Antihydrophobic Cosolvent Effects in Organic Displacement Reactions
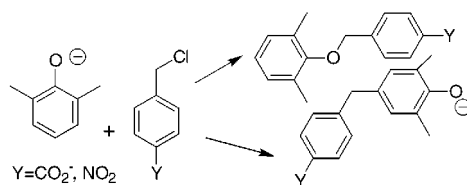
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ABSTRACT

Rates of reactions in water can be modified by the presence of antihydrophobic cosolvents such as ethanol and DMSO, which lower the energies of nonpolar surfaces. The rate effects reflect changes both in the solvation of nonpolar surfaces and also in the solvation of polar groups. The effects have been sorted out for some displacement reactions, revealing the geometry of an interesting branching reaction whose two paths show different antihydrophobic effects.

Diels−Alder reactions in water solution can be accelerated[1] and made more selective[2,3] by the hydrophobic effect, the tendency of hydrocarbon surfaces to avoid a water interface by association with other hydrocarbons.[4] The effect is increased by salts such as LiCl that cause electrostriction of the water, increasing the energy needed to produce a cavity that can accommodate a dissolved hydrocarbon. The hydrophobic effect is decreased by some solutes such as urea, guanidinium cation, and perchlorate anion that we have termed *antihydrophobic agents*.[5] In water they act to denature proteins by decreasing the energy cost of exposing hydrocarbon side chains to the water solvent and increase the solubility of hydrocarbons in water.

We have shown that the principal source of the antihydrophobic effect of the denaturants is to assist hydrocarbon solvation in water, presumably by bridging between the hydrocarbon and the water.[6]

We saw that the benzoin condensation in water was accelerated by the prohydrophobic solute LiCl but slowed by the antihydrophobic solute lithium perchlorate.[7] This indicated that the transition state for the reaction had some overlap of the two phenyl groups in the transition state. Ethanol and other alcohols also increase the solubility of hydrocarbons in water by helping to solvate them. For quantitative studies we decided that modest amounts of such cosolvents would be preferable to antihydrophobic salts such as guanidinium chloride, where salt effects might be a problem.

We have described the use of antihydrophobic cosolvents such as ethanol to determine the detailed geometry of transition states in some organic reactions.[8−10] We showed that the $\delta\Delta G°$ value for hydrophobic molecules, the change in standard free energy when small amounts of ethanol or other alcohols were added to the water solvent, was proportional to the amount of exposed similar hydrophobic surface. In particular, the increased solubility in water when small amounts of ethanol were added, expressed as $\delta\Delta G°$, was twice as large for compounds with two exposed phenyl rings as for compounds with only one phenyl group. When the phenyl rings were partially eclipsed, as in benzoin or in (Z)-1,2-diphenyloxirane, the $\delta\Delta G°$ value reflected the frac-

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(2) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901.
(3) Grieco, P.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897 and later work.
(4) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317.
(5) Breslow, R.; Halfon, S. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 6916.
(6) Breslow, R.; Guo, T. S. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 167.

(7) Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 1596.
(8) Breslow, R.; Connors, R. *J. Am. Chem. Soc.* **1995**, *117*, 6601.
(9) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923.
(10) Breslow, R.; Connors, R.; Zhu, Z. *Pure Appl. Chem.* **1996**, *68*, 1527.

tion of the two phenyl rings that mutually overlapped and was thus not exposed to solvent.

If the transition state (TS) of a reaction has the same amount of exposed hydrophobic surface as occurs in the starting materials, and if the cosolvent has no effect other than to help solvate hydrophobic surfaces, then the rate of the reaction should be unaffected by adding the cosolvent to the water solution. That is, the $\Delta G°$ value of the TS will be lowered to the same extent as that of the starting materials, and so the activation energy will be unchanged, as will the rate. If the TS is less hydrophobic than the starting materials, for example if some hydrophobic surface is hidden in the TS, the cosolvent should slow the reaction by an amount corresponding to the difference in $\delta\Delta G°$ for starting materials and TS. If the TS is more hydrophobic than the starting materials, the reaction will be faster with the added cosolvent. The detailed mathematical treatment of the effects has been published elsewhere.[10]

We showed[10] that the addition of ethanol to water solvent slowed the Diels−Alder dimerization of 1,3-cyclopentadiene, the Diels−Alder addition of maleimides to 9-(hydroxy-methyl)anthracene, and the cyanide-catalyzed benzoin condensation of benzaldehyde. From the detailed results, the deduced geometries of the TSs for these reactions were consistent with expectation and with quantum mechanical calculations.

Displacement Reactions. We also described some studies of the effect of ethanol cosolvent on displacement reactions in water, such as the reaction of *N*-methylaniline and of phenoxide ion with *p*-carboxybenzyl chloride. The aniline nucleophile is of course using electrons that are part of the π system, so it was reasonable to expect that it would displace on the benzyl chloride so as to stack the two phenyl rings on each other (Figure 1). Consistent with this, we saw that antihydrophobic ethanol slowed the reaction.
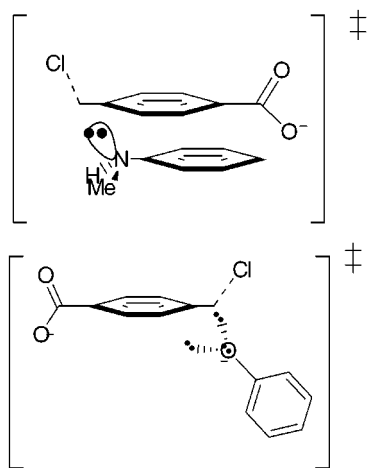

Figure 1. Proposed geometries in the displacement TSs.

In contrast, there was essentially no rate change on going from pure water solvent to 20 volume % ethanol/80 volume

% water solution for displacement by phenoxide ion on *p*-carboxybenzyl chloride. We concluded that the phenoxide ion uses n electrons, not π electrons, for the nucleophilic attack (Figure 1), so the two phenyl rings do not shield each other from solvent in the TS. Of course, the oxygen π electrons are conjugated with the phenyl ring in the product ether; we proposed that with the use of n electrons this conjugation is not disrupted in the TS.

However, we did raise the concern that the addition of ethanol to water could have other effects related to poorer solvation of charges and hydrogen bonding, not simply better solvation of hydrophobic surfaces.[11] To examine this, we have expanded the number of nonhydrophobic control reactions and devised experiments to separate the effects. For example, we find that displacement by methoxylamine on 2-bromoacetamide is 20% slower in the mixed solvent; the polar TS is more poorly solvated because of the lower dielectric constant and possibly some change in hydrogen-bonding ability[12] in the mixed solvent.

If charge is lost in the TS, the less polar mixed solvent can accelerate the reaction. The reactions of methyl mesylate and methyl iodide with phenoxide ion showed large *rate increases*−60% and 110%, respectively−upon addition of 20 volume % ethanol. The difference reflects different solvation demand by the leaving groups. In the reaction with *N*-methylaniline, on the other hand, only about a 10% rate increase is observed.

Cyanide ion, with a basicity similar to that of phenoxide ion, showed rate increases with added EtOH of 70% in the reaction with methyl iodide and 20% with methyl mesylate. We conclude that a part of the rate increase upon addition of ethanol is due to altered solvation of the nucleophile lone pairs, but the larger rate effect in the reaction of phenoxide involves an additional factor. In phenoxide ion the negative charge is delocalized into the benzene ring, making it less hydrophobic. As the transition state is approached, the charge is lost, the ring becomes more hydrophobic, and the reaction should be accelerated by ethanol.

As further evidence for this, we have examined the reaction of hydroquinone dianion with methyl iodide and methyl mesylate. The ethanol cosolvent effects were only as large as those for cyanide ion nucleophile, not the larger effects seen with phenoxide ion nucleophile. The hydroquinone dianion never becomes hydrophobic, since only part of one of the two delocalized charges is neutralized in the TSs.

We have simulated the effect of ethanol in lowering the $\Delta G°$ value of a solute in water by calculating the energy change when a molecule of ethane is brought up to contact with a benzene derivative in water.[11] The interactions were calibrated against experimentally measured solubility perturbations to account for both the effectiveness of ethanol in stabilizing the benzene rings and the fraction of the time that there is any interaction with ethanol at all in this dilute ethanol solution. As we described, when ethane was brought

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(12) Symons, M. C. R. *Acc. Chem. Res.* **1981**, *14*, 179.

nucleophile	electrophile	k water	ethanol	DMSO	$k_{20\% \text{ EtOH}}/k_{\text{water}}$	$k_{20\% \text{ DMSO}}/k_{\text{water}}$
phenoxide ion	*p*-carboxybenzyl chloride	0.053	0.051	0.053	0.97	1
phenoxide ion	*p*-nitrobenzyl chloride	0.024	0.028	0.031	1.2	1.3
phenoxide ion	methyl iodide	0.001	0.0021	0.0035	2.1	3.5
phenoxide ion	methyl mesylate	0.022	0.036	0.04	1.6	1.8
N-methylaniline	*p*-carboxybenzyl chloride	0.55	0.42	0.33	0.75	0.6
N-methylaniline	methyl iodide	0.036	0.042		1.17	
N-methylaniline	methyl mesylate	0.11	0.115		1.07	
cyanide ion	methyl iodide				1.7	2.5
cyanide ion	methyl mesylate				1.2	1.2
2,6-dimethylphenoxide ion (O-alk)	*p*-carboxybenzyl chloride	0.018	0.02	0.023	1.06	1.25
2,6-dimethylphenoxide ion (C-alk)	*p*-carboxybenzyl chloride	0.032	0.02	0.018	0.65	0.56
2,6-dimethylphenoxide ion (O-alk)	*p*-nitrobenzyl chloride	0.019	0.024		1.26	
2,6-dimethylphenoxide ion (C-alk)	*p*-nitrobenzyl chloride	0.018	0.01		0.56	

up to the aromatic face of phenoxide anion, the calculated $\delta\Delta G°$ value was one-third as large as with phenol. The decrease in interaction energy will also decrease the fraction of time that there is interaction of the ethanol with the surface; therefore, most if not all of the antihydrophobic solvation of a phenyl ring by 20 volume % ethanol should be absent in a phenoxide ion. Hydrophobic character will be brought in as the phenoxide ion loses charge in a displacement reaction.

Ethane interactions with the protonated anilinium cation and with *N*-methylaniline cation radical were also calculated. The protonated cation had essentially the same interaction energy as did neutral *N*-methylaniline, but the cation radical had no net interaction with ethane. Thus, delocalized charge decreases the hydrophobic character of the benzene ring, positive as well as negative charge, but charge localized on the anilinium nitrogen has little effect on the aromatic surface.

The two effects—change in solvation of polar groups, and change in solvation of hydrophobic surfaces—can be sorted out to some extent by substituting DMSO for ethanol. At 20 volume % in water, DMSO is 50% more effective than is ethanol at solubilizing phenyl derivatives, the antihydrophobic effect. However, it is much more polar than ethanol. For example, nucleophilic displacements by *N*-methylaniline on *p*-carboxybenzyl chloride and on iodoacetamide show essentially the same slowing (25% and 30%) in the mixed ethanol/water solvent relative to water, but with DMSO/water the effect is larger (40%) in the *p*-carboxybenzyl chloride case but smaller (10%) with iodoacetamide (Table 1). From this we conclude that there is loss of hydrophobicity in the TS for the benzyl chloride case, in addition to effects of polarity in both cases.

We had reported the rate decrease with ethanol in this reaction of *p*-carboxybenzyl chloride and *N*-methylaniline previously and concluded that this reflected a TS with stacking of the two phenyl groups (Figure 1).[10] This may be true, but the benzyl chloride will also become less hydrophobic if the TS has some benzylic cation character, with charge delocalized into the phenyl ring, as is generally believed to be true for substitutions at benzylic carbons.

Polar effects also complicate the interpretation of cosolvent effects in the reaction of phenoxide ion with *p*-carboxybenzyl chloride. We had reported that this reaction shows almost no rate effect with ethanol in water and concluded that the two phenyl groups are not stacked in the TS (Figure 1).[10] However, our new studies indicate that the loss of charge by phenoxide ion in the TS (a Hammett plot with substituted phenols shows that ca. one-third of the charge is lost) should lead to a rate increase with ethanol, while the rate will be slowed by benzylic cation character in the TS for benzylic substitution and by weaker solvation of the departing Cl$^-$. Do the rate-increasing and -decreasing effects compensate quantitatively? If so, there is no room left for hydrophobic stacking, supporting our previous conclusions.

Support for the idea that the two phenyl groups do not stack in the transition state for displacement by phenoxide ion on *p*-carboxybenzyl chloride comes from our reexamination of the reaction of 2,6-dimethylphenoxide ion (**1**) with the benzyl chloride **2**. We had reported that this reaction slows in the mixed ethanol/water solvent.[10] The overall reaction of **1** with **2** does indeed slow in the mixed solvent, but the situation is more interesting than that.

In water solution, but not in pure ethanol or DMSO, there are actually two products from the reaction of **1** with **2**: the ether **3**, which is formed in all solvents, and the para coupling product **4**, which is not formed in solvents other than water (Figure 2). We also see para coupling as well as O-alkylation of **1** with *p*-nitrobenzyl chloride (Table 1). We see only oxygen alkylation when we change the nucleophile to unsubstituted phenoxide or react methylated **1** with methyl mesylate or bromoacetamide electrophiles. There are earlier reports of carbon alkylation of some phenoxides in strong hydrogen-bonding solvents, which was ascribed to ionic solvation.[13]

(13) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148, and earlier papers.
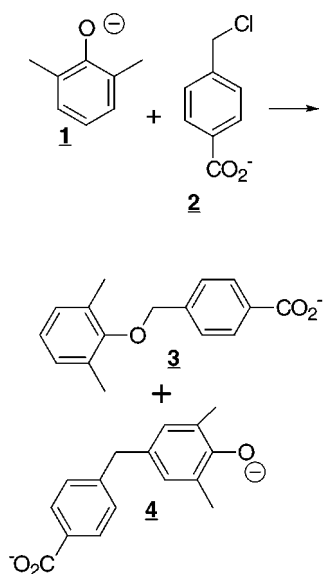
Figure 2. O-Alkylation and C-alkylation, with unstacked and stacked TS geometries, respectively.

C-alkylation should be oblique (Figure 3), to avoid putting the phenyl ring atop the O⁻, and such oblique stacking lets the *o*-methyl group contribute to the hydrophobic effect.
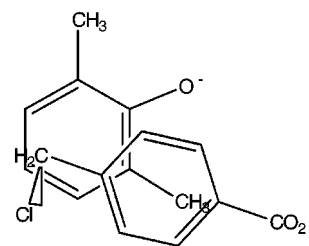

Figure 3. Oblique overlap in the para coupling of **2** with **1**.

As the data in Table 1 show, the reaction forming ether **3** shows a negligible 6% rate increase with 20 volume % ethanol in water, but the major para coupling reaction to form **4** is 35% slowed by ethanol. With **5** there is a 26% rate increase in 20% ethanol for O-alkylation (reflecting loss of charge from the phenoxide but no hydrophobic loss from **5**, whose TS will not have benzylic cation character) and a 44% rate decrease for C-alkylation.

We propose that coupling in the para position involves stacking of the two phenyl rings, while O-alkylation does not. Such stacking would be favored by the hydrophobic effect in water. As mentioned, there is no para coupling with nonmethylated phenoxide ion and *p*-carboxybenzyl chloride, where the hydrophobic effect would be smaller. Stacking in

The contrast in ethanol effects (Table 1) between *p*-carboxybenzyl and *p*-nitrobenzyl chloride supports our proposal. Benzyl cation character will be smaller with the nitro group, and Cl⁻ solvation effects should be no larger; thus, only stacking in the C-alkylation can account for the large ethanol effect in the nitro case.

Obviously the polarity effects in these displacement reactions make the interpretation of cosolvent effects more complicated than was the case for the Diels−Alder reactions, for instance. However, it seems that with appropriate control reactions, and the contrast between ethanol and DMSO cosolvent effects, it is possible to use the rate effects of antihydrophobic cosolvents to help elucidate the geometries of transition states, even in some displacement reactions. In any case, the solvation of hydrophobic substrates by such antihydrophobic cosolvents must be considered in any interpretation of cosolvent effects on reactions in water solution.