Benzylphenol Derivatives as Antioxidants for Autoxidation of Tetralin

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A series of 4-benzylphenols, 2-methyl-4-benzylphenols, 4-methyl-2-benzylphenols and 4-methoxy-2-benzylphenols have been prepared and evaluated as antioxidants for tetralin at 60 °C by means of an oxygen-absorption method. Very good activities have been observed with a series of 4-methoxy-2-benzylphenols. The electrochemical oxidation potentials of these compounds were determined using linear-sweep voltammetry. The antioxidative activities were found to correlate with both the ^{13}C NMR chemical shifts (δ) of the *ipso*-carbon of the OH substituent and their peak potentials (E_p).

During the course of our studies of phenol derivatives as antioxidants,[1-5] compounds containing a diarylmethyl group with a phenolic hydroxyl group showed high activities as antioxidants for paraffin wax,[1,2] lard,[3] vitamin A,[4] mineral oils,[5] and greases.[5] In a recent study of benzylphenols,[6] 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. Furthermore, the antioxidative activities of the benzylphenols increased with a decrease of the ^{13}C NMR chemical shifts (δ) of the *ipso*-carbon of the OH substituent.[6]

In this paper, the antioxidative activities of twenty compounds of four series of benzylphenols were evaluated by means of an oxygen-absorption method and are discussed in connection with their ^{13}C NMR chemical shifts and electrochemical oxidation data.

Experimental

Measurements. All the boiling and melting points were uncorrected. ^{13}C NMR spectra were recorded on a JNM-PS-100/EC-100 FT spectrometer operating at 25.15 MHz with complete proton decoupling. The pulse width and repetition time were 10.2 μs (for a 45° pulse) and 6 s, respectively. The spectra were observed as 2 mmol cm^{-3} solutions in $(CD_3)_2CO$ with a spectral width of 6250 Hz. Chemical shifts were referred to internal standard TMS. Mass spectra were obtained with a JEOL JMS-01SG Mattauch-Herzog double-focusing mass spectrometer at an ionizing voltage of 75 eV. GLC analyses were carried out on a Yanagimoto gas chromatograph(model GCG-550-T) using a 1.50-m column packed with Silicone SE-30 (10% wt).

Antioxidants. The benzylphenol derivatives studied in this work were as follows; 4-benzylphenol (**1**), 4-(α-methylbenzyl)phenol (**2**), 4-(α-ethylbenzyl)phenol (**3**), 4-(α-isopropylbenzyl)phenol (**4**), 4-benzhydrylphenol (**5**), 2-methyl-4-benzylphenol (**6**), 2-methyl-4-(α-methylbenzyl)phenol (**7**), 2-methyl-4-(α-ethylbenzyl)phenol (**8**), 2-methyl-4-benzhydrylphenol (**9**), 2-methyl-4-(α, α-dimethylbenzyl)phenol (**10**), 4-methyl-2-benzylphenol (**11**), 4-methyl-2-(α-methylbenzyl)phenol (**12**), 4-methyl-2-(α-ethylbenzyl)phenol (**13**), 4-methyl-2-(α-isopropylbenzyl)phenol (**14**), 4-methyl-2-benzhydrylphenol (**15**), 4-methoxy-2-benzylphenol (**16**), 4-methoxy-2-(α-methylbenzyl)phenol (**17**), 4-methoxy-2-(α-ethylbenzyl)phenol (**18**), 4-methoxy-2-(α-isopropylbenzyl)phenol (**19**), and 4-methoxy-2-benzhydrylphenol (**20**).

Compounds **1**—**20** were prepared by Friedel-Crafts benzylations of the corresponding phenols in nitromethane using a catalyst for the desired time at a suitable temperature.[7,8] The reaction conditions for benzylations were as follows: (1) The reactions of the corresponding phenols with benzyl chloride or α-methylbenzyl chloride using $AlCl_3$ as the catalyst (1.0/1.0/0.1 molar ratio) at 60—70 °C gave the corresponding products, **1**, **7**, and **16**, respectively, (2) the reactions of the corresponding phenols with benzyl chloride using $ZnCl_2$ (1.0/1.0/0.1) at 25—45 °C gave products **6** and **11**, (3) the reactions of the phenols with α-ethylbenzyl alcohol, α-isopropylbenzyl alcohol, or benzhydrol using $ZnCl_2$ (1.0/1.0/1.0) at 25—45 °C gave products **3**, **4**, **5**, **8**, **9**, **13**, **14**, **15**, **18**, **19**, and **20**, respectively, and (4) the reactions of the phenols with styrene or α-methylstyrene using concd H_2SO_4 (1.0/1.0/1.0) at 30—60 °C gave products **2**, **10**, **12**, and **17**.

Each reaction was monitored using GLC analysis. The compound obtained was characterized by chemical shifts in the ^{13}C NMR spectrum. The physical properties and the results of elemental analyses of compounds **1**—**20** (prepared here) are summarized in Table 1.

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 during and after the induction period were determined in the usual way.[9]

Tetralin used for the test 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 Denko HB-107A function generator in connection with a potentionstat Hokuto Denko HA-

TABLE 1. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF **1**—**20** COMPOUNDS

Compound No.	Mp θ_m/°C or Bp θ_b/°C(Pa)	Yield/%	δ_c				Found (Calcd) (%)		M+
			CH_3 or OCH_3	$CH_3(\alpha)$	$CH_3CH_2(\alpha)$	$(CH_3)_2CH(\alpha)$	C	H	
1	82.0—83.0	17.0					84.96 (84.75)	6.32 (6.57)	184
2	57.7—58.1	62.1		22.5			84.42 (84.81)	6.95 (7.12)	198
3	67.4—68.1	29.5			13.0; 29.2		84.72 (84.87)	7.84 (7.60)	212
4	62.0—62.9	26.5				21.9; 32.1	84.77 (84.91)	8.04 (8.02)	226
5	112.5—113.0	48.3					87.40 (87.66)	6.33 (6.20)	260
6	131 (133)	55.1	15.8				84.95 (84.81)	7.10 (7.12)	198
7	151 (133)	84.1	16.1	22.2			84.75 (84.87)	7.67 (7.60)	212
8	125 (133)	53.5	16.0		12.6; 28.8		84.73 (84.91)	8.10 (8.02)	226
9	99.8—100.3	67.5	16.2				87.88 (87.56)	6.40 (6.61)	274
10	121 (133)	20.3	16.4	{29.0 {29.7			85.02 (84.91)	8.13 (8.02)	226
11	133—134 (133)	61.5	20.5				84.76 (84.81)	7.25 (7.12)	198
12	142 (133)	40.4	20.7	20.7			84.58 (84.87)	7.69 (7.60)	212
13	128—129 (133)	36.6	20.9		13.1; 28.4		84.54 (84.91)	8.10 (8.02)	226
14	129—130 (133)	23.1	20.4			{21.4; 21.8 {31.2	84.81 (84.96)	8.56 (8.39)	240
15	133.2—134.1	79.2	20.7				87.35 (87.56)	6.53 (6.61)	274
16	96.6—98.1	42.0	55.2				78.65 (78.48)	6.63 (6.59)	214
17	63.9—64.8	52.8	55.4	20.9			78.88 (78.92)	7.08 (7.06)	228
18	84.4—85.0	45.6	55.5		12.9; 28.2		79.01 (79.31)	7.50 (7.49)	242
19	155.6—156.0	20.7	55.5			{21.6; 22.0 {31.5	79.88 (79.65)	7.85 (7.86)	256
20	110.8—111.2	40.4	55.5				82.84 (82.73)	6.26 (6.25)	290

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

Activities of Antioxidants. Data regarding the activities of compounds **1**—**20** (denoted by the induction period, the stoichiometric factor, and the rates of the oxygen absorption) are listed in Table 2.

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;[13,14]

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

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

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

Termination: $$2\text{RO}_2\cdot \xrightarrow{k_t} \text{non-radical products} \tag{4}$$

$$\text{RO}_2\cdot + \text{ArOH} \xrightarrow{k_{inh}} \text{ROOH} + \text{ArO}\cdot \tag{5}$$

TABLE 2. ACTIVITIES OF ANTIOXIDANTS ALONG WITH ^{13}C CHEMICAL SHIFTS OF THE *ipso*-CARBON OF THE OH SUBSTITUENT AND THE OXIDATION POTENTIALS

Compound No.	IP/min	$n^{a)}$	$-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t^{b)}$ mol dm^{-3} min^{-1} (I) $\times 10^6$	(II) $\times 10^4$	δ_c/ppm	E_p/V	i_p/μA
1	62	0.45	17.3	5.7	156.0	1.512	92.2
2	56	0.40	15.9	5.2	156.2	1.530	93.7
3	69	0.50	15.5	5.7	156.0	1.519	89.5
4	69	0.50	12.9	5.9	155.4	1.490	89.3
5	50	0.36	14.3	6.4	156.2	1.526	72.3
6	186	1.34	12.0	2.6	153.7	1.388	76.3
7	177	1.27	13.1	1.9	153.8	1.403	79.0
8	182	1.31	12.3	1.5	153.7	1.371	45.9
9	168	1.21	10.6	4.1	154.2	1.386	51.8
10	157	1.13	11.4	8.4	153.5	1.359	62.5
11	213	1.53	9.2	2.0	153.0	1.351	52.8
12	252	1.81	8.1	1.7	152.1	1.323	51.2
13	221	1.59	8.1	1.7	153.2	1.349	52.5
14	217	1.56	10.3	1.7	152.6	1.341	51.3
15	215	1.55	9.6	3.1	153.0	1.339	51.8
16	434	3.12	3.1	7.3	149.0	1.040	55.8
17	452	3.25	3.0	7.3	148.7	1.023	52.9
18	460	3.31	3.1	7.1	149.1	1.049	55.4
19	454	3.27	3.3	7.9	148.8	1.043	51.5
20	406	2.92	3.3	7.2	149.3	1.055	49.9
Control	22			8.6			

a) The stoichiometries were determined at 60 °C by the induction-period method,[9,10] by using the values, the activity factor of the initiator, 0.6,[11] and the rate constant of decomposition of the initiator, 6.0×10^{-4} min^{-1} (the mean from the data in Ref. 12). b) The rates of oxygen absorption; (I) for an inhibited autoxidation during IP and (II) for an uninhibited oxidation after IP.

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

where RH denotes the organic substrate (tetralin) and $\mathrm{RO_2}\cdot$ 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. The induction period and the rates of inhibited and uninhibited oxidations can be represented by Eqs. I, II, and III, respectively;

$$\mathrm{IP} = n[\mathrm{ArOH}]/R_\mathrm{i} \qquad (\mathrm{I})$$

$$-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t = k_\mathrm{p}R_\mathrm{i}[\mathrm{RH}]/nk_\mathrm{inh}[\mathrm{ArOH}] \qquad (\mathrm{II})$$

$$-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t = k_\mathrm{p}(R_\mathrm{i}/2k_\mathrm{t})^{1/2}[\mathrm{RH}] \qquad (\mathrm{III})$$

where R_i is the rate of the chain initiation.

As can be seen from Table 2, the characterizations of the antioxidative activities can be expressed by three values: IP, n, and $-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t$. These values are thought to be dependent on the structures of the phenol nuclei with various substituents at different positions. The length of IP increased in the order of **16**—**20** (4-methoxyphenols)> **11**—**15** (4-methylphenols)> **6**—**10** (2-methylphenols)> **1**—**5** (phenols). In each series, the compounds with an α-alkyl substituent possessed a longer IP than that of the α-phenyl substituent. Compounds **16**—**20** with a 4-methoxyl group exhibit much longer IP and, thus, higher stoichiometric factors (around n=3) in comparison with those of **1**—**15**.

For oxygen absorption during IP, much lower rates were found in compounds **16**—**20**, while higher rates were observed for **1**—**15**, (particularly **1**—**5**). According to Eq. II, the rate is proportional to the reciprocal of n. This relation is clearly illustrated in Fig. 1. On the other hand, the rates after IP are quite complicated. When all ArOH are consumed by reactions 5 and 6 (up to IP), the rate of autoxidation obeys Eq. III and is equal to that of the control test. In fact, the rates of **10** and **16**—**20** are close to 8.6. However, **1**—**15** (except for **10**) show much lower rates. This means that the retardation ability persists even after IP is over due to some products of the antioxidant. Figure 2 shows the tendency of IP values to increase with decreasing rates of **1**—**15** (except for **10**). Particularly, both groups **1**, **6** and **11** and **5**, **9** and **15** (with an α-phenyl substituent) show linear relations. This indicates the influence of a 2-methyl or 4-methyl substituent.

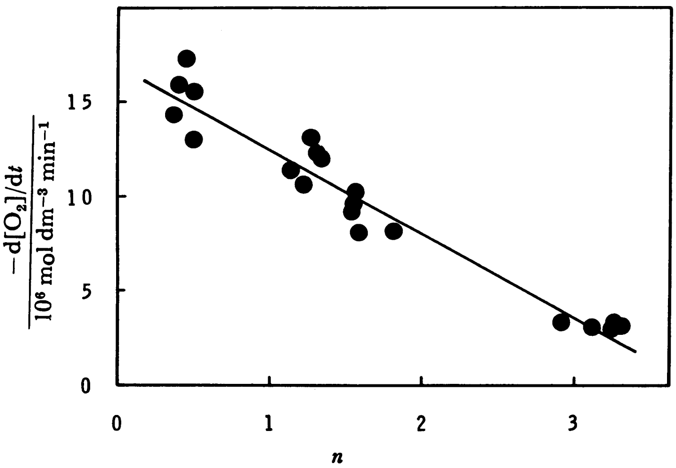

Fig. 1. plot of n vs. the rate of oxygen absorption; $r=$ 0.969.

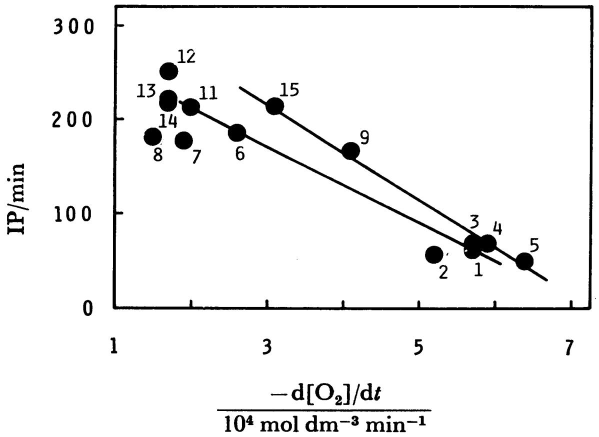

Fig. 2. Plot of IP vs. the rate of oxygen absorption.

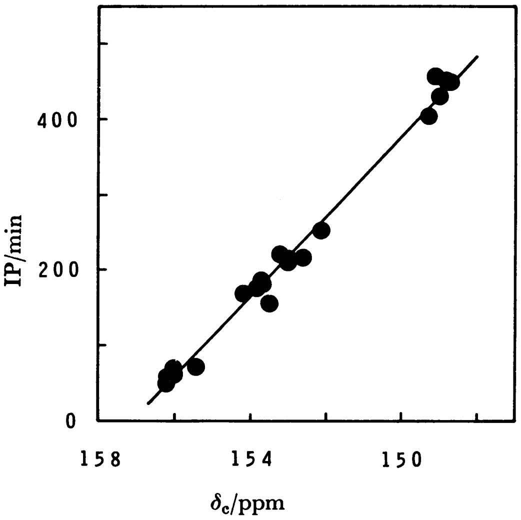

Fig. 3. Plot of IP vs. ^{13}C chemical shift of the *ipso*-carbon of OH; $r=0.994$.

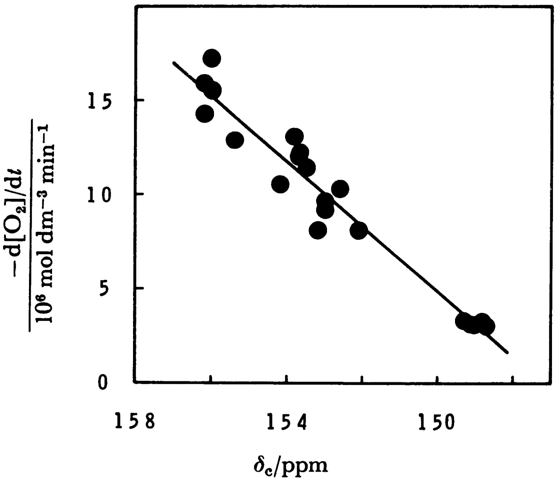

Fig. 4. Plot of the rate of oxygen absorption vs. ^{13}C chemical shift of the *ipso*-carbon of OH; $r=0.972$.

Correlations of Antioxidative Activities with ^{13}C Chemical Shifts and Oxidation Potentials. In order to understand the factors and mechanisms govering antioxidative activities of compounds **1**—**20**, several attempts were made to plot their IP values and the rates of oxygen absorption against the *ipso*-carbon chemical shifts of the OH substituents and the electrochemical oxidation potentials, respectively. The data used in this attempt are listed in Table 2.

Figure 3 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 the decreasing of the chemical shifts, and that the electron density on the *ipso*-carbon of the OH substituent governs antioxidative activity. In a previous paper,[15] we proved that the 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. According to a proposal by Morokuma *et al.*,[16] this will necessarily decrease the electronegativity of the oxygen atom and make the Coulomb integral of the σ orbital on the oxygen more positive. In the inhibition processes (reactions 5 and 6) the reactivities of phenolic hydrogen and the phenoxyl radical are the controlling factors. The reactivity of phenolic hydrogen for an attack on a peroxyl radical (electronegative radical) is greatly elevated by an increased π-electron density on the oxygen. Consequently, the reactivity of the phenoxyl radical produced can be elevated by an increased π-electron density.

Figure 4 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. From Eq. II, it is seen that the rate is proportional to

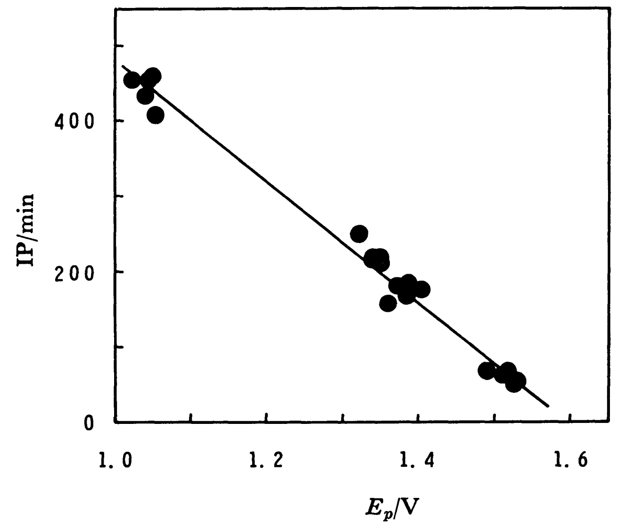

Fig. 5. Plot of IP *vs.* E_p; $r=0.993$.

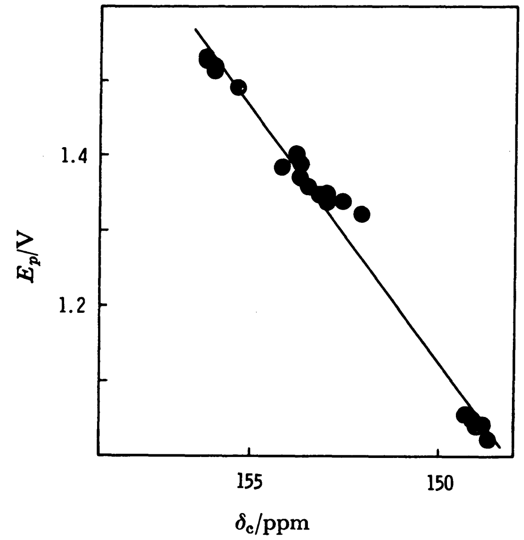

Fig. 6. Plot of E_p *vs.* ^{13}C chemical shift of the *ipso*-carbon of OH; $r=0.993$.

the reciprocal of n and k_{inh}. As was mentioned above, the activity of an 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.

The IP values show a linear relationship with the E_p values, as can be seen in Fig. 5. The IP values increase with a decreasing value of the oxidation potentials. In general, when the oxidation of a molecule is carried out at some potential, the reaction involves an initial electron loss, followed by proton migration. It is, therefore, thought that the simplicity of one-electron and one-proton transfers can be displayed by lower E_p values. In addition, there is the linear relationship between the *ipso*-carbon chemical shifts of the OH substituents and the E_p values, as can be seen in Fig. 6. This indicates that the easiness of one-electron and one-proton transfers is greatly increased by an increased electron density at the *ipso*-carbon of the OH substituent. The IP values were determined under an oxygen atmosphere while the electrochemical oxidations were performed in a solvent. The IP and E_p values were obtained for the different systems. Although the mechanism of the initial step of the inhibition is still unsettled, the above facts indicate that the oxidation of the phenol derivatives in these different systems proceed by a similar mechanism.

In conclusion, the ^{13}C chemical shift of the *ipso*-carbon of the OH substituent and the E_p value made it possible to estimate the antioxidative activity of a series of benzylphenol derivatives.

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