Solvent Effects on the Rates and Mechanisms of Reaction of Phenols with Free Radicals

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ABSTRACT
The rates of formal abstraction of phenolic hydrogen atoms by free radicals, Y• + ArOH → YH + ArO•, are profoundly influenced by the hydrogen-bond-accepting and anion-solvation abilities of solvents, by the electron affinities and reactivities (Y−H bond dissociation enthalpies) of radicals, and by the phenol's ring substituents. These apparently simple reactions can occur by at least three different, nonexclusive mechanisms: hydrogen atom transfer, proton-coupled electron transfer, and sequential proton-loss electron transfer. The delicate balance among these mechanisms depends on both the environment and the reactants. The main features of these mechanisms are described, together with some interesting kinetic consequences.

The autoxidation of organic materials, RH, as varied as lubricating oils, edible fats, and lipids in living organisms, are free radical chain reactions:

$$\textit{Initiation:}\ \text{Formation of R}^\bullet \tag{1}$$

$$\textit{Propagation:}\ \text{R}^\bullet + \text{O}_2 \rightarrow \text{ROO}^\bullet \tag{2}$$

$$\text{ROO}^\bullet + \text{RH} \rightarrow \text{ROOH} + \text{R}^\bullet \tag{3}$$

$$\textit{Termination:}\ \text{ROO}^\bullet + \text{ROO}^\bullet \rightarrow \text{nonradical products} \tag{4}$$

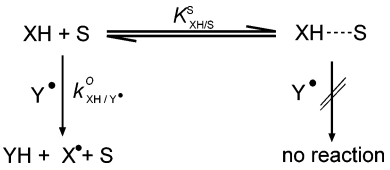
The rates of these oxidative degradations can be decreased by the addition of low concentrations of phenols because peroxyl radicals react more rapidly with phenols than with RH, that is, $k_5 \gg k_3$.[1] Aryloxyl radicals generally trap a (second) peroxyl because they are too unreactive to continue the chain:

$$\text{ROO}^\bullet + \text{ArOH} \rightarrow \text{ROOH} + \text{ArO}^\bullet \tag{5}$$

$$\text{ROO}^\bullet + \text{ArO}^\bullet \rightarrow \text{non-radical products} \tag{6}$$

In 1964, values of k_3/k_5 were reported for four phenols in up to 12 solvents.[2] These ratios increased with increasing solvent polarity, for example, with *para*-cresol, ratios were 2.1×10^{-3} in decane and 36×10^{-3} in acetonitrile,

Scheme 1. HAT and a "Normal" Kinetic Solvent Effect



changes that were attributed to reductions in k_5 caused by hydrogen bond (HB) formation between the phenolic hydroxyl group and HB-accepting (HBA) solvents.

Later, Scaiano and co-workers[3] employed laser flash photolysis (LFP) to show that reaction 7 exhibited kinetic

$$t\text{-RO}^\bullet + \text{ArOH} \rightarrow t\text{-ROH} + \text{ArO}^\bullet \tag{7}$$

solvent effects (KSEs), for example, for phenol k_7 ($M^{-1}\ s^{-1}$) $= 3.3 \times 10^8$ in benzene, 1.5×10^7 in *tert*-butanol, and 4.7×10^6 in pyridine. These KSEs were also attributed to HB formation by the phenol.

Hydrogen Atom Transfer (HAT) and "Normal" KSEs

Systematic studies of KSEs for reaction 7, and for related reactions such as reaction 8, only began in 1995,[4] 2 years

$$t\text{-RO}^\bullet + t\text{-BuOOH} \rightarrow t\text{-ROH} + t\text{-BuOO}^\bullet \tag{8}$$

after it had been demonstrated that HAT from saturated,[5] reaction 9, and unsaturated[6] hydrocarbons by alkoxyls

$$t\text{-RO}^\bullet + c\text{-C}_6\text{H}_{12} \rightarrow t\text{-ROH} + c\text{-C}_6\text{H}_{11}^\bullet \tag{9}$$

exhibited no KSEs, for example,[5] at 30 °C, $k_9 = (1.2_4 \pm 0.1_2) \times 10^6\ M^{-1}\ s^{-1}$ in six solvents including CCl_4, *t*-BuOH, MeCN, and $MeCO_2H$. This meant that the large KSEs found for reactions 7 and 8 were not due to a solvent modulation of *t*-RO• reactivity and must, therefore, be due to a modulation of the reactivities of these hydroxylic substrates, that is, to HB formation.

The KSEs for HAT from a HB donor (HBD) substrate, XH, to a radical, Y•, were accounted for *quantitatively* via Scheme 1 and three accompanying assumptions: (i) Each XH molecule can HB with only one molecule of HBA solvent, S. (ii) The equilibrium constant for HB formation, $K^S_{XH/S}$, is independent of the properties (e.g., dielectric constant) of the surrounding medium. (iii) HAT cannot occur from the HB complex, XH···S, for steric reasons. It occurs only from "free" XH, and this reaction possesses a characteristic rate constant, $k^0_{XH/Y•}$, that is equal in magnitude to the measured rate constant in a non-HBA solvent, that is, a saturated hydrocarbon.

According to Scheme 1, the experimental rate constant for HAT in a HBA solvent, S, is given by

$$k^S_{XH/Y•} = k^0_{XH/Y•}/(1 + K^S_{XH/S}) \tag{I}$$

This equation led to the prediction that for any two

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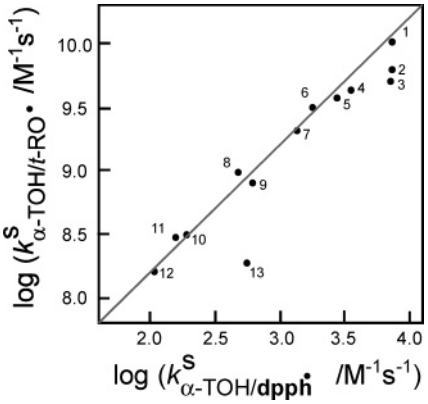


FIGURE 1. Log/log plot for the reactions of α-tocopherol with *tert*-butoxyl and 2,2-diphenyl-1-picrylhydrazyl. Solvent designations: *n*-pentane (1), *n*-octane (2), *n*-hexadecane (3), tetrachloromethane (4), chlorobenzene (5), benzene (6), anisole (7), acetonitrile (8), acetic acid (9), methyl acetate (10), ethyl acetate (11), γ-valerolactone (12), and *tert*-butanol (13). The line in this figure has a slope = 1.0. Reproduced from ref 7. Copyright 1995 American Chemical Society.

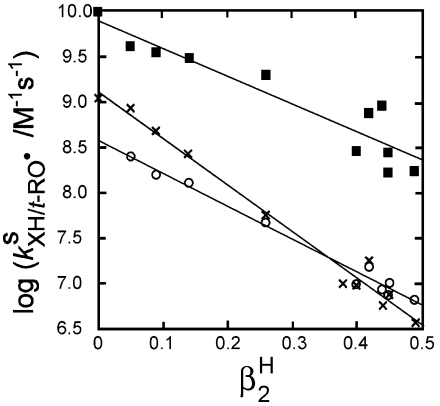


FIGURE 2. Plots of log($k^S_{\mathrm{XH}/t-\mathrm{RO}^\bullet}$, M^{-1} s^{-1}) vs the β_2^H value for the solvent, S, for XH = α-tocopherol (■), phenol (×), and *tert*-butyl hydroperoxide (○). Reproduced from ref 10. Copyright 2001 American Chemical Society.

solvents, S^1 and S^2, the ratio $k^{S^1}_{\mathrm{XH/Y}^\bullet}/k^{S^2}_{\mathrm{XH/Y}^\bullet}$, *would be independent of the reactivity of* Y•, that is, independent of the absolute values of $k^{S^1}_{\mathrm{XH/Y}^\bullet}$. This prediction was quickly confirmed[7] using as Y•'s both highly reactive *t*-RO• radicals (kinetics using LFP) and the very much less reactive, stable, and strongly colored 2,2-diphenyl-1-picrylhydrazyl (**dpph•**) radical (kinetics using a simple spectrophotometer). Two XH substrates were employed, phenol using eight solvents and another phenol, α-tocopherol (α-TOH, vitamin E), using 13 solvents. Plots of $\log(k^S_{\mathrm{PhOH/RO}^\bullet})$ versus $\log(k^S_{\mathrm{PhOH/dpph}^\bullet})$ and of $\log(k^S_{\alpha-\mathrm{TOH/RO}^\bullet})$ versus $\log(k^S_{\alpha-\mathrm{TOH/dpph}^\bullet})$, see Figure 1, gave straight lines with slopes of unity and only a few "outlier" solvents. In any one solvent, the rate constant for the RO• reaction was larger than that for the **dpph•** reaction by a factor of 1.6 × 10^6 for α-TOH and by an astonishing 1 × 10^{10} for phenol. For α-TOH, there were three outliers. Two were due to the RO• reaction being diffusion-limited in two alkanes, hexadecane (3) and octane (2). The third outlier was *tert*-butanol (13), *also the only outlier solvent in the phenol plot.*

In any analysis of solvent effects on chemical reactions, it is customary to seek a linear relationship between some empirical solvent parameter and the logarithm of the rate constant for the reaction, that is, a linear free-energy relationship. The β_2^H values of Abraham et al.[8] provide the most reliable scale of relative HBA activities. (The earlier β-constants purporting to measure the same quantities contain significant contributions from anion solvation abilities.)[9] The β_2^H constants represent a general thermodynamically related scale of solute HB basicities in CCl_4 and range in magnitude from 0.00 for alkanes to 1.00 for hexamethylphosphortriamide (the strongest organic base). Values of β_2^H are determined using IR spectroscopy to measure equilibrium constants for 1:1 complex formation between XH, the HB donor (HBD), and a "calibrated" HBA, B, in CCl_4 at room temperature.[8]

$$\mathrm{XH} + \mathrm{B} \overset{K^{\mathrm{CCl_4}}_{\mathrm{HX/B}}}{\rightleftharpoons} \mathrm{XH}\cdots\mathrm{B} \qquad (10)$$

Plots of $\log(k, M^{-1} s^{-1})$ against β_2^H for reaction 7 (ArOH = PhOH and α-TOH) and reaction 8 gave straight lines, see Figure 2.[10] Straight lines were also obtained with many other phenols[10] and with aniline.[11] The slopes of all these lines are proportional to Abraham et al.'s[12] α_2^H constants for XH. Values of α_2^H are determined using "calibrated" HBAs in the same manner as β_2^H constants. They provide a measure of the relative abilities of solutes to act as HBDs and range in magnitude from 0.00 (alkanes) to ~1 for strong acids (CF_3CO_2H).[12] The KSEs for HAT from phenols, hydroperoxides, aniline, and hydrocarbons are *quantitatively* described by[10]

$$\log(k^S_{\mathrm{XH/Y}^\bullet}, M^{-1} s^{-1}) = \log(k^0_{\mathrm{XH/Y}^\bullet}, M^{-1} s^{-1}) - 8.3\alpha_2^H\beta_2^H \qquad (II)$$

This equation even applies to the radical/radical reaction 11 for which $k^{\mathrm{H_2O}}_{\mathrm{HOO}^\bullet/\mathrm{HOO}^\bullet} \approx 10^6$ M^{-1} s^{-1} both by calculation

$$\mathrm{HOO}^\bullet + \mathrm{HOO}^\bullet \rightarrow \mathrm{HOOH} + \mathrm{O_2} \qquad (11)$$

and by experiment.[13] Indeed, eq II applies whether the reaction occurs by a simple HAT mechanism involving the motion of a proton with one of its bonding electrons or by proton-coupled electron transfer (PCET) in which the proton moves between two electron pairs and the accompanying fifth electron moves between nonbonding orbitals, see below.

In Figure 2, the final point for each substrate corresponds to the solvent, *tert*-butanol. Since these three points fall close to the best lines through all points, they must reflect the HBA activity of *tert*-butanol. This means that the deviant *tert*-butanol point in Figure 1 must arise because the α-TOH/**dpph•** reaction is considerably faster than expected from this solvent's HBA activity (β_2^H). This and the similar deviant behavior of the PhOH/**dpph•** reaction in *tert*-butanol were the first anomalous KSEs where a *formal* HAT reaction was faster than predicted by eq II.

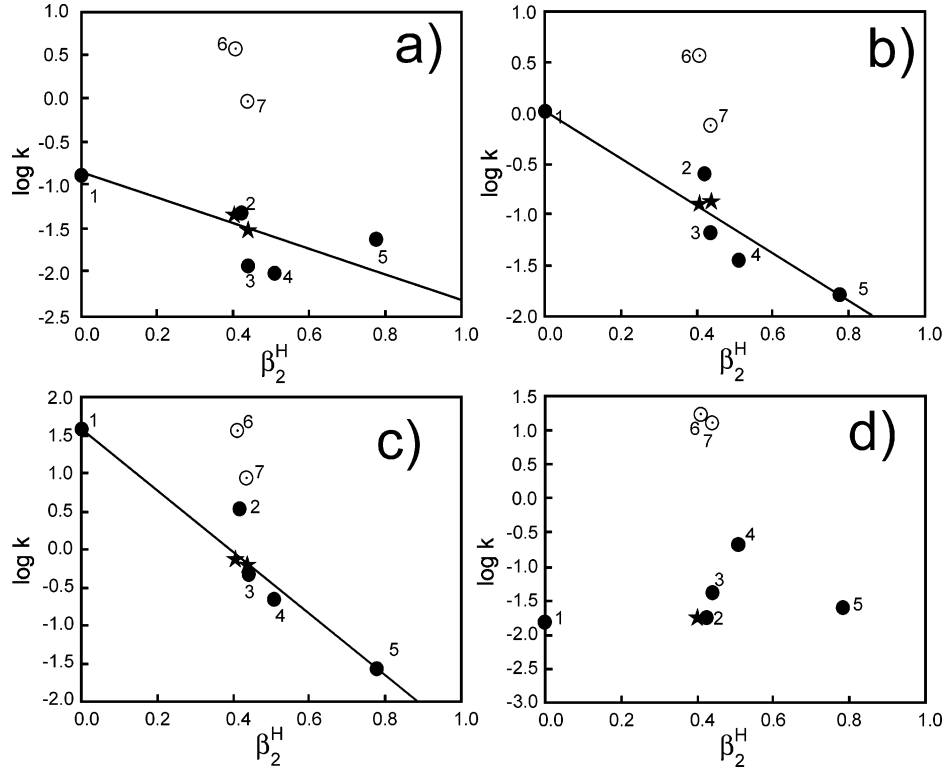


FIGURE 3. Log($k^S_{ArOH/dpph\bullet}$, M^{-1} s^{-1}) vs β_2^H: (a) 2,6-*t*-Bu_2-phenol, (b) 2,6-*t*-Bu_2-4-Me-phenol, (c) 2,4,6-Me_3-phenol, and (d) 2,6-*t*-Bu_2-4-CN-phenol. Non-alcoholic solvents are given as filled circles: *n*-heptane (1), di-*n*-butyl ether (2), acetonitrile (3), THF (4), and DMSO (5). Open circles denote alcoholic solvents: methanol (6) and ethanol (7). Rates in acidified (10 mM acetic acid) alcohols are shown by filled stars: methanol (left) and ethanol (right). The star in plot d denotes methanol containing 1.7 M acetic acid. The lines in plots a−c were drawn using only data for the five nonalcoholic solvents. Modified from ref 16.

Anomalous KSEs and Sequential Proton-Loss Electron Transfer (SPLET)

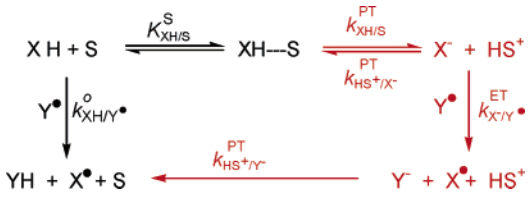
Exploratory studies of HAT from α-TOH to cumylperoxyl[14] and to alkyl[15] radicals showed that in *tert*-butanol the peroxyl reaction was significantly faster than predicted by eq II (i.e., ROO• behaved like **dpph•**) but the alkyl reaction occurred at the "expected" rate (i.e., R• behaved like RO•).

The high reactivity of RO• prohibited kinetic measurements in alcohols other than *tert*-butanol. This restriction does not apply to **dpph•**, a radical isoelectronic with peroxyls and widely used in "antioxidant" studies. Values of $k^S_{ArOH/\mathbf{dpph\bullet}}$ were determined by monitoring the loss of **dpph•** spectrophotometrically at 517 nm ($\epsilon \approx 11\,000$ M^{-1} cm^{-1}) using a stopped-flow instrument.[16] A large excess of ArOH was generally employed, and the complete loss of **dpph•** occurred with pseudo-first-order kinetics with 13 phenols in numerous alcohol and nonalcoholic solvents with rates proportional to the concentration of ArOH; that is, these reactions followed bimolecular kinetics:[16]

$$-\mathrm{d}[\mathbf{dpph\bullet}]/\mathrm{d}t = k_{exptl}[\mathrm{ArOH}][\mathbf{dpph\bullet}] \qquad \text{(III)}$$

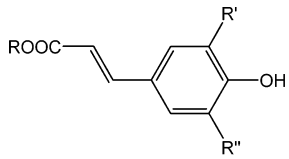
However, rate constants in alcohols were larger than predicted by eq II.[16] In fact, for some 2,6-di-*tert*-butyl-4-sustituted phenols, *the rate constants in methanol and ethanol were even larger than those in heptane*! Moreover, the very acidic 2,6-di-*tert*-butyl-4-cyanophenol's rate constants in nonalcoholic, polar solvents, such as acetonitrile, THF, and DMSO, were also greater than those in heptane.[16] Rate constants for phenols in alcohols were increased by the addition of 2 mM sodium methoxide and were decreased by added acetic acid (Figure 3). It was concluded[16] that ArOH/**dpph•** reactions could occur by a *combination* of the classical HAT mechanism and a process involving the phenoxide anion, later dubbed[17] sequential proton-loss electron transfer, SPLET, see Scheme 2. In all solvents examined, these ArOH/**dpph•** reactions followed bimolecular kinetics, both under HAT-only conditions (non-ionizing solvents and ionizing solvents containing sufficient acetic acid to eliminate SPLET) and when SPLET contributed ~10% to 99% to k_{exptl}.[16]

Scheme 2. "Anomalous" Kinetic Solvent Effect



The SPLET mechanism was discovered independently by Foti et al.[18] during a kinetic study of the reactions with

dpph• of some cinnamic acids and esters (reaction 12) in methanol and ethanol:



R = H, Me; R', R" = H, Me, OMe (12)

The key observation was that the esters were 3−5 times more reactive than the acids, a result interpreted as "self-suppression" of phenol ionization by the carboxylic acid, that is, self-suppression of SPLET in the acids.[18]

Factors Affecting the HAT/SPLET Mechanistic Duo

The rate of consumption of **dpph•**, or more generally Y•, is given by

$$-\mathrm{d}[\mathrm{Y}^\bullet]/\mathrm{d}t = k^{\mathrm{HAT}}[\mathrm{XH}][\mathrm{Y}^\bullet] + k^{\mathrm{ET}}[\mathrm{X}^-][\mathrm{Y}^\bullet] \qquad \text{(IV)}$$

The relative contributions of HAT and SPLET are sensitive to both reactants and solvent. Since k^{ET} will normally be much greater than k^{HAT}, even a very low X^- concentration can produce a large rate enhancement.

The rate of HAT, and hence its contribution to the measured rate, is given by eq II. The rate of SPLET will be influenced by all factors that affect XH ionization and the electron affinity of Y•:

1. Role of XH in XH Ionization. Other things being equal, the concentration of X^- in solvents that support ionization will increase with an increase in XH acidity. For phenols, electron-withdrawing substituents (EWS) increase O−H bond dissociation enthalpies[19] and hence decrease k^{HAT}, but they also increase phenol acidities and hence increase X^- concentration. However, the EWS's phenoxide stabilizing effects will decrease k^{ET}, and thus the EWS's overall effects on SPLET's contribution to the measured rate are difficult to forecast.

2. Role of Solvent in XH Ionization. The degree of ionization of XH depends on both a bulk property of the solvent, its relative permittivity (dielectric constant), ϵ_r, and a molecular property, its relative ability to solvate, and hence stabilize, anions (X^-), as quantified by Swain et al.'s *A* values.[9,20,21] HAT will generally dominate XH/Y• reactions in solvents having low ϵ_r and *A* values, notably alkanes (1.8 and 0.00), but also 1,4-dioxane (2.2, 0.19) and ethyl acetate (6.0, 0.21). SPLET will be favored in solvents having high ϵ_r and *A* values, notably water (78, 1.00), but also methanol (33, 0.75) and ethanol (25, 0.66).

3. Electron Affinity (EA) of Y•. In water, EA(Y•) can be quantified by the one-electron reduction potential, E^0_{red}, of the Y•/Y^- couple, a quantity that for ROO•/ROO^- has been shown to correlate linearly with the pK_a of ROOH.[22] The enhanced rate constants found in *tert*-butanol for the reactions of phenol or α-TOH with **dpph•**[7,16] (**dpph**-H, pK_a 8.5) and cumylperoxyl[14] ($PhMe_2COOH$, pK_a 13) but not with *tert*-alkoxyl[10,11] (Me_3COH, pK_a = 19.2) and primary alkyl[15] ($PhCMe_3$, pK_a ~50) arise because the first two of these four radicals have EAs great enough for them to oxidize phenoxide anions (SPLET), while the EAs of the last two radicals are too low for similar electron transfers (ET). However, even when there is positive driving force for the $X^- + Y^\bullet \rightarrow X^\bullet + Y^-$ ET, there may be insufficient ionization of XH for significant SPLET. For example,[23] in acetonitrile (ϵ_r = 36, *A* = 0.37), the anion of an α-TOH analog has $E^0_{\mathrm{ox}} = -0.47$ V (vs SCE) and is rapidly oxidized by a **dpph•** analog (E^0_{red}(**dpph•**) = 0.18 V vs SCE) but the **dpph•** reactions with α-TOH[7] and other phenols[7,16] apparently occur solely by HAT; see, for example, Figure 1, point 8.

XH + Y• Reactions in Water

The unique properties of water make ET far more common in it than in organic solvents.

Kinetic studies of XH + Y• reactions using pulse radiolysis have largely been confined to water, but in compensation, there is pH control and ability to generate radicals having a wide range of reduction potentials. With peroxyls, for example,[24] E^0_{red} vs NHE range from 0.71 V ($Me_3COO^\bullet$), through 0.94 V ($MeOO^\bullet$) and 1.23 V ($ClCH_2OO^\bullet$) to 1.44 V ($Cl_3COO^\bullet$), while the O−H bond dissociation enthalpies (BDEs, kcal/mol) and pK_a's (in italics) of the corresponding hydroperoxides are 88, *13* (Me_3COOH); 92, *11*; 96, *9.5*; and 101, *8.7* (Cl_3COOH), so the rates of both ET and HAT reactions increase along this series of peroxyls.[25] The oxidation potentials of phenoxides, E_{ox}, are known to correlate linearly with their parent phenols' pK_a's.[26]

The one-electron oxidation of phenoxide, $ArO^- \rightarrow ArO^\bullet + e^-$, is thermodynamically preferred over the one-electron oxidation of the corresponding phenol, $ArOH \rightarrow ArO^\bullet + H^+ + e^-$. For example, at pH 10, E_{ox} of 2,4,6-tri-*tert*-butylphenol and its phenoxide are +0.13 V and −0.093 V, respectively.[27] Thus, even a slight degree of phenol ionization can contribute significantly to its measured rate of reaction with a one-electron acceptor, a phenomenon well-known to the pulse radiolysis fraternity.[28] Indeed, the pK_a of XH can generally be obtained from plots of $k_{(\mathrm{XH/X^-})+\mathrm{Y}^\bullet}$ against pH, and for polyhydroxylated aromatics such as flavonoids, these plots have been shown to fit their several pK_a's.[29]

Proton-Coupled Electron Transfer (PCET)

Identity reactions ($XH + X^\bullet \rightarrow X^\bullet + XH$, and other nearly thermoneutral reactions) involving HAT between two oxygen atoms have long been known to have much higher rate constants and much lower activation enthalpies and Arrhenius pre-exponential factors than HAT between two carbon atoms.[30] For many years, this was attributed to differences in triplet repulsion between the two heavy atoms in the transition state $(X^\uparrow\ H^\downarrow\ X^\uparrow)^\ddagger$.[31] In 2002, this explanation was shown to be invalid by Shaik et al.,[32] but with serendipidous timing, a new and simple explanation for $(O^\bullet + HO)/(C^\bullet + CH)$ differences was soon provided by Mayer et al.[33] Their DFT calculations showed that the transition states for the $PhO^\bullet$ + PhOH and $PhCH_2^\bullet$ +

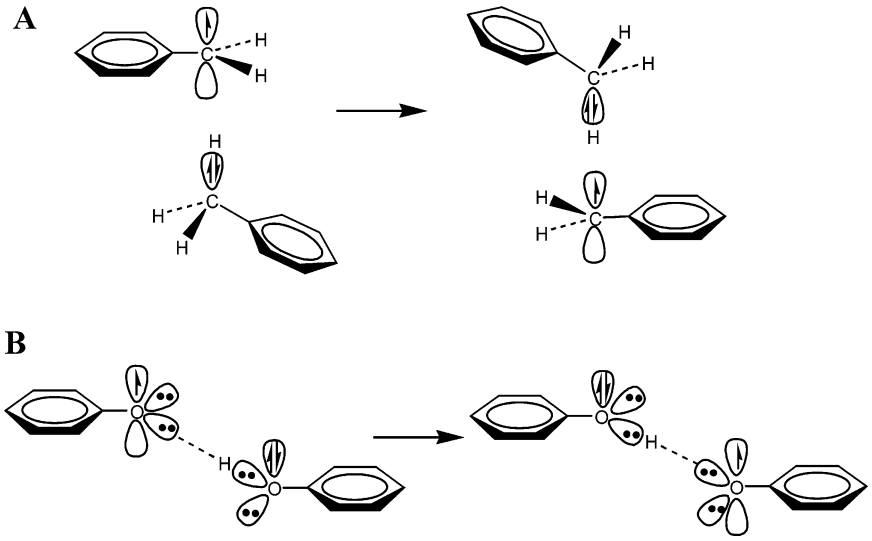


FIGURE 4. (A) HAT for benzyl/toluene and (B) HAT(PCET) for phenoxyl/phenol.

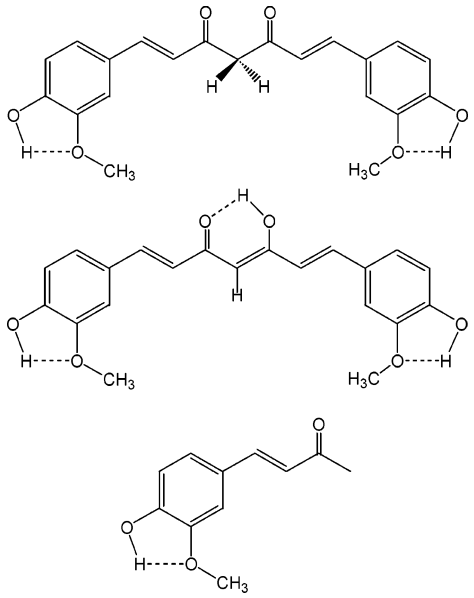
$PhCH_3$ had quite different structures (Figure 4). In the benzyl/toluene reaction (Figure 4A), HAT involves transfer of a proton with one of its bonding electrons. However, in the phenoxyl/phenol reaction, a pre-transition state HB complex is formed between the OH and a *lone pair* on O•, the proton is then transferred from its two bonding electrons to the radical's lone pair, while the accompanying electron moves from the 2p lone pair on the phenol to the radical's singly occupied molecular orbital (SOMO) (Figure 4B). The formation of the HB complex has adverse entropic effects on the rate of the phenoxyl/phenol reaction, but these are outweighed by favorable enthalpic effects arising from the closer approach of the two oxygens in Figure 4B (2.40 Å) than the two carbons in Figure 4A (2.72 Å).[33] This closer proximity of the two oxygens is primarily due to the smaller atomic radius of oxygen than of carbon[34] (further enhanced by the attractive HB). The barrier between reactants and products is, therefore, lower and narrower for $PhO^{\bullet} + PhOH$ than for $PhCH_2^{\bullet} + PhCH_3$ (which may encourage a significant contribution to the inter-oxygen HAT rate from quantum-mechanical tunneling of the proton).

HAT for the phenoxyl/phenol reaction is called proton-coupled electron transfer (PCET) with the proton and five electrons playing a major role in the transition state. The term HAT is reserved for benzyl/toluene and like reactions (proton and three electrons). Because the KSEs described earlier for ArOH/Y• (and similar) reactions are due to the ground-state properties of ArOH *the magnitude of the KSE must be identical for both a HAT mechanism (e.g., alkyl•/ArOH) and a PCET mechanism (e.g., ROO•/ArOH).* Therefore, henceforth HAT(PCET) will be used when discussing KSEs for either, or both, of these non-SPLET mechanisms.

Some Interesting Features of HAT(PCET) and SPLET Reactions

1. Extremely Fast Initial Rates. These were first observed immediately (<100 ms) after mixing solutions of curcumin (Chart 1, see also below) and **dpph•** in methanol (Figure 5A) or ethanol.[17] These fast initial rates ($k_{exptl}^{MeOH} = 16\,000$ M^{-1} s^{-1}) were greatly reduced by the addition of just 5 mM acetic acid (72 M^{-1} s^{-1}, Figure 5B), although complete suppression of SPLET required 1 M acid (3.6 M^{-1} s^{-1}).[17] These short duration, very fast reactions were followed by slower (but still rapid) first-order loss of **dpph•** (Figure 5A). The initial fast chemistry was attributed to reaction with **dpph•** of curcumin anions present at low equilibrium concentrations in alcohols. These "preformed" anions are quickly depleted, and ionization of curcumin (XH) then becomes partially rate-limiting (Scheme 2). Extremely fast initial rates were also observed for the dehydrozingerone (half-curcumin)/**dpph•** reaction in methanol and ethanol[17] and for the 2,2′-methylene-bis(4-methyl-6-*tert*-butylphenol) (BIS, see below)/**dpph•** reaction in five non-alcoholic solvents.[21]

Chart 1. Curcumin (Diketo and Keto−Enol Forms) and Dehydrozingerone



2. An ArOH/dpph• Reaction That Is Zero-Order in dpph• Concentration in Certain Solvents. All the reac-

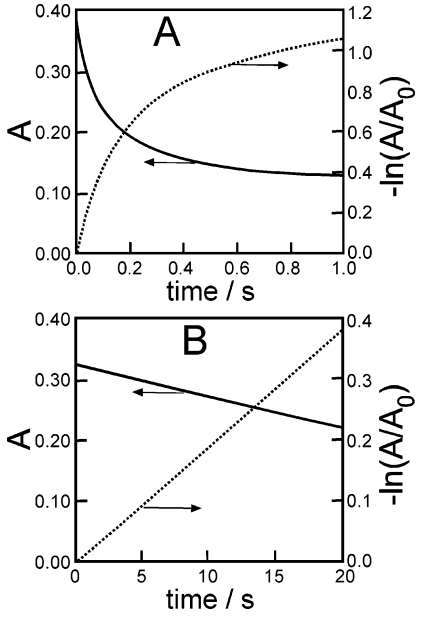
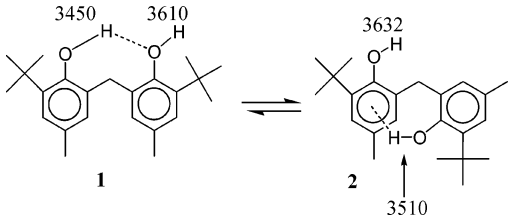


FIGURE 5. Decay of 3 μM dpph• in reaction with 0.37 mM curcumin in methanol (A) and in methanol/5 mM acetic acid (B). Reproduced from ref 17. Copyright 2004 American Chemical Society.

Chart 2. BIS Structures and Four O−H Fundamental Stretching Frequencies (cm^{-1}) Assigned[21]



tions described above follow bimolecular kinetics whether HAT(PCET) or SPLET is dominant. For SPLET, this indicates that ionization of XH is faster than the capture of X^- by Y•, that is, $k^{PT}_{XH/S}[XH\cdots S] > k^{ET}_{X^-/Y\bullet}[X^-][Y\bullet]$, see Scheme 2. However, we discovered one phenol/**dpph•** reaction where in five solvents (out of 20 examined) and after the initial (<100 ms) rapid consumption of "preformed" phenoxide (see above), ionization becomes rate-determining.[21] This phenol is 2,2′-methylene-bis(4-methyl-6-*tert*-butylphenol) or BIS (see Chart 2). In acetonitrile, benzonitrile, acetone, cyclohexanone, and DMSO, the initial very fast BIS/**dpph•** reaction with "preformed" anion follows the usual bimolecular kinetics (eq III); thereafter, the reaction slows and, while remaining first-order in BIS, becomes zero-order in **dpph•**, see Figure 6, that is,[21]

$$-\mathrm{d}[\mathbf{dpph}^\bullet]/\mathrm{d}t = k_{\mathrm{exptl}}[\mathrm{BIS}] \qquad \text{(V)}$$

The reactions zero-order in **dpph•** yielded BIS ionization rate constants, $k^{PT}_{XH/S}[S]$, ranging from 0.2 s^{-1} (acetone) to 3.3 s^{-1} (benzonitrile).[21]

The secret behind the BIS/**dpph•** reaction's unique zero-order kinetics lies in BIS's solution properties and structure. Its IR spectrum in CCl_4 reveals four O−H stretching bands that we have assigned (**1** and **2** in Chart 2).[21] However, in HBA solvents, both OH groups form

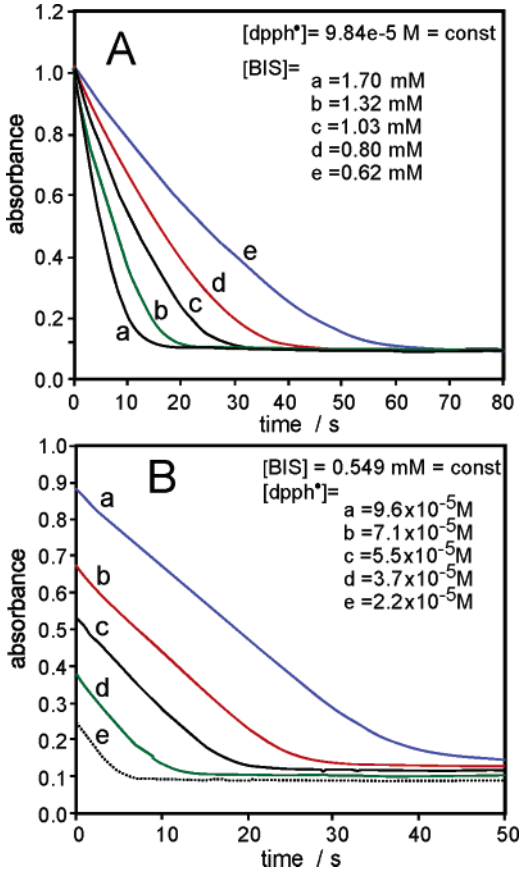
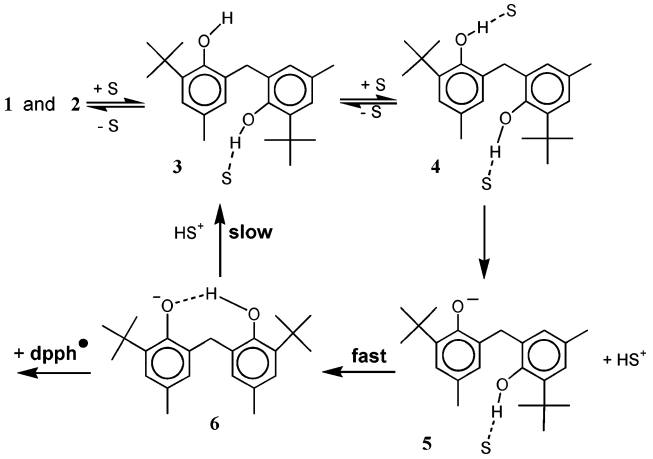


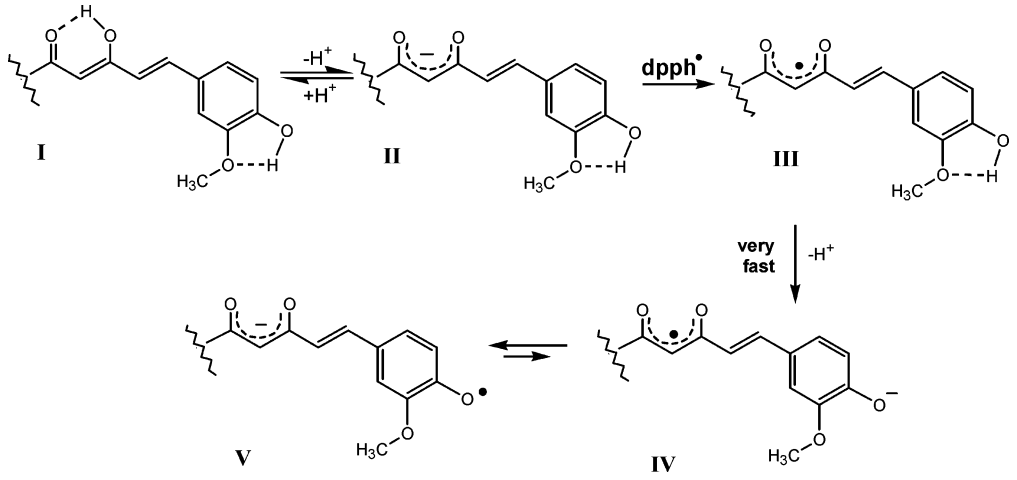
FIGURE 6. Change in dpph• absorbance during reaction with BIS in acetone: (A) $[dpph^\bullet]_0$ = constant, $[BIS]_0$ = various; (B) $[BIS]_0$ = constant, $[dpph^\bullet]_0$ various. Reproduced from ref 21. Copyright 2005 American Chemical Society.

Scheme 3. BIS/dpph• Reactions Zero-order in dpph• Concentration



intermolecular HBs (**4**, Scheme 3). For BIS and other aromatic diols that form intramolecular OH···OH HBs (e.g., catechols), the intramolecular HBs in the radical, OH···O•, and in the anion, OH···O^-, are considerably stronger than that in the starting molecule. As a consequence, the "free" OH groups have low O−H BDEs[35−38] (which makes them excellent H-atom donors),[18,36−40] are quite acidic, and are fairly strong HBDs.[40] In BIS, the "free" OH in **1** (3610 cm^{-1}) will be the reactive center for HAT-(PCET) and for SPLET, which was significant in all but a

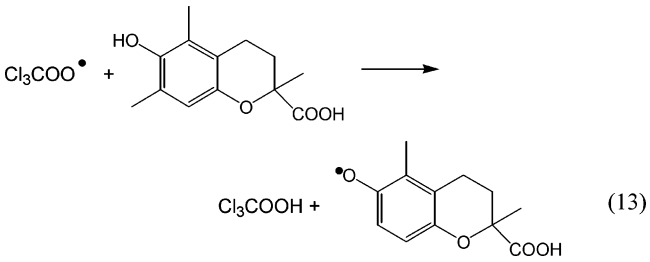
Scheme 4



few solvents. Therate-determining step (rds) for those reactions zero-order in **dpph•** is ionization of BIS (**4** → **5**, Scheme 3). The initially formed anion, **5**, is rapidly stabilized by intramolecular HB formation, **6**. This retards the reverse proton transfer (**6** → **3**) and permits these unusual SPLET kinetics.

3. Resolution of the Curcumin Antioxidant Controversy. Curcumin, the yellow pigment in tumeric and curry, has been claimed to have many health benefits, benefits generally ascribed to its radical-trapping properties. Indeed, curcumin has been claimed to be a "superb H-atom donor" on the basis of kinetic measurements in polar solvents with the H-atom donor being the central methylene group.[41,42] However, these claims were rejected by Barclay et al.[43] who demonstrated that inhibition of the autoxidation of methyl linoleate and styrene in chlorobenzene by curcumin was strictly due to its phenolic hydroxyl groups. We discovered[17] that these contrasting conclusions arose from the use of polar[41,42] (SPLET dominant) and nonpolar[43] (HAT(PCET) dominant) solvents. The importance of SPLET in the curcumin/**dpph•** reaction in polar, but not in nonpolar, solvents is illustrated by the following rate constants (M^{-1} s^{-1}): 1.6×10^4 in methanol; 3.6 in methanol/1 M acetic acid; 1.4 in dioxane. Since curcumin's most acidic site is its enolic hydroxyl and since 2,4-pentanedione ($pK_a \approx 9$) reacted with **dpph•** in polar, ionizing solvents but did not react in nonpolar solvents, the curcumin/**dpph•** reaction in polar solvents was formulated as in Scheme 4. The keto−enol moiety in neutral curcumin (**I**, Chart 1 and Scheme 4) deprotonates to form the anion, **II**, this transfers an electron to **dpph•**, and the product, **III**, contains the strong EW group, [−C(O)CHC(O)−]•, which increases the acidity of the phenolic hydroxyls, one of which deprotonates to give **IV**. Finally, the negative charge migrates to the central keto−enol moiety, **V**.

4. Even Two Bulk Solvent Parameters Failed To "Unscramble" the HAT(PCET)/SPLET Mechanistic Combo. As mentioned earlier, Cl_3COOH and **dpph**-H have similar pK_a's, and therefore their radicals have roughly similar EAs and predilections for SPLET chemistry. However, $Cl_3COO^•$ is a far better HAT(PCET) reactant than **dpph•**:[25] BDEs (kcal/mol) Cl_3COO-H, 101; **dpph**-H, 78.5. In one of the few pulse radiolysis studies not confined to water, Neta and co-workers[44,45] measured k_{13} for the $Cl_3COO^•$/Trolox reaction in 15 solvents:



(13)

Values of k_{13}^S (M^{-1} s^{-1}) ranged from 5.8×10^8 (H_2O) through 4.6×10^7 (CCl_4) to 9.2×10^6 (acetone). In the earlier work[44] (13 solvents), $\log(k_{13}^S, M^{-1} s^{-1})$ gave a best fit using two solvent parameters, dielectric constant and solvent basicity, with $R^2 = 0.97$, "but only after removing CCl_4 and water from the set of correlated data".[45] The later study[45] added two carefully selected solvents, *N*-methylformamide (high ϵ_r, low basicity) and triethylamine (low ϵ_r, high basicity), but in both k_{13} was more than an order of magnitude lower than predicted by the earlier[44] correlation equation. The best $\log(k_{13}^S/M^{-1}s^{-1})$ correlation ($R^2 = 0.94$) was again obtained with two parameters but now these were the solvents' cohesive energy density and pK_a, but again CCl_4 was not included because: "its basicity is unknown. To fit CCl_4 to the same line, it would have to have a p*K*a value in acetonitrile of 11.9, close to that of pyridine, which is very unlikely."[45]

As first suggested in 1996[46] and as will be obvious to readers of this Account, the $Cl_3COO^•$/Trolox reaction will occur primarily by HAT(PCET) in solvents with low ϵ_r and low basicity and primarily by SPLET in solvents of high ϵ_r and high basicity. There seems little likelihood that $\log(k_{13}^S, M^{-1} s^{-1})$ could ever be correlated with *bulk* solvent properties in view of this reaction's dual mechanisms.

Future Work

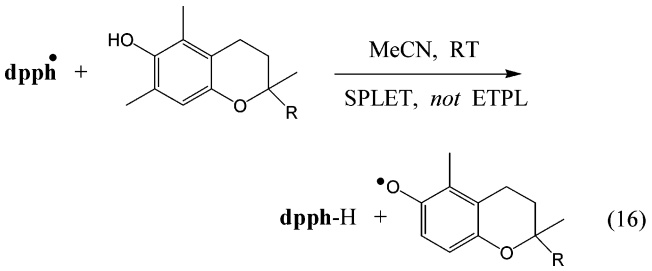
Is There Really a *Fourth* Mechanism for Formal Y$^\bullet$ + ArOH → YH + ArO$^\bullet$ Reactions? A fourth mechanism for these reactions (Y$^\bullet$ = ROO$^\bullet$ and **dpph**$^\bullet$) involving electron transfer then proton transfer, ETPT, reaction 14, has

$$Y^\bullet + ArOH \rightarrow Y^- + [ArOH]^{\bullet+} \rightarrow ArO^\bullet + H^+ \quad (14)$$

frequently been invoked both by experimentalists[44,45,47] and theoreticians.[48] Some radical/alkylaromatic hydrocarbon oxidations in polar solvents occur by ETPT, for example,[49]

$$NO_3^\bullet + 4\text{-}MeOC_6H_4CH_3 \xrightarrow[4 \times 10^7\ M^{-1}\ s^{-1}]{MeCN,\ RT} NO_3^- + [4\text{-}MeOC_6H_4CH_3]^{\bullet+} \rightarrow 4\text{-}MeOC_6H_4C^\bullet H_2 + H^+ \quad (15)$$

However, claims[47b] for an ETPT mechanism for two ArOH/**dpph**$^\bullet$ reactions (reaction 16, R = CH_3 and $C_{16}H_{33}$) are



(16)

without merit. These reactions have been unequivocally demonstrated to occur by SPLET.[50]

Nevertheless, we believe that under appropriate conditions ArOH/Y$^\bullet$ reactions *might* occur by an ETPT-like mechanism. However, *this would actually be a PCET process in which the proton and electron go to different (initial) acceptors*. That is, in HBA solvents, the phenol will largely be H-bonded to a solvent molecule. Electron transfer to Y$^\bullet$ (or a non-radical electron acceptor) creates a H-bonded radical cation, and since radical cations are very much more acidic than their neutral parents, proton loss will be extremely fast, possibly even concerted with ET.

$$Y^\bullet + ArOH\cdots S \xrightarrow{ET} Y^- + Ar\overset{\bullet+}{O}H\cdots S \xrightarrow{v.\ fast} Y^- + ARO^\bullet + HS^+ \quad (17)$$

Indeed, oxidation of the phenol tyrosine in a tyrosine–ruthenium complex has been reported to occur by both processes: a concerted single-step reaction (pH-dependent) and ETPT (pH-independent) with the proton going into bulk water in both cases.[51,52] ETPT dominates at low pH and the concerted process at high pH. Similar ETPT or concerted reactions, in which the proton does not go to a tyrosine-oxidizing high-valent metal ion but to a neighboring base, are believed operative in certain enzymes.[51,52] To discover whether any ArOH/Y$^\bullet$ reactions in homogeneous solution occur by such a mechanism will require additional work.

Potential Biological Relevance. The importance of diets rich in plant-derived "antioxidants" (such as resveratrol) is frequently touted by the media and in the scientific literature. These "antioxidants" contain (poly)-hydroxylated aromatic rings. Researchers using in vitro model systems have almost always assumed that reaction between their putative antioxidant and the radical employed occurs by a HAT(PCET) mechanism. However, the relevance of such work to human health is questionable because SPLET is a much more probable mechanism in many of these systems and, more importantly, in biofluids such as blood plasma and cellular cytosol. Further research is required to determine the importance of SPLET in vivo using biologically relevant antioxidants and radicals.

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