Chemistry on the Decay of the Phenoxy Radical from Butylated Hydroxytoluene

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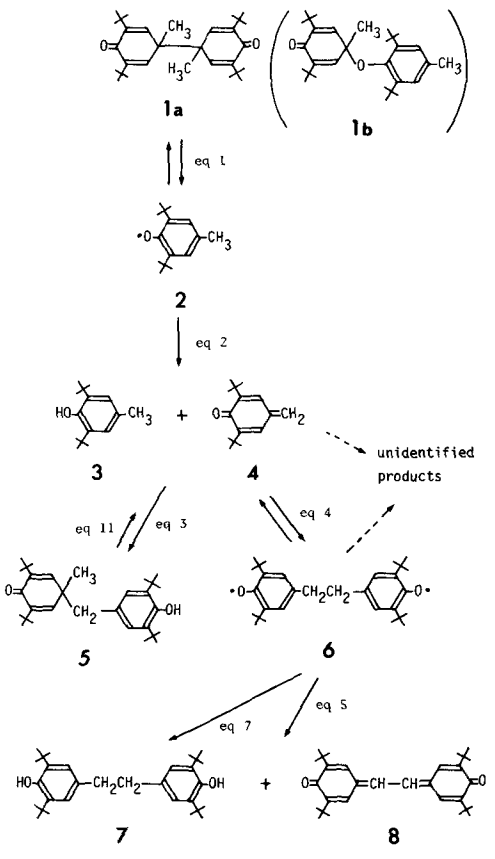
Decay of unstable 2,6-di-*tert*-butyl-4-methylphenoxy radical (2) was investigated in various solvents. Radical 2 was conveniently generated by dissociation of bis(methylcyclohexadienone) (1a), unstable dimer of 2, in solution. The products were butylated hydroxytoluene (3), 1,2-bis(4-hydroxyphenyl)ethane (7), 4,4′-stilbenequinone (8), and 4-(4-hydroxybenzyl)cyclohexadienone (5). Unidentified products also were formed. The formation of 5 was favored in polar solvents, but was not subject to catalysis with Et_3N or HCl. In contrast, the rates of formation of 7 and 8 appeared to be independent of solvent polarity. The mechanism of formation of the dimeric products *via* reactive intermediate quinone methide 4, generated from 2 by disproportionation, is discussed. Gradual disintegration of 5 in solution into 3 and 4 was investigated.

KEY WORDS: Butylated hydroxytoluene, dimer formation, phenoxy radical, quinone methide, solvent effect.



SCHEME 1

Establishing the chemistry on the fate of the unstable phenoxy radical 2 (Scheme 1) from butylated hydroxytoluene (BHT, 3) is essential for the full account of the activity of 3 as a widely used synthetic antioxidant (1). It is also useful for study of the metabolism of 3. Phenoxy radical 2 and quinone methide 4, generated by disproportionation of 2, have been suggested as reactive metabolites of 3, and have been thought to be responsible for the toxic effects exerted by 3 (2–4). 4,4′-Stilbenequinone 8 has also been suggested as a metabolite (3).

Chemistry on the decay of 2 has been studied by generating it from 3 with a variety of dehydrogenating agents (5–7). As the ultimate products, 1,2-bis(4-hydroxyphenyl)ethane 7 and 8 have been obtained. The study on the decay of 2 may, however, be complicated because an oxidant employed to produce 2 may dehydrogenate not only 3, but also phenolic products such as 7 (8–10). In addition, most of the previous studies on the decay of 2 appeared to have lacked detailed product analyses. Therefore, these reactions were investigated carefully by generating 2 with a different method. The method was simply to allow bis(methylcycohexadienone) **1a** to dissolve in a solvent (11). Compound **1a**, obtained by dimerization of 2 (12), is a "canned phenoxy radical (1)" because it readily dissociates in solution to generate 2. Another advantage of the method is that 2 can be generated in any solvent of choice. Structure **1a** has been proposed recently instead of the earlier quinol ether structure **1b** (11).

EXPERIMENTAL PROCEDURES

^1H nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ on a Hitachi (Tokyo, Japan) R-20B spectrometer (60 MHz). Infrared (IR) spectra were taken in $CHCl_3$ with a Hitachi EPI-G3 spectrophotometer. Column chromatography was conducted by using Merck SiO_2 60 (Darmstadt, Germany). Thin-layer chromatography (TLC) was run on SiO_2.

Decay of phenoxy radical 2 derived from dimer 1a (Table 1). A solvent (8 mL) was added to solid **1a** (12) (800 mg, 1.83 mmol). The mixture was magnetically stirred at 30°C in a tightly screw-capped bottle until it became homogeneous. The following approximate times (min) were required for the complete dissolution of **1a** in solvents shown in parentheses; 1 (CH_2Cl_2), 4 (CCl_4), 4 (benzene), 10 (ether), 11 (Et_3N), 15 (pyridine), 18 (hexane), 22 (AcOEt), 33 (acetone), 100 (dimethyl formamide, DMF), 340 (acetonitrile), and 480 or more (dimethyl sulfoxide, DMSO). The resultant solution in the capped bottle was let stand at 30°C for 4 hr or 20 hr, and evaporated under reduced pressure to leave a residue. The mixture after the reaction in pyridine, acetone containing hydrochloric acid, DMF, or DMSO was poured into water, and extracted with petroleum ether. The extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to leave a residue.

A typical chromatographic procedure with SiO_2 (25 g) is presented here for the residual mixture of products (0.80 g) from the reaction in benzene (run 7). Elution with petroleum ether gave 182 mg (45%) of phenol 3 (^1H NMR and TLC) as colorless crystals. Further elution afforded 1,2-bis(4-hydroxyphenyl)ethane 7 (250 mg, 31%) as yellow crystals, identical with an authentic sample (12) (^1H NMR, IR and TLC). Further elution gave a light yellow solid, which was a mixture of 7 (30 mg, 4%) and 5 (see

TABLE 1

Decay of Phenoxy Radical 2[a]

Run	Solvent[b]	Yield (%, mol/mol 1a × 100) 3	5	7	8
1	Hexane	58	12	38	5.7
2	Et_3N	61	13	34	7.3
3	Et_3N[c]	59	13	35	6.9
4	CCl_4	48	16	40	3.4
5	CCl_4[c]	50	15	41	3.2
6	Ether	49	20	34	3.7
7	Benzene	45	20	35	2.1
8	AcOEt	45	34	21	1.6
9	Acetone	47	41	15	1.4
10	Acetone[c]	44	40	16	1.1
11	Acetone/HCl[d]	51	40	13	0.9
12	CH_2Cl_2	42	31	26	1.0
13	Pyridine	41	45	17	2.0
14	Acetonitrile	48	43	11	0.9
15	DMF	37	52	12	0.8
16	DMSO	27	71	4	0.6

[a]Unless otherwise stated, the reactions were carried out for 20 hr.

[b]The solvents are listed in order of increasing solvent polarity. As a measure of solvent polarity, Swain's empirical parameters were arbitrarily adopted (ref. 29).

[c]Reaction for 4 hr.

[d]Acetone containing a catalytic amount of 0.05 N HCl (0.05 mol/mol 1a).

TABLE 2

Decay of Dienone 5

Solvent	Conversion of 5 (%)	Yield[a] (%[b]) 3	7
Hexane	43	21	18
CCl_4	54	25	27
Et_3N[c]	0	0	0
Pyridine[c]	ca. 0	trace	trace
Acetone	42	21	14
Acetone/HCl[d]	15	7	1
DMF	42	22	16

[a]In addition, 8 was formed in small quantities.

[b](Mol/mol 5 employed) × 100.

[c]Stilbenequinone 8 was not formed.

[d]Acetone containing a catalytic amount of 6 N HCl (0.35 mol/mol 5).

below) (20 mg, 3%) as estimated by ^1H NMR spectroscopy. Continued elution yielded 2,6-di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-4-methylcyclohexa-2,5-dien-1-one (5) (143 mg, 18%) as yellow crystals—pale yellow crystals from diisopropylether, identical with an authentic sample (13) (m.p., ^1H NMR, IR and TLC), m.p. 108–109°C dec. [lit. m.p. 115–117°C (13) and 116°C (14)]; MS *m/e* 438 (M^+). *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.00; H, 10.72. Further recrystallization did not raise the melting point. Elution with petroleum ether/benzene (10:1) provided a semi-crystalline mixture (27 mg), which was treated with a small amount of MeOH. The mixture was filtered hot to afford 4,4′-stilbenequinone 8 (17 mg, 2.1%) as reddish orange crystals, identical with an authentic sample (15) (^1H NMR, IR and TLC). The filtrate contained little 8. Elution with benzene gave an oily mixture of products (85 mg). The mixture contained two major components, which were not characterized [R_f 0.24 and 0.15 respectively, with petroleum ether/benzene (6:1)]. A control experiment, conducted by dissolving 1a in deaerated benzene and leaving the resulting solution under an atmosphere of nitrogen for 20 hr, gave essentially the same result as run 7.

Decay of dienone 5 (Table 2). A solution of 5 (300 mg, 0.68 mmol) in a solvent (8 mL) was kept at 30°C for 70 hr in a screw-capped bottle. The reaction mixture was evaporated under reduced pressure to leave a residue. The mixture from the reaction in pyridine, DMF, or acetone containing hydrochloric acid was poured into water and extracted with petroleum ether. The extract was washed with water, dried and evaporated under reduced pressure to leave a residue. The residual mixture of products was chromatographed on SiO_2 (15 g) as described above.

Oxidation of BHT (3) with alkaline potassium ferricyanide. A solution of 3 (880 mg, 4.00 mmol) in benzene (10 mL) was added to a solution of potassium ferricyanide (2.90 g, 8.8 mmol) and KOH (2.0 g) in water (20 mL). The mixture was vigorously stirred for 8 min under an atmosphere of nitrogen. After removal of the aqueous layer, the organic layer was washed with water and was allowed to stand at room temperature for 23 hr. The reaction mixture was evaporated to leave a residue, which was chromatographed (SiO_2, 25 g) as described above to afford 3 (89 mg, 10% recovery), 5 (155 mg, 18%), 7 (356 mg, 41%) and 8 (139 mg, 16%).

Reduction of bromocyclohexadienone 16 with Hg. Mercury (2.40 g) was added to a solution of 16 (16) (1.195 g, 4.00 mmol) in ether (10 mL). The mixture was stirred vigorously under an atmosphere of nitrogen at room temperature for 17 hr. The mixture was filtered, and the filtrate was evaporated to leave a residue, which was chromatographed (SiO_2, 25 g) as described above to afford 3 (224 mg, 51%), 5 (76 mg, 9%), 7 (426 mg, 49%), and 8 (11 mg, 1%).

Decay of quinone methide 4, prepared from benzyl bromide 9 and Et_3N, in the presence and absence of BHT (3). A solution of Et_3N (404 mg, 4.00 mmol) in pentane (20 mL) was added dropwise to a stirred solution of 9 (17) (1.196 g, 4.00 mmol) in pentane (200 mL). After a few minutes, the mixture was filtered, and the filtrate containing 4 was mixed with a solution of 3 (880 mg, 4.00 mmol) in pentane (50 mL). The mixture was concentrated to a small volume (*ca.* 20 mL) at atmospheric pressure (bath temperature, 45°C). The concentrate was kept at 30°C for 22 hr. The reaction mixture was evaporated under reduced pressure to leave a residue, which was chromatographed (SiO_2, 30 g) as described above to furnish 3 (382 mg, 43% recovery), 5 (150 mg, 9%), 7 (816 mg, 47%) and 8 (74 mg, 4%).

A solution of 4 (4 mmol) in pentane (220 mL), prepared in the manner described above, was concentrated to a small volume (*ca.* 20 mL) at atmospheric pressure. The concentrate was kept at 30°C for 21 hr. The reaction mixture was evaporated at atmospheric pressure. These operations were carried out under an atmosphere of nitrogen. The residue (0.88 g) was chromatographed (SiO_2, 20 g) as described above to provide 7 (129 mg, 29% based on Eqs. [4] and [5]) and 8 (209 mg, 48%). Elution with benzene afforded an oily mixture (531 mg), which principally con-

tained two unidentified products. These unknown substances were shown by TLC to be identical with those obtained from the decay of **1a** (see above). They also were obtained from the other reactions involving **4** conducted in the present study.

Reaction of quinone methide 11 with phenol 12. A solution of **11** (18) (230 mg, 1.0 mmol) and **12** (1.033 g, 5.0 mmol) in benzene (2 mL) was allowed to stand at 60°C for 65 hr. The mixture was evaporated under reduced pressure to leave a residue, which was chromatographed (SiO_2, 25 g). Elution with petroleum ether gave unreacted **12**. Elution with petroleum ether/benzene (10:1) gave an oily mixture of **11** (100 mg, 43% recovery) and **14** (see below) (55 mg) as estimated by ^1H NMR spectroscopy. Further elution afforded 1,1-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane **14** as light yellow crystals (148 mg, 83% in total based on the reacted **11**)—colorless crystals from hexane, m.p. 157–158°C [lit. (19) m.p. 156°C]. The ^1H NMR spectrum was in agreement with that reported for **14** (19).

RESULTS AND DISCUSSION

Prior to preparative-scale studies, the process of reaction at 30°C after dissolution of **1a** in CCl_4 (0.23 mol/L) was followed by ^1H NMR spectroscopy. Initially, the mixture principally contained **3** and **4**:

$$\mathbf{1a} \rightleftarrows \mathbf{2}\ \mathbf{2} \qquad [1]$$

$$\mathbf{2}\ \mathbf{2} \rightarrow \mathbf{3} + \mathbf{4} \qquad [2]$$

With the elapse of time, the quantity of reactive intermediate **4** decreased slowly, and new signals due to products increasingly appeared in the spectrum. After 4 hr, the mixture contained *ca.* 15% of the proposed amount of **4**. Only a trace amount of **4** survived after 20 hr. In the preparative-scale run in CCl_4, therefore, the mixture obtained by dissolving **1a** (0.23 mol/L) was allowed to wait for 20 hr at 30°C for work-up. The products isolated after column chromatography included **3** (48%), **7** (40%) and **8** (3.4%). In addition, a crystalline product was obtained in 16% yield, which proved to be 4-(4-hydroxybenzyl)cyclohexadienone **5**. In spite of a number of studies on the oxidation of **3**, **5** has seldom been obtained (13,14), and the formation of this phenolic product in low yields has received only limited attention.

The decay of **2** by use of **1a** was similarly undertaken in other solvents inert to **4** (Table 1). The yield of **5** was variable (12–71%) but tended to increase as solvent polarity increased. The formation of **5** was particularly facile in DMSO (run 16). In contrast, the yields of **7** and **8** were relatively high in nonpolar solvents. Stilbenequinone **8** always remained a minor product. In addition, two unidentified compounds were produced, both of which moved slower than **5**, **7** or **8** on a TLC plate. These uncharacterized products were identical with those obtained when **4** was allowed to decay spontaneously in the absence of **3** (see below).

The favored formation of **5** in polar solvents may suggest that it is the product of polar 1,6-addition of **3** to **4**:

$$\mathbf{3} + \mathbf{4} \rightarrow \mathbf{5} \qquad [3]$$

Conjugate addition of nucleophiles, including phenols, to quinone methides or vinyl quinone methides is well known (20–22). In general, it can be accelerated by acid or base such as Et_3N. The decay of **4** derived from **1a** in Et_3N, however, afforded only low yield of **5** (run 2). Apparently, Et_3N in the reaction is serving only as a relatively nonpolar solvent. The reaction to give **5** in acetone (run 9) was not improved by addition of a catalytic amount of hydrochloric acid (run 11). An alternative mechanism appears to be formation of the charge-transfer complex from **3** (donor) and **4** (acceptor) in the rate-determining step. The more detailed mechanism of the formation of **5** awaits closer examination.

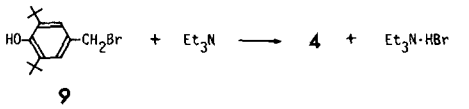
Quinone methide **4** has been suggested to dimerize to give biradical **6**. Recently this dimerization has been shown to be reversible (23):

$$\mathbf{2}\ \mathbf{4} \rightleftarrows \mathbf{6} \qquad [4]$$

Dimeric products reportedly are formed in equimolar amounts by disproportionation of **6** (1,5–7):

$$\mathbf{2}\ \mathbf{6} \rightarrow \mathbf{7} + \mathbf{8} \qquad [5]$$

Spontaneous decay of **4** (in the absence of **3**) was reinvestigated under anaerobic conditions by generating **4** in pentane by the reaction of benzyl bromide **9** with Et_3N:



9 [6]

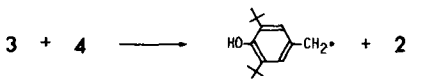
Products **7** and **8** were obtained only in low yields (29% and 48%, respectively, of the theoretical amounts based on Eqs. [4] and [5]). Formation of two unidentified products was substantial (more than 50% by weight of the crude product). These uncharacterized substances were, as described above, always found in the decay of **2**. The result indicates that there is an additional reaction(s) by which **4** and/or **6** decays spontaneously.

It is evident that Eqs. [4] and [5] account for only a small fraction of **7** formed from the decay of **2**, because the yield of **7** always overwhelmed that of **8**. The rest of **7** was probably formed by hydrogenation of **6** with **3** (24):

$$\mathbf{6} + \mathbf{2}\ \mathbf{3} \rightarrow \mathbf{7} + \mathbf{2}\ \mathbf{2} \qquad [7]$$

It is presumed that the rates of formation of **7** and **8** are controlled by that of dimerization of **4** (Eq. [4], forward reaction) because the subsequent reactions (Eq. [4], backward reaction, Eqs. [5] and [7]) are assumed to be quite fast, owing to the instability of biradical **6**. The relatively high yields of **7** and **8** in nonpolar solvents will be the result of the relative slowness of the competitive reaction of **4** with **3** (Eq. [3]) in these solvents, and the rate of dimerization of **4** (Eq. [4]) is probably independent of solvent polarity.

It might still be suspected that **7** (if not all) was the product of dimerization of 4-hydroxybenzyl radical **10** rather than that of Eq [7]. Generation of **10** may be considered if Eq. [3] proceeds stepwise:

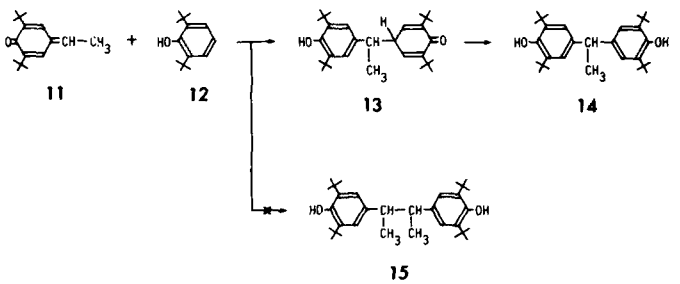


10 [8]

$$10 + 2 \rightarrow 5 \quad [9]$$

$$2\ 10 \rightarrow 7 \quad [10]$$

Such supposition is not without reason, since hydrogenation or electrochemical reduction of quinone methides has been shown to generate 4-hydroxybenzyl radicals, which dimerize to give 1,2-bis(4-hydroxyphenyl)ethane derivatives (25,26). The reported hydrodimerization of 2,6-di-*tert*-butyl-4-isopropenyl quinone methide with Zn/AcOH may also involve intermediary formation of a 4-hydroxybenzyl radical (27). Eq. [8] may or may not be affected by solvent polarity, but the subsequent, and presumably equally rapid, radical coupling processes (Eqs. [9] and [10]) may not be. If Eqs. [8–10] are involved in the present study, the formation of 5 and 7 would be subject to the same or a similar solvent effect, contrary to the fact. Exposure of quinone methide 11 [which is known to be much more stable than 4 and does not undergo spontaneous dimerization similar to Eq. [4] (18)], to excess phenol 12 in benzene at 60°C provided 1,1-bis(4-hydroxyphenyl)ethane 14 slowly, but in high yield. Product 14 may have arisen *via* intermediate dienone 13. The mechanism of the formation of 13 from 11 and 12 may be reasonably assumed to be analogous to that of 5 from 4 and 3. In this reaction, however 1,2-bis(4-hydroxyphenyl) ethane 15 was not obtained at all. In conclusion, it is unlikely that 5 and 7 are formed from the common intermediate radical 10.



11 12 13 14 15

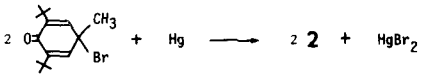
It has been reported that 5 is not quite stable in benzene solution and disintegrates slowly into 3 and 4 (the reverse reaction of Eq. [3]) (13):

$$5 \rightarrow 3 + 4 \quad [11]$$

The spontaneous decay of 5 was studied by allowing a solution of 5 to stand at 30°C for 70 hr (Table 2). The decomposition of 5 was significant in hexane, CCl_4, acetone and DMF, but there was no apparent dependency of its rate on solvent polarity. The products obtained after work-up were 3, 7 and 8, suggesting that Eq. [11] is followed by Eqs. [4], [5] and [7]. Rather unexpectedly, 5 was found to be stable in Et_3N under the given conditions. The decay of 5 also was slow in pyridine. It also was retarded in acetone containing a catalytic amount of hydrochloric acid. The results imply that the distribution of products from the decay of 1a (Table 1) might be different from what would result if 5 were stable in solution, and that the apparent dependency (or independence) of product formation on solvent polarity might even need re-evaluation. The following observations, however, indicate that the differences are not large.

The decay of 2 in CCl_4 (run 4) was repeated, but the mixture obtained by dissolving 1a was allowed to stand at 30°C for only 4 hr instead of 20 hr. The reaction mixture, which was to contain a considerable amount of 4 (see above), was evaporated. Chromatography of the residue afforded 3, 5, 7 and 8 in essentially the same quantities as those from the prolonged reaction (run 5). The reactions involving 4 were thus remarkably enhanced during the process of concentration. The product distributions from the reactions in Et_3N and in acetone showed similar independence on the reaction time (compare runs 3 with 2, and 10 with 9, respectively). The disintegration of product 5 in these solvents during the short period of reaction will not be significant in quantity.

The following facts will suffice to prove that the formation of 5 may be observed as commonly as that of 7 and 8, irrespective of means by which 2 is generated. Dienone 5 was isolated in 18% and 9% yields, respectively, from oxidation of 3 with alkaline potassium ferricyanide in benzene under appropriate conditions (see Experimental) and from reduction of 4-bromocyclohexadienone 16 with Hg in ether:



16 [12]

Dienone 5 was also obtained in 9% yield from the reaction of 4, generated in pentane by Eq. [6], in the presence of an equimolar amount of added 3. In these reactions, 7 and 8 were formed, as was reported by other groups who previously studied similar reactions (15,17,24,28).

Phenolic dienone 5 might be involved in the antioxidant activity and metabolism of BHT (3), although bimolecular reactions, Eq. [2] and, consequently, Eq. [3] may have little chance to occur *in vivo* where the concentration of 2 is quite low. Antioxidant activity as well as biological activity of 5, therefore, may deserve investigation.

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