

## Quantitative Antihydrophobic Effects as Probes for Transition State Structures. 1. Benzoin Condensation and Displacement Reactions

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Received March 3, 1995

With prohydrophobic agents such as LiCl, and antihydrophobic agents such as LiClO<sub>4</sub> or guanidinium chloride, one can diagnose hydrophobic effects in the transition states of Diels–Alder reactions and the benzoin condensation.<sup>1,2</sup> There is a correlation of some antihydrophobic effects on solubilities and binding constants with calculated hydrophobic surface areas.<sup>3</sup> We now find that we can use the quantitative aspects of antihydrophobic effects to estimate the amount of hydrophobic surface that is solvent-accessible in the transition states (TSs) of various reactions. This furnishes a picture of the geometries of those transition states that is not easily available by other methods.

In order to minimize ionic effects on the rates, we use neutral antihydrophobic agents such as ethanol in limited concentrations in water. Ethanol increases the solubility of a hydrophobic substrate such as benzaldehyde, lowering its free energy (decreasing its activity coefficient) by assisting solvation.<sup>4</sup> One expects that the magnitude of the effect, in free energy terms, should be proportional to the amount of hydrophobic surface in the substrate (eq 1), and that is what we find.

$$\delta\Delta G^\circ(2) = \rho_H \delta\Delta G^\circ(1) \quad (1)$$

$$\text{Therefore, } \log(S/S_0)_2 = \rho_H \log(S/S_0)_1 \quad (2)$$

where  $\rho_H$  is the hydrophobic surface area ratio for the two substrates of similar type,  $S_0$  is the solubility in water, and  $S$  is the solubility in the presence of a cosolvent.

As the simplest test, the solubility of benzamide in water at 25 °C increases by 1.46-fold with 10 vol % 1,4-butanediol, but that of *N*-phenylbenzamide increases by 2.14-fold (Table 1). Thus,  $\rho_H$  is 2.0, the ratio for the two phenyl groups held apart by the *s-trans* amide group. With 20% v/v butanediol, the ratio is 1.95. By contrast, benzoin (**1**) has only 150% of the exposed hydrophobic surface area of a benzaldehyde molecule by this test, consistent with overlap of ~50% of one face of each phenyl group by the other, since they are not held apart. Other examples are listed in Table 1.

We have established that the rate of the displacement reaction of hydroxylamine with sodium iodoacetate is unaffected by ethanol up to 20% v/v (Table 2). Similarly, there is no effect on the rate of reaction of sodium thiomethoxide with sodium chloroacetate (Table 2). Thus, as expected, such limited amounts of a less polar solvent do not significantly affect the ability of water to solvate ionic transition states. With hydrophobic reactants, the situation is different. The cosolvents can markedly increase hydrocarbon solubilities in water, so the free energies of starting materials, of products, and of transition states are lowered by such cosolvents (Figure 1). The starting material and product effects are seen in solubilities, while the transition state effects are seen in the rates.

For example, in the benzoin condensation (Figure 2), a benzaldehyde cyanohydrin anion reacts with a benzaldehyde

**Table 1.** Relative Solubilities of Various Solutes at 25 °C in Water and with 10 and 20% 1,4-Butanediol Added, and Their Hydrophobic Surface Areas,  $\rho_H$ , Relative to That of Benzaldehyde Calculated from Eq 2

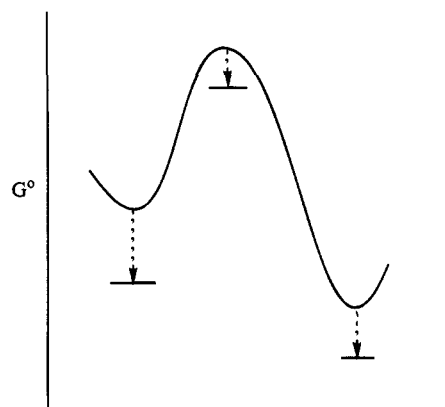
solute	butanediol, vol %	$S/S_0^a$	$\rho_H$
benzaldehyde	10	1.51	1.000
	20	2.22	1.000
benzene	10	1.47	0.93
	20	1.94	0.83
benzamide	10	1.46	0.92
	20	2.12	0.94
<i>p</i> -tolualdehyde	10	1.56	1.08
	20	2.46	1.13
3,5-dimethylbenzaldehyde	10	1.77	1.39
	20	3.11	1.42
2-naphthaldehyde	10	2.00	1.68
	20	3.52	1.58
benzoin	10	1.90	1.56
	20	3.37	1.52
<i>N</i> -phenylbenzamide	10	2.14	1.84
	20	4.31	1.83

<sup>a</sup> Substrate solubility in the mixed solvent divided by that in water.

**Table 2.** Relative Rate Constants for Some Displacement Reactions in Water and with Added Ethanol at 25 °C, and the Values of  $h$  Calculated from Eq 3 and from the Solubility Ratio ( $S/S_0$ ) for Benzaldehyde

nucleophile	electrophile	EtOH, vol %	$k_0/k^a$	$h^b$
H <sub>2</sub> N–OH	sodium iodoacetate	20	1.00	0.00
		10	0.97	–0.05
CH <sub>3</sub> S–Na	sodium chloroacetate	20	0.88	–0.10
		10	1.09	0.16
imidazole	sodium iodoacetate	20	1.32	0.23 <sup>c</sup>
		10	1.09	0.16
PhS <sup>–</sup> Li <sup>+</sup>	PhCH <sub>2</sub> Cl	20	1.08	0.07
		10	0.98	–0.04
PhS <sup>–</sup> Na <sup>+</sup>	sodium 4-(chloromethyl)benzoate	20	0.98	–0.02
		10	1.26	0.43
Ph–NHMe	sodium 4-(chloromethyl)benzoate	20	1.59	0.38

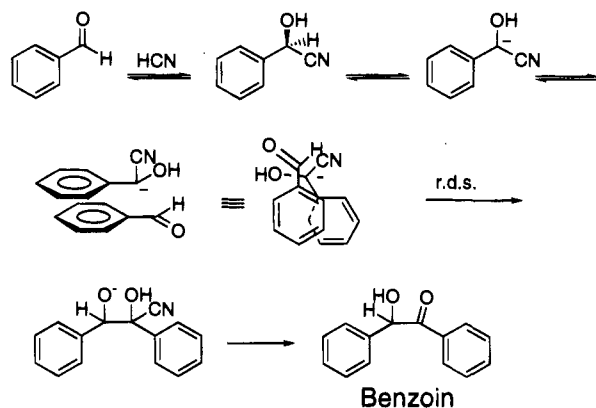
<sup>a</sup> Rate constant in water divided by the rate constant in the mixed solvent. <sup>b</sup> Expressed as a fraction of the hydrophobic surface of benzaldehyde. Negative values mean that ethanol lowers the free energy of the transition state *more* than that of the reactants, speeding the reaction. The small negative effects in this table are essentially zero. <sup>c</sup> Expressed as the equivalent amount of benzaldehyde hydrophobicity, not a physically meaningful comparison in this case.



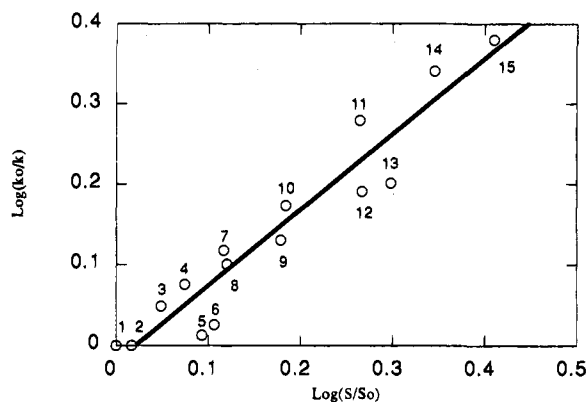
**Figure 1.** Lowering of the free energies of reactants, products, and transition state in water by an added antihydrophobic cosolvent.

molecule in the transition state, and our previous work<sup>1</sup> indicated that there is some overlap of the two phenyl groups. The free energy of the starting materials will be lowered by the effect of added ethanol on two exposed phenyl groups; if they were also fully exposed to solvent in the transition state, it would be

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**Figure 2.** Benzoin condensation, with partially overlapping face-to-face phenyl groups.



**Figure 3.** Plot of the effect of cosolvents (vol %) on the solubility of benzaldehyde in water at 25 °C versus the effect on the rate of the benzoin condensation in water at 65 °C, according to eq 3. The points are numbered: 1, water; 2, 5% ethylene glycol; 3, 10% ethylene glycol; 4, 15% ethylene glycol; 5, 5% *n*-propanol; 6, 5% 1,4-butanediol; 7, 10% ethanol; 8, 20% ethylene glycol; 9, 10% 1,4-butanediol; 10, 10% *n*-propanol; 11, 20% ethanol; 12, 15% 1,4-butanediol; 13, 15% *n*-propanol; 14, 20% 1,4-butanediol; 15, 20% *n*-propanol.

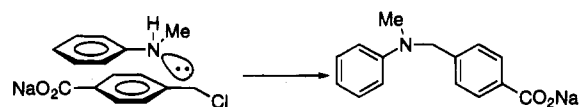
lowered by the same amount, and there would be no rate effect. However, we see that the rate is slowed, indicating that some hydrophobic surface is hidden in the TS. Equation 3 shows the expected relationship:

$$\log(k_0/k) = h \sum \log(S/S_0) \quad (3)$$

where  $k_0$  is the rate constant in water,  $k$  is the rate constant in the presence of the antihydrophobic agent, the starting material solubility perturbations are summed over all reactants, and  $h$  is a function of the amount of hydrophobic surface that becomes inaccessible to solvent in the transition state.

In the benzoin condensation, both reactants carry a phenyl group, and  $h$  is the fraction of the total hydrophobic surface that becomes covered in the transition state. If the transition state had no exposed hydrophobic surface at all, the decrease of free energy of two reactants would make the  $\log(k_0/k)$  show twice the effect of the  $\log(S/S_0)$ .

In Figure 3, we plot the effect of various concentrations of different alcohol additives on benzaldehyde solubility (at 25 °C) and on the rate constant for the benzoin condensation (at 65 °C). It is clear that eq 3 is followed. However, to derive  $h$ , we need data at the same temperature, and since we had trouble determining benzaldehyde solubility at 65 °C, we used benzamide, which is similar (Table 1). With 10% ethanol and 10% 1,4-butanediol, we obtained  $S/S_0$  values of 2.30 and 2.54, respectively, which taken with their rate effects correspond to  $h$  of 0.16, while with 20% ethanol and 10% propanol, we obtained  $S/S_0$  of 5.33 and 3.00, respectively, leading to  $h$  values



**Figure 4.** Displacement reaction showing considerable packing of the phenyl groups in the transition state.

of 0.19. If each face of a benzene ring contributes 40% of its hydrophobic surface, with 20% for the edge, this  $h$  would correspond to 40–42% coverage of a face of each phenyl group in the TS. The carbanion orbital overlaps  $\pi^*$  of the carbonyl by a back-side approach (Figure 2), so the phenyls are only partially occluded.

We have examined some displacement reactions at 25 °C involving a phenyl group on each reactant (Figure 4). For instance, the reaction of *N*-methylaniline with 4-(chloromethyl)benzoic acid shows an  $h$  of 0.36 (taking benzaldehyde solubility data again as the reference) (Table 2), showing that the two phenyl groups essentially occlude each other in the transition state. This is expected for overlap of the  $sp^3$  hybrid orbital of the nucleophile with the  $\sigma^*$  orbital of the halide, which aligns the phenyl groups.

However, some related reactions show surprising effects. The displacement reaction of sodium thiophenoxide with 4-(chloromethyl)benzoic acid shows no effect (Table 2) on 10 or 20% ethanol, indicating no shielding of the phenyl groups in the TS. Similarly, the displacement reaction of lithium thiophenoxide with benzyl chloride shows an  $h$  of only 7–16% (Table 2), indicating almost no shielding of the phenyls. By increasing the concentration of the nucleophile, we saw that this latter reaction shows second-order kinetics, so it is not a simple  $S_N1$  reaction.

A nonstacking geometry may indicate that the nucleophile attacks an intimate ion pair,<sup>5</sup> or more likely there may be a single-electron transfer mechanism.<sup>6</sup> Alternatively, the thiophenoxide ion might perform an  $S_N2$  displacement using electrons in the plane of its ring, not perpendicular to it, so the phenyls do not stack face-to-face. In any case, the distinction in the TS geometries for displacement by an amine and by a thiolate is revealed by our method and is an important mechanistic fact.

Shielding is an obvious way to diminish the exposed hydrophobic surface in the TS, but there may be another factor to be considered. The displacement reaction by imidazole on sodium iodoacetate shows some slowing when alcohol is added (Table 2), in contrast to the absence of an effect with nucleophilic hydroxylamine or thiomethoxide anion. It seems unlikely that the imidazole ring becomes sterically shielded, but it does acquire a delocalized positive charge in the TS. This should diminish the hydrophobic energy and thus the ability of ethanol to lower it.

We believe that this new quantitative approach to transition state structures will have wide application. We have also applied it in Diels–Alder reactions.<sup>7</sup> This technique tells us about the geometries of transition states in *water* solvent, but the hydrophobic accelerations of these reactions normally involve only a few kilocalories. Thus the relative transition state energies are similar to those in other solvents, and presumably the geometries as well. This will be especially true in cases, such as those in the present paper, in which the geometry of the reacting centers dictates the geometries of the rigidly attached hydrophobic groups. This is presumably why the benzoin condensation used a geometry that did not maximize the hydrophobic shielding.

**Acknowledgment.** This work was supported by the NIH and the ONR.

JA9507168

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(7) Breslow, R.; Zhu, Z., unpublished work.