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How Solvent Modulates Hydroxyl Radical Reactivity in Hydrogen Atom Abstractions

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Abstract: The hydroxyl radical (HO•) is a highly reactive oxygen-centered radical whose bimolecular rate constants for reaction with organic compounds (hydrogen atom abstraction) approach the diffusion-controlled limit in aqueous solution. The results reported herein show that hydroxyl radical is considerably *less reactive* in dipolar, aprotic solvents such as acetonitrile. This diminished reactivity is explained on the basis of a polarized transition state for hydrogen abstraction, in which the oxygen of the hydroxyl radical becomes highly negative and can serve as a hydrogen bond acceptor. Because acetonitrile cannot participate as a hydrogen bond donor, the transition state cannot be stabilized by hydrogen bonding, and the reaction rate is lower; the opposite is true when water is the solvent. This hypothesis explains hydroxyl radical reactivity both in solution and in the gas phase and may be the basis for a "containment strategy" used by Nature when hydroxyl radical is produced endogenously.

Solvent polarity can have a huge effect on the kinetics of reactions involving or forming charged species in solution. In contrast, reactions of neutral radicals are much less sensitive to solvent polarity effects, mainly because charged species are not involved, and there is not a significant change in dipole moment in the progression from reactants to transition state. Because of this, other subtler solvent properties such as viscosity or internal pressure can influence the rate of certain radical reactions; such solvent effects are much more difficult to detect in polar reactions because they are masked by the overwhelming effect of solvent polarity.[1]

For example, solvent viscosity can affect the rate and product distribution when radical caged-pairs (geminate or diffusive) are involved. Internal pressure can influence rate if there is a difference in the volume of the reactants compared to the transition state ($\Delta V_{\mathrm{act}} \neq 0$) and can influence the relative rate of some radical reactions. However, these solvent effects are generally small, with changes in rate or product distribution not much greater than an order of magnitude.[1] Consequently, instances where solvent *dramatically* affects the rate or selectivity of reactions involving neutral radicals are rare and noteworthy.

The classic example of a significant solvent effect in a radical reaction involves free radical chlorinations of alkanes conducted in benzene solvent. The chain-carrying chlorine atom forms a complex with benzene, lowering its reactivity and increasing its selectivity (by nearly 2 orders of magnitude) in hydrogen atom abstractions.[1,2] A more recent example of a significant solvent effect was reported by Ingold and co-workers, who found that rate constants for hydrogen atom abstractions from phenols were reduced in solvents where the phenol was stabilized by hydrogen bonding.[3] In this case, it was the reactivity of the substrate, not the radical, that was diminished as a result of a solute/solvent interaction.

The hydroxyl radical (HO•) is an extremely reactive oxidant, important in chemistry, biology, medicine, materials, and the environment. In biology, hydroxyl radical is recognized as the most reactive of the so-called reactive oxygen species (ROS). Cancer, arthritis, and Parkinson's disease are but a few of the ailments that are linked to hydroxyl radical. Despite it's role in disease, HO• is also a vital part of the body's natural defense mechanisms. Reactive oxygen species are produced endogenously as a means of destroying foreign antigens or abnormal cells. It is often stated that in biological systems, hydroxyl radical reacts with the first molecule it encounters.

Hydroxyl radical is also important in atmospheric chemistry because of its ability to oxidize volatile organic pollutants and has been referred to as the atmosphere's "detergent."[4] Recently, Vöhringer-Martinez et al. examined the role of water in the gas-phase reaction of the hydroxyl radical with acetaldehyde, reporting that a water concentration of 3% led to an increase in the rate of hydrogen abstraction (abstraction taking place from the aldehydic hydrogen).[5] Their hypothesis that hydrogen bonding to water in the transition state lowered the reaction barrier raises several intriguing questions: Why is hydrogen bonding to water more important in the transition state as compared to reactants? Is this stabilization unique to substrates with functional groups that are capable of hydrogen bonding (such as the carbonyl group in acetalaldehyde)? Is this stabilization also important for reactions of hydroxyl radical in solution? In short, how general is this phenomenon, and can we understand it on the molecular level?

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(1) Tanko, J. M.; Suleman, N. K. Solvent Effects in the Reactions of Neutral Free Radicals. In *Energetics of Organic Free Radicals*; Simões, J. A. M., Greenberg, A., Liebman, J., Eds.; Chapman & Hall: New York, 1996; pp 224−293.

(2) Russell, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 4987–4996.

(3) Litwinienko, G.; Ingold, K. U. *Acc. Chem. Res.* **2007**, *40*, 222–230.

(4) Li, S.; Matthews, J.; Sinha, A. *Science* **2008**, *319*, 1657–1660.

(5) Vöhringer-Martinez, E.; Hansmann, B.; Hernandez-Soto, H.; Francisco, J. S.; Troe, J.; Abel, B. *Science* **2007**, *315*, 497–501.

10.1021/ja903856t

Until recently, pulse radiolysis was one of a few means of generating hydroxyl radical in solution for the determination of absolute reaction rates. Because this technique, by definition, involves the radiolysis of water, solution-phase studies of hydroxyl radical kinetics have largely been conducted in water.[6] As a result, relatively little is known about the reactivity of HO• in other solvents. Recent developments have made it possible to study the hydroxyl radical in a nonaqueous environment through the use of photolabile hydroxyl radical precursors. *N*-Hydroxypyridine-2-thione (PSH), developed by Zard et al.,[7] is one such precursor that, when photolyzed at 355 nm, cleanly produces the hydroxyl radical. Because the radical byproduct (pyrithyl radical) is relatively stable, decaying on a microsecond time scale, this precursor is an ideal candidate for studying the hydroxyl radical kinetics in solution via laser flash photolysis (LFP).[8]

Platz et al.[8b,c] developed a method for "visualizing" the hydroxyl radical, which does not have a convenient absorption in the UV−vis: hydroxyl radical addition to the ortho and para positions of *trans*-stilbene produces an adduct with an absorption at 392 nm, allowing *trans*-stillbene to act as a viable spectroscopic probe for monitoring HO• kinetics. These workers also noted a solvent effect on HO• reactivity. The rate constant for addition to aromatics (*trans*-stilbene, benzene) was observed to be lower in acetonitrile compared to water. Molecular orbital calculations supported the notion that this was due to a polarized transition state, reminiscent of the polar effect introduced by Russell,[9] Walling,[10] and others[11] for hydrogen atom abstraction reactions (*vide infra*). Other studies reporting Hammett parameters for HO• addition reactions to aromatic compounds have given negative $\rho+$ values, consistent with the buildup of negative charge on the hydroxyl moiety in the transition state.[12] The strong dipole that is formed in the transition state has the ability to be stabilized by the surrounding solvent.

Very little is known about the kinetics of hydrogen abstractions by HO• in nonaqueous solvents. Amplified by high level molecular orbital calculations, the observations reported herein provide answers to all of the questions posed above and a comprehensive understanding of HO• reactivity in solution and the gas phase, correcting what we now believe to be some of the misconceptions pertaining to the chemistry of hydroxyl in solution.

Experimental Section

Materials. All of the solvents and fine chemicals used in this study were obtained from Sigma-Aldrich. Liquid substrates were distilled and *N*-hydroxypyridine-2-thione was recrystallized prior to use.

Apparatus. Steady-state UV−vis spectra were recorded on a Hewlett-Packard diode array UV−vis spectrophotometer (HP 8452A). Laser flash photolysis experiments were conducted using an Applied Photophysic LKS.60 spectrometer using the third harmonic of a Continuum Surelite I-10 Nd:YAG laser (4−6 ns pulse, 355 nm). Transient signals were monitored by a Hewlett-Packard Infinium digital oscilloscope and analyzed with the Applied Photophysics SpectraKinetic Workstation software package (v. 4.59).

Table 1. Rate Constants for Hydrogen Abstraction by HO• from Various Organic Substrates in CH_3CN and H_2O[a]

substrate	$k_H(CH_3CN) \times 10^{-7}$ ($M^{-1}\ s^{-1}$)	$k_H(H_2O) \times 10^{-7}$ ($M^{-1}\ s^{-1}$)	$k_H(H_2O)/k_H(CH_3CN)$
$(CH_3)_3CC(CH_3)_3$	5.83 (±0.61)		
$CH_3(CH_2)_4CH_3$	4.48 (±0.79)	660[b]	147
$CH_3(CH_2)_5CH_3$	6.24 (±0.88)	770[b]	123
c-C_6H_{11}-CH_3	4.22 (±0.28)	710[b]	168
c-C_6H_{12}	6.72 (±0.99)	610[b]	90
$(CH_3)_2CHCH(CH_3)_2$	12.0 (±3.90)		
$CH_3(CH_2)_3OH$	4.20 (±0.98)	420 (±33.4)[c−f]	100
CH_3CH_2OH	8.28 (±3.20)	193 (±10.4)[c−e,g−j,l−p,ee]	23
$(CH_3)_2CHOH$	7.19 (±1.72)	200 (±24.0)[c,d,g,i,q−s]	28
CH_3OH	5.90 (±0.67)	95 (±4.4)[c−g,i,k,m,n]	16
$(CH_3)_3COH$	3.62 (±0.03)		
$(CH_3CH_2)_2O$	4.56 (±1.00)	355 (±127)[s,t]	78
$CH_3OC(CH_3)_3$	4.35 (±0.35)	160[t]	37
$CH_3CH_2OC(CH_3)_3$	1.78 (±0.63)	225 (±88)[u,v]	126
C_4H_8O (THF)	3.50 (±0.65)	410[t]	117
CH_2Cl_2	7.63 (±0.89)	8.8 (±1.8)[w−y]	1.2
$(CH_3)_2CO$	3.21 (±1.16)	11.3 (±2.7)[d,f,i,s]	3.5
$CHBr_3$	8.41 (±2.32)	10.5 (±0.97)[w,z]	1
$CHCl_3$	4.85 (±0.92)	1.74 (±1.4)[w,aa−dd]	0.35
$ClCH_2CO_2H$	5.09 (±0.96)	4.3[f]	0.85

[a] The rate constants in water were obtained from the Notre Dame Radiation Laboratory database (http://www.rcdc.nd.edu/index.html); these values were verified by consulting the original papers. [b] Reference 17. [c] Reference 18. [d] Reference 19. [e] Reference 20. [f] Reference 21. [g] Reference 22. [h] Reference 23. [i] Reference 24. [j] Reference 25. [k] Reference 26. [l] Reference 27. [m] Reference 28. [n] Reference 29. [o] Reference 30. [p] Reference 31. [q] Reference 32. [r] Reference 33. [s] Reference 34. [t] Reference 35. [u] Reference 36. [v] Reference 37. [w] Reference 38. [x] Reference 39. [y] Reference 40. [z] Reference 41. [aa] Reference 42. [bb] Reference 43. [cc] Reference 44. [dd] Reference 45. [ee] Reference 46.

Laser Flash Photolysis (LFP). Substrates were prepared in acetonitrile or in an acetonitrile/water cosolvent and deoxygenated prior to photolysis. (Steady-state UV−vis spectra were recorded to verify that *N*-hydroxypyridine-2-thione was the only species absorbing at the excitation wavelength). In all LFP experiments, a fixed concentration of *trans*-stilbene (0.0015 M) was utilized as a spectroscopic probe, monitoring the signal buildup at 392 nm. Low laser power (*ca.* 10−20 mJ) was used in all experiments to eliminate any laser power dependency to the observed rate constants thereby minimizing the contributions of radical−radical reactions and other artifacts. Substrate concentrations were varied over a factor of at least 10 over 5−7 separate experiments.

Calculations. Electronic structure calculations were performed using either the Spartan 04[13] molecular modeling software or Gaussian 03.[13]

Results and Discussion

Rate constants for the reaction of HO• with a variety of substrates in acetonitrile are summarized in Table 1. Compared to *tert*-butoxyl radical,[14] rate constants for hydrogen abstraction by hydroxyl radical are generally 2−3 orders of magnitude greater. The high reactivity of HO• is accompanied by low selectivity. For aliphatic hydrogens, the per-hydrogen reactivity is approximately tertiary (13.9) > secondary (1.4) > primary

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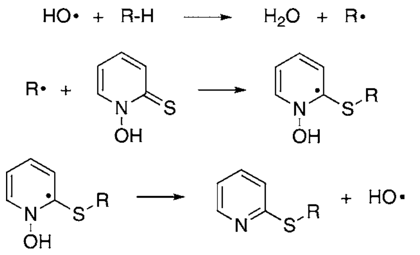
(6) Xu, G.; Chance, M. R. *Chem. Rev.* **2007**, *107* (8), 3514–3543.
(7) Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *47*, 6869–6872.
(8) (a) Aveline, B. M.; Kochevar, I. E.; Redmond, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 9699–9708. (b) DeMatteo, M. P.; Poole, J. S.; Shi, X.; Sachdeva, R.; Hatcher, P. G.; Hadad, C. M.; Platz, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7094–7109. (c) Poole, J. S.; Shi, X.; Hadad, C. M.; Platz, M. S. *J. Phys. Chem. A.* **2005**, *109*, 2547–2551.
(9) Russell, G. A. Reactivity, Selectivity, and Polar Effects in Hydrogen Atom Transfer Reactions. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons, Inc.: New York, 1973; Vol. I pp 275−331.
(10) Walling, C. *Free Radicals in Solution*; John Wiley & Sons, Inc.: New York, 1957.
(11) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35.
(12) (a) Merga, G.; Rao, B. S. M.; Mohan, H.; Mittal, J. P. *J. Phys. Chem.* **1994**, *98*, 9158–9164. (b) Anbar, M.; Meyerstein, D.; Neta, P. *J. Phys. Chem.* **1966**, *70*, 2660–2662.
(13) Frisch, M. J. et al. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.

(1.0), based upon a multiple regression analysis of the results (assuming the global rate constant to be the sum of contributions from each type of hydrogen). For the alcohols, the hydrogen of the hydroxyl group is about 3 times more reactive than a primary, aliphatic hydrogen.

A reviewer has vehemently argued that the results reported herein, as well as the earlier results of Platz et al., are not attributable to hydroxyl radical. Rather, it was suggested that at the low substrate concentrations used in these experiments (millimolar), HO• would instantaneously abstract hydrogen from acetonitrile solvent, present in large excess, forming •CH$_2$CN, and that it was the kinetics of •CH$_2$CN that was observed by laser flash photolysis. (It was also suggested that the photolysis byproduct, PyrS•, might also be a contributor to the observed kinetics.) However, as noted by others, acetonitrile is an exceptional solvent in that it is “extremely unreactive towards ‘electrophilic’ oxygen-centered radicals.”[15] The evidence against potential roles for either •CH$_2$CN or PyrS• is reviewed and discussed in detail in Supporting Information.

Scheme 1



To provide new evidence that eliminates •CH$_2$CN from consideration as a hydrogen atom abstractor under these conditions, some of the laser flash experiments were repeated using a solvent devoid of abstractable hydrogens, specifically, Freon 113 (1,1,2-trichlorotrifluoroethane). In this solvent, the rate constants for hydrogen abstraction from cyclohexane and methanol were $7.3\ (\pm 0.5) \times 10^{7}$ and $9.2\ (\pm 1.1) \times 10^{7}$ M^{-1} s^{-1}, respectively, nearly identical to those measured in acetonitrile (Table 1).

Preparative-scale experiments were performed in acetonitrile, using cyclohexane and 2,3-dimethylbutane as substrates. The photoinitiated (350 nm) reaction of PSH with alkanes yields the corresponding sulfides in good yield, presumably via the chain mechanism depicted in Scheme 1.[7]

To ascertain relative reactivities of primary, secondary, and tertiary hydrogens, competition experiments were conducted using 2,3-dimethylbutane as the source for primary and tertiary hydrogens and cyclohexane as the source for secondary hydrogens. Rather than being present in millimolar concentrations as with the laser flash experiments, the hydrocarbon substrates were used as cosolvents. The derived relative reactivities in acetonitrile, tertiary (15.2) > secondary (3.9) > primary (1.0), compare favorably to the values estimated from the laser flash results (*vide supra*), consistent with the role of HO• as the hydrogen abstractor.

Unfortunately, these experiments do not *prove* that the observed chemistry is attributable to hydroxyl radical. Rather, they only eliminate other reasonable alternative explanations. In addition to the aforementioned *trans*-stilbene adducts with PyrS• and •CH$_2$CN, Platz and co-workers also considered and eliminated triplet stilbene and stilbene radical cation as species giving rise to the 392 nm transient. Computational studies provided no evidence for HO•/CH$_3$CN complexes to explain the diminished reactivity of hydroxyl radical in acetonitrile; our results in Freon 113 add additional support to this conclusion. On the basis of the laser flash results and the accompanying product studies, hydroxyl radical emerges as the most likely explanation for the observed chemistry.

Table 1 also summarizes rate constants for reactions of HO• in water obtained from the literature. In cases where more than one value was available, these were averaged and reported with 95% confidence limits. For hydrocarbons, the rate constants for hydrogen abstraction by HO• are nearly 2 orders of magnitude *lower* in acetonitrile than in water solvent. When the substrate possesses an electronegative substituent (halogen, carbonyl, etc.), this difference diminishes to much less than an order of magnitude. However, the solvent effect is restored; the rate constants in water are again about 2 orders of magnitude greater than in acetonitrile when the substrate bears an electron-donating group such as alkoxyl or hydroxyl.

The results in Table 2 extend these observations: In going from neat acetonitrile to a 90% acetonitrile/water cosolvent, the

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(14) Finn, M.; Friedline, R.; Suleman, N. K.; Wohl, C. J.; Tanko, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7578–7584.
(15) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *93*, 466–470.
(16) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1990.
(17) Rudakov, E. S.; Volkova, L. K.; Tret’yakov, V. P. *React. Kinet. Catal. Lett.* **1981**, *16*, 333–337.
(18) Buxton, G. V.; Greenstock, C. L.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1988**, *17*, 513–886.
(19) Willson, R. L.; Greenstock, C. L.; Adams, G. E.; Wageman, R.; Dorfman, L. M. *Int. J. Radiat. Phys. Chem.* **1971**, 211–220.
(20) Adams, G. E.; Boag, J. W.; Michael, B. D. *Trans. Faraday Soc.* **1965**, *61*, 1417–1424.
(21) Adams, G. E.; Boag, J. W.; Currant, J.; Michael, B. D. In *Pulse Radiolysis*; Ebert, M., Keene, J. P., Swallow, A. J., Baxendale, J. H., Eds.; Academic Press: New York, 1965; pp 131−143.
(22) Motohashi, N.; Saito, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1842–1845.
(23) Park, H.-R.; Getoff, N., Z. *Z. Naturforsch. A: Phys. Sci.* **1992**, *47A*, 985–991.
(24) Wolfenden, B. S.; Willson, R. L. *J. Chem. Soc., Perkin Trans.* **1982**, 805–812.
(25) Matheson, M. S.; Mamou, A.; Silverman, J.; Rabani, J. *J. Phys. Chem.* **1973**, *77*, 2420–2424.
(26) Elliot, A. J.; McCraken, D. R. *Radiat. Phys. Chem.* **1989**, *33*, 69–74.
(27) Buxton, G. V. *Trans. Faraday Soc.* **1970**, *66*, 1656–1660.
(28) Baxendale, J. H.; Khan, A. A. *Int. J. Radiat. Phys. Chem.* **1969**, *1*, 11–24.
(29) Neta, P.; Dorfman, L. M. *Adv. Chem. Ser.* **1968**, *81*, 222–230.
(30) Heckel, E.; Henglein, A.; Beck, G. *Ber. Bunsenges. Phys. Chem.* **1966**, *70*, 149–154.
(31) Matthews, R. W.; Sangster, D. F. *J. Phys. Chem.* **1965**, *69*, 1938–1946.
(32) Elliot, A. J.; Simsons, A. S. *Radiat. Phys. Chem.* **1984**, *24*, 229–231.
(33) Greenstock, C. L.; Ng, M.; Hunt, J. W. *Adv. Chem. Ser.* **1968**, *81*, 397–417.
(34) Thomas, J. K. *Trans. Faraday Soc.* **1965**, *61*, 702–707.
(35) Eibenberger, J. Vienna University, Vienna, Austria, 1980.
(36) Karpel Vel Leitner, N.; Papailhou, A.-L.; Croue, J.-P.; Peyrot, J.; Dore, M. *Ozone Sci. Eng.* **1994**, *16*, 41–54.
(37) Mezyk, S. P.; Cooper, W. J.; Bartels, D. M.; O’Shea, K. E.; Wu, T. *J. Phys. Chem. A* **2001**, *105*, 3521–3526.
(38) Haag, W. R.; Yao, C. C. D. *Environ. Sci. Technol.* **1992**, *26*, 1005–1013.
(39) Getoff, N. *Radiat. Phys. Chem.* **1991**, *37*, 673–680.
(40) Emmi, S. S.; Beggiato, G.; Casalbore-Miceli, G.; Fuochi, P. G. *J. Radioanal. Nucl. Chem., Lett.* **1985**, *93*, 189–197.
(41) Lal, M.; Mahal, H. S. *Radiat. Phys. Chem.* **1992**, *40*, 23–26.
(42) Rezansoff, B. J.; McCallum, K. J.; Woods, R. J. *Can. J. Chem.* **1970**, *48*, 271–276.
(43) Anbar, M.; Meyerstein, D.; Neta, P. *J. Chem. Soc. B* **1966**, 742–747.
(44) Chutny, B. *Collect. Czech. Chem. Commun.* **1966**, *31*, 358–361.
(45) Bednar, J.; Teply, J. *Collect. Czech. Chem. Commun.* **1960**, *25*, 842–851.
(46) Adams, G. E.; Boag, J. W.; Michael, B. D. *Trans. Faraday Soc.* **1965**, *61*, 492–505.

Table 2. Rate Constants for Hydrogen Abstraction by HO• from Various Organic Substrates in 90% CH_3CN/H_2O and 100% CH_3CN

substrate	$k_H(CH_3CN/H_2O) \times 10^{-7}$ (M^{-1} s^{-1})	$k_H(CH_3CN) \times 10^{-7}$ (M^{-1} s^{-1})	k_H $(CH_3CN/H_2O)/k_H(CH_3CN)$
$CH_3(CH)_4CH_3$	11.3 (±1.04)	4.48 (±0.79)	2.5
c-C_6H_{12}	15.2 (±0.68)	6.72 (±0.99)	2.3
$(CH_3)_2CHCH(CH_3)_2$	16.8 (±0.81)	12.0 (±3.90)	1.4
CH_3CH_2OH	11.1 (±0.80)	8.28 (±3.20)	1.3
$CHBr_3$	8.33 (±0.84)	8.41 (±2.32)	1.0
$CHCl_3$	4.26 (±1.06)	4.85 (±0.92)	0.9

rate constants increase by about a factor of 2 for the hydrocarbons but remain virtually unchanged for substrates with electronegative substituents. (Higher proportions of water could not be used because of solubility problems.)

Walling,[10] Russell,[2] and others[11] have argued for the importance of a polar transition state for hydrogen atom abstraction reactions. These results can be explained by taking their ideas one step further (Figure 1): because oxygen is more electronegative than carbon and hydrogen, in the transition state for hydrogen abstraction, electron density is pulled toward the oxygen of the hydroxyl radical, giving it a partial negative charge and a partial positive charge on the RH portion of the transition state. This development of negative charge on the oxygen of the hydroxyl radical affords the opportunity for the solvent (H_2O) to stabilize the transition state through its polarity and/or ability to participate in hydrogen bonding. Table 2 shows that for hydrocarbons even 10% addition of water has a significant effect on the rate because the transition state is so highly polarized.

In contrast, when the substrate possesses electronegative substituents (e.g., halogen, carbonyl), the transition state is less polarized because the substituent competes for electron density; there is less transfer of negative charge to the oxygen of the hydroxyl radical and hydrogen bonding interactions are expected to be weaker, thus explaining why there is little to no rate enhancement in going from acetonitrile to water for these substrates. It should be noted that the hydrogen on the hydroxyl radical (not involved in the reaction) bears substantial positive charge in the reactant, transition state, and product. Although this hydrogen can also participate in hydrogen bonding, this interaction does not affect the relative energies because the charge on this hydrogen remains constant in the progression from reactant to transition state to product.

For alcohols and ethers, where H-abstraction also occurs at the α-carbon, we hypothesize that the electron-withdrawing properties of oxygen in the substrate (manifested through an inductive effect) are offset by the resonance stabilization afforded by the lone pair of electrons (Scheme 2). This resonance effect would thus allow the oxygen of the hydroxyl radical to become highly negative so that hydrogen bonding interactions would again become important. Presumably the effect of oxygen diminishes with distance so that the β-hydrogens (and beyond) are aliphatic in nature, and the solvent effect on their reactivity is similar to the alkanes.

To test these hypotheses, and assess how atomic charges on individual atoms vary in the progression from reactants → transition state → product, molecular orbital calculations were performed on the pertinent species for the reactions (a) $CH_4 + HO\bullet \rightarrow CH_3\bullet + H_2O$, (b) $Cl_3CH + HO\bullet \rightarrow Cl_3C\bullet + H_2O$, and (c) $HOCH_3 + HO\bullet \rightarrow HOCH_2\bullet + H_2O$ at various levels of theory. In Figure 2, the charges obtained from a natural population analysis at the MP2(full)/aug-cc-pVQZ//UHF/6-311G* levels are reported. It should be noted that every level of theory (AM1, B3LYP/6-311G*, UHF/6-311G*) employed gave virtually the same qualitative results. As the reactants approach the transition state, the hydrogen being transferred becomes substantially more positive, and the oxygen becomes more negative, consistent with the notion of a polarized transition state. However, the *degree* of polarization is far greater for CH_4 and CH_3OH compared to $CHCl_3$, as expected on the basis of the preceding discussion. The negative charge on the oxygen of hydroxyl radical in the transition state means that this oxygen can be a hydrogen bond acceptor.

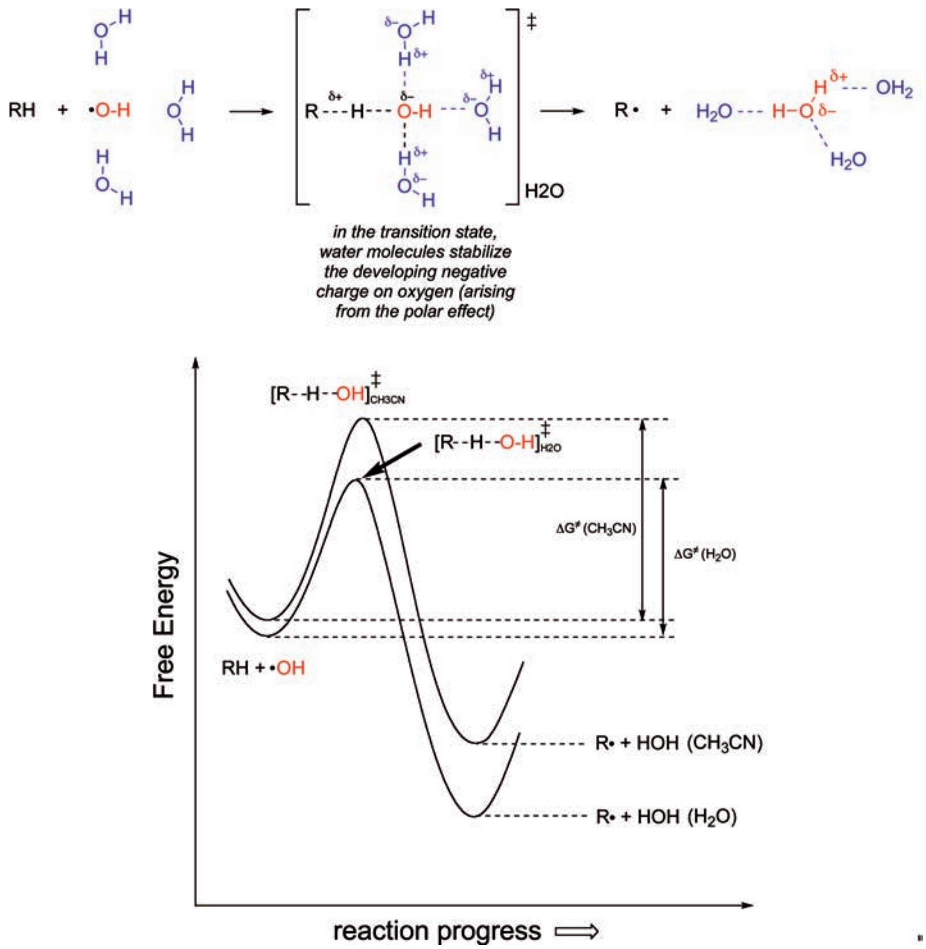
As noted, there are in principle two contributors to the observed solvent effect. In addition to hydrogen bonding, it is also possible that solvent polarity plays a role in stabilizing the transition state (relative to the reactants). However, the following analysis strongly suggests that hydrogen bonding interactions in the transition state, rather than a simple solvent polarity effect, is the etiology of the effect.

The free energy of solvation of a polar molecule in a polar solvent can be estimated by the Kirkwood equation and applied to the reaction between two polar molecules $A + B \rightarrow$ transition state (ts) via activated complex theory.[16] The magnitude of the solvent effect depends on the dipole moment (μ) and radius (r) of the transition state relative to reactants, and the dielectric constant (ε) of the solvent as expressed in eq 1, where $\ln k_0$ refers to the rate constant in a solvent of dielectric constant of unity, ε_0 is the permittivity of vacuum, and N, π, R, and T have their usual meanings.

$$\ln k = \ln k_0 + \frac{1}{4\pi\varepsilon_0}\frac{N}{RT}\left(\frac{\mu_{\mathrm{ts}}^2}{r_{\mathrm{ts}}^3} - \frac{\mu_{\mathrm{A}}^2}{r_{\mathrm{A}}^3} - \frac{\mu_{\mathrm{B}}^2}{r_{\mathrm{B}}^3}\right)\left(\frac{\varepsilon - 1}{2\varepsilon + 1}\right) \qquad (1)$$

Using the dipole moments and radii for CH_4, HO•, and $(CH_4/HO\bullet)^\ddagger$ obtained from CCSD(T)/aug-cc-pVDZ calculations based on MP2/aug-cc-pVDZ geometries (*vide infra*), the rate is actually predicted to be slightly *greater* in acetonitrile than water ($k_{CH_3CN}/k_{H_20} = 1.01$). This result makes sense because one of the reactants (hydroxyl radical) possesses a significant dipole moment; the transition state has a slightly lower dipole moment and a larger radius. The increased rate in water thus cannot arise simply because it is a more polar solvent than acetonitrile, but rather because it is able to stabilize the developing negative charge on the hydroxyl radical in the transition state by acting as a hydrogen bond donor. It should also be noted that the results obtained in Freon 113 add further support to this hypothesis because (a) the rate constants are the same as in acetonitrile, and (b) Freon 113 has a substantially lower dielectric constant than acetonitrile.

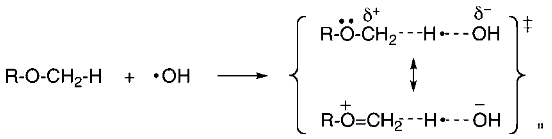
To further assess the contribution of dipolar interactions to the observed rate enhancement in water, electronic-structure theory calculations of the $HO\bullet + CH_4 \rightarrow H_2O + CH_3\bullet$ reaction barrier were calculated using implicit solvation models. CCSD(T)/aug-cc-pVDZ calculations with the polarized continuum model (PCM) using geometries and frequencies calculated at the MP2/aug-cc-pVDZ level indicate that the reaction in water should be *slower* than in acetonitrile or the gas phase. In effect, the barrier for the PCM calculations using water as a solvent in the PCM model (6.76 kcal/mol) is larger than the barrier when using acetonitrile as a solvent (5.86 kcal/mol). Both barriers are larger than the gas-phase barrier at that level (5.03 kcal/mol). These predictions (based upon the PCM model, which does not account for implicit hydrogen bonding) are in stark contrast with the experimental results in water solvent. This "disparity" is easily



in the transition state, water molecules stabilize the developing negative charge on oxygen (arising from the polar effect)

Figure 1. Formation of a polarized transition state for hydrogen atom abstraction from a hydrocarbon by hydroxyl radical. When water is the solvent, the free energy of the transition state is lowered relative to that of the reactants because of hydrogen bonding of water to the developing negative charge on the hydroxyl moiety.

Scheme 2



reconciled if the transition state for hydrogen atom abstraction is stabilized by hydrogen bonding in water solvent.

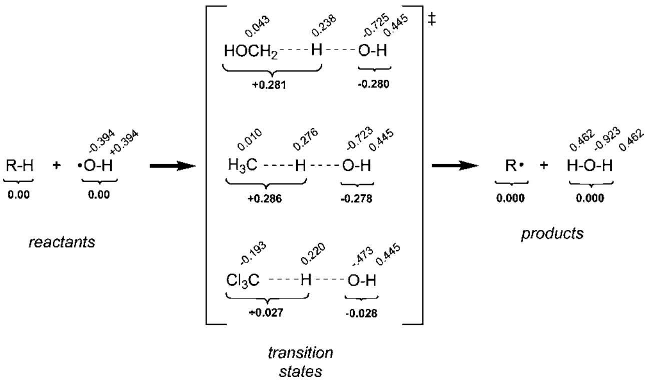
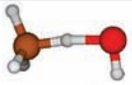
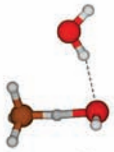
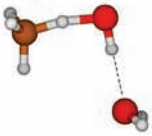
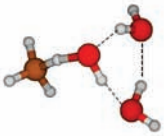
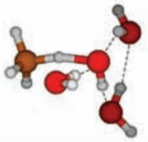


Figure 2. Atomic charges for the reaction of hydroxyl radical with CH_4, CH_3OH, and $CHCl_3$ obtained from natural population analysis of the reactants, transition states, and products at the MP2(full)/aug-cc-pVQZ//UHF/6-311G* levels.

As a final confirmation of this interpretation, the effect of solvent water molecules on the minimum-energy reaction path of the $HO\bullet + CH_4 \rightarrow H_2O + CH_3\bullet$ reaction was calculated. Geometry optimizations and frequency calculations were conducted at the MP2/aug-cc-pVDZ level, and energies were refined at the CCSD(T)/aug-cc-pVDZ level. Qualitatively, when water molecules were added to the calculations for the $HO\bullet/CH_4$ reaction, the resulting transition state clearly shows that the water molecules properly align so as to stabilize the developing charges as hypothesized. Quantitatively, the magnitude of the stabilization is consistent with the magnitude of the observed kinetic solvent effect.

Table 3 shows the calculated barriers and calculated relative rate constants for $HO\bullet + CH_4 \rightarrow H_2O + CH_3\bullet$ with various water molecules hydrogen bonding to different sites of the $HO\bullet/CH_4$ system either as donors or acceptors. One water molecule acting as hydrogen-bond donor to the OH radical reduces the barrier by 1.52 kcal mol^{-1}. On the other hand, if the solvating water molecule acts as hydrogen-bond acceptor, the barrier increases by 0.32 kcal mol^{-1}. If one water molecule acts as hydrogen-bond donor and another one as hydrogen-bond acceptor, the barrier decreases by 1.14 kcal mol^{-1}. This decrease is almost a perfect balance between the 1.52 kcal mol^{-1} decrease and 0.32 kcal mol^{-1} increase in the barriers of the transition states with only one molecule acting as donor or acceptor, respectively, suggesting that the effect of individual water molecules might be additive. Attempts to study the reaction in

Table 3. Barriers of the HO• + CH_4 → H_2O + CH_3• Reaction with Various Levels of Solvation[a]

	# of waters	# of HB acceptors	# of HB donors	Barrier (kcal/mol)	k_{rel}
	0	0	0	5.04	1.0
	1	0	1	3.48	13.9
	1	1	0	5.25	0.7
	2	1	1	3.90	6.8
	3	1	2	2.37	90.2

[a] Energies calculated at the CCSD(T)/aug-cc-pVDZ level using geometries and harmonic frequencies obtained at the MP2/aug-cc-pVDZ level. The barriers correspond to enthalpies of activation at 0 K.

which two water molecules act as hydrogen-bond donors failed to locate the appropriate reagents conformation. In effect, even though a transition state in which two water molecules are acting as hydrogen-bond donors was located, optimizations of the OH radical with two water molecules acting as hydrogen-bond donors always led to the isomer in which one water molecule acts as hydrogen-bond donor and the other is an acceptor.

Finally, the barrier of the HO• + CH_4 → H_2O + CH_3• reaction, with two water molecules acting as hydrogen bond donors and one water molecule acting as hydrogen bond acceptor, was calculated. The decrease in the barrier for this solvation level with respect to the unsolvated system is 2.37 kcal mol^{-1} with a relative rate enhancement consistent with experimental results. Various attempts to include additional water molecules that are in direct contact with the HO• at the transition state led to solvation of any of the three water molecules forming the first solvation sphere, as expected.

Conclusions

The hypothesis that the hydroxyl radical reacts through a polar transition state is fully supported by the experimental and theoretical data obtained in this study. As a consequence of this polarization, hydrogen bonding to water stabilizes the transition state, resulting in larger rate constants when water is the solvent. This explanation also predicts that the *magnitude* of the solvent effect will decrease when electronegative substituents are present on the α-carbon of the substrate. The solvent effect is also significant when the substrate possesses electron-donating substituents, presumably because of competing inductive (electron-withdrawing) and resonance (electron-donating) effects.

These results extend the observations of Platz and co-workers,[8b,c] who argued for a highly polarized transition state for the addition of HO• to aromatic substrates to explain a nearly 2 orders of magnitude diminution in rate in acetonitrile compared to water. For these additions, calculations suggested that the hydroxyl moiety was nearly anionic in the transition state, providing a clear opportunity for water stabilization via hydrogen bonding. The effect water has on modulating HO• reactivity has enormous implications. In biological systems, this means that HO• may be less reactive in the hydrophobic regions of a cell than previously believed, i.e., hydroxyl radical does not necessarily react with the first molecule it encounters. Indeed, Nature may use this as a containment strategy when hydroxyl radical is produced naturally within cells.

On the basis of rate measurements in water, reactions of HO• were generally thought to be diffusion-controlled. Consequently, it has been assumed that attempts to protect against the damaging effects of HO• through the use of antioxidants are doomed to failure because a successful defense strategy requires a degree of selectivity to be demonstrated by the reactive radical. The radical must react preferentially with antioxidant, rather than the molecule or materials that one is trying to protect, in order for any defense system to be effective. Our results demonstrate that such selectivity might be attainable in a hydrophobic environment.

Finally, it should be stressed that the ideas presented herein provide a molecular-level understanding of hydroxyl radical reactivity both in solution and the gas phase.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0548129, CHE-0547543) and in part by the Macromolecular Interfaces with Life Sciences (MILES) Integrative Graduate Education and Research Traineeship (IGERT) of the National Science Foundation under Agreement No. DGE-0333378 in the form of fellowships to S.M. and S.Z.D.T. is a Cottrell Scholar of Research Corporation. We thank Profs. T. Daniel Crawford and Naushadalli K. Suleman for helpful discussions.

Supporting Information Available: Discussion of the role of •CH_2CN and PyrS• in these experiments, details of the product studies and competition experiments, representative transient traces, k_{obs} versus concentration plots, the absolute energies and optimized geometries of all calculated structures, and the complete Gaussian 03 citation. This material is available free of charge via the Internet at http://pubs.acs.org.

JA903856T