Communications to the Editor

Inhibition Kinetics of Chain-Breaking Phenolic Antioxidants in SDS Micelles. Evidence That Intermicellar Diffusion Rates May Be Rate-Limiting for Hydrophobic Inhibitors Such as α-Tocopherol

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As chain-breaking inhibitors of lipid autoxidation, phenols compete with an autoxidizable lipid, LH, for a chain-carrying peroxy radical, LOO•, to terminate the chain process.

$$\text{Propagation: } LOO^\bullet + LH \xrightarrow{k_p} LOOH + L^\bullet \xrightarrow{O_2} LOO^\bullet \text{ etc.} \quad (1)$$

$$\text{Inhibition: } LOO^\bullet + ArOH \xrightarrow{k_{inh}} LOOH + ArO^\bullet \xrightarrow{LOO^\bullet} \text{nonradical products} \quad (2)$$

Early measurements of k_{inh} in homogeneous solution[1] have been followed by experiments employing more biologically relevant systems such as water-borne liposomes[2] and micelles.

In studies of the food antioxidant 3-butylated hydroxyanisole (3-BHA) and other phenols, we have employed linoleic acid as an oxidation substrate micellized in SDS,[3] following reports[4-6] that autoxidation of such dispersions follows classical rate laws in both uninhibited (eq 3) and inhibited (eq 4) reactions.

$$\text{uninhibited rate law: } -d[O_2]/dt = k_p[LH](R_i)^{1/2}/(2k_t)^{1/2} \quad (3)$$

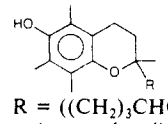
$$\text{inhibited rate law: } -d[O_2]/dt = k_p[LH]R_i/nk_{inh}[inh] + R_i \quad (4)$$

The present paper reports that by making use of a simple technique[7] to determine the partitioning of solute between aqueous and micellar phases, it is possible to quantify the manner in which the power of an inhibitor is moderated by its ability to enter the locus of autoxidation, the micelle. More importantly, it reveals that intermicellar diffusion may be rate-limiting.

Results in Table I[8] are principally for commercial phenolic food additives, α-tocopherol, and derivatives of "Trolox"[9] (tocopherol models). Equation 4 *appears* to be obeyed in all cases, since plots of inhibited rate versus 1/[inh] are linear as 1/[inh] approaches zero and show intercepts, equal to the rate of initiation, R_i, in good agreement with values of R_i determined by the lag period method.[10] As expected, the effectiveness of phenols with an appreciable solubility in water is attenuated by their failure to partition into the micellar phase (e.g., Trolox itself, at pH 7). This represents the first quantitative consideration of the influence of partitioning on the effectiveness of an antioxidant. What was unexpected was that α-tocopherol is by no means the most potent antioxidant in this micellar system; it is considerably less effective than the Trolox esters or even the simple 2,5-di-*tert*-butyl-4-methoxyphenol. By contrast, α-tocopherol and its five-membered ring analogue are the most effective phenolic scavengers known for peroxy radicals in homogeneous solution.[11]

Two features of the micellar system might account for the failure of α-tocopherol[12] to provide the best protection against autoxidation.[14] First, the relative spatial distributions[15] of to-

Table I. Distribution Coefficients and Inhibition Rate Constants for the Reaction of Phenols with Linoleoylperoxy Radicals in Buffered SDS Micelles[3]

phenol (inh)	k_{inh} (effective),[a] 10^2 M^{-1} s^{-1}	f[b]	k_{inh} (intrinsic),[c] 10^2 M^{-1} s^{-1}
phenol	0.19	0.11	1.7
2-*tert*-butylphenol	14	0.77	19
2,6-di-*tert*-butyl-4-methylphenol (BHT)	340	0.97	350
2-*tert*-butyl-4-methoxyphenol (BHA)	250	0.77	330
2,5-*tert*-butyl-4-methoxyphenol	1300[d]	0.88	1500
			
R = $((CH_2)_3CHCH_3)_3CH_3$ (α-tocopherol)	600	1	600
COOH (≡CO_2^-) "Trolox"	100	0.02	5000[e]
$COOCH_3$	3500[d]	0.94	3700
$COOC_2H_5$	3300[d]	0.95	3500
$COOC_4H_9$	2900[d]	0.97	2900
$COOC_8H_{17}$	3300[d]	1	3300
$COOCH_2C_7F_{15}$	1300[d]	1	1300
$COOC_{10}H_{21}$	3600[d]	1	3600

[a] Effective inhibition rate constant for eq 2, calculated from eq 4 taking $n = 2.0$[13] and $k_p = 100$ M^{-1} s^{-1} (Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 793-802), although a lower value may be more appropriate (Barclay, L. R. C.; Locke, S. J.; MacNeil, J. M. Vankessel, J. *Can. J. Chem.* **1985**, *63*, 2633). [b] Fraction of phenol in micellar pseudophase under reaction conditions. Determined according to ref 7. [c] k_{inh}(intrinsic) can be recalculated from eq 4 by using new values for [inh] that reflect its partitioning into the micellar phase. This simplifies to k_{inh}(intrinsic) = k_{inh}(effective)/f. [d] Such low concentrations of these inhibitors were required that consumption was considerable. This has been allowed for at a rate of $R_i/2$ for concentrations applied to eq 4; this uncertainty causes values of k_{inh} to be reproducible to ±ca. 30%. For less reactive phenols, reproducibility was typically ±5-10%. [e] The error associated with the determination of small f values[7] makes this value uncertain.

(1) (a) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791-7792. (b) Burton, G. W.; Le Page, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472-6477.

(2) (a) Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7792-7794. (b) Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6478-6485.

(3) Concentrations for the total reaction volume (10 mL): Linoleic acid, 3 mM; SDS, 15 mM; sodium phosphate buffer, 50 mM (pH 7.0). Reactions at 40.0 °C, initiated by di-*tert*-butyl hyponitrite (0.3 mM). Rates measure by O_2 electrode.

(4) Yamamoto, Y.; Haga, S.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1260-1264.

(5) (a) Barclay, L. R. C.; Lock, S. J.; MacNeil, J. M. *Can. J. Chem.* **1983**, *61*, 1288-1290. (b) Barclay, L. R. C.; Lock, S. J.; MacNeil, J. M. *Can. J. Chem.* **1985**, *63*, 366-374. (c) Barclay, L. R. C.; Locke, S. J.; MacNeil, J. M.; VanKessel, J.; Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 2479-2481.

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(7) Burkey, T. J.; Griller, D.; Lindsay, D. A.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 1983-1985.

(8) Values of k_{inh} (Table I) are for reaction 2 based in the micellar phase. Reaction in the aqueous phase should be negligible since LOO• will partition overwhelmingly into the micellar phase.

(9) Trolox (Hoffman La Roche) = 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

(10) Boozer, C. E.; Hammond, G. S.; Hamilton, C. E.; Sen, J. N. *J. Am. Chem. Soc.* **1955**, *77*, 3233-3237.

(11) 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.

(12) Samples of α-tocopherol were pure by spectroscopy, HPLC, and by the lag period method compared with standard inhibitors.[1b,10,13]

(13) Winterle, J.; Dulin, D.; Mill, T. *J. Org. Chem.* **1984**, *49*, 491-495.

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copherol and linoleoylperoxy radical within the micelle might be unfavorable. However, since there is no significant variation in k_{inh} for the C_1–C_{10} hydrocarbon esters of Trolox, which presumably will have very different solubilization sites if this argument operates, this feature is considered unimportant. The alternative, which we prefer, is that diffusion of the highly lipophilic phenols, e.g., tocopherol, between micelles may be so slow as to limit the scavenging process. The most potent phenols in Table I suppress autoxidation to around 10% of its uninhibited rate at a ratio of phenol molecules to micelles of 1:100. For the phenol to protect ca. 100 micelles so effectively, its intermicellar diffusion (i.e., the frequency with which it "visits" each micelle) must be rapid compared to the lifetime of a linoleoylperoxy radical.[16,17]

In a similar case where the rate of a bimolecular free-radical process was retarded by entrainment within SDS micelles, the rate constant for exit of mesitylthiyl radicals from SDS was estimated at 2×10^3 s^{-1}.[18] The more hydrophobic α-tocopherol should exit more slowly,[19] although the degree of acceleration provided by its amphipathic nature[20] is unclear. We estimate the pseudo-first-order rate constant ($=k_p$[LH]) for the propagation reaction of LOO$^\bullet$ (eq 1) to be 75 s^{-1} in our system, so exit rates of this order, with 100 micelles to be visited, would be rate-limiting. Where exit from the micelle is a rate-controlling step, eq 4 is inapplicable without modification.

Thus, it seems that the hydrophobic phytyl tail of α-tocopherol, apparently chosen by nature to *retain* vitamin E in biomembranes,[21] inhibits intermicellar transfer. In this behavior, micelles can be compared to liposomes where, for example,[22] α-tocopherol has been found to be reluctant to exchange among phosphatidylcholine liposomes—in contrast to analogues that lack the phytyl tail and exchange freely. A requirement for facile diffusion may be one reason why small and relatively polar phenols are often superior to α-tocopherol as food antioxidants.[23,24] We may also be witnessing the onset of such behavior in the series of Trolox esters studied. Values of k_{inh} are fairly constant for the C_1–C_{10} hydrocarbon esters but the highly hydrophobic $C_7F_{15}CH_2$ compound (Table I) is appreciably less effective. We believe that this is due to a hydrophobic effect rather than to steric or electronic effects.

Our uninhibited reactions obey eq 3 in that oxygen uptake is first order in linoleic acid (0.95), half-order in initiator (0.60), and reciprocal three-halves order in micellised SDS (−1.53). Bimolecular termination therefore operates and, since the chance that two autoxidation chains initiate in the same micelle is essentially nil,[25] this is evidence that linoleoylperoxy radicals diffuse freely from one micelle to another.[26] For extremely hydrophobic antioxidants such as α-tocopherol, it is probably the diffusion of the chain-carrying peroxy radical to the phenol rather than the reverse that provides the (rate-limiting) mechanism for encounter and consequent scavenging.[27]

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Registry No. SDS, 151-21-3; BHT, 128-37-0; BHA, 121-00-6; LOO$^\bullet$, 86683-30-9; linoleic acid, 60-33-3; 2-*tert*-butylphenol, 88-18-6; 2,5-di-*tert*-butyl-4-methoxyphenol, 1991-52-2; α-tocopherol, 59-02-9; trolox, 56305-04-5; phenol, 108-95-2; di-*tert*-butyl hyponitrite, 14976-54-6; trolox methyl ester, 86646-83-5; trolox ethyl ester, 103960-43-6; trolox butyl ester, 103960-44-7; trolox octyl ester, 103960-45-8; trolox (perfluoroheptyl)methyl ester, 103960-46-9; trolox decyl ester, 103960-47-0.

(14) Estimates of k_{inh} for α-tocopherol in homogeneous solution include 3.2×10^6 M^{-1} s^{-1} (polystyrylperoxy in PhCl)[11] and 5.1×10^5 M^{-1} s^{-1} (methyl linoleoylperoxy in *t*-BuOH: Niki, E.; Saito, T.; Kawakami, A.; Kamiya, Y. *J. Biol. Chem.* **1984**, *259*, 4177–4182).

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(16) That intermicellar diffusion is rapid compared with inhibition for smaller phenols is found in the close correspondence between relative reactivities measured in the course of this work and those determined in homogeneous solution (e.g., Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744–1751); absolute comparison of k_{inh} from the present work with homogeneous systems may not be justified.

(17) Diffusive encounter of species A and B is known to be slowed if diffusion of either component is impeded (e.g., Torney, D. C.; McConnell, H. M. *Proc. R. Soc. London, Ser. A* **1983**, *387*, 147–170).

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(24) Poor antioxidant activity of α-tocopherol in aqueous dispersions with a water-soluble initiator has been noted previously.[4]

(25) The initiator[3] partitions almost entirely into the aqueous phase (method of ref 7).

(26) Another indication that each autoxidation chain is not confined within any single micelle is that at low initiation rates, chain lengths in excess of 70 were seen whereas each micelle contains only about 17 linoleic acid molecules.

(27) The exit rate of amphiphilic molecules from their micelles is strongly dependent on their chain length.[20] The value for hexadodecyl sulfate has been estimated at 6×10^4 s^{-1} and the exit rate for linoleate anion from SDS might be expected to be similar.

Carbon Monoxide Cleavage by (silox)$_3$Ta (silox = *t*-Bu$_3$SiO$^-$)

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The initial step in the Fischer–Tropsch (F–T)[1] process is thought to be the dissociative adsorption of CO to provide surface oxide and carbide.[2] The latter surface species are modeled[3] by late metal, carbonyl cluster carbides,[4] whose formation is often accompanied by the release of CO_2 ($2CO \rightarrow$ carbide + CO_2). Although carbonylation of metal alkyls[5] and hydrides[6] has resulted in CO cleavage, existing early metal carbides[7] have not been prepared by direct scission of the carbon–oxygen bond. With CO coupling promoted by low-valent early metal centers providing

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