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Antioxidant Activities of Vitamin E Analogues in Water and a Kamlet−Taft *β*-Value for Water[1]

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Abstract: Rate constants for hydrogen atom abstraction from two water-soluble α-tocopherol (α-**T**OH, vitamin E) analogues by *tert*-butoxyl radicals have been measured at room temperature in four solvents, including water. The results imply that H-atom abstraction from α-TOH is 3.9 times slower in water than in benzene and yield a "reliable" Kamlet−Taft *β* solvent parameter for water of 0.31. Literature rate constants for H-atom abstraction by peroxyl radicals from α-**T**OH in SDS micelles and in phospholipid micelles are, respectively, about 100 and 1000 times lower than in styrene. Since only a small fraction of the observed rate diminution can be attributed to hydrogen bonding of α-**T**OH to water it is concluded that in these heterogeneous systems much of the α-**T**OH is physically inaccessible to the attacking radicals. Whether this is also true for α-**T**OH in the biological membranes in living animals remains to be determined.

α-Tocopherol (α-**T**OH, vitamin E) is a biologically important and very effective lipid-soluble, radical-trapping antioxidant.[3] In organic solvents α-**T**OH reacts more rapidly with peroxyl

$$X^{\bullet} + \alpha\text{-}\mathbf{T}\text{OH} \rightarrow XH + \alpha\text{-}\mathbf{T}\text{OH}^{\bullet} \tag{1}$$

radicals,[4] alkoxyl radicals,[5,6] and carbon-centered radicals[5] than nearly all other phenols.[7] The phenolic hydroxyl group of α-**T**OH is crucial for antioxidant activity.[4,10] However, in egg phosphatidylcholine bilayers (which are excellent models for biomembranes) it has been shown that this hydroxyl group is located near the phosphate moiety of the lipid matrix,[11] i.e., it resides mainly in the aqueous-lipid interfacial region.[12] The location of the hydroxyl group of α-**T**OH in bilayers is particularly intriguing in view of our recent demonstration that the rate constants for hydrogen atom abstraction from α-**T**OH (reaction 1, $X^{\bullet}$ = *tert*-butoxyl, $BO^{\bullet}$, and 2,2-diphenyl-1-picrylhydrazyl, $DPPH^{\bullet}$) decreased dramatically as the hydrogen

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(3) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194−201.

(4) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065.

(5) Evans, C.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4589−4593.

(6) Valgimigli, L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 9966−9971.

(7) Only one class of phenols has been discovered which contains more active radical-trapping agents than α-**T**OH.[4,8] Several naphthols are also more active than α-**T**OH.[9]

(8) Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950−5951. Ingold, K. U.; Burton, G. W.; Foster, D. O.; Zuker, M.; Hughes, L.; Lacelle, S.; Lusztyk, E.; Slaby, M. *FEBS Lett.* **1986**, *205*, 117−120. Ingold, K. U.; Burton, G. W.; Foster, D. O.; Hughes, L. *FEBS Lett.* **1990**, *267*, 63−65. Gilbert, J. C.; Pinto, M. *J. Org. Chem.* **1992**, *57*, 5271−5276.

(9) (a) See, e.g.: Barclay, L. R. C.; Vinqvist, M. R.; Mukai, K.; Itoh, S.; Morimoto, H. *J. Org. Chem.* **1993**, *58*, 7416−7420. (b) Barclay, L. R. C.; Edwards, C. D.; Mukai, K.; Egawa, Y.; Nishi, T. *J. Org. Chem.* **1995**, *60*, 2739−2744.

(10) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472−6477.

(11) Perly, B.; Smith, I. C. P; Hughes, L.; Burton, G. W.; Ingold, K. U. *Biochim. Biophys. Acta* **1985**, *819*, 131−135.

(12) The hydrophobic $C_{16}H_{33}$ "tail" of α-**T**OH goes deep into the membrane, see: Ekiel, I. H.; Hughes, L.; Burton, G. W.; Jovall, P. A.; Ingold, K. U.; Smith, I. C. P. *Biochemistry* **1988**, *27*, 1432−1440.

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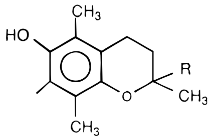
bond accepting (HBA) ability of the solvent increased.[6,13] Thus, because of its physical location in biomembranes we would expect the hydroxyl group of α-**T**OH to be largely hydrogen bonded, in which case the ability of α-**T**OH to trap radicals would be seriously impaired. In fact, there is some experimental evidence that this is true for $X^\bullet$ = peroxyl ($ROO^\bullet$). Thus, at 30 °C, $k_1(ROO^\bullet + \alpha\text{-}\mathbf{T}OH) = 6.8 \times 10^6\ M^{-1}\ s^{-1}$ in cyclohexane (at 25 °C),[16] $3.2 \times 10^6\ M^{-1}\ s^{-1}$ in styrene,[4] $2.3 \times 10^5\ M^{-1}\ s^{-1}$ in *tert*-butyl alcohol,[17,18] $9.5 \times 10^4\ M^{-1}\ s^{-1}$ (at ca. 25 °C) in ethanol,[19] 1.7×10^4,[17] 3.7×10^4,[20] and $6.0 \times 10^4\ M^{-1}\ s^{-1}$ (at 40 °C)[21,22] in SDS micelles,[23] and $3 \times 10^3\ M^{-1}\ s^{-1}$ in a phospholipid bilayer.[24,25] Unfortunately, the kinetic measurements in the non-homogeneous systems (micelles and bilayers) might reflect *either* a reduction in the reactivity of the α-**T**OH because of the HBA effect of the aqueous phase *or* the fact that much of the α-**T**OH was physically inaccessible to the peroxyl radicals, *or both* the above.[28] Indeed, Castle and Perkins[21] have pointed out that diffusion of highly lipophilic phenols (such as α-**T**OH) between SDS micelles is probably so slow that it limits their ability to scavenge the $ROO^\bullet$ radicals and that it is probably the diffusion of $ROO^\bullet$ to the α-**T**OH rather than the reverse that provides the (rate-limiting) mechanism for encounter and consequent $ROO^\bullet$ scavenging.[29] Our recent prediction[14] and subsequent demonstration[6] that kinetic solvent effects on reaction 1[30] are independent of the nature and reactivity of $X^\bullet$ provided hope that some firm decision could be made as to the cause of the low reactivity of α-**T**OH toward peroxyl radicals in biphasic systems.

Herein we report absolute rate constants for hydrogen atom abstraction from two water-soluble models of α-**T**OH by alkoxyl radicals in water and in three organic solvents of differing HBA ability and the results are discussed in relation to our earlier study of solvent effects on hydrogen abstraction from α-**T**OH. One of the water-soluble α-**T**OH models was (*S*)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) and the other was the corresponding hydroxytetramethylchromanacetic acid (HCAA).



α-**T**OH, R = $C_{16}H_{33}$

Trolox, R = COOH

HCAA, R = CH_2COOH

From the time of its discovery[31] Trolox has been found to be a highly active antioxidant, being even superior to α-**T**OH in a number of food preservation tests[32] and for the protection of oils of cosmetic interest.[33] Trolox is also of considerable potential biological and clinical importance since it has been shown to prevent both liver necrosis and lipid peroxidation in rats poisoned with bromobenzene[34] and to reduce myocardial infarction in canine models.[35] Moreover, kinetic solvent effects on the reactions of Trolox with halogenated methylperoxyl radicals, particularly $Cl_3COO^\bullet$, have been extensively investigated by Neta and co-workers.[36]

We used HCAA as well as Trolox because earlier kinetic studies had shown that it is a better mimic of α-**T**OH than Trolox.[4]

Results

Absolute rate constants, $k^{s}_{ArOH/BO}$ for reaction of *tert*-butoxyl radicals with Trolox and HCAA were measured by nanosecond laser flash photolysis in the usual way.[5,6,14,15] In the organic solvents the *tert*-butoxyl radicals were generated "instantaneously" by 308 nm LFP of di-*tert*-butyl peroxide and in water

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[13] The same is true for H-atom abstraction from phenol,[6,14,15] *tert*-butyl hydroperoxide,[14] and aniline.[15]

[14] Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929−2930.

[15] MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 1316−1321.

[16] Jovanovic, S. V.; Jankovic, I.; Josimovic, L. *J. Am. Chem. Soc.* **1992**, *114*, 9018−9021.

[17] Barclay, L R. C.; Baskin, K. A.; Locke, S. J.; Schaeffer, T. D. *Can. J. Chem.* **1987**, *65*, 2529−2540.

[18] In *tert*-butyl alcohol at 37 °C the $ROO^\bullet$ + α-**T**OH rate contant has also been reported to be $5.1 \times 10^5\ M^{-1}\ s^{-1}$. See: Niki, E.; Saito, T.; Kawakami, A.; Kamiya, Y. *J. Biol. Chem.* **1984**, *259*, 4177−4182. However, as Barclay *et al.*[17] have pointed out this value may be quite unreliable because it was based on an $ROO^\bullet$ + RH rate constant measured in solution under different conditions.

[19] Jore, D.; Patterson, L. K.; Ferradini, C. *J. Free Radicals Biol. Med.* **1986**, *2*, 405−410.

[20] Pryor, W. A.; Strickland, T.; Church, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 2224−2229.

[21] Castle, L.; Perkins, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6381−6382.

[22] The same criticism as in footnote 18 was levelled by Barclay *et al* [17] against Castle and Perkins' [21] rate constant in SDS micelles.

[23] Some other antioxidants structurally related to α-**T**OH have also been shown to be about 100 times less reactive towards peroxyl radicals in an SDS micellar system than in styrene.[9b]

[24] Barclay, L R. C.; Baskin, K. A.; Locke, S. J.; Vinqvist, M. R. *Can. J. Chem.* **1989**, *67*, 1366−1369. Barclay, L R. C.; Baskin, K. A.; Dakin, K. A.; Locke, S. J.; Vinqvist, M. R. *Can. J. Chem.* **1990**, *68*, 2258−2269.

[25] The $ROO^\bullet$ + PhOH reaction has also been demonstrated to show a solvent effect in homogeneous solutions which is attributable to hydrogen bonding between the phenol and HBA solvents.[26] For example,[26] at −32 °C $\log(k_{PhOH/ROO}\ /M^{-1}\ s^{-1})$ = 2.71, 2.58, 1.89, 1.55, 0.80, 0.75, and 0.74 in hexane, chlorobenzene, valeric acid, ethyl acetate, *n*-butanol, di-*n*-butyl ether, and acetone, respectively. The $ROO^\bullet$ + PhCHO reaction shows no significant solvent effects.[26] The rate constant ratio, $k_1(ROO^\bullet + \alpha\text{-}\mathbf{T}OH)/k(ROO^\bullet$ + methyl linoleate), has been reported to be 1.5×10^4, 1.0×10^4, 6.8×10^3, 5.4×10^3, 3.7×10^3 and 3.2×10^2 in acetonitrile, hexane, methanol, ethanol, SDS micelles, and phosphatidyl choline liposomes, respectively, at 37 °C.[27] The smaller antioxidant activity in protic solvents was attributed to hydrogen bonding. Unfortunately, these are only rate constant ratios and it appears unlikely to us that this ratio should, e.g., be greater in acetonitrile than in hexane.

[26] Tavadyan, L. A.; Mardoyan, V. A.; Nalbandyan, A. B. *Sov. J. Chem. Phys.* **1990**, *5*, 2537−2556.

[27] Iwatsuki, M.; Tsachiya, J.; Komuro, E.; Yamamoto, Y.; Niki, E. *Biochim. Biophys. Acta* **1994**, *1200*, 19−26.

[28] For some interesting observations and discussions regarding the inhibition of peroxidation of phospholipid bilayers by water-soluble α-**T**OH analogues and their partitioning between the bilayer and the water, see: Barclay, L. R. C.; Vinqvist, M. R. *Free Radical Biol. Med.* **1994**, *16*, 779−788. Barclay, L. R. C.; Artz, J. D.; Mowat, J. J. *Biochim. Biophys. Acta* **1995**, *1237*, 77−85.

[29] In SDS/linoleic acid mixed micelles different phenols show much more similar antioxidant activities[17,20,21] than is the case in homogeneous hydrocarbon solvents.[4] This "levelling effect" in the micelles presumably arises from a combination of differential partitioning of the phenols between the aqueous and lipid phases, differential diffusional effects within and between micelles, and differential changes in absolute reactivities because of hydrogen bonding to the water. However, it is important to note that even in these apparently simple SDS/linoleic acid micelle systems there must be some as yet unrecognized complications. Thus, the effective antioxidant activity of α-**T**OH relative to Trolox (*vide infra*) has been reported to be 0.61,[17] 0.34,[20] and 6.0 [21] while the effective antioxidant activity of 2,6-di-*tert*-butyl-4-methylphenol relative to Trolox has been reported to be 0.10[20] and 3.4[21]!

[30] And also for hydrogen atom abstraction from phenol.[6]

[31] Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil. Chem. Soc.* **1974**, *51*, 200−203.

[32] Cort, W. M.; Scott, J. W.; Arouj, M.; Mergens, W. J.; Cannalonga, M. A.; Osadca, M.; Harley, H.; Parrish, D. R.; Pool, W. R. *J. Am. Oil. Chem. Soc.* **1975**, *52*, 174−178. Cort, W. M.; Scott, J. W.; Harley, J. H. *Food Technol. (Chicago)* **1975**, *29*, 46−50.

[33] Scott, J. W.; Cort, W. M. *Cosmet. Toiletries* **1976**, *91*, 39−44.

[34] Casini, A. F.; Pompello, A.; Comporti, M. *Am. J. Pathol.* **1985**, *118*, 225−237.

[35] Mickle, D. A. G.; Li, R.-K.; Weisel, R. D.; Birnbaum, P. L.; Wu, T.-W.; Jackowski, G.; Madonik, M. M.; Burton, G. W.; Ingold, K. U. *Ann. Thorac. Surg.* **1989**, *47*, 553−557.

[36] (a) Neta, P.; Huie, R. E.; Maruthamutha, P.; Steenken, S. *J. Phys. Chem.* **1989**, *93*, 7654−7659. (b) Alfassi, Z. B.; Huie, R. E.; Kumar, M.; Neta, P. *J. Phys. Chem.* **1992**, *96*, 767−770. (c) Alfassi, Z. B.; Huie, R. E.; Neta, P. *J. Phys. Chem.* **1993**, *97*, 7253−7257.

Table 1. Absolute Rate Constants for Hydrogen Atom Abstraction by *tert*-Butoxyl Radicals ($k^{s}_{ArOH/BO}$) and Poly(peroxystyryl)peroxyl Radicals ($k^{s}_{ArOH/ROO}$) from (*S*)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic Acid (Trolox), (*S*)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid (HCAA), and α-Tocopherol (α-**T**OH) in Various Solvents at 298 ± 2 K for *tert*-Butoxyl and 303 K for the Peroxyl Radicals[a]

	$10^{-8}k^{s}_{ArOH/BO}$/M^{-1} s^{-1}				$10^{-5}k^{s}_{ArOH/ROO}$/M^{-1} s^{-1} [b]
ArOH	$C_6H_5OCH_3$	CH_3CN	$CH_3C(O)OC_2H_5$	H_2O	$C_6H_5CH{=}CH_2$
Trolox	16	5.2	2.0	17.5	11
HCAA	19	8.5	3.2	8.4	19[c]
α-**T**OH	20[d]	9.4[d]	2.9[d]		32

[a] Estimated experimental error ±10−15% for all LFP-derived rate constants (see ref 6). [b] Rate constants for reactions of these phenols with poly(peroxystyryl)peroxyl radicals measured at 303 K by the inhibited autoxidation of styrene method (see ref 4). [c] The corresponding propionic acid has $k = 37 \times 10^5$ M^{-1} s^{-1} (see ref 4). [d] From ref 6.

$$\mathrm{Me_3CO^{\bullet} + ArOH \xrightarrow{k^{S}_{ArOH/BO}} Me_3COH + ArO^{\bullet}} \qquad (2)$$

by 308 nm LFP of *tert*-butyl monoperoxysuccinate (BMPS), reaction 3. The carbonyloxyl radical which is also produced

$$\mathrm{Me_3COOC(O)CH_2CH_2COOH \xrightarrow[308\ nm]{h\nu} Me_3CO^{\bullet} + {}^{\bullet}OC(O)CH_2CH_2COOH} \qquad (3)$$

in reaction 3 will undergo a very rapid decarboxylation,[37] reaction 4, and the resulting primary alkyl radical will be too

$$\mathrm{{}^{\bullet}OC(O)CH_2CH_2COOH \rightarrow CO_2 + {}^{\bullet}CH_2CH_2COOH} \qquad (4)$$

unreactive toward the phenols to interfere with the measurement of $k^{s}_{ArOH/BO}$.[38] These rate constants were measured at 298 ± 2 K in each solvent in the presence of five different concentrations of Trolox and HCAA (typically in the range 7×10^{-4} to 4×10^{-3} M) by monitoring the pseudo-first-order growth of the ArO$^{\bullet}$ radicals at 420 nm (rate constant = k_{exptl}). The absolute second-order rate constants were obtained by the method of least squares:

$$k^{s}_{exptl} = k^{s}_{0} + k^{s}_{ArOH/BO}[\mathrm{ArOH}]$$

The results are summarized in Table 1 and some of our earlier kinetic data on the Me$_3$CO$^{\bullet}$ + α-**T**OH reaction[6] are included in this Table for comparison. The final column of Table 1 lists the rate constants for hydrogen atom abstraction from these phenols by poly(peroxystyryl)peroxyl radicals measured at 303 K in styrene as solvent in this laboratory some ten years ago.[4]

A few LFP experiments were carried out in the organic solvents using BMPS in place of di-*tert*-butyl peroxide as the *tert*-butoxyl source. Identical kinetic data were obtained though the BMPS generally gave somewhat weaker ArO$^{\bullet}$ signals.

Discussion

The *tert*-butoxyl radical kinetic data in the three organic solvents and the earlier peroxyl radical kinetic data in styrene[4] show that HCAA is a better model for α-**T**OH than is Trolox. We conclude, therefore, that the rate constant for hydrogen abstraction from α-**T**OH by *tert*-butoxyl in water, $k^{H_2O}_{TOH/BO}$ would be about 8×10^8 M^{-1} s^{-1}.

In earlier work[15] on kinetic solvent effects for hydrogen atom abstraction from phenol by cumyloxyl radicals we reported that our rate data could be correlated with various empirical measures of the HBA activities of the different solvents. We chose to correlate our results with Abraham *et al.*'s β_2^{H} solvent parameters[39] despite the fact that this is a scale of solute hydrogen bond basicities in CCl$_4$, rather than a scale for neat solvents. This choice was made simply because the β_2^{H} scale is the most extensive of all the scales measuring solvent HBA activities. A linear free energy plot of log($k^{s}_{PhOH/CumO}$/M^{-1} s^{-1}) vs β_2^{H} gave an excellent correlation. For unknown reasons, our rate measurements on the *tert*-butoxyl/α-**T**OH reaction in different solvents[6] do not correlate as well with β_2^{H} as was the case for phenol. However, a reasonable correlation is obtained by using the original β values of Taft and co-workers[40] which refer to the HBA activities of neat solvents. This plot is shown in Figure 1 for those solvents for which Taft *et al.*[40] give "reliable" β-values.[41] Excluded from this plot are our kinetic measurements in hexadecane, octane, and CCl$_4$ because the Me$_3$CO$^{\bullet}$/α-**T**OH reaction is partially diffusion-controlled in these

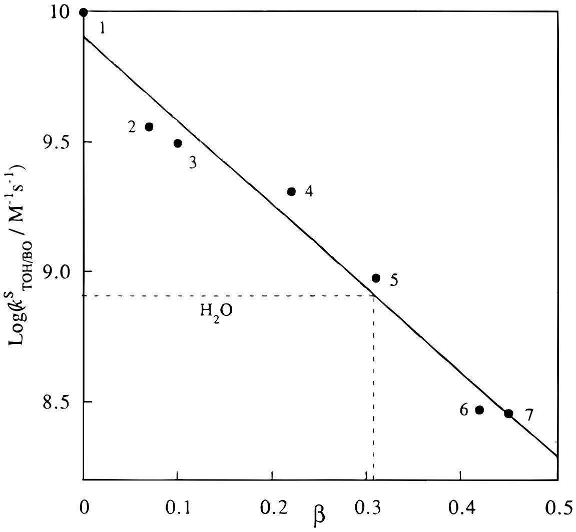

Figure 1. Plot of log ($k^{s}_{TOH/BO}$/M^{-1} s^{-1}) for abstraction of the phenolic hydrogen atom from α-tocopherol by *tert*-butoxyl radicals in various solvents vs the β values for these solvents. The rate constants were measured at 298 ± 2 K (see ref. 6) and the β values were taken from ref 40 (see ref 42). The solvents are the following: 1, *n*-pentane; 2, chlorobenzene; 3, benzene; 4, anisole; 5, acetonitrile; 6, methyl acetate; 7, ethyl acetate.

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(37) See, e.g.: Hilborn, J. W.; Pincock, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 2683−2686.

(38) Primary alkyl radicals abstract hydrogen from α-**T**OH with a rate constant of 1.7×10^6 M^{-1} s^{-1} at 70 °C in benzene, see: Evans, C.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4589−4593.

(39) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521−529. See also: Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Taft, R. W.; Morris, J. J.; Taylor, P. J.; Laurence, C.; Berthelot, M.; Doherty, R. M.; Kamlet, M. J.; Abboud, J.-L. M.; Sraidi, K.; Guihéneuf, G. *J. Am. Chem. Soc.* **1988**, *110*, 8534−8536. Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *Tetrahedron Lett.* **1989**, *30*, 2571−2574. Laurence, C.; Berthelot, M.; Helbert, M.; Sraidi, K. *J. Phys. Chem.* **1989**, *93*, 3799−3802. Abraham, M. H.; Lieb, W. R.; Franks, N. P. *J. Pharm. Sci.* **1991**, *80*, 719−724.

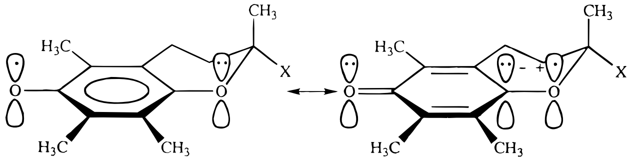
(40) Kamlet, M. J.; Abboud, J. L.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877−2887 and references cited therein. See also: Marcus, Y.; Kamlet, M. J.; Taft, R. W. *J. Phys. Chem.* **1988**, *92*, 3613−3622.

(41) This plot therefore excludes the points for acetic acid (no β value), *tert*-butyl alcohol (a non-reliable β = 1.01), and water (a non-reliable β = 0.18).

solvents,[6] i.e., $k^{\mathrm{s}}_{\mathrm{TOH/BO}}$values are reduced for reasons of viscosity not hydrogen bonding. Our rate constant of 8×10^8 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for the $\mathrm{Me_3CO^{\bullet}}$/α-**T**OH reaction in water would fall on this correlation line if $\beta(\mathrm{H_2O}) = 0.31$. We consider this β value to be "reliable". It may be compared with a "reliable" $\beta_2^{\mathrm{H}}(\mathrm{H_2O}) = 0.38$,[39] in which connection we note a solvent's β value is generally somewhat smaller than its β_2^{H} value.[42] Thus, water is not a very strong hydrogen bond acceptor in comparison to *tert*-butyl alcohol, for example, though it is a better acceptor than originally suggested.[40,41]

Our present kinetic results with the α-**T**OH analogue, HCAA, in water shed new light on earlier measurements of the rate constants for the reactions of peroxyl radicals with α-**T**OH in non-homogeneous, water−lipid systems.[17,20−24] As was mentioned in the Introduction, we have recently demonstrated that kinetic solvent effects on reaction 1 are independent of the nature and reactivity of $\mathrm{X^{\bullet}}$.[6] That is, for $\mathrm{X^{\bullet}} = \mathrm{Me_3CO^{\bullet}}$ (BO) and DPPH in two solvents A and B, $k^{\mathrm{A}}_{\mathrm{TOH/BO}}/k^{\mathrm{B}}_{\mathrm{TOH/BO}} \approx k^{\mathrm{A}}_{\mathrm{TOH/DPPH}}/k^{\mathrm{B}}_{\mathrm{TOH/DPPH}}$ despite the fact that in the same solvent the *tert*-butoxyl reaction is 1.6×10^6 times faster than the DPPH reaction.[6] There is just sufficient evidence to indicate that this principle can be extended to $\mathrm{X^{\bullet}} = \mathrm{ROO^{\bullet}}$. Thus, $k^{\mathrm{PhH}}_{\mathrm{TOH/BO}}/k^{\mathrm{Me_3COH}}_{\mathrm{TOH/BO}} = 31 \times 10^8/1.8 \times 10^8 = 17$,[6] while $k^{\mathrm{PhCH{=}CH_2}}_{\mathrm{TOH/ROO}} = 3.2 \times 10^6\ \mathrm{M^{-1}\ s^{-1}}$ [4] and $k^{\mathrm{Me_3COH}}_{\mathrm{TOH/ROO}} = 2.3 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$ [17,18] for a ratio of 14 provided benzene and styrene have similar HBA activities.[43] Since $k^{\mathrm{PhH}}_{\mathrm{TOH/BO}}/k^{\mathrm{H_2O}}_{\mathrm{TOH/BO}} = 31 \times 10^8/8 \times 10^8 = 3.9$ and, again assuming that benzene and styrene have roughly equal HBA activities, we can estimate that $k^{\mathrm{H_2O}}_{\mathrm{TOH/ROO}} \approx k^{\mathrm{PhCH{=}CH_2}}_{\mathrm{TOH/ROO}}/\ 3.9 = 3.2 \times 10^6/3.9 = 8 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$. This estimated rate constant for the $\mathrm{ROO^{\bullet}}$ + α-**T**OH reaction in water is greater than the measured rate constants for the same reaction in *tert*-butyl alcohol, viz.,[17] $2.3 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$ or ethanol, viz.,[19] $9.5 \times 10^4\ \mathrm{M^{-1}\ s^{-1}}$. More importantly, it is much greater than the rate constants measured in SDS micelles dispersed in water, viz., $1.7 \times 10^4\ \mathrm{M^{-1}\ s^{-1}}$, [17] $3.7 \times 10^4\ \mathrm{M^{-1}\ s^{-1}}$,[20] and $6.0 \times 10^4\ \mathrm{M^{-1}\ s^{-1}}$,[21,22] and in a phospholipid bilayer dispersed in water, viz.,[24] $3 \times 10^3\ \mathrm{M^{-1}\ s^{-1}}$. It seems highly unlikely that the SDS micelles and the phospholipid bilayer could contain HBA molecules that were so very much better HBA's than water or *tert*-butyl alcohol (which is a slightly stronger HBA than esters).[42] As Castle and Perkins[21] proposed, therefore, it would appear probable that in mixed water−lipid systems the *principal* reason for the small magnitudes of $k_{\mathrm{TOH/ROO}}$ is that much of the α-**T**OH was physically inaccessible to the peroxyl radicals[46] and that the rate retarding effect due to hydrogen bonding is only of secondary importance.[47] In this connection, physical inaccessibility is more likely to be connected to inter-lipid particle differences in composition than to intraparticle diffusional difficulties. That is, some of the lipid particles may not have contained α-**T**OH and so they could undergo relatively rapid oxidation despite the fact that other particles (and, hence, the total reaction system) contained significant quantities of α-**T**OH. Whether α-**T**OH in the biological membranes of living animals is also, in part, physically inaccessible to bio-generated peroxyl radials remains a major challenge for future research.

The interesting observation that Trolox is less reactive than α-**T**OH in organic solvents but more reactive than the α-**T**OH analogue, HCAA, in water is readily accounted for in terms of the inductive effect of Trolox's carboxyl group.[4] That is, in organic solvents the C(O)OH moiety is electron-withdrawing ($\sigma_{\mathrm{I}} = 0.30$)[49] and this will impair the ability of the 2p-type lone pair on the ring oxygen to participate in the stabilization of the phenoxyl radical. In water at pH 7, on the other hand, the carboxyl group will be ionized and the $\mathrm{C(O)O^-}$ group is strongly electron-releasing ($\sigma_{\mathrm{I}} = -0.19$),[49] which will enhance the ability of ring oxygen's 2p-type lone pair to stabilize the phenoxyl radical. This difference between the C(O)OH and $\mathrm{C(O)O^-}$ groups becomes relatively unimportant in HCAA because of the electronically "insulating" effect of the adjacent methylene group.[50]



Finally, it is interesting to compare the kinetic solvent effect found in the present work for the Trolox/$\mathrm{BO^{\bullet}}$ reaction (Table 1) with the much more extensive kinetic data obtained by Neta et al.[36] on the Trolox/$\mathrm{Cl_3COO^{\bullet}}$ reaction. The $\mathrm{Cl_3COO^{\bullet}}$ radical is not an "ordinary" alkylperoxyl since it is highly electron-deficient and oxidizes most substrates by electron transfer.[36] It was found that the Trolox/$\mathrm{Cl_3COO^{\bullet}}$ kinetic data could be roughly correlated by the two-parameter linear free energy relation:[36c]

$$\log(k^{\mathrm{s}}_{\mathrm{Trolox/CCl_3COO}}/\mathrm{M^{-1}\ s^{-1}}) = C_0 + C_1\delta_{\mathrm{H}}^2 + C_2\mathrm{p}K_{\mathrm{a}}$$

where δ_{H}^2 is the square of Hildebrand's solubility parameter (i.e., it is the cohesive energy density) for the solvent and $\mathrm{p}K_{\mathrm{a}}$ was used as a measure of the proton-removal capability of the solvent (i.e., as an alternate to the more normal hydrogen bond acceptor parameter, β[40]). However, the correlation did not include the point for $\mathrm{CCl_4}$ because "its basicity is unknown. (Moreover) To fit $\mathrm{CCl_4}$ to the same line, it would have to have a $\mathrm{p}K_{\mathrm{a}}$ value in acetonitrile of 11.9, close to that of pyridine, which is unlikely".[36c]

We suggest that a solution to this "$\mathrm{CCl_4}$ problem" is that the Trolox/$\mathrm{Cl_3COO^{\bullet}}$ reaction occurs by two independent pathways which are influenced differently by a solvent's physical properties. First, the reaction is a straightforward hydrogen atom abstraction in solvents of low dielectric constant and low basicity (reaction 5). This accounts for the fact that the rate constants

$$\mathrm{Cl_3COO^{\bullet}} + \mathrm{ArOH} \rightarrow \mathrm{Cl_3COOH} + \mathrm{ArO^{\bullet}} \qquad (5)$$

decrease along the solvent series $\mathrm{CCl_4}$ > dioxane > ether ($10^{-7}k_5/\mathrm{M^{-1}\ s^{-1}}$ = 4.6, 1.5, and 1,4, respectively)[36c] because

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(42) For the solvents shown in Figure 1 the β and β_2^{H} values are: pentane, 0, 0; chlorobenzene, 0.07, 0.09; benzene, 0.10, 0.14; anisole, 0.22, 0.26; acetonitrile, 0.31, 0.44; methyl acetate, 0.42, 0.40; ethyl acetate, 0.45, 0.45. The β_2^{H} value for *tert*-butyl alcohol is 0.49.

(43) This check is important because the absolute reactivity of the $\mathrm{DPPH^{\bullet}}$ radical, as measured by hydrogen atom abstraction from a hydrocarbon, is higher in *tert*-butyl alcohol than in most other solvents (in which it maintains the same reactivity).[6,44] The reactivity of alkoxyl radicals, as measured by hydrogen atom abstraction from hydrocarbons, is the same in all solvents, including *tert*-butyl alcohol.[45]

(44) Valgimigli, L. Unpublished results.

(45) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466−470.

(46) The same explanation is likely to apply to other lipid-soluble, phenolic antioxidants in SDS micelles.[9b,21,23]

(47) Hydrogen bonding between phenol and hydrogen bond accepting solvents has been demonstrated to increase the effective PhO−H bond dissociation energy.[48]

(48) Wayner, D. D. M.; Lusztyk, E.; Pagé, D.; Ingold, K. U.; Mulder, P.; Laarhoven, L. J. J.; Aldrich, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 8737−8744.

(49) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251.

(50) Intramolecular hydrogen bonding between the C(O)OH group and the ring oxygen atom may also affect the reactivities of the carboxylic acids, see ref 4.

of the increase in the hydrogen bond accepting abilities of these solvents ($\beta = 0.00$, 0.37, and 0.47, respectively). Second, the reaction becomes an electron transfer in solvents with high dielectric constants and high basicities (reaction 6).

$$\mathrm{Cl_3COO^\bullet + ArOH \rightarrow Cl_3COO^- + ArO^\bullet + H^+} \qquad (6)$$

In some cases, this may involve a solvent-assisted proton loss (reaction 7).

$$\mathrm{Cl_3COO^\bullet + ArOH + S \rightarrow Cl_3COO^- + ArO^\bullet + SH^+} \qquad (7)$$

Electron transfer, with or without solvent-assisted proton removal, would explain the high rates found in the relatively good hydrogen bond accepting solvents, water, formamide, triethylamine,[51] and pyridine, viz.,[36c] $10^{-7}\ k_{6/7}/\mathrm{M^{-1}\ s^{-1}} = 58$, 27, 9.5, and 8.0. A number of solvents yielded rate constants lower than the value found in CCl_4 but not as small as might have been expected if the reactions had occurred solely by a hydrogen atom transfer which was retarded by hydrogen bonding of the Trolox, e.g., *tert*-butyl alcohol ($k = 2.1 \times 10^7$ $\mathrm{M^{-1}\ s^{-1}}$, β non-reliable,[41] $\beta_2^{\mathrm{H}} = 0.49$),[42] acetone ($k = 0.92 \times 10^7\ \mathrm{M^{-1}\ s^{-1}}$, $\beta = 0.48$), and acetonitrile ($k = 1.2 \times 10^7\ \mathrm{M^{-1}\ s^{-1}}$, $\beta = 0.31$). In these and other solvents it appears possible that both hydrogen atom abstraction and electron transfer play a role in the overall reaction.

Experimental Section

Materials. Solvents were of the purest grade commercially available and were used without further purification. (*S*)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) was a commercial sample (Aldrich, 98%) and was used as received. (*S*)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid (HCAA) was available from previous studies (purity 99% by HPLC on a 150 × 4.6 mm, 3 μm particle size C-18 column eluted at 1.0 mL/min with EtOH/H_2O (92:8, v/v) using 295 nm detection). Di-*tert*-butyl peroxide (Aldrich, 98%) was percolated through activated basic alumina immediately prior to use (to remove any traces of *tert*-butyl hydroperoxide). *tert*-Butyl monoperoxysuccinate (BMPS)[52] was synthesized according to the results of a mathematical optimization[53] of the method proposed by Davies *et al.*[54] Succinic anhydride (6.0 g; 0.06 mol) was dissolved in 70 mL of acetone at 40 °C and 0.065 mol (8% excess) of *tert*-butyl hydroperoxide (Aldrich) were added, immediately followed by 2.37 g (0.03 mol) of pyridine. The reaction mixture was stirred for 15 min at 40−45 °C, then cooled, diluted with chloroform, washed with hydrochloric acid (1:3; 2 × 50 mL) and water (1 × 30 mL), and dried ($MgSO_4$). The solvent and unreacted hydroperoxide were removed under vacuum (10 mmHg) at room temperature. The white solid was recrystallized from Et_2O/hexane to give white crystalline BMPS that was pure by TLC (benzene/acetone, 9:1; $R_f = 0.1$). Yield = 75%; mp 56 °C (lit. mp 54 °C,[53] 58−59 °C[54]); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 2.63 (t, 2H, $J = 6$ Hz), 2.73 (t, 2H, $J = 6$ Hz), 3.01 (s, 1H).

Laser Flash Photolysis (LFP). The laser flash photolysis equipment and experimental procedures have been adequately described in earlier publications.[5,6,14,15,45,55] Experiments were carried out in cells made of 7 mm × 7 mm Suprasil quartz tubing. *tert*-Butoxyl radicals were generated by 308 nm LFP of solutions of di-*tert*-butyl peroxide (0.22 M) or *tert*-butyl monoperoxysuccinate (0.13 M) at 298 ± 2 K in the presence of the hydrogen atom donating substrate (the peroxide concentrations were chosen so as to give an O. D. ∼0.3 at the laser wavelength). When experiments were performed in water the pH was adjusted to 7.0 by addition of concentrated NaOH. The reaction was followed by monitoring the growth in the aroxyl radicals' absorption at 420 nm. Pseudo-first-order rate constants (k^s_{exptl}) were determined by fitting digitally averaged growth curves arising from five to ten laser flashes. Absolute second-order rate constants ($k^s_{\mathrm{ArOH/BO}}$) were calculated by least-squares fitting of k^s_{exptl} vs [ArOH] for five different ArOH concentrations in the range $(7-40) \times 10^{-4}$ M ($r > 0.99$). The ArOH concentrations were chosen so that k^s_{exptl} was in the range $(2-50) \times 10^5\ \mathrm{s^{-1}}$.

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[51] The β value for triethylamine is 0.71,[40] not 0.00 as given in ref 36c.

[52] The IUPAC name for this compound is 3-[(*tert*-butyldioxy)carbonyl]-propionic acid.

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