Antioxidant Activities of Dihydric Phenol Derivatives for the Autoxidation of Tetralin

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The antioxidant activities of dihydric phenols, such as catechol, resorcinol, and hydroquinone, and their twenty-three alkyl and benzyl substituted derivatives were evaluated by means of an oxygen-absorption method at 60 °C for determining the oxidation of tetralin. Catechols exhibited a much higher stoichiometric factor (2.0—2.3) compared with those of other compounds. The stoichiometric factors of hydroquinones (0.6—1.1) are almost half those of catechols, and are lower for the resorcinols (0.3—0.6). In addition, the rates of oxidation during the induction period (R_{inh}) were 1.1—1.6×10^{-6}, 3.0—3.8×10^{-6}, and 13.3—18.4×10^{-6} M min^{-1} for catechols, hydroquinones, and resorcinols, respectively. According to these results, catechols and hydroquinones are efficient antioxidants, and their activities may be dependent on the stability of phenoxyl radicals as oxidation products due to the formation of the quinone structure. Furthermore, the stability of phenoxyl radicals derived from catechols is higher than that of those from hydroquinones. In spite of having two OH substituents, resorcinols behave as monohydric phenols in the reaction with peroxyl radicals.

Antioxidants play an important role in the protection of biomolecules from lipid peroxidation and damage to membranes, which can result in the initiation and/or progression of a number of diseases.[1,2] Therefore, various kinds of natural and synthetic phenolic compounds have generally been used as chain-breaking inhibitors of the peroxyl radicals. For instance, tocopherols, flavonoid and ubiquinols act as free radical scavengers and exhibit excellent antioxidative activities.[3—7]

We have previously reported that phenolic compounds with diarylmethylene moieties, such as benzylphenols and alkylidenebisphenols, showed high antioxidant activities.[8,9] In addition, the rates of oxidation during the induction period were found to closely correlate with both the ^{13}C NMR chemical shifts of the *ipso*-carbon of the OH substituent and the electrochemical oxidation potentials. The ^{13}C chemical shifts of the *ipso*-carbon of the OH substituent and the electrochemical oxidation potential indicate the total π-electron density of the oxygen atom and the simplicity of the one-electron and one-proton transfers, respectively. Namely, the antioxidant activities of the benzylphenols and alkylidenebisphenols were governed by the ability of one-electron and one-proton transfers following the hydrogen abstractions which are dependent upon the π-electron density of the oxygen atom.

On the other hand, although the polyhydric phenols often found in plants and animals are well known as effective antioxidants, the exact mechanisms of the antioxidant action and the effects of introducing the substituents on the phenol nuclei are not clearly understood. The mechanisms of antioxidant activities of polyhydric phenols are complicated by the interaction of each OH substituent due to resonance effects and intramolecular hydrogen bonds. However, it would be expected that the reactivity of phenolic hydrogen on polyhydric phenols can be estimated to a certain extent by incorporation with the reactivities of two OH substituents existing in each position, such as *ortho*, *meta*, and *para*.

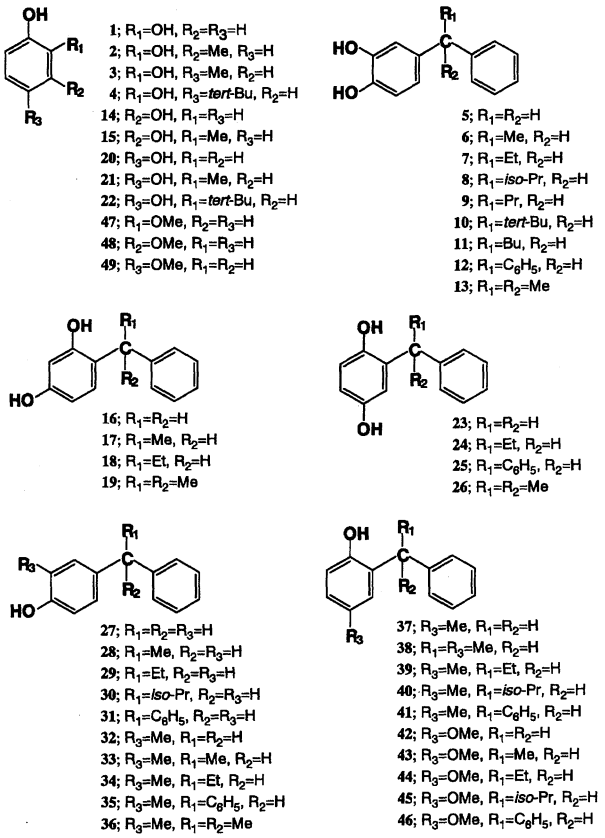
In the present study, therefore, the antioxidant activities of the dihydric phenols, such as catechol, resorcinol, and hydroquinone, containing alkyl and benzyl groups as substituents, were evaluated using an oxygen-absorption method at 60 °C for determining the oxidation of tetralin. In addition, their antioxidant activities are discussed in connection with their ^{13}C NMR chemical shifts and electrochemical oxidation potentials.

Experimental

Measurements. ^{13}C NMR spectra were recorded on a Hitachi R-90H FT spectrometer at 22.66 MHz with complete proton decoupling. The spectra were observed using a 2 M solution in $(CD_3)_2CO$ (1 M=1 mol dm^{-3}). Chemical shifts were referenced to TMS.

Antioxidants. The 26 dihydric phenol derivatives studied in this work are shown in Scheme 1.

The commercially available compounds, **1**, **2**, **3**, **4**, **14**,



Scheme 1.

15, **20**, **21**, **22**, **47**, **48**, and **49**, were further purified by recrystallization from a mixture of benzene and hexane. The other compounds used in this work were prepared by Friedel–Crafts benzylations of the corresponding phenols in nitromethane for the desired time at a suitable temperature.[10,11] The reaction conditions for benzylations were as follows: (1) The reactions of the corresponding phenols with benzyl chloride using $AlCl_3$ as the catalyst (1.0/1.0/0.3 molar ratio) at 60—70 °C gave the corresponding products, **5**, **16**, and **23**; (2) the reactions of the phenols with α-ethylbenzyl alcohol, α-isopropylbenzyl alcohol, α-propylbenzyl alcohol, α-*t*-butylbenzyl alcohol, α-butylbenzyl alcohol, or diphenylmethanol using $ZnCl_2$ (1.0/1.0/1.0) at 40—50 °C gave products, **7**, **8**, **9**, **10**, **11**, **12**, **18**, **24**, and **25**; and (3) the reactions of the phenols with styrene or α-methylstyrene using concd H_2SO_4 (1.0/1.0/0.5) at 60—85 °C gave products, **6**, **13**, **17**, **19**, and **26**. The structures were confirmed by the ^{13}C and ^1H NMR spectra and by elemental analyses.

Determination of the Antioxidant Activity for Tetralin. The measurement of the oxygen-absorption rate was performed with an isobaric gas-absorption apparatus with a closed-flow system (2.0±0.1 L oxygen h^{-1}) provided with an electrolyzer using 50 ml of tetralin containing an antioxidant (1 mM) and azobisisobutyronitrile (AIBN) as the initiator (10 mM). The oxidation temperature was kept at 60±0.1 °C and the oxygen absorption was periodically measured in a constant-pressure closed system. The induction period (t_{inh}) and the oxidation rates during the induction period (R_{inh}) were determined in the usual way.[12,13] Tetralin used for the test was purified by shaking with concentrated sulfuric acid, dried with sodium, and distilled under an inert atmosphere.

Electrochemical Determination. Linear-sweep voltammograms were recorded for each compound (1 mM) in acetonitrile with $LiClO_4$ (0.1 M) as the supporting electrolyte. The counter and working electrodes were made of platinum and the working electrode potential was referenced to Ag/AgCl. Potential sweeps were generated using a Hokuto Denko HB-107A function generator in connection with a Hokuto Denko HA-104 potentiostat. All measurements at a scan rate of 200 mV s^{-1} were carried out at 25±0.1 °C using a constant-temperature bath under a nitrogen atmosphere. The acetonitrile was of optically pure grade and was free from water.

Results

Figure 1 shows examples of oxygen-absorption curves for the oxidation of tetralin initiated using AIBN at 60 °C. After a very brief induction period, a constant rate of oxygen absorption was observed in the control solution in the absence of an antioxidant. When benzylcatechol (**5**) or benzylhydroquinone (**23**) was added to the tetralin, oxidation was strongly suppressed, and there was a measurable induction period. On the other hand, in the presence of benzylresorcinol (**16**), the rate of oxygen absorption was less suppressed, and a low induction period was observed.

The autoxidation of organic substrates initiated with AIBN and inhibited by phenol derivatives proceeds by the following chain-reaction schemes.[13]

$$\text{Initiation:}\quad \text{AIBN};\ \text{RH} \xrightarrow{O_2} \text{RO}_2\cdot \tag{1}$$

$$\text{Propagation:}\quad \text{RO}_2\cdot + \text{RH} \xrightarrow{k_p} \text{ROOH} + \text{R}\cdot \tag{2}$$

$$\text{R}\cdot + \text{O}_2 \xrightarrow{\text{fast}} \text{RO}_2\cdot \tag{3}$$

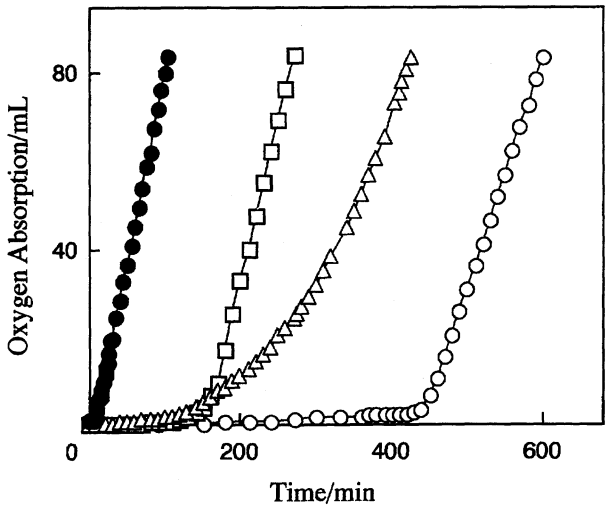


Fig. 1. Rate of oxygen uptake in the oxidation of tetralin initiated by 10 mM AIBN in the absence and presence of 1 mM dihydric phenols at 60 °C under oxygen. ●: control, ○: benzylcatechol, △: benzylresorcinol, □:benzylhydroquinone.

$$\text{Termination}: 2RO_2\cdot \xrightarrow{2k_t} \text{non-radical products} \quad (4)$$

In the above, RH denotes tetralin in this work and $RO_2\cdot$ is the peroxyl radical. In the presence of a chain-breaking phenolic antioxidant, ArOH, the oxidation chains are shortened, chain termination by reaction 4 is suppressed, and termination occurs instead by reactions 5 and 6, where n represents the stoichiometric factor which is the number of radicals trapped by each molecule of antioxidant.[13]

$$RO_2\cdot + ArOH \xrightarrow{k_{inh}} ROOH + ArO\cdot \quad (5)$$

$$(n-1)RO_2\cdot + ArO\cdot \xrightarrow{fast} \text{non-radical products} \quad (6)$$

The induction period (t_{inh}) and the rate of oxidation (R_{inh}) are represented by Eqs. 7 and 8, respectively,

$$t_{inh} = n[ArOH]/R_i, \quad (7)$$

$$R_{inh} = k_p R_i[RH]/nk_{inh}[ArOH], \quad (8)$$

where k_p is the propagation rate constant of the chain reaction, R_i is the rate of the chain initiation, and k_{inh} is the rate constant of reaction 5.

From the above equations, the characterizations of the antioxidative activities can be expressed by three values: t_{inh}, n, and k_{inh}. However, the value of k_{inh} is difficult to that obtain experimentally. Consequently, instead of this value the rate of oxygen absorption (R_{inh}) in Eq. 8 was used.

The induction period and stoichiometric factors for the dihydric phenols are given in Table 1, along with the results of inhibition by benzylphenols[8] for a comparison. The t_{inh} values of dihydric phenols were affected by the positions of the OH groups. That is, the t_{inh} values decreased in the order catechols>hydroquinones>resorcinols. The t_{inh} values for the catechol derivatives are the same, within experimental error, as those for the catechol. The values for resorcinols increased considerably due to a combination of differential electronic and steric effects as a result of introducing substituents on the phenol ring. On the other hand, hydroquinone showed higher t_{inh} values than did the hydroquinone derivatives.

At first, the stoichiometric factor (n) for the antioxidants tested was obtained from Eq. 7. The rate of initiation (R_i) was determined from the induction period measured in the presence of 2,6-di-*t*-butyl-4-methylphenol (BHT) under the same conditions, for which $n=2$ was assumed.[14]

Catechols exhibited a much higher stoichiometric factor (2.0—2.3) compared with those of other compounds. This means that catechols can trap two peroxyl radicals. On the other hand, the n values of hydroquinones and resorcinols were almost half that obtained in the presence of an equal amount of catechols.

Regarding the rates of oxygen absorptions (R_{inh}) during the induction period, the catechols and hydroquinones have a smaller R_{inh} than do the resorcinols.

Table 1. Antioxidant Activities of Dihydric Phenols and Benzylphenols along with ^{13}C Chemical Shifts of the *ipso*-Carbon of the OH Substituents and the Oxidation Potentials

Compd No.	t_{inh} min	n a)	R_{inh} b) $\times 10^6$ M min^{-1}	δ_c c) ppm	δ_c' d) ppm	E_p e) V
1	472	2.3	1.3	145.5	145.5	1.155
2	462	2.2	1.1	143.9	144.9	1.134
3	471	2.3	1.3	143.3	145.4	1.054
4	416	2.0	1.6	142.7	144.6	1.079
5	446	2.2	1.5	143.8	145.4	1.150
6	446	2.2	1.4	143.6	145.3	1.095
7	449	2.2	1.2	143.6	145.3	1.090
8	447	2.2	1.6	143.4	145.2	—
9	433	2.1	1.3	143.5	145.2	—
10	445	2.1	1.6	143.8	144.9	—
11	438	2.1	1.4	143.7	145.4	—
12	425	2.1	1.5	143.9	145.1	—
13	459	2.2	1.1	143.2	144.8	1.125
14	53	0.3	18.4	158.9	158.9	1.500
15	69	0.3	16.4	156.7	156.7	1.365
16	124	0.6	14.6	156.0	157.0	1.370
17	132	0.6	13.3	155.5	156.6	1.360
18	118	0.6	14.9	155.9	156.5	1.250
19	78	0.4	15.9	156.5	157.4	1.310
20	234	1.1	3.0	150.7	150.7	1.020
21	155	0.7	3.6	148.8	150.7	0.980
22	128	0.6	3.8	149.1	150.3	0.995
23	159	0.8	3.1	148.3	150.8	0.960
24	137	0.7	3.6	148.0	150.7	0.970
25	175	0.8	3.4	148.1	150.6	0.970
26	139	0.7	3.8	148.3	150.9	1.020
27	62	0.3	17.3	156.0	—	1.512
28	56	0.3	15.9	156.2	—	1.530
29	69	0.3	15.5	156.0	—	1.519
30	69	0.3	12.9	155.4	—	1.490
31	50	0.2	14.3	156.2	—	1.526
32	186	0.9	12.0	153.7	—	1.388
33	177	0.9	13.1	153.8	—	1.403
34	182	0.9	12.3	153.7	—	1.371
35	168	0.8	10.6	154.2	—	1.386
36	157	0.8	11.4	153.5	—	1.359
37	213	1.0	9.2	153.0	—	1.351
38	252	1.2	8.1	152.1	—	1.323
39	221	1.1	8.1	153.2	—	1.349
40	217	1.0	10.3	152.6	—	1.341
41	215	1.0	9.6	153.0	—	1.339
42	434	2.1	3.1	149.0	—	1.040
43	452	2.2	3.0	148.7	—	1.023
44	460	2.2	3.1	149.1	—	1.049
45	454	2.2	3.3	148.8	—	1.043
46	406	2.0	3.3	149.3	—	1.055
BHT	414	(2.0)	12.0	152.1	—	1.345
Control	22	—	—	—	—	—

a) Stoichiometric factor determined from relative to BHT as a standard. b) Rates of oxygen uptake for an inhibited oxidation during induction period. c) ^{13}C chemical shift of the *ipso*-carbon of OH substituent obtained at lower field. d) ^{13}C chemical shift of the *ipso*-carbon of OH substituent obtained at higher field. e) Oxidation potential in acetonitrile at 25 °C.

Based on these results, catechols and hydroquinones should react with peroxyl radicals more quickly than resorcinols. Thus, the chain propagation by reaction 2 is strongly suppressed by catechols and hydroquinones.

According to Eq. 8, the R_{inh} value varies inversely with the product of n and k_{inh}. Figure 2 shows plots of the n values against the R_{inh} values of the dihydric phenols and benzylphenols. Excellent linear correlations of the slope (r=0.990) were obtained for the catechols and hydroquinones, while different relationships were obtained for the cases of the resorcinols and benzylphenols (r=0.969). From these relationships, it is considered that the k_{inh} values for catechols and hydroquinones, resorcinols and benzylphenols are nearly equal.

Discussion

Recently, we reported on studies of hydrogen abstractions from phenolic compounds using ab initio molecular orbital calculations, and concluded that the gain or loss of electrons in the reaction states may be correlated with the ^{13}C chemical shifts of the *ipso*-carbon of the OH substituent and the values of the t_{inh} as antioxidant activity.[15,16] Consequently, in order to understand the factors and mechanisms governing antioxidant activities of dihydric phenols, several attempts were made to investigate the relationship among their t_{inh} values and the R_{inh} values relative to the ^{13}C NMR chemical shifts (δ_c) of the *ipso*-carbon of the OH substituent by comparing these data with previously reported data for benzylphenols.[8] The data used in this attempt are listed in Table 1.

The δ_c values were 142.7—145.5, 148.0—150.7, and 155.5—158.9 for catechols, hydroquinones and resorcinols, respectively. This result is in good agreement with the antioxidant activities of each compound denoted by the values of t_{inh}, n, and R_{inh}. That is, the antioxidant activities of dihydric phenols increased with increasing the total π-electron density of the oxygen atom.

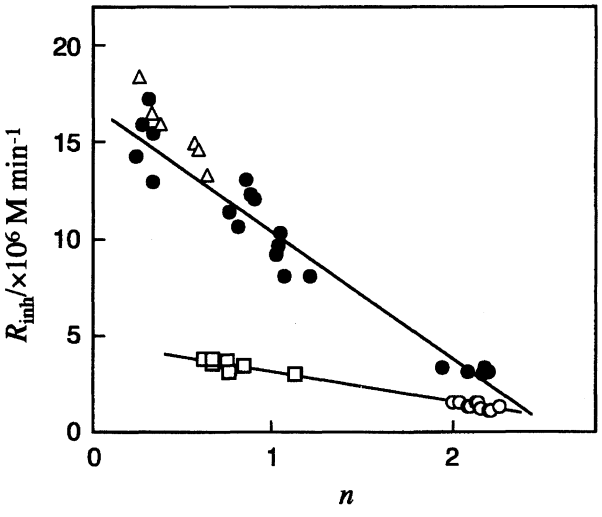


Fig. 2. Plot of stoichiometric factor, n, against the rate of oxygen uptake during the induction period in the oxidation of tetralin initiated by AIBN. ○: catechols, △: resorcinols, □: hydroquinones, ●: benzylphenols.

When an oxygen atom exists in a position *ortho* or *para* to the OH substituents on the aromatic ring, it is expected that the electron density of the *ipso*-carbon of the OH substituents will increase by delocalization into the π-electron system of the aromatic ring. Indeed, the δ_c values of catechols and hydroquinones are smaller than that of resorcinols. In order to consider the role of OH substituents on each position of the aromatic ring, the antioxidant activities of dihydric phenols and their monomethyl ethers are therefore compared. The antioxidant activities of dihydric phenols and the corresponding methoxyphenols are listed in Table 2.

The antioxidant activity of catechol is decreased markedly by monomethyl etherification. That is, the values of t_{inh} and n of catechol (**1**) are about five-fold, and the R_{inh} value is twelve-fold lower than that of *o*-methoxyphenol (**47**). In contrast, the t_{inh} and n values of *p*-methoxyphenol (**49**) are two-fold higher than those of hydroquinone (**20**), but their R_{inh} value is almost the same. Thus, *p*-methoxyphenol can react with more peroxyl radicals than hydroquinone at the same reaction rate. Ingold et al.[17] reported that the rate constant for the hydrogen abstraction by peroxyl radicals for α-tocopherol and related compounds depends on the degree of stabilization of the phenoxyl radical. Stabilization of the phenoxyl radical depends on both the extent of the orbital overlap between the 2p lone pair on the *para* oxygen atom and the aromatic π-electron system and on the electron-donating ability of the group bonded to the *para* oxygen atom. In the case of *p*-methoxyphenol, the methyl group bonds to the *para* oxygen atom and acts as an electron donor. That is, the phenoxyl radical of *p*-methoxyphenol is more stable than that of hydroquinone. Therefore, the increases in the values

Table 2. Antioxidant Activities of Dihydric Phenols and Methoxyphenols along with ^{13}C Chemical Shifts of the *ipso*-Carbon of the OH Substituents and the Oxidation Potentials

Compd No.	t_{inh} min	n [a]	R_{inh} [b] $\times10^6$ M min^{-1}	δ_c [c] ppm	E_p [d] V
1	472	2.3	1.3	145.5	1.155
47	96	0.5	15.9	145.7	1.284
14	53	0.3	18.4	158.9	1.500
48	56	0.3	16.1	156.9	1.527
20	234	1.1	3.0	150.7	1.020
49	462	2.2	3.0	149.6	1.181

a) Stoichiometric factor determined from relative to BHT as a standard. b) Rates of oxygen uptake for an inhibited oxidation during induction period. c) ^{13}C chemical shift of *ipso*-carbon of OH substituent. d) Oxidation potential in acetonitrile at 25 °C.

of t_{inh} and n are due to stabilization of the phenoxyl radical. The antioxidant activity of *m*-methoxyphenol (**48**) is almost same as that of resorcinol (**14**). Based on this fact, the OH substituents on resorcinols react individually for peroxyl radicals without interaction among each OH substituent. The residual OH substituent may then induce a retardation effect after the induction period shown in Fig. 1.

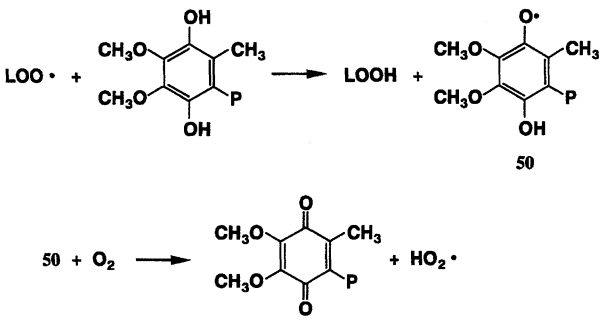
Alanko et al.[18] reported that the stoichiometric factor and the relative peroxyl radical scavenging rate constant (IC_{50}) for dihydric phenols was determined using a luminescent assay to be 7.4 and 0.086 μM for catechol, 3.1 and 0.091 μM for hydroquinone, and 0.85 and 4.6 μM for resorcinol, respectively. Although the stoichiometric factors appeared to be three-fold higher, these results showed a tendency similar to our results for the autoxidation of tetralin initiated with AIBN.

The electrochemical oxidation potentials (E_p) showed a different tendency for other antioxidant parameters, such as the t_{inh}, n and R_{inh} values listed in Table 1. That is, the hydroquinones exhibited much lower E_p values compared with other compounds. A similar tendency was reported in that the oxidation potentials of dihydric phenols at pH 7 are 0.53, 0.46, and 0.81 V for catechol, hydroquinone, and resorcinol, respectively.[19] This means that the one-electron and one-proton transfers occur more easily in the hydroquinones than in catechols and resorcinols. In a previous paper,[8] we proved that the ease of one-electron and one-proton transfers is greatly increased by an increased electron density at the *ipso*-carbon of the OH substituent, which can increase the antioxidant activities. However, no linear relationship was obtained between the E_p values and the t_{inh} values or δ_c values for dihydric phenols. Based on these facts, it is speculated that the E_p values of the hydroquinones could not reflect the ability of the hydrogen abstraction by peroxyl radicals denoted in reaction 5. Therefore, the simplicity of one-electron and one-proton transfers was not related to peroxyl radical scavenging ability in the case of hydroquinones. These results suggest that hydroquinones could not act as effective radical scavengers, whereas the hydrogen abstraction occurred more easily compared with catechols and resorcinols.

In fact, the hydroquinones scavenge only one-half of the peroxyl radicals compared with the catechols, as demonstrated by the n values. When hydrogen abstraction occurs, hydroquinone may immediately change to *p*-quinone, which is a stable form. This reversible process is well-known in which hydroquinone may be oxidized to quinone and quinone may be reduced to hydroquinone. In biological membranes, the *p*-quinone derivatives such as ubiquinones play an important role in the transmembrane electron and proton transport systems through the reversible process of conversion to the ubiquinols.[20] It is therefore considered that electron and proton transfers easily occurred without a peroxyl radical scavenging in the hydroquinones. Furthermore, Iwatsuki et al.[21] reported that the ubiquinols forms the hydroperoxyl radical from the interaction of oxygen and ubisemiquinone radical (**50**) denoted in Scheme 2. Since the hydroperoxyl radical is active and capable of initiating chain oxidation, ubiquinol shows less antioxidant activity.

On the other hand, when an oxygen atom exists at the *o*-position of an OH substituent, an intramolecular hydrogen bond forms between the hydrogen atom of the OH substituent and the oxygen atom at the *o*-position. In addition, the strength of the hydrogen bond may be increased in the case of *o*-methoxyphenol due to an inductive effect of the methyl group. Therefore, hydrogen abstraction from the OH substituent is suppressed by the formation of a hydrogen bond in *o*-methoxyphenol. On the contrary, there is a free hydrogen atom in catechol, although an OH substituent forms the intramolecular hydrogen bond. Furthermore, the electron density of the oxygen atom may be elevated by delocalization of the π-electron system of an adjacent oxygen atom on the aromatic ring. Therefore, it is considered that the simplicity of hydrogen abstraction from the OH substituent and the stability of the resulting phenoxyl radical increase in catechols due to a resonance effect and the formation of an intramolecular hydrogen bond.

In conclusion, the t_{inh} values and stoichiometric factors of catechols are about two-fold higher than those of hydroquinones. Thus, catechols can react with more peroxyl radicals than hydroquinones. The R_{inh} values of catechols are almost half those of hydroquinones. Based on these facts, the differences in the radical scavenging abilities of catechols and hydroquinones are considered to be dependent upon the stability of the phenoxyl radicals. Therefore, the stability of the phenoxyl radicals derived from catechols is higher than that of those from hydroquinones due to the intramolecular hydrogen bond and delocalization of the π-electron system of the aromatic ring. On the other hand, in the case of the hydroquinones, which convert to *p*-quinones, it is presumed that the hydrogen abstraction occurring later plays the role of electron transportation rather than radical scavenging in the oxidation reaction. Furthermore, the antioxidant activities of the resorcinols, which could not



Scheme 2.

convert to the quinones, are lowest in the dihydric phenols, and showed a tendency similar to that of monohydric phenols. Consequently, the antioxidant activities of the dihydric phenols are affected by the position of the OH substituents because of the difference in both the electron density of the oxygen atom and the stability of phenoxyl radicals as oxidation products.

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