Kinetic Solvent Effects on Hydroxylic Hydrogen Atom Abstractions Are Independent of the Nature of the Abstracting Radical. Two Extreme Tests Using Vitamin E and Phenol[1]

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Abstract: Rate constants have been measured at 25 °C in 13 solvents (S) for abstraction of the phenolic hydrogen atom from α-tocopherol (TOH) by *tert*-butoxyl ($BO^\bullet$), $k^{S}_{TOH/BO}$, and by 2,2-diphenyl-1-picrylhydrazyl ($DPPH^\bullet$), $k^{S}_{TOH/DPPH}$, and in eight solvents for abstraction of the phenolic hydrogen atom from phenol by cumyloxyl, $k^{S}_{PhOH/CumO}$, and $DPPH^\bullet$, $k^{S}_{PhOH/DPPH}$. Over the range of solvents examined $k^{S}_{TOH/BO}$ and $k^{S}_{TOH/DPPH}$ vary by a factor of ca. 65, and $k^{S}_{PhOH/CumO}$ and $k^{S}_{PhOH/DPPH}$ vary by a factor of ca. 120. In accordance with a prediction,[5] the kinetic solvent effect is essentially identical for the same substrate and is independent of the attacking radical. That is, for almost any pair of solvents, A and B $(k^{A}_{TOH/BO}/k^{B}_{TOH/BO})/(k^{A}_{TOH/DPPH}/k^{B}_{TOH/DPPH}) \approx 1.0$. The same applies with phenol as the substrate. Exceptions to this 1:1 relationship occur when one of the reactions becomes partly diffusion-controlled and in the solvent *tert*-butyl alcohol in which $DPPH^\bullet$ shows a larger reactivity than would be expected. The absolute magnitudes of the alkoxyl and DPPH rate constants in the same solvent differ by a factor of over 1 000 000 (10^6) for α-tocopherol and by 10 000 000 000 (10^{10}) for phenol! We have therefore confirmed, under extreme conditions, a new, unifying principle for free radical chemistry in solution.

The rates of radical reactions are commonly assumed to be independent of the solvent.[3] We have demonstrated that this assumption is fully justified for hydrogen atom abstraction from cyclohexane by cumyloxyl radicals.[4] However, we have also demonstrated the occurrence of dramatic solvent effects on the rates of H-atom abstraction from phenol and *tert*-butyl hydroperoxide by the same radical.[5] These very large solvent effects were attributed to hydrogen bond formation between the substrate, XOH, and hydrogen bond accepting (HBA) solvents, S. The magnitude of this kinetic solvent effect (KSE) is therefore determined by the strength of the interaction between XOH, the hydrogen bond donor (HBD), and the HBA solvent. This led us to predict that the magnitude of a KSE (i.e., the rate constant ratio, k^A/k^B, measured in two solvents, A and B) would "depend on the Lewis acidity of XOH, (but would) generally be independent of the nature of the radical which abstracts the hydrogen atom".[5] That is, for the reaction

$$XOH + Y^\bullet \rightarrow XO^\bullet + YH \tag{1}$$

the ratio of the measured rate constants in solvents A and B will generally be independent of the structure of Y, i.e.,[6] $(k^{A}_{XOH/Y})/(k^{B}_{XOH/Y})$ = constant (for the same XOH).

We have now confirmed this prediction using phenol and α-tocopherol (vitamin E) as hydrogen atom donating reactants, XOH, and two $Y^\bullet$ radicals having grossly different absolute reactivities in hydrogen atom abstraction. Phenol was chosen as one XOH because some of the necessary kinetic data were already available.[5] α-Tocopherol (α-TOH) was selected as the other XOH because of its biological importance,[7] because it is one of the most reactive peroxyl-radical-trapping phenolic antioxidants,[7] and because there is some isolated evidence that the rates of hydrogen abstraction from this compound are solvent dependent.[8] The highly reactive $Y^\bullet$ radicals were alkoxyls, cumyloxyl ($CumO^\bullet$) in the case of phenol and *tert*-butoxyl ($BO^\bullet$) in the case of α-TOH.[15] A single, relatively unreactive $Y^\bullet$ radical was chosen, 2,2-diphenyl-1-picrylhydrazyl ($DPPH^\bullet$), because of the ease with which its decay kinetics could be monitored in a conventional spectrophotometer via its strong visible absorption.

Results

Kinetic Measurements with the Alkoxyl Radicals. The usual laser flash photolysis (LFP) technique was employed.[4,5,9] *Tert*-butoxyl and cumyloxyl radicals were generated "instantaneously" by 308 nm LFP of their parent peroxides at 298 ± 2 K. In the α-TOH/$BO^\bullet$ experiments the concentrations of α-TOH typically ranged from 2×10^{-4}–10×10^{-4} M in "fast" solvents and from 10×10^{-4}–50×10^{-4} M in "slow" solvents, while in the PhOH/$CumO^\bullet$ experiments the PhOH concentrations typically ranged from 1–5 × 10^{-3} M in "fast" and from 5–475

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[3] Curran, D. P. *Synthesis* **1988**, 417–439, 489–513. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Revs.* **1991**, *91*, 1237–1286.

[4] Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466–470.

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

[6] Previously,[5] the subscript employed was *n* which served to denote both the substrate and the reaction (two substrates but a common reactant radical, see text). In the present work we have employed a different substrate and two different H-atom abstracting radicals, $Y^\bullet$. We denote the rate constants as $k^{S}_{XOH/Y}$, i.e., with the necessary three identifying symbols.

[7] Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194–201.

[8] Abstraction by $BO^\bullet$:[9] $k(298\ K) = 3.8 \times 10^9\ M^{-1}\ s^{-1}$ in BOOB/C_6H_6 (1:1, v/v); $= 6.6 \times 10^8\ M^{-1}\ s^{-1}$ in "wet" CH_3CN. Abstraction by $ROO^\bullet$: $k(303\ K) = 3.2 \times 10^6\ M^{-1}\ s^{-1}$ in styrene;[10] $= 2.3 \times 10^5\ M^{-1}\ s^{-1}$ in BOH;[11] $= 1.7 \times 10^4\ M^{-1}\ s^{-1}$ [11] and $3.7 \times 10^4\ M^{-1}\ s^{-1}$ [12] in SDS micelles; $= 3 \times 10^3\ M^{-1}\ s^{-1}$ in a phospholipid bilayer;[13] and a not quantified study in hexane, acetonitrile, methanol, and ethanol.[14]

[9] Evans, C.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4589–4593.

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$\times\ 10^{-3}$ M in "slow" solvents. The rates of reactions 2 and 3

$$\text{CumO}^{\bullet} + \text{PhOH} \xrightarrow{k^{S}_{\text{PhOH/CumO}}} \text{CumOH} + \text{PhO}^{\bullet} \quad (2)$$
$$(\lambda_{\max} = 485\ \text{nm})$$

$$\text{BO}^{\bullet} + \alpha\text{TOH} \xrightarrow{k^{S}_{\text{TOH/BO}}} \text{BOH} + \alpha\text{-TO}^{\bullet} \quad (3)$$
$$(\lambda_{\max} = 420\ \text{nm})$$

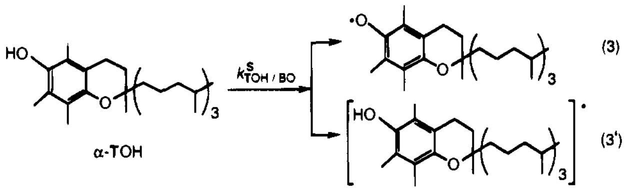
were monitored by following the pseudo-first-order decay of CumO$^{\bullet}$ and growth of α-TO$^{\bullet}$, respectively.[15] Variation of the experimental first-order rate constant, k^{S}_{exptl}, with substrate concentration was linear ($r \geq 0.99$), and absolute second-order rate constants were obtained by the method of least squares:

$$k^{S}_{\text{exptl}} = k^{S}_{0} + k^{S}_{\text{PhOH/CumO}}[\text{PhOH}]$$

$$k^{S}_{\text{exptl}} = k^{S}_{0} + k^{S}_{\text{TOH/BO}}[\alpha\text{-TOH}]$$

These kinetic data are given in Table 1.

In the PhOH/CumO$^{\bullet}$ system the only plausible chemical process is abstraction of the phenolic hydrogen atom, reaction 2. For the α-TOH/BO$^{\bullet}$ system in addition to abstraction of the phenolic hydrogen, reaction 3, there is the possibility of a concomitant hydrogen atom abstraction from one or more of the many C−H bonds in α-TOH (primary and secondary benzylic and primary, secondary, and tertiary aliphatic). Our experimental procedure does not distinguish between reaction 3 and abstraction from C−H, reaction 3′. That is, $k^{S}_{\text{TOH/BO}}$ is actually a "global" rate constant which includes all sites and modes of BO$^{\bullet}$ attack on α-TOH.



To investigate the importance of reaction 3′ relative to reaction 3, we synthesized the methyl ether of α-tocopherol (α-TOMe). This compound was too unreactive for LFP measurements with the cumyloxyl radical. For this reason the rate constant, k_4, for reaction of the ether with *tert*-butoxyl radicals was determined by competition kinetics with triphenylsilane, reaction 5. *Tert*-butoxyl radicals were generated by conventional photolysis of their parent peroxide with 300 nm light in

$$\text{BO}^{\bullet} + \alpha\text{-TOMe} \xrightarrow{k_4} \text{BOH} + [\alpha\text{-TOMe}]^{\bullet} \quad (4)$$

$$\text{BO}^{\bullet} + \text{Ph}_3\text{SiH} \xrightarrow{k_5} \text{BOH} + \text{Ph}_3\text{Si}^{\bullet} \quad (5)$$

a Rayonet photochemical reactor in benzene as solvent. The decrease in the concentrations of α-TOMe and Ph3SiH was monitored at different times, *t*, by GC/MS. A simple kinetic treatment yields

$$k_4 \ln\left(\frac{[\text{Ph}_3\text{SiH}]_{t=0}}{[\text{Ph}_3\text{SiH}]_t}\right) = k_5 \ln\left(\frac{[\alpha\text{-TOMe}]_{t=0}}{[\alpha\text{-TOMe}]_t}\right)$$

Our analytical results yielded $k_4 = 0.24\ k_5$. Since $k_5 \approx 1.0 \times 10^{7}\ \text{M}^{-1}\ \text{s}^{-1}$,[17] we obtain $k_4 \approx 2.4 \times 10^{6}\ \text{M}^{-1}\ \text{s}^{-1}$. Thus, the rate constant for hydrogen abstraction from α-TOMe by *tert*-butoxyl radicals is nearly two orders of magnitude smaller than any of our measured $k^{S}_{\text{TOH/BO}}$ rate constants (see Table 1). Since there are excellent reasons for believing that the magnitude of k_4 will not depend on the solvent,[4] it is clear that we can neglect reaction 3′ and equate $k^{S}_{\text{TOH/BO}}$ with reaction 3.

Kinetic Measurements with DPPH$^{\bullet}$. The rates of reaction of the DPPH$^{\bullet}$ radical with phenol and α-TOH were measured at 298 K after rapidly mixing stock solutions of the two reactants.[18] Since the reaction of DPPH$^{\bullet}$ with phenols is reversible the experimental conditions were chosen so as to

$$\text{DPPH}^{\bullet} + \text{PhOH} \xrightarrow{k^{S}_{\text{PhOH/DPPH}}} \text{DPPH}_2 + \text{PhO}^{\bullet} \quad (6)$$

$$\text{DPPH}^{\bullet} + \alpha\text{-TOH} \xrightarrow{k^{S}_{\text{TOH/DPPH}}} \text{DPPH}_2 + \alpha\text{-TO}^{\bullet} \quad (7)$$

avoid (or minimize) interference from the back reaction (see Experimental Section). Initial reagent concentrations were chosen so as to give convenient reaction rates with, typically, $[\text{DPPH}^{\bullet}] = 1 \times 10^{-6}$ or 5×10^{-5} M (according to substrate) and with five to eight different concentrations of the substrate in the range $(5-20) \times 10^{-2}$ M for phenol and $(2-10) \times 10^{-5}$ M for α-TOH (see supporting information).[19] The pseudo-first-order decay of DPPH$^{\bullet}$ was monitored at its band maximum (512−530 nm, depending on the solvent) relative to an isobestic point (424−440 nm, depending on the solvent and substrate). Second-order rate constants obtained in the usual way (i.e., via plots of k^{S}_{exptl} vs [substrate]) are given in Table 1.

Discussion

Dramatic kinetic solvent effects (KSEs) are shown by the kinetic data in Table 1. For example, the rate constants for abstraction of the phenolic hydrogen atom of α-TOH by DPPH$^{\bullet}$ and by BO$^{\bullet}$ decrease by factors of ~67 and ~60, respectively, on changing the solvent form *n*-pentane to γ-valerolactone. Similarly, the rate constants for hydrogen abstraction from phenol by DPPH$^{\bullet}$ and CumO$^{\bullet}$ decrease by factors of ~107 and ~136, respectively, on changing the solvent from *n*-octane to ethyl acetate.

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(10) 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.

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

(12) Pryor, W. A.; Strickland, T.; Church, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 2224−2229.

(13) 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.

(14) Iwatsuki, M.; Tsuchiya, J.; Komuro, E.; Yamamoto, Y.; Niki, E. *Biochim. Biophys. Acta* **1994**, *1200*, 19−26.

(15) These two alkoxyl radicals have essentially equal reactivity in H-atom abstractions. They were chosen for convenience in the LFP experiments. In the PhOH/CumO$^{\bullet}$ experiments the reaction was monitored via the decay of the CumO$^{\bullet}$ radical's absorption at 485 nm in the visible.[4,5,16] (At 485 nm the PhO$^{\bullet}$ does not absorb to any measurable extent, see: Johnston, L. J.; Mathivanan, N.; Negri, F.; Siebrand, W.; Zerbetto, F. *Can. J. Chem.* **1993**, *71*, 1655−1662.) In the α-TOH/BO$^{\bullet}$ experiments the kinetics were monitored via the growth of the α-TO$^{\bullet}$ radical's absorption at 420 nm in the visible (where BO$^{\bullet}$ does not absorb).[16]

(16) Avila, D. V.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 6576−6577. Avila, D. V.; Ingold, K. U.; Di Nardo, A. A.; Zerbetto, F.; Zgierski, M. Z.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 2711−2718.

(17) Chatgilialoglu, C.; Ingold, K. U.; Lusztyk, J.; Nazran, A. S.; Scaiano, J. C. *Organometallics* **1983**, *2*, 1332−1335.

(18) Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1995**, *60*, 5456−5467.

(19) There is good evidence that there is little or no self-association of α-tocopherol or phenol under our experimental conditions. In the first place all plots of k^{S}_{exptl} vs [XOH] gave excellent straight lines ($r > 0.99$ generally). Secondly, the equilibrium constants for substrate dimerization at 30 °C in CCl4 are fairly small (e.g., 4.7 M^{-1} [20] or lower [21] for phenol).

Table 1. Absolute Rate Constants for Abstraction of the Phenolic Hydrogen Atom from α-Tocopherol (TOH) and Phenol (PhOH) in Various Solvents at 298 ± 2 K[c]

	solvent	10^{-8} $k^S_{TOH/BO}$ (M^{-1} s^{-1})	10^{-2} $k^S_{TOH/DPPH}$ (M^{-1} s^{-1})	10^{-7} $k^S_{PhOH/CumO}$ [a] (M^{-1} s^{-1})	10^{3} $k^S_{PhOH/DPPH}$ (M^{-1} s^{-1})
1	*n*-pentane	99	74		
2	*n*-octane	60	74	110[b]	160
3	*n*-hexadecane	50	73		
4	carbon tetrachloride	42	36	86	93
5	chlorobenzene	36	27	48	59
6	benzene	31	18	28	31
7	anisole	20	14	5.6	7.2
8	acetonitrile	9.4	4.9		
9	acetic acid	7.7	6.2	1.8	3.1
10	methyl acetate	3.0	1.9		
11	ethyl acetate	2.9	1.6_5	0.81[b]	1.5
12	γ-valerolactone	1.6_5	1.1		
13	*tert*-butyl alcohol	1.8	5.7	0.36	2.9

[a] Data are from ref 5 unless otherwise noted. [b] Measured in the present work. We thank Dr. P. A. MacFaul for making one of these measurements. [c] The abstracting radicals are *tert*-butoxyl (BO•), cumyloxyl (CumO•), and diphenylpicrylhydrazyl (DPPH•).

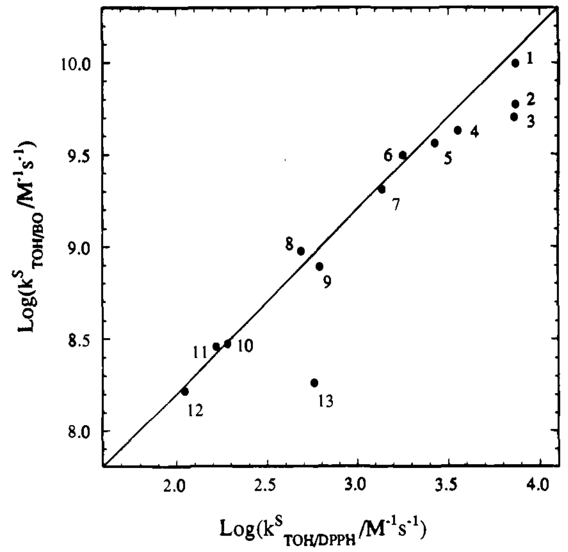

Figure 1. Plot of log ($k^S_{TOH/BO}$) for the reaction of α-tocopherol with *tert*-butoxyl radicals vs log ($k^S_{TOH/DPPH}$) for its reaction with 2,2-diphenyl-1-picrylhydrazyl radicals. The number beside each point corresponds to the solvent listed in Table 1 (plus 4% by volume BOOB for the BO• reactions). The line in this figure has a slope = 1.0.

Even more dramatic is the confirmation of our prediction[5] that the magnitude of the KSE on XOH/Y• reactions would be essentially independent of the nature of Y•. Thus, Figure 1 shows a plot of log ($k^S_{TOH/BO}/M^{-1}$ s^{-1}) vs log ($k^S_{TOH/DPPH}/M^{-1}$ s^{-1}) with the numbers beside each point corresponding to the solvents listed in Table 1. The straight line on this graph has been drawn with a slope = 1.0, and most of the points fall very close to this line (the exceptions are discussed below). What is truly astonishing is just how well most of our experimental results fit our prediction considering that in the same solvent the absolute magnitudes of the two rate constants differ by a factor of over one million. That is,

$$k^S_{TOH/BO}/k^S_{TOH/DPPH} \approx 1.6 \times 10^6$$

for almost any solvent.

Even more striking are the results with phenol (see Figure 2). Once again, the straight line on this plot of log ($k^S_{PhOH/CumO}/$ M^{-1} s^{-1}) vs log ($k^S_{PhOH/DPPH}/M^{-1}$ s^{-1}) has been drawn with a slope = 1.0, and all but one of the points fall very close to this line. In this set of experiments the absolute magnitudes of the two rate constants in the same solvent differ by a factor of 10 000 000 000! That is,

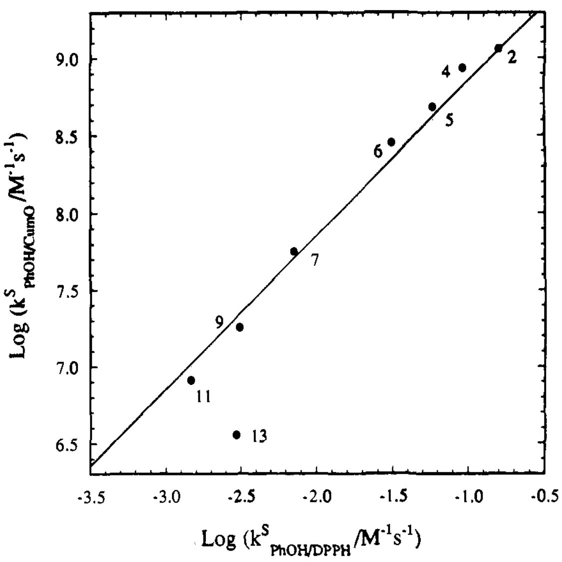

Figure 2. Plot of log ($k^S_{PhOH/CumO}$) for the reaction of phenol with cumyloxyl radicals vs log ($k^S_{PhOH/DPPH}$) for its reaction with 2,2-diphenyl-1-picrylhydrazyl radicals. The number beside each point corresponds to the solvent listed in Table 1 (plus 2% $(CumO)_2$ for the CumO• reactions). The line in this figure has a slope = 1.0.

$$k^S_{PhOH/CumO}/k^S_{PhOH/DPPH} \approx 1.0 \times 10^{10}$$

It would be difficult to imagine a more dramatic confirmation of our prediction that KSEs for hydrogen atom abstraction from XOH substrates will not, in general, depend on the nature of the attacking radical.

We turn now to a consideration of those few solvents where the points in Figures 1 and 2 deviate to a significant extent from the lines (slope = 1.0) drawn on these figures. For α-TOH in the "fast" solvents it is clear that there can be a diffusional limitation on the magnitude of $k_{TOH/BO}$. Thus, in the three paraffins, $k_{TOH/BO}$ rises from 50 to 60 to 99 × 10^8 M^{-1} s^{-1} in *n*-hexadecane (**3**), *n*-octane (**2**), and *n*-pentane (**1**), respectively, a change in *k* which parallels the decrease in viscosity along this series, viz., η (18 °C) = 3.55, 0.56, and 0.24 cP, respectively.[22] In contrast, in these same three solvents $k_{TOH/DPPH}$ is constant within experimental error (see Table 1). We conclude that in hexadecane and octane, and also probably to some small extent in pentane, the α-TOH/BO• reaction rate is partly diffusion-controlled. This is not surprising for a reaction for which the nondiffusion limited rate constant in alkanes would appear to be slightly greater than 10^{10} M^{-1} s^{-1}. The reaction in CCl_4, η = 1.04 cP, may also be partially diffusion-controlled (see point **4** in Figure 1).

The rate of the PhOH/CumO• reaction is only about 20% as large as the rate of the α-TOH/BO• reaction. Not surprisingly, therefore, the PhOH/CumO• reaction shows no sign of diffusion control in *n*-octane (**2**) and CCl_4 (**4**), see Figure 2.

Only in *tert*-butyl alcohol (**13**) is deviant behavior observed with α-TOH and PhOH. The observed deviation implies either

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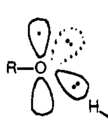
(20) Clotman, D.; van Lerberghe, D.; Zeegers-Huyskens, Th. *Spectrochim. Acta Part A* **1970**, *26*, 1621–1631.

(21) (a) Maguire, M. M.; West, R. *Spectrochim. Acta* **1961**, *17*, 369–378. (b) Coggeshall, N. D.; Saier, E. L. *J. Am. Chem. Soc.* **1951**, *73*, 5414–5418. (c) Powell, D. L.; West, R. *Spectrochim. Acta* **1964**, *20*, 983–991.

(22) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983–4992.

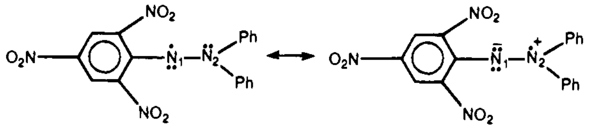
that the alkoxyl reactions are unexpectedly slow, or that the DPPH$^\bullet$ reactions are unexpectedly fast, or both. We suggest that the observed deviations are due mainly (or even entirely) to unusually fast DPPH$^\bullet$ reactions. This suggestion is based on two observations made rather early in our KSE studies during measurements of the rate constants for hydrogen atom abstraction from phenol and *tert*-butyl hydroperoxide (BOOH) by the cumyloxyl radical. In the preliminary report,[5] we noted that a plot of log ($k^{S}_{PhOH/CumO}$/M^{-1} s^{-1}) vs log ($k^{S}_{BOOH/CumO}$/M^{-1} s^{-1}) gave "an excellent straight line". If such a plot of our data is made, the point for *tert*-butyl alcohol falls on the line. Secondly, we observed (but did not report because of space limitations) that our kinetic data correlated extremely well with some of the empirical solvent parameters which measure the relative HBA abilities of solvents which are Lewis bases.[23] Thus, a plot of log ($k^{S}_{PhOH/CumO}$/M^{-1} s^{-1}) vs (for example) Abraham's[24,25] β_2^H value for each solvent, *including tert*-butyl alcohol, gave a good straight line. These early observations have been fully confirmed and will be reported in detail later.[26,27] They imply that insofar as phenol is concerned, *tert*-butyl alcohol is not an "unusual" HBA solvent. Therefore, we conclude that the "deviations" of the *tert*-butyl alcohol points in Figures 1 and 2 are most probably due to an enhanced reactivity of DPPH$^\bullet$ in this solvent.

The foregoing conclusion is especially intriguing in view of our earlier proof that the reactivity of the cumyloxyl radical in hydrogen abstraction is independent of the solvent within experimental error.[4] We assume that the cumyloxyl radical will act as a HBA in *tert*-butyl alcohol, but, since its reactivity remains essentially unchanged (in hydrogen atom abstraction from cyclohexane), we presume that any hydrogen bonding must involve an oxygen 2p-type lone pair of electrons rather than the unpaired electron,[28] i.e., **A**.

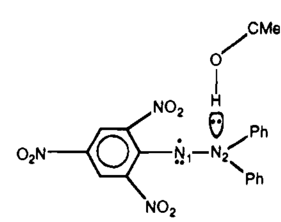


A

In contrast to alkoxyl radicals, the DPPH$^\bullet$ radical can act as a HBA at a heteroatom adjacent to that which formally bears the unpaired electron. The unpaired electron in DPPH$^\bullet$ (as in other hydrazyl radicals)[29,30] is conjugatively delocalized from its formal site at N_1, canonical structure **B**, onto the neighboring nitrogen atom, N_2, canonical structure, **C** (as well as being delocalized into the aromatic rings). The two hydrazyl nitrogen atoms of DPPH produce rather similar EPR hyperfine splittings (e.g.,[30] $a(N_1) = 9.7$ G, $a(N_2) = 7.9$ G in hydrocarbon solvents at room temperature) which implies that canonical structures **B** and **C** are of roughly equal importance. If a hydrogen bond is formed between a HBD solvent molecule (such as *tert*-butyl alcohol)[31] and one of the hydrazyl nitrogen atoms of DPPH$^\bullet$, it will almost certainly be with N_2, structure **D**, because the picryl group is very strongly electron-withdrawing. Such hydrogen-bonding would prevent, or at least reduce, conjugative electron delocalization. Thus, the electron would become more localized on N_1, and the radical's reactivity would increase.[32]



B **C**



D

In some earlier work from this laboratory we reported that the rate constants for the trapping of transient carbon-centered radicals by stable nitroxide radicals were solvent dependent.[22] The observed KSEs were attributed to solvent effects on the relative importance of the two canonical nitroxide structures

This radical–radical reaction was also unexpectedly fast in alcoholic solvents, a result which was attributed to the formation of a hydrogen bond between the alcohol and nitroxide.

Most of our KSE work serves to demonstrate that there is no thermodynamically significant interaction between radicals and solvents which can alter reaction rates. The unexpectedly high reactivity of DPPH$^\bullet$ toward phenols and of nitroxides toward carbon-centered radicals in alcoholic solvents is, therefore, particularly intriguing and raises two important questions we hope to pursue in later work. First, will DPPH$^\bullet$ (in contrast to alkoxyl radicals) abstract hydrogen from hydrocarbons more rapidly in alcohols than in other organic solvents? Second, will peroxyl radicals

exhibit KSEs similar to those found for alkoxyl radicals[33] or to those found for DPPH$^\bullet$?[34]

The KSEs reported herein (and earlier)[5] are clearly due to hydrogen bonding between the substrate, XOH, acting as a HBD

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[23] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Verlag Chimie: Weinheim, Germany, 1988.

[24] 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.

[25] The β_2^H values provide a general, thermodynamically related, scale of solute hydrogen-bond basicities in CCl_4.

[26] MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* Submitted for publication.

[27] Banks, J. T.; Ingold, K. U.; Lusztyk, J. Manuscript in preparation.

[28] We have previously pointed out that a hydrogen bond is more likely to involve an oxygen 2p-type lone pair than the unpaired electron on the same oxygen atom, see: Foti, M.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 9440–9447.

[29] Lunazzi, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 5558–5560 and references cited.

[30] Neugebaur, F. A. In *Landolt-Börnstein, New Series, Magnetic Properties of Free Radicals*; Fischer, H., Hellwege, K.-H., Eds.; Springer Verlag: Berlin, 1979; Vol. 9cl, pp 40–92.

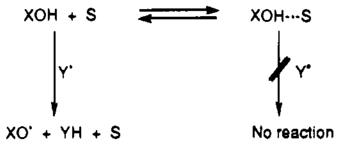
[31] There is nothing "unusual" about acetic acid (see Figure 1) presumably because DPPH$^\bullet$ is not a sufficiently strong HBA to break up the acetic acid dimers which prevail in the neat acid.

[32] The distribution of spin density between the two nitrogen atoms in hydrazyl radicals is very easily perturbed.[29] In alkyl hydrazyls it is even sensitive to the inductive effect of the alkyl groups, e.g.,[29] $H\dot{N}NR_2$, $a(N_1/N_2) = 9.8/11.6$ G; $R\dot{N}NHR$, $a(N_1/N_2) = 12.7/9.1$ G; $R\dot{N}NR_2$, $a(N_1/N_2) = 11.8/10.3$ G.

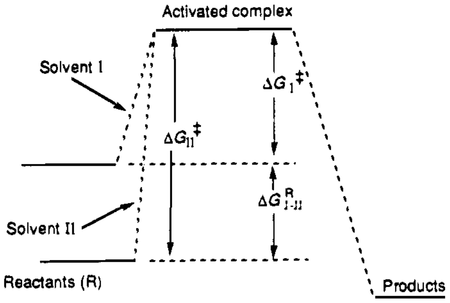
[33] I.e., no KSE for C–H abstraction, large KSE for O–H abstraction, moderate KSE for NH abstraction.[26]

[34] I.e., unexpectedly fast abstractions in alcohols.

and the solvent acting as a HBA. The kinetic model advanced in our preliminary communication[5] involved reactive nonhydrogen bonded XOH and nonreactive hydrogen bonded XOH, viz.,



Although this model has the virtue that it is easy to comprehend, we now recognize that it is an oversimplification of a complex situation which would probably be better represented by less specific and therefore more general models.[23,35] In terms of transition-state theory and with the assumption that the KSE arises entirely from the differential solvation of the reactants by the different solvents we can represent the situation in a relatively nonsolvating solvent, I, and in a more solvating solvent, II, by means of the following one-dimensional Gibbs free energy diagram:[36]



Our measured rate constants can be used to calculate the difference in the Gibbs energy of solvation of the reactants for any pair of solvents, i.e.,

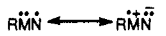
$$\log(k^{I}/k^{II}) = \Delta G^{R}_{I-II}/2.3RT$$

Thus, for example, for α-TOH as the hydrogen atom donor in the solvent pair, *n*-pentane/ethyl acetate, ΔG^{R}_{1-11} can be calculated to be 2.1_8 kcal/mol,[37] while for phenol as the hydrogen atom donor the kinetic data for the equivalent solvent pair (*n*-octane/ethyl acetate) yields $\Delta G^{R}_{2-11} = 2.8_5$ kcal/mol.[38] Since the reactivities of alkoxyl radicals in hydrogen atom abstractions are unaffected by solvent[4] these ΔG^{R} values must be assigned entirely to preferential solvation of the reactant phenols in ethyl acetate relative to the *n*-alkane. As would be expected, the stronger acid, phenol, which also has a sterically unprotected hydroxyl group, is more strongly solvated by HBA solvents than α-tocopherol.

Similar Gibbs energy calculations for the *n*-alkane/*tert*-butyl alcohol solvent pairs show that the unexpectedly high reactivity of DPPH• in *tert*-butyl alcohol corresponds to a free energy difference of nearly 1 kcal/mol, i.e., $\Delta G^{R(\text{alkoxyl})}_{1(2)-13} - \Delta G^{R(\text{DPPH})}_{1(2)-13} = 0.9_5$ kcal/mol.[39]

Conclusions

We have predicted and herein confirmed a new unifying principle for free radical chemistry in solution. Provided rate constants have been measured for the reaction of one radical with a substrate in a range of solvents, then a measurement of the rate constant for reaction of the same substrate with some different radical need be made in only one of these solvents for values in all the other solvents to be predicted accurately. We believe this principle will prove to be extremely valuable despite the fact that it may occasionally be invalid in HBD solvents such as alcohols. At the present time, these alcoholic exceptions would appear to be confined to radicals which can undergo conjugative electron delocalization.



Experimental Section

Materials. Solvents were of the purest grade commercially available. They were used without further purification except for γ-valerolactone (Aldrich) which was percolated through activated basic alumina until it had an O.D. < 0.01 at λ = 308 nm (measured in a 1.0 cm quartz cuvette).

Phenol (Aldrich) was purified by recrystallization from hexane (purity > 99% by GC/MS). 2*R*,4′*R*,8′*R*-α-Tocopherol, α-TOH (natural vitamin E, Chemalog), was purified by column chromatography on silica gel (Aldrich, grade 923, 100–200 mesh) eluting with (92:8, v/v) hexane/ethyl acetate (purity 100% by HPLC on a 150 × 4.6 mm, 3 μm particle size C-18 column eluted at 1.0 mL/min with MeOH/*i*-PrOH (95:5, v/v), using 295 nm detection). The methyl ether of α-tocopherol (α-TOMe) was synthesized by cautious addition of a solution of α-TOH in anhydrous DMF to a cooled (0 °C) and stirred suspension of NaH (1.4 equiv) in DMF under a stream of nitrogen, following which the mixture was warmed to room temperature and MeI (1.4 equiv) was added. After 45 min, brine was added, and the α-TOMe was extracted with ether, washed with water, and dried ($MgSO_4$). Removal of the ether solvent under vacuum yielded a yellow oil which was purified by column chromatography on silica gel (hexane/ethyl acetate, 97:3, v/v): yield 85%, purity > 95% by GC/MS (444, M^+ (100), 179 (90)), ^{1}H-NMR 3.7 ppm (3 H, s, $ArOCH_3$).

Diphenylpicrylhydrazil, DPPH• (BDH, Poole, UK), was 98% pure by HPLC (260 nm, $MeOH/H_2O$, 5:1 v/v). Di-*tert*-butyl peroxide (Aldrich, 98%) was percolated through activated basic alumina immediately prior to use (to remove any traces of *tert*-butyl hydroperoxide). Dicumyl peroxide (Aldrich) was purified by recrystallization from methanol.

Laser Flash Photolysis (LFP). The laser flash photolysis equipment and experimental procedures have been adequately described in earlier publications.[40] Experiments were carried out in cells made of 7 × 7 mm² Suprasil quartz tubing. *Tert*-butoxyl and cumyloxyl radicals were generated by 308 nm LFP of solutions of di-*tert*-butyl peroxide (0.22 M) or dicumyl peroxide (0.13 M) 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). Pseudo-first-order rate constants (k^{S}_{exptl}) were determined at 298 ± 2 K using digitally averaged decay or growth curves from five to ten laser flashes. Absolute second order rate constants ($k^{S}_{\text{XOH/Y}}$) were calculated by least-squares fitting of k^{S}_{exptl} vs [XOH] for five different XOH concentrations (see Results). The XOH concentrations were chosen so that k^{S}_{exptl} was in the range $(2-50) \times 10^5\ s^{-1}$. Full kinetic data are given as supporting information.

Reaction of BO• with α-TOMe. A benzene solution containing α-TOMe (1.9×10^{-3} M), Ph_3SiH (1.0×10^{-3} M), BOOB (2.5 M), and *n*-dodecane (as an internal standard) was prepared in a 7 × 7 mm² Suprasil quartz cuvette by mixing concentrated stock solutions of the reactants and was deoxygenated by purging with argon. The sample was irradiated for 30 min with 300 nm UV light in a Rayonet photochemical reactor at 298 ± 2 K. The composition of the solution was analyzed at different times by GC/MS before and during the

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(35) We thank an anonymous referee for his persistent encouragement of us to use the transition-state approach.

(36) See ref 23, pp 121–129.

(37) DPPH•/BO• data, $2.2_5/2.1_0$ kcal/mol.

(38) DPPH•/CumO• data, $2.7_7/2.9_3$ kcal/mol.

(39) α-TOH substrate DPPH•/BO• data, $1.5_1/2.3_6$ kcal/mol, difference = 0.8_5 kcal/mol. PhOH substrate DPPH•/CumO• data, $2.3_6/3.4_1$ kcal/mol, difference = 1.0_5 kcal/mol.

(40) Kazanis, S.; Azarani, A.; Johnston, L. J. *J. Phys. Chem.* **1991**, *95*, 4430–4435.

irradiation. The areas of the chromatographic peaks due to α-TOMe and Ph_3SiH (relative to that of the internal standard) were taken as a measure of the relative concentrations of the two competing substrates and used to calculate the ratio of their rate constants for hydrogen abstraction by BO•, k_4/k_5 (see Results). A parallel experiment with a solution which contained no BOOB showed no decline in the concentrations of α-TOMe or Ph_3SiH.

Kinetic Measurements with DPPH•. Concentrated, deoxygenated stock solutions of PhOH or α-TOH were rapidly mixed with thermostated, deoxygenated solutions of DPPH• in the same solvent. The DPPH solution was contained in a 10 × 10 mm^2 quartz cuvette sitting within a Hewlett Packard 8425A diode array spectrophotometer, and the decay of the DPPH• was monitored at its band maximum relative to an isobestic point. These two wavelengths were determined for each solvent by a few preliminary measurements and are available as supporting information. Initial concentrations of DPPH• and XOH were chosen so as to give a reasonable reaction rate under pseudo-first-order conditions (typically 1×10^{-6} M DPPH• with $(2-10) \times 10^{-5}$ M α-TOH and 5×10^{-5} M DPPH• with $(5-20) \times 10^{-2}$ M PhOH). For each solvent five to eight measurements were made of k^{S}_{exptl}, and absolute second-order rate constants, $k^{S}_{\text{XOH/DPPH}}$, were calculated by least-squares fitting of plots of k^{S}_{exptl} vs [XOH] ($r > 0.99$, generally). The back reaction, i.e., $XO^{\bullet} + DPPH_2 \rightarrow XOH + DPPH^{\bullet}$, was judged to be unimportant under our conditions since good first order plots were obtained for at least the first 70% of reaction. Full kinetic data are given as supporting information.

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Supporting Information Available: Tables of kinetic data for the BO• and DPPH• reactions (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the joumal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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