

Determining the Geometries of Transition States by Use of Antihydrophobic Additives in Water

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Received January 20, 2004

ABSTRACT

The quantitative effect of cosolvents on the water solubility of hydrophobic substrates can be correlated with the effect on reaction rates to determine the geometries of transition states for Diels–Alder reactions, the benzoin condensation, and alkylations of phenoxide ions and aniline. Some of these reactions have transition states with packing of hydrophobic surfaces and some do not. Methods were devised to sort out the effect of the cosolvents on solvation of hydrophobic surfaces and the effect on solvation of polar groups. The result is a set of geometries for these reactions that is consistent with theory.

Introduction

For the understanding of how reactions occur, one of the most fundamental questions is what is the structural geometry of the transition state? Transition states (TSs) are fleeting species whose structures cannot yet be determined by standard methods. However, knowing the TS structure will tell us how the reactants approach each other during a reaction. It will also tell us how to catalyze the process and let us check the predictions of such TS geometry from theoretical methods. Modern theory is powerful, but it needs to be validated with key experimental facts. The structure of a TS can be calculated—indeed, the entire geometry and energy profile of a reaction can be calculated—but it is important to check the predictions so as to establish which theoretical methods can be trusted.

In the course of our studies of hydrophobic effects on organic reactions we realized that we had a powerful new method to determine transition-state geometries for certain reactions performed in water.

In a previous review in *Accounts of Chemical Research*¹ we described our early work on the Diels–Alder (DA) reaction in water solution^{2–4} in which we discovered that such reactions are accelerated by the hydrophobic effect. This conclusion was supported by the rate effects of salts such as LiCl that increase the hydrophobic effect in water and of others such as guanidinium chloride that decrease hydrophobicity. We also described the decelerating effect of LiClO₄ and guanidinium perchlorate, which are also

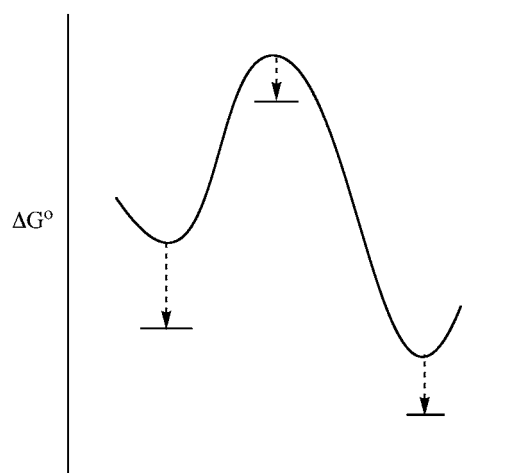


FIGURE 1. Typical reaction free energy plot. The curve symbolizes the reaction in water, while the downward arrows indicate that the free energies of hydrophobic reactants, transition states, and products in water can be lowered by added cosolvents such as ethanol.

antihydrophobic agents.¹ Others also examined DA reactions in water.^{5,6} We studied the benzoin condensation and saw that it was accelerated in water due to the hydrophobic effect, as evidenced by the prohydrophobic and antihydrophobic salt effects.⁷

After that early work we asked a more basic question: Can the magnitude of the rate effects caused by antihydrophobic agents in water be used to deduce the geometry of transition states (TSs) for common reactions? The idea is shown in the simple reaction plot of Figure 1. In this plot we show both the free energies of reactants (R), TS, and products (P) in water and also the free energies if an antihydrophobic agent is added to the water. The hydrophobic effect reflects the high energy of a water–hydrocarbon interface, and antihydrophobic additives lower this energy. We have shown^{8,9} that this results from insertion of the antihydrophobic agent between water and hydrocarbon, not by affecting the structure of water.

In the plot of Figure 1 the lowered energy of the starting materials can be measured by the effect of the additive on their solubility; the same is true for the products. The lowered energy of the TS is reflected in the rate change for the reaction when the additive is present. If the additive lowers the energy of the TS less than it lowers the energy of R, as the plot indicates, the additive will slow the rate. If TS and R are lowered to the same extent, there will be no rate effect and the rate could even increase if the additive lowered the TS energy more than it lowered that of R. This indeed happens with phenoxide ion alkylations (see below).

The *energies* of TSs relative to Rs are, of course, easily derived from the rates of the reactions. We hoped that we would be able to deduce the *geometries* of the TSs from the rate effects of antihydrophobic additives. First, we needed to show that such additives lower the free energies of hydrophobic solutes in water in proportion to the amount of exposed similar hydrophobic surface. Next, we

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needed to show that the observed rate effects of such additives on reactions where we knew the TS geometries were indeed reflecting the amount of exposed hydrophobic surface in the TS. If this was successful (it was), we then needed to apply this method to cases where the geometry of the TS was not known to learn how much hydrophobic surface was exposed in their TSs. Of course, we also had to show that the only significant rate effect of the additives was the result of antihydrophobic solvation of exposed hydrophobic surfaces in the TS or at least sort out other solvent effects. This was the most challenging requirement.

We also had to see that our conclusions had sensible explanations and agreed with (or acted as a check on) the predictions of modern theoretical treatments. The latter is a general need. There is no problem in calculating the exact pathways, geometries, and energies along the pathways for chemical reactions using modern quantum and molecular mechanics. However, since such calculations involve approximations, the question always is are the calculations correct? We hoped that our experimental method to determine the geometries of transition states would help validate the theoretical methods.

Choosing the Antihydrophobic Agents

Although our early work used antihydrophobic salts, we changed to neutral compounds to minimize the effects that salts could have on ionic strengths. Thus, most of our new work was done with ethanol and other alcohols as additives and with dimethyl sulfoxide (DMSO).¹⁰

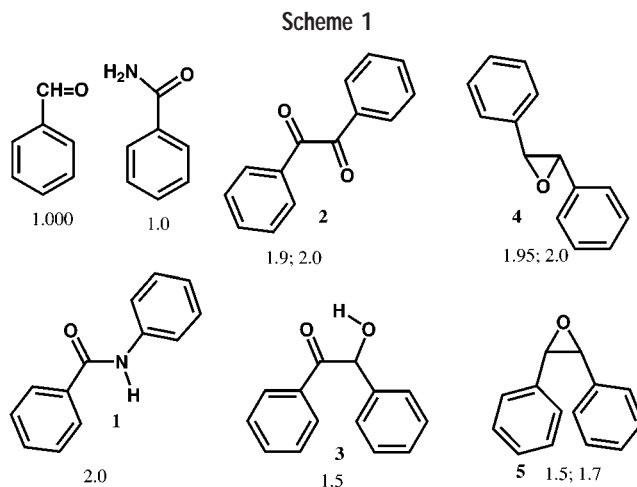
In the first such study¹¹ we saw that the ability of 1,4-butanediol to increase the solubility of some hydrophobic compounds followed a simple pair of equations, eqs 1 and 2

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

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

Here $\delta\Delta G^\circ$ is the change in the free energy of solution (ΔG° is the free energy of the dissolved compound minus the free energy of the pure compound) when a cosolvent is added to the water. Also, ρ_H is the ratio of the hydrophobic surface of compound 2 relative to that of compound 1 (e.g., two unstacked phenyls versus one similar phenyl group), and eq 1 simply indicates that the additive changes the free energy of a compound in water solution in proportion to the area of its similar hydrophobic surface. This is reasonable but was not yet established. Equation 2 simply indicates that such free energy changes will be reflected in the solubility changes that the additive produces, and since solubility is an equilibrium constant, the free energy change can be derived from the difference in logs of the solubilities with (S) and without (S_0) the antihydrophobic additive, for example, the butanediol.

Values of S and S_0 were determined for various compounds at 25 °C. The critical point is that eqs 1 and 2 were obeyed with both 10% and 20% (v/v) added butanediol



and that with both concentrations the *N*-phenylbenzamide (1), with two phenyl groups in an extended geometry, had *twice* the ρ_H as simple benzamide and benzamide had the same ρ_H as benzene. The solubilities of benzene and benzamide in water are, of course, not the same, but the *change* in solubility, as a ratio with and without the additive, was the same. The additive was solvating the same amount of hydrophobic surface in benzene and benzamide and twice as much surface in *N*-phenylbenzamide.

In later work we expanded these solubility studies. Again, using 1,4-butanediol as additive and comparing benzil (2) with benzaldehyde, we saw that ρ_H was 1.9 with 10% additive and 2.0 with 20%.¹² The two phenyls in benzil are fully exposed because of the preferred geometry induced by the two carbonyl dipoles. Interestingly, in benzoin (3), our method indicates that ρ_H is only 1.5 relative to benzaldehyde, Scheme 1. There is partial overlap of the two phenyls in 3, and about 25% of each total phenyl surface is hidden from the water solvent and thus not accessible to stabilization by the additives.

We see something similar in the *E*- and *Z*-stilbene oxides (4 and 5, respectively). The value of ρ_H for the *E* isomer, in which the two phenyls cannot overlap, is 2.03 and 1.95 relative to benzamide, using in this case 10% and 20% (v/v) of *tert*-butyl alcohol as cosolvent. However, for the *Z* isomer 5 the values of ρ_H are only 1.6 ± 0.1 , reflecting partial phenyl overlap in this isomer.

Rate Effects and Transition-State Geometries

Diels–Alder Reactions. As described above, the effects of antihydrophobic cosolvents—such as 1,4-butanediol or *tert*-butyl alcohol—on the water solubilities of compounds with hydrophobic phenyl groups are indeed quantitative indications of the amount of phenyl surface exposed to the solvent. Thus, we explored the possibility that the change in free energy of transition states with such cosolvents, as indicated in Figure 1, might also reflect the amount of hydrophobic surface that is exposed in the TS. The cosolvent effect on the free energy of the substrates could be determined from solubility changes, so the rate effect of the cosolvent would directly reflect its effect

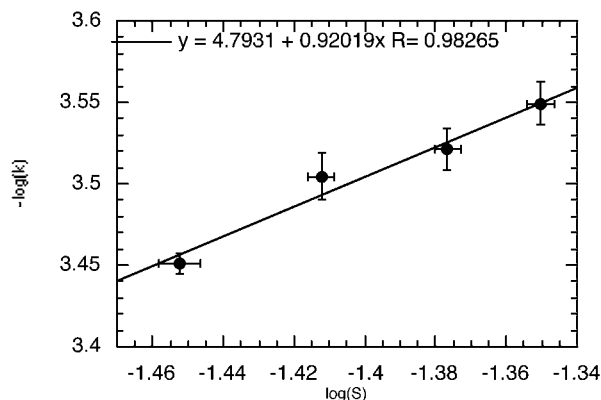
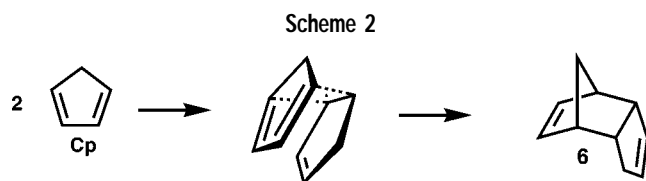


FIGURE 2. Plot of $\log(S)$, the solubility of cyclopentadiene (M), vs $-\log(k)$, the second-order rate constant for Diels–Alder dimerization of cyclopentadiene ($M^{-1} s^{-1}$) at 25 °C in water (left point) containing 5%, 10%, and 15% v/v of ethanol. The slope of 0.92 indicates loss of contact by 92% of a cyclopentadiene equivalent with the solvent in the transition state, ca. one face of each reactant. The numbers, such as the slope indicated of 0.92019, are the result of the plotting program and should not be taken seriously beyond the first one or two decimals.



on the energy of the TS relative to the effect on the substrates. Did that TS energy change tell us what the geometry of the TS was? It did only if there were no other causes of the change, such as solvent *polarity* effects on TS energies.

Sangwan and Schneider reported¹³ that the Diels–Alder dimerization of 1,3-cyclopentadiene (Cp) to form the endo product **6** is accelerated in water solution, Scheme 2. For this hydrocarbon dimerization it is unlikely that the TS has significant polar character, so changes in solvent polarity with added cosolvent should not be important. Also, the TS geometry is predictable—essentially face-to-face—so we viewed this reaction as a check on our methodology.

We investigated it at 25 °C with 5%, 10%, and 15% (v/v) ethanol cosolvent, determining both the Cp solubilities and second-order rate constants for the dimerization (Figure 2).¹⁴ From this we saw that the TS had $46 \pm 6\%$ less solvent-accessible surface than the two original Cps. This corresponds to pretty much face-to-face geometry in the TS, with only one face of each Cp and some edges still solvent accessible.

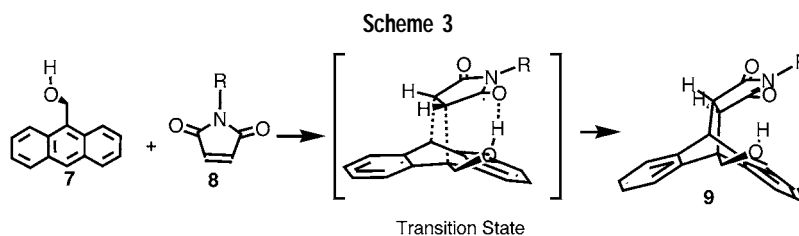
We calculated the geometry of this Cp dimerization TS using the AM1 program¹⁵ and then the solvent-accessible surface of this TS using Macromodel.¹⁶ The result was a prediction of 38% coverage of each Cp, on the edge of our measured result.

The reactions between 9-(hydroxymethyl)anthracene **7** and various *N*-substituted maleimides **8** to afford **9** are also accelerated by hydrophobic effects.¹ Thus, we examined the solubilities of **7** and a series of *N*-alkylmaleimides **8** in water and dilute aqueous solutions (1/10 (v/v) in water) of ethanol, 2-propanol, and *tert*-butyl alcohol.¹⁴ We also determined the effect of these cosolvent solutions on the rates of Diels–Alder reactions to afford adducts **9**, Scheme 3.

Two interesting points emerged. First of all, the data for the reactions to form **9** all showed that the maleimides **8** cover about 30% of the surface of **7** in the TS, as expected from a TS covering a little more than one-half of one face of the anthracene ring. Again, a combined AM1 and Macromodel calculation was consistent with this picture of the TS for this Diels–Alder reaction. Second, from the solubilities of the *products* **9** in water and with the cosolvents, we determined that in these products only ca. 10% of the surfaces were now not solvent accessible. Models show that this is sensible for **9**. The originally flat anthracene, still quite flat at the TS for the reaction, is bent in products **9** such that much of the surface hidden by the maleimide in the TS is open to solvent again in the products.

Benzoin Condensation. In one of our earliest studies, we showed that the benzoin condensation—in which two benzaldehydes formed benzoin (**3**) with cyanide catalysis—involves hydrophobic interaction of the two phenyl groups in the TS.⁷ The reaction was much faster in water than in other solvents, and the rate was increased by the addition of LiCl, which increases the hydrophobic effect, and slowed by the addition of LiClO₄, which is antihydrophobic. Thus, we applied our new quantitative approach to this reaction.¹¹

Using ethanol, *n*-propanol, and 1,4-butanediol as additives, we compared their solubility effects on the benzaldehyde starting material with their rate effects on the benzoin condensation. A plot of the free energy effect of the various cosolvents on benzaldehyde solubility vs the energy effect on reaction rate was reasonably linear, with 15 points corresponding to different solvent mixtures, supporting the idea that the major rate effect of the cosolvents again reflects the solvation of exposed hydrophobic surfaces in the TS.



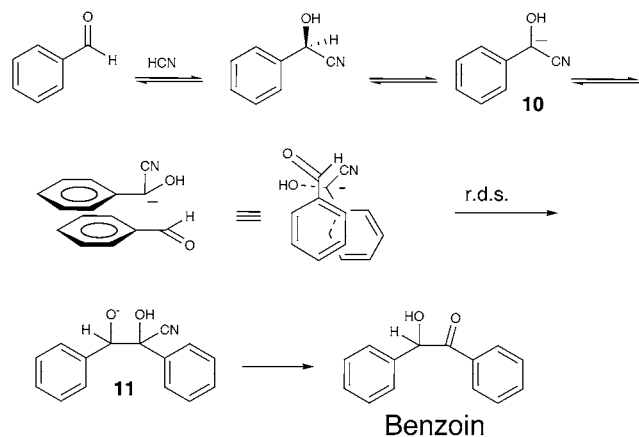


FIGURE 3. Benzoin condensation. Our method indicates a transition state with only partial phenyl–phenyl overlap, consistent with the expected approach direction of the carbanion to the aldehyde group.

With this interpretation, the TS has ca. 40% of one face of each benzene ring covered by the other ring, corresponding to a mechanism in which the cyanohydrin anion **10** approaches the benzaldehyde carbonyl group (under our concentration conditions, this is the rate-determining step) from the back of the carbonyl group, with the cyanohydrin anion electronic orbital overlapping π^* of the carbonyl group. As Figure 3 shows, this mechanism would lead to partial, but only partial, overlap of the two phenyl groups in the transition state.

In contrast to the situation with the Diels–Alder reactions described above, this benzoin condensation involves charged groups. The cyanohydrin anion will certainly be stabilized by polar solvents (as will the cyanide ion in equilibrium with it) and so will the oxyanion in the first adduct (**11**). If our cosolvents are decreasing the polarity of the water medium and thus changing the solvation of charged groups, how do we know how much this contributes to the change in rates? In fact, most previous researchers assumed that such cosolvent effects on reaction rates *mainly* reflect changes in charge solvation, and they ignored the change in solvation of hydrophobic surfaces (see below).

With the benzoin condensation just discussed, the reasonable parallel between cosolvent effects on benzaldehyde solubility in water—which is certainly the result of solvation of the benzene ring by the cosolvents—and the cosolvent effects on rates supports our assignment that the extent of phenyl ring accessibility to solvent in the TS is the major reason for the cosolvent rate effects. Perhaps in this case the conversion of a cyanohydrin anion **10** to an oxyanion **11** leads to compensation of the simple polar effects. However, we wanted to apply our new methodology to the study of simple displacement reactions, in which compensation of polar solvation effects is less likely and in any case cannot be assumed.

Alkylation Reactions. In one of our earliest studies,¹¹ we examined the reaction of thiophenoxide ion **12** with a water-soluble benzyl chloride, sodium 4-(chloromethyl)benzoate (**13**). We saw that the reaction rate in water was unaffected by the addition of ethanol, suggesting that the

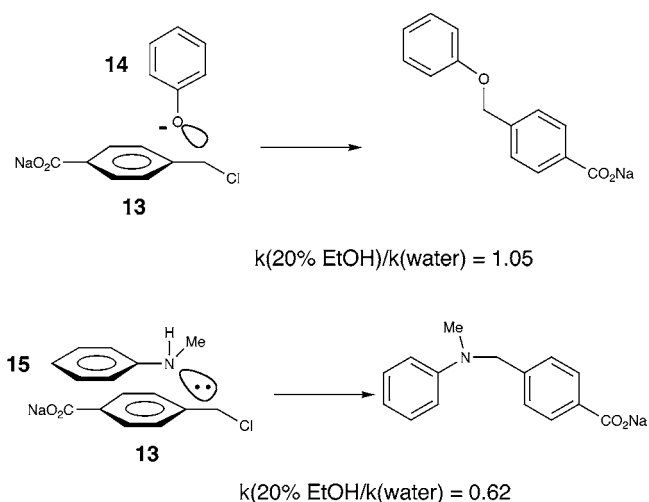


FIGURE 4. Nucleophilic substitutions on a soluble benzylic chloride (**13**) in water by phenoxide ion (**14**) and *N*-methylaniline (**15**). The rate effects of ethanol cosolvent indicate that the phenoxide reaction has a transition state lacking phenyl–phenyl overlap, while such overlap is present in the aniline reaction.

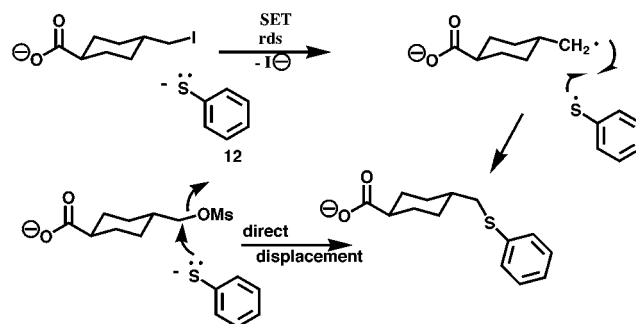


FIGURE 5. Thiophenoxide ion (**12**) displaces an iodide using the single-electron-transfer (SET) mechanism but a direct S_N2 mechanism with the mesylate leaving group.

two phenyl groups are not overlapping in the TS (ignoring possible polar effects.) We later saw that this lack of a cosolvent rate effect was also true in the reaction of **13** with phenoxide ion **14**.¹² By contrast, the reaction of **13** with *N*-methylaniline **15** in water was significantly slowed by added ethanol.

We concluded that the alkylation of phenoxide ion involves the use of two of its *n* unshared electrons, not the two electrons that are conjugated with the phenyl π system, and that the geometry of the attack is as shown in Figure 4. By contrast, the alkylation of *N*-methylaniline must, of course, involve its nitrogen electron pair that is conjugated with the phenyl π system, and the geometry is as shown in Figure 4, with significant overlap of the phenyl rings. However, only with our later work (see below) were we able to sort out the contributions from solvation of polar groups.¹⁷ Interestingly, after this further work the mechanisms pictured in Figure 4 are still supported. With the thiophenoxide ion nucleophile we were also able to find evidence that a single-electron-transfer mechanism (Figure 5) occurs with a benzylic iodide but not with a benzylic mesylate.¹⁸

Solvent Polarity or Hydrophobic Solvation? As mentioned above, adding ethanol to water increases the

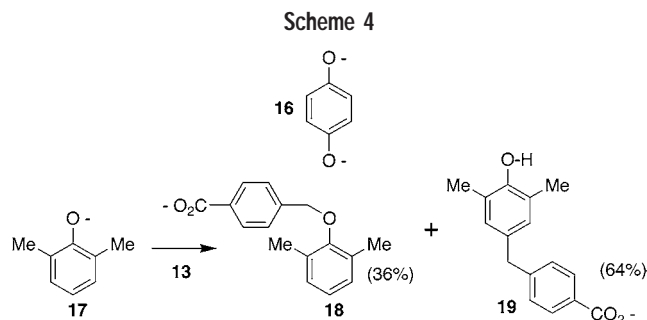
stability of dissolved hydrophobic species, thus increasing their solubility, but it also decreases the polarity of the solvent medium. In reactions with ionic species it was critical to sort out these two effects in interpreting the changes in reaction rates. As one approach we examined DMSO as an additive, instead of ethanol.¹⁷ We were pleasantly surprised to discover that 20% (v/v) DMSO is more effective than 20% (v/v) ethanol in increasing the solubility of hydrocarbon species such as phenyl methyl ether in water, so DMSO is a more potent antihydrophobic agent. However, the dielectric constant of aqueous DMSO is 77.1, almost as high as the 78.5 of pure water, but that for the ethanol solution is only 72.1. Thus, if the rate effects from adding DMSO are larger than the effects from adding ethanol, we are dealing with antihydrophobic solvation of nonpolar surfaces, while if the ethanol effects are larger we are dealing with simple solvent polarity changes. Hydrogen bonding by the water solvent can also change with these cosolvent additions.

We examined some control reactions to validate this conclusion.¹⁷ We saw evidence for polar effects with cosolvent ethanol in some simple displacements where no hydrophobic character is involved, such as the reaction of cyanide ion with methyl mesylate and methyl iodide. This is in line with the earlier proposal by Ingold that poorer solvation of an attacking nucleophile by a less polar solvent would lead to a rate acceleration.^{19,20} However, the alkylation of phenoxide ion, whose basicity is similar to that of cyanide ion, showed a much larger rate increase with added ethanol than does cyanide ion.

Some of this increase must also reflect the polarity change, but we concluded^{17,21} that an additional factor for the phenoxide ion is an *increase* in hydrophobicity during the methylation reactions. The phenoxide ion, with its charge delocalized into the ring, is less hydrophobic as a result than is phenyl ether. Our Hammett plots with substituted phenoxide ions indicate that ca. 30% of the phenoxide ion charge is lost at the TS for such reactions, leading to an increase in hydrophobicity.

The proposal that alkylation of phenoxide ion leads to an increase in hydrophobicity is supported by the results with *p*-nitrophenoxide ion instead of phenoxide ion. Alkylation of *p*-nitrophenoxide ion does not lead to the large increase in hydrophobicity that we saw with simple phenoxide ion. In the nitro anion the charge is distributed between the phenolic oxygen and the *nitro* group, so the ring carbons have little charge and the hydrophobicity of the phenyl ring is not diminished by charge delocalization.

Another support for our proposal comes from the result of monoalkylating hydroquinone dianion (**16**). This alkylation does *not* lead to large antihydrophobic cosolvent effects since the product is still a delocalized phenoxide ion with little hydrophobicity. Finally, we calculated the hydrophobicities of phenoxide ion and phenol by a quantitative method described elsewhere.^{17,21} This method also predicts that the delocalized negative charge in the phenoxide ion will greatly diminish the hydrophobicity of the phenyl group.



S_N2 displacements on benzylic halides such as **13** involve transition states in which there is some positive charge delocalized into the benzene ring. That is, the S_N2 transition state has some of the character of an S_N1 reaction, with the nucleophile and leaving group coordinated on opposite faces. Our studies indicated that this transition-state charge delocalization would significantly decrease the hydrophobicity of the benzene ring, as also predicted by our computations.^{17,21} Thus, in the alkylation of phenoxide ion by a benzylic halide such as **13**, the increased hydrophobicity of the phenoxide in the TS is at least partially compensated by a decreased hydrophobicity of the benzylic component. If they actually cancel, our observation that there is no antihydrophobic cosolvent effect does indeed support the TS shown in Figure 4. However, we needed stronger evidence.

The most striking confirmation of our conclusion that phenoxide ion is alkylated at its *n* electrons as shown in Figure 4, without hydrophobic packing by benzylic halides such as **13**, is found in our experimental results in the alkylation by **13** of methyl-substituted phenoxides such as **17**. In water we see that there is both *O*-alkylation (36%) to form **18** and *C*-alkylation (64%) to form **19**, Scheme 4.

Such alkylations had been studied previously by Kornblum^{22–27} and Curtin,²⁸ among others, who had seen that the *C*-alkylation occurred in water but not in normal organic solvents. They proposed that the water solvated the oxyanion of **17**, slowing *O*-alkylation so the otherwise slower *C*-alkylation could win out. However, we find that this choice—of *O*-alkylation vs *C*-alkylation—is actually the result of a difference in the *hydrophobic character* of the TSs for the two different reactions, a difference that matters in water but not in ordinary organic solvents.

The most striking evidence is from our kinetic results that show that the cosolvents ethanol and DMSO do *not* slow the *O*-alkylation but instead slightly accelerate it, with DMSO being more effective.¹⁷ This is consistent with some acceleration as the phenoxide ion becomes more hydrophobic but again indicates that *O*-alkylation involves the use of oxygen *n* electrons with no hydrophobic packing in the TS. However, the cosolvents do greatly slow the *C*-alkylation process, with DMSO again being more effective. This indicates that the TS for *C*-alkylation has *lost* hydrophobicity. With the same starting materials, the reactions go to two different TSs with grossly different hydrophobic character!

Without the added methyl groups, simple phenoxide ion did not undergo *C*-alkylation under our conditions.

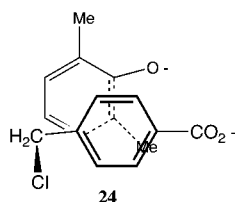
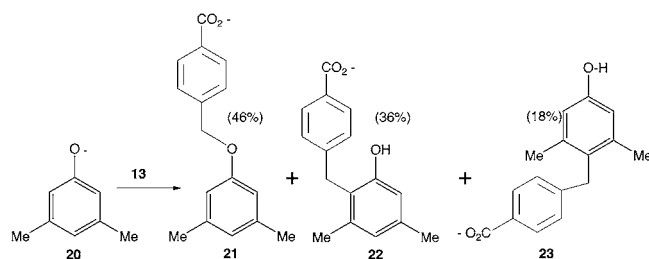


FIGURE 6. Phenyl–phenyl overlap in the transition state for C-alkylation of 2,6-dimethylphenoxide ion by benzylic chloride **13**. No such overlap is seen in the competing O-alkylation.

Scheme 5



More interestingly, the methyl groups did not have to be ortho to the phenoxide ion. Indeed, compound **20** underwent O-alkylation to afford **21** (46%) but also C-alkylation to form both **22** (18%) and **23** (36%), Scheme 5. As models show, a transition state such as **24** can be promoted in water by the extra hydrophobic interaction that the methyl groups introduce, Figure 6. This TS uses the oxygen π electrons, delocalized into the ring, and involves serious coverage of one face of a benzene ring in each reactant. Such a transition state, and related ones for the other phenoxide derivatives such as **20**, is the only reasonable possibility to explain all the data.

We also saw that with the anion of *p*-methylphenol there was 16% alkylation of the ortho phenyl ring position by **13**, but with non-hydrophobic *p*-substituents such as methoxyl or cyano, there was only O-alkylation.

Although the other studies described above certainly strongly supported the mechanisms shown in Figure 4, this work clearly shows that the C-alkylation of substituted phenoxides by **13** involves hydrophobic packing of the reagents and the O-alkylation does not. Thus, even in a case like this where there are charged groups whose solvation will be affected by nonpolar cosolvents in water, it is possible to sort out the effects and determine the part that reflects not the polarity but the geometry of the transition state.

Our studies were performed in water solution, along with some additives, so one might wonder whether the conclusions are general for reactions in *organic* solvents. This remains to be established in detail. However, we find that even in water the phenoxide ion does not pack onto the benzylic halide in O-alkylation, so as to minimize the exposed hydrophobic surface. Instead, it uses the oxygen n electrons so as to avoid breaking up the conjugation of the oxygen π electrons with the phenyl ring, and it uses the π electrons only when it must, in ring alkylations. Surely in other solvents, with no hydrophobic driving force that would promote ring packing, it will also adopt a transition state like that shown in Figure 4.

Finally, we need to point out that many physical organic studies have been performed in water with cosolvents such as ethanol added, but previous authors have interpreted the rate effects of the cosolvent exclusively in terms of the solvation of ions by solvents of altered polarity. For example, Grunwald and Winstein studied the solvolysis of *tert*-butyl chloride in various solvents and interpreted the rate effects in terms of the *Y* value of the solvent, its ability to solvate the *tert*-butyl cation and chloride anion.²⁹ However, the starting *tert*-butyl chloride is itself quite nonpolar and hydrophobic, and thus its solubility in water is greatly increased by added ethanol, so its energy is lowered.

By our rough estimate,³⁰ as much as one-half of the rate decrease in this solvolysis caused by the ethanol results from the decreased hydrophobicity of *tert*-butyl cation relative to *tert*-butyl chloride, while the rest is of it is indeed caused by the polarity effects on the ions. Thus, I urge that in interpreting such solvent effects chemists remember the contribution from antihydrophobic solvation and perhaps its extension to related effects in other polar solvents. The energies are significant and easy to determine.

Conclusions

(1) The free energy effect on solubility of nonpolar solutes in water caused by antihydrophobic cosolvents such as ethanol is proportional to the amount of similar hydrophobic surface in the solute.

(2) This results from solvation of the hydrophobic surfaces by the cosolvent, not from some effect on water structure.

(3) The effect of the cosolvents on the rates of reaction of nonpolar substrates, such as the Diels–Alder dimerization of cyclopentadiene, reflects the amount of hydrophobic surface of the substrates that becomes hidden from solvent in the transition state of the reaction.

(4) For this dimerization, the geometry of the transition state predicted from this rate effect of cosolvents is consistent with that calculated by theoretical methods.

(5) The perturbation of solubilities and rates by cosolvents in water also indicates a transition state for the Diels–Alder reaction of an anthracene derivative with maleimide dienophiles that is reasonable. The method also indicates that the product has opened up much of the hydrophobic surface that was hidden in the transition state for this reaction.

(6) When this technique is applied to the benzoin condensation, it indicates a transition state with only partial overlap of the phenyl groups of the reactants, consistent with a theoretically reasonable geometry for the reaction.

(7) In the alkylation of phenoxide ion by a benzyl halide there is no overlap of the phenyl groups in the transition state. This indicates that the phenoxide reacts with its nonconjugated n electrons, not its π electrons, with a geometry that is extended even though the packing of the phenyl groups would be favored in water.

(8) By contrast, with *N*-methylaniline as nucleophile, the geometry involves the use of the conjugated nitrogen electrons, as it must, leading to packing of the two phenyl groups in the transition state.

(9) With thiophenoxide ion as nucleophile, there is evidence for a single-electron-transfer mechanism when iodide is the leaving group.

(10) Nonpolar cosolvents in water can solvate hydrophobic surfaces, but they can also lower the polarity of the medium and diminish the solvation of charges. A number of techniques were used to sort out the two effects.

(11) DMSO is more potent as an antihydrophobic agent than is ethanol, but DMSO lowers the polarity of the water solution less. Thus, in reactions where the solvation of nonpolar surfaces in the starting materials and transition states is the important factor the DMSO causes the larger effects.

(12) Hydrophobic character can diminish in transition states because the geometry hides some surface from the solvent, but charge delocalization can also play a role. The alkylation of phenoxide ion—which has low hydrophobicity because its charge is delocalized into the ring—leads to an increase in hydrophobic character as that charge is neutralized during reaction. Similarly, the transition states for alkylations by benzylic halides have some delocalized positive charge—even in strictly S_N2 reactions—so this can cause a decrease in the hydrophobicity of transition states for such alkylations.

(13) These effects were demonstrated in appropriate control reactions and are also consistent with a novel method for the theoretical estimation of the hydrophobicity of various phenyl species such as phenoxide ion and benzyl cation.

(14) Phenoxide ions with methylated phenyl groups can be alkylated on both their oxygens and their ortho and para phenyl positions. These *C*-alkylations occur in water but not in organic solvents. The cosolvent effects on rates show that ethanol and DMSO increase the rate of *O*-alkylation but diminish the rates of *C*-alkylations. This is consistent with our model in which *O*-alkylation does not involve phenyl overlap in the transition state but *C*-alkylation does involve such overlap. This conflicts with previous proposals by others for such cosolvent effects and supports our conclusions about the geometry of the *O*-alkylation process.

(15) While these geometries for transition states were determined in water solution, it is likely that they are reasonably general. Even in water the *O*-alkylation of phenoxide ion did not adopt a geometry with phenyl packing to minimize the hydrocarbon–water interface, since that would have broken the conjugation of the oxygen electrons with the phenyl group.

(16) It is important that the interpretation of cosolvent effects on reaction rates, such as the rate of ionization of *tert*-butyl chloride, takes account of the change in hydrophobic solvation as the nonpolar substrate goes to a polar cation. This affects the rate along with the well-understood

polarity effects that determine the stabilization of the polar ionic products.

I thank my co-workers listed in the references for their intellectual and experimental contributions. The work has been supported over the years by the National Science Foundation and the National Institutes of Health.

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AR040001M