Substituted Thiobisphenols as Antioxidants: Correlation Between Antioxidant Activities and ^{13}C Chemical Shifts

Tatsuo Yamamura[a], **Kazunori Tanaka**[b], **Shogo Tomiyama**[b], **Shinryu Sai**[b],
Fukiko Yamada[b] **and Tomihiro Nishiyama**[b],*
[a]Shiga Central Research Laboratories, Noevir Co. Ltd., Yokaichi, Shiga 527, Japan and [b]Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan

ABSTRACT: The antioxidant activities of ten thiobisphenols were evaluated by an oxygen-absorption method at 60°C in tetralin and determination of peroxide values at 160°C in paraffin. For the 4,4′-thiobisphenols, alkyl groups *ortho* to the phenolic hydroxyl groups increased the induction period compared to that of other thiobisphenols for both oxidation of tetralin and paraffin. The data on electrochemical oxidation potentials that were determined by linear-sweep voltammetry and the ^{13}C nuclear magnetic resonance chemical shifts (δ) of these compounds were associated with antioxidant activities. In particular, the activities exhibited during the induction period closely correlated with the ^{13}C chemical shifts of ipso-carbon of the OH substituent.

JAOCS 72, 1047–1052 (1995).

KEY WORDS: Antioxidant, ^{13}C chemical shifts, oxidation potential, paraffin, tetralin, thiobisphenol.

During the course of our studies of phenol derivatives as antioxidants for hydrocarbons and other organic materials, we have concluded that phenolic compounds that contain hydroxy-substituted diarylmethylene moieties, such as benzylphenols and alkylidenebisphenols, show high antioxidant activities (1–3). These phenol derivatives act as chain-breaking antioxidants. Their antioxidant activity is related to both the ^{13}C nuclear magnetic resonance (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 the one-electron and one-proton transfers after the hydrogen abstractions, which are dependent upon the total π-electron density of the oxygen atom.

On the other hand, the long-standing antioxidants that contain sulfur atoms are well known as effective peroxide decomposers and are synergistic in combination with chain-breaking antioxidants (4,5). Therefore, it can be expected that the coexistence of the phenolic hydroxyl group and a sulfur atom in one molecule increases its antioxidant activity, predominantly at elevated oxidation temperatures.

In this study, in view of the activities as chain-breaking inhibitors and peroxide decomposers, 2,2′- or 4,4′-thiobisphenols that contain methyl and/or *tert*-butyl groups as substituents were evaluated by an oxygen-absorption method at 60°C in tetralin and by determination of peroxide values at 160°C in paraffin, respectively. In addition, their antioxidant activities are discussed in connection with their ^{13}C NMR chemical shifts and electrochemical oxidation potentials to make a comparison with ethylidenebisphenols for clarifying the role of the bridging S atom.

EXPERIMENTAL PROCEDURES

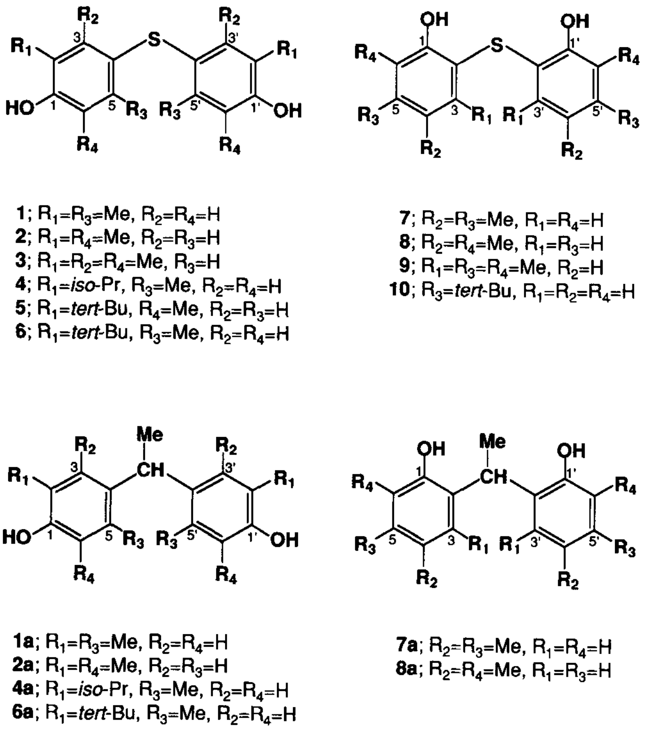
Measurements. NMR spectra were recorded with a Hitachi R-9OH FT spectrometer (Tokyo, Japan) operating at 90 MHz for ^{1}H and 22.7 MHz for ^{13}C NMR with complete proton decoupling. The spectra were observed in a 1 M solution in $(CD_3)_2CO$. Chemical shifts were referenced to tetramethylsilane (TMS). Gas–liquid chromatography (GLC) analyses were carried out on a Yanagimoto (Kyoto, Japan) gas chromatograph (model GCG-G 1800-T) in a 1.5-m column packed with Silicone SE-30 (10% wt). Liquid chromatography was carried out on a Shimadzu (Kyoto, Japan) model LC-6A with a Shim-pack CLC–ODS column.

Antioxidants. Ten thiobisphenol derivatives and one sulfide studied in this work were 4,4′-thiobis(2,5-dimethylphenol) (**1**), 4,4′-thiobis(2,6-dimethylphenol) (**2**), 4,4′-thiobis(2,3,6-trimethylphenol) (**3**), 4,4′-thiobis(2-isopropyl-5-methylphenol) (**4**), 4,4′-thiobis(2-*tert*-butyl-6-methylphenol) (**5**), 4,4′-thiobis(2-*tert*-butyl-5-methylphenol) (**6**), 2,2′-thiobis(4,5-dimethylphenol) (**7**), 2,2′-thiobis(4,6-dimethylphenol) (**8**), 2,2′-thiobis(3,5,6-trimethylphenol) (**9**), 2,2′-thiobis(5-*tert*-butylphenol) (**10**), and diphenyl sulfide (**11**) (Scheme 1).

Preparation. Commercially available compounds **5**, **6**, and **11** were further purified by recrystallization from a mixture

---

*To whom correspondence should be addressed.



1; R_1=R_3=Me, R_2=R_4=H
2; R_1=R_4=Me, R_2=R_3=H
3; R_1=R_2=R_4=Me, R_3=H
4; R_1=*iso*-Pr, R_3=Me, R_2=R_4=H
5; R_1=*tert*-Bu, R_4=Me, R_2=R_3=H
6; R_1=*tert*-Bu, R_3=Me, R_2=R_4=H

7; R_2=R_3=Me, R_1=R_4=H
8; R_2=R_4=Me, R_1=R_3=H
9; R_1=R_3=R_4=Me, R_2=H
10; R_3=*tert*-Bu, R_1=R_2=R_4=H

1a; R_1=R_3=Me, R_2=R_4=H
2a; R_1=R_4=Me, R_2=R_3=H
4a; R_1=*iso*-Pr, R_3=Me, R_2=R_4=H
6a; R_1=*tert*-Bu, R_3=Me, R_2=R_4=H

7a; R_2=R_3=Me, R_1=R_4=H
8a; R_2=R_4=Me, R_1=R_3=H

SCHEME 1

of benzene and hexane. Other known compounds used in this work were prepared by known methods or simple modifications thereof (6–9). For example, compounds **1–4** and **7–10** were prepared by the usual method (6) involving the reaction of the corresponding phenol with thionyl chloride in chloroform solution. These compounds **1–10** gave satisfactory results for elemental analyses and ^{1}H NMR chemical shifts.

Determination of antioxidant activity for tetralin. 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. It contained 50 mL of tetralin with 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 (IP) and the oxidation rates were determined both during and after IP (2,3).

Determination of antioxidant activity for paraffin. Activities of **1–10** in paraffin (m.p. 52–54°C; Wako Pure Chemical Co., Osaka, Japan) were evaluated by measuring the time required to oxidize the paraffin to a given extent by dry-air blowing (2 L h^{-1}) at 160°C. The antioxidant was added as an aliquot of an ethanol solution to 50 g melted paraffin. To remove the ethanol, the mixture was heated under reduced pressure, and then poured into a glass test tube (3.5 cm diameter) (10). The constant-temperature oil bath was equipped with an immersion heating element to control temperature to ±0.5°C. The rate of oxidation of the paraffin was followed by measuring the peroxide value. The IP was defined as the time required to obtain a peroxide value of 50 (10).

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 with a Hokuto (Tokyo, Japan) Denko HB-107A function generator in connection

TABLE 1
^{13}C Chemical Shifts for Compound 1–11[a]

Compound	C_1	C_2	C_3	C_4	C_5	C_6	R_1	R_2	R_3	R_4
1	155.2	123.3	134.6	124.9	137.8	117.5	15.7		20.2	
1a	153.4			136.2						
2	153.9	125.9	132.6	126.9	132.6	125.9	16.7			16.7
2a	151.6		138.7							
3	153.7	125.2	136.9	126.6	132.4	123.5	13.2	16.8		17.4
4	154.7	134.4	130.7	125.4	137.9	118.2	23.1 27.5		20.3	
4a	152.4			136.4						
5	154.5	126.1	132.3	126.6	128.5	138.3	16.8			30.4 35.4
6	155.5	119.4	138.2	125.2	131.4	135.4		20.2		30.2 35.3
6a	153.6			135.5						
7	155.8	118.2	136.4	129.4	139.9	117.7		18.7	19.6	
7a	151.9	129.9								
8	153.5	121.1	133.3	130.6	132.9	126.0		20.8		17.1
8a	149.8	132.8								
9	156.4	117.2	139.8	121.8	139.3	125.1	20.5		21.5	13.0
10	156.8	117.5	134.7	118.3	154.2	113.2			31.7 35.3	
11	127.8	129.9	131.5	136.2	131.5	129.9				

[a] The data of **1a, 2a, 4a, 6a, 7a,** and **8a** are taken from Reference 3.

with a Hokuto Denko HA-104 potentiostat. All measurements at the scan rate of 200 mV s^{-1} were carried out at 25 ± 0.1°C in a constant-temperature bath under a nitrogen atmosphere.

RESULTS AND DISCUSSION

The ^{13}C chemical shifts of compounds **1–11**. The ^{13}C signals for **1–11** were easily assigned by using the known chemical shift rules on the parameters (11), and the results are given in Table 1. These shifts are thought to be dependent on the structures of the phenol nuclei with R_{1-4} substituents and bridging S atom.

The δ values of the C_1 carbons, the ipso-carbons of the OH substituent, shifted due to both substituent and steric effects produced by the *ortho-* and *para-*substituents and the bridging S atom. On the other hand, the C_2 values in **7–10**, the ipso-carbons of S in the 2,2′-series, exhibited higher upfield shifts in comparison with the C_4 values in **1–6**, the ipso-carbons of S in the 4,4′-series.

From the standpoint of the chemical shifts of both ipso-carbons of the OH substituents and bridging S atom already mentioned, compounds **1–10** may be divided into two groups; the 4,4′-series (**1–6**) and the 2,2′-series (**7–10**), as shown in Figure 1. In each group, the value of the ipso-carbon of OH is inversely related to that of S. These results suggest that the electron density of the ipso-carbon of the bridging S atom was governed by both the position of the OH substituent and the total π-electron density of the oxygen atom.

Furthermore, compared to the corresponding ethylidenebisphenols, the C_1 values exhibit lower downfield shifts of 1.8–3.9 ppm, whereas the C_2 and C_4 values exhibit higher upfield shifts of 10.3–11.7 ppm (see Table 1). That is, although the shifts are small, the electron densities of the ipso-carbon of the OH substituent are influenced by the bridging S atom.

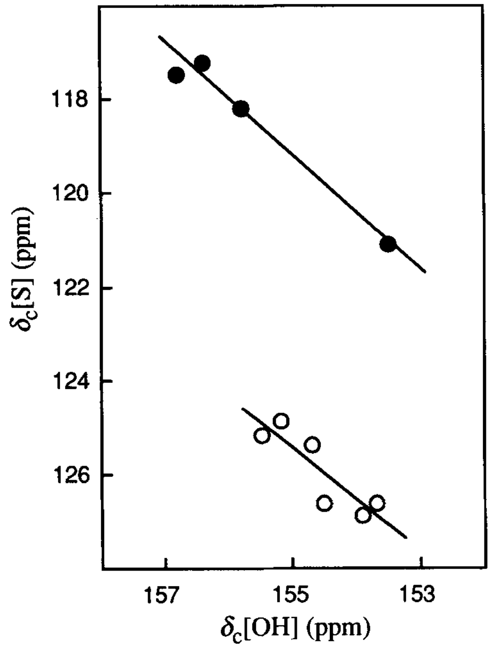


FIG. 1. Relationship between ^{13}C chemical shift of the ipso-carbon of OH and S: ○, 4,4′-series, ●, 2,2′-series.

Activities of antioxidants. Data regarding the activities of compounds **1–11**, denoted by their IP values, the stoichiometric factor (n), which is the number of radicals trapped by each molecule of antioxidant (12), the rates of oxygen absorption, and the oxidation potential (E_p), along with those of some ethylidenebisphenols, are listed in Table 2.

The autoxidation of tetralin at 60°C was initiated by AIBN, and the inhibition by phenol derivatives can be described by the following chain-reaction schemes (12), where RH denotes tetralin or paraffin and $RO_2\bullet$ is the peroxyl radical:

$$\text{Initiation: AIBN; RH} \xrightarrow{O_2} RO_2\bullet \qquad [1]$$

$$\text{propagation: } RO_2\bullet + RH \xrightarrow{k_p} ROOH + R\bullet \qquad [2]$$

$$R\bullet + O_2 \longrightarrow RO_2\bullet \qquad [3]$$

$$\text{termination: } 2RO_2\bullet \xrightarrow{k_t} \text{nonradical products} \qquad [4]$$

In the presence of a chain-breaking phenolic antioxidant, ArOH, the oxidation chains are terminated by Reactions 5 and 6, where n represents the stoichiometric factor for the antioxidant.

$$RO_2\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO\bullet \qquad [5]$$

$$(n\text{-}1)RO_2\bullet + ArO\bullet \longrightarrow \text{nonradical products} \qquad [6]$$

Consequently, the IP and the rates of inhibited and uninhibited oxidations can be represented by Equations 7, 8, and 9, where R_i is the rate of the chain initiation:

$$IP = n[ArOH]/R_i \qquad [7]$$

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

and

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

From these equations, the characterizations of the antioxidative activities can be expressed by three values: IP, n, and k_{inh}. However, the value of k_{inh} is difficult to experimentally obtain. Consequently, instead of this value, the rate of oxygen absorption in Equation 8 was used.

The IP values of the 4,4′-series for tetralin were greater than those of the 2,2′-series. Of these compounds, **2** and **3** exhibit a much longer IP and thus higher n values, in comparison with those of the other thiobisphenols.

TABLE 2
Activities of Antioxidants Along with the Oxidation Potentials for Compounds 1–11[a]

Compound	IP[b] (min)	n[c]	$-d[O_2]/dt$[d] ($M\ min^{-1}$) (I) × 10^6	(II) × 10^4	IP[e] (h)	E_p (V)
1	495	3.56	7.8	2.2	14.8	1.11
1a	425	3.06	8.9	3.1	6.0	
2	655	4.72	5.4	3.1	19.2	0.95
2a	670	4.82	4.5	5.7	8.0	
3	645	4.64	4.8	3.2	18.0	0.96
4	528	3.80	7.1	2.3	13.7	1.07
4a	508	3.66	7.1	5.6		
5	540	3.89	7.4	2.1	16.5	1.02
6	514	3.70	7.3	2.1	13.6	1.07
6a	420	3.02	7.1	3.7		
7	355	2.56	10.7	3.3	7.5	1.21
7a	591	4.26	5.1	4.3	7.9	
8	556	4.00	6.3	3.9	10.8	1.03
8a	912	6.57	2.7	5.9	12.6	
9	270	1.94	14.7	2.9	7.0	1.30
10	260	1.87	15.4	2.7	6.4	1.32
11	11		25.5	7.9		
Control	6			9.1		

[a] The data of **1a, 2a, 4a, 6a, 7a,** and **8a** except for the induction period (IP) values of paraffin, were taken from Reference 3.
[b] IP values for tetralin.
[c] The stoichiometries were determined at 60°C by the IP method (Ref. 13).
[d] The rates of oxygen absorption; (I) for an inhibited autoxidation during IP and (II) for after IP.
[e] The IP values for paraffin.

For oxygen absorption rates during IP [see (I) in Table 2], relatively lower rates were found for **2**, **3**, and **8**. According to Equation 8, the rate varies inversely with the product of n and k_{inh}. Figure 2 shows that the rates vary inversely with n and shows an approximately linear relationship. From this relation, it is thought that the k_{inh} values of compounds **1–10** are nearly equal. On the other hand, the rates after IP [see (II) in Table 2], occur in the range of $(1.0–3.9) \times 10^{-4}$. Generally, when all antioxidants are consumed by Reactions 5 and 6, the rate of autoxidation obeys Equation 9 and is nearly equal to that of the control test (2,3). In the thiobisphenol series, none of the observed rates are close to 9.1, and are much lower than those of the corresponding ethylidenebisphenols (see Table 2). This means that the retardation ability persists, even after IP is over, due to the antioxidant activity of the bridging S atom. Therefore, it is expected that thiobisphenols react not only as the chain-breaking inhibitor but also as the peroxide decomposer.

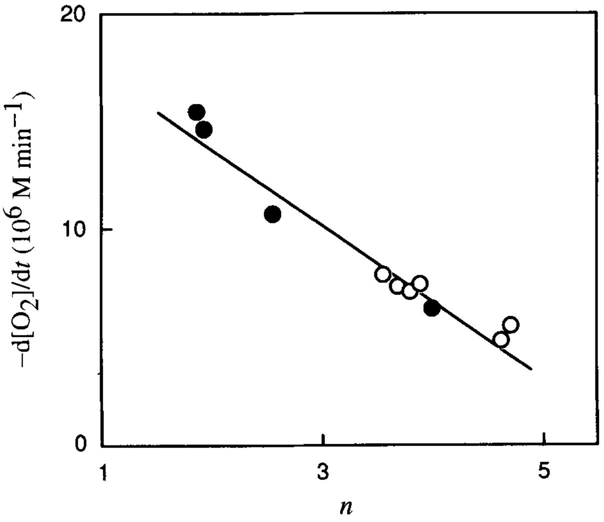


FIG. 2. Relationship between the stoichiometric factor (n) and the rate of oxygen absorption during the induction period for the oxidation of tetralin: ○, 4,4′-series, ●, 2,2′-series.

Correlations of antioxidant activities with ^{13}C NMR chemical shifts. Recently, we reported on studies of the hydrogen abstractions of phenolic antioxidants in the chain process of antioxidation by *ab initio* molecular orbital calculations (14). The experimental results showed that the gain or loss of electrons in the reaction states may be correlated to the experimental data, the ^{13}C chemical shifts of the ipso-carbon of the OH substituent, and the values of the IP as antioxidant activity (15,16). Consequently, to understand the factors and mechanisms governing the activities, several attempts were made to plot their IP values and the rates of oxygen absorption vs. the ipso-carbon chemical shifts of the OH substituent, respectively. The data are taken from Tables 1 and 2. Figure 3 shows the relationship between IP values and the ipso-carbon chemical shifts of the OH substituent. The plotted points fall on a different line but show a linear relation in each group. This fact indicates that the IP values increase with a decrease

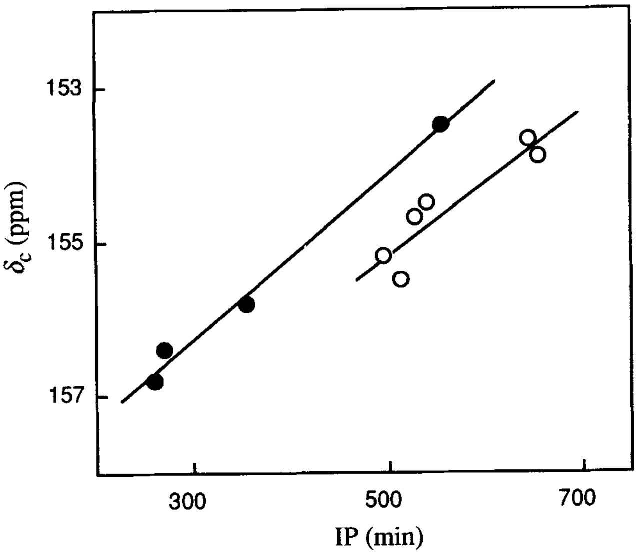


FIG. 3. Relationship between the induction period (IP) for tetralin and ^{13}C chemical shift of the ipso-carbon of OH: ○, 4,4′-series, ●, 2,2′-series.

in the chemical shifts of the ipso-carbon of the OH substituent in each group. Therefore, the IP values are governed by the electron densities of the ipso-carbons of the OH substituent. Figure 4 shows the linear relationship of the rate of oxygen absorption of (I) with the ipso-carbon chemical shifts of the OH substituent. The rate of (I) in each group increases with increasing ipso-carbon shifts of OH. Namely, by increasing the electron density of the ipso-carbon of OH, the rate (I) decreases. These facts indicate that the antioxidant activities expressed by the values of *n*, IP, and the rate of oxygen absorption are influenced by the electron densities of the OH substituent (2,3).

Therefore, it is considered that these thiobisphenols as antioxidants for autoxidation of tetralin at 60°C act as a chain-breaking inhibitor of the peroxyl radical (15,16). It is well known that the bridging S atom acts as a peroxide decomposer (4,5). As shown in Table 2, the IP values for **7** and **8** are greatly inferior to those of **7a** and **8a**, that have an ethylidene group. On the contrary, the IP values for **1**, **4**, and **6** are larger than those of **1a**, **4a**, and **6a**, respectively. There are some differences between the compounds of the 2,2′-series and 4,4′-series. In the 2,2′-series, the structures of **7** and **8** might be thought to have hydrogen bonds between the bridging S atom and the OH substituent at the *ortho*-positions (17).

Furthermore, a previous study suggests 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 (18). Stabilization of the phenoxyl radical depends on both the extent of orbital overlap between the 2p lone pair on the *para* oxygen atom and the aromatic π-electron system, and the electron-donating ability of the group bonded to the *para* oxygen atom. Thus, the heteroatom substituent at the position *para* to the hydroxyl group, the bridging S atom in the 4,4′-tiobisphenols, may be important in increasing antioxidant activity.

Antioxidant activity for paraffin. Activities of compounds **1–10** for paraffin at 160°C were evaluated by determining peroxide value. The IP values are listed in Table 2. The compounds of the 4,4′-series (**1–6**) exhibited a higher IP compared with those of the 2,2′-series. In particular, compounds **2** and **3** exhibit a much larger IP. As Figure 5 shows, this fact holds for linear relations with the ^{13}C chemical shifts of the ipso-carbon of the OH substituent in each group. The IP values in each case increase with a decrease in the chemical shifts of the ipso-carbon of OH. This is similar to the phenomenon in the case of tetralin at 60°C.

However, the IP values of the 4,4′-series are much greater

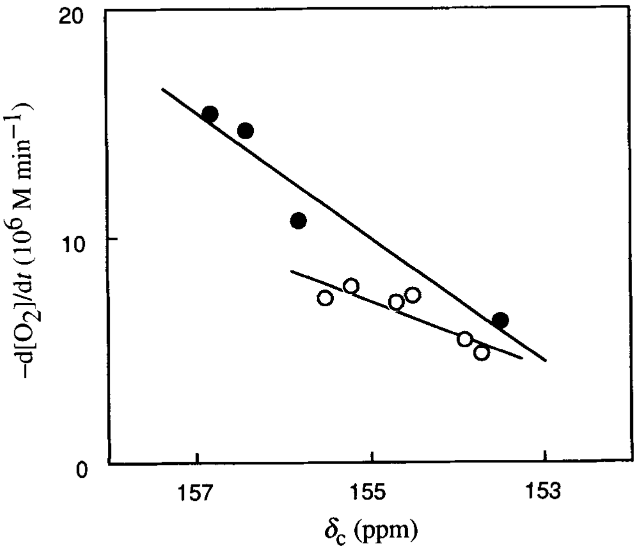


FIG. 4. Relationship between the ipso-carbon chemical shift of OH and the rate of oxygen absorption during induction period for tetralin: ○, 4,4′-series, ●, 2,2′-series.

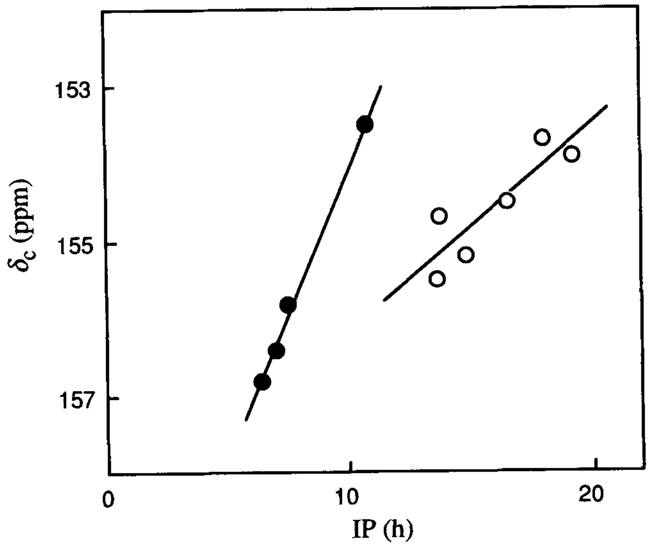


FIG. 5. Relationship between the induction period (IP) for paraffin and the ipso-carbon chemical shift of OH: ○, 4,4′-series, ●, 2,2′-series.

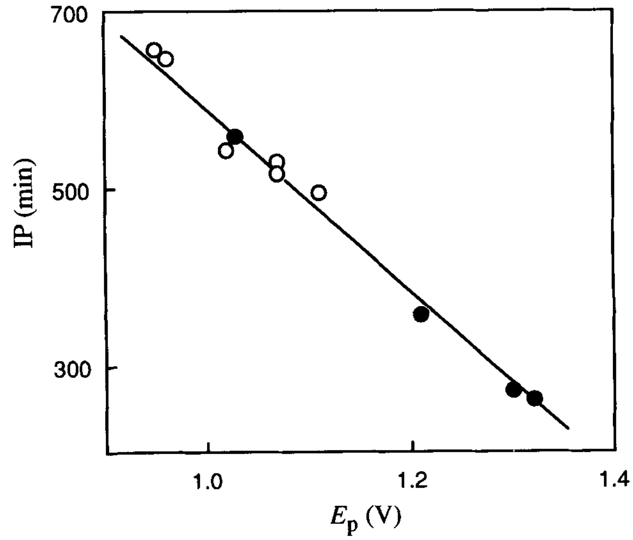


FIG. 6. Relationship between the oxidation potential (E_p) and the induction period (IP) for tetralin: ○, 4,4′-series, ●, 2,2′-series.

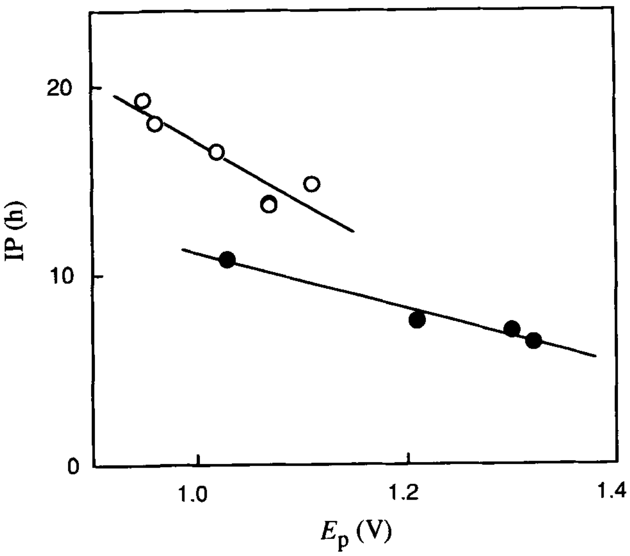


FIG. 7. Relationship between the oxidation potential (E_p) and the induction period (IP) for paraffin: ○, 4,4′-series, ●, 2,2′-series.

than those of the 2,2′-series for paraffin when compared to tetralin. For paraffin, the activity may be determined as the peroxide decomposer, including the activity as a chain-breaking inhibitor (4). Therefore, it can be assumed that the high IP values of the 4,4′-series in paraffin reflect the decomposition of hydroperoxides by the bridging S atom. The effect of sulfur as a peroxide decomposer is small in the 2,2′-series compared to the 4,4′-series. The difference between the 4,4′-series and the 2,2′-series on IP values may be due to the formation of the intramolecular hydrogen bond in the 2,2′-series.

Correlation of antioxidant activity with the oxidation potential (E_p*).* The IP values of compounds **1–10** show a linear relationship with the E_p values in the case for tetralin as can be seen in Figure 6. On the other hand, Figure 7 shows that the plotted points fall on individual lines for the 4,4′-series and 2,2′-series in paraffin. In each case, however, the IP values increase with decreasing E_p values. 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 showed 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, based on the ^{13}C NMR chemical shifts.

From the above facts, it may be considered that the IP values for both tetralin and paraffin primarily depend on the simplicity of the hydrogen abstraction of the phenolic OH governed by the electron transfer. Although the IP values for tetralin were governed by only the hydrogen abstraction, the IP values for paraffin were influenced both by the hydrogen abstraction and, after decomposition of the hydroperoxides, by the bridging S atom. Consequently, the thiobisphenols acted primarily as chain-braking antioxidants as well as other phenol derivatives, such as the benzylphenols and alkylidenebisphenols, and then acted as a peroxide decomposer after the hydrogen abstraction by the peroxyl radicals.

REFERENCES

1. Yamada, F., T. Nishiyama and Y. Nakai, *J. Am. Oil Chem. Soc. 60*:1651 (1983).
2. Yamada, F., T. Nishiyama, Y. Suzuura and T. Yamamura, *Bull. Chem. Soc. Jpn. 58*:115 (1985).
3. Yamada, F., T. Nishiyama, M. Yamamoto and K. Tanaka, *Ibid. 62*:3603 (1989).
4. Jirackova, L., and J. Pospisil, *Eur. Polym. J. 10*:975 (1974).
5. Scott, G., *Bull. Chem. Soc. Jpn. 61*:165 (1988).
6. Oae, S., M. Yoshihara and W. Tagaki, *Ibid. 40*:951 (1967).
7. Oae, S., and M. Yoshihara, *Ibid. 41*:2082 (1968).
8. Oae, S., and C. Zalit, *J. Am. Chem. Soc. 82*:5359 (1960).
9. Fujisawa, T., M. Yamamoto and G. Tsuchihashi, *Synthesis*:624 (1972).
10. Morawetz, H., *Ind. Eng. Chem. 41*:1442 (1949).
11. Ewing, D.F., *Org. Magn. Reson. 12*:499 (1979).
12. Burton, G.W., and K.U. Ingold, *J. Am. Chem. Soc. 103*:6472 (1981).
13. Horswill, E.C., J.A. Howard and K.U. Ingold, *Can. J. Chem. 44*:985 (1966).
14. Binkley, J.S., R.A. Whiteside, R. Krishnan, R. Seeger, D.J. DeFrees, H.B. Schlegel, S. Topiol, L.R. Kahn and J.A. Pople, *GAUSSIAN 80*, Carnegie Mellon University, Pittsburg, 1980.
15. Tanaka, K., S. Sakai, S. Tomiyama, T. Nishiyama and F. Yamada, *Bull. Chem. Soc. Jpn. 64*:2677 (1991).
16. Tomiyama, S., S. Sakai, T. Nishiyama and F. Yamada, *Ibid. 66*:299 (1993).
17. Pivcova, H., L. Jirackova and J. Pospisil, *J. Polym. Sci., Polym. Symp. 40*:283 (1973).
18. Burton, G.W., T. Doba, E.J. Gabe, L. Hughes, F.L. Lee, L. Prasad and K.U. Ingold, *J. Am. Chem. Soc. 107*:7053 (1985).

[Received August 10, 1994; accepted June 8, 1995]