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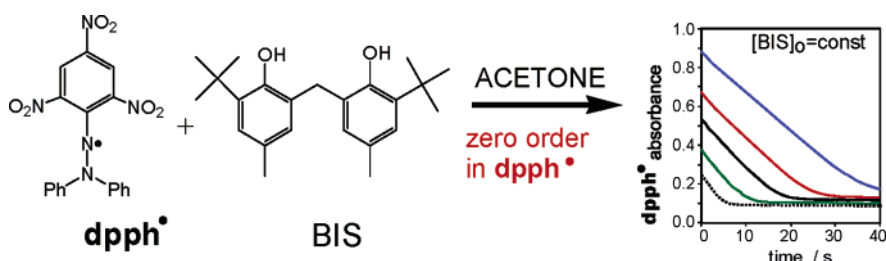
Abnormal Solvent Effects on Hydrogen Atom Abstraction. 3. Novel Kinetics in Sequential Proton Loss Electron Transfer Chemistry

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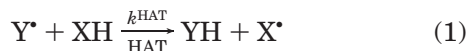


A prolonged search involving several dozen phenols, each in numerous solvents, for an ArOH/2,2-diphenyl-1-picrylhydrazyl (**dpph**[•]) reaction that is first-order in ArOH but zero-order in **dpph**[•] has reached a successful conclusion. These unusual kinetics are followed by 2,2'-methylene-bis(4-methyl-6-tert-butylphenol), BIS, in five solvents (acetonitrile, benzonitrile, acetone, cyclohexanone, and DMSO). In 15 other solvents the reactions were first-order in both BIS and **dpph**[•] (i.e., the reactions followed "normal" kinetics). The zero-order kinetics indicate that in the five named solvents the BIS/**dpph**[•] reaction occurs by sequential proton loss electron transfer (SPLET). This mechanism is not uncommon for ArOH/**dpph**[•] reactions in solvents that support ionization, and normal kinetics have always been observed previously (see Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433 and Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 5888). The zero-order kinetics found for the BIS/**dpph**[•] reaction in five solvents, S, imply that BIS ionization has become the rate-determining step (rds, rate constants 0.20–3.3 s^{−1}) in the SPLET reaction sequence: S + HOAr ⇌ S[−] + HOAr $\xrightarrow{\text{rds}}$ SH⁺ + [−]OAr $\xrightarrow{\text{dpph}^{\bullet}}$ SH⁺ + [•]OAr + **dpph**[−] → S + [•]OAr + **dpph**-H, where ArOH = BIS. Some properties specific to BIS that may be relevant to its relatively slow ionization in the five solvents are considered.

Introduction

The rates of hydrogen atom transfer (HAT) from a wide variety of substrates, XH (hydrocarbons,¹ aniline,² *tert*-butyl hydroperoxide,³ phenol,^{2–5} ring-substituted phenols,^{4–8} and aromatic diols^{8,9}) by a number of radicals, Y[•] (*tert*-alkoxyl, 2,2-diphenyl-1-picrylhydrazyl (**dpph**[•]), alkyl-

peroxyl, and alkyl) have revealed that reaction 1 exhibits large kinetic solvent effects (KSEs) when XH is a hydrogen bond donor (HBD) and the reaction is carried out in a hydrogen bond acceptor (HBA) solvent, S. These very extensive kinetic results have been rationalized by the simple chemistry shown in Scheme 1.^{3,5}



According to Scheme 1, there is no HAT from the hydrogen-bonded XH (XH–S) and the reaction involves

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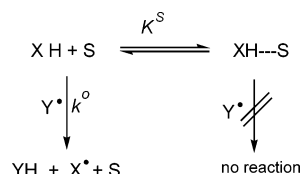
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SCHEME 1. Cause of a KSE in a HAT Reaction



only that fraction of XH that is not H-bonded. This “free” XH reacts with Y^\bullet by HAT that occurs with a characteristic, solvent-independent rate constant, k^0 . This characteristic rate constant is the same as the rate constant measured in non-HBA solvents, notably saturated hydrocarbons. Kinetic analysis of Scheme 1 relates the experimentally measured rate constant for the reaction of XH with Y^\bullet by a HAT mechanism, k^{HAT} , in any solvent, S, to the characteristic rate constant and the equilibrium constant for H-bond formation as shown in eq 2:^{3,5}

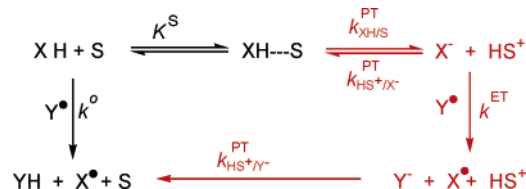
$$k^{\text{HAT}} = k^0 / (1 + K^S[S]) \quad (2)$$

Room-temperature KSEs for the many XH/ Y^\bullet reactions investigated have been shown to be extremely well correlated by empirical eq 3:⁵

$$\log(k^{\text{HAT}}/\text{M}^{-1} \text{ s}^{-1}) = \log(k^0/\text{M}^{-1} \text{ s}^{-1}) - 8.3\alpha_2^{\text{H}}\beta_2^{\text{H}} \quad (3)$$

In this equation, α_2^{H} is Abraham et al.’s¹⁰ parameter quantifying the relative HBD activities of XH (range 0.00 for alkanes to ~1 for strong organic acids), and β_2^{H} is Abraham et al.’s¹¹ parameter quantifying the relative HBA activities of S (range 0.00 for alkanes to 1.00 for hexamethylphosphoramide, the strongest organic HBA). More than 500 α_2^{H} values and more than 500 β_2^{H} values are known.^{10,11}

Equation 3 has proven to be a very useful mechanistic probe for XH/ Y^\bullet reactions. If the kinetic data in several solvents fit eq 3 or, equivalently, yield a straight line when logarithms of the experimental rate constants are plotted against β_2^{H} , there is a HAT mechanism in all the solvents examined. Under these circumstances, the XH/ Y^\bullet reaction is said to exhibit a *normal* KSE. The reactions of phenols and ring-substituted phenols with, for example, *tert*-alkoxyl radicals *all* exhibit normal KSEs.^{2,5,7} However, very early in this work,⁴ it was discovered that although the KSEs were normal with XH = phenol and α -tocopherol and $Y^\bullet = \text{dpph}^\bullet$ in most solvents, they were abnormal in *tert*-butyl alcohol. Specifically, for both substrates the rate constants in *tert*-butyl alcohol were about five times greater than would have been expected on the basis of the HBA activity (i.e., β_2^{H} value) of this alcohol. Enhanced rate constants (sometimes very much enhanced) were subsequently observed in the reactions of various phenols with dpph^\bullet in many alcohols.¹² These abnormal KSEs were attributed to the occurrence in these systems of a new reaction path leading to the same products.¹² This new mechanism was later named sequential proton loss electron transfer (SPLET).¹³

SCHEME 2. Origin of KSEs in a Mixed HAT and SPLET Reaction^a

^a The SPLET reaction is shown in red.

The SPLET mechanism, which was independently discovered by Foti et al.,¹⁴ is consistent with the high reactivity of a phenolate anion toward a dialkyl-substituted dpph^\bullet reported by Nakanishi et al.¹⁵ SPLET is shown in Scheme 2 (in red) as an extension of the HAT mechanism (in black) from Scheme 1.

In Scheme 2, the rate constants for proton and electron transfer are indicated by k^{PT} and k^{ET} , respectively. Although all the reactions in this scheme will be reversible (e.g., $k_{\text{PhOH/dpph}^\bullet}^0 < k_{\text{dpph}^\bullet\text{-H/PhO}_2}^0$), this complexity has been ignored for three of the reactions in favor of simplicity.

Consistent with Scheme 2, the SPLET mechanism has been shown experimentally to be favored with respect to the underlying, and always present, HAT process in solvents that support XH ionization (notably methanol among organic solvents), with XH having low $\text{p}K_{\text{a}}$'s and with electron-deficient Y^\bullet (e.g., dpph^\bullet).¹² In many solvents, the rates of ArOH/dpph^\bullet reactions are increased by the addition of base (e.g., sodium methoxide) and decreased by the addition of acid (e.g., acetic acid).^{12,13} These changes in rate reflect a base-induced increase and an acid-induced decrease in the degree of phenol ionization and hence in the importance of the SPLET mechanistic pathway.

In our recent work on KSEs, the kinetics of ArOH/dpph^\bullet have been monitored by following the loss of dpph^\bullet spectrophotometrically at 517 nm ($\epsilon \approx 11\,000 \text{ M}^{-1} \text{ cm}^{-1}$)¹⁶ using a rapid-mixing, stopped-flow apparatus.^{9a,b,12,13} A large excess of ArOH was generally employed, and the complete loss of dpph^\bullet occurred with “clean” first-order kinetics, with just the four exceptions noted below. Rates of ArOH/dpph^\bullet reactions were *always* directly proportional to the ArOH concentration. Therefore, the vast majority of the ArOH/dpph^\bullet reactions examined follow “clean” bimolecular kinetics (eq 4).

$$-d[\text{dpph}^\bullet]/dt = k_{\text{exptl}}[\text{ArOH}][\text{dpph}^\bullet] \quad (4)$$

This was the case for “HAT-only” conditions (nonionizing solvents and ionizing solvents containing sufficient acetic acid to completely suppress the SPLET process), for conditions where SPLET contributed $\geq 90\%$ to k_{exptl} , and

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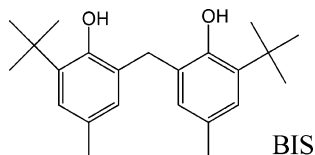
for conditions where the HAT and SPLET processes were more evenly matched.

The four exceptions mentioned above would not have been discovered without the stopped-flow equipment. This is because the anomalous kinetics occurred within <100 ms of mixing methanol and ethanol solutions of curcumin and dehydrozingerone (sometimes called “half curcumin”, pK_a 9.1 in water/methanol, 1:1 v/v) with solutions of **dp ph^{\bullet}** in the same solvents.¹³ These very initial reactions were >1000 times as rapid as the same reactions carried out in the presence of 5 mM acetic acid, despite the fact that the rates with 5 mM acid were still 1 order of magnitude greater than those for the “HAT only” reactions that were observed only at much higher concentrations of acetic acid.¹³ The four short duration, fast reactions were followed by slower (but still rapid) first-order loss of **dp ph^{\bullet}** . The initial, fast processes were attributed to reactions of **dp ph^{\bullet}** with the anions, X^- , of the substrates, XH, that would have been present at low equilibrium concentrations in the alcohols (see reaction labeled k^{ET} in Scheme 2). These “preformed” anions are quickly depleted, and ionization of XH (the proton loss portion of SPLET) then becomes *partly* rate-determining (see reaction labeled $k_{\text{XH/S}}^{\text{PT}}$ in Scheme 2).

Substrate ionization in an $\text{ArOH}/\text{dp $\text{ph}^{\bullet}$$ reaction occurring by the SPLET mechanism that is truly the rate-determining step (rds) would have an interesting and readily observed kinetic consequence. Specifically, in the second (slower) stage of the reaction after the “preformed” ArO^- has been rapidly consumed, the loss of **dp ph^{\bullet}** should follow zero-order kinetics. That is, the reaction should obey eq 5, rather than eq 4.

$$-d[\text{dp ph^{\bullet} }] / dt = k_{\text{exptl}} [\text{ArOH}] \quad (5)$$

Extensive kinetic studies on $\text{ArOH}/\text{dp $\text{ph}^{\bullet}$$ reactions involving numerous monophenols and many solvents failed to reveal a single example of eq 5 kinetics. However, our efforts were rewarded when we extended our studies to bisphenols and discovered that 2,2'-methylene-bis(4-methyl-6-*tert*-butylphenol):



BIS

designated hereafter as BIS, sometimes exhibited the sought-after kinetics. In a 20-solvent study, eq 4 was obeyed throughout the entire $\text{BIS}/\text{dp $\text{ph}^{\bullet}$$ reaction in 15 of the solvents, but only in the very initial stages in the remaining five solvents. In these five solvents, after the initial, very fast reaction with the “preformed” BIS^- anion, the kinetics changed to become “clean” zero-order in **dp ph^{\bullet}** (i.e., the rate law changed from eq 4 to eq 5). These kinetic solvent effects on what, at first sight, might be thought to be a simple hydrogen atom abstraction are described herein.

Results

Kinetics of $\text{BIS}/\text{dp $\text{ph}^{\bullet}$$ Reaction in Different Solvents. Overview. Decay of **dp ph^{\bullet}** (initial concentration

TABLE 1. Bimolecular Rate Constants, $k^{\text{S}}/\text{M}^{-1} \text{ s}^{-1}$, for the $\text{BIS}/\text{dp $\text{ph}^{\bullet}$$ Reaction in 20 Solvents^a

	solvent ^b	β_2^{H} ^c	k^{S}		solvent ^b	β_2^{H} ^c	k^{S}
1	$\text{CH}_3(\text{CH}_2)_5\text{CH}_3$	0.00	57	11	1,4-dioxane	0.47	0.31
2	CCl_4	0.05 ^d	25	12	EtCOEt	0.48	6.5
3	$\text{PhH} + 1 \text{ M Ph}_2\text{CO}$	0.20 ^e	7.0	13	PhCOMe	0.48	87
4	HC(O)OMe	0.38	1.0	14	<i>t</i> -BuCOMe	0.49	0.64
5	MeOH	0.41	2100	15	MeCOMe	0.50	460^f
6	PhCN	0.42	620^f	16	THF	0.51	1.4
7	MeCN	0.44	15000^f	17	$(\text{CH}_2)_5\text{CO}$	0.52	240^f
8	EtOH	0.44	1300	18	<i>c</i> -(C_3H_5) ₂ CO	0.53	1500
9	<i>t</i> -BuCN	0.44	13	19	γ -valerolactone	0.55	1300
10	MeC(O)OEt	0.47	12	20	Me₂SO	0.78	160^f

^aFull data with errors are given in the Supporting Information.

^bSolvents are listed in order of increasing β_2^{H} values. The solvents are identified in parts A and B of Figure 1 by the numbers in this column. ^cReference 11. ^dReference 5. ^eEstimated from β_2^{H} (benzene) = 0.14 and β_2^{H} (benzophenone) = 0.47 and the mole fractions of the two components of this solvent mixture. ^fThis rate constant refers only to very initial stages of the reaction (0 to <100 ms) where the reaction is first-order in both BIS and **dp ph^{\bullet}** .

$3\text{--}8 \times 10^{-5} \text{ M}$) was monitored to completion¹⁷ in the presence of excess BIS at five or more different BIS concentrations in 20 solvents (see Supporting Information). In all solvents the rate of loss of **dp ph^{\bullet}** was directly proportional to the concentration of BIS. In 15 of the solvents the **dp ph^{\bullet}** loss followed pseudo-first-order kinetics for the entire reaction that can be represented as:



Bimolecular rate constants in each solvent, $k^{\text{S}}/\text{M}^{-1} \text{ s}^{-1}$, were calculated from the linear least-squares slopes¹⁸ derived from plots of k_{exptl} versus [BIS], eq 7.

$$k_{\text{exptl}} = \text{const} + k^{\text{S}}[\text{BIS}] \quad (7)$$

The k^{S} values in these 15 solvents are recorded in Table 1 in normal type. The solvents have been listed in order of increasing HBA activity, that is, increasing β_2^{H} which, for a “clean” HAT process, would mean also in order of decreasing k^{S} , with the value in heptane, viz., $k^0 = 57 \text{ M}^{-1} \text{ s}^{-1}$, being the largest (see eq 3). It is obvious that in several of these 15 solvents the reaction being monitored is not a HAT process because $k^{\text{S}} > k^0$.

For the other five solvents (listed in bold face in Table 1), the same kinetics (i.e., first-order in both **dp ph^{\bullet}** and [BIS]) applied *only* in the period immediately (<100 ms) following the rapid (~1–5 ms) mixing of the **dp ph^{\bullet}** and BIS solutions. The “initial” k^{S} values (eq 7) are given in Table 1 in bold face (the zero-order kinetics that follow this initial (fast) reaction phase are described later). In these five solvents the k^{S} values are also considerably greater than k^0 (Table 1). Indeed, a plot of $\log k^{\text{S}}$ for all 20 solvents against β_2^{H} provides a rather fine “shotgun pattern” (Figure 1A) rather than the straight line (slope

(17) This is never all the way to zero absorbance at 517 nm because **dp ph^{\bullet}** -H absorbs weakly at this wavelength ($\epsilon \approx 400 \text{ M}^{-1} \text{ cm}^{-1}$) and because the BIS oxidation product(s) also absorb at this wavelength; see various figures in the text and Supporting Information.

(18) In all the kinetic work reported herein the overwhelming majority of the R^2 values were 0.99 (see Supporting Information).

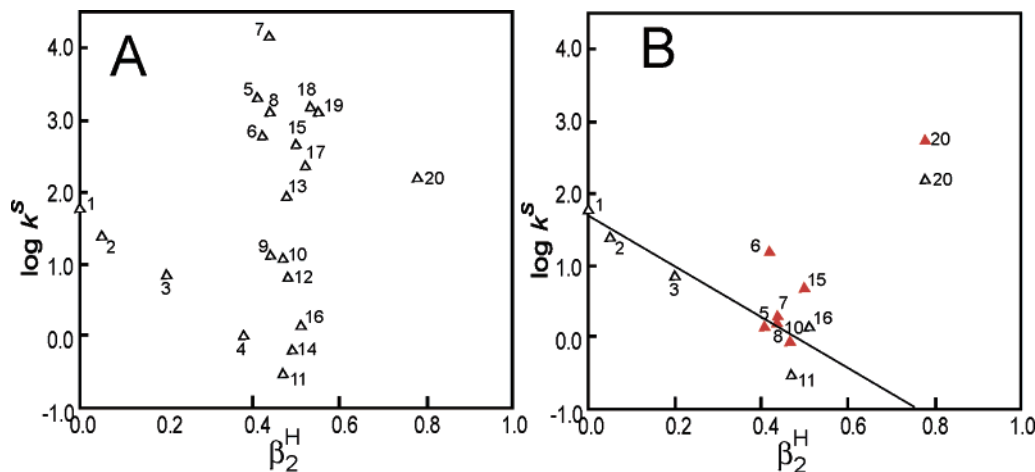


FIGURE 1. Plots of $\log k^S$ for the BIS/dpph \cdot reaction in different solvents against β_2^H . (A) All 20 solvents, data from Table 1. (B) Five solvents selected as being unlikely to support BIS ionization (Δ , Table 1) and seven solvents containing 1 M acetic acid (red \blacktriangle , Table 2). The least-squares straight line in (B) has been drawn ignoring the points for solvents 6, 15, and 20.

TABLE 2. Bimolecular Rate Constants, $k^S/\text{M}^{-1} \text{s}^{-1}$, for the BIS/dpph \cdot Reaction in Seven Solvents Containing Acetic Acid^a

	[acetic acid]/ mM solvent ^b	A^c	ϵ_r^d	k^S			
				0	10 mM	100 mM	1000 mM
5	MeOH	0.75	32.7	2100	9.1	3.6	1.4
6	PhCN	—	25.2	620^e	750	23	15
7	MeCN	0.37	35.9	15000^e	5700	274	2.0
8	EtOH	0.66	24.6	1300	36	3.1	1.7
10	MeC(O)OEt	0.21	6.0	12	12	1.6	0.9
15	MeCOMe	0.25	20.6	460^e	13000	1550	4.9
20	Me ₂ SO	0.34	46.5	160^e	890	4900	520

^a Full data with errors are given in the Supporting Information.

^b See footnote b to Table 1. ^c For solvent acity, see ref 44. ^d For permittivity (dielectric constant), see: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley: Weinheim, Germany, 2003. ^e See footnote f to Table 1.

$= -8.3\alpha_2^H$) expected (eq 3) if there is a HAT mechanism in all solvents. This suggests that the scatter in Figure 1A is largely¹⁹ due to contributions from the SPLET mechanism (Scheme 2).

The HAT-Only Reactions and the Determination of α_2^H for BIS by Kinetics and by IR Spectroscopy.

The effects of acetic acid on the BIS/dpph \cdot KSEs were explored using seven solvents chosen because they were judged to be capable of supporting the ionization of BIS and had structural features representative of other solvents that were also likely to support BIS ionization. Bimolecular rate constants, k^S , were measured in the presence of 10, 100, and 1000 mM acetic acid in the seven selected solvents, and the results are presented in Table 2. Those solvents shown in bold face in Table 1 are also shown in bold face in Table 2, though it should be noted that with all concentrations of acetic acid the reactions were not zero-order in [dpph \cdot] (i.e., they did not follow the kinetics observed in the nonacidified solvents; see below).

(19) For sterically nonhindered phenols, scatter in such plots appears to arise solely from the SPLET mechanism. However, for sterically hindered phenols (e.g., BIS, see later) scatter also arises from the fact that the strength of the hydrogen bond between the phenol and the HBA depends on the HBA's size and shape as well as on its HBA activity toward nonhindered phenols.¹²

In all our earlier ArOH/dpph \cdot KSE work,^{12,13} 10 mM acetic acid either had no effects on k^S (i.e., no SPLET occurred in the solvent) or it reduced k^S relative to the rate constant in the nonacidified solvent (i.e., there was partial or complete suppression of SPLET and $k^S \rightarrow k^{\text{HAT}}$). For the BIS/dpph \cdot reaction, in contrast, the addition of 10 mM acetic acid causes the values of k^S to increase substantially in acetone and DMSO and to increase slightly in benzonitrile (see Table 2). In acetone and benzonitrile, k^S decreases on increasing the acetic acid concentration to 100 mM and decreases still further with 1 M acid. In DMSO, k^S reaches a maximum with 100 mM acetic acid and even with the addition of 1 M acid k^S remains larger than in the nonacidified solvent.

Earlier work^{12,13} has shown that for ArOH/dpph \cdot reactions the SPLET mechanism is either completely or nearly completely suppressed by 1 M acetic acid, meaning that the measured rate constant, k^S , now reflects the underlying HAT process, k^{HAT} . The logarithms of the 1 M acetic acid rate constants have therefore been plotted (in red) against β_2^H in Figure 1B together with $\log k^S$ (in black) for those neat solvents that are unlikely to support a kinetically significant SPLET process (viz., solvents 1, 2, 3, 11, and 16). A rather good straight line is obtained provided the benzonitrile (6), acetone (15), and DMSO (20) data points are ignored. The deviations of these three data points from the line suggest that in these three solvents the ionization of BIS is incompletely suppressed by 1 M acetic acid.

The line in Figure 1B has a slope of -3.5 , indicating that the “best” α_2^H value for BIS is $-3.5/-8.3 = 0.42$ for this array of 11 solvents.²⁰ Since an α_2^H value for BIS (or any related diol) has not been previously reported, “solvent-specific” α_2^H values were determined by the usual IR method^{5,10,12,13} using two of Abraham's¹⁰ “calibrated” HBA's: DMSO gave $\alpha_2^H = 0.49$ and acetonitrile gave $\alpha_2^H = 0.40$ (for full details see the Supporting Information). These two “solvent-specific” IR-derived α_2^H

(20) The word “best” has been used because sterically congested phenols do not possess a single, unique α_2^H value; see footnote 19 and ref 12.

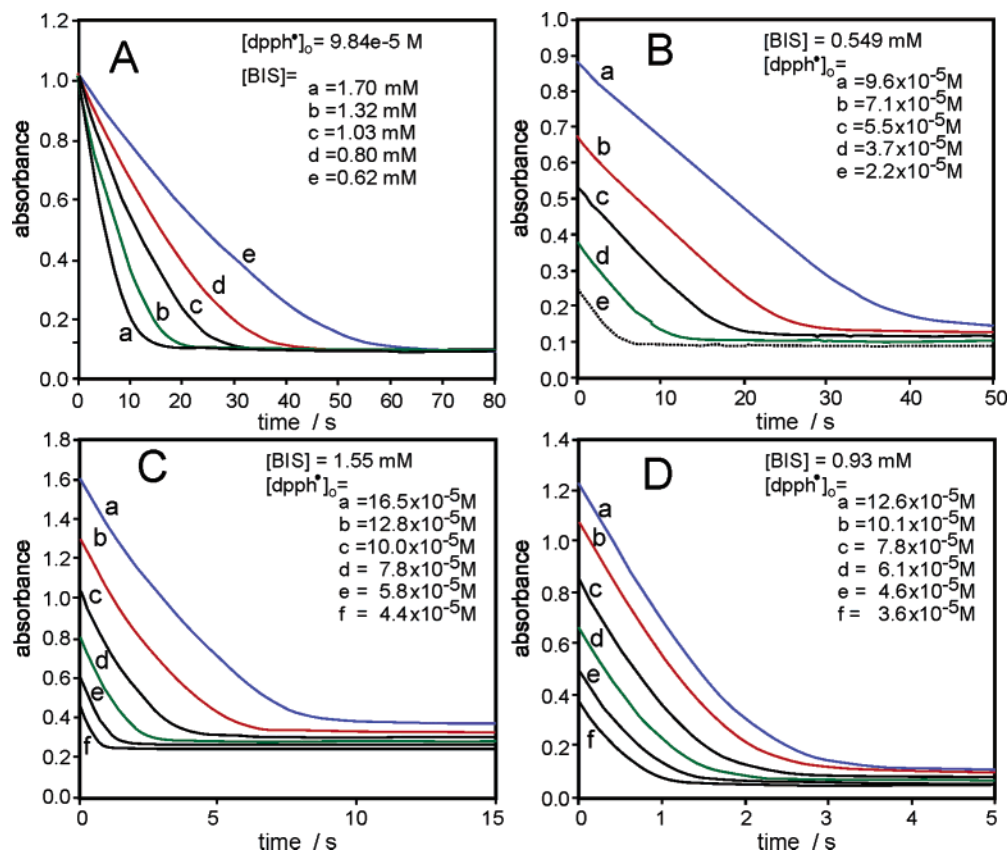


FIGURE 2. Decay of dpph^\bullet during the reaction with BIS in acetone (A and B), in DMSO (C), and in benzonitrile (D). In the reactions shown in (A), the initial concentrations of dpph^\bullet were always the same and the initial concentrations of BIS were varied. In the reactions shown in (B, C and D), the initial concentrations of [BIS] were always the same in each panel and the initial concentrations of dpph^\bullet were varied. All concentrations are given in the legends within each panel.

values for BIS nicely bracket the “best” kinetics-derived α_2^{H} value of 0.42.

The Reactions that are Zero-Order in $[\text{dpph}^\bullet]$. These kinetics (i.e., reactions following the rate law described by eq 5, with the rds being deprotonation of phenol) were observed to commence some 100 ms after mixing BIS and dpph^\bullet solutions in five solvents: benzonitrile, acetonitrile, acetone, cyclohexanone, and DMSO. They do not occur immediately after the reagent solutions are mixed because during the first few tens of milliseconds the dpph^\bullet is reacting with, and hence destroying, the equilibrium concentration of “preformed” BIS anion (see Introduction). The dpph^\bullet solutions are stable for days in four of these five solvents. However, in cyclohexanone the dpph^\bullet slowly decays. This we attribute to its reaction with the 1.2% enol present in neat cyclohexanone²¹ by analogy with other ketone(enol)/ dpph^\bullet reactions we have studied.¹³ Because of this side reaction, consideration will henceforth only be given to the other four solvents. Typical kinetic traces are shown in Figure 2 (acetone (15) panels A and B; DMSO (20), panel C; benzonitrile (6), panel D). These traces and data in the Supporting Information demonstrate that these reactions are first-order in [BIS] (e.g., Figure 2A) and zero-order in $[\text{dpph}^\bullet]$ (e.g., parts B, C, and D in Figure 2).

Discussion

The KSEs observed in BIS/ dpph^\bullet reactions are familiar, for the most part. That is, in all solvents the rates of the initial reactions are directly proportional to the concentration of BIS and to the concentration of dpph^\bullet . In the majority of the 20 solvents examined these bimolecular kinetics are followed until complete consumption of dpph^\bullet , although the very initial stages of the reaction are often much faster than the later stages. As with other $\text{ArOH}/\text{dpph}^\bullet$ reactions,^{12–14} SPLET (Scheme 2) is the dominant reaction mechanism in solvents that can support the ionization of ArOH . Initially, the dpph^\bullet will react with the low concentration (if any) of “preformed” phenoxide anion present in equilibrium with the phenol. This involves a very rapid electron transfer and occurs with bimolecular kinetics (eq 4). Once all the preformed anion has been consumed, the reaction rate slows and the SPLET mechanism takes control with kinetics again described by eq 4. The pre-ionization of ArOH and the SPLET process can generally be suppressed, or even eliminated, leaving just the “background” HAT mechanism, by the addition of acetic acid.

All the foregoing aspects of BIS/ dpph^\bullet reaction kinetics are familiar, in view of our earlier work.^{12,13} What is unfamiliar and has not previously been observed in $\text{ArOH}/\text{dpph}^\bullet$ reactions involving monophenols,^{4,5,8,12–14} catechols,^{8,9} or naphthalene diols⁹ is a process that is first-order in $[\text{ArOH}]$ but zero-order in $[\text{dpph}^\bullet]$. The following

(21) Solomons, T. W. G. *Organic Chemistry*, 6th ed.; Wiley: New York, 1996.

discussion will therefore focus on the zero-order kinetics found for BIS/dpph[•] reactions in certain solvents.

Kinetic Requirements for an XH/Y[•] Reaction To Be Zero-Order in [Y[•]]. Two conditions must be met: (i) the SPLET mechanism must completely dominate the HAT process and (ii) proton transfer from ArOH to the solvent, S, must be the rds in the SPLET pathway. Application of the steady-state approximation to Scheme 2 yields:

$$[X^-] = \frac{K^S k_{XH/S}^{PT} [XH] [S]}{k_{HS^+/X^-}^{PT} [HS^+] + k^{ET} [Y^*]} \quad (8)$$

and hence:

$$-\frac{d[Y^*]}{dt} = \frac{K^S k_{XH/S}^{PT} k^{ET} [XH] [S] [Y^*]}{k_{HS^+/X^-}^{PT} [HS^+] + k^{ET} [Y^*]} \quad (9)$$

The reaction will follow zero-order kinetics provided:

$$k^{ET} [Y^*] \gg k_{HS^+/X^-}^{PT} [HS^+] \quad (10)$$

in which case:

$$-d[Y^*]/dt = K^S k_{XH/S}^{PT} [XH] [S] \quad (11)$$

Intramolecular H-Bonding and Structures of BIS in Solution. The secret of the BIS/dpph[•] reaction's unique zero-order kinetics must lie in the solution properties and structures of BIS. In 1950, an early IR study of BIS revealed two O–H stretching bands.²² In 1965, IR measurements with better resolution showed that BIS actually has four O–H stretching bands, two of which are barely resolved.²³ It was suggested that BIS adopted a number of conformations that “may be in equilibrium.”²³ The O–H bands were assigned to “free” OH, to OH hydrogen bonded to the “other” aromatic ring, OH–Ar, and to OH hydrogen bonded to the “other” OH group, OH–OH.²³ The presence of four O–H stretching bands has been confirmed in three later publications,^{24–26} though their reported frequencies in CCl₄²⁷ and the conformers suggested were not always in agreement.²⁸

We have confirmed that BIS has four O–H stretching bands (Figure 3) and agree broadly with their original assignments by Cairns and Eglinton.²³ That is, the bands at 3632 and 3610 cm^{−1} are assigned to “free” OH groups, that at 3510 cm^{−1} to OH that is H-bonded to the adjacent aromatic ring, and that at 3450 cm^{−1} to OH that is

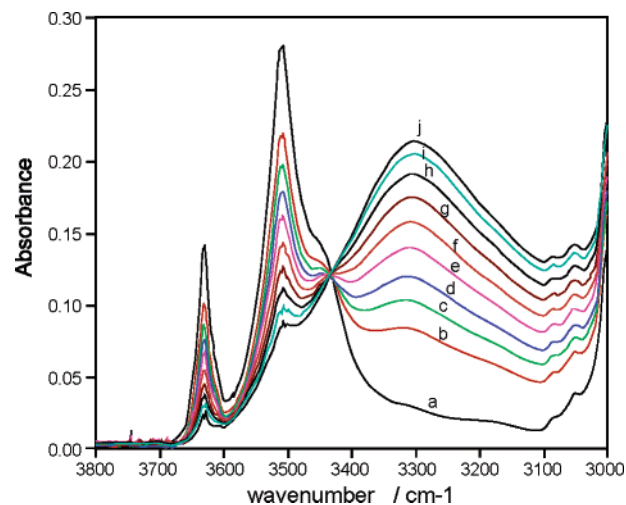
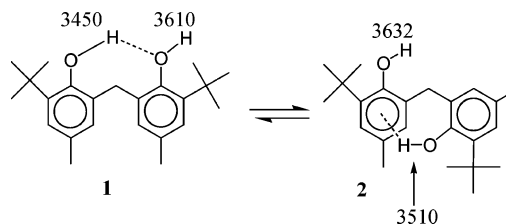


FIGURE 3. OH stretching region of the IR spectrum of 13.4 mM BIS in CCl₄ containing various concentrations of DMSO (in mM): (a) 0.0, (b) 9.1, (c) 13.6, (d) 18.2, (e) 24.2, (f) 32.3, (g) 43.1, (h) 57.4, (i) 76.5, (j) 98.4. The free OH band at 3632 cm^{−1} was used for calculation of the concentration of nonintermolecularly hydrogen-bonded BIS.

SCHEME 3. ν_{OH}/cm^{-1} for BIS Conformers in CCl₄



hydrogen bonded to the oxygen atom of the adjacent phenol. However, we suggest that in CCl₄ all conformers present in reasonable abundance will have one intramolecular hydrogen bond. The electron-withdrawing (EW) effect of these intramolecular hydrogen bonds will cause the band due to the remaining “free” OH to shift to lower wavenumbers than those for the OH bands in 2-*tert*-butyl-4,6-dimethylphenol and 2,4,6-trimethylphenol. For meta- and para-substituted phenols the OH fundamental stretching frequencies, ν_{OH} , correlate very well with the substituents’ Hammett σ -constants with EW substituents shifting ν_{OH} to smaller wavenumbers.^{30,31} The EW effect of the intramolecular hydrogen bonds on the neighboring “free” OH groups will be greater for the OH–OH hydrogen bond than for the OH–Ar hydrogen bond. Our assignment of the four OH stretching bands of BIS in CCl₄ is shown in Scheme 3. For simplicity, this representation is two-dimensional but it is certain that the two aromatic rings of BIS will not be coplanar in any stable conformer.^{28,29,33}

(22) Coggeshall, N. D. *J. Am. Chem. Soc.* **1950**, *72*, 2836–2844.

(23) Cairns, T.; Eglinton, G. *J. Chem. Soc.* **1965**, 5906–5913.

(24) Kovac, S.; Solcaniova, E.; Baxra, J. *Tetrahedron* **1971**, *27*, 2823–2830.

(25) Pivcova, H.; Jirackova, L.; Pospisil, J. *J. Polym. Sci., Polym. Symp.* **1973**, *40*, 283–295.

(26) Arzamanova, I. G.; Naiman, M. I.; Romm, I. P.; Tovbin, U. K.; Guryanova, E. N.; Gurvich, Y. A.; Logvinenko, R. M. *Zh. Fiz. Khim.* **1981**, *55*, 1554–1555.

(27) Band maximum frequencies (in cm^{−1}): 3639, 3620, 3516, 3450 (ref 23); 3648, 3623, 3516, 3444 (ref 24); 3627, 3610, 3506, 3436 (ref 25); 3651, 3635, 3516, 3454 (ref 26). Our work (Figure 3 and Scheme 3) yields: 3632, 3610, 3510, 3450.

(28) Most notably, any OH–OH hydrogen-bonded conformers of BIS were ignored in ref 24. The crystal structure of BIS reveals an intramolecular OH–OH hydrogen bond with the “free” OH (on the right in structure 1, Scheme 3) twisted out of the plane of the aromatic ring to which it is attached.²⁹

(29) Chetkina, L. A.; Zavodnik, V. E.; Bel’skii, V. K.; Arzamanova, I. G.; Naiman, M. I.; Gurvich, Ya. A. *Zh. Struct. Khim.* **1984**, *25*, 109–113. English translation: *J. Struct. Chem.* **1985**, *25*, 935–939.

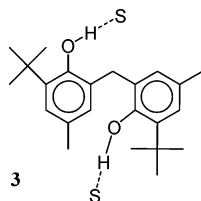
(30) Ingold, K. U. *Can. J. Chem.* **1960**, *38*, 1092–1098.

(31) ν_{OH} values for para-substituted 2-*tert*-butyl, 2,6-di-*tert*-butyl, 2-methyl, and 2,6-dimethylphenols also correlate with σ_p .^{30,32}

(32) (a) Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 471–480. (b) Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 111–121.

(33) According to DFT calculations, the conformers of bis(2-hydroxyphenyl)methane also have noncoplanar aromatic rings; see: Katsyuba, S.; Chernova, A.; Schmutzler, R.; Gronenberg, J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 67–71.

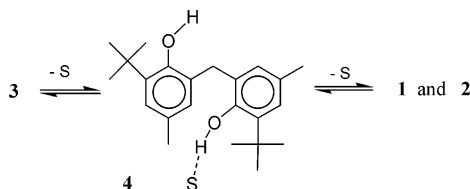
The two intramolecular hydrogen bonds formed by BIS in CCl_4 (Scheme 3) do not exist in the presence of >100 mM DMSO (see Figure 3). Similarly, the BIS analogue in which the two 4-methyl groups were replaced by two ethyl groups showed only a single broad band in diethyl ether (3350 cm^{-1})²³ and in pyridine (3185 cm^{-1}).²⁴ Thus, in strong and even in moderately strong HBA solvents, BIS adopts conformation **3**.



This facile breaking of the BIS intramolecular H-bonds (**1** and **2**) by HBA solvents indicates that they are relatively weak and stands in contrast to the virtual inability of such solvents to cleave the intramolecular OH–OH hydrogen bonds in catechols and 1,8-naphthalene diols.^{9a,34}

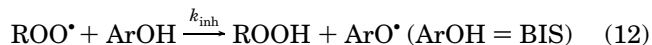
The BIS/dpph[•] Reaction. The HAT process in non-HBA solvents will involve only conformers **1** and **2**. In catechols (and naphthalene diols), the OH–OH intramolecular hydrogen bond lowers the bond dissociation enthalpy (BDE) of the “free” OH relative to, for example, that of the OH BDE in hydroquinone.^{35,36} This is because the fairly strong OH–OH hydrogen bond in these aromatic diols becomes stronger by several kcal/mol in the radical OH–O[•] hydrogen bond.^{9b,35,36} By analogy, the most reactive site for HAT in BIS is expected to be the “free” OH in **1**. Thus, in a saturated hydrocarbon and on a molar basis, BIS would be expected to show a similar, or slightly enhanced, reactivity toward **dpph[•]** compared with 2-*tert*-butyl-4,6-dimethylphenol ($\text{Bu}^t\text{Me}_2\text{-phenol}$) and 2,4,6-trimethylphenol ($\text{Me}_3\text{-phenol}$), but to be much less reactive than catechol. The experimental rate constants ($\text{M}^{-1}\text{ s}^{-1}$) are: BIS, 57 (Table 1); $\text{Bu}^t\text{Me}_2\text{-phenol}$, 17;³⁷ $\text{Me}_3\text{-phenol}$, 40;³⁷ and catechol,^{9b} 1800. Thus, the HAT ability of BIS is consistent with its structure.

In HBA solvents, the HAT reactions of BIS will involve the mono-desolvated form, **4**, or, less probably, the di-desolvated forms **1** and **2**.



The BIS/**dpph[•]** reaction would therefore be predicted to exhibit a normal KSE provided any SPLET process was suppressed because of the solvent's low permittivity (dielectric constant, ϵ_r) or by the addition of acetic acid. This normal KSE is shown in Figure 1B, and the derived

kinetic α_2^{H} value for BIS (0.42) is consistent with the two values obtained by IR (0.49 and 0.40), *vide supra*. Indeed, from the viewpoint of the BIS/**dpph[•]** KSEs and reaction rates, BIS *generally* behaves as a “normal”, moderately acidic,³⁸ moderately sterically crowded phenolic HBD. The generally “normal” behavior of BIS is also indicated by by Pedulli and co-workers⁴⁰ study of the BIS/ ROO^{\bullet} reaction:



These workers found that the autoxidation of styrene (4.3 M in chlorobenzene at $30\text{ }^{\circ}\text{C}$) was retarded by BIS and the duration of the induction period corresponded to an overall stoichiometric factor, n , equal to 4 (i.e., 4 ROO^{\bullet} /BIS) as befits a bisphenol. Initially, there was strong inhibition during which 2 ROO^{\bullet} per BIS were consumed and k_{inh} was found to be $5.0 \times 10^5\text{ M}^{-1}\text{ s}^{-1}$.⁴⁰ Weaker inhibition followed for the remaining 2 ROO^{\bullet} per BIS with $k_{\text{inh}} = 2.0 \times 10^3\text{ M}^{-1}\text{ s}^{-1}$.⁴¹ For comparison, under similar experimental conditions with $\text{ArOH} = \text{Me}_3\text{-phenol}$, $k_{\text{inh}} = 8.5 \times 10^4\text{ M}^{-1}\text{ s}^{-1}$ and $n = 2$.⁴² Thus, BIS is slightly more reactive than $\text{Me}_3\text{-phenol}$ toward both ROO^{\bullet} and **dpph[•]** in poor and non-HBA solvents, respectively. These results are consistent with the slightly lower O–H BDE for a BIS homologue,⁴³ viz.⁴⁰ 81.2 kcal/mol, compared with that for $\text{Me}_3\text{-phenol}$, 82.7 kcal/mol.⁴⁰

In two respects, however, the BIS/**dpph[•]** reactions exhibit behavior that has not previously been encountered. The first relates to the effect on the reaction rates in certain solvents of added acetic acid. In earlier $\text{ArOH}/\text{dpph}^{\bullet}$ kinetic work with many phenols in numerous solvents,^{12,13} the addition of acetic acid either had no effect on the reaction rate (indicating a HAT-only reaction) or caused the rate to decline monotonically (to the HAT limit) as the acid concentration increased (indicating a SPLET process). The rates of the BIS/**dpph[•]** reactions decline monotonically with increasing acetic acid concentrations in only three of the seven solvents in which the effect of acid was explored (Table 2). In two of the seven solvents, acetone (**15**) and DMSO (**20**), the rates in the presence of 10 mM acetic acid are definitely

(37) Kinetic data on the reactions of $\text{Bu}^t\text{Me}_2\text{-phenol}$ and $\text{Me}_3\text{-phenol}$ with **dpph[•]** in various solvents are given in the Supporting Information.

(38) The pK_{a} of BIS has not been reported. Two much less sterically congested homologues in which both of the *tert*-butyl groups of BIS had been replaced either by two H-atoms or by two CH_3 groups have been titrated with base in isopropyl alcohol/benzene, 1:1 v/v.³⁹ For both compounds, one OH group was much more acidic than the other, a result consistent with their monoanions having structures analogous to **6**.

(39) Sprengling, G. R. *J. Am. Chem. Soc.* **1954**, *76*, 1190–1193.

(40) Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2003**, *68*, 5198–5204.

(41) Initially, one ring of BIS is oxidized to a peroxy-cyclohexadienone, the carbonyl group of which promotes the formation of a strong intramolecular hydrogen bond from the OH group on the second ring. It is this hydrogen bond that makes the second phenolic hydrogen atom more difficult to abstract.⁴⁰

(42) 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.

(43) One H-atom in the methylene bridge was replaced by a methyl group because the BIS radical was not sufficiently persistent to allow the O–H BDE in BIS to be determined.⁴⁰

(44) Swain, C. G.; Swain, M. S.; Powell, A. L.; Alunni, S. *J. Am. Chem. Soc.* **1983**, *105*, 502–513.

(34) Foti, M. C.; DiLabio, G. A.; Ingold, K. U. *J. Am. Chem. Soc.* **2003**, *125*, 14642–14647.

(35) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183.

(36) (a) Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *167*, 928–931. (b) Lucarini, M.; Pedulli, G. F.; Guerra, M. *Chem.–Eur. J.* **2004**, *10*, 933–939.

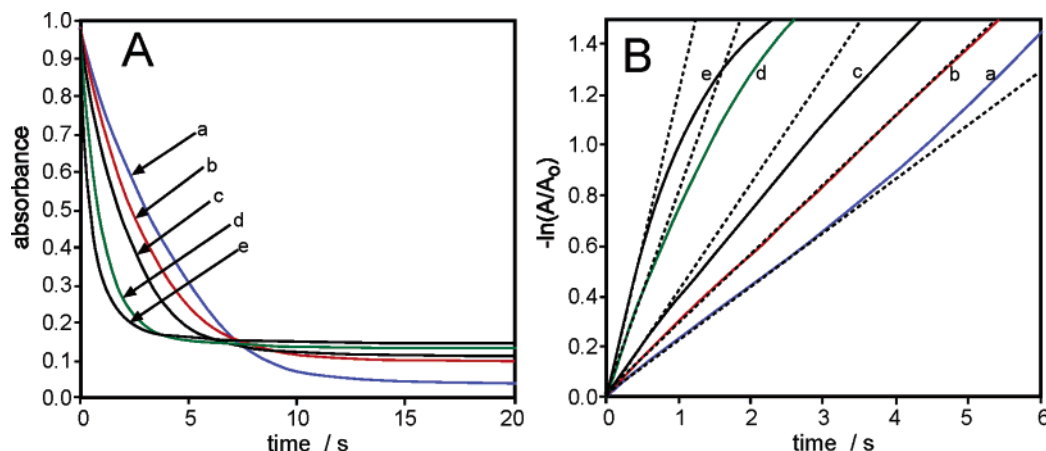
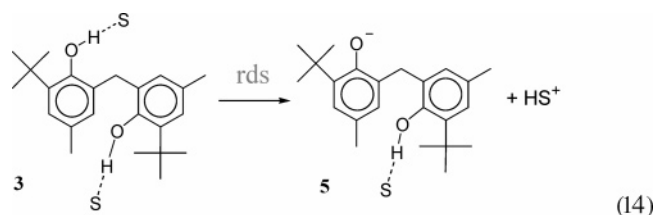


FIGURE 4. (A) Kinetic traces showing the loss of **dpph•** (initial concentration 9.5×10^{-5} M) during reaction with 2.5×10^{-4} M BIS in dry acetone (a) and in acetone containing water at concentrations of 0.36 (b), 0.56 (c), 1.20 (d), and 1.44 M (e). (B) Plots of the negative logarithms of normalized absorbance obtained from the kinetic curves in (A). The dashed straight lines show that curve (a) does not but that curves (b–e) do follow first-order kinetics.

greater than the rates in the absence of acid. This acetic acid-induced rate increase suggests that the concentration of the “preformed” BIS anion has been increased by the added acid. Although this suggestion is counterintuitive, it may be a consequence of the relative anion-solvating abilities of acetic acid and the solvents. Relative anion solvating abilities are described by Swain et al.’s⁴⁴ solvent acity parameters, A (scales range from 0.0 for alkanes to 1.0 for water). The A value for acetic acid is 0.93, which means that it will solvate the BIS anion much more strongly than, for example, acetone ($A = 0.25$) or DMSO⁴⁵ ($A = 0.34$); see Table 2.

The second unusual aspect of BIS/**dpph•** reactions, and the *raison d’être* for the present article, is those reactions that are zero-order in **[dpph•]**. Such kinetics are consistent with the ionization of BIS being the rds reaction 14:

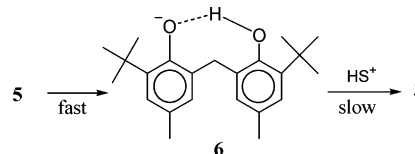


The five linear decay traces for the BIS/**dpph•** reaction in acetone that are shown in Figure 2B have a mean slope of -0.021_4 absorbance units/s (see Supporting Information). Conversion of absorbance into **[dpph•]** yields $k_{\text{XH/S}}^{\text{PT}}[\text{BIS}][\text{acetone}] = 1.1 \times 10^{-5} \text{ M s}^{-1}$ and, since **[BIS]** was $5.5 \times 10^{-5} \text{ M}$ in these five experiments, $k_{\text{XH/S}}^{\text{PT}}[\text{acetone}] = 0.20 \text{ s}^{-1}$, which is the rate constant for BIS ionization in acetone. Rate constants for BIS ionization in the other three solvents in which it could be measured are: benzonitrile, 3.30 s^{-1} ; acetonitrile, 1.4 s^{-1} ; and DMSO, 0.91 s^{-1} .^{46,47} As a reviewer kindly pointed out, the protonation of the BIS anion will be close to diffusion-controlled (i.e., in Scheme 2, $k_{\text{HS}^+/\text{X}^-}^{\text{PT}} \approx 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$). It follows that the dissociation constant for BIS, $K_a(\text{BIS})$, in these four solvents ranges from 4.0×10^{-11} to $2.8 \times 10^{-10} \text{ M}$.⁴⁹

The addition of low concentrations of water ($\beta_2^{\text{H}} = 0.38$)¹¹ is not expected to have much effect on either the

solvation of BIS or on its conformational equilibria in acetone ($\beta_2^{\text{H}} = 0.50$).¹¹ However, the added water ($\epsilon_r = 78.4$) would be expected to increase the rate of BIS ionization above that in neat acetone ($\epsilon_r = 20.6$). In the event, the rate of the BIS/**dpph•** reaction in acetone was increased by the addition of water (see Figure 4A), and the reaction became first-order in **[dpph•]** (see Figure 4B). This result also suggests that ionization of **3** may well be the rds in the five abnormal solvents.

Structure **5** is not intended to represent the most stable conformer of the BIS monoanion. The stable conformer of the monoanion is expected to have an intramolecular OH–O[−] hydrogen bond (i.e., **6**).



The intramolecular H-bond in **6** is likely to retard the reverse proton-transfer step, **6** + $\text{HS}^+ \rightarrow \text{3}$ ($k_{\text{HS}^+/\text{X}^-}^{\text{PT}}$ in Scheme 2). A slow reverse proton-transfer reaction is a

(45) Another possible reason for the unusual behavior of the BIS + DMSO + $\text{CH}_3\text{CO}_2\text{H}$ system (in comparison with other acidified systems) lies in the fact that the acidities of carboxylic acids change much more than the acidities of phenols on passing from water (or alcohols) to DMSO. For example, the $\text{p}K_a$'s for acetic acid in water and in DMSO are 4.7 and 12.6, respectively ($\Delta\text{p}K_a = 7.9$). For 2,6-dinitrophenol, the $\text{p}K_a$'s in water and DMSO are 3.7 and 4.9, respectively ($\Delta\text{p}K_a = 1.2$); see: Isutsu, K. *Electrochemistry in Nonaqueous Solutions*; Wiley-VCH: Weinheim, Germany, 2002; Chapter 3, pp 66–67. For some other carboxylic acids and phenols, the $\Delta\text{p}K_a$'s are: 6.8, benzoic acid; 6.0, chloroacetic acid; 1.44, 2,4-dinitrophenol; and -1.38 , picric acid.

(46) The rates of these zero-order reactions are, of course, much greater than the rates of the HAT-only reactions in these four solvents. The latter can be calculated from eq 2, using $k^0 = 57 \text{ M}^{-1} \text{ s}^{-1}$ (Table 1), $\alpha_2^{\text{H}} = 0.42$ for BIS, and the appropriate β_2^{H} value for the solvent. In acetone ($\beta_2^{\text{H}} = 0.50$), for example, this procedure yields $k^{\text{HAT}} = 1.0 \text{ M}^{-1} \text{ s}^{-1}$. The zero-order in **[dpph•]** traces in acetone shown in Figure 2B were obtained with **[dpph•]** = $(2.2\text{--}9.6) \times 10^{-5} \text{ M}$. Therefore, in this solvent $k^{\text{HAT}}[\text{dpph•}] = 1.0 \times (2.2\text{--}9.6) \times 10^{-5} = (2.2\text{--}9.6) \times 10^{-5} \text{ s}^{-1}$, which is very much smaller than $k_{\text{XH/S}}^{\text{PT}}[\text{acetone}]$, viz. 0.20 s^{-1} .

(47) These rate constants are 3 or 4 orders of magnitude smaller than the rate constants for the deprotonation of nitrophenols in water.⁴⁸

(48) Eigen M.; Kustin, K. *J. Am. Chem. Soc.* **1960**, *82*, 5952–5953.

necessary condition for the overall kinetics to be zero-order in **[dpph[•]]**, that is, $k_{\text{HS}^+/X^-}^{\text{PT}}$ must be $\ll k^{\text{ET}}[\text{Y}^{\bullet}]$ (see eq 10 and Scheme 2). We therefore tentatively suggest that the formation of an intramolecular H-bond in this BIS monoanion is the reason that the BIS/**dpph[•]** reaction exhibits zero-order kinetics in a few neat solvents.⁵⁰

The discovery of ArOH/**dpph[•]** reactions that follow zero-order kinetics in **dpph[•]** in certain solvents provides strong support for the occurrence of the SPLET mechanism in some of these systems. Whether such kinetics are also obtained for any ArOH/ROO[•] reaction in biological systems remains to be determined.

Experimental Section

Materials. Because phenol/**dpph[•]** reaction kinetics in methanol, ethanol, acetone, and acetonitrile are sensitive to traces of acids and bases, these solvents were fractionally distilled over a small amount of **dpph[•]** and a few beads of an ion-exchange resin prior to use. All other solvents were of the highest commercially available purity and were used as received. Commercial BIS was recrystallized twice from *n*-hexane, and the crystals were dried under vacuum.

Kinetic Measurements. These were made following the procedure described previously.^{12,13} Decays of **dpph[•]** (initial concentrations $3\text{--}8 \times 10^{-5}$ M) in the presence of excess BIS at known concentrations were monitored at 517 nm on an Applied Photophysics stopped-flow spectrophotometer, SX 18 MV, equipped with a 150 W xenon lamp at ambient temperature. The rate constants presented in Tables 1 and 2 are mean values from at least two independent sets of measurements of several pseudo-first-order rate constants, k_{exptl} . Values of k^{S} were calculated using eq 7 in the Results. For additional details, see the Supporting Information.

(49) For example, the first K_{a} for 2,2'-methylenebis(4-methylphenol) dissociation in methanol is 3.3×10^{-11} M (see: Takemura, H. *J. Inclusion Phenom.* **2002**, *42*, 169–186.)

(50) The possibility that the zero-order kinetics arise from some other conformational property that is unique to BIS or its monoanion cannot be ruled out.

Determination of α_2^{H} by IR. The method has been described previously.^{12,13} A Shimadzu FTIR 8201PC apparatus with a 1.03 mm CaF₂ cell was employed, and a baseline correction was made using the same concentration of the HBA in CCl₄. Values of [BIS]_{free} were determined from the intensities of the band at 3632 cm⁻¹ (resolution 1 cm⁻¹, 20 scans). The detailed procedure and the tables and figures for BIS and for Bu^tMe₂-phenol, OH_{free} = 3618 cm⁻¹ (OH group pointing toward the 6-methyl substituent) and 3650 cm⁻¹ (OH group pointing toward the 2-*tert*-butyl substituent)³¹ are given in the Supporting Information.

Acknowledgment. We are extremely grateful to several anonymous reviewers for their thoughtful and helpful comments and criticisms. G.L. thanks the Department of Chemistry, Warsaw University, for Grants BW-1637/06/04 and BW-1681/07/05.

Supporting Information Available: Detailed kinetic data for reactions of BIS with **dpph[•]** in 20 solvents and in seven acidified solvents (Tables S1–S19), for the reaction of Bu^tMe₂-phenol in heptane, ethanol, and acetone (Table S20), for the reaction of Me₃-phenol in 14 solvents (Table S21) and plot of the logarithms of the Me₃-phenol kinetic data against β_2^{H} (Figure S2), plots of **dpph[•]** decay in its reaction with BIS in neat acetonitrile and in acidified acetonitrile (Figure S1), plots and parameters used for calculation of HB equilibrium constants, K , between BIS and DMSO and acetonitrile plus calculated α_2^{H} parameters (Figures S3, S4 and Tables S22–S24), first-order plots of the **dpph[•]**/Bu^tMe₂-phenol reaction in neat acetone (Figure S5), IR plots and parameters used for calculation of HB equilibrium constants, K and α_2^{H} for Bu^tMe₂-phenol versus DMSO (Figures S6, S7 and Table S25), plots of kinetic traces of **dpph[•]** decay in its reaction with BIS in neat DMSO and DMSO containing 10, 100, and 1000 mM acetic acid (Figure S8), plots of **dpph[•]** decay in its reaction with BIS in acetone that were used for the determination of the rates of BIS ionization (Figure S9), and plots of **dpph[•]** decay in its reaction with BIS in acetonitrile (Figure S10). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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