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Litwinienko, Gregorz; Ingold, K. U.

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## Abnormal Solvent Effects on Hydrogen Atom Abstractions. 1. The Reactions of Phenols with 2,2-Diphenyl-1-picrylhydrazyl (dpph<sup>•</sup>) in Alcohols

Grzegorz Litwinienko<sup>\*,1</sup> and K. U. Ingold

National Research Council, 100 Sussex Drive, Ottawa, Ontario, Canada, K1A 0R6

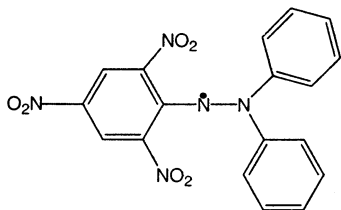
grzegorz.litwinienko@nrc.ca

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Rate constants,  $k_{\text{ArOH/dpph}^{\bullet}}^{\text{s}}$ , for hydrogen atom abstraction from 13 hindered and nonhindered phenols by the diphenylpicrylhydrazyl radical, **dpph<sup>•</sup>**, have been determined in *n*-heptane and a number of alcoholic and nonalcoholic, hydrogen-bond accepting solvents. Abnormally enhanced values of  $k_{\text{ArOH/dpph}^{\bullet}}^{\text{s}}$  have been observed in alcohols. It is proposed that this is due to partial ionization of the phenols and a very fast electron transfer from phenoxide anion to **dpph<sup>•</sup>**. The popular assessment of the antioxidant activities of phenols with **dpph<sup>•</sup>** in alcohol solvents will generally lead to an overestimation of their activities.

### Introduction

In 1958, Blois<sup>2</sup> suggested that the decolorization of the 2,2-diphenyl-1-picrylhydrazyl radical, **dpph<sup>•</sup>**,



in ethanol solutions would provide a convenient method for measuring the total concentration of antioxidants in biological materials. Because of its speed and simplicity this method for assaying the total antioxidant content in foods and plant products has become extremely popular.<sup>3</sup> By and large, these bio-antioxidants are phenols and it is interesting to note that kinetic studies on **dpph<sup>•</sup>**/phenol reactions also began in the late 1950s.<sup>4</sup> Initially, rate measurements were carried out in benzene, toluene, and CCl<sub>4</sub>, and were only extended to alcoholic solvents

in 1982.<sup>5</sup> Systematic studies on the kinetic solvent effects (KSEs) of **dpph<sup>•</sup>**/phenol reactions began in 1995.<sup>6</sup> The results of these<sup>6</sup> and other studies on the solvent effects on the kinetics of reactions between various radicals, Y<sup>•</sup>, and phenols, ArOH, and other substrates capable,<sup>7–15</sup> or not capable<sup>16–19</sup> of acting as hydrogen bond donors (HBDs) have confirmed that the large KSEs observed for H-atom abstractions from phenols are mainly, or possibly solely, a consequence of hydrogen bonding to the solvent, S, when S is a hydrogen bond acceptor (HBA). Intermolecularly hydrogen-bonded ArOH is essentially unreactive to all Y<sup>•</sup> (due to steric protection of the OH group by S), with only the “free”, non-hydrogen-bonded ArOH being reactive<sup>6–14</sup> (see Scheme 1, for Y<sup>•</sup> = **dpph<sup>•</sup>**). The

(1) Permanent address: Warsaw University, Department of Chemistry, Pasteur 1, 02-093 Warsaw, Poland.

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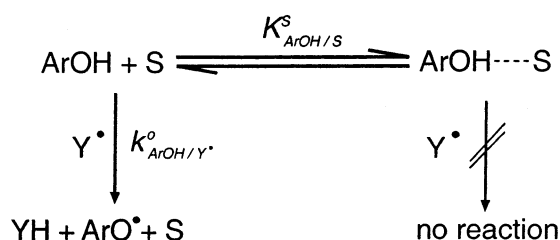
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## SCHEME 1



concentration of free ArOH depends on the total [ArOH] and on the equilibrium constant,  $K_{\text{ArOH/S}}^{\text{s}}$ . The experimentally observed rate constant in solvent, S,  $k_{\text{ArOH/Y}}^{\text{s}}$ , is given by,

$$k_{\text{ArOH/Y}}^{\text{s}} = \frac{k_{\text{ArOH/Y}}^{\circ}}{1 + K_{\text{ArOH/S}}^{\text{s}}[\text{S}]} \quad (\text{I})$$

where  $k_{\text{ArOH/Y}}^{\circ}$  is the rate constant for reaction of  $\text{Y}^{\bullet}$  with non-hydrogen-bonded ArOH, i.e.,  $K_{\text{ArOH/S}}^{\text{s}}$  is the experimental rate constant in a non-HBA solvent (such as an alkane) at concentrations of ArOH sufficiently low that there is no ArOH self-association via H-bonding.

The enthalpy of the ArOH...S hydrogen bond (and hence the magnitude of  $K_{\text{ArOH/S}}^{\text{s}}$  and  $k_{\text{ArOH/Y}}^{\text{s}}$ ) depends on the HBD ability of ArOH and the HBA ability of S. The former is most conveniently quantified (on a relative scale ranging from 0.00 to ca. 1.0) by Abraham et al.'s  $\alpha_2^{\text{H}}$  values<sup>20</sup> and the latter is most conveniently quantified (again on a relative scale from 0.00 to 1.00) by Abraham et al.'s  $\beta_2^{\text{H}}$  values.<sup>21</sup> Kinetic solvent effects on H-atom abstractions by highly reactive and relatively unreactive  $\text{Y}^{\bullet}$  from substrates having a wide range of  $\alpha_2^{\text{H}}$  values and solvents having a wide range of  $\beta_2^{\text{H}}$  values can be accurately described (and predicted) by a simple equation, viz.,<sup>13</sup>

$$\log k_{\text{ArOH/Y}}^{\text{s}} = \log k_{\text{ArOH/Y}}^{\circ} - 8.3\alpha_2^{\text{H}}\beta_2^{\text{H}} \quad (\text{II})$$

It should be noted that eq II implies that the relative magnitude of a KSE depends on the  $\beta_2^{\text{H}}$  value of S but does not depend on the reactivity of  $\text{Y}^{\bullet}$ . This has been amply confirmed<sup>6,9-11,13,19</sup> and eq II has been found to be remarkably general. However, even in early work,<sup>6</sup> an alcoholic solvent, *tert*-butyl alcohol, was found to give anomalous results for H-atom abstraction from phenol and  $\alpha$ -tocopherol by **dp<sup>ph</sup>** but normal (i.e., "expected"; eq II) results for H-abstraction from these two substrates by *tert*-alkoxyl radicals. That is, the H-abstraction rate constants with the *tert*-alkoxyl radicals were depressed (relative to  $k_{\text{ArOH/RO}}^{\circ}$ ) by the amount expected from the  $\beta_2^{\text{H}}$  value of *tert*-butyl alcohol (0.49)<sup>21</sup> and the depression observed for a dozen or so other HBA solvents with known  $\beta_2^{\text{H}}$  values.<sup>6-8,13</sup> However, with **dp<sup>ph</sup>** the rate constants for H-abstraction from both phenol and  $\alpha$ -tocopherol were five times greater than expected in *tert*-butyl alcohol.<sup>6</sup> A similar rate enhancement (actually, a less than expected rate reduction) in *tert*-butyl alcohol

was also found for H-abstraction from  $\alpha$ -tocopherol by peroxy radicals<sup>9</sup> but not for H-abstraction from the same substrate by the neophyl radical,<sup>10</sup>  $\text{PhCMe}_2\text{CH}_2^{\bullet}$ . Some proposed explanations for the **dp<sup>ph</sup>**/ArOH anomalous KSEs in *tert*-butyl alcohol have been ruled out experimentally.<sup>18</sup>

Kinetic studies of H-atom abstractions by *tert*-alkoxyl radicals in alcoholic solvents have been confined to *tert*-butyl alcohol (despite its mp of 25 °C and high viscosity) because most other alcohols are themselves highly reactive H-atom donors to alkoxy radicals. This restriction (based on thermodynamic considerations) does not apply to H-abstractions from phenols by the **dp<sup>ph</sup>** radical:



and during a study designed to explore the applicability of eq II to sterically hindered phenols some highly anomalous KSEs were encountered in alcoholic solvents.

## Results and Discussion

Steric protection of the OH group in 2,6-di-*tert*-butylphenols does not prevent the formation of a hydrogen bond with suitable HBAs.<sup>23</sup> As would be expected, rate constants for the reactions at room temperature of **dp<sup>ph</sup>** with five 2,6-di-*tert*-butylphenols generally declined monotonically as the HBA abilities of the following solvents increased: heptane < di-*n*-butyl ether < acetonitrile < tetrahydrofuran (THF) < dimethyl sulfoxide (DMSO), see Table 1, which includes the  $\beta_2^{\text{H}}$  values for the solvents. Indeed, plots of  $\log k_{\text{ArOH/dp}^{\text{ph}}}^{\text{s}}$  vs  $\beta_2^{\text{H}}$  for at least some of these 2,6-Bu<sup>t</sup><sub>2</sub>-phenols are quite reasonable (see Figure 1a,b). For 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol these kinetic data yield (via eq II)  $\beta_2^{\text{H}} = 0.29$ . Of course, steric hindrance of hydrogen bond formation by 2,6-Bu<sup>t</sup><sub>2</sub>-phenols will depend on the size and shape of the HBA molecule.<sup>24</sup> Thus, the hindered phenols are not expected to have  $\alpha_2^{\text{H}}$  values which are universally applicable (as is the case for unhindered phenols). We were, therefore, pleasantly surprised by the (admittedly very rough) correlation of  $\log k_{\text{ArOH/dp}^{\text{ph}}}^{\text{s}}$  for 2,6-Bu<sup>t</sup><sub>2</sub>-phenol and 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol with  $\beta_2^{\text{H}}$  for these five solvents (Figure 1, parts a and b, respectively). To explore this matter further, we have measured the equilibrium constants for hydrogen bond formation between 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol and four HBAs (acetonitrile, THF, DMSO, and pyridine) by IR spectroscopy.<sup>25</sup> These four HBAs have been "calibrated" by Abraham et al.<sup>20</sup> and the measured equilibrium constants therefore can be converted to the  $\alpha_2^{\text{H}}$  values which are given in Table 2. This table also contains an

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(24) In the case of strongly hindered phenols, the shape and size of the HBA molecule is a very important factor for H-bond formation. For example, the OH fundamental stretching frequency of 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol in heptane occurs at 3655 cm<sup>-1</sup>. A broad, lower frequency band due to an intermolecular hydrogen bond has been observed for this phenol in only a few neat solvents for which the HBA atom is relatively "exposed", e.g. dioxane (3431 cm<sup>-1</sup>) and THF (3400 cm<sup>-1</sup>). An intermolecular H-bond is not formed in diethyl ether nor in di-*n*-butyl ether (ref 23a).

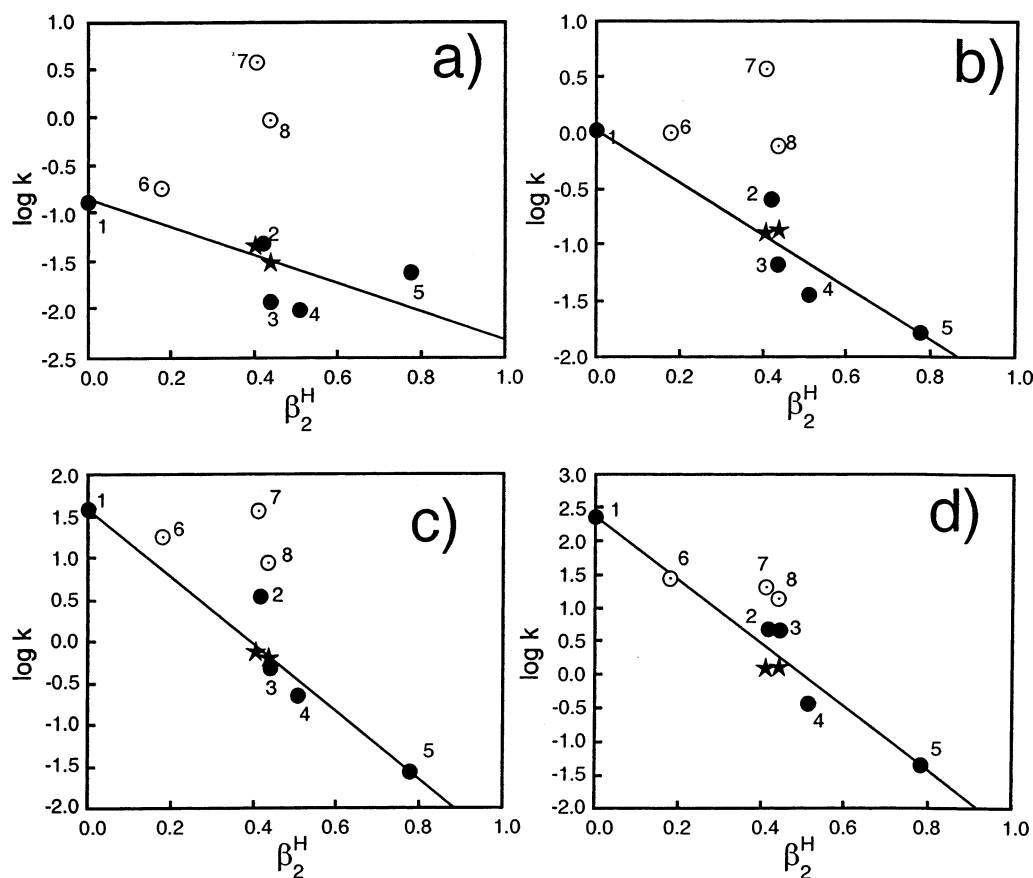
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**TABLE 1. Bimolecular Rate Constants ( $M^{-1} s^{-1}$ ) for H-atom Abstraction from Thirteen Phenols by  $dpph^{\bullet}$  Radicals in Five Nonalcoholic Solvents at Ambient Temperatures**

phenol substituents <sup>a</sup> ( $\beta_2^H$ )	$pK_a^b$	heptane (0.00) <sup>c</sup>	<i>n</i> -butyl ether (0.42) <sup>c</sup>	acetonitrile (0.44) <sup>c</sup>	THF (0.51) <sup>c</sup>	DMSO (0.78) <sup>c</sup>
2,6-Bu <sup>t</sup> <sub>2</sub> -4-MeO	12.15	22.6	6.7	1.5	0.53	0.74
2,6-Bu <sup>t</sup> <sub>2</sub> -4-Me	12.23	1.1	0.27	0.090	0.033	0.016
2,4,6-Bu <sup>t</sup> <sub>3</sub>	12.19	1.0	0.33	0.15	0.028	0.021
2,6-Bu <sup>t</sup> <sub>2</sub>	11.70	0.13	0.052	0.013	0.010	0.025
2,6-Bu <sup>t</sup> <sub>2</sub> -4-CN	8.70	0.022	0.025	0.050	0.23	0.030
2,4,6-Me <sub>3</sub> (0.37)	10.9	40	3.8	0.56	0.24	0.031
2,6-Me <sub>2</sub> -4-Cl		4.9	0.61	0.086	0.023	0.039
2,6-Me <sub>2</sub>	10.60	4.5	0.41	0.22	0.031	0.014
2,6-Me <sub>2</sub> -4-CN		0.013	0.013	0.011	0.023	0.0021
4-MeO (0.57)	10.24	240	4.9	5.0	0.40	0.048 <sup>d</sup>
4-Me (0.57)	10.3	2.8	0.038	0.064	0.0053	0.023
4-Bu <sup>t</sup> (0.56)	10.3	2.3	0.045	0.034	0.0047	0.014
none (0.60)	10.0	0.19 <sup>e</sup>	0.004	0.019	0.0006	0.0076

<sup>a</sup> Reliable values of  $\alpha_2^H$  are given in parentheses. All values are from ref 20 apart from 2,4,6-Me<sub>3</sub> (taken from ref 13). <sup>b</sup> Phenol  $pK_a$  values are from ref 22. <sup>c</sup>  $\beta_2^H$  values are from ref 21. <sup>d</sup> This value was taken from ref 13, our measurements gave rate constants five times greater (see Supporting Information, Table S5). <sup>e</sup> Literature rate constants for phenol +  $dpph^{\bullet}$  in *n*-octane are 0.19  $M^{-1} s^{-1}$  (ref 6) and 0.22  $M^{-1} s^{-1}$  in *n*-heptane (ref 13).



**FIGURE 1.** Logarithms of the rate constants for hydrogen atom abstraction from phenols by the  $dpph^{\bullet}$  radical: (a) 2,6-Bu<sup>t</sup><sub>2</sub>-phenol, (b) 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol, (c) 2,4,6-Me<sub>3</sub>-phenol, and (d) 4-MeO-phenol. Nonalcoholic 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: 2,2,2-trifluoroethanol (6), methanol, (7) and ethanol (8). Acidified (10 mM acetic acid) alcohols are shown as asterisks: methanol (left) and ethanol (right). Straight lines were constructed by using data for the five nonalcoholic solvents only. (2,2,2-Trifluoroethanol has a much lower nucleophilicity and  $\beta_2^H$  value than other alcohols. It was used as a solvent only with the four phenols shown in this figure.)

$\alpha_2^H$  value estimated for 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol from an NMR determination of its equilibrium constant with acetone.<sup>26</sup> For this phenol, the  $\alpha_2^H$  values calculated from IR and NMR data range from 0.18 to 0.25, in fair agreement with the KSE-derived value of 0.29.

Although the KSEs for the reaction of  $dpph^{\bullet}$  with four of the 2,6-Bu<sup>t</sup><sub>2</sub>-phenols are reasonably well behaved in heptane, butyl ether, acetonitrile, THF, and DMSO, this is obviously not the case for 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol nor is it the case for *any* of these hindered phenols in alcohol

**TABLE 2. Equilibrium Constants ( $K_{\text{ArOH/S}}^{\text{s}}$ /M<sup>-1</sup>) for Hydrogen Bond Formation between 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol and Four Solvents Measured by IR and One Solvent Measured by <sup>1</sup>H NMR and the Corresponding Calculated Values of  $\alpha_2^{\text{H}}$ <sup>a</sup>**

solvent	method	$K_{\text{ArOH/S}}^{\text{s}}$	$\alpha_2^{\text{H}}$
acetonitrile	IR	0.45	0.24
THF	IR	0.37	0.18
DMSO	IR	2.17	0.25
pyridine	IR	0.98	0.23
acetone	NMR	0.35 <sup>b</sup>	0.18

<sup>a</sup> See Supporting Information, Tables S13–S14 and Figures S1–S4, for details. <sup>b</sup> Equilibrium constant taken from ref 26.

solvents, see Table 3. In particular, the rate constants for 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol, 2,6-Bu<sup>t</sup><sub>2</sub>-phenol, and 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol were *larger* in methanol ( $\beta_2^{\text{H}} = 0.41$ ) than in heptane by factors of 3.4, 28, and an astonishing 940, respectively. Rate constants for the five 2,6-Bu<sup>t</sup><sub>2</sub>-phenols were also measured in ethanol, 2-propanol, and *tert*-pentanol (2-methylbutan-2-ol, which is a liquid at room temperature unlike *tert*-butyl alcohol), see Table 3. In these alcohols the rate constants for these hindered phenols were lower than in heptane with the exception of 2,6-Bu<sup>t</sup><sub>2</sub>-phenol in ethanol and 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol in all the alcohols except *tert*-pentanol (Table 3). Moreover, for 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol the rate constants in the four polar, non-hydroxylic solvents (di-*n*-butyl ether, acetonitrile, THF, and DMSO) were *also* higher than those in heptane (see Table 1).

A survey of four 2,6-Me<sub>2</sub>-phenols and four sterically nonhindered phenols revealed slightly higher rate constants in methanol than in heptane for some of the 2,6-Me<sub>2</sub>-phenols but rate constants for these phenols were lower than in heptane in all other alcohols, see Table 3. For all the nonhindered phenols, rate constants in methanol and in all other alcohol solvents were lower than those in heptane. Nevertheless, for all 2,6-Me<sub>2</sub>-phenols and all the unhindered phenols, almost all the rate constants measured in alcohols were larger than would be predicted by eq II (see Figure 1c,d and Supporting Information).

As has been the case in all our earlier KSE studies<sup>6–9,13–18</sup> we employed the purest solvents commercially available. The methanol anomaly forced us to reassess this policy and the methanol was therefore subjected to purification by fractional distillation (center cut, reflux ratio 10:1). However, this purified methanol gave essentially identical kinetic results to those obtained when methanol was used “straight from the bottle”.

Further purification of the methanol was therefore undertaken and the reason for the anomalous kinetic results in alcoholic solvents became clear (eventually) following the use of methanol distilled from calcium hydride (to remove any last traces of water from the purchased anhydrous methanol). To our surprise, ArOH/**dpph**<sup>•</sup> rate constants measured in this CaH<sub>2</sub>-distilled solvent were much greater than those in the unpurified

methanol. These results suggested that traces of basic materials were carried over with the distillate. That this was probably the case was indicated by the deliberate addition of base to the methanol. For example, the addition of a methanolic solution of sodium methoxide to unpurified methanol so as to obtain a final [NaOMe] = 1.7 × 10<sup>-4</sup> M gave ArOH/**dpph**<sup>•</sup> rate constants which were much greater than those in the unpurified methanol: viz., phenol, 0.21 vs 0.038 M<sup>-1</sup> s<sup>-1</sup>; 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol, 63 vs 3.7 M<sup>-1</sup> s<sup>-1</sup>; and 2,4,6-Me<sub>3</sub>-phenol, 780 vs 43 M<sup>-1</sup> s<sup>-1</sup>. Thus, the anomalous ArOH/**dpph**<sup>•</sup> KSEs in alcoholic solvents would appear to be due to the presence of traces of phenoxide anions, ArO<sup>-</sup>. The phenoxide anion would be expected to react very rapidly in these solvents with the highly electron-deficient **dpph**<sup>•</sup> radical.



This conclusion is consistent with four observations reported above. First, the alcohol anomaly is greatest for methanol, the alcohol that best supports ionization. Second, the methanol/alcohol anomalies are most obvious for the 2,6-Bu<sup>t</sup><sub>2</sub>-phenols. This is because these phenols have a much poorer ability to act as HBDs than most phenols (cf.  $\alpha_2^{\text{H}}$  values given in Tables 1 and 2). For this reason, the reduction in the rate constants due to hydrogen bonding with an HBA solvent, e.g., an alcohol, is relatively small, which allows the rate accelerating effect due to ArO<sup>-</sup> formation to show up much more clearly than is the case for less hindered and unhindered phenols with their higher  $\alpha_2^{\text{H}}$  values. However, there is still a very substantial KSE anomaly (rate enhancement relative to rate constants expected from equation II) in methanol for all these unhindered and relatively unhindered phenols (vide infra), it is just not so obvious because  $k_{\text{ArOH/dpph}^\bullet}^{\text{MeOH}}$  is smaller than  $k_{\text{ArOH/dpph}^\bullet}^{\text{heptane}}$ . Third, the only 2,6-Bu<sup>t</sup><sub>2</sub>-substituted phenol for which the rate constants in methanol, ethanol, and 2-propanol are larger than in heptane is the most acidic of the hindered phenols, and hence the most prone to anion formation, viz., 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol (see the pK<sub>a</sub> values given in Table 1). Fourth, the alcohol anomaly was first observed for the reactions of phenol and  $\alpha$ -tocopherol with **dpph**<sup>•</sup> in *tert*-butyl alcohol.<sup>6</sup> There was no *tert*-butyl alcohol anomaly in the reactions of these two phenols with *tert*-alkoxy radicals,<sup>6</sup> nor for H-atom abstraction from tocopherol by the neophyl radical,<sup>10</sup> but this anomaly occurred in the peroxy radical/tocopherol reaction.<sup>9</sup> With hindsight, it is clear that anomalously high rates of H-atom abstraction from phenols in *tert*-butyl alcohol were due to the formation of traces of phenoxide anions which were highly reactive toward radicals derived from parent molecules having low pK<sub>a</sub> values (**dpph**<sup>•</sup>/**dpph**-H pK<sub>a</sub> = 8.5<sup>27</sup> and ROO<sup>•</sup>/ROOH pK<sub>a</sub> = 12.8<sup>28</sup>) but not toward radicals derived from parent molecules having high pK<sub>a</sub> values (RO<sup>•</sup>/ROH pK<sub>a</sub> = 15.1–19.2<sup>29</sup> and PhCMe<sub>2</sub>CH<sub>2</sub><sup>•</sup>/PhCMe<sub>2</sub> pK<sub>a</sub> ~ 50<sup>30</sup>).

(27) Luca, C.; Ionita, P.; Constantinescu, T. *Rev. Roum. Chim.* **1994**, *39*, 1141–1151.

(28) Richardson, W. H. In *The chemistry of peroxides*; Patai S., Ed.; Wiley: New York, 1983; Chapter 5, pp 129–160.

(29) The pK<sub>a</sub> values for RO<sup>•</sup>/ROH are 15.1 (MeOH), 15.9 (EtOH), 16.1 (*n*-propanol, *n*-butanol), 17.1 (2-propanol), and 19.2 (*tert*-butyl alcohol, *tert*-pentanol), see ref 22.

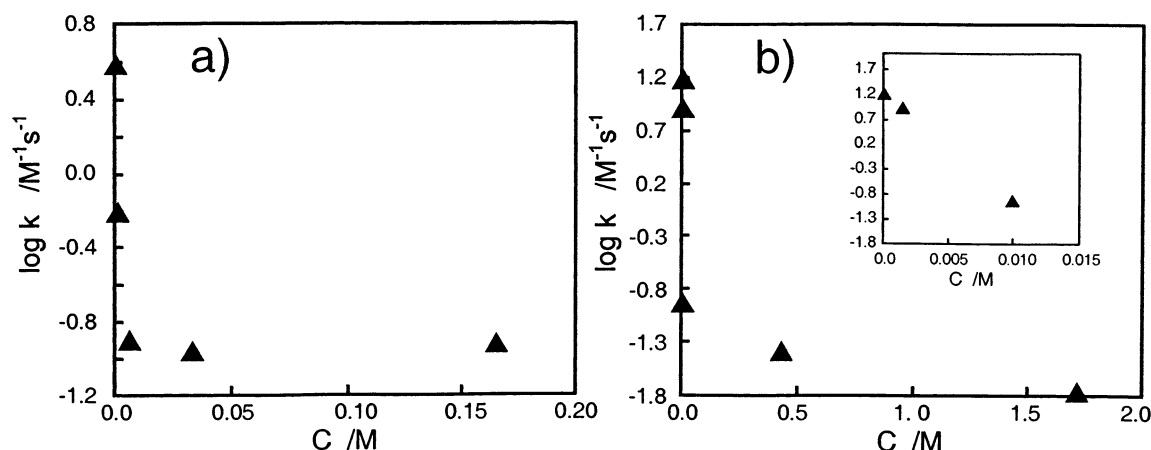
(25) See refs 13–15 for experimental conditions used for IR measurements of this type, the only difference being that we had to use much higher concentrations of HBAs in CCl<sub>4</sub> (up to 70% acetonitrile, THF, DMSO, and pyridine). See Experimental Section and Supporting Information for details.

(26) Wawer, I.; Keçki Z. *Ber. Bunsen-Ges.* **1976**, *80*, 522–525.

**TABLE 3. Bimolecular Rate Constants ( $M^{-1} s^{-1}$ ) for H-Atom Abstraction from 13 Phenols by  $\text{dpph}^{\bullet}$  Radicals in *n*-Heptane, Methanol, Ethanol, 2-Propanol, *tert*-Pentanol (2-Methylbutan-2-ol), and Acidified Methanol at Ambient Temperatures**

phenol substituents ( $\beta_2^H$ )	heptane (0.00) <sup>a</sup>	MeOH (0.41) <sup>a</sup>	EtOH (0.44) <sup>a</sup>	<i>iso</i> -PrOH (0.47) <sup>a</sup>	<i>tert</i> -C <sub>5</sub> OH (0.49) <sup>a</sup>	MeOH/H <sup>+</sup> <sup>b</sup>	
						10 mM	100 mM
2,6-Bu <sup>t</sup> <sub>2</sub> -4-MeO	22.6	3.9	3.9	6.8	8.8	1.8	1.9
2,6-Bu <sup>t</sup> <sub>2</sub> -4-Me	1.1	3.7	0.86	0.35	0.48 <sup>c</sup>	0.13	0.12
2,4,6-Bu <sup>t</sup> <sub>3</sub>	1.0	0.35	0.13	0.34	0.45	0.11	0.12
2,6-Bu <sup>t</sup> <sub>2</sub>	0.13	3.9	0.88	0.050	0.053	0.056	0.044
2,6-Bu <sup>t</sup> <sub>2</sub> -4-CN	0.022	16	13	7.7	0.0038	0.12	0.017 <sup>d</sup>
2,4,6-Me <sub>3</sub>	40	43	8.4	0.89	1.6	0.52	0.50
2,6-Me <sub>2</sub> -4-Cl	4.9	e	0.092	0.11	0.17	0.076	0.064
2,6-Me <sub>2</sub>	4.5	4.6	3.5	0.32	0.31	0.32	0.087
2,6-Me <sub>2</sub> -4-CN	0.013	0.014	0.0061	0.0073	0.0048	0.0068	0.0032
4-MeO	240	18	14	3.1	1.2	1.2	0.99
4-Bu <sup>t</sup>	2.3	0.74	0.57	0.19	0.012	0.019	0.017
4-Me	2.8	0.59	0.54	0.17	0.013	0.019	0.015
none	0.19	0.038	0.010	0.017	0.0066	0.0046	0.0037

<sup>a</sup>  $\beta_2^H$  values were taken from ref 21. <sup>b</sup> Methanol containing acetic acid (10 and 100 mM unless otherwise noted). <sup>c</sup> A reported  $k^s$  for this reaction in *tert*-butyl alcohol was  $0.41 M^{-1} s^{-1}$  (ref 11). <sup>d</sup> Concentration of acetic acid = 1.7 M, the rate constants for this reaction at other concentrations of acetic acid are listed in Table 4. <sup>e</sup> The results obtained for this phenol were irreproducible for reasons we did not explore. One set of measurements gave a value  $0.12 M^{-1} s^{-1}$  and another independent set of measurements gave  $4.0 M^{-1} s^{-1}$  (both results are presented in Table S6 in the Supporting Information).

**FIGURE 2.** Plots of the logarithm of the bimolecular rate constant for reaction of  $\text{dpph}^{\bullet}$  with 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol (a) and 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol (b) at ambient temperature in methanol vs added acetic acid concentration. The inset in panel b shows the dependence for the concentration range 0–10 mM.

Final confirmation that the formation of traces of phenoxide anions in alcoholic solvents enhances the apparent magnitude of  $k_{\text{ArOH/dpph}}^{\text{ROH}}$  was obtained by simply adding a small amount of acid to the unpurified methanol.<sup>31</sup> We found that 10 mM acetic acid was sufficient to reduce the rate constant for reaction of  $\text{dpph}^{\bullet}$  with most, but *not* all, phenols to a limiting value (meaning that the rate constant was not significantly reduced further by the addition of 100 mM acid), see Table 3. For example, the effects of variable acetic acid concentrations on  $k_{\text{ArOH/dpph}}^s$  for the weak acid 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol ( $\text{p}K_a = 12.2$ ) show that only a small concentration of acid (ca. 7 mM) is required to reduce the rate constant to a limiting value (see Figure 2a), whereas

**TABLE 4. Bimolecular Rate Constants ( $k_{\text{ArOH/dpph}}^s$ ) at Ambient Temperatures for the Reaction of 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol and 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol with  $\text{dpph}^{\bullet}$  in Methanol Containing Various Concentrations (C) of Acetic Acid**

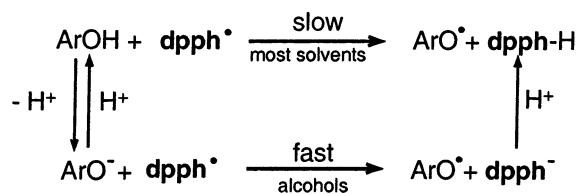
2,6-Bu <sup>t</sup> <sub>2</sub> -4-Me-phenol		2,6-Bu <sup>t</sup> <sub>2</sub> -4-CN-phenol	
C/mM	$k_{\text{ArOH/dpph}}^s/M^{-1} s^{-1}$	C/mM	$k_{\text{ArOH/dpph}}^s/M^{-1} s^{-1}$
0.0	3.7	0.0	16
0.1	0.62	1.5	8.4
6.7	0.13	10.0	0.12
10.0	0.12	440	0.040
33.3	0.11	1710	0.017
166	0.12		

for the much more strongly acidic 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol ( $\text{p}K_a = 8.7$ ), the rate constant was only reduced to the same value as in heptane even with acetic acid concentrations as high as 1.7 M (see Table 4 and Figure 2b). The 10 and 100 mM acetic acid modulated rate constants are given in the two right-hand columns of Table 3 and the rate constants measured with 10 mM acetic acid added to methanol and ethanol are shown as asterisks

(30) Smiths, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001.

(31) Addition of mineral acids or formic or acetic acid at a concentration higher than 2 M causes a slow decolorization of  $\text{dpph}^{\bullet}$ .<sup>32</sup> However, under our experimental conditions solutions of  $\text{dpph}^{\bullet}$  in alcohols containing less than 1 M acetic acid gave rate constants for  $\text{dpph}^{\bullet}$  decolorization which were 3 to 4 orders of magnitude smaller than the rate constants for the  $\text{dpph}^{\bullet}$  + phenol reactions. The acid-catalyzed decomposition of  $\text{dpph}^{\bullet}$  can therefore be neglected.

## SCHEME 2



on the plots of  $\log k_{\text{ArOH/dpph}^\bullet}^s$  vs  $\beta_2^{\text{H}}$  in Figure 1. Similar large effects induced by the addition of acetic acid were observed in *n*-propanol, e.g.,  $k_{\text{ArOH/dpph}^\bullet}^s$  ( $\text{M}^{-1} \text{s}^{-1}$ ) for *n*-propanol (*n*-propanol +  $\text{H}^+$ ) are 7.20 (0.77) for 2,4,6-Me<sub>3</sub>-phenol, 13 (1.0) for 4-MeO-phenol, and 0.4 (0.2) for 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol, but the effects in *tert*-pentanol were much smaller, e.g. 1.6 (1.1) for 2,4,6-Me<sub>3</sub>-phenol, see Table S15, Supporting Information.

## Conclusions

Abnormal kinetic solvent effects were first observed during studies of H-atom abstraction from two phenols by the **dpph**<sup>•</sup> radical.<sup>6</sup> In that work it was discovered that the rate constants in *tert*-butyl alcohol were higher than would be predicted from the H-bond accepting ability ( $\beta_2^{\text{H}}$  value) of this solvent. Enhanced rate constants have now been shown to be a general feature of phenol/**dpph**<sup>•</sup> reactions not only in alcohols but also, for phenols with low  $\text{p}K_{\text{a}}$  values, in non-hydroxylic, polar solvents (cf. rate constants for the 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol/**dpph**<sup>•</sup> reaction in di-*n*-butyl ether, acetonitrile, THF and DMSO, Table 1). These rate enhancements are due to partial (even very partial) ionization of the phenol (in those solvents which can support ionization) and a very fast electron transfer from the phenoxide anion to the **dpph**<sup>•</sup> radical, see Scheme 2. This “side” reaction that has such profound kinetic consequences (in the absence of an acid) has no precedent known to us in any solvent other than water.<sup>33</sup>

It is clear that our results bring into question all previous kinetic studies of H-atom abstractions from phenols in alcoholic solvents.<sup>34</sup> However, they also imply that the use of **dpph**<sup>•</sup> in ethanol to “titrate” for total antioxidants in foods and plant extracts remains a

(32) Solomon, D. H.; Swift, J. D. *J. Polym. Sci. A* **1965**, *3*, 3107–3116.

(33) Electron transfer from un-ionized phenols to electrophilic radicals is occasionally proposed to be the rate-controlling step (followed by rapid proton loss) as an alternative to direct H-atom abstraction.

(34) A large fraction of the papers identified in ref 3 involved studies on **dpph**<sup>•</sup> + antioxidant reactions in alcoholic solvents (generally methanol or ethanol).

perfectly valid procedure since the stoichiometries of reactions 1 and 2 will be the same.

## Experimental Section

**Infrared Measurements of  $\alpha_2^{\text{H}}$ .** Experiments were done in CCl<sub>4</sub> (distilled over P<sub>2</sub>O<sub>5</sub>) with dry THF, acetonitrile, pyridine, and DMSO as HBAs and with a Midac M FTIR spectrophotometer 120 series and CaF<sub>2</sub> cell with path length ca. 2.5 mm. The concentration of free 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol was determined by using a calibration curve (solutions of the phenol in CCl<sub>4</sub>). Values of  $K_{\text{ArOH/S}}^s$  were obtained from the slopes of straight lines of ( $[\text{ArOH}]_0/[\text{ArOH}]_{\text{free}}$ ) vs concentration of noncomplexed HBA (see Figures S1–S4, Table S13, and explanations to Table S14.) A more detailed description of similar IR measurements of  $\alpha_2^{\text{H}}$  has been given in refs 13–15.

**Measurements of Rate Constants for the Reaction of Phenols with **dpph**<sup>•</sup>.** The procedure used to determine  $k^s$  was common to all solvents and phenols. Solutions of **dpph**<sup>•</sup> and the phenol 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**<sup>•</sup> in the presence of a known concentration of 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  $23 \pm 2$  °C. The concentration of **dpph**<sup>•</sup> was  $(8.5 \pm 1.0) \times 10^{-5}$  M. Phenols were always used in large excess over [**dpph**<sup>•</sup>]. The concentrations of phenols are given in Tables S1–S12, from which the  $[\text{ArOH}]_0/[\text{dpph}^\bullet]_0$  ratios can be calculated. The decays of the **dpph**<sup>•</sup> absorbancies were analyzed as pseudo-first-order processes to yield  $k_{\text{ex}}/s^{-1}$ . Plots of  $k_{\text{ex}}$  vs phenol concentration were linear and their slopes gave the second-order rate constants,  $k^s$ . Kinetic parameters and mean values  $k^s$  with estimated errors are collected in Tables S1–S12.

**Acknowledgment.** We thank Dr. Dave Carlsson for the use his FTIR instrument and Shuqiong Lin for synthesis of 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol. G.L. thanks The Foundation for Polish Science (FNP) for receipt of a Postdoctoral Fellowship.

**Supporting Information Available:** Detailed kinetic data for reactions of the phenols with **dpph**<sup>•</sup> in neat solvents (Tables S1–10) and acidified methanol (Tables S11 and S12), infrared data used for calculation of equilibrium constants for 2,6-Bu<sup>t</sup><sub>2</sub>-4-Me-phenol H-bond formation with acetonitrile, THF, pyridine, and DMSO (Table S13 and Figures S1–S4) and other parameters from which  $\alpha_2^{\text{H}}$  values were calculated (Table S14), comparison of rate constants for reactions of four phenols with **dpph**<sup>•</sup> in neutral and acidified *n*-propanol and ethanol (Table S15), a typical plot of **dpph**<sup>•</sup> decay after mixing with a methanolic solution of 2,6-Bu<sup>t</sup><sub>2</sub>-4-CN-phenol (Figure S5). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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