Antioxidant Synergism Between Butylated Hydroxyanisole and Butylated Hydroxytoluene

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ABSTRACT: Decay of the 2,6-di-*tert*-butyl-4-methylphenoxy radical [butylated hydroxytoluene (BHT)-radical] in the presence of butylated hydroxyanisole (BHA) was investigated in 1,2-dimethoxyethane with or without triethylamine. BHT-radical was conveniently generated by dissociation of its unstable dimer in solution. The products were BHT, 3,3′-di-*tert*-butyl-5,5′-dimethoxy-2,2′-dihydroxybiphenyl (BHA-dimer), 2,6-di-*tert*-butyl-*p*-quinone methide (QM), 1,2-*bis*(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane, and 3,3′,5,5′-tetra-*tert*-butyl-4,4′-stilbenequinone. The reaction without added triethylamine gave larger quantities of the last two products and BHA (recovery), whereas the reaction with it provided larger quantities of the first two products. The marked difference in the product distribution can be accounted for by a series of reactions including reversible dehydrogenation of BHA with BHT-radical, which generates 2-*tert*-butyl-4-methoxyphenoxy radical (BHA-radical) and BHT, reversible dimerization of BHA-radical, which affords an intermediary *bis*(cyclohexadienone), and spontaneous and base-catalyzed prototropic rearrangement of the intermediate into BHA-dimer. Products of coupling between BHT-radical and BHA-radical were not obtained. BHA was found to undergo facile acid-catalyzed addition to QM, providing two isomeric *bis*(hydroxyphenyl)methanes. The results help to elucidate the mechanism of antioxidant synergism between BHA and BHT and may suggest that the synergism can be affected by base or acid.

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KEY WORDS: Antioxidant synergism, butylated hydroxyanisole, butylated hydroxytoluene, effect of acid, effect of base, fate of phenoxy radicals involved.

Activity of phenolic antioxidants involves scavenging of peroxy free radicals that are generated during the free-radical processes in autoxidation of oils and fats. Phenolic antioxidants scavenge the peroxy radicals by hydrogen donation to produce hydroperoxides and phenoxy free radicals. Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are among such antioxidants and have been shown to be synergists with one another (1–3). The mechanism of the synergistic effect has not been fully disclosed. In connection with this mechanism, dehydrogenation of a mixture of BHA and BHT has been studied. BHT is preferentially consumed in chemical (4–6) and biochemical (7) dehydrogenation (or one-electron oxidation) of the mixture. This is in sharp contrast to the observation that BHA is consumed faster than BHT when they are subjected to dehydrogenation separately under comparable conditions. To account for the apparent anomaly, it has been proposed that BHA is dehydrogenated first to give 2-*tert*-butyl-4-methoxyphenoxy radical (BHA-radical) in the dehydrogenation of a mixture with BHT, but that the BHA-radical abstracts hydrogen from BHT, thus regenerating BHA and generating 2,6-di-*tert*-butyl-4-methylphenoxy radical (BHT-radical). The synergistic effect of BHA and BHT on inhibiting autoxidation of oils and fats has been explained analogously—BHA acts as the scavenger (or inhibitor) of the peroxy radicals while BHT acts as the synergist, the regenerator of BHA from BHA-radical.

In principle, dehydrogenation of a phenol by a phenoxy radical is a reversible process. The reverse reaction of dehydrogenation of BHT with BHA-radical (dehydrogenation of BHA with BHT-radical), however, has not been considered seriously in most of the studies described mentioned previously on the cooxidation of BHA and BHT. We studied the reaction of the BHT-radical with BHA and report information obtained regarding the antioxidant synergism between BHA and BHT. To generate the BHT-radical selectively and efficiently in the presence of BHA, a dimer of BHT-radical, *bis*(1-methyl-3,5-di-*tert*-butyl-4-oxo-cyclohexa-2,5-dienyl) (BHT-dimer), was employed. BHT-dimer is relatively stable in the solid state but dissociates readily in solution to generate BHT-radicals (8–11). This method for generating a BHT-radical employs neither BHT nor a dehydrogenating agent, which may dehydrogenate phenolic products as well. A BHT-radical generated by this means has been shown to dehydrogenate phenols to give BHT and new phenoxy radicals, which couple with more BHT-radicals (10). The decay of the BHT-radical, generated analogously in the absence of an added phenol, also has been studied (11).

EXPERIMENTAL PROCEDURES

^{1}H (90 MHz) and ^{13}C (22.6 MHz) nuclear magnetic resonance (NMR) spectra were obtained in chloroform-*d* on a Hitachi (Tokyo, Japan) R-1900 spectrometer. Infrared (IR) spectra were taken in chloroform with a Hitachi EPI-G3 spectrophotometer. Column chromatography was conducted on

Merck Silica gel 60 (SiO_2; Darmstadt, Germany). Thin-layer chromatography (TLC) was run on Merck SiO_2 60 F_{254} with petroleum ether/benzene (6:1) as the developing solvent. 2-*tert*-Butyl-4-methoxyphenol (BHA), purchased from Tokyo Chemical Industry (Tokyo, Japan), was recrystallized from petroleum ether, m.p. 58–59.5°C.

Decay of BHT-radical in the presence of BHA. BHA (1.350 g, 7.5 mmol) in either 1,2-dimethoxyethane (DME; 13 mL; run 1) or DME (13 mL) and triethylamine (Et_3N; 0.5 mL; run 2) was added to BHT-dimer (9) (1.314 g; 3 mmol). The mixture was stirred at 30°C in a stoppered flask, and the solid BHT-dimer was dissolved within 30 s. The homogeneous mixture was allowed to stand at 30°C for 30 min. The mixture was diluted with benzene (200 mL) and was shaken vigorously for 15 min with 50% dimethylamine (Me_2NH; 1 mL). The mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure to leave a residual mixture of products.

The residue from run 1 was chromatographed on SiO_2 (100 g). Elution with petroleum ether gave 448 mg (34%) of BHT as colorless crystals as was confirmed by ^1H NMR and TLC. Elution with petroleum ether/benzene (5:1) provided 1,2-*bis*(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane (BE) (468 mg, 36%) as yellow crystals. Recrystallization from benzene gave pure BE as light-yellow crystals, identical to an authentic sample (9) (^1H NMR, IR, and TLC), m.p. 171.5–173°C [lit. (9) m.p. 167–168°C]. Further elution gave a semi-crystalline mixture (151 mg), which was washed with methanol to yield 3,3′,5,5′-tetra-*tert*-butylstilbene-4,4′-quinone (STBQ) (83 mg, 6%) as reddish-brown crystals, identical to an authentic sample (12) [^1H NMR, infrared (IR), and TLC], m.p. 315°C [lit. (12) m.p. 310–311°C]. Further elution gave a semi-crystalline mixture, which was washed with petroleum ether to afford 3,3′-di-*tert*-butyl-5,5′-dimethoxy-2,2′-dihydroxybiphenyl (BHA-dimer) (106 mg, 10%) as colorless crystals, m.p. 228–230°C [lit. (13) m.p. 228–229°C]. The ^1H NMR spectrum agreed with that reported by Butsugan *et al.* for BHA-dimer (13). The petroleum ether filtrate was evaporated to dryness to leave a light-brown oil (762 mg), which consisted almost exclusively of unreacted BHA. Further elution provided BHA (374 mg, 84% recovery in total) as light-brown crystals. Elution with ether gave a crystalline mixture (184 mg), which was recrystallized from petroleum ether (5 mL) with active charcoal (0.1 g) to furnish *N,N*-dimethyl-3,5-di-*tert*-butyl-4-hydroxybenzylamine (BA) (85 mg, 5%) as yellow crystals, identical to an authentic sample (14) (^1H NMR, IR, and TLC), m.p. 91.5–93.5°C [lit. (14) m.p. 92–93.5°C]. The ^1H NMR signals appeared at δ 7.06 (*s*, 2 H), 5.10 (*s*, 1 H), 3.32 (*s*, 2 H), 2.22 (*s*, 6 H), and 1.44 (*s*, 18 H), and IR absorption was observed at 3620 cm^{-1}.

The semi-crystalline residue from run 2 was washed with petroleum ether to yield BHA-dimer (429 mg). The filtrate was evaporated, and the residue was chromatographed in the manner described above for the residue from run 1. An additional amount of BHA-dimer (170 mg, 56% in total) was obtained by chromatography.

*Reaction of 2,6-di-*tert*-butyl-p-quinone methide (QM) with BHA.* Triethylamine (610 mg, 6 mmol) in DME (5 mL) was added dropwise to a solution of 3,5-di-*tert*-butyl-4-hydroxybenzyl bromide (15) (1.793 g, 6 mmol) in DME (200 mL) at 0°C over a period of *ca.* 3 min. After stirring the mixture at 0°C for 10 min, it was filtered into a flask that contained a solution of BHA (1.620 g, 9 mmol) in DME (30 mL). Colorless crystals were obtained (1.01 g; 93% as triethylammonium bromide).

In run 1, the contents of the flask were concentrated to a small volume (*ca.* 30 mL) under reduced pressure below 35°C. The concentrate in a stoppered flask was allowed to stand at 30°C for 30 min. The mixture was diluted with benzene (200 mL) and vigorously shaken with 50% Me_2NH (1 mL) for 15 min. The mixture was washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed in the manner described previously for the residue from run 1 of the decay of BHT-radical in the presence of BHA.

In run 2, 70% perchloric acid ($HClO_4$; 6 drops) were added to the contents of the flask before concentration. The concentrate was allowed to stand at 30°C for 10 min. The mixture, no longer containing QM as indicated by TLC, was poured into water and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. The oily residue was dissolved in petroleum ether and stored at –20°C. Filtration afforded a colorless crystalline mixture, which was sublimed at 83°C under reduced pressure (17 Torr). The sublimate (216 mg), obtained as colorless crystals, consisted exclusively of BHA. The light-yellow crystalline residue (679 mg) consisted exclusively of 2′,4-dihydroxy-3,3′,5-tri-*tert*-butyl-5′-methoxydiphenylmethane (Adduct 1). Recrystallization from diisopropyl ether provided pure Adduct 1 as colorless crystals, m.p. 105–107.5°C [lit. (3) m.p. 106–107°C]. The ^1H NMR and IR spectra agreed with those reported by Kurechi and Kato (3) for Adduct 1. The ^{13}C NMR signals appeared at δ 152.72, 152.42, 146.78, 138.06, 136.29, 128.24, 127.45, 124.67, 112.82, 111.96, 55.52, 37.35, 34.76, 34.30, 30.22, and 29.64. The petroleum ether filtrate was evaporated, and the residue was chromatographed on SiO_2 (150 g) with petroleum ether/benzene (5:1). The first fraction gave BE (81 mg, 6%). The second fraction gave a crystalline mixture (780 mg); recrystallization from petroleum ether yielded an additional amount of Adduct 1 (453 mg, 47% in total). The third fraction furnished 4,5′-dihydroxy-3,4′,5-tri-*tert*-butyl-2′-methoxydiphenylmethane (Adduct 2) (697 mg, 29%) as light-orange crystals. Recrystallization from hexane gave pure Adduct 2 as light-yellow crystals, m.p. 126–127°C. The ^1H NMR signals appeared at δ 7.03 (*s*, 2 H), 6.80 (*s*, 1 H), 6.31 (*s*, 1 H), 5.01 (*s*, 1 H, exchangeable with deuterim oxide), 4.34 (*s*, 1 H, exchangeable with deuterium oxide), 3.80 (*s*, 3 H), 3.77 (*s*, 2 H), 1.41 (*s*, 18 H), and 1.39 (*s*, 9 H). The ^{13}C NMR signals appeared at δ 151.75, 150.71, 147.54, 135.53, 133.91, 130.95, 128.97, 125.65, 118.12, 110.22, 56.16, 35.06, 34.55, 34.27, 30.34, and 29.61; IR absorptions appeared at 3620 and 3580 cm^{-1}. Analysis: Calculated for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61;

found: C, 78.30; H, 9.80. The final fraction, obtained by elution with dichloromethane, gave an additional amount of unreacted BHA (456 mg, 41% recovery in total). Duplication of the above experiments gave nearly identical results.

RESULTS AND DISCUSSION

Upon addition of a solution of an excess of BHA (2.5 mol equivalent) in DME, a solid of BHT-dimer dissolved quickly at 30°C. During the course of the dissolution, the mixture displayed a transient, light-green color due to a BHT-radical. The yellow color of the resulting homogeneous mixture suggested that the decay of the BHT-radical was complete (10). The solution was allowed to stand at 30°C for 30 min and treated with Me_2NH. This treatment rapidly and quantitatively converted QM, one of the products, as indicated by TLC, into BA. QM is a labile and reactive species, which can exist only in a relatively dilute solution. The products isolated after subsequent work-up were BHT, QM (obtained as BA), STBQ, BE, and BHA-dimer, and their yields are listed in Table 1 (run 1). STBQ is another quinone methide, but it was found to be practically stable to the Me_2NH treatment. The reaction in DME containing Et_3N also was conducted, and the results were compared (Table 1, run 2). The reaction without added Et_3N gave a higher yield of BE, whereas the reaction with the added base provided much greater quantities of BHT and BHA-dimer. STBQ was not obtained from run 2. More BHA was recovered from run 1 than from run 2. The marked difference in product distribution may be interpreted as follows (Scheme 1). BHA is reversibly dehydrogenated by the BHT-radical, which results in the formation of BHT and BHA-radical. This BHA-radical undergoes dimerization to afford an unstable *bis*(cyclohexadienone) intermediate (Prodimer). The dimerization of the BHA-radical is reversible, and Prodimer is recycled back to the parent phenoxy radical. Alternatively, Prodimer undergoes relatively slow and irreversible prototropic rearrangement, spontaneously giving BHA-dimer, and the rearrangement is greatly facilitated by Et_3N. Formation of *bis*(cyclohexadienone)s as the primary product is common in phenoxy radical C-C coupling (16,17). Most of these primary products cannot be isolated because they dissociate into the parent phenoxy radicals and/or undergo prototropic rearrangement. However, some of them are stable enough to allow isolation and structure determination (10,18). Rapid and quantitative base (such as Et_3N)-catalyzed prototropic rearrangement of 4-hydrocyclohexa-2,5-dienones into phenols has been confirmed (10,19). In the presence of Et_3N (run 2), therefore, the BHA-radical is consumed preferentially by the efficient transformation into BHA-dimer *via* Prodimer, and a large quantity of BHT is also obtained. In the absence of Et_3N (run 1), in contrast, the formation of BHA-dimer from the BHA-radical is slow, and the radical is consumed mainly by dehydrogenating the BHT, thus regenerating large quantities of BHA- and BHT-radical. BHT-radical can be irreversibly converted to QM by disproportionation (20) or hydrogen donation to BHA-radical (6,7). QM dimerizes to give a biradical, which can be degraded into STBQ and BE (11). Reversibility of the dimerization of QM recently has been proved (21). BE also can be formed from the biradical after hydrogen donation by BHA or BHT (20). A diphenyl ether type of dimer of BHA-radical is known (3,6), but it was not obtained from our runs.

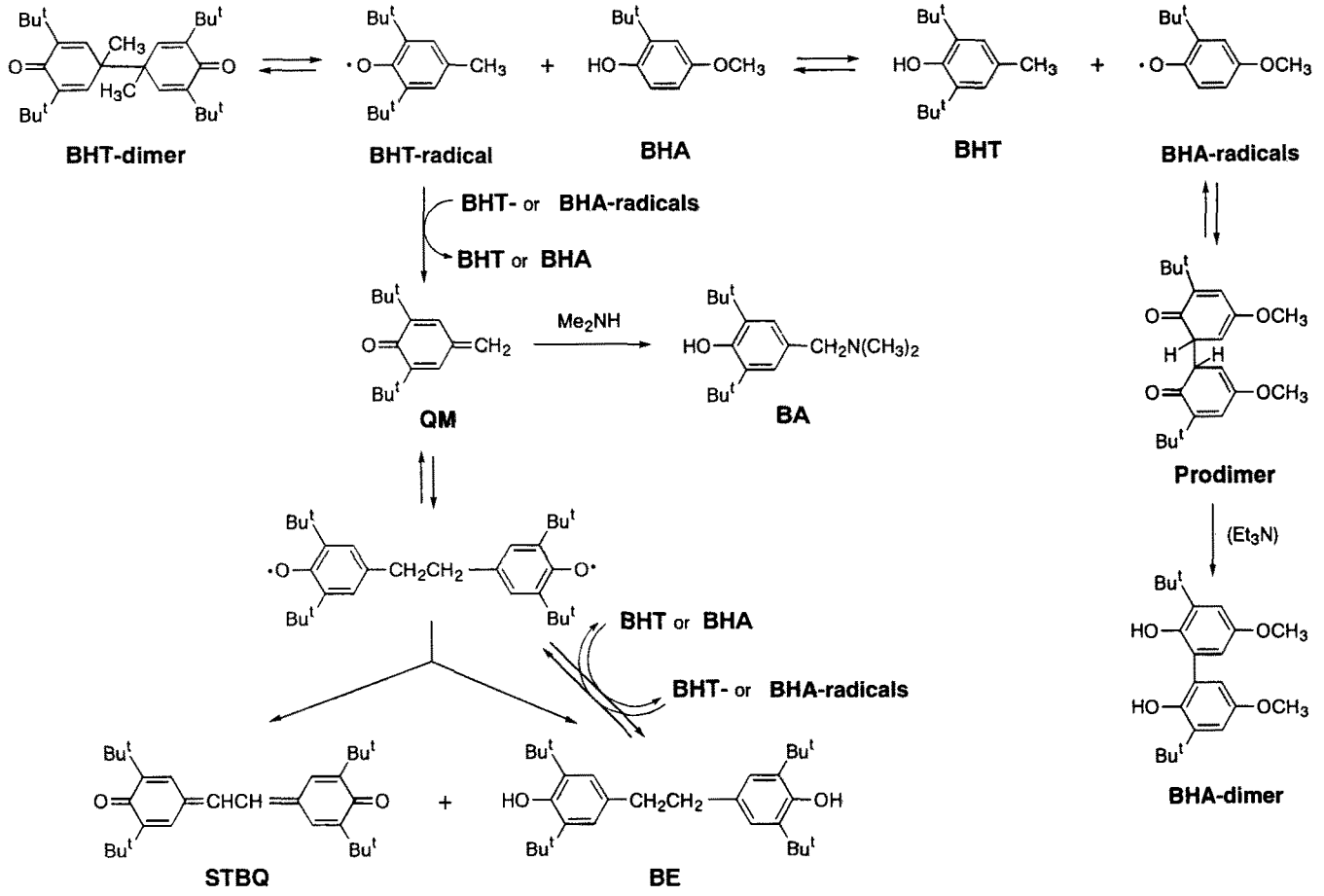
The results prove that abstraction of hydrogen from BHA by BHT-radicals is quite facile, although they provide little information regarding the rate of the reaction relative to the reverse reaction (hydrogen donation from BHT to the BHA-radical). It is emphasized that the faster consumption of BHT in the dehydrogenation of a mixture with BHA (described previously) can be ascribed at least partly to the reversibility of the dimerization of the BHA-radical to give Prodimer, and it is possible that the dehydrogenation of BHA with a BHT-radical has been underestimated in previous accounts of this fact.

Generation of a new phenolic product(s) acting as a potent antioxidant(s) is another explanation for the antioxidant synergism between BHA and BHT. In this context, we had expected to obtain a phenolic cyclohexadienone, the product of cross-coupling of the BHA- and BHT-radicals, from run 2, in particular (Equation 1). The BHT-radical can undergo analogous coupling with a number of phenoxy radicals (10). No indication, however, was obtained that the phenolic cyclohexa-

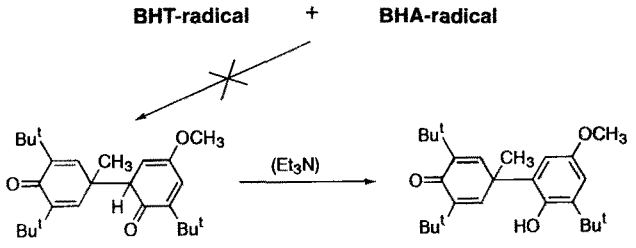
TABLE 1
Decay of 2,6-Di-*tert*-Butyl-4-Methylphenoxy Radical (BHT-radical) in the Presence of Butylated Hydroxyanisole (BHA)[a,b]

Run	Additive	Recovery of BHA (%)	Yield (%)				
			BHT[c]	QM[c,d]	STBQ[e]	BE[e]	BHA-dimer[e]
1	None	84	34	5	6	36	10
2	Et_3N	51	64	7	0	11	56

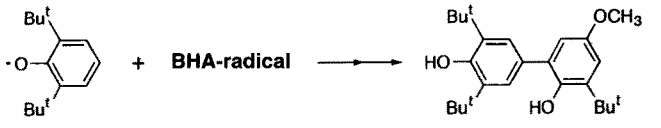
[a]See Scheme 1 for the structures of butylated hydroxytoluene (BHT)-radical, BHA, BHT-dimer, BHT, 2,6-di-*tert*-butyl-*p*-quinone methide (QM), 3,3′,5,5′-tetra-*tert*-butylstilbene-4,4′-quinone (STBQ), 1,2-*bis*(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane (BE), BHA-dimer, and *N,N*-dimethyl-3,5-di-*tert*-butyl-4-hydroxybenzylamine (BA).
[b]Conducted by using BHT-radical (6 mmol), generated by dissociation of BHT-dimer, and BHA (7.5 mmol).
[c](mol/mol BHT-radical) × 100.
[d]Isolated as BA.
[e](mol/mol BHT-radical) × 2 × 100.



SCHEME 1



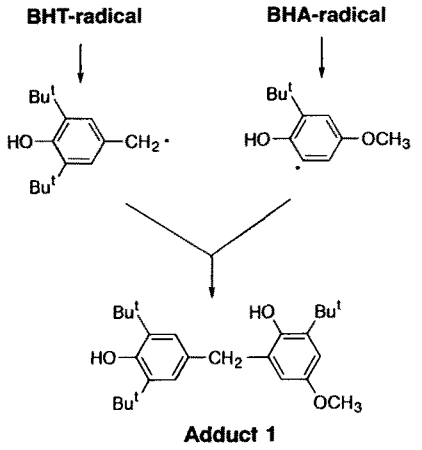
EQUATION 1



EQUATION 2

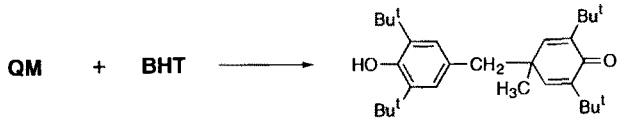
dienone or other products of coupling between the two radicals were formed in run 1 or run 2. Cross-coupling products have not been reported either from other reactions involving BHA- and BHT-radicals. It may, therefore, be concluded that BHA-radical and BHT-radical cannot couple with each other and that hydrogen transfer (yielding BHA and QM) is the only reaction between these radicals. It is, however, notable that the BHA-radical and 2,6-di-*tert*-butylphenoxy radical can undergo cross-coupling (22) (Equation 2).

Adduct 1 was also a possible phenolic product, but it was not obtained from our reactions. Adduct 1 has been isolated among other products by Kurechi and Kato (3) from photochemical cooxidation of BHA and BHT, and was shown to be an excellent antioxidant although, reportedly, the photochemical process was extremely inefficient, and the yield of Adduct 1 was low. Photochemical generation of BHA-radical and BHT-radical, their isomerization into a 2-hydroxyphenyl radical and a 4-hydroxybenzyl radical, respectively, and cross-coupling of the resulting radicals have been assumed to account for the formation of Adduct 1 (Equation 3). The mechanism, however, appeared to be questionable because such radical–radical isomerizations have not been generally accepted, although the isomerization of BHT-radical into the benzyl radical was once considered to account for formation of BE by oxidative dimerization of BHT (15). It was assumed that Adduct 1 is the product of the addition of BHA to QM. To test this assumption, QM was generated by treating 3,5-di-*tert*-butyl-4-hydroxybenzyl bromide with Et_3N, and the mixture was allowed to react in DME in the presence of BHA. After 30 min, the reaction at 30°C was interrupted by treatment with Me_2NH. As Table 2 (run 1) shows, decay of QM



EQUATION 3

was incomplete, and Adduct 1 was not produced. The major products were the dimeric products (STBQ and BE) from QM. Lack of formation of Adduct 1 was not unexpected because, as described previously, the reaction of BHT-radical in the presence of BHA, involving generation of QM, did not result in Adduct 1. The reaction of QM and BHA was drastically altered when it was carried out in the presence of a catalytic amount of $HClO_4$ (Table 2, run 2). The decay of QM was completed rapidly. Only a small quantity of BE was formed, and STBQ was no longer obtained. Instead, Adduct 1 was obtained as the principal product. The physical and spectral properties of the product were in full accordance with those reported for Adduct 1. In addition, a new phenolic substance was isolated which by microanalysis seemed to be isomeric with Adduct 1. The resemblance of the ^1H NMR spectral pattern of the new product to that of Adduct 1 indicated that it was a positional isomer of Adduct 1. Thus, the spectrum suggested the presence of two equivalent aromatic protons (δ 7.03), three *tert*-butyl groups (two of which are equivalent) (δ 1.41 and 1.39), two hydroxyl groups (δ 5.01 and 4.34), a methoxyl group bound to an aromatic ring (δ 3.80), and a methylene group linking aromatic rings (δ 3.77). In the aromatic region, two signals were also observed at δ 6.80 (*s*; 1 H) and 6.31 (*s*; 1 H). Little or no coupling between these protons suggested that they were *para*-coupled. Hence, the



EQUATION 4

product was assigned the structure of 4,5′-dihydroxy-3,4′,5-tri-*tert*-butyl-2′-methoxydiphenylmethane (Adduct 2). The ^{13}C NMR and IR spectra also were compatible with the given structure (see the Experimental Procedures section). The total yield of Adduct 1 and Adduct 2 amounted to 76% of QM employed. The formation of Adduct 1 and Adduct 2 may be the result of protonation of QM and electrophilic attack by the resulting benzyl cation on BHA in the positions activated by the hydroxyl and the methoxyl groups (Scheme 2). The addition of BHA to QM formally resembles that of BHT to QM, giving a phenolic dienone, but the reaction mechanisms may be different because the latter addition is not catalyzed by acid but is accelerated in polar solvents (11) (Equation 4). The photochemical formation of Adduct 1 from a mixture of BHA and BHT may be similarly ascribed to the addition of BHA to QM, catalyzed by an acidic substance, contaminating the starting materials, or by an acidic product. The possibility may also be considered that the addition can proceed slowly without a catalyst or is photochemically induced.

As shown here, the reactions involving BHA, BHT, and the phenoxy radicals derived from them can be affected by acid or base. This may suggest that the synergistic effect of BHA and BHT can be significantly altered by adding acid or base as a third component to the antioxidation system.

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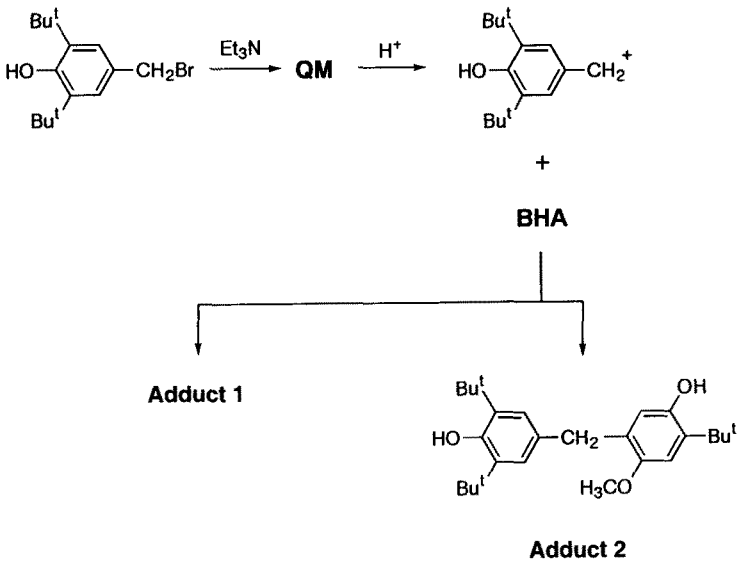
TABLE 2
Reaction of QM with BHA[a,b]

Run	Additive	Time (min)	Recovery of QM[c] (%)	Recovery of BHA (%)	Yield (%) STBQ[d]	BE[d]	BHA-dimer[d]	Adduct 1[e]	Adduct 2[e]
1	None	30	24	89	24	30	7	0	0
2	70% $HClO_4$	10	0	41	0	6	trace	47	29

[a]See Scheme 1 or Scheme 2 for the structures of QM, BHA, STBQ, BE, BHA-dimer, Adduct 1, Adduct 2, and BA. Abbreviations as in Table 1.
[b]Conducted by using QM (6 mmol), generated by treating 3,5-di-*tert*-butyl-4-hydroxybenzyl bromide with triethylamine, and BHA (9 mmol).
[c]Isolated as BA.
[d](mol/mol QM) × 2 × 100.
[e](mol/mol QM) × 100.



SCHEME 2

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