

## Quantitative Antihydrophobic Effects as Probes for Transition State Structures. 2. Diels–Alder Reactions

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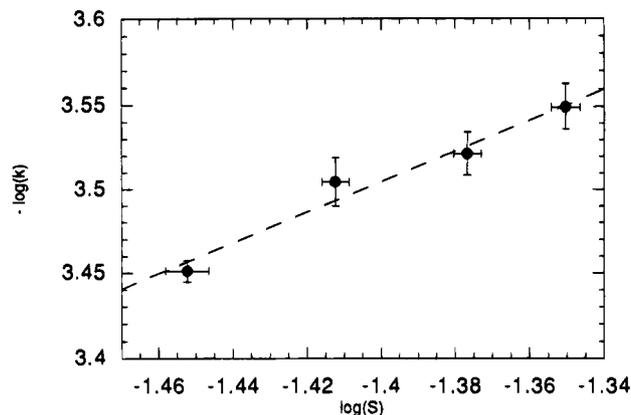
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In a previous paper<sup>1</sup> we described the use of antihydrophobic alcohol cosolvents in water to establish quantitative relationships between solubilities and rates in the benzoin condensation and in some displacement reactions. The idea, in brief, is that a small amount of an alcohol cosolvent will not interfere with the ability of water to solvate ionic transition states (activated complexes), as we demonstrated,<sup>1</sup> but that the cosolvent will be recruited into the transition state to help solvate the hydrophobic portions. The induced solubility perturbations reflect the solvation of the reactants by the cosolvent. We showed that the  $\delta\Delta G^\circ$  induced by such antihydrophobic cosolvation is proportional to the amount of hydrophobic surface that is exposed to water, and we present further evidence for this here. The rate effects caused by the cosolvents reflect the difference in solvation of reactants and transition states.

The  $\delta\Delta G^\circ$  for reactants and products can be evaluated simply by measuring their increased solubility induced by the cosolvents. The effects of the cosolvents on reaction rates can be used to deduce the amount of hydrophobic surface that becomes buried as reactants proceed to the transition states. The relationship is expressed in eq 1, where  $h$  describes the fractional loss of solvent-accessible hydrophobic surface in the transition state (ts).<sup>1,2</sup>

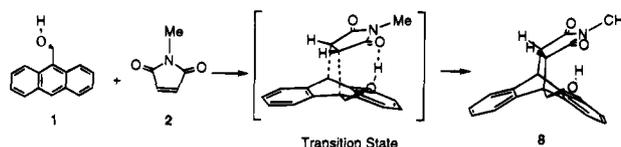
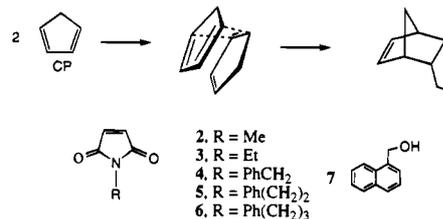
$$\log(k_t/k) = h \sum \log(S/S_0) \quad (1)$$

In this paper we extend this study to a series of Diels–Alder reactions. The simplest is the dimerization of 1,3-cyclopentadiene (CP), whose rate is accelerated in water.<sup>3</sup> We have measured the solubility of CP in water and in 0.5/10, 1/10, and 1.5/10 (v/v) ethanol in water at 25 °C and its dimerization rates under the same conditions. The solubilities and the second-order rate of disappearance of CP by dimerization were determined by HPLC assay (C-18 reverse phase) of the saturated solution, and all measurements were repeated at least five times. The data are plotted according to a transform of eq 1 in Figure 1. From the slope,  $2h$  has a value of  $0.92 \pm 0.12$ , indicating that  $46 \pm 6\%$  of each CP is no longer solvent accessible in the ts. This presumably indicates complete occlusion of one face of each CP by the other, with additional shielding by the unshown hydrogens, a reasonable ts for endo addition. The errors are large relative to those in our other studies using this technique since here a 15% ethanol cosolvent induces a solubility increase of only 25% and a rate decrease of only 20%. The rate and solubility values themselves are accurate (standard error of the mean)<sup>5</sup> to 2% and 1%, respectively.



**Figure 1.** Plot of  $\log(S)$  for the solubility of cyclopentadiene (M) vs  $-\log(k)$  of the second-order rate constant ( $M^{-1} s^{-1}$ ) for Diels–Alder dimerization of cyclopentadiene in water and in ethanol/water solutions of 5/100, 10/100, and 15/100 v/v at 25 °C. The slope of the line is  $0.92 \pm 0.12$  and corresponds to  $2h$  of eq 1 (which can be rearranged to  $2h \log S = C - \log k$ ). The superimposed error bars are  $\pm 1$  standard error of the mean,<sup>5</sup> considering all the data (eight solubility determinations and 5–10 rate determinations at each solvent composition). The value of  $2h$  is  $\pm 1$  standard deviation (of the mean values of the data from the calculated line). As discussed in the text, the errors are larger than in our other studies using this technique, since the cosolvent effects on rates and solubilities are relatively small here.

As previously,<sup>1</sup> the ambiguity here has to do with the amount of hydrophobic surface contributed by the faces and the edge of CP, respectively, and the extent to which a face-to-face ts would interfere with edge solvation as well as face solvation. These are matters to be addressed in further developing this novel method for determining the geometry of transition states. We have calculated the transition state geometry for CP dimerization using the AM1 program incorporated in the SPARTAN package,<sup>6</sup> and the solvent accessible surface at a 3.0 Å contour from the van der Waals surface using MacroModel.<sup>7</sup> This predicts 38% coverage of each CP, which is on the edge of our estimated range above.



The reactions between 9-(hydroxymethyl)anthracene (1) and various N-substituted maleimides 2–6 are also accelerated by hydrophobic effects.<sup>8–10</sup> We examined the solubility of 1–6 and of 1-(hydroxymethyl)naphthalene (7) and some other hydrocarbon derivatives (9–12) in water ( $S_0$ ) and ( $S$ ) in dilute

(6) Spartan, version 3.0; Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92715.

(7) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGust, F.; Hasel, W. MacroModel, version 3.5; Department of Chemistry, Columbia University, New York, NY 10027.

(8) Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(9) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.

(10) Breslow, R.; Rizzo, C. *J. Am. Chem. Soc.* **1991**, *113*, 4340–4341.

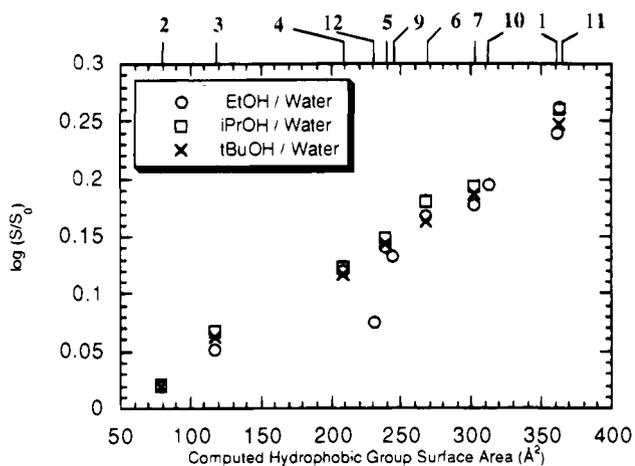
(1) Breslow, R.; Connors, R. *J. Am. Chem. Soc.* **1995**, *117*, 6601–6602.

(2) When two identical reactants are involved, as in cyclopentadiene dimerization,  $h$  is simply the fractional loss of exposed surface. When the reactants are different, as in the other Diels–Alder reactions of this paper,  $h$  is more complex, since the more hydrophobic reactant contributes more to its value. An example is given here for the weakly hydrophobic N-methylmaleimide and the strongly hydrophobic anthracene-9-carbinol.

(3) Sangwan, N. K.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223–1227. Our second-order rate constant in water solution is 46 times lower than that reported in their paper; their reported value is anomalously high compared with the values in other solvents and is probably in error (cf. ref 4).

(4) Jorgensen et al. (Jorgensen, W. L.; Blake, J. F.; Lim, D.; Severance, D. L. *J. Chem. Soc., Faraday Trans.* **1990**, 1727–1732) discuss the likelihood of this error and cite a private communication from L. K. Steffen and J. Gajewski with a value for the acceleration of CP dimerization in water that is in agreement with our own observed rate constant.

(5) This error measure is shown at the urging of a referee and an editor. It is smaller than the standard deviation by a factor of  $N^{1/2}$ , where  $N$  is the number of independent measurements of a quantity.



**Figure 2.** Plot of  $\log(S/S_0)$  for compounds 1–7 and benzene (9), naphthalene (10), biphenyl (11), and cyclopentadiene (12) in water ( $S_0$ ) and ( $S$ ) in water with 1/10 v/v of ethanol (O), of 2-propanol (□), and *tert*-butyl alcohol (×) at 25 °C, vs the calculated solvent accessible surface area of the R groups in 2–6 and of the hydrocarbon segments of 1 and 7 and of 9–12. The slope of the plot from ethanol–water has a value of  $0.00080 \text{ \AA}^{-2}$ .

aqueous solutions (1/10 v/v in water) of ethanol, 2-propanol, and *tert*-butyl alcohol by UV assay of the saturated solutions. We also computed the geometries of these compounds and their water accessible surface areas using the MM3 force field in Macromodel.<sup>7</sup> As Figure 2 shows,<sup>11</sup> there is a clear linear correlation between the  $\log(S/S_0)$ , which is proportional to the cosolvent perturbation  $\delta\Delta G^\circ$ , and the calculated water accessible surface area of the R groups in the maleimides and the hydrocarbon groups in 1, 7, and 9–12. Since the solubility of 2, the *N*-methylmaleimide, is so little perturbed by our cosolvents, we neglect the maleimide ring itself in calculating the hydrophobic surface.

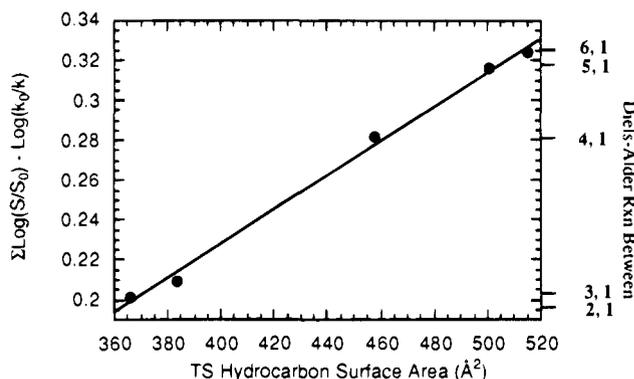
All three alcohols are equally effective,<sup>11</sup> at 1/10 v/v in water, in slowing a Diels–Alder addition reaction of a particular maleimide in the set 2–6 with 1 (but *different* maleimides respond to different extents, as described below). For *N*-methylmaleimide (2) the reaction with 1 is 17% slower in 1/10 ethanol in water, so  $\log(k_0/k)$  is  $0.08 \pm 0.01$ . For the same solvent,  $\log(S/S_0)$  is  $0.26 \pm 0.01$  for 1 and only  $0.02 \pm 0.001$  for 2. Thus  $h$  has a value of 0.29. Since the contribution of 2 to the  $\delta\Delta G^\circ$  is only 8% that of 1, this means that a little over one-quarter of the surface of 1 has been covered by the maleimide in the transition state. This is a reasonable picture for this reaction.

$$\delta\Delta G^\circ_{\text{ts}} = 2.3RT(\sum \log(S/S_0)_{\text{reactants}} - \log(k_0/k)) \quad (2)$$

An equivalent treatment is that of eq 2. This says that the ability of the cosolvent to lower the free energy of the transition state can be calculated from the rate and solubility effects. From eq 1 of the previous paper,<sup>1</sup> this can be used to derive a value of  $\rho_H$ , the surface area ratio for the transition state relative to starting materials. The value from the above data is 0.71, another way of expressing the 29% loss of available surface.

The final product has more accessible surface than the transition state. The adduct 8 between 1 and 2 has a  $\log(S/S_0)$  of 0.233 in 1/10 v/v ethanol in water compared with water alone, corresponding to a solvent accessible hydrophobic surface area 90% that of 1. Some of this change relative to the ca. 70% in the transition state may reflect an increased hydrophobic contribution from the now saturated maleimide group, but it also reflects the more open structure of 8 compared with the transition state.

(11) The similar effects of 1/10 ethanol, 2-propanol, and *tert*-butyl alcohol are explained when the molarity of each solvent is multiplied by the calculated<sup>7</sup> water accessible area of the solvent molecules themselves. The resulting total water accessible hydrophobic surface areas of the three cosolvents used in this study are almost the same, and their effects on substrate solubility are similar.



**Figure 3.** Correlation of the calculated hydrophobic surface areas of the Diels–Alder transition states—with lowest energy maximum packing of hydrocarbon segments together—with their free energies of solvation using 1/10 v/v ethanol vs water. As described, the transition state solvent exposed surface areas were calculated using the AM1 method for geometries and Macromodel for solvent accessible surface. The free energies of transition state solvation were obtained from eq 2. The line has a slope of  $0.00086 \text{ \AA}^{-2}$ .

We have calculated the transition state geometries for reactions of 1 with 2–6 using the AM1 program incorporated in the SPARTAN package,<sup>6</sup> and related them to the perturbable hydrophobic surface area in the transition states for the reactions, from eq 2.

The results are plotted in Figure 3. There is a good correlation for transition states calculated with geometries that allow the hydrophobic components of the maleimides 2–6 to pack onto 1. Furthermore, the slope of the line ( $0.00086 \text{ \AA}^{-2}$ ) is essentially the same as that ( $0.00080 \text{ \AA}^{-2}$ ) from Figure 2, for substrate solubility perturbation vs calculated area. This indicates that solvation effects on hydrophobic surfaces in the transition states are similar to those in normal molecules, at least in this case.

The relatively simple model used does not make distinctions among hydrophobic surfaces of various types, e.g., aromatic and aliphatic. In the aromatic series, no distinction has been made between edge and face, and they are not likely to be equivalent. Furthermore, some of the correlations described here are with calculated geometries, subject to the uncertainties of the calculations. However, our conclusions that a full face of each CP ring is covered in the ts for dimerization and that about 25% of the anthracene surface is covered in the ts for *N*-methylmaleimide addition are direct results of our solubility and rate measurements and are quite reasonable.

More work will be needed to establish the fine points, and limitations, of this approach to the determination of transition state structures, but the early results are promising.<sup>12–14</sup>

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**Supporting Information Available:** Experimental details (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfiche version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) There is a huge literature (e.g., ref 13, 14) on solvent effects on reaction rates, but we are not aware of any other work that relates solubility effects to rate effects as we have done here and previously (ref 1).

(13) For a study of the effect of alcohol cosolvents on some Diels–Alder reaction rates in water, cf.: (a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J. B. *J. Am. Chem. Soc.* **1992**, *114*, 5440.

(14) For a review of some relevant work and proposals of Engberts on rate effects of cosolvents, see: Blokzijl, W.; Engberts, J. B. In *Structure and Reactivity in Aqueous Solution*; Cramer, C. J., Truhlar, D. G., Eds.; ACS Symposium Series 568; American Chemical Society: Washington, DC, 1994; Chapter 21.