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Fluorophobic Acceleration of Diels−Alder Reactions

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It is now well established that the rates of certain Diels−Alder reactions in aqueous media show dramatic accelerations relative to those in organic solvents.[1] Over the years, these have been alternatively ascribed to hydrophobic association of the reacting partners,[1a] micellar catalysis,[2] solvophobicity,[3] high internal solvent pressure,[2c] cohesive energy density,[4] solvent polarity,[5] and hydrogen bonding[6] (Lewis acid type catalysis by association to a more polarized transition state). In nonaqueous media, however, solvent effects on Diels−Alder reactions are small, a typical characteristic of reactions with isopolar transition states.[7] Theoretical studies have concluded that a combination of enforced hydrophobic interactions and Lewis acid type catalysis are the main contributors to the rate enhancement in water.[8] The hydrophobic component of the rate enhancement is derived from the removal of solvent accessible nonpolar surface area in the transition state. We hypothesized that for such reactions having large negative volumes of activation,[9] the solvophobic properties of other liquids might lead to rate enhancements similar to those observed in water.

Recently fluorous (highly fluorinated) solvents have been employed in catalysis,[10a] molecular self-assembly,[11] combinatorial chemistry,[10b] and organic separation methodology.[12] Fluorocarbon solvents show poor miscibility and lower solvating power than normally associated with nonpolar organic liquids ("fluorophobic effect"). Hildebrand and Scott[13] have accounted for such properties based on a solubility parameter δ, the square root of the cohesive energy density of a solvent. Fluorous liquids are characterized by low values of δ, signifying exceedingly low propensities for intermolecular interactions. Thus these form an independent phase in most organic solvents and in water. At first glance, these seemed appropriate solvents to test our hypothesis of fluorophobic acceleration.

We wish to report here that certain Diels−Alder reactions show dramatic rate accelerations in fluorous solvents with enhancements approaching those in water.[14] The kinetics of the Diels−Alder reaction of dienophile *N*-ethylmaleimide (**2**; 1 mM) and 9-hydroxymethylanthracene (**1**; 0.03 mM) was followed at 45 °C by disappearance of **1** at 382 nm in various solvents. The bimolecular rate constants and the saturation solubilities of **1** in various solvents are reported in Table 1. The reactions in perfluorohexane and FC-75 were conducted with 2% v/v isooctane to solubilize **1** and to maintain stable solutions. It is clear that the rate of the reaction is fastest in water and slowest in organic solvents. The reaction shows significant rate enhancements in water and fluorous media (perfluorohexane and FC-75) over traditional organic solvents. Indeed, the rates in fluorous solvents are only a factor of ~4.2 ($\Delta\Delta G^{\ddagger} \sim +0.91$ kcal/mol at 45 °C) slower than those in water. In fluorinated solvents where solubility of the reactants is not compromised, the rate acceleration is no longer observed. For instance, in perfluorobenzene and trifluoroethanol, the observed reaction rates are in the hydrocarbon regime. Thus, an inverse relationship exists between the observed rates and saturating solubility of reactant **1**.Table 1 shows that the fluorous liquids and water have the lowest solvating abilities for the starting materials. These data suggest that the thermodynamic chemical potentials of the reactants and the transition state assume high values in these solvents.[15] Given that roughly 25% of the surface area of 9-hydroxymethylanthracene (the more fluorophobic solute) is removed from the solvent in the transition state,[16] the chemical potential of the transition state is likely raised to a lesser extent in water and in the fluorous solvents leading to enhanced rates. The rate effect in water is more pronounced due to presence of hydrogen bonding functionalities.[17,18] Breslow et al. have demonstrated a relationship between reaction rate and the solvophobic surface area that becomes inaccessible in the transition state.[19]

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[16] Solvent exposed surface areas were estimated using AM1 minimized rigid geometries for the reactants and the transition state with a spherical probe of radius 1.4 Å. The transition state structure was calculated using the semiempirical AM1 package incorporated in SPARTAN Pro v1.2 from Wavefunction, Inc.

[17] It is unlikely that hydrogen bonding is the primary reason for the observed rate enhancements in water given that trifluoroethanol with its strong hydrogen bond donating capabilities does not enhance the reaction rate in a similar manner.

[18] Rideout et al. have suggested that the lower rates in methanol and acetonitrile (compared to isooctane or *n*-hexane) are due to less effective hydrogen bonding between the reactants in the transition state.[1a]

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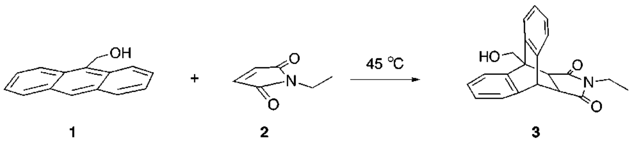
Table 1. Rate Constants for Diels−Alder Reaction between 9-Hydroxymethylanthracene and *N*-Ethylmaleimide at 45 °C and Saturation Solubilites of **1**

solvent	k_2[a]	k_{rel}	δ[b]	$[\mathbf{1}]_s$ (mM)[c]
perfluorohexane[d]	5345 ± 308	49.5	5.9	<0.005
FC-75[d,e]	4562 ± 404	42.2	6.1[f]	<0.005
n-hexane	776 ± 80	7.2	7.3	1.24 ± 0.1
di-*n*-butyl ether	245 ± 16	2.3	7.6[g]	20.9 ± 0.5
perfluorobenzene	152 ± 26	1.4	8.1	11.22 ± 0.4
acetonitrile	108 ± 10	1.0	11.8	29.5 ± 0.7
methanol	337 ± 60	3.1	14.3	29.9 ± 1.3
trifluoroethanol	841 ± 114	7.8		18.1 ± 1.9
water	22300 ± 720	206	23.4	0.027 ± 0.005

[a] Second-order rate constants ($\times 10^5$ $M^{-1}\cdot s^{-1}$). Data are the averages of at least three sets of triplicate runs.[22] Uncertainty represents 2 standard deviations. Initial conditions were 9-hydroxymethylanthracene (0.015−0.035 mM) and *N*-ethylmaleimide (0.3−1.4 mM). [b] Solubility parameter $\delta = (\Delta E^v/v)^{1/2}$ in $(\text{cal}\cdot\text{cm}^{-3})^{1/2}$, where ΔE^v and v are the molar energy of vaporization and molal volume of the pure solvent, respectively. [c] Saturation solubilities of **1** as determined by UV−vis spectroscopy at 25 °C. [d] Reactions contained 2% isooctane (v/v) for solubilizing 9-anthracenecarbinol and maintaining stable solutions. [e] FC-75 is a perfluoro cyclic ether (CAS registry no. 335-36-4; perfluoro-2-*n*-butyl-THF) with molecular formula $C_8F_{16}O$. [f] Estimated from data in ref 23. [g] Estimated from data in ref 24.

Scheme 1



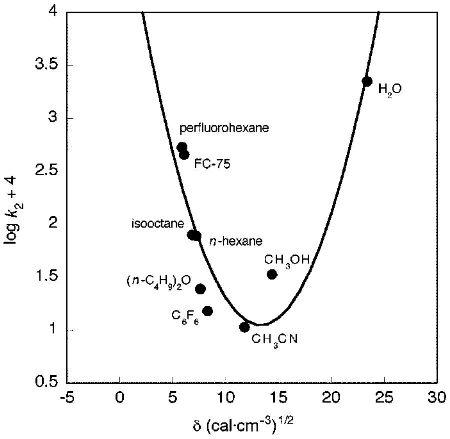


Figure 1. Semilogarithmic plot of log *k* (for reaction of **1** and **2**) with Hildebrand solubility parameter δ for a total of 9 solvents ($r = 0.90$).[25]

Our results are in agreement with these findings.[20] Figure 1 shows the parabolic dependence of the bimolecular rate constant with Hildebrand's solubility parameter δ in a semilogarithmic plot. Strictly, such correlations are more relevant for nonpolar solvents and solutes only;[21] however, the plot serves to highlight higher reaction rates on both ends of the Hildebrand solubility parameter scale.

Jorgensen and co-workers have argued that since the hydrophobic surface area that becomes inaccessible during Diels−Alder additions of different dienophiles to a given diene is roughly equal, solvophobic effects in principle should contribute a constant factor to the overall rate enhancement.[8c] Indeed, their investigations using Monte Carlo and ab initio methods have pointed to a constant factor of ~10 ($\Delta\Delta G^{\ddagger} \sim 1.5$ kcal/mol) in the case of cyclopentadiene reacting with various dienophiles. The remainder of the rate enhancement has been attributed to enhanced polarization in the transition state resulting in stability from strengthening of H-bonds with water.[8a,b] Since the fluorous solvents used in these studies have no hydrogen bond donating capability, the lower rate enhancements from those seen in water are readily explained. The 10−50-fold rate enhancement ($\Delta\Delta G^{\ddagger} \sim 1.4$−$2.5$ kcal/mol at 45 °C) observed in these solvents is within the expected range anticipated on the basis of solvophobicity alone.

In summary, we have demonstrated that fluorous media accelerate reactions with large negative volumes of activation despite being extremely nonpolar and having low internal pressures and cohesive energy densities. A solvophobic mechanism is inferred as solvent exposed surface area is removed upon going from the reactants to the transition state. While current parametric models do not allow accurate calculation of Gibbs energies of solvation in fluorous liquids,[26] mechanistic investigations should lead to a better understanding of solvation energetics in these systems and decouple the entropic and enthalpic contributions to the rate enhancement. With this study, we envision the introduction of a new reaction medium for the simultaneous execution and acceleration of appropriately chosen organic reactions.

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Supporting Information Available: HPLC analysis of product formation, data fitting procedures, and structural characterization of Diels−Alder adduct **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In the absence of solvophobic components, reaction rates in *n*-hexane and perfluorohexane are similar (e.g. Diels−Alder reaction of 1,4-naphthoquinone and cyclopentadiene: Myers, K. E.; Kumar, K. Unpublished observations).

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