7MeBA could arise either from the conformational differences of the adducts formed on DNA, from the lesser selectivity of the dihydrodiol epoxides of DMBA versus 7MeBA in reactions with DNA, from differences in extent of DNA modification, from difficulties in repairing DMBA–DNA damage,[34] or any combination of these differences associated with methyl substitution in the bay region.

Registry No. **1a**, 133645-02-0; **1a** + (*R*)Gt, 133551-46-9; **1a** + (*S*)Gt, 133646-13-6; **1a** + (*S*)Gc, 133645-03-1; **1a** + (*S*)At, 133551-47-0; **1a** + (*R*)At, 133645-04-2; **1a** + (*S*)Ac, 133645-05-3; **1a** + (R)Ac, 133645-06-4; **1a** + (*R*)Gc, 133645-07-5; **1b**, 130856-45-0; **1b** + (*R*)Gc, 133551-48-1; **1b** + (*S*) Gc, 133645-08-6; **1b** + (*R*)Gt, 133645-09-7; **1b** + (*S*)Gt, 133645-10-0; **1b** + (*S*)Ac, 133551-49-2; **1b** + (*R*)Ac, 133645-11-1; **1b** + (*S*)At, 133694-83-4; **1b** + (*R*)At, 133645-12-2; dAMP, 653-63-4; dGMP, 902-04-5.

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Structure–Activity Relationship in the Quenching Reaction of Singlet Oxygen by Tocopherol (Vitamin E) Derivatives and Related Phenols. Finding of Linear Correlation between the Rates of Quenching of Singlet Oxygen and Scavenging of Peroxyl and Phenoxyl Radicals in Solution

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The rate of quenching of $^1O_2$ by 17 kinds of tocopherol derivatives, including α-, β-, γ-, and δ-tocopherols, and five structurally related phenols has been measured spectrophotometrically in ethanol at 35 °C. The result indicates that the overall rate constants, k_Q ($k_Q = k_q + k_r$, physical quenching + chemical reaction), increase as the total electron-donating capacity of the alkyl substituents on the aromatic ring increases. The log of the rate constants, k_Q, was found to correlate with their half-peak oxidation potentials, $E_{P/2}$; the tocopherols that have smaller $E_{P/2}$ values show higher reactivities. Tocopherols 11 and 12 with a five-membered heterocyclic ring were found to be 1.73 and 1.21 times more active than α-tocopherol, respectively, which has the highest antioxidant activity among natural tocopherols and related phenols. Two benzodipyran derivatives 16 and 17 having no OH group were also found to be 1.63 and 1.33 times more active than the α-tocopherol. The quenching rates, k_Q, observed were found to be related linearly to the rates k_1 and k_3 of scavenging of peroxyl and phenoxyl radicals by these tocopherols, respectively, reported previously by Burton et al. and by Mukai et al., except for the benzodipyran derivatives. The result indicates that the relative reactivities, that is, relative antioxidant activities of phenolic antioxidants in homogeneous solution, do not depend on singlet oxygen ($^1O_2$), peroxyl radical (LOO•), and substituted phenoxyl radical (PhO•) reacted. Further, the result indicates that the properties of the transition states in the singlet oxygen quenching and free radical scavenging reactions by tocopherol are similar, suggesting a charge-transfer intermediate.

Introduction

Vitamin E compounds (α-, β-, γ-, and δ-tocopherols) are well-known as scavengers of active free radicals (LOO•, LO•, and HO•) generated in biological systems.[1,2] Recently, Burton et al.[3] have reported absolute second-order rate constants, k_1, for the reaction of α-, β-, γ-, and δ-tocopherols and related phenols with poly(styrylperoxyl)peroxyl radicals using the inhibited autoxidation of styrene method (reaction 1).

$$\mathrm{LOO\bullet + Toc} \xrightarrow{k_1} \mathrm{LOOH + Toc\bullet} \qquad (1)$$

It was observed that the second-order rate constants, k_1, of tocopherols decrease in the order of $\alpha > \beta \approx \gamma > \delta$-tocopherol. We reported that the absolute reactivities of tocopherols to LOO• increase as the total electron-donating capacity of the alkyl substituents at the aromatic ring increases.[4,5] For the tocopherols log k_1 was found to correlate roughly with the sum of Brown's σ^+ constants ($\Sigma\sigma^+$). Further, the log of the second-order rate constants, k_1, obtained for the tocopherols was found to correlate with their half-peak oxidation potentials, $E_{P/2}$; the tocopherols which have smaller $E_{P/2}$ values show higher reactivities.

On the other hand, tocopherols can also act as an efficient scavenger of singlet oxygen ($^1O_2$).[6-8] It was shown that α-tocopherol scavenges $^1O_2$ by a combination of physical quenching (k_q) and chemical reaction (chemical quenching, k_r). Because $k_q \gg k_r$, the quenching process is almost entirely "physical"—that is, α-tocopherol deactivates ~120 $^1O_2$ molecules before being destroyed by chemical reaction[6] (reaction 2).

$$^1O_2 + \mathrm{Toc} \xrightarrow{k_Q} \text{physical quenching + chemical reaction} \qquad (2)$$

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† Department of Chemistry.

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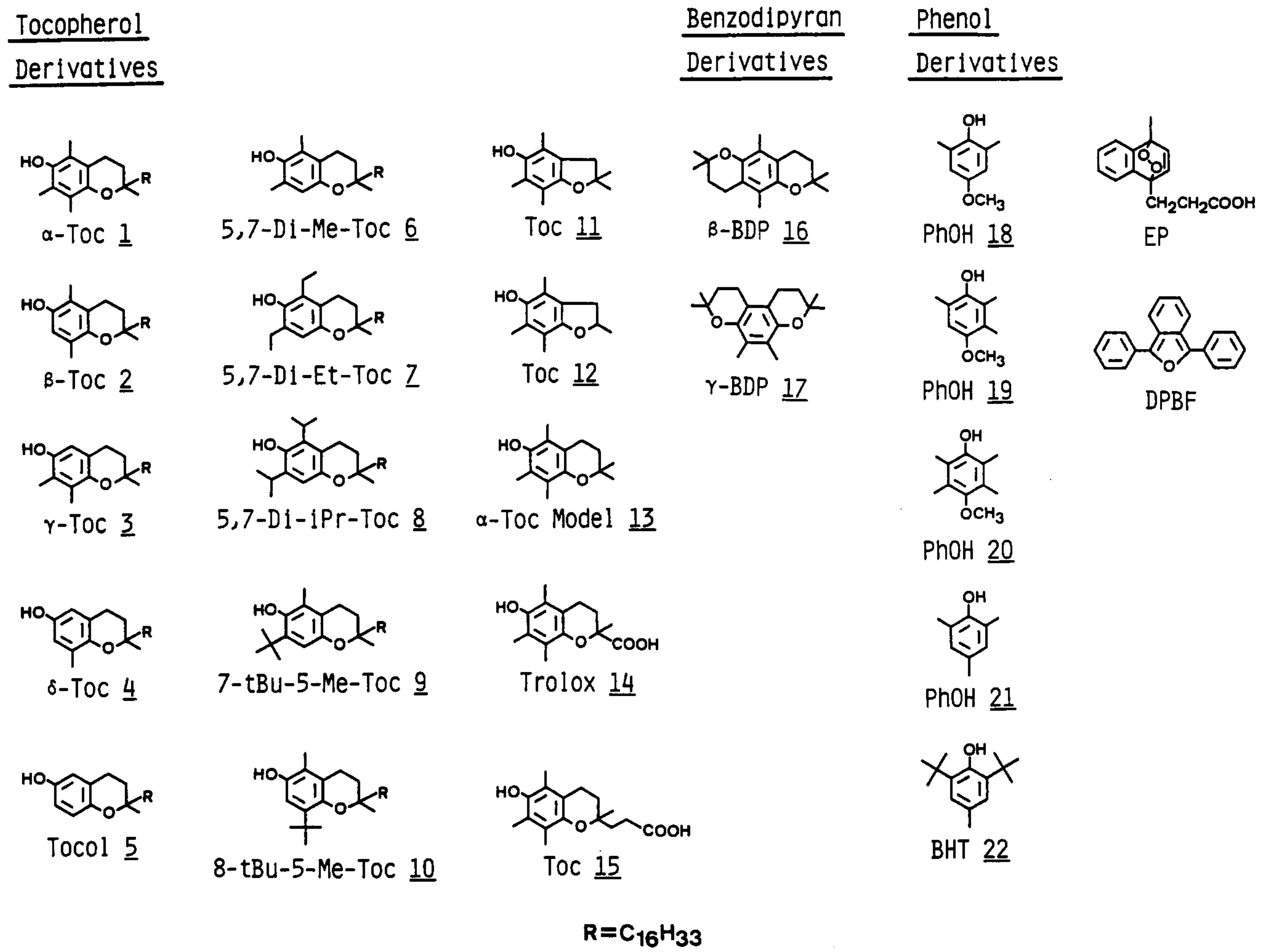

Figure 1. Molecular structures of tocopherols 1–15, benzodipyrans 16 and 17, phenols 18–22, EP, and DPBF.

Grams and Eskins[9] have studied the chemical reaction of $^1O_2$ with α-, β-, γ-, and δ-tocopherols. They demonstrated that the reactivities of tocopherols toward singlet oxygen correlate well with their biological activity and suggested that one of the functions of vitamin E might be to protect membrane lipids from oxidative damage by $^1O_2$. Yamauchi and Matsushita[10] have reported absolute second-order rate constants for the physical quenching (k_q) and chemical reaction (k_r) of α-, γ-, and δ-tocopherols with $^1O_2$, produced by methylene blue photosensitization in ethanol. They have found that the overall rate constants, k_Q, ($k_Q = k_q + k_r$, physical quenching + chemical reaction) decrease in the order $\alpha > \gamma > \delta$-tocopherol. However, systematic kinetic studies of the quenching reaction of singlet oxygen by tocopherols have not been performed.

Recently, many kinds of new tocopherol derivatives have been synthesized in our laboratory, and second-order rate constants, k_3, for H-atom abstraction by substituted phenoxyl radicals (PhO•) (2,6-di-*tert*-butyl-4-(4-methoxyphenyl)phenoxyl) have been measured spectrophotometrically by the stopped-flow method as a model reaction of tocopherols with unstable free radicals (LOO•, LO•, and HO•) in biological systems (reaction 3).[4,5,11-13]

$$\mathrm{PhO\bullet + Toc \xrightarrow{k_3} PhOH + Toc\bullet} \qquad (3)$$

The relative k_3 values ($\alpha:\beta:\gamma:\delta$ = 100:44:47:20) obtained by the stopped-flow technique are in good agreement with the k_1 values (100:41:44:14) obtained by the inhibited autoxidation of the styrene method, although the absolute values are ~600 times smaller than those for the reaction of tocopherols with the poly(styrylperoxyl)peroxyl radical in chlorobenzene.[11] The result suggests that the relative reactivities, that is, relative antioxidant activities of tocopherols in homogeneous solution, do not depend on the kinds of radicals (substituted phenoxyl and peroxyl radicals) used, even though the absolute rates are considerably different. For the tocopherol derivatives log k_3 was also found to correlate with their half-peak oxidation potentials, $E_{P/2}$.

In the present work, the rate (k_Q) of quenching of singlet oxygen ($^1O_2$) by 17 kinds of tocopherol derivatives, including α-, β-, γ-, and δ-tocopherol, and five structurally related phenols (see Figure 1) has been measured in ethanol at 35 °C and compared to those (k_1 and k_3) of scavenging of peroxyl and phenoxyl radicals in tocopherols and related phenols.[3,5,13]

Experimental Section

Determination of Quenching Rate Constants. Singlet oxygen ($^1O_2$) was generated by the thermal decomposition of the 3-(1,4-epidioxy-4-methyl-1,4-dihydro-1-naphthyl)propionic acid (EP) (see Figure 1).[14,15] 2,5-Diphenyl-3,4-benzofuran (DPBF)

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Table I. Second-Order Rate Constants (k_Q, k_3, and k_1), Relative Rate Constants (k_Q(Toc)/k_Q(α-Toc)), and Half-Peak Oxidation Potentials ($E_{P/2}$)

compds	this work 10^{-8} k_Q (M^{-1} s^{-1})	K_Q(Toc)/ k_Q(α-Toc)	Mukai et al.[5,13] $10^{-3}k_3$ (M^{-1} s^{-1})	Burton et al.[3] 10^{-6} k_1 (M^{-1} s^{-1})	$E_{P/2}$ (mV vs SCE)
		Tocopherol Derivatives			
α-tocopherol 1	2.06	1.00	5.12	3.20	860
β-tocopherol 2	1.53	0.74	2.24	1.30	920
γ-tocopherol 3	1.38	0.67	2.42	1.40	930
δ-tocopherol 4	0.53	0.26	1.00	0.44	990
tocol 5	0.28	0.14	0.56		1050
5,7-Di-Me-Toc 6	0.97	0.47	2.39	1.80	890
5,7-Di-Et-Toc 7	0.95	0.46	2.48		890
5,7-Di-iPr-Toc 8	1.13	0.55	2.51		890
7-tBu-5-Me-Toc 9	1.22	0.59	2.97		880
8-tBu-5-Me-Toc 10	1.63	0.79	3.62		970
Toc 11	3.57	1.73	6.99	5.70	810
Toc 12	2.50	1.21	6.17	5.40	840
α-Toc model 13	1.96	0.95	4.20	3.80	870
Trolox 14	0.81	0.39	2.23	1.10	890
Toc 15	1.80	0.87	3.10	3.70	850
		Benzodipyran Derivatives			
β-BDP 16	3.35	1.63			880
γ-BDP 17	2.75	1.33			890
		Phenol Derivatives			
PhOH 18	0.25	0.12	0.48	0.94	970
PhOH 19	0.68	0.33	0.96	1.30	940
PhOH 20	0.14	0.068	0.035	0.39	1070
PhOH 21	0.038	0.018	0.017	0.085	1260
BHT 22	0.034	0.017	0.035	0.014	1240

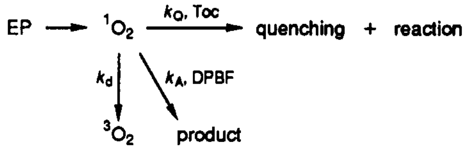
was used as standard compound. The total quenching rate constants k_Q (= k_q + k_r) for the reaction of $^1O_2$ with tocopherols and related phenols were determined by Young's technique[16] (see Scheme I). Solutions containing EP (4.6×10^{-4} M), DPBF (4.30×10^{-5} M), and various amounts of tocopherol (0–30 mM) in ethanol were reacted at 35 °C. The disappearance of DPBF was measured at 411 nm. The details of experiments are reported in previous papers.[14,15]

Materials. *d*-α-, β-, γ-, δ-Tocopherols and tocopherol 15 were kindly supplied by Eisai Co., Ltd. Tocopherol derivatives 5–10 (tocol 5, 5,7-dimethyltocol 6, 5,7-diethyltocol 7, 5,7-diisopropyltocol 8, 7-*tert*-butyl-5-methyltocol 9, and 8-*tert*-butyl-5-methyltocol 10) were synthesized by condensation of isophytol with the corresponding alkylhydroquinone, as reported in a previous paper.[5] α-Tocopherol model 13 was prepared according to the method of Nilsson et al.[17] 2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (tocopherol 11) was prepared according to the method of Burton et al.[3] Benzo[1,2-*b*:4,5-*b*′]dipyran (β-BDP 16) and benzo[1,2-*b*:4,3-*b*′]dipyran (γ-BDP 17) compounds were synthesized by condensation of 2-methyl-3-buten-2-ol to the corresponding alkylhydroquinone, according to the method of Nilsson et al.[17]

Phenol derivatives 18–20 were prepared according to the method of Ramirez et al.[18] Trolox 14, 2,4,6-trimethylphenol (21), and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT; 22) are commercially available. 3-(1,4-Epidioxy-4-methyl-1,4-dihydro-1-naphthyl)propionic acid (EP) was prepared by the published procedure.[14] 2,5-Diphenyl-3,4-benzofuran (DPBF) is commercially available.

2,3-Dihydro-5-hydroxy-2,4,6,7-tetramethylbenzofuran (Tocopherol 12). Tocopherol 12 was prepared by refluxing the trimethylhydroquinone and allyl chloride in dioxane with stannous chloride and concentrated HCl, according to a procedure similar to that used by Fujisawa et al.[19] to prepare vitamin K_1–chromanol: mp 137.5–138.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.45 (d, 3 H, J = 6.1 Hz, 2-CH_3), 2.11 (s, 6 H, 4- and 7-CH_3), 2.13 (s, 3 H, 6-CH_3), 2.71 (dd, 1 H, J = 15.3, 8.0 Hz, 3-H), 3.21 (dd, 1 H, J = 15.3, 8.8 Hz, 3-H), 4.18 (s, 1 H, 5-OH), 4.81–4.89 (m, 1 H, 2-H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.36; H, 8.43.

Scheme I



Results and Discussion

Second-Order Rate Constant, k_Q, for the Reaction of $^1O_2$ with Tocopherols and Related Phenols. The overall rate constants k_Q (=k_q + k_r) for the reaction of $^1O_2$ with tocopherols and related phenols were determined in ethanol by eq 4 derived from the steady-state treatment

$$S_0/S_s = 1 + [(k_q + k_r)/k_d][\mathrm{Toc}] \qquad (4)$$

of Scheme I[14-16] where S_0 and S_s are slopes of the first-order plots of disappearance of the $^1O_2$ acceptor, DPBF, in the absence and presence of tocopherol, respectively. k_d is the rate of deactivation of $^1O_2$ in ethanol. S_0/S_s vs [Toc] plots for α-, β-, γ-, and δ-tocopherols are shown in Figure 2. The overall rate constants (k_Q) were calculated by using the value of k_d in ethanol ($k_d = 8.3 \times 10^4$ s^{-1}) reported by Merkel and Kearns.[20]

Similarly, tocopherol derivatives 5–17 and related phenols 18–22 were reacted with the $^1O_2$ in ethanol. The k_Q values obtained are summarized in Table I. Data are means of four or five experiments. For each tocopherol derivative, experimental error in the k_Q value was ±8% at maximum.

As described in a previous section, Yamauchi and Matsushita[10] have reported absolute second-order rate constants for the physical quenching (k_q) and chemical reaction (k_r) of α-, γ-, and δ-tocopherols with $^1O_2$, produced by methylene blue photosensitization in ethanol (reaction 2). The $^1O_2$ quenching rate constants, k_q, for α-, γ-, and

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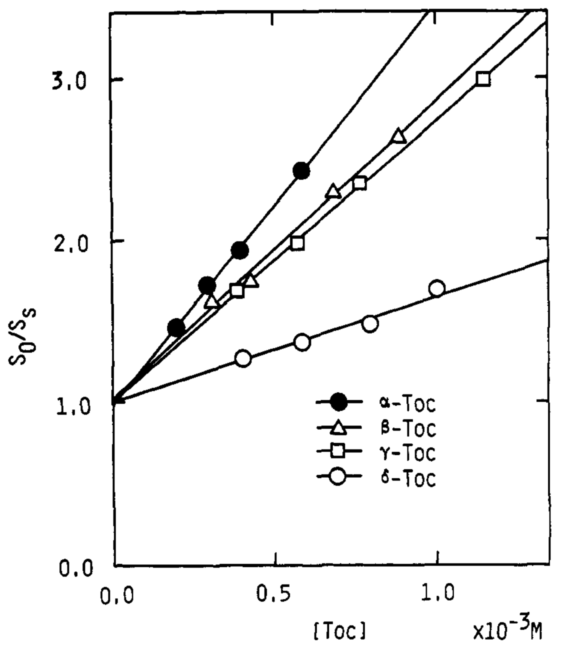

Figure 2. Plot of S_0/S_S vs concentrations of α-, β-, γ-, and δ-tocopherols.

δ-tocopherols in ethanol were estimated to be 2.6 × 10^8, 1.8 × 10^8, and 1.0 × 10^8 M^{-1} s^{-1}, respectively. And the rate constants, k_r, for the chemical reaction between each tocopherol and $^1O_2$ were 6.6 × 10^6, 2.6 × 10^6, and 0.7 × 10^6 M^{-1} s^{-1} for α-, γ-, and δ-tocopherols, respectively, in ethanol at 20 °C. Subsequently, the overall rate constants, k_Q ($k_Q = k_q + k_r$), obtained are 2.67 × 10^8 (α-Toc), 1.83 × 10^8 (γ-Toc), and 1.01 × 10^8 (δ-Toc) M^{-1} s^{-1}. In the present work, we have determined the overall rate constants, k_Q, for the reaction of α-, β-, γ-, and δ-tocopherols with $^1O_2$ generated by the thermal decomposition of the naphthalene 1,4-*endo*-peroxide in ethanol using a spectrophotometer. The relative k_Q values (α:γ:δ = 100:67:26), that is, relative antioxidant activities of α-, γ-, and δ-tocopherols, obtained by the present work are in agreement with those (100:69:38) reported by Yamauchi and Matsushita, although the absolute k_Q values are 23–47% smaller than those for the reaction of corresponding tocopherols with the $^1O_2$ produced by methylene blue photosensitization.

When the second-order rate constants observed for 5,7-dimethyltocol **6** having two methyl groups at ortho positions are compared with that of α-tocopherol, the former is only ~47% as reactive as the latter. Further, β- and γ-tocopherols are 74 and 67% as reactive as α-tocopherol, respectively, whereas δ-tocopherol is only ca. 26% as reactive as α-tocopherol and tocol **5** is only ca. 14% as reactive as α-tocopherol. On the other hand, the rate constants of tocopherol compounds **6–9** having two alkyl substituents at the ortho position of the OH group are similar to each other, suggesting that the effect of steric hindrance on the reaction rate is small. The result indicates that the quenching rate, that is, the antioxidant activity of these tocopherols, varies depending on the number of alkyl substituents. Consequently, we can expect that the quenching rate of these tocopherol compounds relates to the total electron-donating character of the alkyl group substituents on the aromatic ring.

The results listed in Table I demonstrate that two tocopherols **11** and **12** with a five-membered heterocyclic ring are 1.73 and 1.21 times as reactive as α-tocopherol, which has the highest antioxidant activity among natural tocopherols. Two benzodipyran compounds **16** and **17** having no OH group were also found to be 1.63 and 1.33 times more active than the α-tocopherol, respectively. However, tocopherols **14** and **15** and phenol derivatives **18–22** showed less reactivity than α-tocopherol. Therefore, tocopherol **11** with a five-membered heterocyclic ring has the highest antioxidant activity among phenolic antioxidants including natural tocopherols, tocopherol derivatives, and related phenols in solution.

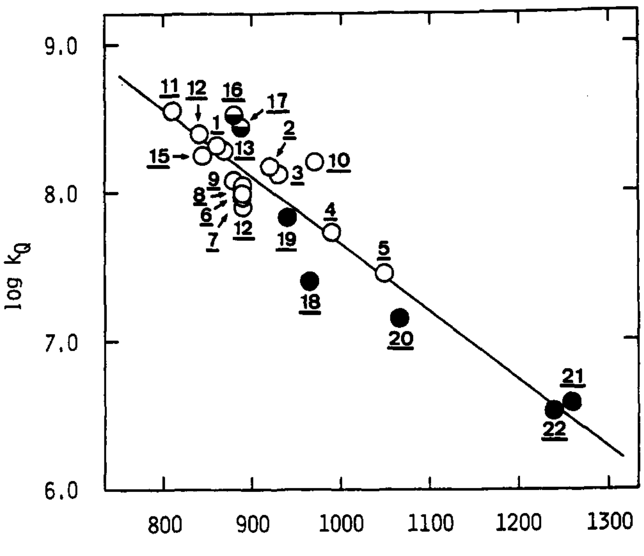

Figure 3. Plot of log k_Q vs $E_{P/2}$ for tocopherols **1–15** (○), benzodipyrans **16** and **17** (◒), and phenols **18–22** (●).

Correlation between log k_Q and $E_{P/2}$. Measurements of half-peak oxidation potential, $E_{P/2}$, of tocopherols **1–11** have been reported in previous papers.[5,13] Similarly, half-peak oxidation potentials have been measured for tocopherols **12–15**, two BDP compounds **16** and **17**, and related phenols **18–22** using cyclic voltammetry. These values are listed in Table I. The values of log k_Q for tocopherols and related compounds have been plotted against $E_{P/2}$. As shown in Figure 3, a plot of log k_Q vs $E_{P/2}$ is linear over most of the range with a slope of −4.5 V^{-1} (correlation coefficient = −0.94). The tocopherols that have smaller $E_{P/2}$ values show higher reactivities.

Thomas and Foote[21] have extensively studied the reaction of $^1O_2$ with alkyl-substituted phenols. They have found that para-substituted 2,6-di-*tert*-butylphenols show a linear correlation between the log of the total rate of $^1O_2$ removal and their half-peak oxidation potential, $E_{P/2}$. Saito et al.[14,15] and Thomas et al.[21] suggested that the most plausible scheme is a charge-transfer reaction between $^1O_2$ and phenol, leading to products by means of superoxide and phenol radical cation. In the present work, the log of the second-order rate constants, k_Q, obtained for tocopherols and related phenols was found to correlate with their half-peak oxidation potentials, $E_{P/2}$. These facts suggest that the transition state in the earlier $^1O_2$ quenching reaction by tocopherols has the property of the charge-transfer intermediate.

Linear Correlation between the Rates of Quenching of Singlet Oxygen and Scavenging of Peroxyl and Phenoxyl Radicals in Solution. Recently, we have reported second-order rate constants, k_3, for the reaction of tocopherol derivatives **1–11** with a substituted phenoxyl radical (PhO•) in ethanol using a stopped-flow spectrophotometer (reaction 3).[5,11-13] Similarly, we have measured the rate constants, k_3, for the reaction of tocopherols **12–15**,

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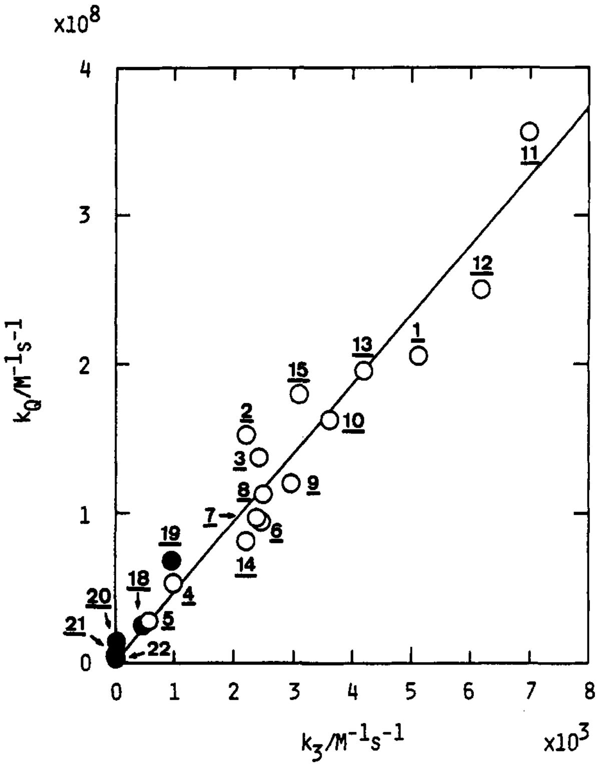

Figure 4. Plot of k_Q vs k_3 for tocopherols 1–15 (○) and phenols 18–22 (●).

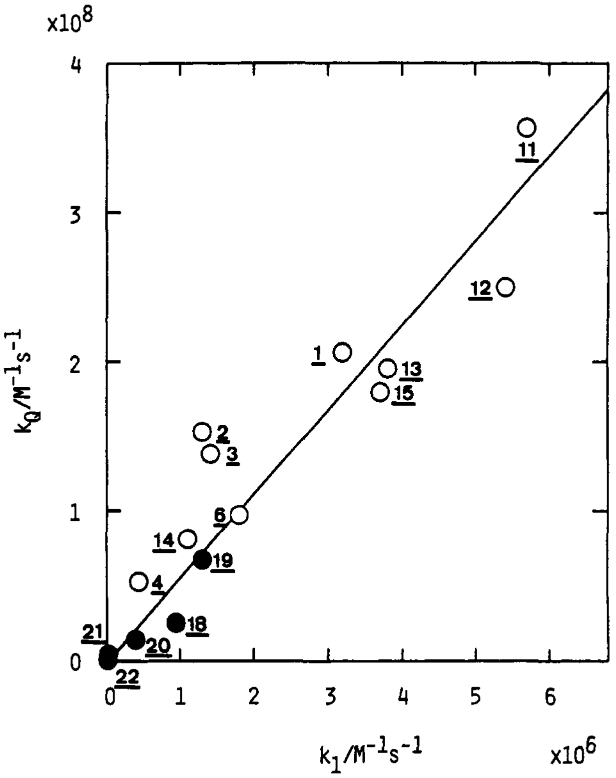

Figure 5. Plot of k_Q vs k_1 for tocopherols (○) and phenols (●).

BDP compounds 16 and 17, and related phenols 18–22 with PhO• in ethanol at 25.0 °C. The rate constants, k_3, obtained are summarized in Table I. As expected, BDP 16 and 17 having no OH group did not react with PhO•, although these compounds show very high activity for the quenching of $^1O_2$. For the tocopherol derivatives 1–15 and related phenols 18–22, log k_3 was found to correlate with their half-peak oxidation potentials, $E_{P/2}$ (correlation coefficient = −0.95).[4,5] As described in a previous section, Burton et al.[3] have reported the k_1 values for the reaction of α-, β-, γ-, and δ-tocopherols and related phenols with peroxyl radical (reaction 1). These values are also listed in Table I. A plot of log k_1 vs $E_{P/2}$ is also linear over most of the range with a slope of −5.0 V^{-1} (correlation coefficient = −0.96).[4]

In the present work, we have found that the log of the quenching rates of $^1O_2$ by 15 kinds of tocopherol derivatives and five structurally related phenols correlates with their half-peak oxidation potential, $E_{P/2}$. Therefore, the values of k_Q have been plotted against k_1 and k_3, respectively. As shown in Figures 4 and 5, the k_Q values were found to correlate linearly with the k_1 values (correlation coefficient = 0.94) and the k_3 values (correlation coefficient = 0.97), respectively. The ratios of k_Q to k_1 and k_Q to k_3 were estimated to be 56 and 4.6 × 10^4 from the gradient in Figures 4 and 5, respectively (eqs 5 and 6). The result

$$k_Q = 56k_1 \tag{5}$$

$$k_Q = (4.6 \times 10^4)k_3 \tag{6}$$

suggests that the relative reactivities, that is, relative antioxidant activities of phenolic antioxidants in homogeneous solution, do not depend on whether singlet oxygen ($^1O_2$), peroxyl radical (LOO•), or substituted phenoxyl radical (PhO•) is the reactive species. Consequently, if we could determine the quenching rate k_Q of $^1O_2$ by phenolic antioxidants in solution, we can presume the scavenging rates k_1 and k_3 of free radicals using eqs 5 and 6 and vice versa.

As described in a previous section, it was suggested that the transition state in the $^1O_2$ quenching reaction by tocopherols and related phenols has the property of the charge-transfer intermediate.[14,15,21] Further, the rate of quenching of singlet oxygen by phenolic antioxidants was found to correlate with those of scavenging of peroxyl and phenoxyl radicals in solution, respectively. These facts indicate that the properties of the transition states in the above singlet oxygen quenching and free-radical scavenging reactions by phenolic antioxidants are similar to each other, suggesting charge-transfer intermediate.

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