Synthesis and Antioxidant Activity of 4*H*-1,3-Benzodioxin-6-ol Derivatives: New Vitamin E Analogs

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4*H*-1,3-Benzodioxin-6-ol (HBD) derivatives **1**—**5**, new tocopherol (Vitamin E) analogs, have been synthesized by condensation of acetaldehyde with the corresponding hydroquinone. For each HBD derivative except for **4**, two diastereomeric isomers were produced. These stereoisomers were separated by column chromatography and the configuration of each isomer was identified by two dimensional NMR techniques and ESR measurements of the HBD radicals. The second-order rate constants, k_s, for the reaction of 9 kinds of HBD derivatives with substituted phenoxyl radical (PhO·) in ethanol have been measured with a stopped-flow spectrophotometer. These HBD derivatives reacted at rates that were only about 5—20% of those observed with the corresponding tocopherols. The logs of the second-order rate constants, k_s, obtained for HBD derivatives were found to correlate with their peak oxidation potentials, E_p. Electron spin resonance measurements were done for HBD radicals in toluene, and the proton hyperfine coupling constants, a_i^H, and g_{iso}-values were determined. The log of the rate constants, k_s, was also found to correlate with the sum of the hyperfine coupling constants ($a_5^H+a_7^H$) at 5- and 7-positions of both HBD radicals and tocopheryloxyl radicals, that is, the unpaired π-spin densities ($\rho_5+\rho_7$) at the two ortho carbon atoms.

It is well-known that Vitamin E (α-, β-, γ-, δ-tocopherols, Toc) is localized in biomembranes and scavenges active free radicals (LOO·, LO·, and HO·) generated in biological systems.[1,2] The scavenging actions of the above free radical by Vitamin E have been ascribed to the initial oxidation by an oxyl radical of the phenolic hydroxyl group, producing a tocopheryloxyl radical (Toc·) which in turn combines with another oxyl radical (Fig. 1). In fact, Yamauchi et al.[3] have succeeded in isolating the reaction products of the α-tocopheryloxyl radical with peroxyl radicals of methyl linoleate (Toc-LOO), by using high-performance liquid chromatography.

$$\text{LOO}\cdot + \text{Toc} \xrightarrow{k_1} \text{LOOH} + \text{Toc}\cdot \quad (1)$$

$$\text{LOO}\cdot + \text{Toc}\cdot \longrightarrow \text{LOO-Toc} \quad (2)$$

Mukai et al.[4,5] have measured the second-order rate constants, k_s, for the reaction of α-, β-, γ-, and δ-tocopherols and tocol with 2,6-di-*t*-butyl-4-(4-methoxyphenyl)phenoxyl radical (abbreviated to substituted phenoxyl (PhO·)) (see Fig. 2) in ethanol solution, using a stopped-flow spectrophotometer. It was observed that the rate constants, k_s, or tocopherols decrease in the order of $\alpha>\beta\approx\gamma>\delta$-tocopherol>tocol.

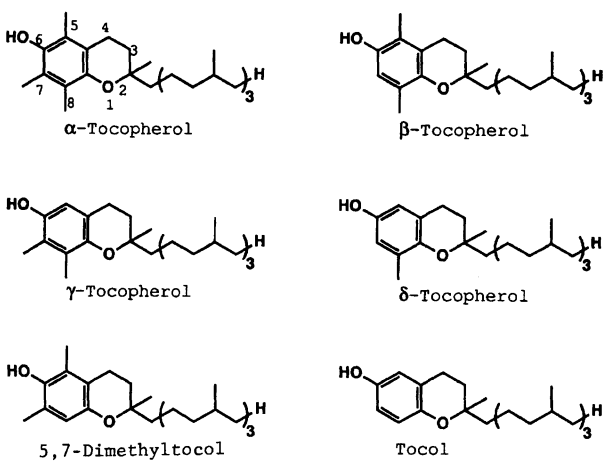

Fig. 1. Molecular structures of tocopherols.

$$\text{PhO}\cdot + \text{Toc} \xrightarrow{k_s} \text{PhOH} + \text{Toc}\cdot \quad (3)$$

The result indicates that the k_s values increase as the total electron-donating capacity of the methyl substituents on the aromatic ring increases. Log k_s obtained for Toc's was found to correlate with the sum of the Hammett's σ constants, $\sum\sigma$, the sum of the Brown's σ^+ constants, $\sum\sigma^+$, and their peak oxidation potentials, E_p; the tocopherols that have smaller E_p values show higher reactivities.[5—7] The Vitamin K_1-chromanol and K_1-chromenol were found to be 6.9 and 4.5 times more active than the α-tocopherol, respectively; that is, the Vitamin K_1-chromanol and K_1-chromenol have the highest antioxidant activity among phenolic antioxidants including natural tocopherols, tocopherol derivatives, and related phenols.[8] In fact, as expected from the larger π-electron system in K_1-chromanol and K_1-chromenol than that in α-tocopherol, the peak oxidation potentials of K_1-chromanol and K_1-chromenol are smaller than that of α-tocopherol.

On the other hand, Burton et al.[9—11] have reported the second-order rate constants, k_1, for the reaction of α-tocopherol and some related phenols (for example, 4-methoxyl-2,3,5,6-tetramethylphenol) with poly(styryl)peroxyl radicals (LOO·). By comparing the k_1 for α-tocopherol with those found for structurally related phenols that lacked the 6-membered heterocyclic ring, they suggested that the structure of this ring was

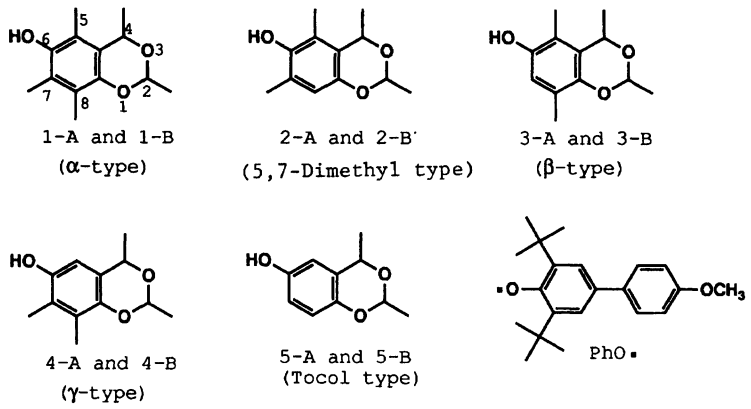

Fig. 2. Molecular structures of 4*H*-1,3-benzodioxin-6-ol (HBD) derivatives and substituted phenoxyl radical (PhO·).

largely responsible for the high reactivity of α-tocopherol. That is, the high reactivity of α-tocopherol has been attributed to strong orbital overlap between the 2p type lone pair on the para oxygen atom and the aromatic π-system. Furthere, they found that a better tocopherol compound is 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (tocopherol **6**), which has a five-membered heterocyclic ring instead of the six-membered one in α-tocopherol.[11—13] They reported that the reaction rate of tocopherol **6** is 1.8 times higher than that of α-tocopherol. The high reactivity of tocopherol **6** has been attributed to stereoelectric factors relating to the orientation of the p-type lone pair of the oxygen at the 1-position with respect to the aromatic ring. Several investigators, including us, have prepared many tocopherol compounds.[6—8,11—23] However, the numbers of the tocopherol compounds having higher antioxidant activity than α-tocopherol are very limited.[8,11,12,22]

Therefore, in this work, we prepared nine kinds of 4*H*-1,3-benzodioxin-6-ol (abbreviated to HBD) derivatives, new Vitamin E analogs, which have a different type of six-membered heterocyclic ring from that of natural tocopherol (see Fig. 2). So, if the extent of the π-conjugation between the 2p-type lone pair on the para oxygen atom (O_1) and aromatic π-electron system in HBD derivatives is larger than that in tocopherols, we can expect high antioxidant activity for these compounds. We have measured the reaction rates, k_s, of HBD derivatives with PhO· radical in ethanol solution. The peak oxidation potentials, E_p, have also been measured, by using cyclic voltammetry technique. ESR studies have been done for the radicals produced by the PbO_2 oxidation of HBD derivatives. The results were compared to those of tocopherols, and the structure-activity relationship in the antioxidant action of HBD has been discussed.

Results

Structure of the 4*H*-1,3-Benzodioxin-6-ol (HBD) Derivatives. *trans*- and *cis*-2,4-Dimethyl-4*H*-1,3-benzodioxin-6-ol (HBD **5-A** and **5-B** (tocol type) (see Fig. 2) were synthesized by condensation of acetaldehyde with the hydroquinone, by a procedure similar to that used by Denisov et al.[24] to prepare HBD **5**. Although Denisov et al. reported a kind of reaction product for HBD **5**, two diastereomeric isomers (**5-A** and **5-B**) of unknown stereochemistry were obtained in this work. Fortunately, these stereoisomers (**5-A** : **5-B**=about 76 : 24 measured by gas chromatography) could be separated by column chromatography and the configuration of each isomer was identified by 2D NMR. Cross-signals attributable to ^{4}J–"W" coupling between H_2 and H_4 was observed in the long-range COSY spectra of the minor isomer (**5-B**) (Fig. 3).[25] Therefore, the minor isomer has a *cis* configuration between H_2 and H_4 in accord with the structure (2,4)-*cis*-**5-B** given in the Fig. 4.[26,27] On the other hand, the major isomer (**5-A**) has a *trans* configuration between H_2 and H_4, because cross-signals are not observed in the long-range COSY spectra.

Similarly, 2,4-dimethyl-4*H*-1,3-benzodioxin-6-ol derivatives **1**, **2**, **3**, and **4** were prepared by condensation of acetaldehyde with the corresponding hydroquionone. Two diastereomers with *tarns*- and *cis*-configurations were obtained for each of the HBD derivatives **1**, **2**, **3**, and the configuration of each isomer was identified by 2D NMR. Only one diastereomer with *trans*-configuration (HBD **4-A**) was obtained for HBD **4**. The reason for this remarkable stereoselectivity is not clear.

As shown in Fig. 4, the *cis* isomer as well as the *trans* one has two possible conformational isomers ($H_2^aH_4^{a'}/H_2^eH_4^{e'}$ and $H_2^eH_4^{a'}/H_2^aH_4^{e'}$), respectively. The observed conformations of the *cis* and *trans* forms were assigned to be $H_2^aH_4^{a'}$ and $H_2^eH_4^{a'}$, respectively, by comparing the hyperfine coupling constants (a_2^H and a_4^H) of HBD-B and -A radicals with those of the corresponding tocopheryloxyl radical, as described later.

The Second-Order Rate Constants, k_s, for the Reaction of HBD with Substituted Phenoxyl Radical. The oxidation rates of HBD **1**—**5** (-**A** and -**B**) by substituted phenoxyl radical (PhO·) were studied by spectrophotometry, using a stopped-flow technique in the presence of excess HBD in ethanol.[4] PhO·

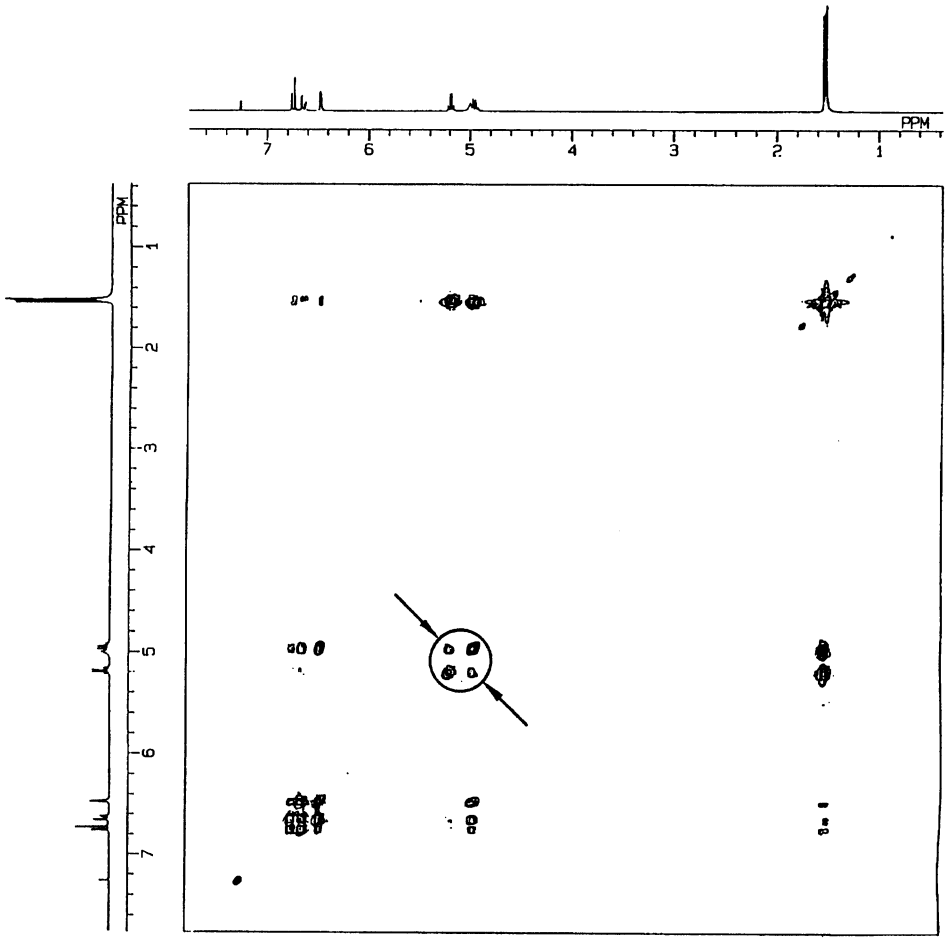

Fig. 3. Long-range COSY spectra of HBD **5-B** compound.

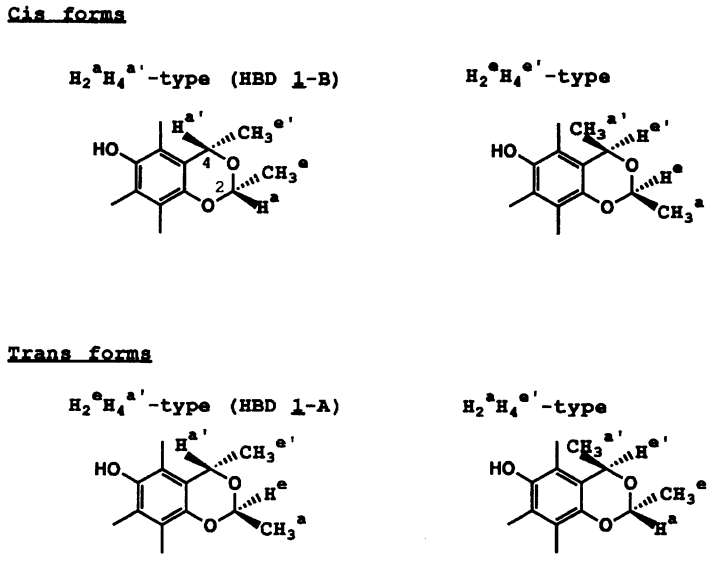

Fig. 4. Stereoisomers of HBD **1**.

was stable in the absence of HBD and showed an absorption peak at $\lambda_{max}=376$ nm ($\varepsilon=17600$ M^{-1} cm^{-1} (1 M=1 moldm^{-3})) and 580 nm ($\varepsilon=4280$ M^{-1} cm^{-1}) in ethanol. By adding an ethanol solution of HBD (1.00—2.50$\times10^{-3}$ M) to an ethanol solution of PhO· (4.00$\times10^{-5}$ M) (1:1 in volume) at 25 °C, the absorption peak of PhO· immediately decreased. The rate was measured by following the decrease in absorbance at 376 and 580 nm of PhO·. The pseudo-first-order rate constants, k_{obsd},

$$-d[PhO\cdot]/dt = k_{obsd}[PhO\cdot] = k_s[HBD][PhO\cdot] \quad (4)$$

were measured by varying the concentration of HBD. The second-order rate constants, k_s, were calculated from the measured k_{obsd} values according to Eq. 4. The k_s values of HBD derivatives at 25 °C are listed in Table 1, in comparison with those of α-, β-, γ-, and δ-tocopherol, tocol, and 5,7-dimethyltocol.[5)]

The peak oxidation potentials, E_p for HBD derivatives were measured in acetonitrile by using cyclic voltammetry, according to the reported procedure.[7,28)] The observed results are listed in Table 1.

ESR Studies of the HBD Radicals. HBD derivatives were oxidized with PbO_2 in toluene under a vacuum. The HBD radicals produced are comparatively stable, and showed well-resolved ESR spectra at room temperature. The observed species were assigned to the primary phenoxyl-type radicals formed from the parent HBD derivatives by abstraction of a phenolic hydrogen atom. For example, Fig. 5 shows the ESR spectra of both HBD **1-A** and **1-B** radicals. The spectrum of HBD **1-A** radical can be reconstructed with five groups 3, 3, 3, 1, and 1 equivalent protons, showing five different hyperfine couplings (6.39, 4.88, 1.18, 1.31, and 0.84 G), respectively. These splittings were assigned to the methyl protons at C-5 ($a_5^{CH_3}$=6.39 G), C-7 ($a_7^{CH_3}$=4.88 G) and C-8 ($a_8^{CH_3}$=1.18 G), and methine protons at C-4 (a_4^{CH}=1.31 G) and C-2 (a_2^{CH}=0.84 G), taking the analysis of the α-tocopheryloxyl into account.[29,30)] A computer simulation of the ESR spectrum using the above coupling constants of HBD **1-A** radical reproduced the experimental spectrum. Similarly, ESR spectra of the other HBD radicals were analyzed. Values of the hyperfine couplings and g_{iso}-values obtained are summarized in Table 2, together with those of tocopheryloxyl radicals.[29,30)]

Table 1. Second-Order Rate Constants (k_s) and Relative Rate Constants for Oxidation of HBD Derivatives by PhO· Radical in Ethanol at 25.0 °C and Peak Oxidation Potentials (E_p) for HBD Derivatives

Compounds	k_s[a)] $M^{-1}s^{-1}$	E_p vs. SCE[b)] mV	(%)[c)]
HBD **1-A** (*trans*)	674	960	13.2
1-B (*cis*)	980	970	19.1
α-Toc	5120	860	100
HBD **2-A** (*trans*)	309	1050	12.9
2-B (*cis*)	458	1030	19.2
5,7-Dimethyl-Toc	2390	890	100
HBD **3-A** (*trans*)	286	1050	12.8
3-B (*cis*)	431	1030	19.2
β-Toc	2240	920	100
HBD **4-A** (*trans*)	505	1040	20.9
4-B (*cis*)	—	—	—
γ-Toc	2420	930	100
HBD **5-A** (*trans*)	39.6	1200	7.07
5-B (*cis*)	28.3	1240	5.05
Tocol	560	1050	100
δ-Toc	1000	990	

a) Experimental errors < ±5%. b) Experimental errors ≦ ±20 mV. c) k_s (HBD)/k_s (tocopherol)×100.

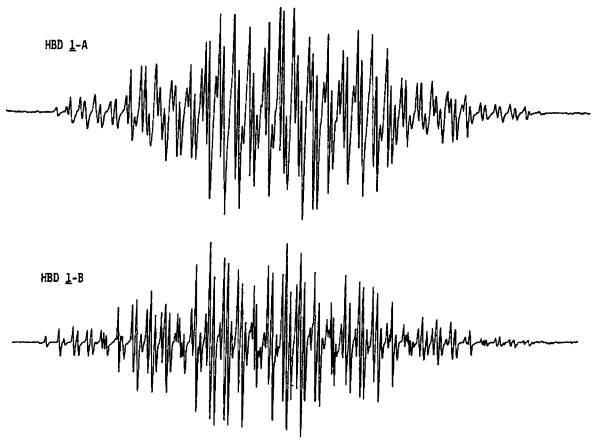

Fig. 5. ESR spectra of HBD **1-A** and **1-B** radicals in toluene.

Discussion

Antioxidant Activity of HBD Derivatives. As listed in Table 1, the k_s values of HBD derivatives increase with increasing numbers of methyl substituents at the aromatic ring. By plotting the $\log k_s$ values against the sums of Hammett σ of all the methyl substituents on the phenol ring ($\sum\sigma$), a linear correlation between $\log k_s$ and $\sum\sigma$ is obtained (correlation coefficient = −0.94).[5)] Further, the values of $\log k_s$ for HBD derivatives have been plotted against E_p, together with those of tocopherols. As shown in Fig. 6, a good linear correlation between $\log k_s$ and E_p has been observed (correlation coefficient = −0.98).[5,7)] The result indicates that the phenolic antioxidants with smaller E_p values show higher reactivities toward active free radicals.

Both the HBD **1-A** and **1-B** derivatives (α-type) as well as α-tocopherol have three methyl substituents at 5-, 7-, and 8-positions of the aromatic ring. Therefore, if the extent of orbital overlap between the 2p type lone pair on the para oxygen atom and the aromatic π-electron system in HBD **1-A** and **1-B** derivatives is larger than that in α-tocopherol, the HBD **1-A** and **1-B** radicals produced by the reaction of HBD **1-A** and **1-B** with PhO· are more stabilized, and, thus, the reaction rate constants, k_s, will increase.[10,11)] However, to our regret, the HBD **1-A** and **1-B** are only about 13.2 and 19.1% as reactive as α-tocopherol, respectively. The existence of the oxygen atom at the 3-position and/or two methyl substituents at the 2- and 4-positions in 6-mem-

Table 2. Hyperfine Splittings (a_i^H) (in gauss) of the Tocopheryloxyl and HBD Radicals in Toluene

Racidals	a_i^H/gauss 5 CH_3	7 CH_3	8 CH_3	4 CHorCH$_2$	2 CH	g_{iso}
HBD **1-A** (*trans*)	6.39	4.88	1.18	1.31	0.84	2.00469
1-B (*cis*)	6.26	4.80	1.15	1.57	2.34	2.00476
α-Toc	5.98	4.57	0.94	1.47		2.00471
	CH_3	CH_3	H	CHorCH$_2$	CH	
HBD **2-A** (*trans*)	6.15	5.01	1.10	1.40	0.81	2.00469
2-B (*cis*)	6.07	4.95	1.03	1.52	2.40	2.00469
5,7-Dimethyl-Toc	5.91	4.64	0.90	1.42		2.00460
	CH_3	H	CH_3	CHorCH$_2$	CH	
HBD **3-A** (*trans*)	6.76	4.78	0.96	1.60	1.20	2.00476
3-B (*cis*)	6.56	4.71	0.92	1.66	2.60	2.00483
β-Toc	6.20	4.50	0.85	1.70		
	H	CH_3	CH_3	CHorCH$_2$	CH	
HBD **4-A** (*trans*)	6.06	5.20	1.38	2.32	0.70	2.00487
4-B (*cis*)	—	—	—	—	—	—
γ-Toc	5.93	4.77	1.17	1.17		
	H	H	H	CHorCH$_2$	CH	
HBD **5-A** (*trans*)	5.86	5.43	0.88	2.75	0.88	2.00490
5-B (*cis*)	6.19	5.32	0.91	2.26	1.67	2.00497
Tocol	5.78	5.08	0.66	1.32		
	H	H	CH_3	CH_2		
δ-Toc	6.21	4.72	1.04	1.42		

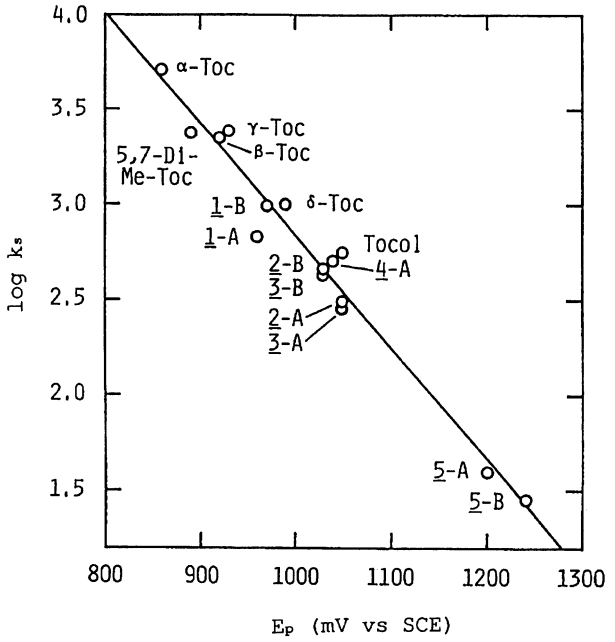

Fig. 6. Plot of log k_s vs. E_p for tocopherol and HBD compounds.

bered heterocyclic ring of HBD compounds induced an undesirable change in the π-conjugation between the 2p type lone pair on the para oxygen atom and the aromatic π-electron system. Similarly, the k_s values of HBD derivatives **2**, **3**, **4**, and **5** are smaller than those of the corresponding tocopherol derivatives (see Table 1). On the other hand, the reaction rates, k_s, of all the HBD derivatives except for HBD **5** were larger than that of 3,5-di-*t*-butyl-4-hydroxytoluene (BHT, k_s=35.0 $M^{-1}s^{-1}$), which is the most popular synthetic antioxidant. For example, the k_s value of HBD **1-A** is 19 times as large as that of BHT.

The Correlation between log k_s and the Sum of Unpaired Spin Densities ($\rho_5+\rho_7$) at the C_5 and C_7 Positions. As listed in Table 1, the reactivity of α-tocopherol, HBD **1-A** and HBD **1-B** compounds with three methyl substituents at aromatic ring, respectively, decreases in the order of α-tocopherol (5120 $M^{-1}s^{-1}$)>HBD **1-B** (980 $M^{-1}s^{-1}$)>HBD **1-A** (674 $M^{-1}s^{-1}$). On the other hand, the sum of the hyperfine couplings, ($a_5^{CH_3}+a_7^{CH_3}$), by the two ortho methyl groups in the corresponding radical increases in the order of α-tocopherol (10.55 G)<HBD **1-B** (11.06 G)<HBD **1-A** (11.27 G). Similarly, the rate constants k_s of 5,7-dimethyltocol, HBD **2-A**, and **2-B** decrease in the order of 5,7-dimethyltocol>HBD **2-B**>HBD **2-A**, and, inversely, the values of ($a_5^{CH_3}+a_7^{CH_3}$) increase in the order of 5,7-dimethyltocol<HBD **2-B**<HBD **2-A**. Burton et al.[11] have reported that for some 2,6-dimethylphenols log k_1 can be correlated with the extent of stabilization of corresponding phenoxyl radicals as measured by the unpaired spin density at the two ortho carbon atoms (C_2 and C_6). They found a rough correlation between log k_1 and ($a_2^{CH_3}+a_6^{CH_3}$).

Generally, the experimental values of spin densities (ρ_i^π) at the aromatic ring are estimated by using the following equation 5,

$$a_i^H = Q^H\rho_i^\pi, \quad a_i^{CH_3} = Q^{CH_3}\rho_i^\pi \tag{5}$$

where Q^H and Q^{CH_3} values were taken to be 25 G and 27 G for ring protons and methyl protons, respectively, in this work.[31] Therefore, the values of log k_s for tocopherols and HBD compounds have been plotted against the sum of the unpaired spin densities ($\rho_5+\rho_7$) at the C_5 and C_7 positions of the aromatic rings of the tocopheryloxyl and HBD radicals. As shown in Fig. 7, there is, in fact, a rough correlation between log k_s and ($\rho_5+\rho_7$) (correlation coefficient=−0.84).

As described in a previous section, the antioxidant activity of tocopherol compounds increases as the total electron-donating capacity of the alkyl substituents on the aromatic ring increases. α-Tocopherol with three methyl substituents at the aromatic ring is 9.3 times as reactive as tocol without methyl substituents. Similarly, HBD **1-A** and **1-B** with three methyl substituents are 17—35 times as reactive as HBD **5-A** and **5-B** without methyl substituents. On the other hand, Burton et al. have reported that the antioxidant activity of tocopherol compounds depends on the extent of orbital overlap between the 2p-type lone pair on the para oxygen atom (O_1) and the aromatic π-system, that is, the structure of the 6-membered heterocyclic ring in toco-

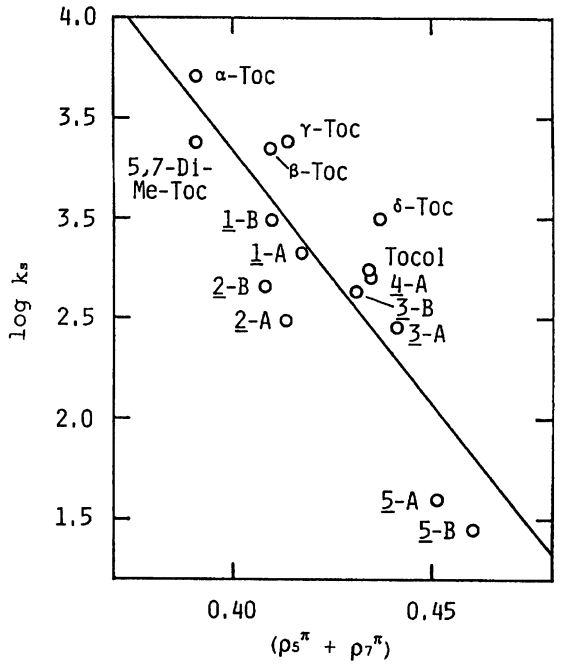

Fig. 7. Plot of $\log k_s$ vs. $(\rho_5^\pi + \rho_7^\pi)$ for tocopheryloxyl and HBD radicals.

pherol. In fact, the reaction rate of α-tocopherol is 7.6 and 5.2 times higher than those of HBD **1-A** and **1-B**, respectively, which have different 6-membered heterocyclic rings. Similarly, the reaction rate of tocol is 14 and 20 times higher than those of HBD **5-A** and **5-B**, respectively. These results suggest that both the effects, that is, i) the total electron-donating capacity of the methyl substituents and ii) the extent of orbital overlap, contribute largely to the antioxidant activity of tocopherols.

The Structure of Conformational Isomer and Heterocyclic Ring in HBD Derivatives. As described in a previous section, two diastereomers with *trans*- and *cis*-configurations between H_2 and H_4 were obtained for each of the HBD derivatives **1**, **2**, **3**, and **5** but not **4**. The configuration of each isomer was identified by 2D NMR techniques. Only one diastereomer with *trans*-configuration (HBD **4-A**) was obtained for HBD **4**. Further, as shown in Fig. 4, the *cis* form has two kinds of conformational isomers ($H_2^aH_4^{a'}$ and $H_2^eH_4^{e'}$ conformations), because of the stereochemistry due to H_2 and H_4 atoms. And similarly the *trans* form also has two isomers ($H_2^eH_4^{a'}$ and $H_2^aH_4^{e'}$).

The magnitude of the β-methylene proton hyperfine splitting (a_β^{CH}) can often be calculated using Heller–McConnell's equation,[32]

$$a_\beta^{CH} = (B_0 + B_2 \cos^2 \theta)\rho_i^\pi \qquad (6)$$

where ρ_i^π denotes the spin density on the carbon atom to which an alkyl group is attached and θ stands for the dihedral angle between the axis of the $2p_z$ orbital on the carbon atom to which the alkyl group is attached and the aliphatic C–H bond of the alkyl group. B_0 and B_2 are empirical parameters and were taken to be 0 and 54 G, respectively, in Eq. 6.

By comparing the hyperfine splittings of HBD **1-A** (*trans*) and **1-B** (*cis*) radicals and α-tocopheryloxyl, a_5^{CH}, a_7^{CH}, and a_8^{CH} are similar to each other, as listed in Table 2. Further, the β-proton hyperfine splitting, a_4^{CH}, at C_4 position is also similar to each other in these radicals. The result suggests that the dihedral angles, θ, in HBD **1-A** and **1-B** are about 30° as observed for α-tocopheryloxyl.[29,33,34] On the other hand, the hyperfine splittings (a_2^{CH}=0.84 G) of the methine proton at C_2 of **1-A** (*trans*) are smaller than that (a_2^{CH}=2.34 G) of **1-B** (*cis*). The result indicates that the methine proton at C_2 of **1-A** (*trans*) takes the equatorial conformation, and the methine proton of **1-B** (*cis*) takes the axial one. Therefore, the conformations of **1-A** (*trans*) and **1-B** (*cis*) were assigned to $H_2^eH_4^{a'}$ and $H_2^aH_4^{a'}$, respectively. Further, it is considered that the heterocyclic ring of **1-A** and **1-B** adopts a half-chair form such as that obtained from the X-ray structure analysis of α-tocopherol model (see Fig. 8).[9,13]

In HBD **1**, **2**, **3**, the steric repulsion forces between the methyl protons at C_5 and neighboring protons of $-CH(CH_3)-$ group at C_4 will be similar to each other and thus the conformations of the heterocyclic ring in **2** and **3** are considered to be similar to that of **1**. In fact, the hyperfine splittings, a_4^{CH} and a_2^{CH}, in *trans* and *cis* forms of HBD **1**, **2**, and **3** are similar to each other. Therefore, the conformations of *trans* and *cis* forms were assigned to $H_2^eH_4^{a'}$ and $H_2^aH_4^{a'}$, respectively. On the other hand, HBD **4** and **5** have no methyl group at the C_5 position, and thus the conformations of the heterocyclic ring in HBD **4** and **5** are considered to be different from that of α-tocopherol. In fact, as listed in Table 2, the hyperfine splittings, a_4^{CH}, of **4** and **5** are 1.4—2.1 times larger than those of HBD **1**, **2**, and **3**, because the dihedral angles of **4** and **5** are thought to be near 0° and those of **1**, **2**, and **3** are thought to be near 30°. Therefore, the conformations of *trans* and *cis* forms in **4** and **5** were assigned to $H_2^eH_4^{a'}$ and $H_2^aH_4^{a'}$, respectively.

If the heterocyclic ring of both the HBD **1-A** and **1-B** has a half-chair form as observed for α-tocopherol, the extent of the π-conjugation between the 2p-type lone pair on the para oxygen atom and the aromatic π-

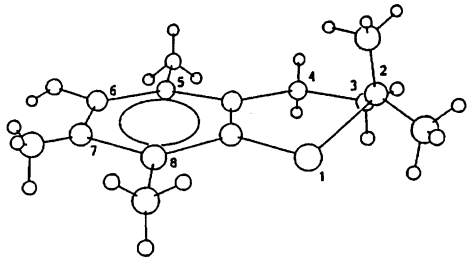

Fig. 8. The structure of α-tocopherol model.

system will be similar to each other in **1-A**, **1-B**, and α-tocopherol. In fact, the k_s and E_p values of HBD **1-A** are similar to the corresponding ones of HBD **1-B**, as listed in Table 1. On the other hand, HBD **1-A** and **1-B** reacted at rates that were only 13.2 and 19.1% of that observed with α-tocopherol, respectively. Further, the E_p values of HBD **1-A** and **1-B** are larger than that of α-tocopherol (see Table 1). These facts will be explained as follows.

As reported in a previous paper, the ENDOR results of α-tocopheryloxyl and its model radical indicate that each of the two β- and γ-methylene protons has an equivalent hyperfine coupling.[29] Further, the equivalence of each of the two β- and γ-methylene protons has also been noted in the NMR spectra of the parent α-tocopherol and its model,[35,36] supporting the above results. The ENDOR (or NMR) and X-ray data would be consistent if the half-chair to half-chair interconversion of the heterocyclic ring was rapid in solution. On the other hand, in the case of HBD **1-A** and **1-B**, the above interconversion of the heterocyclic ring is considered to be locked, because the hyperfine splittings ($a_2^{CH}=0.84$ G and $a_2^{CH}=2.34$ G) of the methine proton at C_2 of **1-A** and **1-B** radicals are very different from each other in solution. If the half-chair to half-chair interconversion of the heterocyclic ring is locked in HBD **1-A** and **1-B**, the π-conjugation between the 2p-type lone pair on the para oxygen atom (O_1) and aromatic π-electron system will be weakened, and thus the k_s value will decrease in HBD **1-A** and **1-B**. Further, the decrease of orbital overlap will induce the increase of E_p value in HBD **1-A** and **1-B**. Similarly, the k_s values of HBD derivatives **2**, **3**, **4**, and **5** will be smaller than those of corresponding tocopherols. However, the reason is not clear at present why the k_s values of HBD **1-A**, **2-A**, and **3-A** are smaller than those of HBD **1-B**, **2-B**, and **3-B**, respectively, and the k_s value of HBD **5-A** is larger than that of HBD **5-B**.

Experimental

Measurements. Proton NMR spectra were observed with JEOL-GX-270 spectrometers with tetramethylsilane as an internal standard. ESR measurements were done using a JEOL-FE-2XG spectrometer with a Takeda-Riken microwave frequency counter. The g_{iso} values were measured relative to the value of Li-TCNQ powder, calibrated with $(KSO_3)_2NO$ ($g=2.0054$). All the ESR spectra have been measured in a sealed, degassed system. The stopped-flow data were obtained on a Unisoku stopped-flow spectrophotometer Model RS-450 by mixing equal volumes of ethanol solutions of substituted phenoxyl (PhO·) and HBD derivative. Cyclic voltammetry was done at 20 °C under an atmosphere of nitrogen with a platinum electrode and a saturated calomel reference electrode in acetonitrile containing 40 mM tetrabutylammonium perchlorate, with a Yanako cyclic voltammetric analyzer Model P-1000H.

Materials. 4*H*-1,3-benzodioxin-6-ol (HBD) derivatives **1-5** were synthesized by condensation of acetaldehyde with the corresponding hydroquinone, according to a procedure similar to that used by Denisov et al.[24] to prepare HBD **5**. Although Denisov et al. reported only one product for HBD **5**, we succeeded in isolating *cis* and *trans* isomers for HBD **1**, **2**, **3**, and **5**, respectively, but not HBD **4**. The configuration of each isomer was identified by measuring the two dimensional NMR (long-range COSY) spectra.[25—27]

The 2,6-di-*t*-butyl-4-(4-methoxyphenyl)phenoxyl (PhO·) was prepared by the method of Rieker et al.[37] The radical concentration of substituted phenoxyl was obtained from the results of the paramagnetic susceptibility measurement at 20 °C. The value was 100% for substituted phenoxyl, assuming the Curie law.

***trans*- and *cis*-2,4,5,7,8-Pentamethyl-4*H*-1,3-benzodioxin-6-ol (HBD 1-A and 1-B (α-Tocopherol Type)).** To a solution of the acetaldehyde (8.8 g, 0.20 mol) in acetic acid (15 ml) and concd HCl (5 ml) was added 2,3,5-trimethylhydroquinone (15.2 g, 0.10 mol) with stirring at 3—5 °C. After being stirred for 2 h at 5 °C, the reaction mixture was poured into ice-water (200 ml). The organic precipitates were separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed sequentially with water, aqueous $NaHCO_3$, and water, and dried over Na_2SO_4. The solvent was evaporated to give a mixture of HBD **1-A** and **1-B** as a white powder. The ratio of *trans* and *cis* isomers was estimated to be about 44 : 56 by gas chromatography. A chromatographic separation (silica gel (Wako-gel C-300), benzene as eluent) gave pure *trans* isomer (**1-A**) (first eluted) and *cis* isomer (**1-B**) (second eluted).

HBD 1-A (*trans*-Isomer, 44%, First Eluted): Mp 124.0—125.5 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta=1.46$ (d, 3H, $J=6.2$ Hz, 2- or 4-CH_3), 1.52 (d, 3H, $J=5.1$ Hz, 2- or 4-CH_3), 2.09 (s, 3H, 5-, 7- or 8-CH_3), 2.12 (s, 3H, 5-, 7- or 8-CH_3), 2.15 (s, 3H, 5-, 7- or 8-CH_3), 4.36 (s, 1H, 6-OH), 4.92 (quartet, 1H, $J=5.1$ Hz, 2- or 4-H), 5.20 (quartet, 1H, $J=6.2$ Hz, 2- or 4-H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. Found: C, 70.70; H, 8.37%.

HBD 1-B (*cis*-Isomer, 56%, Second Eluted): Mp 130.5—131.5 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta=1.53$ (d, 3H, $J=5.1$ Hz, 2- or 4-CH_3), 1.54 (d, 3H, $J=6.6$ Hz, 2- or 4-CH_3), 2.05 (s, 3H, 5-, 7- or 8-CH_3), 2.12 (s, 3H, 5-, 7- or 8-CH_3), 2.16 (s, 3H, 5-, 7- or 8-CH_3), 4.33 (s, 1H, 6-OH), 4.99 (quartet, 1H, $J=6.6$ Hz, 2- or 4-H), 5.30 (quartet, 1H, $J=5.1$ Hz, 2- or 4-H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. Found: C, 70.61; H, 8.17%.

***trans*- and *cis*-2,4,5,7-Tetramethyl-4*H*-1,3-benzodioxin-6-ol (HBD 2-A and 2-B (5,7-Dimethyltocopherol Type)).** HBD **2-A** (*trans*) and **2-B** (*cis*) were obtained in a similar manner to the preparation of HBD **1-A** and **1-B**. The ratio of *trans* and *cis* isomers was estimated to be about 49 : 51.

HBD 2-A (*trans*-Isomer, 49%, First Eluted): Mp 117.0—118.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta=1.48$ (d, 3H, $J=6.3$ Hz, 2- or 4-CH_3), 1.49 (d, 3H, $J=5.1$ Hz, 2- or 4-CH_3), 2.11 (s, 3H, 5- or 7-CH_3), 2.19 (s, 3H, 5- or 7-CH_3), 4.41 (s, 1H, 6-OH), 4.95 (quartet, 1H, $J=5.1$ Hz, 2- or 4-H), 5.19 (quartet, 1H, $J=6.3$ Hz, 2- or 4-H), 6.54 (s, 1H, 8-H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.45; H, 7.69%.

HBD 2-A (*cis*-Isomer, 51%, Second Eluted): Mp 110.0—111.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta=1.50$ (d,

3H, J=5.1 Hz, 2- or 4-CH_3), 1.54 (d, 3H, J=6.7 Hz, 2- or 4-CH_3), 2.07 (s, 3H, 5- or 7-CH_3), 2.20 (s, 3H, 5- or 7-CH_3), 4.32 (s, 1H, 6-OH), 4.99 (quartet, 1H, J=6.7 Hz, 2- or 4-H), 5.30 (quartet, 1H, J=5.1 Hz, 2- or 4-H), 6.53 (s, 1H, 8-H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.09; H, 7.73%.

***trans*- and *cis*-2,4,5,8-Tetramethyl-4*H*-1,3-benzodioxin-6-ol (HBD 3-A and 3-B (β-Tocopherol Type)).** HBD **3-A** (*trans*) and **3-B** (*cis*) were also prepared in a similar way as described above. The ratio of *trans* and *cis* isomers was estimated to be about 32:68.

HBD 3-A (*trans*-Isomer, 32%, First Eluted): Mp 146.0—147.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.48 (d, 3H, J=6.4 Hz, 2- or 4-CH_3), 1.52 (d, 3H, J=5.1 Hz, 2- or 4-CH_3), 2.08 (s, 3H, 5- or 8-CH_3), 2.13 (s, 3H, 5- or 8-CH_3), 4.54 (s, 1H, 6-OH), 4.94 (quartet, 1H, J=5.1 Hz, 2- or 4-H), 5.21 (quartet, 1H, J=6.4 Hz, 2- or 4-H), 6.50 (s, 1H, 7-H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.23; H, 7.76%.

HBD 3-B (*cis*-Isomer, 68%, Second Eluted): Mp 149.5—151.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.53 (d, 3H, J=5.1 Hz, 2- or 4-CH_3), 1.55 (d, 3H, J=6.7 Hz, 2- or 4-CH_3), 2.04 (s, 3H, 5- or 8-CH_3), 2.13 (s, 3H, 5- or 8-CH_3), 4.43 (s, 1H, 6-OH), 5.00 (quartet, 1H, J=6.7 Hz, 2- or 4-H), 5.31 (quartet, 1H, J=5.1 Hz, 2- or 4-H), 6.52 (s, 1H, 7-H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 68.89; H, 7.63%.

***trans*-2,4,7,8-Tetramethyl-4*H*-1,3-benzodioxin-6-ol (HBD 4 (γ-Tocopherol Type)).** HBD **4** was prepared according to the method described above, but gave only *trans* isomer, HBD **4-A**.

HBD 4-A (*trans*-Isomer): Mp 122.0—123.0 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.47 (d, 3H, J=6.4 Hz, 2- or 4-CH_3), 1.54 (d, 3H, J=5.9 Hz, 2- or 4-CH_3), 2.12 (s, 3H, 7- or 8-CH_3), 2.14 (s, 3H, 7- or 8-CH_3), 4.70 (s, 1H, 6-OH), 5.03 (quartet, 1H, J=6.4 Hz, 2- or 4-H), 5.15 (quartet, 1H, J=5.9 Hz, 2- or 4-H), 6.32 (s, 1H, 5-H). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.47; H, 7.83%.

***trans*- and *cis*-2,4-Dimethyl-4*H*-1,3-benzodioxin-6-ol (HBD 5-A and 5-B (Tocol Type)).** HBD **5-A** (*trans*) and **5-B** (*cis*) were also prepared in a similar way as described above. The ratio of *trans* and *cis* isomers was estimated to be about 76:24.

HBD 5-A (*trans*-Isomer, 76%, First Eluted): Viscous oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.51 (d, 3H, J=6.4 Hz, 2- or 4-CH_3), 1.52 (d, 3H, J=5.2 Hz, 2- or 4-CH_3), 4.76 (s, 1H, 6-OH), 5.06 (quartet, 1H, J=6.4 Hz, 2- or 4-H), 5.18 (quartet, 1H, J=5.2 Hz, 2- or 4-H), 6.51—6.73 (m, 3H, 5-, 7- or 8-H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%. Found: C, 65.69; H, 6.78%.

HBD 5-B (*cis*-Isomer, 24%, Second Eluted): Mp 117.0—118.5 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.52 (d, 3H, J=5.0 Hz, 2- or 4-CH_3), 1.54 (d, 3H, J=6.7 Hz, 2- or 4-CH_3), 4.96 (quartet, 1H, J=6.7 Hz, 2- or 4-H), 5.00 (s, 1H, 6-OH), 5.19 (quartet, 1H, J=5.1 Hz, 2- or 4-H), 6.47—6.76 (m, 3H, 5-, 7- or 8-H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%. Found: C, 66.41; H, 6.64%.

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