Antioxidant activities of tetrakis(4-hydroxyphenyl)pentanes and tetrakis(4-hydroxyphenyl)-*p*-xylenes

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A series of tetrakis(4-hydroxyphenyl)pentanes and tetrakis(4-hydroxyphenyl)-*p*-xylenes having relatively high molecular weights (550–810) were prepared and evaluated as antioxidants for tetralin at 60°C by means of an oxygen-absorption method. Introduction of alkyl groups to the *ortho* positions of the phenolic hydroxyl group was shown to improve antioxidant activities for both series of compounds.

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On a préparé une série de tétrakis(4-hydroxyphényl)pentanes et de tétrakis(4-hydroxyphényl)-*p*-xylènes de poids moléculaires relativement élevés (550–810) et on les a évalués comme antioxydants pour le tétraline, à 60°C, par une méthode d'absorption de l'oxygène. On a démontré que l'introduction de groupes alkyles en positions *ortho* du groupe hydroxyle du phénol améliore les activités antioxydantes dans les deux séries de composés.

[Traduit par la Rédaction]

Introduction

In chemical industries, antioxidants have commonly been used to prevent deterioration due to the oxidation of organic materials, for example, petroleum hydrocarbons, lubricating oils, rubbers, polymers, and foodstuffs (1). The oxidation upon storage at room temperature or during various processes at high temperature have been well recognized as radical chain reactions. Antioxidants such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) and *tert*-butylated hydroxyanisole (BHA) react as chain-breaking inhibitors of the peroxyl radical. BHT and BHA are, however, relatively volatile and, consequently, of somewhat limited use at higher temperatures owing to their loss through vaporization. The development of antioxidants having high molecular weights (2) and the fixation of antioxidants to polymer chains (3, 4) are well-established methods to reduce the volatility of antioxidants.

During the course of our studies on phenol derivatives as antioxidants (5, 6), we have found that the introduction of the benzyl group at *ortho*- and (or) *para*-positions of the phenolic hydroxyl group improved the antioxidant activities. Furthermore, benzylphenols containing alkyl groups at both *ortho* positions for the phenolic hydroxyl group showed high activities as antioxidants.

On this basis, we expected that 1,1,5,5,-tetrakis(4-hydroxyphenyl)pentanes (**1–5**) and α,α,α′,α′-tetrakis(4-hydroxyphenyl)-*p*-xylenes (**6–11**) would act as better antioxidants compared with BHT or BHA, since they have four active phenolic moieties and alkyl or benzyl groups at the *ortho*- and or *para*-positions of the phenol skeleton. Herein, we wish to report the preparation of compounds **1–11** (Fig. 1) and their antioxidant activities evaluated by means of an oxygen-absorption method.

Results and discussion

Figure 2 shows the results of the autoxidation of tetralin initiated by 2,2′-azo-bis(isobutyronitrile) AIBN), in the presence of tetrakisphenols **1–11** and BHT as antioxidants, along with a control test in the absence of an antioxidant. The control curve was observed without any appreciable induction period (IP). On the contrary, the rates of oxygen uptake in the presence of tetrakisphenols were remarkably suppressed.

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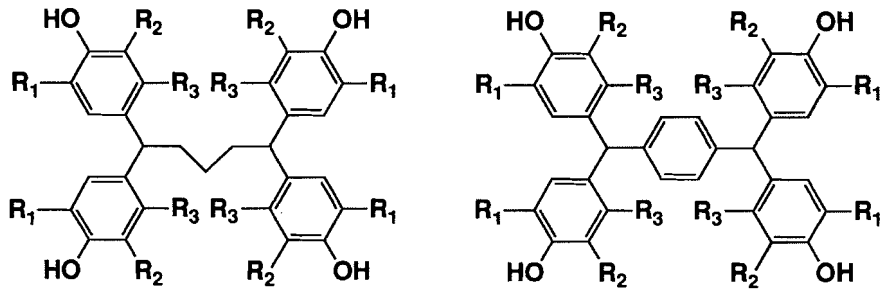
First, the antioxidant activities of the tetrakis(4-hydroxyphenyl)pentanes and tetrakis(4-hydroxyphenyl)-*p*-xylenes were compared. In comparison with **1** and **6** having 2,5-dimethyl substituents on phenol rings, the IP value of **1** showed a slightly higher value (see IP values in Table 1). However, the IP values of **2** and **7**, **3** and **8**, and **5** and **10** showed almost the same values.

Next, the positions of the alkyl substituents on the phenol rings on their antioxidant effect were compared. The relative antioxidant potency of the tetrakis(4-hydroxyphenyl)pentanes was observed in the order **3** > **2** > **4**,**5** > **1**. Similarly, the IP values of the tetrakis(4-hydroxyphenyl)-*p*-xylenes decreased in the order **8**,**11** > **7** > **10** > **9** > **6**. In particular, for compounds **2**, **3**, **7**, **8**, and **11** having two alkyl substituents at *ortho* positions of OH groups, the IP values were 2.5–3.0 times larger than that for BHT. These results indicated that the factors which enhance the peroxyl radical trapping ability of tetrakisphenols are greatly dependent on the position of the ring substituents of the phenol nuclei. These factors are, first, alkyl substitution at both *ortho* positions and, second, a bulky substitution at the *ortho* position.

The stoichiometric factors (n) for all the antioxidants examined are listed in Table 1. Compounds **2**, **3**, **7**, **8**, and **11** exhibited much higher stoichiometric factors (5.2–6.0) in comparison with those of other compounds. This means that these four compounds react with five to six pieces of peroxyl radicals, respectively.

Table 1 also shows the rates of oxygen consumption after IP. As can be seen from Table 1, relatively lower rates were observed for all classes of tetrakisphenols in comparison with BHT. When all ArO· radicals are consumed, the rate of autoxidation should be equal to that of the control test. In fact, the rate of oxygen consumption after IP of BHT was close to the control value. On the other hand, the rates of oxygen consumption of compounds **1–11** were not close to the control value, but much lower. This means that the retardation ability persists, even after IP is over, owing to some transformation products of the antioxidant.

In conclusion, we have synthesized a series of tetrakisphenols. Among these compounds, the compounds having two alkyl substituents at *ortho* positions of OH groups, such as **2**, **3**, **7**, **8**, and **11**, exhibited significant antioxidant effect. However, no influence of the structure between tetrakis(4-hydroxyphenyl)pentanes and tetrakis(4-hydroxyphenyl)-*p*-xylenes on their antioxidant effect was observed.



1, $R_1=R_3=CH_3$, $R_2=H$
2, $R_1=R_2=CH_3$, $R_3=H$
3, $R_1=R_2=R_3=CH_3$
4, $R_1=CH(CH_3)_2$, $R_2=H$, $R_3=CH_3$
5, $R_1=C(CH_3)_3$, $R_2=H$, $R_3=CH_3$

6, $R_1=R_3=CH_3$, $R_2=H$
7, $R_1=R_2=CH_3$, $R_3=H$
8, $R_1=R_2=R_3=CH_3$
9, $R_1=CH(CH_3)_2$, $R_2=H$, $R_3=CH_3$
10, $R_1=C(CH_3)_3$, $R_2=H$, $R_3=CH_3$
11, $R_1=R_2=CH(CH_3)_2$, $R_3=H$

FIG. 1. 1,1,5,5-Tetrakis(4-hydroxyphenyl)pentanes (**1–5**) and α,α,α′,α′-tetrakis(4-hydroxyphenyl)-*p*-xylenes (**6–11**).

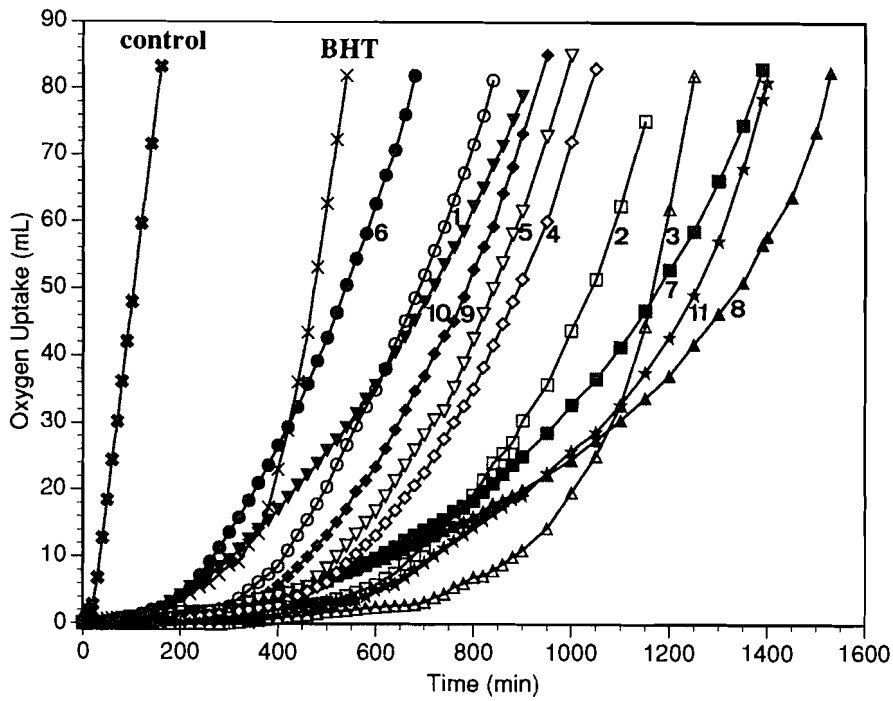


FIG. 2. Rate of oxygen uptake in the oxidation of tetralin in the absence and presence of antioxidant.

We are planning to test the toxicity of **1–11** and the antioxidant activities for other substrates.

Experimental

General

Melting points were measured on a Yanaco MP-J3 micro melting apparatus and uncorrected. Infrared spectra were determined with a Perkin-Elmer model 1600 grating infrared spectrophotometer using a potassium bromide pellet. Nuclear magnetic resonance spectra were recorded with a Jeol GSX-400 spectrometer operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C. Unless otherwise noted, the solvent was $(CD_3)_2CO$ and chemical shifts are given with respect to TMS.

Determination of antioxidant activities

The volume of oxygen consumption was determined as a function of time under 760 Torr (1 Torr = 133.3 Pa) of O_2 (5). The oxidation temperature was kept at 60 ± 0.1°C. The IP was determined graphically (7, 8) on the plot of oxygen consumption versus time as the point of intersection of a line of the rate of oxygen uptake after the inhibitor was consumed and a line tangent to the curve with a slope equal to half of the slope of the line after the inhibitor was consumed. Stoichiometric factors (n) were determined at 60°C by the IP method (9, 10).

Materials

Tetralin was washed with concentrated sulfuric acid, aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, and distilled under nitrogen before use. AIBN was recrystallized from methanol.

The tetrakis(4-hydroxyphenyl)pentanes **1–5** and tetrakis(4-hydroxyphenyl)-*p*-xylenes **6–11** were prepared by the condensation reaction of glutaraldehyde or terephthalaldehyde with the corresponding phenols in the molecular ratio of one to four in the presence of an acidic catalyst (11, 12). A typical experimental procedure is described for the synthesis of **1**. To the solution of 2,5-dimethylphenol (12.2 g, 0.1 mmol) and glutaraldehyde (2.5 g, 25 mmol) in nitromethane (30 mL), concentrated HCl (1.5 mL) was added dropwise at room temperature.

TABLE 1. Antioxidant activities of tetrakisphenols **1–11**

Compound	mp (°C)	IP (min)	*n*	Rates of oxygen consumption (mL/min)
1	226.2–227.0	493	3.07	0.21
2	206.0–206.5	938	5.16	0.32
3	228.0–229.0	1038	5.56	0.36
4	179.9–181.2	678	4.01	0.25
5	198.8–199.1	672	3.98	0.25
6	>300	384	2.47	0.25
7	248.2–250.0	973	5.31	0.19
8	263.1–263.8	1167	6.04	0.20
9	285.2–285.9	487	3.04	0.18
10	>300	601	3.63	0.22
11	145.1–146.2	1126	5.89	0.26
BHT		376	2.67	0.48
Control		22	—	0.56

After being stirred for 24 h, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with 10% ethyl acetate in hexane as eluants. The first fraction contained 2,5-dimethylphenol. The second fraction was evaporated in vacuo to leave a solid. Recrystallization of the solid from acetone gave 2.8 g (20%) of **1**. The yield, spectral, and analytical data are as follows.

1,1,5,5-Tetrakis(2,5-dimethyl-4-hydroxyphenyl)pentane (1)
^{1}H nmr δ: 1.81–1.88 (m, 6H), 2.04 (s, 12H), 2.06 (s, 12H), 2.89 (br s, 4H), 3.95 (t, J = 7.3 Hz, 2H), 6.52 (s, 4H), 6.77 (s, 4H); ^{13}C nmr δ: 16.1, 19.3, 32.3, 37.0, 42.0, 117.3, 121.7, 130.2, 134.9, 153.7; ir: 3484 cm^{-1} (s, br). Anal. calcd. for $C_{37}H_{44}O_4$: C 80.39, H 8.02; found: C, 79.99, H, 8.10.

1,1,5,5-Tetrakis(3,5-dimethyl-4-hydroxyphenyl)pentane (2)
Yield: 10%; ^{1}H nmr δ: 1.81–1.88 (m, 6H), 2.02 (s, 24H), 2.75 (br s, 4H), 3.44 (t, J = 7.7 Hz, 2H), 6.67 (s, 8H); ^{13}C nmr δ: 16.7, 27.3, 36.8, 50.5, 124.2, 128.4, 138.1, 152.0; ir: 3500 cm^{-1} (s, br). Anal. calcd. for $C_{37}H_{44}O_4$: C 80.39, H 8.02; found: C 80.01, H 7.98.

1,1,5,5,-Tetrakis(2,3,5-trimethyl-4-hydroxyphenyl)pentane (3)
Yield: 11%; ^{1}H nmr δ: 2.03–2.06 (m, 6H), 2.09 (s, 24H), 2.12 (s, 12H), 2.81 (br s, 4H), 3.65 (t, J = 7.7 Hz, 2H), 6.47 (s, 4H); ^{13}C nmr δ: 12.9, 15.3, 16.9, 32.3, 37.2, 43.1, 121.1, 123.5, 127.5, 133.5, 135.3, 151.5; ir: 3480 cm^{-1} (s, br). Anal. calcd. for $C_{41}H_{52}O_4$: C 80.49, H 8.78; found: C 80.20, H 8.48.

1,1,5,5-Tetrakis(2-methyl-5-isopropyl-4-hydroxyphenyl)pentane (4)
Yield: 42%; ^{1}H nmr δ: 1.12 (d, J = 6.8 Hz, 12H), 1.17 (d, J = 6.8 Hz, 12H), 1.85–1.91 (m, 6H), 2.11 (s, 6H), 2.18 (s, 6H), 3.06–3.13 (m, 4H), 4.00 (t, J = 7.0 Hz, 2H), 4.66 (br s, 4H), 6.48 (s, 4H), 6.91 (s, 4H); ^{13}C nmr δ: 19.2, 23.1, 27.4, 27.8, 37.5, 42.4, 117.6, 125.7, 132.2, 134.3, 134.9, 152.5; ir: 3479 cm^{-1} (s, br). Anal. calcd. for $C_{45}H_{60}O_4$: C 81.28, H 9.09; found: C 79.89, H 9.01.

*1,1,5,5-Tetrakis(2-methyl-5-*tert*-butyl-4-hydroxyphenyl)pentane (5)*
Yield: 18%; ^{1}H nmr δ: 0.90 (s, 36H), 1.44–1.51 (m, 6H), 1.69 (s, 12H), 2.42 (br s, 4H), 3.65 (t, J = 7.6 Hz, 2H), 6.13 (s, 4H), 6.64 (s, 4H); ^{13}C nmr δ: 19.0, 27.6, 30.9, 35.0, 37.8, 42.3, 118.8, 126.3, 133.3, 134.4, 134.5, 153.9; ir: 3494 cm^{-1} (s, br). Anal. calcd. for $C_{49}H_{68}O_4$: C 81.62, H 9.51; found: C 81.43, H 9.31.

α,α,α′,α′-*Tetrakis(2,5-dimethyl-4-hydroxyphenyl)*-p-*xylene (6)*
Yield: 15%; ^{1}H nmr (DMSO-d_6) δ: 1.93 (s, 12H), 1.96 (s, 12H), 2.08 (s, 4H), 5.38 (s, 2H), 6.27 (s, 4H), 6.56 (s, 4H), 6.86 (s, 4H); ^{13}C nmr (DMSO-d_6) δ: 15.9, 18.9, 30.7, 48.0, 116.7, 120.0, 129.0, 130.8, 132.6, 133.9, 141.3, 153.2; ir: 3485 cm^{-1} (s, br). Anal. calcd. for $C_{40}H_{42}O_4$: C 81.88, H 7.21; found: C, 81.57, H 7.24.

α,α,α′,α′-*Tetrakis(3,5-dimethyl-4-hydroxyphenyl)*-p-*xylene (7)*
Yield: 22%; ^{1}H nmr δ: 2.13 (s, 24H), 2.85 (s, 2H), 2.88 (s, 2H), 5.23 (s, 2H), 6.99 (s, 4H), 7.01 (s, 4H), 7.33 (s, 4H); ^{13}C nmr δ: 16.7, 55.9, 124.2, 129.1, 129.7, 130.1, 136.6, 143.7, 152.2; ir: 3475 cm^{-1} (m, br). Anal. calcd. for $C_{40}H_{42}O_4$: C 81.88, H 7.21; found: C 81.68, H 7.19.

α,α,α′,α′-Tetrakis(2,3,5-trimethyl-4-hydroxyphenyl)-p-*xylene (8)*
Yield: 29%; ^{1}H nmr δ: 2.06 (s, 12H), 2.08 (s, 12H), 2.17 (s, 12H), 2.87 (br s, 4H), 5.66 (s, 2H), 6.91 (s, 2H), 6.97 (s, 2H), 7.35 (s, 4H); ^{13}C nmr δ: 13.0, 15.8, 17.1, 51.2, 121.0, 124.0, 129.3, 129.9, 134.2, 135.1, 143.4, 152.2; ir: 3510 cm^{-1} (s, br). Anal. calcd. for $C_{44}H_{50}O_4$: C 82.20, H 7.84; found: C 81.87, H 7.79.

α,α,α′,α′-*Tetrakis(2-methyl-5-isopropyl-4-hydroxyphenyl)*-p-*xylene (9)*
Yield: 33%; ^{1}H nmr δ: 1.03 (d, J = 6.6 Hz, 24H), 2.05 (s, 12H), 2.91 (s, 2H), 2.94 (s, 2H), 3.12–3.22 (m, 4H), 5.55 (s, 2H), 6.60 (s, 4H), 6.63 (s, 4H), 6.94 (s, 4H); ^{13}C nmr δ: 19.4, 23.1, 27.6, 49.9, 117.8, 128.1, 130.2, 132.1, 134.5, 135.1, 142.9, 153.1; ir: 3493 cm^{-1} (s, br). Anal. calcd. for $C_{48}H_{58}O_4$: C 82.48, H 8.36; found: C 82.21, H 8.12.

α,α,α′,α′-Tetrakis(2-methyl-5-tert-*butyl-4-hydroxyphenyl)*-p-*xylene (10)*
Yield: 31%; ^{1}H nmr δ: 1.25 (s, 36H), 2.11 (s, 12H), 2.93 (br s, 4H), 5.60 (s, 2H), 6.65 (s, 4H), 6.74 (s, 4H), 6.97 (s, 4H); ^{13}C nmr δ: 19.1, 35.1, 49.8, 118.9, 128.8, 130.2, 133.2, 133.9, 135.3, 143.1, 154.4; ir: 3481 cm^{-1} (s, br). Anal. calcd. for $C_{52}H_{66}O_4$: C 82.71, H 8.81; found: C 82.80, H 8.80.

α,α,α′,α′-Tetrakis(3,5-diisopropyl-4-hydroxyphenyl)-p-*xylene (11)*
Yield: 11%; ^{1}H nmr δ: 1.07 (d, J = 6.6 Hz, 48H), 2.75 (s, 2H), 2.79 (s, 2H), 3.22–3.28 (m, 8H), 5.31 (s, 2H), 6.81 (s, 8H), 6.99 (s, 4H); ^{13}C nmr δ: 23.5, 27.6, 57.1, 125.1, 129.8, 135.3, 137.3, 144.4, 149.7; ir: 3495 cm^{-1} (s, br). Anal. calcd. for $C_{56}H_{74}O_4$: C 82.92, H 9.19; found: C 82.61, H 9.08.

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