November, 1989] © *1989 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***62**, 3603—3608 (1989)* 3603

Substituted Bisphenols as Antioxidants for Autoxidation of Tetralin

Fukiko Yamada,* Tomihiro Nishiyama, Masahiro Yamamoto, and Kazunori Tanaka
Department of Applied Chemistry, Faculty of Engineering, Kansai University,
Yamatecho, Suita, Osaka 564

(Received March 16, 1989)

The antioxidative activities of nineteen compounds of seven series of alkylidene- and benzylidenebisphenols were evaluated by means of an oxygen-absorption method at 60 °C for tetralin. The electrochemical oxidation potentials determined using linear-sweep voltammetry and the ^{13}C NMR chemical shifts (δ) of these compounds were obtained. These data were associated with the antioxidative activities. In particular, the activities exhibited by the induction period (min) were found to closely correlate with the ^{13}C chemical shifts of the ipso-carbon of the OH substituent (corr. coeff.=0.991). Very good activities have been observed with a series of 2,2′-alkylidene- and benzylidenebis(4,6-dimethylphenol) derivatives.

In recent studies of benzylphenol derivatives as antioxidants,[1,2] we found that the introduction of a benzyl group to the para- and/or ortho-positions of the hydroxyl group on the benzene ring improved the antioxidative activities of phenols and that these activities increased with a decrease in the ^{13}C NMR chemical shifts (δ) of the ipso-carbon of the OH substituent. Subsequently, on the basis of these facts, we proposed the idea of obtaining a superior antioxidant in each series.[3] Namely, the introduction of a substituent would contribute to providing an upfield shift of the ipso-carbon of the OH substituent, resulting in a superior antioxidant. In our previous paper[2] a series of 4-methoxy-2-benzylphenols was reported as being very good antioxidants. By applying the above-mentioned idea, it was found that 2,2′-ethylidenebis(4-methoxyphenol) has a very good antioxidative activity, superior to those of a series of 4-methoxy-2-benzylphenols.[2,3] Consequently, the present work was directed toward the preparation of several series of substituted bisphenols as antioxidants.

In the present study, the antioxidative activities of nineteen compounds were evaluated by means of an oxgen-absorption method and are discussed in connection with their ^{13}C NMR chemical shifts and electrochemical oxidation data.

Experimental

Measurements. All melting points were uncorrected. ^{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 as a 1 mmol cm^{-3} solution in $(CD_3)_2CO$. Chemical shifts were referred to internal TMS. GLC analyses were carried out on a Yanagimoto gas chromatograph (model GCG-G 1800-T) using a 1.50-m column packed with Silicone SE-30 (10% wt). Liquid chromatography was carried out on a Shimadzu model LC-6A using Shim-pack CLC-ODS column.

Antioxidants. The bisphenol derivatives studied in this work were as follows; 2,2′-ethylidenebis(4,5-dimethylphenol) (**1**), 2,2′-propylidenebis(4,5-dimethylphenol) (**2**), 2,2′-ethylidenebis(4,6-dimethylphenol) (**3**), 2,2′-propylidenebis(4,6-dimethylphenol) (**4**), 2,2′-isobutylidenebis(4,6-dimethylphenol) (**5**), 2,2′-benzylidenebis(4,6-dimethylphenol) (**6**), 4,4′-ethylidenebis(2,5-dimethylphenol) (**7**), 4,4′-propylidenebis(2,5-dimethylphenol) (**8**), 4,4′-benzylidenebis(2,5-dimethylphenol) (**9**), 4,4′-ethylidenebis(2,6-dimethylphenol) (**10**), 4,4′-propylidenebis(2,6-dimethylphenol) (**11**), 4,4′-benzylidenebis(2,6-dimethylphenol) (**12**), 4,4′-ethylidenebis(2-isopropyl-5-methylphenol) (**13**), 4,4′-propylidenebis(2-isopropyl-5-methylphenol) (**14**), 4,4′-ethylidenebis(2-*t*-butyl-5-methylphenol) (**15**), 4,4′-propylidenebis(2-*t*-butyl-5-methylphenol) (**16**), 4,4′-isobutylidenebis(2-*t*-butyl-5-methylphenol) (**17**), 4,4′-benzylidenebis(2-*t*-butyl-5-methylphenol) (**18**), and 4,4′-methylenebisphenol (**19**).

Compounds **1**—**18** were prepared by a condensation of the corresponding phenol and aldehyde, respectively, in nitromethane using concd HCl as the catalyst for the desired time at a suitable temperature.[4] The general method for the preparation is as follows. To a well-stirred solution of phenol (0.1—0.2 mol) and aldehyde (0.09—0.18 mol) in nitromethane (50 ml), concd HCl (0.06—0.12 mol) was added dropwise. The reaction mixture was kept at a constant temperature. The progress of the reaction was followed by means of GLC analysis. After being stirred for a suitable length of time, the reaction mixture was cooled, and dichloromethane was added. The mixture was washed with cold water until freed from acidity. The extract was evaporated to give the crystalline product. The product was recrystallized from the hexane–dichloromethane (2:1). The product purified was characterized by chemical shifts in the ^{13}C NMR spectrum. The reaction conditions, results, and the physical properties of the products are summerized in Table 1.

Compoud **19** was commercially available and was purified by recrystallization; mp 157.5—157.8 °C.

Determination of Antioxidative Activity. Measurements of oxygen-absorption rates were performed with an isobaric gas-absorption apparatus under a closed-flow system (2.0± 0.1 L oxygen/h) provided with an electrolyser using 50 cm^3 of tetralin containing an antioxidant (0.001 mol dm^{-3}) and azobis(isobutyronitrile) as the initiator (0.01 mol dm^{-3}). The oxidation temperature was kept at 60±0.1 °C and oxygen absorption was periodically measured in a constant-pressure closed system. Satisfactory and reproducible data were obtained.

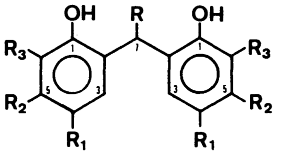
The induction period (IP) and the oxidation rates both

Table 1. Conditions, Results, and Physical Properties of the Products **1**—**18**

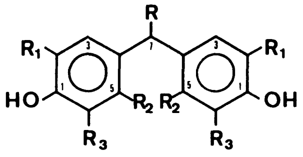
Compound	Molar ratio [P]/[A]$^{a)}$	Temp/°C	Time/h	Yield/%	Mp θ_m/°C	Found (%)		Calcd (%)	
						C	H	C	H
1	1.2/1.0	25	8	23.2	143.5—144.3	79.86	8.23	79.96	8.20
2	2.0/1.0	25	7	34.4	139.7—140.5	79.98	8.53	80.24	8.51
3	1.1/1.0	50—60	10	36.0	134.0—134.5	79.68	8.47	79.96	8.20
4	1.1/1.0	70—80	12.5	3.5	130.5—131.2	79.95	8.48	80.24	8.51
5	1.3/1.0	70—80	68.3	11.1	156.3—156.9	80.41	8.86	80.50	8.78
6	1.8/1.0	70—80	17	26.9	108.5—109.0	82.83	7.48	83.09	7.28
7	0.8/1.0	50—60	2	12.2	219.0—219.8	79.77	8.19	79.96	8.20
8	1.3/1.0	45—55	4	18.3	193.5—194.1	80.09	8.53	80.24	8.51
9	1.8/1.0	25	3	15.6	229.0—229.6	82.82	7.29	83.09	7.28
10	1.3/1.0	25	5.2	25.3	140.7—141.0	79.81	8.18	79.96	8.20
11	1.3/1.0	25	86.7	27.1	119.7—120.2	79.95	8.52	80.24	8.51
12	1.3/1.0	60—70	24.5	35.4	162.9—163.4	82.81	7.29	83.09	7.28
13	1.1/1.0	25	1	25.4	178.5—179.4	80.60	9.34	80.94	9.26
14	0.9/1.0	25	4	21.7	203.2—204.1	80.89	9.46	81.13	9.47
15	1.8/1.0	60—70	5	27.5	203.0—203.8	80.98	9.66	81.31	9.67
16	1.8/1.0	80—90	6	17.4	193.7—194.3	81.02	9.86	81.47	9.85
17	1.7/1.0	60—70	4	14.3	236.5—237.0	81.37	10.03	81.62	10.01
18	1.9/1.0	70—80	3	27.4	202.9—203.5	83.32	8.67	83.61	8.71

a) Molar ratio of the corresponding phenol and aldehyde.

Table 2. Carbon-13 Chemical Shifts for Compounds **1**—**19**



1 and **2**; R_1=R_2=Me
3, **4**, **5**, and **6**; R_1=R_3=Me



7, **8**, and **9**; R_1=R_2=Me
10, **11**, and **12**; R_1=R_3=Me
13 and **14**; R_1=*i*-Pr, R_2=Me
15, **16**, **17**, and **18**; R_1=*t*-Bu, R_2=Me

Compound	Carbon									
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	R_1	R_2	R_3
1	151.9	129.9	127.9	128.6	134.9	117.3	29.4	18.4	18.8	
2	152.4	128.9	128.1	128.8	134.9	117.4	37.7	19.2	19.5	
3	149.8	132.8	125.8	129.5	129.8	124.9	30.8	21.0		16.9
4	150.1	131.6	125.5	129.7	129.5	124.8	38.0	20.8		16.7
5	150.7	131.8	126.3	130.2	129.7	125.4	44.9	21.3		17.3
6	151.0	131.0	128.9	129.0	130.4	125.0	44.9	21.1		17.0
7	153.4	121.5	129.4	136.2	134.3	117.3	36.5	15.9	18.9	
8	153.8	121.9	130.4	135.2	135.1	117.7	44.4	16.7	19.7	
9	153.8	121.3	132.0	134.0	135.1	117.5	49.7	16.0	19.3	
10	151.6	123.9	127.9	138.7			44.1	16.9		16.9
11	151.6	123.9	128.1	137.5			52.7	16.9		16.9
12	151.9	123.9	129.8	136.1			56.2	16.7		16.7
13	152.4	132.3	125.1	136.4	133.9	117.6	37.0	23.3 27.6	19.1	
14	152.6	132.5	125.8	135.1	134.6	117.8	44.5	23.5 27.7	19.6	
15	153.6	133.9	125.5	135.5	133.2	118.5	36.7	30.0 34.9	18.7	
16	153.4	134.0	126.0	134.4	133.1	118.5	44.1	30.3 35.1	19.2	
17	153.3	134.0	126.4	134.6	133.3	118.3	49.4	30.4 35.2	19.9	
18	153.9	133.2	126.1	134.7	132.9	118.6	49.8	30.0 34.9	19.0	
19	155.6	115.4	129.9	133.2			40.0			

during and after the induction period were determined in the usual way.[2,5]

Tetralin was purified by shaking with concd sulfuric acid, dried with sodium, and distilled under an inert atmosphere.

Electrochemical Determination. Linear-sweep voltammograms were recorded for each compound (0.001 mol dm^{-3}) in acetonitrile with $LiClO_4$ (0.1 mol dm^{-3}) as a supporting electrolyte. The counter and working electrodes were made of platinum and the working electrode potential was referred to Ag/AgCl. Potential sweeps were generated by a Hokuto Deko HB-107A function generator in connection with a potentionstat Hokuto Denko HA-104. All the measurements at the 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 and Discussion

The ^{13}C NMR Chemical Shifts of Compounds 1—19. The ^{13}C signals in **1**—**19** were easily assigned using the known chemical shift rules on the parameters[6,7] and the results are given in Table 2. At first glance these shifts are thought to be dependent in the structures of the phenol nuclei with R_{1-3} substituents and various R substituents.

The δ value of C-1 carbon in compound **19** exhibits the lowest downfield shift in comparison with those of the compounds listed in the table. On the contrary, in compounds **3**—**6**, the C-1 values exhibit higher upfield shifts due to both substituent and steric effects produced by, ortho-, para-methyl, and R substituents.

In our previous study on benzylphenols,[6] it was found that the methylene carbons show signal shifts mainly due to the mesomeric effect of the OH substituent, and that in the case of ortho-substituted benzyl compounds, the methylene carbon signals exhibit upfield due to both mesomeric and steric effects. In this work, C-7 carbons correspond to the methylene carbons of benzylphenols[6] and the δ values of C-7 are influenced by the effects mentioned above. Furthermore, these shifts are greatly affected by each substituent R in the order methyl, ethyl, isopropyl, and phenyl.

Activities of Antioxidants. Data regarding the activities of compounds, **1**—**19** along with commercially available antioxidants, BHT and BHA, denoted by the induction period (IP), the stoichiometric factor (n), the rates of the oxygen absorption, and the oxidation potential (E_p) are listed in Table 3.

The autoxidation of tetralin at 60 °C was initiated by azobis(isobutyronitrile) (AIBN) and the inhibition by phenol derivatives can be described by the following chain-reaction schemes:[2,9,10]

Initiation:
$$\text{AIBN; RH} \xrightarrow{O_2} RO_2\cdot \tag{1}$$

Propagation:
$$RO_2\cdot + RH \xrightarrow{k_p} ROOH + R\cdot \tag{2}$$

$$R\cdot + O_2 \longrightarrow RO_2\cdot \tag{3}$$

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

$$RO_2\cdot + ArOH \xrightarrow{k_{inh}} ROOH + ArO\cdot \tag{5}$$

$$(n-1)RO_2\cdot + ArO\cdot \longrightarrow \text{non-radical products,} \tag{6}$$

where RH denotes tetralin in this work and $RO_2\cdot$ is the peroxyl radical. In the presence of an antioxidant, ArOH, the oxidation chains become shortened, termination 4 is suppressed, and reactions 5 and 6 occur instead of 4. Consequently, the induction period and the rates of inhibited and uninhibited oxidations can be represented by Eqs. 7, 8, and 9, respectively:

$$IP = n[ArOH]/R_i, \tag{7}$$

$$-d[O_2]/dt = k_pR_i[RH]/nk_{inh}[ArOH], \tag{8}$$

and

$$-d[O_2]/dt = k_p(R_i/2k_t)^{1/2}[RH], \tag{9}$$

where R_i is the rate of the chain initiation.

From the above equations, the characterizations of the antioxidative activities can be expressed by three

Table 3. Activities of Antioxidants along with the Oxidation Potentials for Compounds **1**—**19**

Compound	IP/min	n a)	$-d[O_2]/dt$ b) mol dm^{-3} min		E_p/V
			(I)×10^6	(II)×10^4	
1	591	4.26	5.1	4.3	1.315
2	555	4.00	4.9	3.1	1.320
3	912	6.57	2.7	5.9	1.260
4	815	5.87	3.6	5.4	1.285
5	768	5.53	3.6	4.6	1.280
6	776	5.59	4.5	4.3	1.300
7	425	3.06	8.9	3.1	1.350
8	382	2.75	8.0	3.0	1.350
9	349	2.51	8.7	2.8	1.355
10	670	4.82	4.5	5.7	1.355
11	650	4.68	6.3	5.2	1.345
12	639	4.60	4.5	4.5	1.350
13	508	3.66	7.1	5.6	1.335
14	502	3.61	7.4	4.6	1.335
15	420	3.02	7.1	3.7	1.360
16	415	2.99	7.1	3.6	1.360
17	378	2.72	8.0	3.3	1.340
18	360	2.59	8.9	3.0	1.350
19	134	0.96	10.7	5.2	1.400
BHT	376	2.67	18.4	7.7	
BHA	408	2.91	8.1	6.1	
Control	22			8.6	

a) The stoichiometries were determined at 60 °C by the induction period method.[5,8] b) The rates of oxygen absorption; (I) for an inhibited autoxidation during IP and (II) for an uninhibited oxidation after IP.

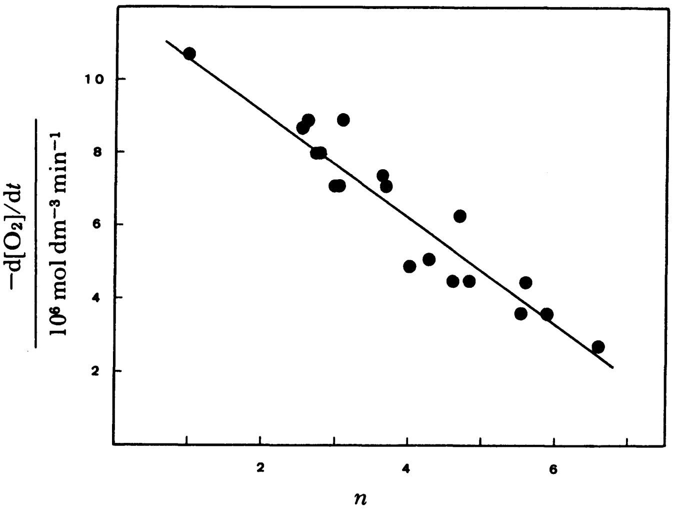


Fig. 1. Plot of n vs. the rate of oxygen absorption.

values: IP, n, and k_{inh}. However, the value of k_{inh} is difficult to obtain experimentally. Consequently, instead of this value the rate of oxygen absorption in Eq. 8 was used.

As can be seen from Table 3, the values are thought to be dependent on the structures of the phenol nuclei with various substitutents at different positions. The IP values increased in the order **3**—**6** (4,6-dimethylphenol)>**10**—**12** (2,6-dimethylphenol)>**1** and **2** (4,5-dimethylphenol)>**13** and **14** (2-isopropyl-5-methylphenol)>**7**—**9** (2,5-dimethylphenol)⩾ **15**—**18** (2-*t*-butyl-5-methylphenol)>**19** (phenol). In each series, the compounds with the α-methyl or α-ethyl substituent possessed a longer IP than that of the α-phenyl substituent. Compounds **3**—**6** exhibit a much longer IP and, thus, higher stoichiometric factors, 5.5—6.6 in comparison with those of other compounds.

For oxygen absorption during IP (see (I) in Table 3), relatively lower rates were found in compounds **3**—**5**, while higher rates were observed for **7**—**9** and **17**—**19**. In particular, BHT exhibited the highest rate. According to Eq. 8, the rate varies inversely as the product of n and k_{inh}. In the range around 1 to 6 of n, the data showed an approximately linear relationship, as can be seen in Fig. 1. From this relation, it is thought that the k_{inh} values of compounds **1**—**18** are nearly equal. On the other hand, the rates after IP (see (II) in Table 3) are quite complicated. When all ArOH are consumed by reactions 5 and 6 (up to IP), the rate of autoxidation obeys Eq. 9 and is nearly equal to that of the control test. All of the observed rates are not close to 8.6, but are much lower. This means that the retardation ability persists, even after IP is over, due to some products of the antioxidant.

Correlations of Antioxidative Activities with ^{13}C NMR Chemical Shifts. In order to understand the factors and mechanisms govering the antioxidative activities of compounds **1**—**19**, several attempts were made to plot their IP values and the rates of oxygen absorption against the ipso-carbon chemical shifts of the OH substituets (C-1 shifts in Table 2). The data used in this attempt are listed in Tables 2 and 3.

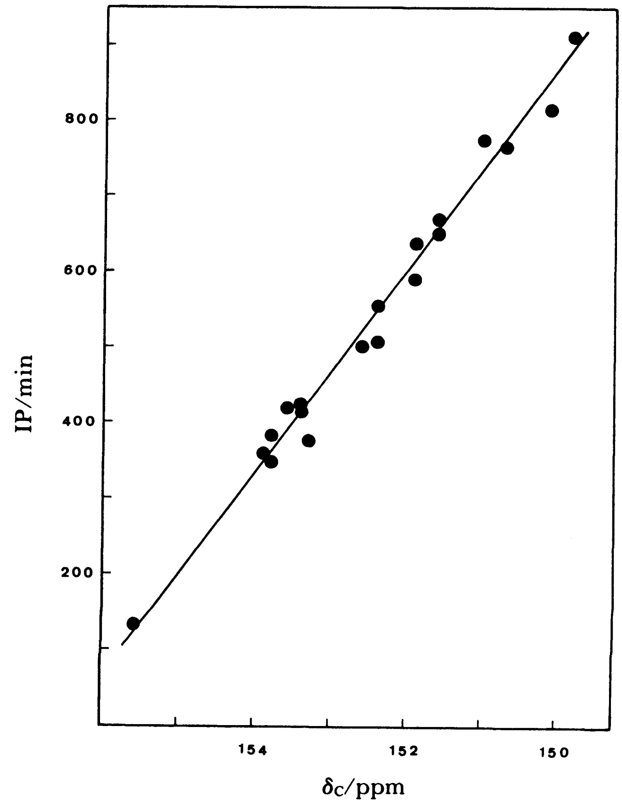


Fig. 2. Plot of IP vs. ^{13}C chemical shift of the ipso-carbon of OH, r=0.991.

Figure 2 shows the relation between the IP values and the ipso-carbon chemical shifts of the OH substituents. The plotted points fall on a straight line. This fact indicates that the IP values increase with a decrease in the chemical shifts, and that the electron density on ipso-carbon of the OH substituent governs the antioxidative activities. In a previous paper[11)] we proved that, on the basis of the ^{13}C chemical shifts of p-substituted benzylbenzenes, electron transmission through the system by a resonance interaction is the most important factor for the α-carbon. It is, therefore, thought that electron transmission through the ipso-carbon to the oxygen atom in phenols depends mostly upon the resonance contribution. Consequently, the total π-electron density of the oxygen atom may be increased by increasing the electron density of the ipso-carbon atom. This will necessarily decrease the electronegativity of the oxygen atom and make the Coulomb integral of the σ orbital on the oxygen more positive.[12)] In the inhibition processes, reactions 5 and 6, the reactivities of phenolic hydrogen and phenoxyl radical are the controlling factors. The reactivity of phenolic hydrogen for an attack of a peroxyl radical, electrophilic radical, is greatly elevated by an increased

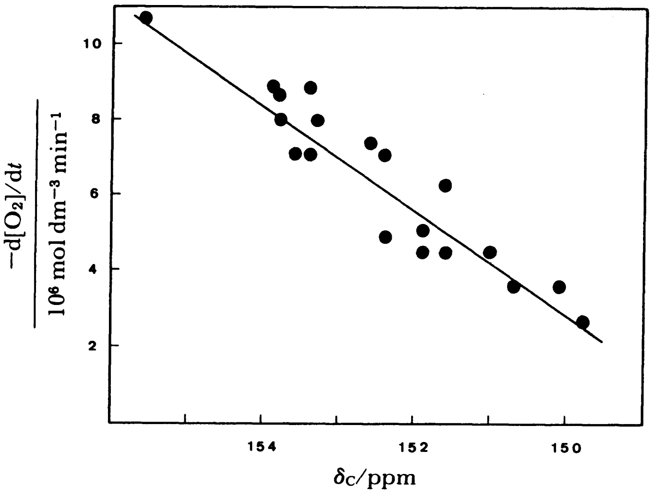


Fig. 3. Plot of the rate of oxygen absorption vs. ^{13}C chemical shift of the ipso-carbon of OH.

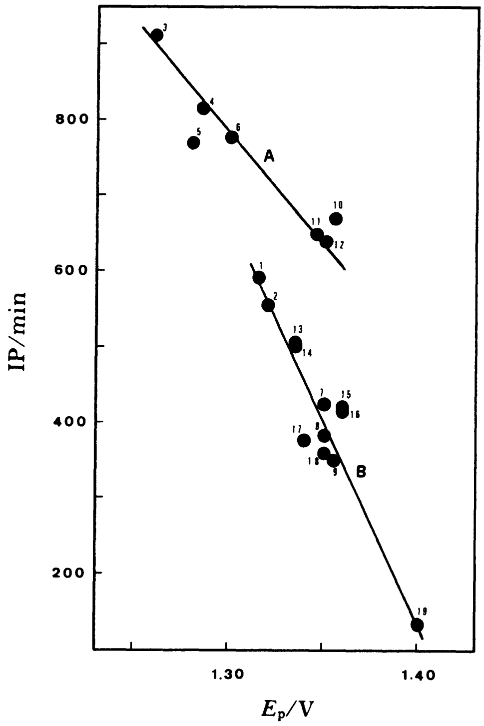


Fig. 4. Plot of IP vs. E_p.

π-electron density on the oxygen. The reactivity of the phenoxyl radical produced can be elevated by the increased π-electron density.

From the reasons mentioned above, the ipso-carbon chemical shifts of the OH substituents may be considered as being reliable and objective indications of the reactivities in the inhibition processes.

Figure 3 also shows a linear relation between the rates of oxygen absorption during IP and the ipso-carbon chemical shifts of the OH substituents. The rates increase with increasing chemical shifts. This indicates that the activity of the antioxidant, which can be expressed by both n and k_{inh} values, is greatly elevated by an increased π-electron density on the phenolic oxygen, as was mentioned above.

Correlations of Antioxidatiove Activities with Oxidation Potentials. As can be seen in Fig. 4, the IP values show two linear relationships, A and B, with the E_p values. Compounds having points plotted on line A have great steric effects on the OH substituent. The other compounds having points plotted on line B have a somewhat weak steric effect (see the structures and ^{13}C NMR data in Table 2). When the oxidation of a molecule is carried out at some potential, the reaction involves an initial electron loss, followed by proton migration. The simplicity of these transfers can be seen by the lower E_p values. In a previous paper[2] 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, on the basis of the ^{13}C NMR chemical shifts.

In compounds **7** (on line B) and **10** (on line A), their E_p values are nearly equal (see also Table 3), while the IP values and the ^{13}C chemical shifts (Table 2) of the ipso-carbons of the OH substituents show considerable differences. In ^{13}C NMR data, the steric compression shift due to the substituent can be easily detected. For example, the OH substituent of 4-(α-methylbenzyl)phenol[2] or compound **19** is not sterically crowded. Consequently, their ipso-carbons of the OH substituents exhibit the shifts at δ 156.2[2] and 155.6 (Table 2), respectively. Compound **7**, having one methyl substituent at the ortho-position of the OH substituent, exhibits a shift at δ 153.4, while compound **10**, having two methyl substituents at both ortho-positions of the OH substituent, exhibits a shift at δ 151.6. This shift is 1.8 ppm upfield from that in **7**. Thus, compounds having sterically hindered phenol moieties, such as **3—6** and **10—12**, show very good antioxidative activities.

These facts indicate that in these compounds the electrochemical oxidation in solution and the inhibition reaction for autoxidation under an oxygen atmosphere proceed by a similar mechanism. However, there are some differences in the reaction mechanisms between the initial steps of both oxidations. Consequently, the contribution of the steric effect to the OH substituent appeared to be an important factor.

The present work was supported by a Grant-in-Aid for Scientific Research No. 62550619 from the Ministry of Education, Science and Culture.

References

1) F. Yamada, T. Nishiyama, and Y. Nakai, *J. Am. Oil Chem. Soc.*, **60**, 1651 (1983).

2) F. Yamada, T. Nishiyama, Y. Suzuura, and T. Yamamura, *Bull. Chem. Soc. Jpn.*, **58**, 115 (1985).

3) F. Yamada, T. Nishiyama, and Y. Suzuura, *Chem. Express*, **1**, 319 (1986).

4) F. Yamada, T. Nishiyama, M. Yamamoto, K. Tanaka, S. Sai, and T. Yamamoto, *Chem. Express*, **3**, 495 (1988).

5) C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen, *J. Am. Chem. Soc.*, **77**, 3233 (1955).

6) Y. Nakai and F. Yamada, *Org. Magn. Reson.*, **11** 607 (1978).

7) a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York (1972); b) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York (1972).

8) E. C. Horswill, J. A. Howard, and K. U. Ingold, *Can. J. Chem.*, **44**, 985 (1966).

9) a) Y. Kamiya, "Yuki-sanka-hanno," Gihodo, Tokyo (1973), Chaps. 5 and 13; b) J. A. Howard, "Free Radicals," ed by J. K. Kochi, Wiley, New York (1973), Vol. II, Chap. 12.

10) G. W. Burton and K. U. Ingold, *J. Am. Chem. Soc.*, **103**, 6472 (1981).

11) Y. Nakai, T. Takabayashi, and F. Yamada, *Org. Magn. Reson.*, **13**, 94 (1980).

12) K. Morokuma, H. Kato, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **36**, 541 (1963).