X-Ray Crystallographic Studies of Vitamin E Derivatives. Relationship between Antioxidant Activity and Molecular Structure

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Synopsis. Molecular structures of vitamin E derivatives were analyzed with X-ray diffraction. The relationship between the antioxidant activity and the molecular structure of vitamin E is discussed.

Vitamin E (α-, β-, γ-, and δ-tocopherols) inhibits the autoxidation of organic molecules, and the mechanism has been studied extensively by numerous investigators.[1—4] Furthermore, vitamin E is present in cellular membranes and edible oils and acts as an antioxidant by protecting polyunsaturated lipids or fatty acids from peroxidation.

The antioxidant properties of tocopherols (TocH's) have been ascribed to proton transfer (hydrogen transfer) from the OH group in TocH's by a lipid dioxyl radical (LOO·). The proton transfer (hydrogen transfer) produces a tocopheroxyl radical (6-chromanyloxyl radical from tocopherol, Toc·), which combines with another lipid dioxyl radical (reactions 1 and 2).[5,6]

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

$$\mathrm{LOO\cdot + Toc\cdot} \rightarrow \text{Non-radical products} \quad (2)$$

We have measured the second-order rate constant of TocH with stable phenoxyl radical (2,6-di-*t*-butyl-4-(4-methoxyphenyl)phenoxyl), k_s, with a stopped-flow spectrophotometer.[7—14] The decreasing order of k_s is as follows: α-TocH > β-TocH ≈ γ-TocH > δ-TocH > tocol. Burton et al. suggested that the difference in antioxidant activity between α-TocH and 2,3,5,6-tetramethyl-4-methoxyphenol is due to the extent of orbital overlap between the 2*p*-type lone pair on the ring oxygen or the methoxy oxygen and the aromatic π electron system.[15—18]

In this report, we have studied the molecular structures of TocH derivatives (Fig. 1) to discover whether or not the orbital overlap is a dominant factor governing the antioxidant activity of TocH's as explained by Burton et al. We have analyzed the molecular structures of TocH derivatives by X-ray diffraction and the results were compared with those by ab initio calculations and ENDOR.[19—21]

Experimental

Preparation of α-TocH model (2,2,5,7,8-pentamethyl-6-chromanol, **1**), β-TocH model (2,2,5,8-tetramethyl-6-chromanol, **2**), γ-TocH model (2,2,7,8-tetramethyl-6-chromanol, **3**), 5,7-Di-Me-TocH model (2,2,5,7-tetramethyl-6-chromanol, **4**), and a tocol model (2,2-dimethyl-6-chromanol, **5**) was reported in previous papers.[8,22] 2,2,7,7-Tetramethyl-2,3,4,7,8,9-hexahydrobenzo[1,2-*b*:4,5-*b*′]dipyran (**6**) and 2,2,5,7,7,10-hexamethyl-2,3,4,7,8,9-hexahydrobenzo[1,2-*b*:4,5-*b*′]dipyran (**7**) were synthesized in procedures described previously.[20,22,23] Single crystals of **1**—**7** used in this study were obtained by recrystallization from various solvents; mixed solvent of petroleum ether and diethyl ether (**1** and **7**), methanol (**2**), petroleum ether (**3** and **6**), mixed solvent of petroleum ether and benzene (**4**), and benzene (**5**). We could not obtain single crystals of δ-TocH.

The setup and the experimental procedures for the X-ray diffraction were described in detail elsewhere.[24] Briefly, the measurements were made with a Rigaku AFC5R automated four-circle diffractometer with a graphite-monochromatized Cu $K\alpha$ or Mo $K\alpha$ radiation source. The complete data of the X-ray diffraction are deposited as Document No. 66048 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Results and Discussion

Crystal data of **1**—**7** are listed in Table 1. As an example, a molecular perspective view of **2** is shown in Fig. 2, together with the numbering system for the atoms discussed in this paper. Phenyl rings of **1**—**4** are non-planar, while those of **5**—**7** are planar. As widely recognized,[25] the molecular structures obtained from the X-ray analysis agreed well with the optimized geometries obtained from ab initio calculations in previous papers.[19,21]

The extent of orbital overlap between the 2*p*-type

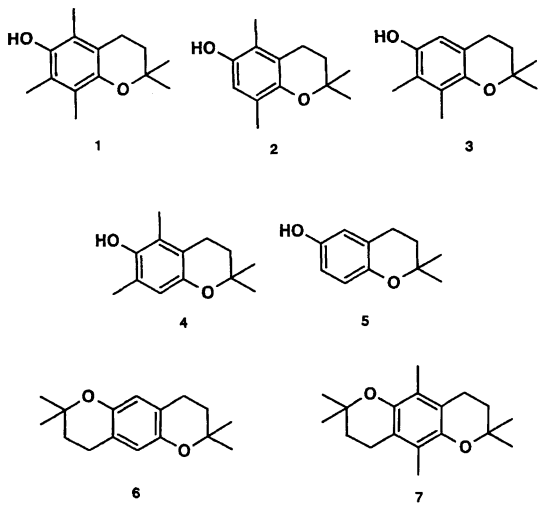

Fig. 1. Structures of models for TocH's studied in this work.

Table 1. Crystal Data for **1**—**7**

	1	**2**	**3**	**4**	**5**	**6**	**7**
Crystal system	Triclinic	Orthorhombic	Monoclinic	Monoclinic	Tetragonal	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$Pbca$	$C2/c$	$P2_1/n$	$I4_1/a$	$P2_1/c$	$P2_1/c$
a/Å	10.843	15.734	22.729	5.684	25.288	6.089	8.040
b/Å	13.304	17.321	10.353	14.844	25.288	10.616	9.365
c/Å	9.155	8.551	24.236	13.666	6.263	11.279	10.392
α/°	103.68	—	—	—	—	—	—
β/°	97.18	—	123.20	98.66	—	100.19	90.47
γ/°	91.05	—	—	—	—	—	—
Z	4	8	16	4	16	2	2
Source[a]	Cu $K\alpha$	Mo $K\alpha$	Cu $K\alpha$	Mo $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
$2\theta_{max}$/°	123.0	55.0	123.0	55.0	123.0	123.0	123.0
R[b]	0.040	0.060	0.043	0.045	0.038	0.059	0.038
R_w[b]	0.049	0.061	0.051	0.044	0.043	0.079	0.045

a) Cu $K\alpha$; λ=1.54178 Å. Mo $K\alpha$; λ=0.71069 Å. b) Final refinement yield.

Table 2. Torsional Angles (θ and θ_γ) of **1**—**7** Obtained by X-Ray Analysis, Ab Initio Calculation, and ENDOR and k_s

	1[a]	**2**	**3**[a]	**4**	**5**	**6**[b]	**7**
θ/°							
X-Ray analysis[c]	15.3 18.5	19.7	5.9 14.9	24.2	18.0	9.9	16.7
ab initio Calculation	21.0	21.4	18.9	—	20.1	—	—
ENDOR[d]	Large	Large	Small	Large	Small	Small	Large
θ_γ/°							
X-Ray analysis[e]	11.6 10.7	16.7	20.5 12.4	7.9	14.1	20.2	13.3
ab initio Calculation	10.8	12.4	14.6	—	15.0	—	—
ENDOR	≈0[d]	≈0[d]	≈30[d]	2.4[f]	≈30[d]	29.9[g]	1.1[g]
k_s[h]/M^{-1} s^{-1}	5.12×10^3	2.24×10^3	2.42×10^3	2.39×10^3	0.56×10^3	—	—

a) There are two structurally-different molecules in a unit cell. b) The crystal has disorder and there is a small amount of a structurally-different molecule in the crystal. Since its occupancy is only 0.294, errors in its θ and θ_γ are large. Accordingly, θ and θ_γ of the other molecule alone are given in this table. c) Average of torsional angles C2–O1–C8A–C4A and C2–O1–C8A–C8. d) Estimated from the structure of the model molecule with ENDOR. e) Average of torsional angles C3–C4–C4A–C5 and C3–C4–C4A–C8A. f) Obtained for 7-*t*-butyl-2,2,5-trimethyl-6-chromanyloxyl. g) Obtained for the cation radical. h) Obtained for α-, β-, γ-, and 5,7-dimethyl-TocH's, and tocol.

lone pair on the ring oxygen and the aromatic π electron system is summarized in Table 2. θ and θ_γ denote the torsional angle between the O1–C2 bond and the aromatic ring and the torsional angle between the C3–C4 bond and the aromatic ring, respectively. The larger the orbital overlap, the smaller the θ. The minimum and maximum orbital overlaps are obtained with θ_γ=0 and 30°, respectively.[19—21]

As described in a previous section, Burton et al. suggested that the larger the orbital overlap, the higher the antioxidant activity.[15—18] They showed that θ's of α-TocH and 2,3,5,6-tetramethyl-4-methoxyphenol are 16 and 89°, respectively, and the ratio of k_1 of α-TocH to that of 2,3,5,6-tetramethyl-4-methoxyphenol is about 8.2. However, the results of the X-ray analyses (θ and θ_γ in Table 2) show that the extent of orbital overlap between the 2*p*-type lone pair on the ring oxygen and the aromatic π electron system in TocH's is similar to one another. If the orbital overlap were a dominant factor governing the antioxidant activity of TocH as explained by Burton et al., k_s's of TocH's would be similar to one another. Actually k_s is correlated to the number of methyl groups bonded to the phenyl ring and the decreasing order of k_s is as follows: α-TocH>β-TocH≈γ-TocH>tocol.[7—14] The ratio of k_s of α-TocH to that of tocol is about 9.1. Therefore, at least within the scope of these TocH's, the orbital overlap cannot be a dominant factor governing the antioxidant activity. However, in TocH with a 5-membered heterocyclic ring, the increase in the extent of orbital overlap induces the increase in k_s as shown previously.[14]

In previous paper,[7—14,19—21] we showed that the antioxidant activity of TocH in reaction 1 depends on the facility of the charge transfer from TocH to LOO·. This view is consistent with our previous experimental results that the decreasing order of k_s is as follows: α-TocH>β-TocH≈γ-TocH>tocol. The ratio of k_s of α-TocH to that of tocol is about 9.1.[7—14] On the other

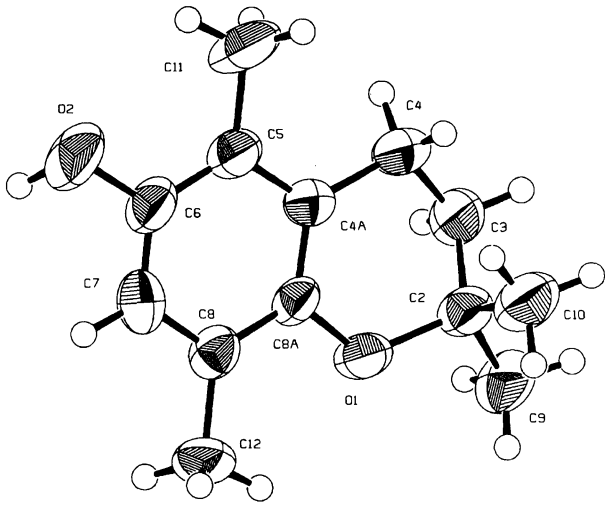

Fig. 2. Perspective view of **2** and numbering system for atoms.

hand, the ratio of k_1 of α-TocH to that of 2,3,5,6-tetramethyl-4-methoxyphenol is about 8.2.[15—18] Thus, it seems that both of the facility of the charge transfer and the extent of orbital overlap contributes to the high antioxidant activity of α-TocH.

In previous papers,[20,21] we obtained the molecular structure of the cation and neutral radicals of model molecules for TocH's by the use of ENDOR. θ's and θ_γ's thus obtained are also listed in Table 2. We then discussed the relationship between the antioxidant activity and the observed molecular structure of the cation and neutral radicals. However, the molecular structure of the neutral molecule obtained from this X-ray analysis is not similar to that of the cation or neutral radical of the model molecule as shown in Table 2. On the other hand, we obtained the molecular structures of TocH's from ab initio calculations.[19,21] The molecular structures obtained from the X-ray analysis are consistent with those from the ab initio calculation rather than those from ENDOR (Table 2).

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References

1) G. W. Burton and K. U. Ingold, *Acc. Chem. Res.*, **19**, 194 (1986), and references cited therein.

2) E. Niki, *Yuki Gosei Kagaku*, **47**, 902 (1989), and references cited therein.

3) L. R. C. Barclay, K. A. Baskin, S. J. Locke, and M. R. Vinqvist, *Can. J. Chem.*, **67**, 1366 (1989).

4) W. A. Pryor, T. Strickland, and D. F. Church, *J. Am. Chem. Soc.*, **110**, 2224 (1988).

5) G. W. Burton and K. U. Ingold, *J. Am. Chem. Soc.*, **103**, 6472 (1981).

6) E. Niki, A. Kawakami, M. Saito, Y. Yamamoto, J. Tsuchiya, and Y. Kamiya, *J. Biol. Chem.*, **260**, 2191 (1985).

7) K. Mukai, Y. Watanabe, Y. Uemoto, and K. Ishizu, *Bull. Chem. Soc. Jpn.*, **59**, 3113 (1986).

8) K. Mukai, S. Yokoyama, K. Fukuda, and Y. Uemoto, *Bull. Chem. Soc. Jpn.*, **60**, 2163 (1987).

9) K. Mukai, K. Fukuda, and K. Ishizu, *Chem. Phys. Lipids*, **46**, 31 (1988).

10) K. Mukai, K. Fukuda, K. Tajima, and K. Ishizu, *J. Org. Chem.*, **53**, 430 (1988).

11) K. Mukai, Y. Kageyama, T. Ishida, and K. Fukuda, *J. Org. Chem.*, **54**, 552 (1989).

12) K. Mukai, K. Okabe, and H. Hosose, *J. Org. Chem.*, **54**, 557 (1989).

13) A. Kuranaka, K. Sawada, U. Nagashima, S. Nagaoka, and K. Mukai, *Vitamins*, **65**, 453 (1991).

14) S. Nagaoka, A. Kuranaka, H. Tsuboi, U. Nagashima, and K. Mukai, *J. Phys. Chem.*, **96**, 2754 (1992).

15) G. W. Burton, Y. Le Page, E. J. Gabe, and K. U. Ingold, *J. Am. Chem. Soc.*, **102**, 7791 (1980).

16) G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, and K. U. Ingold, *J. Am. Chem. Soc.*, **107**, 7053 (1985).

17) G. W. Burton, L. Hughes, and K. U. Ingold, *J. Am. Chem. Soc.*, **105**, 5950 (1983).

18) T. Doba, G. W. Burton, and K. U. Ingold, *J. Am. Chem. Soc.*, **105**, 6505 (1983).

19) S. Nagaoka, K. Mukai, T. Itoh, and S. Katsumata, *J. Phys. Chem.*, **96**, 8184 (1992).

20) K. Mukai, Y. Uemoto, M. Fukuhara, S. Nagaoka, and K. Ishizu, *Bull. Chem. Soc. Jpn.*, **65**, 2016 (1992).

21) S. Nagaoka, Y. Uemoto, M. Fukuhara, K. Ishizu, and K. Mukai, *Mag. Reson. Med.*, **2**, 196 (1991).

22) J. L. G. Nilsson, H. Sievertsson, and H. Selander, *Acta Chem. Scand.*, **22**, 3160 (1968).

23) K. Mukai, Y. Uemoto, and K. Ishizu, *Bull. Chem. Soc. Jpn.*, **58**, 1928 (1985).

24) N. Azuma, T. Ozawa, K. Yamawaki, and R. Tamura, *Bull. Chem. Soc. Jpn.*, **65**, 2860 (1992).

25) W. J. Hehre, L. Radom, P. v. R. Schleyer, and J. A. Pople, "Ab Initio Molecular Orbital Theory," John Wiley & Sons, New York (1986).