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Abnormal Solvent Effects on Hydrogen Atom Abstraction. 2. Resolution of the Curcumin Antioxidant Controversy. The Role of Sequential Proton Loss Electron Transfer

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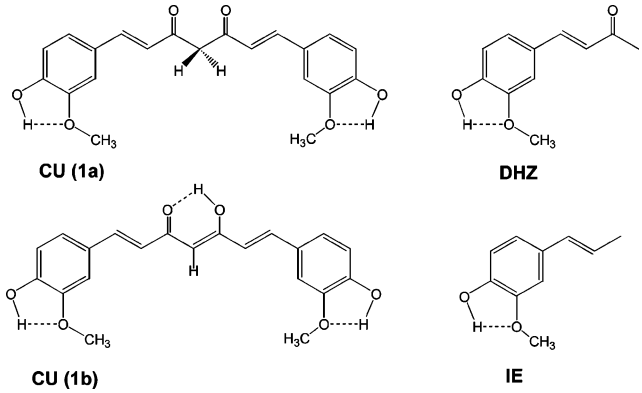
The rates of reaction of 1,1-diphenyl-2-picrylhydrazyl (**dpph•**) radicals with curcumin (**CU**, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), dehydrozingerone (**DHZ**, "half-curcumin"), and isoeugenol (**IE**) have been measured in methanol and ethanol and in two non-hydroxylic solvents, dioxane and ethyl acetate, which have about the same hydrogen-bond-accepting abilities as the alcohols. The reactions of all three substrates are orders of magnitude faster in the alcohols, but these high rates can be suppressed to values essentially equal to those in the two non-hydroxylic solvents by the addition of acetic acid. The fast reactions in alcohols are attributed to the reaction of **dpph•** with the **CU**, **DHZ**, and **IE** *anions* (see *J. Org. Chem*. **2003**, *68*, 3433), a process which we herein name sequential proton loss electron transfer (SPLET). The most acidic group in **CU** is the central keto−enol moiety. Following **CU**'s ionization to a monoanion, ET from the $[-(O)CCHC(O)-]^-$ moiety to **dpph•** yields the neutral $[-(O)CCHC(O)-]^•$ radical moiety which will be strongly electron withdrawing. Consequently, a phenolic proton is quickly lost into the alcohol solvent. The phenoxide anion so formed undergoes charge migration to produce a neutral phenoxyl radical and the keto−enol anion, i.e., the same product as would be formed by a hydrogen atom transfer (HAT) from the phenolic group of the **CU** monoanion. The SPLET process cannot occur in a nonionizing solvent. The controversy as to whether the central keto−enol moiety or the peripheral phenolic hydroxyl groups of **CU** are involved in its radical trapping (antioxidant) activity is therefore resolved. In ionizing solvents, electron-deficient radicals will react with **CU** by a rapid SPLET process but in nonionizing solvents, or in the presence of acid, they will react by a slower HAT process involving one of the phenolic hydroxyl groups.

Introduction

Curcumin (**CU**), 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, **1a**, the yellow pigment of turmeric and curry, exists mainly in the keto−enol form, **1b** (see Chart 1), which is favored by a strong intramolecular hydrogen bond.[1,2]

Many health benefits have been claimed for **CU**,[3] and these have generally been ascribed to its radical-trapping antioxidant properties.[4] Since **CU** is a (bis)phenol, its reported ability to trap lipid peroxyl[5,6] and 1,1-diphenyl-2-picrylhydrazyl[7] (**dpph•**) radicals by donating one of its phenolic H-atoms is consistent with the known mechanism by which other phenols trap peroxyls,[8] alkoxyls,[9−11] and **dpph•**,[9,11,12] reaction 1.

CHART 1. Structures and Abbreviations of the Main Compounds Studied: Curcumin (CU) in the α,γ-Diketo and Keto−Enol Forms (Structures 1a and 1b, Respectively), Dehydrozingerone (DHZ), and Isoeugenol (IE)



$$X^• + ArOH \rightarrow XH + ArO^• \quad (X^• = ROO^•, RO^•, \mathbf{dpph^•}, \text{etc.}) \quad (1)$$

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† Warsaw University.

(1) Tønnesen, H. H. In *Phenolic compounds in food and their effects on health. I. Analysis, Occurrence, and Chemistry*; Ho, C.-T., Lee, C. Y., Huang, M. T., Eds.; ACS Symposium Series 506; American Chemical Society: Washington, DC, 1992; pp 143−153.

(2) Roughley, P. J.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2379−2388. Pedersen, U.; Rasmussen, P. B.; Lawesson, S.-O. *Liebigs Ann. Chem*. **1985**, 1557−1569.

(3) E.g., reduction in blood cholesterol, inhibition of low-density lipoprotein peroxidation, platelet aggregation, HIV replication, cataract formation, etc. Reviews: Leu, T.-H.; Maa, M.-C. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 357−370. Aggarwal, B. B.; Kumar, A.; Bharti, A. C. *Anticancer Res*. **2003**, *23*, 363−398.

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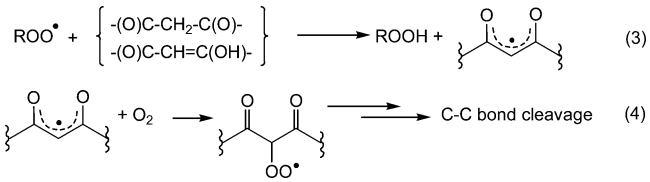
However, since curcumin's phenolic hydrogen atoms are intramolecularly H-bonded to the adjacent methoxy groups, it is expected to be a relatively poor hydrogen atom transfer (HAT) agent, as is illustrated by the rate constants for reaction of **dpph•** in alkane solvents at 298 K with 2-methoxyphenol (0.7 M^{-1} s^{-1})[12] compared with 4-methoxyphenol (240 M^{-1} s^{-1}).[11] Thus, a statement that **CU** is a "superb antioxidant"[13] seems improbable, and at first sight, it is surprising that **CU**'s radical trapping properties have received such attention.[14] There is no doubt that much of this attention can be attributed to suggestions that the α,γ-dicarbonyl moiety (both as the diketone, **1a**, and as the keto−enol, **1b**) is involved in radical trapping.[13,15−18] However, "radical trapping" does not, in and of itself, make an antioxidant. For a compound to be a radical-trapping antioxidant it is essential that the antioxidant-derived radical does not react with dioxygen as this would continue the autoxidation chain. For this reason, among others, phenols are radical-trapping antioxidants; i.e., reaction 2 does not occur.

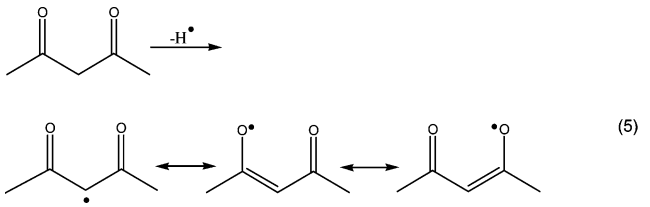
$$ArO^{\bullet} + O_2 \not\rightarrow \qquad (2)$$

In this connection, it is important to note that in 1996 Sugiyama et al.[17] showed that the radicals derived from α,γ-dicarbonyl moieties do react with dioxygen. Specifically, these workers showed that when dimethoxytetrahydrocurcumin (**CU** modified by reduction of the two vinyl (styrene) groups and by methylation of the two phenolic OH groups) was oxidized with peroxyl radicals in oxygen-saturated acetonitrile it underwent C−C bond cleavage at the −(O)CCH_2C(O)− moiety. Bond cleavage was attributed to H-atom abstraction from the central CH_2 group and from the enolic OH group to form a carbon-centered radical which reacted rapidly with dioxygen, a process which eventually leads to C−C bond cleavage, reactions 3 and 4.



Thus, the α,γ-diketone moiety may "trap" peroxyl radicals, but this does not make **CU** a radical-trapping *antioxidant*. Also in 1996, Sreejayan and Rao[7a] reported that a diacetylated **CU** in which both phenol OH groups had been converted to acetyl groups did not react with **dpph•** in ethanol. Similarly, Priyadarsini et al.[7b,c] have reported recently that a methylated **CU** in which both phenolic OH groups had been converted to OCH_3 groups reacted with **dpph•** 1800 times more slowly than **CU**.

Despite this background, in 1999, Jovanovic et al.[13] claimed that **CU** was a "superb H-atom donor." The diketo form was (possibly incorrectly)[19−21] assumed to be the dominant form in their experiments and was "an extraordinarily potent H-atom donor...due to delocalization of the unpaired electron on the adjacent oxygens" (shown as in reaction 5). Certainly, the reported rate constants for H-atom abstraction from the central CH_2 group of **CU** by methyl radicals (3.5×10^9 M^{-1} s^{-1} in 40% aqueous DMSO at pH 5) and *tert*-butoxyl radicals (7.5×10^9 M^{-1} s^{-1} in acetonitrile) are extraordinarily high. Indeed, they would appear to be impossibly high for abstraction of H from any C−H moiety.[22]



Jovanovic et al.'s[13] conclusions were firmly rejected in 2000 by Barclay et al.[6] These workers examined the actual antioxidant activities of **CU**, three curcumin analogues with no phenolic hydroxyl groups and three 2-methoxy-4-alkylphenols by measuring their abilities to inhibit the autoxidation of styrene and methyl linoleate in chlorobenzene at 30 °C. The **CU** analogues with no phenolic hydroxyl groups did not retard oxidation of either substrate, but **CU** and the three methoxy alkylphenols did inhibit oxidation, trapping four and two peroxyl radicals, respectively. Moreover, the rate constant

(4) In iron-catalyzed lipid peroxidation the antioxidant activity of CU and its acetylated derivatives has been ascribed to iron chelation by the α,γ-diketone moiety; e.g., see: Sreejayan, N.; Rao, M. N. A. *J. Pharm. Pharmacol.* **1994**, *46*, 1013−1016. See also: Began, G.; Sudharshan, E.; Udaya Sankar, K.; Appu Rao, A. G. *J. Agric. Food Chem.* **1999**, *47*, 4992−4997.

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(8) (a) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 1851−1864. (b) 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.

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(14) For the 3 year period (2000 to 2002-end), Chemical Abstracts (SciFinder) lists 956 papers with the word *curcumin*. Among this number, 248 papers contain the word pair *curcumin* and *antioxidant*.

(15) Jovanovic, S. V.; Boone, C. W.; Steenken, S.; Trinoga, M.; Kaskey, R. B. *J. Am. Chem. Soc.* **2001**, *123*, 3064−3068.

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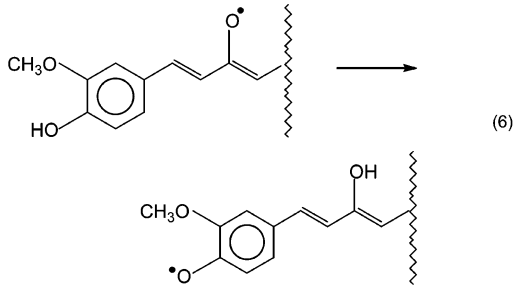
(20) Gorman, A. A.; Hamblett, I.; Srinivasan, V. S.; Wood, P. D. *Photochem. Photobiol.* **1994**, *59*, 389−398.

(21) For 2,4-pentanedione (acetylacetone), the [keto−enol]/[diketo] ratios are 42, 4.8, 2.9, 1.2, and 0.23 in cyclohexane, 1,4-dioxane, methanol, acetonitrile, and water, respectively, and equilibration is extremely slow, e.g., 15 h in methanol. See: Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216−1224.

(22) The fastest authentic C−H abstractions appear to be: $CH_3^{\bullet}$ + 1,4-cyclohexadiene (1.3×10^5 M^{-1} s^{-1})[23] and $Me_3CO^{\bullet}$ + $(CH_3CH_2)_3N$ (1.8×10^8 M^{-1} s^{-1}).[24]

for reaction of **CU** with polyperoxystyreneperoxyl radicals (3.4×10^5 M^{-1} s^{-1}) was exactly twice that of dehydrozingerone (1.7×10^5 M^{-1} s^{-1}), which is sometimes called "half curcumin" (see **DHZ** in Chart 1), and the rate constant for 2-methoxy-4-methylphenol was only slightly lower (1.4×10^5 M^{-1} s^{-1}). These results all demonstrate that the two "halves" of **CU** react independently with peroxyl radicals and that the α,γ-diketo moiety has no antioxidant properties *in these systems*.

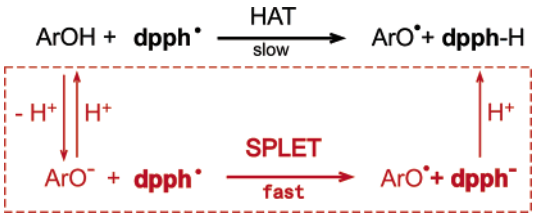
Barclay et al.'s[6] paper and its conclusion "that curcumin is a *phenolic* chain breaking antioxidant" were both ignored a year later by Jovanovic et al.[15] However, in this second paper the original mechanism was modified with the proposal that "the initially generated curcumin alkoxyl radical (see reaction 5) undergoes rapid intramolecular H-shift" to form a phenoxyl radical; i.e., reaction 6.



This proposal was based on the fact that the radical derived from a **CU** analogue with no phenolic hydroxyl groups reacted with dioxygen (reaction 4), whereas the **CU**-derived radical (like other phenoxyl radicals) did not. Nevertheless, reaction 6 is implausible because an intramolecular 1,9-H-atom shift could not possibly occur in this planar radical.

Attempts to determine the most probable site of radical attack on **CU** by theoretical calculations of bond dissociation enthalpies[7b,25] have ignored a basic kinetic fact[26] and, hence, have not helped to resolve the controversy. To us, it appeared reasonable to hypothesize that the disagreements over **CU**'s reactive site arose from the different experimental conditions that had been employed. In *all* publications dealing with radical attack on **CU**, *a direct hydrogen atom transfer (HAT) has been assumed*. Over the past few years, we have shown that HAT rates from phenols to any radical are subject to large kinetic solvent effects (KSEs) in hydrogen-bond-accepting (HBA) solvents.[9−12,28] This is because a phenol molecule that is involved as a hydrogen bond donor (HBD) *to a solvent molecule* is unreactive toward radicals (for steric reasons). The observed rate constants, k^s, involve only noninter-molecularly H-bonded phenol molecules. We demonstrated that for any attacking radical and any HBD substrate the value of k^s in all solvents could be correlated with the rate constant in a non-HB solvent, $k°$, via eq 7[11]

SCHEME 1



$$\log(k^s/M^{-1}\,s^{-1}) = \log(k°/M^{-1}\,s^{-1}) - 8.3\alpha_2^H\beta_2^H \quad (7)$$

with some interesting exceptions.[29] In this equation, α_2^H represents the relative ability of the substrate to donate a HB (range 0 to ca. 1)[30] and β_2^H represents the relative ability of the solvent to accept a HB (range 0 to 1.00).[31]

The *interesting exceptions* referred to above were discovered from the failure of eq 7 to predict HAT rate constants for the reactions of various phenols with **dpph•** in alcohol solvents, the measured rates being higher (sometimes very much higher) than predicted.[29] To explain these anomalies, we proposed a mechanism which we now name as sequential proton loss electron transfer (SPLET). In solvents which support ionization (notably methanol among organic solvents[29]), the experimental rate constant is the sum of the rate constant for the conventional HAT process (Scheme 1, black) and the very much larger rate constant for reaction of the radical with the phenoxide anion,[32,33] the SPLET process (Scheme 1, red). SPLET is favored for reactions of phenols having low pK_a's with electron-deficient radicals having relatively low HAT activities and yielding product molecules having low pK_as, e.g., **dpph•**/**dpph**-H and peroxyls, ROO•/ROOH.[34]

The occurrence of SPLET in methanol and ethanol has also been clearly demonstrated by Foti et al.[32] in a study of the reactions of **dpph•** with some phenolic acids (caffeic, *p*-coumaric, ferulic, and sinapic acids). Rate constants for reactions of the methyl esters of these acids

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(26) Thermochemistry alone does not dictate the relative rates of H-atom abstractions from OH and CH groups. It is well-known that for equal thermodynamic driving forces H-atom abstractions by oxygen-centered radicals (and other radicals) are several orders of magnitude faster from an OH group than from a CH group.[27]
(27) (a) Zavitsas, A. A. *J. Am. Chem. Soc.* **1972**, *94*, 2779−2789. (b) Zavitsas, A. A.; Melikian, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 2757−2763. (c) Zavitsas, A. A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1995**, *117*, 10645−10654, and the many references cited in these three papers.
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(33) A very fast electron transfer from the phenolate anion generated from 2,2,5,7,8-pentamethylchroman-6-ol to 2,2-bis-(4-tert-octylphenyl)-1-picrylhydrazyl radical (DOPPH•) in acetonitrile has been recently reported, see: Nakanishi, M.; Miyazaki, K.; Shimada, T.; Iizuka, Y.; Inami, K.; Mochizuki, M.; Urano, S.; Okuda, H.; Ozawa, T.; Fukuzumi, S.; Ikota, N.; Fukuhara, K. *Org. Biomol. Chem.* **2003**, *1*, 4085−4088.
(34) The pK_a's (in parentheses) for some relevant ion/molecule pairs are:[29] **dpph**$^-$, H$^+$/**dpph**H (8.5); ROO$^-$, H$^+$/ROOH (12.8); Me_3CO^-, H$^+$/Me_3COH (19.2); primary alkyl radical, H$^+$/alkane (ca. 50).

were 3−5 times greater than for the free acids as a consequence of the suppression of ionization of the phenolic OH group by the free carboxylic acid. These experiments nicely confirm the role that phenol ionization can play in the reactions of phenols with **dpph•** in solvents that can support ionization.

With this background information in our possession, we hypothesized that the experimental conditions used in some studies of **CU**'s antioxidant activity would favor a purely HAT process (e.g., ref 6) while the conditions in other studies would favor a large contribution from a SPLET process (e.g., refs 13 and 15). Herein, we provide evidence supporting this hypothesis and thus resolve the **CU** antioxidant controversy. We also provide evidence suggesting that **CU**'s α,γ-keto−enol/diketo moiety probably plays an important role in the reaction of **CU** with **dpph•** in solvents which support ionization.

Results

The **dpph•** radical has served our mechanistic studies of radical/phenol reactions well in the past[9,11,12,28c,29] and has been widely used to measure the hydrogen-atom-donating abilities of natural antioxidants. The rates of reaction 8 with XH (= **CU**, **IE**, **DHZ**, 2-MeO-phenol and 2-MeO-4-Me-phenol) were determined by monitoring the decay of **dpph•** at 517 nm[35] in a stopped-flow apparatus, as described previously.[29]

$$\mathbf{dpph}^{\bullet} + \mathrm{XH} \rightarrow \mathbf{dpph}\mathrm{H} + \mathrm{X}^{\bullet} \qquad (8)$$

The **dpph•** concentration was generally ca. $2-6 \times 10^{-5}$ M, and XH was used in excess. In almost all cases, this produced excellent pseudo-first-order decays of **dpph•** (rate constant, k_{exptl}) and the second-order rate constants for reaction 8, k^s, were calculated from the slopes of plots of k_{exptl} vs [XH], i.e.

$$k_{exptl} = k_o + k^s[\mathrm{XH}] \qquad (9)$$

at XH concentration where XH does not self-associate.

Equation 7 applies only to "pure" HAT reactions. It therefore provides a vital mechanistic tool for quantifying the importance of the SPLET process in different solvents and with different phenols.[29] Unfortunately, $k°$ in eq 7 could not be determined for the **dpph•/CU** reaction because of **CU**'s low solubility in saturated hydrocarbons ($\beta_2^H = 0.00$). We therefore measured k^s for this reaction in two non-hydroxylic solvents, 1,4-dioxane and ethyl acetate, and in two hydroxylic solvents, methanol and ethanol. Dioxane and methanol have been reported to have identical HBA activities (i.e., identical β_2^H values = 0.41).[31] Similarly, ethyl acetate and ethanol have also been reported to have identical HBA activities (β_2^H = 0.45).[31] However, the two hydroxylic solvents have much higher dielectric constants, ϵ, than the two non-hydroxylic solvents and hence have much greater abilities to support ionization and, consequently, the SPLET reaction mechanism (Scheme 1). Results are summarized in Table 1 together with k^s values measured in these four solvents acidified by the addition of (generally relatively low) concentrations of acetic acid as in our earlier work in which the SPLET reaction mechanism was first identified.[29]

TABLE 1. Room-Temperature Bimolecular Rate Constants, k^s (M^{-1} s^{-1}) for the Reactions of dpph• with Curcumin (CU), Dehydrozingerone (DHZ), and Isoeugenol (IE) in Various Solvents and Acidified Solvents[a]

solvent (β_2^H, ϵ)[b]	CH_3CO_2H[c] (mM)	k^s (**CU**)	k^s (**DHZ**)	k^s (**IE**)
1,4-dioxane (0.41,[d] 2.21)	0	1.4	0.33	2.4
dioxane	10	1.4	0.31	2.3
methanol (0.41, 32.63)	0	16 000[e]	1450[e]	1000
methanol	5	72	10	12
methanol	10	47	6.1	7.4
methanol	50	18	2.0	5.5
methanol	100	11	1.0	5.4
methanol	1000	3.6	0.72	6.4
ethanol (0.45, 24.30)	0	9800[e]	790[e]	240
ethanol	5	59	9.4	10
ethanol	10	48	7.3	7.2
ethanol	50	9.2	2.6	6.1
ethanol	100	6.3	1.8	6.3
ethanol	1000	2.8	1.2	6.0
ethyl acetate (0.45, 6.02)	0	9.0	0.72	4.1
ethyl acetate	10	6.7	0.66	4.3
ethyl acetate	1000	1.9	0.65	4.5

[a] k^s values are generally based on at least two independent measurements. Full data, including error limits for k^s, are given in the Supporting Information. [b] β_2^H from ref 31, ϵ from *CRC Handbook of Chemistry and Physics*, 67th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987. [c] β_2^H for propionic and butyric acids = 0.42, not available for acetic acid, and ϵ for CH_3CO_2H = 6.15. [d] This statistically corrected literature value is significantly smaller than the value of 0.47 measured in the present work; see text. [e] The loss of **dpph•** follows excellent pseudo-first-order kinetics in all cases except for **CU** and **DHZ** in neat MeOH and EtOH. Thus, these four rate constants are based on initial rates of decay of **dpph•**.

In methanol, the **dpph•/IE** reaction follows excellent pseudo-first-order kinetics (Figure 1C) but the **dpph•/CU** and **dpph•/DHZ** reactions exhibit a very fast initial loss of **dpph•** followed by a much slower process (Figure 1A,B). Similar results were obtained in ethanol. For all three compounds in both alcohols the addition of as little as 5 mM acetic acid dramatically decreases the reaction rate and all the **dpph•** decay traces now follow pseudo-first-order kinetics (for acidified methanol solvent see Figure 1A′−C′). With higher concentrations of acetic acid the second-order rate constants in both alcohols decline further toward a limiting value which is reached with **IE** at [CH_3CO_2H] ≥ 50 mM, with **DHZ** at [CH_3CO_2H] ≥ 100 mM, and with **CU** at [CH_3CO_2H] ≥ 1000 mM (see Table 1). This behavior is fully consistent with a SPLET reaction for these three substrates in both alcohols. That is, these substrates are partially ionized in alcoholic solvents and their anions react rapidly with the **dpph•** radical. Ionization is suppressed by addition of the acid, and at sufficiently high [CH_3CO_2H], the SPLET process is completely suppressed and the residual slow reaction occurs by HAT.[29] The three substrates are not expected to ionize in dioxane (ϵ = 2.2), and therefore, as expected, their second-order rate constants in this solvent are not changed by the addition of acetic acid (Table 1).

In ethyl acetate, with its higher dielectric constant (ϵ = 6.0), the addition of CH_3CO_2H does not change the

(35) **CU** is yellow with a strong absorption in the 420 to 430 nm region in organic solvents ($\epsilon_{\lambda max} \sim 55\,000$).[16] In none of our work did **CU**'s absorption interfere with our measurements of the rates of decay of **dpph•** at 517 nm ($\epsilon_{\lambda max} \sim 50\,000$).

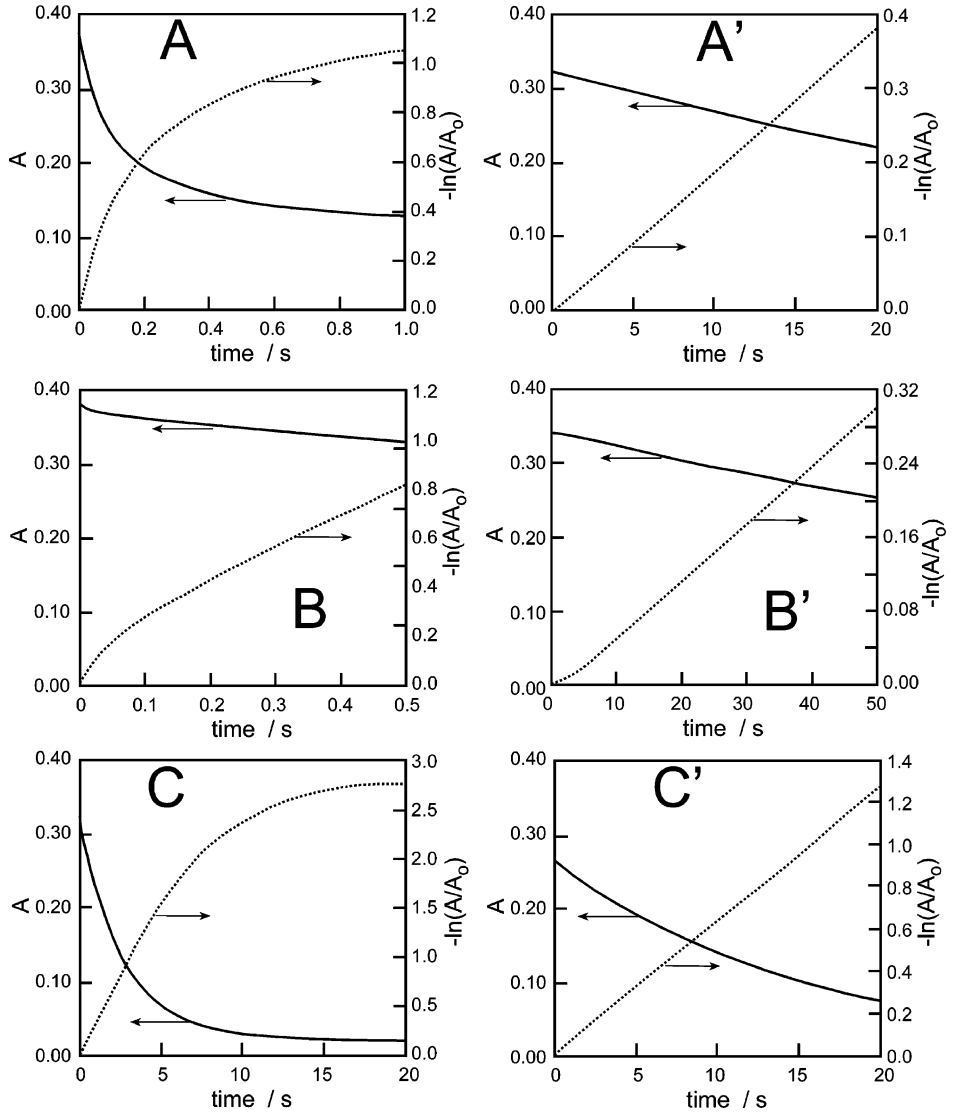


FIGURE 1. Decay of 3 μM **dpph**$^{\bullet}$ in reaction with 0.37 mM **CU**, **DH**Z, and **IE** in MeOH, panels A, B, and C, respectively, and in MeOH containing 5 mM acetic acid, panels A′, B′, and C′, respectively. A = absorbance, A_o = initial absorbance.

second-order rate constants for **DHZ** and **IE** but it does reduce the rate constant for **CU** (Table 1). Clearly, **CU** must be a stronger acid than **DHZ** and **IE** and be partially ionized in ethyl acetate. This is consistent with pK_a values in 1:1 (v/v) water/methanol obtained from the literature for **CU**[36,37] and dimethoxycurcumin and determined in the present work for **DHZ**, **IE**, and two related phenols, 2-MeO-phenol and 2-MeO-4-Me-phenol (see Table 2). More complete pK_a data are given in the Supporting Information.

The limiting HAT rate constants (i.e., k's when SPLET has been suppressed, if necessary, by acetic acid) for the reactions of **dpph**$^{\bullet}$ with **CU**, **DHZ**, and **IE** are all smaller in dioxane than in ethyl acetate, methanol, and ethanol (see Table 1). Such kinetics appeared to be inconsistent with the literature β_2^H values[31] for these solvents (Table 1) which imply (equation 7) that HAT rate constants should, for example, be smaller in ethyl acetate than in dioxane. This caused us to redetermine (unnecessarily, see below) β_2^H for dioxane by the usual infrared (IR) spectroscopic method[31,38] using CCl_4 as solvent and "calibrated" 4-fluorophenol as the HBD (for details see

TABLE 2. Values of pK_a in Water/Methanol (1:1 v/v) from the Literature and Measured in the Present Work[a]

		pK_a
CU	(1)	8.54[b]
	(2)	9.30[b]
	(3)	10.69[b]
(Me$_2$**CU**)[c]		8.75[b]
DHZ		9.12
IE		10.60
2-MeOC$_6$H$_4$OH		10.68
2-MeO-4-MeC$_6$H$_3$OH		10.78

[a] For additional details, see the Supporting Information. [b] See refs 36 and 37. [c] Dimethoxycurcumin is the dimethyl ether of **CU** having no phenolic OH groups.

(36) Borsari, M.; Ferrari, E.; Grandi, R.; Saladini, M. *Inorg. Chim. Acta* **2002**, *328*, 61−68.

(37) All three pK_a's for **CU** are within 2.5 log units of one another and the three ionization processes therefore overlap. We were not able to deconvolute the **CU** potentiometric curve. Fortunately, Bosari et al.[36] had reported some very systematic studies of **CU**'s acidity using potentiometric, spectrophotometric, and NMR methods. The three pK_a of **CU** were assigned by these workers to the ionization of particular OH groups, see Discussion.

TABLE 3. Comparison of Measured Bimolecular Rate Constants (Bold) for the Reactions of dpph• and Four *o*-Methoxyphenols in Ethyl Acetate and Dioxane with Rate Constants Calculated (Italics) from Eq 7[a]

		$k°$ (M^{-1} s^{-1}) (in heptane)	k^s (M^{-1} s^{-1}) (in ethyl acetate)		k^s (M^{-1} s^{-1}) (in dioxane)		
	phenol α_2^H [c]	$\beta_2^H = 0.00$[b]		$\beta_2^H = 0.45$[b]		$\beta_2^H = 0.47$[c]	($\beta_2^H = 0.41$)[b]
DHZ	0.36_1	**7.2**[d]	**0.72**	*0.33*	**0.33**	*0.28*	(*0.43*)
IE	0.29_1	**53**	**4.1**	*4.4*	**2.4**	*3.9*	(*5.5*)
2-MeO	0.29_4[e]	**1.0**	**0.14**	*0.08*	**0.055**	*0.07*	(*0.10*)
2-MeO-4-Me	0.29_2	**7.1**	**0.89**	*0.59*	**0.47**	*0.52*	(*0.73*)

[a] Full data with errors are given in the Supporting Information. [b] Reference 31. [c] This work. [d] In heptane/CCl_4, (1:1 v/v) because of the low solubility of **DHZ** in neat heptane. [e] A value of 0.26 is given in ref 30.

the Experimental Section and Supporting Information). The β_2^H value obtained for dioxane was 0.47, which is fully consistent with the HAT reactions of **CU**, **DHZ**, and **IE** being slightly slower in dioxane than in ethyl acetate ($\beta_2^H = 0.45$).[31] Later, a reviewer pointed out that in Abraham et al.'s original report[31] the log K_B^H value for dioxane is listed as 1.101. When this was converted to a β_2^H value, a statistical factor of 2 was introduced, giving $\beta_2^H = 0.41$.[31] If the statistical factor is ignored, as we believe it should be, β_2^H for dioxane becomes 0.47_5, in excellent agreement with our own measurements.

The validity of eq 7 for intramolecular hydrogen-bonded compounds was also briefly explored using **DHZ**, **IE**, 2-methoxyphenol, and 2-methoxy-4-methylphenol. Unfortunately, **CU** had to be excluded from these studies because it was found to be too insoluble in CCl_4 and heptane. First, the α_2^H values for these four *ortho*-methoxyphenols were measured by the usual IR method,[11,12,29,30] using CCl_4 as solvent and the "calibrated" HBA, DMSO (for details, see the Supporting Information). The α_2^H values for **IE**, 2-methoxyphenol, and 2-methoxy-4-methylphenol are all 0.29 (see Table 3) but that for **DHZ** is appreciably greater (0.36). These results are consistent with the observation that **DHZ** is significantly more acidic than the other three *o*-methoxyphenols (see Table 2). The greater acidity of **DHZ** and its stronger HBD activity can be attributed to the electron-withdrawing effect of its carbonyl group which is conjugated to the aromatic ring para to the hydroxyl group (see Chart 1). Second, the rate constants for the reactions of these four *o*-methoxyphenols with **dpph•** were measured in heptane and for 2-MeO- and 2-MeO-4-Me-phenols in ethyl acetate and dioxane; see Table 3. Values of k^s in these two solvents were then calculated using eq 7 and the $k°$, α_2^H, and β_2^H values given in Table 3. These calculated values are in very satisfactory agreement with our measurements (see Table 3). Notably, the calculated k^s values in dioxane agree better with experiment using the β_2^H value (0.47) measured in the present work instead of the statistically corrected literature value (0.41).

Discussion

For an *apparent* hydrogen atom abstraction (HAT) reaction between X• and ArOH (reaction 1) to occur by a sequential proton loss electron transfer (SPLET) mechanism, three conditions must be met: (i) The radical, X•, must be electron deficient; i.e., XH must have a fairly low pK_a (as is the case for **dpph•**/**dpph**-H (8.5) and ROO•/ROOH (12.8).[29] (ii) The substrate, ArOH, must have a readily "abstractable" and fairly acidic hydrogen atom (as is true for most phenols: $ArOH \rightleftharpoons ArO^- + H^+$; $ArOH + X^\bullet \rightleftharpoons ArO^\bullet + XH$). (iii) The solvent must be able to support partial (or even complete) ionization of the substrate.

The simplest test we have devised which can demonstrate the presence or absence of a SPLET contribution to an (apparent) HAT is to study the effect of added acetic acid on the measured rate constant for the reaction. The ionization of most substrates will be suppressed by added acetic acid (because the substrates will generally be less acidic than CH_3CO_2H). As a consequence, the contribution of SPLET to the overall reaction will be decreased and the measured rate constant will decline. In many cases, SPLET will be completely suppressed at high [CH_3CO_2H] (see ref 29). The measured rate constant will then become independent of the concentration of CH_3CO_2H and will reflect the underlying and much slower HAT process in the solvent in which the reaction was carried out. To prove that these limiting rate constants really do correspond (at least, mainly) to the underlying HAT reaction in any particular solvent it is necessary to show that they are *approximately* of the magnitude dictated by eq 7.[29,39] In the present work, this was achieved by demonstrating that the "limiting" rate constants at high [CH_3CO_2H] in the two ionizing solvents, MeOH and EtOH, were *roughly* equal to rate constants for the same ArOH/X• reaction measured in solvents having similar HBA activities (i.e., similar β_2^H values) *and* little or no ability to ionize ArOH. To confirm that these low dielectric constant solvents (dioxane and ethyl acetate in the present work) truly prevented SPLET it was, of course, essential to also measure rate constants with acetic acid added to these solvents. This check confirmed that **CU**, **DHZ**, and **IE** were not ionized in dioxane (Table 1) and therefore SPLET played no role in this solvent. The same is true for **IE** and, probably, for **DHZ** in ethyl acetate, but **CU** must be partially ionized because the addition of 1 M CH_3CO_2H reduced the rate constant for reaction with **dpph•** by a factor of 4.6 from its value in neat ethyl acetate (Table 1).

First, consideration will be given to HAT from a phenolic hydroxyl group of **CU**, **DHZ**, and **IE** to **dpph•**. These reactions are dominant in dioxane, in strongly acidified methanol and ethanol, and in ethyl acetate, the last strongly acidified for **CU**. A comparison of the rate constants measured under these conditions shows that

(38) (a) Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 485−489. (b) Besseau, F.; Luçon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 101−107.

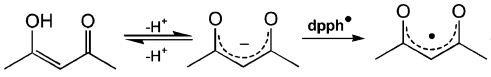
(39) Equation 7 is a remarkably reliable kinetic guideline for "pure" HAT processes (see e.g., Table 3) but it appears to be rarely, if ever, precisely obeyed (see e.g., refs 11, 12, and 29). Too much should not, therefore, be read into any minor kinetic "inconsistencies".

IE is the most reactive HAT substrate, followed by **CU** (even after statistically correcting for the two phenolic groups in this molecule), followed by **DHZ**. This order of reactivity is congruent with expectations based on the fact that electron withdrawing (EW) para substituents increase phenolic O−H bond dissociation enthalpies (BDEs)[40] and hence reduce HAT activities.[11,41] The EW carbonyl group in **DHZ** is conjugated to the aromatic ring. If **CU** existed solely in the diketo form, **1a**, it would (after the statistical correction) be of equal reactivity to **DHZ**. However, in these four solvents/solvent mixtures, **CU** probably exists largely as the keto−enol,[19−21] **1b**, and the −(O)CCH=C(OH)− moiety is expected to be less strongly EW than the simple carbonyl group in DHZ. For this reason, even after the statistical correction, **CU** is a somewhat better HAT agent to **dpph•** than **DHZ**. The absence of a carbonyl group in the para substituent of **IE** makes this compound a more reactive HAT than **CU** and **DHZ**. **IE** is also a more reactive HAT agent than 2-methoxy-4-methylphenol which, in turn, is more reactive that 2-methoxyphenol (Table 3). These results are also congruent with expectations. That is, para substituents which aid electron delocalization in phenoxyl radicals decrease phenolic O−H BDEs and hence increase HAT rates. For these three phenols, the order of increasing HAT rates is, as expected, 4-H < 4-CH_3 < 4-CH=$CHCH_3$. **DHZ** is more interesting. The HAT activity of DHZ is essentially identical to that of 2-methoxy-4-methylphenol. This implies that the O−H bond weakening effect due to electron delocalization into the 4-CH=$CHCOCH_3$ group is countered by bond strengthening arising from the EW nature of this group.[42] The EW character of 4-CH=$CHCOCH_3$ is attested to by the much lower pK_a of **DHZ** than **IE**, 2-methoxy- and 2-methoxy-4-methylphenol and by a reported σ_p^+ (CH=$CHCOCH_3$) = 0.39.[43]

The extremely high rate constants for the reactions of **CU**, **DHZ**, and **IE** with **dpph•** in methanol and ethanol compared with the rate constants in dioxane and ethyl acetate, taken together with the dramatic declines in the rate constants in the two alcohols which are produced by added acetic acid, prove that in the alcohols these reactions occur primarily by the SPLET mechanism. As was pointed out in the Results, the reaction of **IE** in the neat alcohols follows clean pseudo-first-order kinetics (see Figure 1C and Table 1). This means the ionization of **IE** must be faster than its reaction with ca. 3 μM **dpph•**. In contrast, the reactions of **CU** and **DHZ** in the neat alcohols show an initial, very fast reaction followed by a slow (but still rapid) loss of **dpph•** (Figure 1A,B and footnote e in Table 1). These initial fast reactions must correspond to rapid reactions of the **dpph•** with the **CU** and **DHZ** anions present at low equilibrium concentration in the alcohols. These "preformed" anions are quickly depleted and ionization of the much larger concentration of neutral **CU** and **DHZ** becomes partly rate limiting.[44]

The occurrence of SPLET in the reactions of **CU**, **DHZ**, and **IE** with **dpph•** is perfectly reasonable as judged by our earlier work[29] because all three substrates are fairly acidic with **CU** being the strongest acid. The three pK_a's of **CU** have been determined in water/methanol, 1:1 (v/v) as[36] (i) 8.54 for dissociation of the α,γ-keto−enol, (ii) 9.30 for dissociation of the first phenolic hydroxyl group to give the dianion, and (iii) 10.69 for dissociation of the second phenolic hydroxyl and formation of the trianion (see Table 2 and, for more details, the Supporting Information).

The low first pK_a value for the keto−enol moiety in **CU** indicates that in solvents which support ionization the SPLET mechanism most probably involves proton loss from (i.e., ionization of) the α,γ-keto−enol moiety and electron transfer from the resulting $[(O)CCHC(O)]^-$ anion moiety to the **dpph•** radical. That such a reaction can occur was demonstrated using 2,4-pentadione (acetylacetone, AcAc). In dioxane, the reaction of **dpph•** with AcAc followed good pseudo-first-order kinetics but was very slow ($k = (8 \pm 4) \times 10^{-5}$ M^{-1} s^{-1}) and is presumably a HAT reaction. In methanol the initial reaction was much faster ($k = (4 \pm 1) \times 10^{-2}$ M^{-1} s^{-1}) but subsequently the reaction became slower and the overall reaction did not follow pseudo-first-order kinetics. Thus, in this alcohol, the initial fast reaction probably involves electron transfer from the AcAc anion to the **dpph•**.



(10)

In the case of **CU**, the initial electron transfer from the ionized keto−enol moiety (see structure **II** in Scheme 2) to the **dpph•** produces a radical fragment $[(O)CCHC(O)]^•$ (structure **III**), which will be strongly electron withdrawing.[46] Consequently, the pK_a of the phenolic hydroxyl groups will decrease dramatically, and this will lead to proton loss from one of these groups (structure

(40) (a) Mulder, P.; Saastad, O. W.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 4090−4092. (b) Jonsson, M.; Lind, J.; Eriksen, T. E.; Merenyi, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1567−1568. (c) Wayner, D. D. M.; Lusztyk, E.; Ingold, K. U.; Mulder, P. *J. Org. Chem.* **1996**, *61*, 6430−6433. (d) Dorrestijn, E.; Laarhoven, L. J. J.; Arends, I. W. C. E.; Mulder, P. *J. Anal. Appl. Pyrol.* **2000**, *54*, 153−192. (e) Pratt, D. A.; de Heer, M. I.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 5518−5526. (f) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334−340.

(41) (a) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744−1751. (b) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2800−2806.

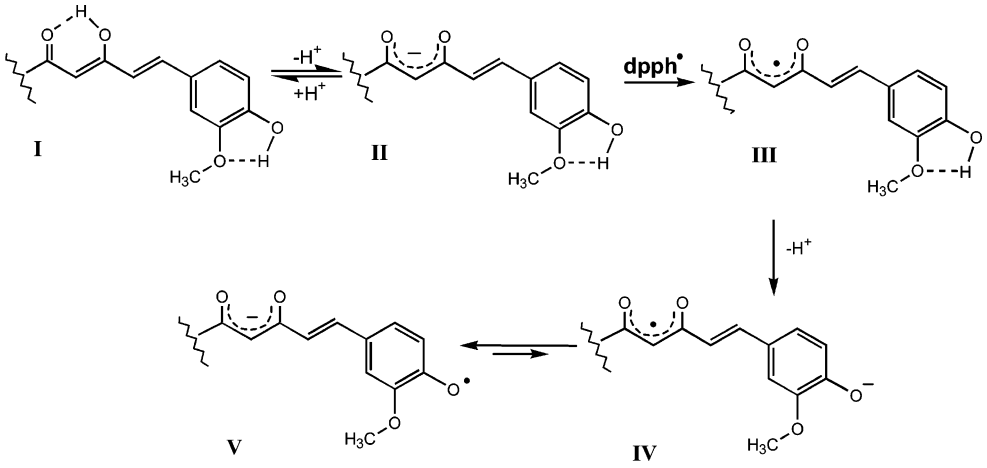
(42) The near equivalence of these two phenolic O−H BDEs is supported by DFT calculations of the differences in O−H BDEs: (4-CH_3COCH=CHC_6H_4O−H − C_6H_5O−H) and (4-$CH_3C_6H_4O$−H − C_6H_5O−H) which are −1.8 and −2.6 kcal/mol, respectively. These calculations were performed using the B3LYP functional with the medium-level model MLM1 as described in: DiLabio, G. A.; Pratt, D. A.; LoFaro, A. D.; Wright, J. S. *J. Phys. Chem. A* **1999**, *103*, 1653−1661.

(43) Saldabol, N. O.; Popelis, Yu. Yu.; Liepin'sh, E. E. *Zh. Org. Khim.* **1980**, *16*, 1494−1497 (English translation, pp 1285−1288).

(44) A truly rate-limiting ionization would cause the slow second stage of **dpph•** loss to follow zero-order kinetics in [**dpph•**] while remaining first order in substrate. This phenomenon has been observed in other **dpph•**/ArOH reactions.[45] Rates of **dpph•** loss in the slow second stages of its reaction with **CU** and **DHZ** in the neat alcohols indicate that the kinetics of ionization and of the **dpph•**/anion reactions are convoluted. Convolution was least for **DHZ** in methanol and in this case the equilibrium concentration of the anion, $[\mathbf{DHZ}^-]_{eq}$, was estimated as follows. At constant [**DHZ**] (0.98 mM) and variable [**dpph•**] (8−91 μM) the roughly linear slow second stages of **dpph•** decay were extrapolated back to zero time to obtain $[\mathbf{dpph•}]_{intercept}$. The differences between the initial concentrations of **dpph•**, $[\mathbf{dpph•}]_o$, and $[\mathbf{dpph•}]_{intercept}$ was plotted against $1/[\mathbf{dpph•}]_o$. A reasonable straight line was obtained with an intercept at $1/[\mathbf{dpph•}]_o = 0$ of 2.6×10^{-6} M (see Supporting Information). This should correspond to $[\mathbf{DHZ}^-]_{eq}$ and the percentage **DHZ** ionized is given by $(100 \times 2.6 \times 10^{-6})/[(980-2.6) \times 10^{-6}] = 0.27\%$.

(45) Litwinienko, G. Unpublished results.

SCHEME 2



IV which will evolve to **V** by migration of the negative charge, see Scheme 2).

That is, in solvents that support ionization, **CU** reacts with electrophilic radicals initially at the ionized α,γ-keto−enol moiety and the resulting neutral radical loses a phenolic proton, thus yielding the same phenoxyl radical, **V**, as would have been formed by HAT from the phenolic hydroxyl group of the **CU** anion (**II**) to the radical (Scheme 2). It must be emphasized that phenoxyl radical formation in ionizing solvents does not occur by Jovanovic et al.'s[15] "rapid intramolecular H-shift", reaction 6, but by loss of a *proton* into the bulk solution from the *neutral* [(O)CCHC(O)]• **CU** radical, **III**. Of course, in solvents which do not support ionization or in which ionization is prevented by the addition of CH_3CO_2H (or other proton source) the SPLET mechanism cannot occur and the reactions will involve only HAT from a phenolic hydroxyl group of the neutral **CU** to the radical. This has already been clearly demonstrated by Barclay et al.[6] in the solvent, chlorobenzene. *Thus, the CU antioxidant controversy is resolved*.

Experimental Section

Materials. 1,4-Dioxane (99+%) and ethyl acetate (99.99%) were used as received. Values of k^s in methanol and ethanol were extremely sensitive to traces of base, the amounts of which vary even in samples of the highest commercially available purity (according to the labels on the bottles). These alcohols were, therefore, fractionally distilled from a small amount of **dpph•** (ca. 1 mg per 500 mL of alcohol) and a few beads of a weakly acidic ion-exchange resin. **IE** (98%, a mixture of cis and trans isomers), **CU** (97%), 2-MeO-phenol (99%), 4-Me-2-MeO-phenol (98%), and 4-fluorophenol (99%) were commercial materials that were used without further purification. Highly purified **DHZ** was a gift; see the Acknowledgment.

Kinetic Measurements. The procedure used to determine k^s was generally the same as described previously.[29] Briefly, solutions of **dpph•** and the phenols were prepared in nitrogen-purged solvents and were kept under nitrogen, with additional nitrogen purging when necessary, until they were taken up into the glass syringes of the stopped-flow apparatus with their gastight Teflon plungers. The decay of **dpph•** in the presence of known concentrations of the phenols was followed at 517 nm on an Applied Photophysics stopped-flow spectrophotometer, SX 18 MV, equipped with a 150 W xenon lamp. All measurements were carried out at 23 ± 2 °C. The concentration of **dpph•** was (4 ± 2) × 10^{-5} M, and the phenols were always used in large excess. The decays of the **dpph•** absorbancies were analyzed as pseudo-first-order processes to yield k_{exptl}/s^{-1}. For the concentrations of phenols used in our experiments (see Tables S1−S23) the plots of k_{exptl} vs phenol concentration were linear and their slopes gave the second-order rate constants, k^s. Mean values k^s with absolute errors (Δk) and statistical parameters are provided in the Supporting Information.

Determination of α_2^H and β_2^H. Values of α_2^H for substrates were determined by monitoring the OH fundamental stretching region of their IR spectrum in CCl_4 at ambient temperatures in the usual manner.[11,29] Each spectrum was collected on a Shimadzu FTIR 8201PC apparatus using a 1.03 mm CaF_2 cell (20 scans with a resolution of 1 cm^{-1}), and the baseline was corrected using solutions having the same concentrations of hydrogen bond acceptor (HBA). Although the OH groups in *o*-methoxyphenols are internally hydrogen bonded, the formation of *intermolecular* HB complex with HBA is still described by

$$ArOH_{free} + HBA_{free} \rightleftharpoons ArOH\cdots HBA_{intermolecular}$$

and the equilibrium constant is given by

$$K^i = \frac{[ArOH\cdots HBA]_{intermolecular}}{[ArOH]_{free}[HBA]_{free}} \qquad (11)$$

where $[ArOH]_{free}$ denotes the concentration of phenol molecules not participating in an *intermolecular* HB. Values of $[ArOH]_{free}$ were determined from the decrease in the peak height of the internally hydrogen bonded OH at about 3560 cm^{-1} for 2-MeO-phenol and 2-MeO-4-Me-phenol, 3557 cm^{-1} for **IE** and 3549 cm^{-1} for **DHZ** (see Figures S5 and S6 in the Supporting Information). Equation 11 can be transformed to the form $[ArOH]_o/[ArOH]_{free} = 1 + K^i [HBA]_{free}$, where $[ArOH]_o$ is the total concentration of phenol and values of K^i were determined from the plots of the ratio $[ArOH]_o/[ArOH]_{free}$ versus $[HBA]_{free}$. Values of α_2^H were calculated using the equations

$$\log K_A^{H_i} = (\log K^i - D_B)/L_B \qquad (12)$$

and

(46) The σ_p (or σ_p^+) value for O• has been estimated to be ca. 2.0[47] though a lower value, closer to that of the strongly electron withdrawing (EW) NO_2 group (σ_p = 0.78), appears to be more probable.[48] In either event the O• moiety is a powerful EW group and the EW character of the [(O)CCHC(O)]• group will therefore be substantial even though it is likely to be somewhat attenuated relative to O• by delocalization of the unpaired electron over the atoms in this group and by conjugation through a vinyl group.

$$\alpha_2^H = (\log K_A^{H_i} + 1.1)/4.636 \quad (13)$$

The HBA was DMSO, a calibrated base for which $L_B = 1.24$ and $D_B = 0.266$.[30]

Values β_2^H for dioxane were calculated from the equation

$$\beta_2^H = (\log K_B^H + 1.1)/4.636 \quad (14)$$

where $\log K_B^H$ is connected to the experimental equilibrium constants K^i by the equation: $\log K^i = L_A \log K_B^H + D_A$ (see ref 31). For the reference acid, 4-fluorophenol, $L_A = 1.000$ and $D_A = 0.000$,[31] and hence $\log K_B^H = \log K^i$. For dioxane plus 4-fluorophenol values of $K^i = 11.58$ and 11.68 were obtained, from which the value of β_2^H is calculated to be 0.47.

Determinations of pK_a. Experimental pK_a values for all the phenols (except **CU**) in water−methanol (1:1) were determined by potentiometric titration: $pK_a = pH + \log([ArOH]/[ArO^-])$ with correction for the OH^- activity (if required) according to the procedure described by Albert and Sergeant.[49] A universal pH-meter, CX-731Elmetron, was used with a combined pH glass electrode calibrated on primary pH standards for nonaqueous and mixed solvents as recommended by IUPAC.[50] A constant ionic strength (0.1 M KCl) was maintained in all experiments. The titrant (KOH in water−methanol 1:1 mixture containing a small quantity of $BaCl_2$ to remove traces of carbonates) and titrated solutions were kept in atmospheres free from carbon dioxide. Tables with experimental data and calculations are given in the Supporting Information.

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Supporting Information Available: Detailed kinetic data for reactions of the **CU**, **DHZ**, **IE**, 2-MeO-phenol and 4-Me-2-MeO-phenol with **dpph•** in neat heptane and in neat and acidified dioxane, methanol, ethanol, and ethyl acetate (Tables S1−S23) and for reaction of AcAc with **dpph•** in neat methanol and in dioxane (Tables S9, S14, S22, and S23), plots of $\log k^s$ vs $[CH_3CO_2H]$ in methanol for the reaction of **CU** + **dpph•** (Figure S1), dependence of the experimental first-order rate constant, k_{exptl}, vs concentration of [AcAc] in methanol (Figure S2), examples of **dpph•** decay traces for fixed initial concentration of **DHZ** and variable initial concentration of **dpph•** in methanol, plot of Δ[**dpph•**] as a function of reciprocal of $[\mathbf{dpph\bullet}]_o$, (Figures S3 and S4), IR spectra of **IE** and **DHZ** in CCl_4 containing various concentrations of DMSO (Figures S5 and S6), plots and parameters used for calculation of the HB equilibrium constants and the α_2^H values for the phenols and β_2^H for dioxane (Figures S7 and S8 and Tables S24−S26), experimental parameters used for the determination of the ionization constants of the phenols in water-methanol (1:1, v/v) solution (Tables S27−S35), and experimental and literature values of pK_a (Table S36). This material is available free of charge via the Internet at http://pubs.acs.org.

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