Haruo Hosoya on the occasion of the 65th birthday.

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mechanism, Eq. (2) [8–11]. Many efforts have been made to investigate the first mechanism, and it was revealed that this pathway was governed by O–H bond dissociation enthalpies (BDEs) of ArOH to certain extent [12–16]. However, the second pathway was given much less attention, especially for the proton–transfer process [17–21], even though the second mechanism seems more important than the first one in polar medium.

$$\mathrm{ROO\cdot + ArOH \rightarrow ROOH + ArO\cdot} \tag{1}$$

$$\mathrm{ROO\cdot + ArOH \rightarrow ROO^{-} + ArOH^{\cdot +} \rightarrow ROOH + ArO\cdot} \tag{2}$$

Our previous study showed that the proton–transfer process pertinent to the monophenolic cation radical was determined to large extent by the O–H proton dissociation enthalpies (PDEs), and the substituent effect on the O–H PDEs was just opposite to that on the O–H BDEs [22]. The difference resulted from the distinct electronic effects on stabilities of phenolic cation radicals and parent phenols [22]. Taking into account that most natural ArOH, such as flavonoids, contain a catecholic moiety, to better understand the antioxidative mechanisms of natural ArOH, it is necessary and interesting to investigate the substituent effects on the O–H PDEs for catecholic cation radicals in terms of intramolecular hydrogen bond (IHB) effect and electronic effect, which is the aim of this paper.

2 METHODS

Density functional theory (DFT) has been successfully used to investigate the substituent effects on O–H BDE [23–28] and O–H PDE [22], so in this paper B3LYP functional [29–31] using the basis set of 6–31G(d,p) was employed to optimize the structures and calculate the O–H PDEs and other parameters of catecholic cation radicals. The procedures are as follows. First, the molecular geometries were optimized with the molecular mechanic method MMX [32], and then, with the semiempirical quantum chemical method AM1 [33]. Finally, (U)B3LYP/6–31G(d,p) was used for the full geometry optimization in gas phase. The zero point vibrational energy (ZPVE) and the vibrational contribution to the energy were scaled by a factor of 0.9805 [34]. Thus, the molecular enthalpy in gas–phase at 298.15 K consists of total electronic energy, scaled ZPVE, scaled vibrational contribution to energy, translational, rotational and PV–work terms. The quantum chemical calculations were accomplished by Gaussian 94 program [35].

According to the definition of O–H PDE and O–H BDE, PDE = $H_r + H_p - H_c$, in which, H_r is the enthalpy for radical generated after proton dissociation, H_p is the enthalpy for proton, 0.00236 hartree, and H_c is the enthalpy for cation radical. BDE = $H_r + H_h - H_p$, in which, H_r is the enthalpy for radical generated after H–abstraction reaction, H_h is the enthalpy for hydrogen atom, –0.49792 hartree, and H_p is the enthalpy for parent molecule.

Although it is clear that the basis set–dependence of substituent effect on O–H BDE is very weak, namely, the relative O–H BDEs calculated by different methods are very similar to one another [23–28], it is still an open question as to the basis set–dependence of substituent effect on O–H PDE. Thus before the normal study, we compared the methyl effects on O–H PDE of catecholic cation radical calculated by different methods. From the PDE difference between Tables 1 and 2, it can be found that the methyl effects vary within ±0.2 kcal/mol against the basis set, despite the absolute O–H PDEs vary around ±5 kcal/mol. Therefore, the basis set–dependence of O–H PDE is negligible and the method employed in this study is acceptable.

Table 1. Total electronic energies (TE, in hartree), thermal corrections to energy (TCE, in hartree), and O–H PDEs (in kcal/mol) for catechol calculated by different methods

Methods	TE$_{\mathrm{C}}$ ^{a}	TE$_{\mathrm{R}}$ ^{b}	TCE$_{\mathrm{C}}$ ^{a}	CTE$_{\mathrm{R}}$ ^{b}	O–H PDE
(U)B3LYP/6–31G	–382.294468	–381.955640	0.116354	0.103573	206.23
(U)B3LYP/6–31G(d)	–382.402842	–382.061272	0.116149	0.103274	207.90
(U)B3LYP/6–31G(d,p)	–382.420415	–382.073070	0.116264	0.103258	211.44
(U)B3LYP/6–31+G(d)	–382.412921	–382.079502	0.115915	0.102978	202.74
(U)B3LYP/6–31+G(d,p)	–382.430349	–382.091347	0.11598	0.102963	206.20
(U)B3LYP/6–311G(2d,2p)	–382.525103	–382.180913	0.116136	0.103046	209.41
(U)B3LYP/6–311+G(2d,2p)	–382.529790	–382.190074	0.115989	0.102939	206.63

^{a} data for cation radical ^{b} data for neutral radical

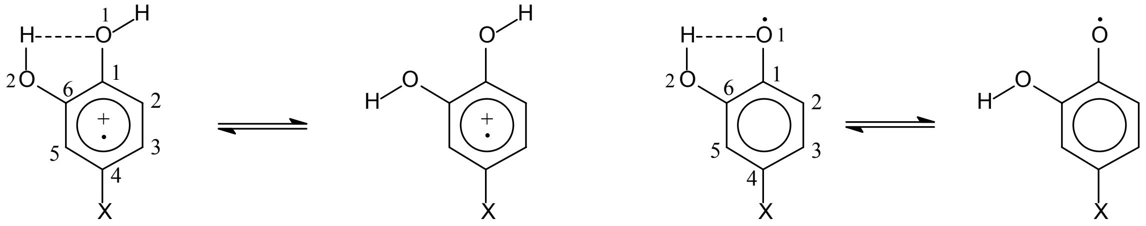
Table 2. Total electronic energies (TE, in hartree), thermal corrections to energy (TCE, in hartree), and O–H PDEs (in kcal/mol) for 4–methyl–catechol calculated by different methods

Methods	TE$_{\mathrm{C}}$ ^{a}	TE$_{\mathrm{R}}$ ^{b}	TCE$_{\mathrm{C}}$ ^{a}	CTE$_{\mathrm{R}}$ ^{b}	O–H PDE
(U)B3LYP/6–31G	–421.611474	–421.266211	0.145634	0.133101	210.43
(U)B3LYP/6–31G(d)	–421.729176	–421.381248	0.145343	0.132700	212.03
(U)B3LYP/6–31G(d,p)	–421.749506	–421.395658	0.145324	0.132520	215.65
(U)B3LYP/6–31+G(d)	–421.740176	–421.400207	0.145043	0.132321	206.99
(U)B3LYP/6–31+G(d,p)	–421.760242	–421.414554	0.144951	0.132145	210.52
(U)B3LYP/6–311G(2d,2p)	–421.863514	–421.512596	0.145110	0.132186	213.73
(U)B3LYP/6–311+G(2d,2p)	–421.868532	–421.521911	0.144956	0.132090	211.07

^{a} data for cation radical ^{b} data for neutral radical

3 RESULTS AND DISCUSSION

The structures, total electronic energies and thermal corrections to energy for catecholic cation radicals and catecholic radicals in different conformations (Scheme 1) were calculated and listed in electronic supplementary information. Accordingly, O–H PDEs, IHB enthalpies and other parameters were obtained and listed in Tables 3–8.



Two conformations of catecholic cation radicals Two conformations of catecholic radicals

Scheme 1

Table 3. O–H PDEs (kcal/mol) and IHB enthalpies (kcal/mol) for catecholic cation radicals in different states. (T = 298.15 K)

X	$\mathrm{PDE_{IHB}}$ [a]	$\mathrm{PDE_{NIHB}}$ [b]	$\mathrm{PDE_{ph}}$ [c]	$\mathrm{H_{IHBc}}$ [d]	$\mathrm{H_{IHBr}}$ [e]	$\mathrm{H_{IHB}}$ [f]	$\mathrm{q_c}$ [g]	$\mathrm{q_r}$ [h]	σ_p^+ [i]	F [j]	$\mathrm{R^+}$ [k]
H	211.44	218.96	211.89	2.06	9.58	7.52	–0.5029	–0.5299	0	0	0
Me	4.21	4.49	6.40	1.92	9.72	7.80	–0.5023	–0.5364	–0.31	0.01	–0.32
F	–3.18	–2.61	–0.73	1.68	9.76	8.08	–0.4933	–0.5304	–0.07	0.45	–0.52
Cl	–2.77	–2.58	0.20	1.78	9.48	7.70	–0.4951	–0.5260	0.11	0.42	–0.31
OH	5.43	6.17	9.75	2.45	10.70	8.25	–0.5010	–0.5442	–0.92	0.33	–1.25
OMe	9.35	9.87	14.09	2.66	10.69	8.03	–0.5065	–0.5482	–0.78	0.29	–1.07
SH	5.69	5.80	10.92	2.51	10.13	7.62	–0.5038	–0.5373	–0.03	0.3	–0.33
SMe	11.39	11.31	17.22	3.02	10.45	7.43	–0.5124	–0.5442	–0.6	0.23	–0.83
$\mathrm{NH_2}$	15.20	15.86	21.46	2.56	10.74	8.18	–0.5099	–0.5567	–1.3	0.08	–1.38
$\mathrm{NMe_2}$	21.69	22.45	29.31	3.14	10.82	7.68	–0.5220	–0.5641	–1.7	0.15	–1.85
CHO	–7.01	–7.48	–5.32	1.34	8.38	7.04	–0.4982	–0.5146	0.73	0.33	0.4
CN	–10.50	–10.70	–8.64	1.71	9.01	7.30	–0.4929	–0.5140	0.66	0.51	0.15
$\mathrm{NO_2}$	–13.00	–13.60	–13.57	1.73	8.41	6.68	–0.4979	–0.5094	0.79	0.65	0.14
$\mathrm{CF_3}$	–6.62	–7.12	–7.22	1.94	8.94	7.00	–0.4997	–0.5203	0.61	0.38	0.23

[a] O–H PDEs of catecholic cation radicals with IHB. The first value is the absolute O–H PDE, and the others are relative to the first value.

[b] O–H PDEs of catecholic cation radicals without IHB. The first value is the absolute O–H PDE, and the others are relative to the first value.

[c] O–H PDEs of monophenolic cation radicals. The first value is the absolute O–H PDE, and the others are relative to the first value. The present values include ZPVE and vibrational contribution to the energy, however, which are very similar to the values only calculated by total electronic energy [22].

[d] IHB enthalpies in catecholic cation radicals, derived from the enthalpy difference between the two kinds of conformations in Scheme 1.

[e] IHB enthalpies in catecholic radicals generated after proton dissociation, derived from the enthalpy difference between the two kinds of conformations in Scheme 1

[f] IHB contributions to O–H PDEs of catecholic cation radicals: $H_{\mathrm{IHBr}} - H_{\mathrm{IHBc}}$.

[g] Mulliken charges of O1 in catecholic cation radicals.

[h] Mulliken charges of O1 in catecholic radicals.

[i] Brown parameter, from ref. 41.

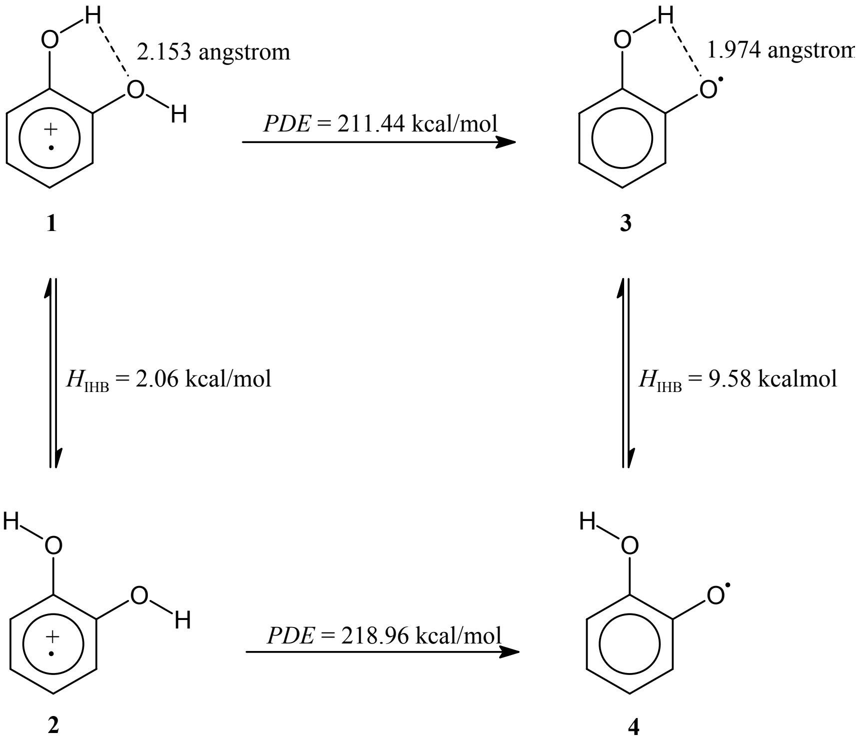
[j] field/inductive parameter, from Ref. [41].

[k] resonance parameter, from Ref. [41].

3.1 O–H PDE of Catecholic Cation Radical

As shown in Table 3, the O–H PDE for catecholic cation radical with IHB, 211.44 kcal/mol, is close to that of phenolic cation radical, 211.89 kcal/mol, suggesting the presence of an *ortho* OH–group has little influence on the O–H PDE. This is different from the *ortho* OH–group effect on O–H BDE that an *ortho* OH–group reduces the O–H BDE approximately 5 ~ 10 kcal/mol [28,36–38]. This also means that the catecholic cation radical would have similar lifetime as phenolic cation radical. However, a recent pulse radiolysis study indicated that the former species was much longer lived than the latter species [21]. An underlying reason may be that other processes than proton dissociation is involved in the decay of catecholic cation radical.

To elucidate the different *ortho* OH–group effect, a thermodynamic scheme for proton dissociation process of catecholic cation radical was constructed (Scheme 2). Obviously, the O–H PDE of **1** is determined by two kinds of substituent effects, the IHB effect and the electronic effect of *ortho* OH–group. The former effect arises from the fact that the IHB in **3**, 9.58 kcal/mol, is much stronger than that in **1**, 2.06 kcal/mol. The difference between the two IHB enthalpies represents the IHB contribution to O–H PDE of **1**, 7.52 (9.58 – 2.06) kcal/mol, which is higher than the IHB effect on O–H BDE of catechol, 5.49 kcal/mol [37]. This stems from the lower IHB enthalpy in **1** than that in parent catechol, 4.09 kcal/mol [37,39]. The electronic effect of *ortho* OH–group on the O–H PDE, represented by the O–H PDE difference between **2** and phenolic cation radical, is 7.07 (218.96 – 211.89) kcal/mol [40]. This is also opposite to the electronic effect on O–H BDE that an *ortho* OH–group reduces the value 4.52 kcal/mol [37], which results from the distinct electronic effects on O–H BDE and O–H PDE [22]. Apparently, the two kinds of effects on O–H PDE of **1** counteract each other, and thus, the *ortho* OH–group effect on O–H PDE is near to zero.



Scheme 2

3.2 4–Substituent Effects on O–H PDEs of Catecholic Cation Radicals

As revealed previously, electron–donating (ED) groups enhanced the O–H PDEs for monophenolic cation radicals, and electron–withdrawing (EW) groups reduced the parameter [22]. This was also observed for catecholic cation radicals that O–H PDEs correlated well with the Brown parameter σ_p^+ [41], regardless of the formation of IHB (Figure 1). The negative correlation coefficient indicates that ED groups tend to raise the O–H PDE, and EW groups have an opposite effect. Furthermore, it is interesting to note that the substituent effect upon O–H PDEs of catecholic cation radicals with or without IHB is comparable to the effect on O–H PDEs of monophenolic cation radicals (Table 3) [42]. Thus, it seems the existence of IHB has little influence on the substituent effect on O–H PDEs. This results from the fact that ED groups increase and EW groups decrease the net charge of O1 in catecholic cation radicals (q_c) and catecholic radicals (q_r) simultaneously (Table 3), hence, ED groups strengthen and EW groups weaken the IHBs of both kinds of radicals as well [43], which induces the two IHB effects offset each other, and the IHB contributions to the relative O–H PDEs only vary within ±1 kcal/mol (Table 3). Thus, electronic contributions to O–H PDEs play a dominant role in the substituent effects, which is similar to the substituent effect on O–H BDEs of catechols [37].

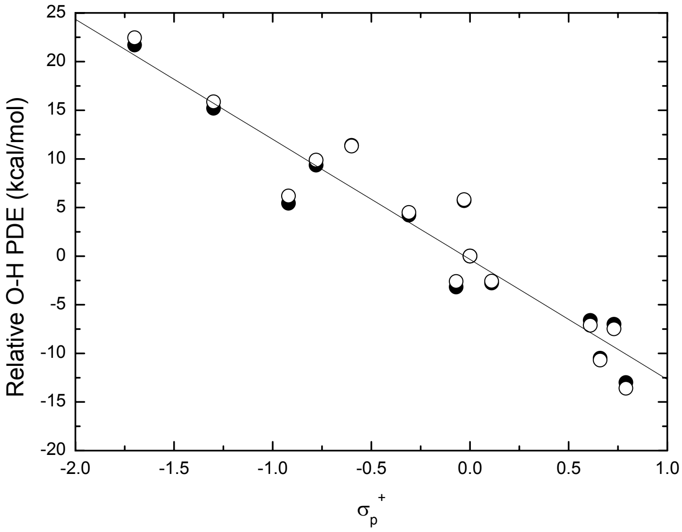


Figure 1. Correlations between relative O–H PDEs of catecholic cation radicals with or without IHB and Brown parameter σ_p^+. (with IHB ●: O–H PDE = –12.35 σ_p^+ – 0.34, r = –0.9543, F = 122.30; without IHB ○: O–H PDE = –12.87 σ_p^+ – 0.31, r = –0.9609, F = 144.43).

A recent study on IHB of *ortho* substituted phenols indicated that the correlation of IHB enthalpy with a single parameter would only be appropriate within a family of compounds [44]. From Table 4, bond length and electron–density of IHB seem appropriate to measure the IHB enthalpy at least in a qualitative fashion. Thus, it is interesting to investigate whether the two parameters are quantitatively effective. Through correlation studies, it was revealed that good linearity only existed between the two parameters and IHB enthalpy of catecholic radicals (Table 5) [45]. Therefore, it is really difficult to find a universal single descriptor to characterize the IHB enthalpy even within the same family of compounds.

As well–known, the 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.*, $\sigma_p^+ = F + R^+$ [41]. Since the O–H PDEs of monophenolic cation radicals were mainly governed by resonance effect [22], it is interesting to investigate whether the O–H PDEs of catecholic cation radicals are mainly determined by resonance effect or not. By correlation studies (Figures 2 and 3), it can be found that the correlation between O–H PDE and R^+ (r = –0.8997) is better than that between O–H PDE and F (r = –0.6756), indicating the hypothesis is reasonable, which will be helpful to elucidate the structure–activity relationship for flavonoid antioxidants that contain a catecholic moiety.

Table 4. B3LYP/6–31G(d,p) calculated bond enthalpies (H_{IHB}, kcal/mol), bond lengths (BL, angstrom) and electron–densities (ED) for IHBs in catecholic cation radicals, parent catechols and catecholic radicals

X	H_{IHBc} [a]	H_{IHBp} [b]	H_{IHBr} [c]	O–H BL_c [a]	O–H BL_p [b]	O–H BL_r [c]	O–H ED_c [a]	O–H ED_p [b]	O–H ED_r [c]
H	2.06	4.09	9.58	2.1525	2.1237	1.9744	0.0183	0.0209	0.0582
Me	1.92	4.10	9.72	2.1544	2.1225	1.9740	0.0178	0.0210	0.0586
F	1.68	4.79	9.76	2.1602	2.1165	1.9747	0.0173	0.0214	0.0578
Cl	1.78	4.06	9.48	2.1644	2.1237	1.9815	0.0171	0.0209	0.0569
OH	2.45	4.88	10.70	2.1554	2.1207	1.9587	0.0173	0.0215	0.0607
OMe	2.66	4.76	10.69	2.1483	2.1229	1.9546	0.0177	0.0213	0.0615
SH	2.51	4.41	10.13	2.1631	2.1253	1.9705	0.0170	0.0210	0.0588
SMe	3.02	3.92	10.45	2.1564	2.1280	1.9644	0.0174	0.0209	0.0601
NH_2	2.56	4.54	10.74	2.1574	2.1178	1.9498	0.0171	0.0217	0.0623
NMe_2	3.14	4.49	10.82	2.1604	2.1305	1.9488	0.0172	0.0209	0.0629
CHO	1.34	3.02	8.38	2.1583	2.1236	1.9888	0.0178	0.0201	0.0548
CN	1.71	3.68	9.01	2.1689	2.1293	1.9923	0.0170	0.0201	0.0546
NO_2	1.73	3.27	8.41	2.1643	2.1300	1.9931	0.0177	0.0199	0.0544
CF_3	1.94	3.26	8.94	2.1613	2.1280	1.9862	0.0178	0.0204	0.0562

[a] data for catecholic cation radicals
[b] data for parent catechols, from Ref. [39b]
[c] data for catecholic radicals, from Ref. [39b]

Table 5. Correlation coefficients between bond enthalpy and bond length and electron–density of IHB in catecholic cation radicals, parent catechols and catecholic radicals

	Catecholic cation radicals	Parent catechols	Catecholic radicals
Bond length	–0.3645	–0.5577	–0.9593
Electron–density	–0.2684	0.9049	0.9655

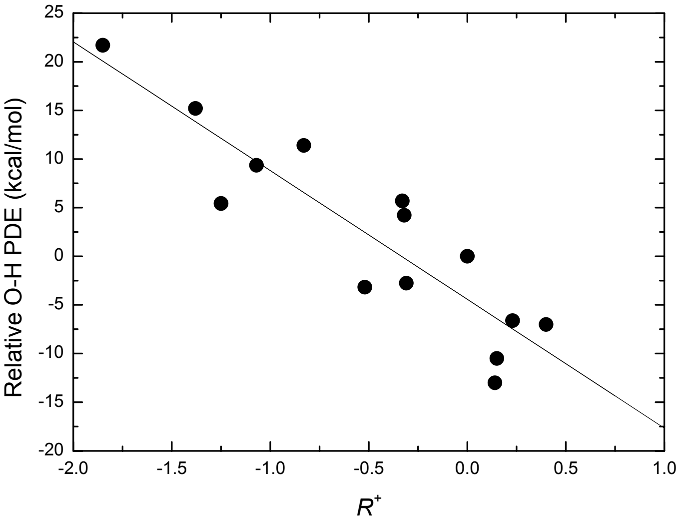


Figure 2. Correlation between relative O–H PDE of catecholic cation radicals with IHB and resonance parameter R^+ ($r = –0.8997$, $F = 50.96$).

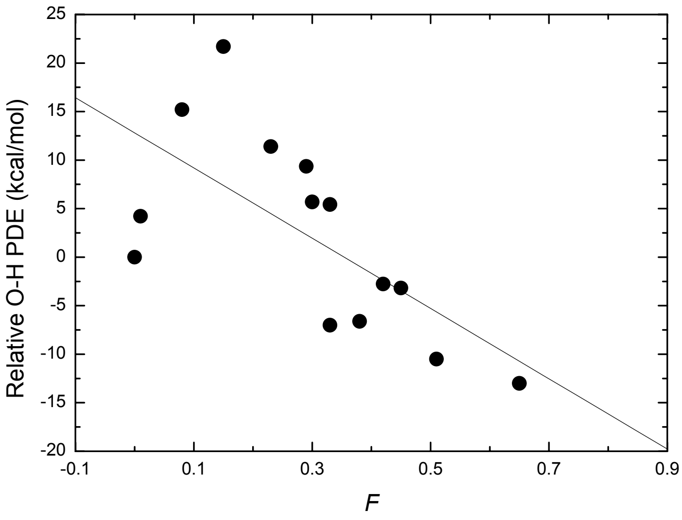


Figure 3. Correlation between relative O–H PDE of catecholic cation radicals with IHB and field/inductive parameter F ($r = -0.6756$, $F = 10.08$).

Furthermore, it is also interesting to test whether bi–parameter correlation will improve the linearity. A regression equation was obtained as: O–H PDE = $2.65 - 11.03\, R^+ - 20.27\, F$ ($r = 0.9644$, $F = 159.50$), indicating the correlation is a little improved comparing with the case where only σ_p^+ is used.

3.3 Correlation Between O–H PDE and Other Parameters

In previous studies, Hermann, Brede and co–workers indicated that the lifetimes (τ_{exp}) of monophenolic cation radicals correlated well with several theoretical parameters, such as spin density at the oxygen, S(O), difference of Mulliken charges at the OH–group, Δq(OH), and at the oxygen, Δq(O), between the cation radical and the singlet ground state [18, 20, 21], which meant that these descriptors were appropriate parameters other than O–H PDE to characterize the proton dissociation ability.

In fact, there exist certain linear relationships between O–H PDE and three kinds of parameters for monophenolic cation radicals (Tables 6 and 7), which is an interesting finding considering the fact that it is difficult to find other parameters than O–H BDE to measure the O–H bond strength [46,47]. However, in the case of catecholic cation radicals, the correlations between O–H PDEs and three kinds of parameters are very poor, regardless of forming IHB or not (Tables 6 and 7). Hence, it seems the description of proton dissociation process is rather more complicated for polyphenolic cation radicals than for monophenolic cation radicals.

Table 6. B3LYP/6–31G(d,p) calculated spin density at the oxygen, *S*(O), difference of Mulliken charges at the OH–group, Δ*q*(OH) and at the oxygen, Δ*q*(O), between the cation radical and the singlet ground state

X	Catecholic cation radicals with IHB			Catecholic cation radicals without IHB			Monophenolic cation radicals		
	S(O)	Δ*q*(OH)	Δ*q*(O)	*S*(O)	Δ*q*(OH)	Δ*q*(O)	*S*(O)	Δ*q*(OH)	Δ*q*(O)
H	0.118	0.149	0.092	0.152	0.174	0.114	0.195	0.212	0.147
Me	0.125	0.150	0.095	0.153	0.171	0.113	0.175	0.195	0.135
F	0.139	0.161	0.103	0.166	0.180	0.120	0.184	0.202	0.139
Cl	0.130	0.151	0.097	0.155	0.170	0.114	0.166	0.186	0.129
OH	0.132	0.155	0.101	0.156	0.173	0.116	0.160	0.183	0.125
OMe	0.126	0.148	0.095	0.149	0.165	0.111	0.149	0.172	0.117
SH	0.117	0.141	0.092	0.138	0.158	0.106	0.132	0.161	0.110
SMe	0.105	0.131	0.085	0.126	0.148	0.099	0.116	0.148	0.100
NH_2	0.120	0.144	0.094	0.142	0.159	0.107	0.133	0.160	0.108
NMe_2	0.103	0.125	0.081	0.125	0.144	0.096	0.111	0.140	0.094
CHO	0.116	0.137	0.084	0.147	0.159	0.104	0.181	0.192	0.133
CN	0.123	0.144	0.091	0.149	0.164	0.108	0.168	0.186	0.128
NO_2	0.115	0.136	0.083	0.148	0.158	0.103	0.203	0.202	0.141
CF_3	0.118	0.143	0.088	0.150	0.165	0.108	0.196	0.204	0.142

Table 7. Correlation coefficients between O–H PDE, O–H BDE and other parameters.

	Catechols with IHB		Catechols without IHB		Monophenols	
	PDE	BDE ^{a}	PDE	BDE ^{a}	PDE	BDE ^{a}
S*(O)*	−0.3449		−0.5828		−0.8940	
Δ*q* (OH)	−0.2921		−0.4232		−0.8523	
Δ*q* (O)	−0.0254		−0.2884		−0.8644	
r(O–H)	−0.9776	0.8892	−0.9811	0.9076	−0.9700	0.9060
ν(O–H)	0.9776	−0.8805	0.9502	−0.8035	0.9680	−0.8152

^{a} parameters for parent molecules are presented in the electronic supplementary information

Table 8. B3LYP/6–31G(d,p) calculated O–H bond length, *r*(O–H) (in angstrom), bond stretching frequency, ν(O–H) (scaled by a factor of 0.98, in cm^{-1}), and bond stretching force constant, *k* (in mDyne/angstrom) for cation radicals.

X	Catecholic cation radicals with IHB			Catecholic cation radicals without IHB			Monophenolic cation radicals		
	r(O–H)	ν(O–H)	*k*	*r*(O–H)	ν(O–H)	*k*	*r*(O–H)	ν(O–H)	*k*
H	0.9721	3688.12	8.9045	0.9730	3676.99	8.8521	0.9751	3647.23	8.7075
Me	0.9719	3690.58	8.9161	0.9727	3686.15	8.8932	0.9738	3663.37	8.7834
F	0.9725	3683.83	8.8848	0.9732	3685.10	8.8893	0.9742	3659.77	8.7679
Cl	0.9723	3686.74	8.8982	0.9729	3689.42	8.9093	0.9736	3665.56	8.7946
OH	0.9716	3693.62	8.9318	0.9722	3704.17	8.9800	0.9729	3677.7	8.8544
OMe	0.9712	3699.21	8.9577	0.9718	3706.84	8.9914	0.9722	3681.57	8.8703
SH	0.9712	3698.44	8.9538	0.9720	3707.61	8.9953	0.9721	3683.26	8.8781
SMe	0.9705	3707.34	8.9962	0.9713	3714.07	9.0256	0.9714	3691.07	8.9148
NH_2	0.9705	3706.84	8.9944	0.9712	3717.93	9.0447	0.9713	3693.89	8.9294
NMe_2	0.9697	3715.96	9.0397	0.9705	3726.05	9.0832	0.9704	3703.89	8.9764
CHO	0.9725	3682.81	8.8792	0.9735	3671.01	8.8231	0.9751	3645.97	8.7009
CN	0.9730	3677.87	8.8558	0.9737	3676.08	8.8469	0.9748	3651.93	8.7299
NO_2	0.9729	3679.15	8.8620	0.9739	3666.13	8.8007	0.9761	3635.67	8.6538
CF_3	0.9725	3683.26	8.8815	0.9732	3672.18	8.8296	0.9754	3643.90	8.6921

In another hand, O–H bond length (*r*(O–H)), bond stretching frequency (ν(O–H)) and bond stretching force constant (*k*), were generally employed to characterize the bond strength. Although the three parameters failed to correlate well with O–H BDE [46], they correlated well with O–H PDE (Tables 7 and 8) [48], suggesting these parameters are better than *S*(O), Δ*q*(OH) or Δ*q*(O) to represent the O–H PDE. Furthermore, the sign of correlation coefficients between O–H BDEs and the descriptors suggest that the higher the ν(O−H) or *k*, the shorter the O−H bond, the lower the O−H BDEs are, which is just opposite to the common understanding that high ν(O−H) or *k* and short O−H bond correspond to high O−H BDE. Therefore, it seems O−H BDE is the only valid parameter to describe the homolysis of O−H bond, whereas, the proton dissociation process can be characterized by various parameters. Furthermore, the good linearity between O−H PDE and *r*(O−H) and ν(O−H) also means that *r*(O−H), ν(O−H) or *k* are appropriate parameters measuring p*K*a values of these cation radicals. In fact, a certain correlation was observed between p*K*a values, *r*(O−H) and ν(O−H) for monophenolic cation radicals [49]. In contrast to the present result, Korth and co–workers proposed that there was no correlation between p*K*a values of *ortho* substituted phenols and ν(O−H) [44]. The presented linearity may come from the fact that the dissociated proton is not hydrogen bonded with the oxygen.

4 CONCLUSIONS

The *ortho* OH–group in catecholic cation radical exerts contradictive effect on O−H PDE. First, the electron–donating property of *ortho* OH–group enhances the O−H PDE. Second, the IHB arising from the OH–group stabilizes the radical and thus beneficial to reduce the O−H PDE. The two effects offset each other, thus the *ortho* OH–group has little influence on the O−H PDE of catecholic cation radical. While substituents at position 4 are involved, the O−H PDEs change drastically. And the substituent effect upon O−H PDEs for catecholic cation radicals has comparable trend as that for monophenolic cation radicals. In addition, apart from O−H PDE, O−H bond length and bond stretching frequency are valid to characterize the proton dissociation process, in contrast to the characterization of homolysis of O−H bond that only BDE is an appropriate parameter.

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Supplementary Material

O–H bond length, bond stretching frequency and bond stretching force constant for catechols and monophenols; optimized structures, total energies and thermal corrections to energies for all calculated molecules.

5 REFERENCES

[1] G. Scott, Antioxidants, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 165–170.
[2] B. Halliwell, R. Aeschbach, J. Loliger, and O. I. Aruoma, The characterization of antioxidants, *Food Chem. Toxic.* **1995**, *33*, 601–617.
[3] O. I. Aruoma, Characterization of drugs as antioxidant prophylactics, *Free Radic. Biol. Med.* **1996**, *20*, 675–705.
[4] G. W. Burton, Y. Le Page, E. J. Gabe, and K. U. Ingold, Antioxidant activity of vitamin E and related phenols. importance of stereoelectronic factors, *J. Am. Chem. Soc.* **1980**, *102*, 7791–7792.
[5] G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, and K. U. Ingold, Autoxidation of biologocal molecules. 4. maximizing the antioxidant activity of phenols, *J. Am. Chem. Soc.* **1985**, *107*, 7053–7065.
[6] M. I. de Heer, P. Mulder, H. G. Korth, K. U. Ingold, and J. Lusztyk, Hydrogen atom abstraction kinetics from

intramolecularly hydrogen bonded ubiquinol–0 and other (poly) methoxy phenols, *J. Am. Chem. Soc.* **2000**, *122*, 2355–2360.

[7] M. C. Foti, E. R. Johnson, M. R. Vinqvist, J. S. Wright, L. R. C. Barclay, and K. U. Ingold, Naphthalene diols: a new class of antioxidants intramolecular hydrogen bonding in catechols, naphthalene diols, and their aryloxyl radicals, *J. Org. Chem.* **2002**, *67*, 5190–5196.

[8] S. Nagaoka, A. Kuranaka, H. Tsuboi, U. Hagashima, and K. Mukai, Mechanism of antioxidant reaction of vitamin E. charge transfer and tunneling effect in proton–transfer reaction, *J. Phys. Chem.* **1992**, 96, 2754–2761.

[9] S. V. Jovanovic, S. Steenken, M. Tosic, B. Marjanovic, and M. G. Simic, Flavonoids as antioxidants, *J. Am. Chem. Soc.* **1994**, *116*, 4846–4851.

[10] S. V. Jovanovic, S. Steenken, Y. Hara, and M. G. Simic, Reduction potentials of flavonoid and model phenoxyl radicals. Which ring in flavonoids is responsible for antioxidant actitity, *J. Chem. Soc. Perkin Trans. 2* **1996**, *11*, 2497–2504.

[11] I. Nakanishi, K. Miyazaki, T. Shimada, K. Ohkubo, S.Urano, N. Ikota, T. Ozawa, S. Fukuzumi, and K. Fukuhara, Effects of metal ions distinguishing between one–step hydrogen–and electron–transfer mechanisms for the radical–scavenging reaction of (+)–catechin, *J. Phys. Chem. A* **2002**, *106*, 11123–11126.

[12] K. Tanaka, S. Sakai, S. Tomiyama, T. Nishiyama, and F. Yamada, Molecular orbital approach to antioxidant mechanisms of phenols by ab initio study, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2677–2680.

[13] S. Tomiyama, S. Sakai, T. Nishiyama, and F. Yamada, Factors influencing the antioxidant activities of phenols by an *ab initio* study, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 299–304.

[14] S. A. B. E. van Acker and L. M. H. Koymans, A. Bast, Molecular pharmacology of vitamin E: Structural aspects of antioxidant activity, *Free Radic. Biol. Med.* **1993**, *15*, 311–328.

[15] E. Migliavacca, P. A. Carrupt, and B. Testa, Theoretical parameters to characterize antioxidants, *Helv. Chim. Acta* **1997**, *80*, 1613–1626.

[16] H. Y. Zhang, Selection of theoretical parameter characterizing scavenging activity of antioxidants on free radicals, *J. Am. Oil Chem. Soc.* **1998**, *75*, 1705–1709.

[17] F. G. Bordwell and J.–P. Cheng, Substituent effects on the stabilities of phenoxyl radicals and the acidities of phenoxyl radical cations, *J. Am. Chem. Soc.* **1991**, *113*, 1736–1743.

[18] R. Hermann, S. Naumov, G. R. Mahalaxmi, and O. Brede, Stability of phenol and thiophenol radical cations–interpretation by comparative quantum chemical approaches, *Chem. Phys. Lett.* **2000**, *324*, 265–272.

[19] M. R. Ganapathi, R. Hermann, S. Naumov, and O. Brede, Free electron transfer from several phenols to radical cations of non–polar solvents, *Phys. Chem. Chem. Phys.* **2000**, *2*, 4947–4955.

[20] R. Hermann, S. Naumov, and O. Brede, Eletron transfer from phenolic compounds to parent n–butyl chloride radical cations—a quantum chemical study of product transient formation and stability, *J. Mol. Struct. (Theochem)* **2000**, *532*, 69–80.

[21] O. Brede, S. Kapoor, T. Mukherjee, R. Hermann, and S. Naumov, Diphenol radical cations and semiquinone radicals as direct products of the free electron transfer from catechol, resorcinol and hydroquinone to parent solvent radical cations, *Phys. Chem. Chem. Phys.* **2002**, *4*, 5096–5104.

[22] H. Y. Zhang, Y. M. Sun, and X. L. Wang, Electronic effects on O–H proton dissociation energies of phenolic cation radicals. A DFT study, *J. Org. Chem.* **2002**, *67*, 2709–2712.

[23] Y. D. Wu and D. K. W. Lai, A density functional study of substituent effects on the O–H and O–CH_3 bond dissociation energies in phenol and anisole, *J. Org. Chem.* **1996**, *61*, 7904–7910.

[24] J. S. Wright, D. J. Carpenter, D. J. McKay, and K. U. Ingold, Theoretical calculation of substituent effects on the O–H bond strength of phenolic antioxidants related to vitamin E, *J. Am. Chem. Soc.* **1997**, *119*, 4245–4252.

[25] T. Brinck, M. Haeberline, and M. Jonsson, A computational analysis of substituent effects on the O–H bond dissociation energy in phenols: polar versus radical effects, *J. Am. Chem. Soc.* **1997**, *119*, 4239–4244.

[26] G. A. DiLabio, D. A. Pratt, A. D. LoFaro, and J. S. Wright, Theoretical study of X–H bond energetics (X= C, N, O, S): application to substituent effects, gas phase acidities, and redox potentials, *J. Phys. Chem. A* **1999**, *103*, 1653–1661.

[27] H. Y. Zhang, Y. M. Sun, and D. Z. Chen, O–H bond dissociation energies of phenolic compounds are determined by field/inductive effect or resonance effect? A DFT study and its implication, *Quant. Struct.–Act. Relat.* **2001**, *20*, 148–152.

[28] J. S. Wright, E. R. Johnson, and G. A. DiLabio, Predicting the activity of phenolic antioxidants: theoretical method, analysis of substituent effects, and application to major families of antioxidants, *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183.

[29] C. Lee, W. Yang, and R. G. Parr, Development of the Colle–Salvetti correlation–energy formula into a functional of the electron density, *Phys. Rev. B* **1988**, *37*, 785–789.

[30] P. J. Stevenes, F. J. Devlin, C. F. Chabalowski, and M. J. Frisch, *Ab initio* calculation of vibrational absorption and circular dichroism spectra using density functional force fields, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[31] A. D. Becke, A new mixing of Hartree–Fock and local density–functional theories, *J. Chem. Phys.* **1993**, *98*,

1372–1377.

[32] J. J. Gajewski, K. E. Gillbert, and J. McKelvey, MMX. An enhanced version of MM2. *Adv. Mol. Model.* **1990**, *2*, 65–92.

[33] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, AM1: a new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

[34] A. P. Scott and L. Radom, Harmonic vibrational frequencies: an evaluation of Hartree–Fock, Møller–Plesset, quadratic configuration interaction, density functional theory, and semiempirical scale factors, *J. Phys. Chem.* **1996**, *100*, 16502–16513.

[35] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al–Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head–Gordon, C. Gonzalez and J. A. Pople, *Gaussian 94*, *Revision E.3;* Gaussian, Inc.: Pittsburgh, PA, 1995.

[36] M. Lucarini, V. Mugnaini, and G. F. Pedulli, Bond dissociation enthalpies of polyphenols: the importance of cooperative effects, *J. Org. Chem.* **2002**, *67*, 928–931.

[37] H. Y. Zhang, Y. M. Sun, and X. L. Wang, Substituent effects on O–H bond dissociation energies and ionization potentials of catechols: A DFT study and its implications in elucidation of structure–activity relationships for flavonoid antioxidants, *Chem–Eur. J.* **2003**, *9*, 502–508.

[38] H. Y. Zhang, On the O–H bond dissociation enthalpy of catechol, *New. J. Chem.* **2003**, *27*, 453–454.

[39] (a) Our previous study indicated that the IHB strength for catechols and catecholic radicals could be characterized to certain extent by the bond length and electron–density of the IHB [39b]. The longer the IHB, and the lower the electron–density on the bond, the weaker the IHB is. As shown in Table 4, the bond lengths of **1**, parent catechol and **3** are in the order: **1** > parent catechol > **3**, and the electron–densities are in the opposite order: **1** < parent catechol < **3**, which is just in line with the IHB enthalpy order: **1** < parent catechol < **3**. (b) H. Y. Zhang, Y. M. Sun and L. F. Wang, A DFT study on intramolecular hydrogen bonds in substituted catechols and their radicals, *Chin. Chem. Lett.* **2003**, *14*, 209–212.

[40] (a) According to the well known proviso $\sigma_o^+ \sim 0.66\sigma_p^+$ [40b, 40c], and the assumption that O–H PDE is proportional with Brown parameter σ^+, one can roughly calculate the electronic effect of *ortho* OH–group on O–H PDE to be: 0.66 × 9.75 = 6.43 kcal/mol, similar to the DFT calculated value. (b) M. Jonsson, J. Lind, T. E. Eriksen and G. Merenyi, O–H bond strengths and one–electron reduction potentials of multisubstituted phenols and phenoxyl radicals. Predictions using free energy relationships, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1567–1568. (c) D. D. M. Wayner, E. Lusztyk, K. U. Ingold and P. Mulder, Application of photoacoustic calorimetry to the measurement of the O–H bond strength in vitamin E (α– and δ–tocopherol) and related phenolic antioxidants, *J. Org. Chem.* **1996**, *62*, 6430–6433.

[41] C. Hansch, A. Leo, and R. W. Taft, A survey of Hammett substituent constants and resonance and field parameters, *Chem. Rev.* **1991**, *91*, 165–195.

[42] The substituent effect on O–H PDEs of catecholic cation radicals is much stronger than that on O–H BDEs of catechols [37]. A similar phenomenon was also observed for monophenolic cation radicals [22].

[43] The correlation coefficients between IHB enthalpies and net charges of O1 are 0.8862 and 0.9536 for catecholic cation radicals and catecholic radicals, respectively. However, the net charge of O1 cannot be used to predict the IHB enthalpy for different families of phenols even in a qualitatively manner. For instance, the net charge of O1 in parent catechol is –0.5946, higher than the charge in catecholic radical, –0.5299, but the IHB enthalpy of the former molecule is much lower than that of the latter molecule [39b].

[44] H. –G. Korth, M. I. de Heer, and P. Mulder, A DFT study on intramolecular hydrogen bonding in 2–substituted phenols: conformations, enthalpies, and correlation with solute parameters, *J. Phys. Chem. A*. **2002**, *106*, 8779–8789.

[45] The parameters for catecholic radicals depend more sensitively on the substituents than other molecules (Table 4), which may be the reason underlying the good linearity.

[46] H. Y. Zhang, Y. M. Sun, G. Q. Zhang, and D. Z. Chen, Why static molecular parameters cannot characterize the free radical scavenging activity of phenolic antioxidants, *Quant. Struct.–Act. Relat.* **2000**, *19*, 375–379.

[47] E. G. Bakalbassis, A. Chatzopoulou, V. S. Melissas, M. Tsimidou, M. Tsolaki and A. Vafiadis, *Ab initio* and density functional theory studies for the explanation of the antioxidant activity of certain phenolic acids, *Lipids* **2001**, *36*, 181–190, and the discussions at below.

[48] Substantially, ν(O–H) has the same meaning as *k*. In fact, there exist very good correlations between the two parameters. Hence, only correlation coefficients associated with ν(O–H) are indicated in Table 7.

[49] The correlation coefficients are –0.941 and 0.938 for *r*(O–H) and ν(O–H), respectively. p*K*a values refer to Ref. [17].