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Scavenging of dpph$^\bullet$ Radicals by Vitamin E Is Accelerated by Its Partial Ionization: the Role of Sequential Proton Loss Electron Transfer

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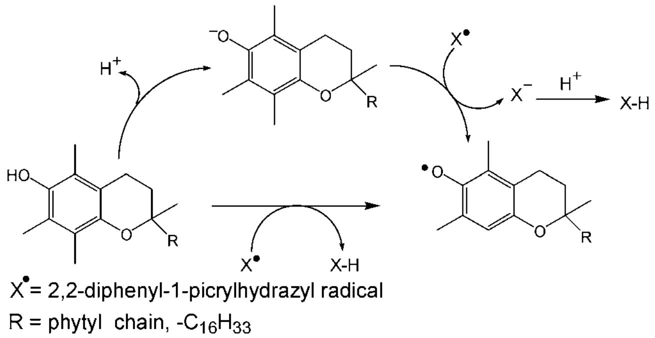
ABSTRACT



Rate constants for reaction of α-tocopherol, 2,2,5,7,8-pentamethyl-6-hydroxychroman, and 2,6-di-*tert*-butyl-4-methylphenol with 2,2-diphenyl-1-picrylhydrazyl radical were measured in solvents of different polarity and H-bond basicity. In ionization supporting solvents besides hydrogen atom transfer (HAT), the kinetics of the process is partially governed by sequential proton loss electron transfer (SPLET). Addition of acetic acid reduces the rate by eliminating SPLET to leave only HAT, while addition of water increases the rate by enhancing phenol deprotonation.

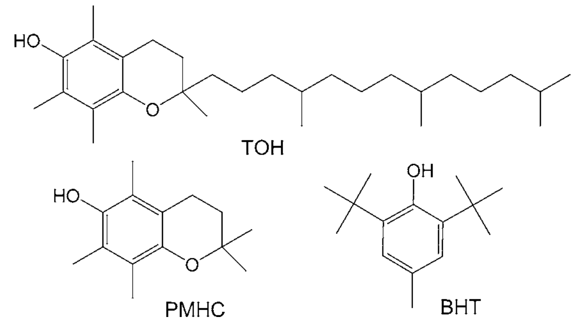


Figure 1. Chemical structures of α-tocopherol (TOH), 2,2,5,7,8-pentamethyl-6-hydroxychroman (PMHC), and 2,6-di-*tert*-butyl-4-methylphenol.

Lipid peroxidation is a free-radical chain process that damages living organisms and can lead to diseases such as artherosclerosis and cancer. In living organisms, "front line" protection against peroxidation is provided by vitamin E. This is a mixture of lipophilic, radical-trapping antioxidants, its most active component being α-tocopherol (TOH, see Figure 1). There is voluminous literature concerning hydrogen atom transfer (HAT) from TOH to carbon-, sulfur-, oxygen-, and nitrogen-centered radicals, X$^\bullet$: TOH + X$^\bullet$ → TO$^\bullet$ + X−H. The high radical-trapping activity of TOH is due to favorable stereoelectronic factors that provide exceptional stabilization to the TO$^\bullet$ radical.[1] Actual radical-trapping rates are also influenced by TOH's environment including the accessibility of TOH molecule to lipid-soluble or water-soluble radicals (which depends on the localization and mobility of TOH)[2] and solvent-mediated

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(1) (a) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc*. **1981**, *103*, 6427−6477. (b) Doba, T.; Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc*. **1983**, *105*, 6505−6506. (c) Burton, G. W.; Doba, T.; Gabe, E. J.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc*. **1985**, *107*, 7053−7065.

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accessibility of the OH group (which gives rise to kinetic solvent effects, KSEs).[3]

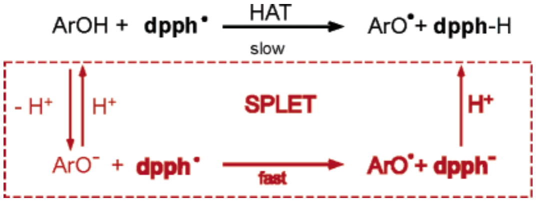
In general, the rates of HAT from phenols to a radical are subject to large KSEs[3−5] because, in hydrogen bond accepting solvents (HBAs), the phenolic hydroxyl group is not accessible to radicals. The measured HAT rate constant in HBAs, k^{HAT}, therefore involves only nonintermolecularly-H-bonded molecules and will be smaller than the rate constant, k^0, in non-HBA solvents (e.g., saturated hydrocarbons). An empirical equation[5] connects k^{HAT} with k^0 by the means of Abraham's parameters α_2^{H} and β_2^{H} (characterizing the relative ability of a phenol to be a hydrogen bond donor,[6] and the relative ability of a solvent to be a hydrogen bond acceptor,[7] respectively)

$$\log k^{\mathrm{HAT}} = \log k^0 - 8.3\,\alpha_2^{\mathrm{H}}\beta_2^{\mathrm{H}} \qquad (1)$$

where the rate constants are expressed in $M^{-1}\,s^{-1}$ units. For any HAT reaction, provided a k^0 or a k^{HAT} value is available, this equation can be used to predict the HAT rate constants in several hundred solvents.[3] Since α_2^{H} and β_2^{H} are positive numbers (range for both, 0 to 1) eq 1 requires that k^{HAT} is always $\leq k^0$.

Apparent exceptions to the $k^{\mathrm{HAT}} \leq k^0$ rule have been observed in solvents that support ionization, particularly alcohols, for reactions between phenols and 1,1-diphenyl-2-picrylhydrazyl (**dpph**$^\bullet$) radicals. These reactions are faster (sometimes much faster) than would be predicted from eq 1. These anomalies were explained by the mechanism named sequential proton loss electron transfer (SPLET),[8,9] which occurs in parallel with HAT. In a solvent, S, that supports ionization the measured rate is the sum of the rates for the HAT (Scheme 1, black) and SPLET (Scheme 1, red) processes. SPLET is favored for reactions of phenols having low pK_a's with electron-deficient radicals that yield products having low pK_a's, e.g., **dpph**$^\bullet$/**dpph**-H and peroxyls ROO$^\bullet$/ROOH.[10]

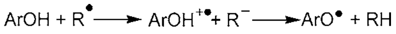
Scheme 1



The SPLET mechanism has been independently discovered by Foti et al.[11] Moreover, the phenolate anion of the vitamin E model compound, PMHC (Figure 1), has been shown to react with a **dpph**$^\bullet$ more rapidly than its parent phenol.[12] Whether the SPLET mechanism will be significant compared with the HAT mechanism will depend on the phenol's acidity, the radical's electron affinity, the ability of the solvent to support phenol ionization, and the ability of the phenol to be a HB donor. SPLET may be supressed by the addition of acetic acid and, with sufficient acetic acid, phenol ionization, and hence SPLET, can be eliminated leaving only the HAT mechanism operative.

Some recent theoretical[13] and experimental[14] papers contain misleading statements that HAT and electron transfer *followed* by proton transfer (ET-PT, Scheme 2) are the only two mechanisms involved in the reactions of radicals with phenols, including PMHC[14] and, hence, are the only two mechanisms responsible for phenols' antioxidant activities. Since both theory[13] and the interpretation of the experimental results[14] contradict our own work with its well supported conclusion that HAT and SPLET are the two mechanisms important in radical + phenol reactions, some new experiments were undertaken to check, in particular, whether the reported enhanced rate of the **dpph**$^\bullet$ + PMHC reaction in methanol compared with acetonitrile is due to ET-PT, as claimed[14] or to SPLET, as we would predict.

Scheme 2



Bimolecular rate constants, k^{S}, were measured for the reactions of **dpph**$^\bullet$ with TOC, PMHC, and 2,6-di-*tert*-butyl-4-methylphenol (BHT), see Figure 1, and are given in Table 1. Considering the BHT data first, it can be seen that the reaction is faster in methanol than in the non-HBA solvent,

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[7] Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521−529.

[8] Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433−3438.

[9] Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 5888−5896.

[10] The pK_a's (in parentheses) for some relevant ion/molecule pairs are[8] **dpph**$^-$, H$^+$/**dpph**H (8.5); ROO$^-$, H$^+$/ROOH (12.8); Me$_3$CO$^-$, H$^+$/Me$_3$COH (19.2); primary alkyl radical, H$^+$/alkane (ca. 50).

[11] Foti, M. C.; Daquino, C.; Geraci, C. *J. Org. Chem.* **2004**, *69*, 2309−2314.

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[14] Nakanishi, I.; Kawashima, T.; Ohkubo, K.; Kanazawa, H.; Inami, K.; Mochizuki, M.; Fukuhara, K.; Okuda, T.; Ozawa, T.; Itoh, S.; Fukuzumi, S.; Ikota, N. *Org. Biomol. Chem.* **2005**, *3*, 626−629.

Table 1. Measured Rate Constants, k^S/M^{-1}s^{-1}, for the Reactions of **dpph$^•$** with TOH, PMHC and BHT in Five Solvents and in Acidified Methanol[a] and (in parentheses) in the Four HBA Solvents the Rate Constants Predicted by eq 1

solvent (β_2^H)[b]	ϵ_r[c]	k^S		
		BHT	TOC	PMHC
α_2^H		0.21[8]	0.37[5]	0.39
n-heptane (0.00)	1.9	1.1[d]	8500	7600
MeCOOEt (0.45)	6.0	0.16 (0.18)	190 (320)	170 (270)
dioxane (0.47)[e]	2.2	0.044 (0.17)	99 (270)	98 (230)
MeCN (0.44)	35.9	0.21 (0.19)	344 (340)	310 (290)
MeOH (0.41)	32.7	2.4[d,f](0.21)	390 (420)	350 (360)
MeOH/10 mM CH_3CO_2H[g]		0.13 [d]	250	280
MeOH/100 mM CH_3CO_2H		0.12[d]	250	230

[a] Values k^S are given with errors usually less than 10%; see the Supporting Information for experimental details and errors. [b] Values of β_2^H from ref 7. [c] Permittivity (dielectric constant), from ref 21. [d] Values from ref 8. [e] Reference 9. This value has not been statistically corrected. [f] Measurements in ref 8 gave k^{MeOH} =3.7 M^{-1} s^{-1}. [g] β_2^H is not available for acetic acid; for propionic and butyric acids it is 0.42.

heptane. This result indicates that the HAT mechanism in methanol (a fairly strong HBA, $\beta_2^H = 0.41$) has become rather unimportant in comparison with some other mechanism (see eq 1). In principle, this other mechanism could be SPLET or the claimed[13,14] ET-PT process. The addition of acetic acid to the methanol-containing BHT will reduce the extent of ionization of this phenol and the measured rate constant might therefore be expected to increase (or remain the same) if the ET-PT mechanism is operative in methanol. In fact, the addition of acetic acid (to obtain 10 and 100 mM concentrations) reduces the rate constant by more than an order of magnitude. This result is fully consistent with the occurrence of SPLET in nonacidified methanol.

Moreover, the rate constants in acidified methanol are the same order of magnitude as those in acetonitrile and ethyl acetate, solvents having similar HBA activities (β_2^H parameters) to methanol, but little or no ability to ionize phenols. More importantly, the rate constants for BHT in acidified methanol are close to the values predicted by eq 1 which yields $0.03 \leq k^{HAT} \leq 0.27$ using the limiting α_2^H values determined earlier for BHT, viz.[8,15] $0.18 \leq \alpha_2^H \leq 0.25$. Similar results were obtained in ethanol, see Table S19 in the Supporting Information.

Although the rate constants for TOH and PMHC in methanol are lower that those in heptane, they are further reduced by acidifying the methanol with acetic acid, indicating a small extent of ionization in nonacidified methanol. Because the acidity of TOC ($pK_a = 11.92$)[16] is similar to that of BHT ($pK_a = 12.2$)[17] the different behavior of these two phenols must be attributed to their different HB donating abilities. For TOH $\alpha_2^H = 0.37$,[5] and for PMHC $\alpha_2^H = 0.39$; see the Supporting Information. Both α_2^H values are considerably larger than $\alpha_2^H = 0.18-0.25$[15] (mean 0.21) determined previously.[8] These parametrs have been combined with the heptane rate constants, k^0, and the β_2^H values for the HBA solvents to predict k^{HAT} values; see the rate constants in parentheses in Table 1. These calculated values of k^{HAT} are generally slightly greater than the experimental rate constants in acidified methanol and in solvents not supporting ionization but, nevertheless, the calculated and experimental rate constants are in very satisfying agreement. All of our new results serve to confirm that HAT and, in suitable solvents, SPLET are the only two mechanisms of any importance in the reaction of **dpph$^•$** with phenols.There is absolutely no solid experimental evidence for the claimed[14] ET-PT mechanism. This claim[14] was largely[18] based on the measured rate constants for the reaction of **dpph$^•$** with PMHC in methanol[19] and in methanol containing millimolar concentrations of pyridine and 2,4-lutidine. These two bases increased the measured rate constants. Peculiarly, in view of the earlier demontration[12] by many of the same authors that the PMHC anion is more reactive toward **dpph$^•$** than PMHC, these increased rates were interpreted as being due to electron transfer to the **dpph$^•$** from PMHC (Scheme 2)[20] rather than to the increased abilities of the mixed solvents to support ionization. However, SPLET provides a much simpler explanation for Nakanishi et al.'s[14] observations and is further supported by our experiments in acidified methanol and ethanol.

We thought that the importance of the SPLET mechanism relative to the HAT mechanism should be increased, with a consequent increase in the measured rate constants, by increasing the dielectric constant (ϵ_r) of the medium. Rate constants were therefore measured for the reaction of BHT and PMHC with **dpph$^•$** in two aprotic solvents, acetonitrile and dioxane, containing increasing amount of water (which is a Lewis base if the PhOH /H_2O acid−base pair is considered). The results are presented in Figures 2 and 3. The different profiles of k^S dependency on [H_2O] correlate

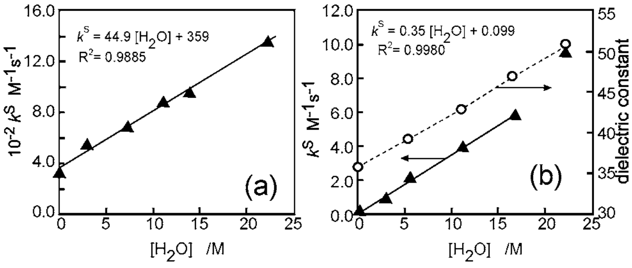

Figure 2. Plot of the rate constants, k^S (black triangles), for **dpph$^•$** reaction with PMHC (panel a) and BHT (panel b) vs water concentration in acetonitrile. The straight line for k^S vs [H_2O] for BHT was constructed without the last point. Panel b contains the values for dielectric constants of acetonitrile−H_2O mixtures (open circles). Values of ϵ_r and k^S for these mixtures are also listed in Tables S1 and S2 (Supporting Information).

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(15) For strongly hindered phenols α_2^H depends on the shape of the hydrogen bond acceptor used as the reference base, see ref 8.

(16) Steenken, S.; Neta, P. *J. Phys. Chem.* **1982**, *86*, 3661−3667.

(17) *Ionisation constants of organic acids in aqueous solution*; Serjeant, E. P., Dempsey, B., Eds.; IUPAC Chemical Data Series, No. 23; Pergamon Press: Oxford, UK, 1979.

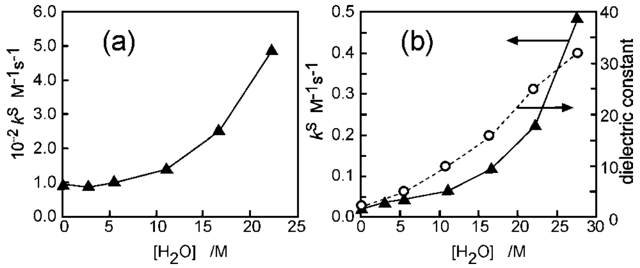

Figure 3. Rate constants, k^S (black triangles), for **dpph•** reaction with PMHC (a) and BHT (b) in dioxane−H_2O plotted against water concentration. Open circles in panel b are the values for dielectric constants of dioxane−water mixtures. Values of ϵ_r and k^S for these mixtures are also listed in Tables S1 and S2 (Supporting Information).

with the changes in ϵ_r of the two water-containing solvents. In acetonitrile−H_2O mixtures the plots k^S vs $[H_2O]$ are linear, as is the plot of ϵ_r vs $[H_2O]$. In dioxane−H_2O both the k^S and dielectric constant plots curve upward to similar extents. Since water strongly supports ionization ($\epsilon_r = 80.4$),[21] the increase in k^S that water induces in acetonitrile−H_2O and dioxane−H_2O mixtures is most simply explained by increased ionization of the two phenols. An alternative explanation, kindly suggested by a reviewer, is that k^S might increase because an increase in the dielectric constant of the solvent would increase the ease of separation of the ion pair formed in the initial step of the ET-PT mechanism, $ArOH + Y^\bullet \rightleftarrows [(ArOH)\cdots Y]^\bullet \rightleftarrows [(ArOH^{\bullet +})\cdots Y^-] \rightarrow$ dissociation of the ion-couple, and thus retard the back reaction. We cannot rule out this explanation but consider ET-PT less likely than the SPLET mechanism for three reasons: (i) acetic acid ($\epsilon_r = 6.2$) strongly retards the reactions in methanol at concentrations as low as 10 mM (Table 1) where any effect of the added acid on the dielectric constant would be very modest, (ii) the reactions in methanol are very strongly accelerated by small amounts of base,[8] and (iii) the reactions in solvents that can support the ionization of phenols frequently have extremely fast initial reactions that reflect the reactions of the **dpph•** with the preionized phenols.[9] Our results in the water-containing solvents are therefore attributed to a water-induced SPLET which quickly dominates the always underlying HAT process, rather than to the operation of an ET-PT mechanism.

In conclusion, vitamin E and other phenols can react with **dpph•** (and other electron deficient radicals such as ROO•) by two different and nonexclusive mechanisms, HAT and SPLET. Ionization of even small fraction of the phenol makes the measured rate constants for the combined HAT and SPLET reaction larger (often much larger) than that for the HAT-only reaction. The relative importance of SPLET can be reduced, or even eliminated, by the addition of acetic acid and can be enhanced by the addition of base. Recent claims[13,14] that these (and similar) reactions occur by a combination of the HAT mechanism and a mechanism involving electron transfer from the phenol to the **dpph•** (the ET-PT mechanism) are completely unfounded. Quite simply, there is no solid experimental evidence in favor of this “third” reaction mechanism. In contrast, there is a great deal of very solid experimental evidence in favor of the “second” mechanism, SPLET.

Acknowledgment. Financial support (Grant No. BW-1681/07/05) is acknowledged. We thank Dr. Keith U. Ingold for helpful disscussions.

Supporting Information Available: The rate constants, k^S, used for Figures 1 and 2 (Table S1 and S2); IR spectra (Figure S1) and other data used for calculation of the equilibrium constant of HB formation between PMHC and DMSO (Figure S2, Table S3); experimentally measured pseudo-first-order rate constants, k_{ex}, used for the calculation of the bimolecular rate constants for the **dpph•**/α-tocopherol, **dpph•**/PMHC and **dpph•**/BHT reactions in heptane, ethyl acetate, acetonitrile, dioxane, methanol, methanol containing CH_3CO_2H, ethanol, ethanol containing CH_3CO_2H, and in acetonitrile−H_2O and dioxane−H_2O systems (Tables S4−S18); and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The presence of large amounts (0.3 M) of Mg^{2+} (a Lewis acid) increased the rate of the **dpph•**/PMHC reaction by a factor of 2.[14] Because metal ions are known to accelerate certain ET reactions this small rate acceleration was used to support the ET-PT mechanism.[14]

(19) The rate constant measured by Nakanishi et al.[14] in methanol (1×10^3 M^{-1} s^{-1}) is three times as large as our value of 350 M^{-1} s^{-1}. Commercially available hydroxylic solvents, even of the highest purity available, often contain traces of base that dramatically accelerate the reaction rate.[8,9] In the present experiments we used MeOH, EtOH, and MeCN freshy distilled over a few beads of ion exchanging resin to remove any traces of base. Our rate constant in methanol is similar to that in acetonitrile, a solvent with a similar HBA activity (Table 1). In contrast, the rate constants measured by Nakanishi et al. are not self-consistent: for the PMHC/**dpph•** reaction k^{MeOH} is three times as large as k^{MeCN} while for the reactions of PMHC with **gavinoxyl•** (a radical that, unlike **dpph•**, is not electron deficient and is therefore unlikely to support the SPLET mechanism) k^{MeOH} is only half as large as k^{MeCN}.

(20) It was found[14] that k^S in MeOH/1.5 mM lutidine, the stronger base, was 30% larger than k^S in MeOH/1.5 mM pyridine. These data show (not unexpectedly) that PMHC does not reach the same degree of ionization in the presence of these two bases. The experiments actually provide additional evidence for the SPLET mechanism, once it is recognized that rate is: $-d[dpph^\bullet]/dt = k^{HAT}[PhOH] + k^{SPLET}[PhO^-]$. Therefore, because $k^{SPLET} \gg k^{HAT}$, even minute amounts of phenol reacting via SPLET can significantly accelerate the overall rate.

(21) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry,* 3rd ed.; Wiley: Weinheim, Germany, 2003.