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Antihydrophobic Cosolvent Effects Detect Two Different Geometries for an S_N2 Displacement and the Change to a Single-Electron-Transfer Mechanism in Related Cases

Ronald Breslow* and Richard Connors

Department of Chemistry, Columbia University
New York, New York 10027

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We have described the use of antihydrophobic cosolvents in water to determine the geometries of transition states for the benzoin condensation[1] and for various Diels−Alder reactions.[2] Our quantitative treatment involved three equations.

$$\delta\Delta G°(2) = \rho_H \cdot \delta\Delta G°(1) \qquad (1)$$

therefore

$$\log(S/S_0)_2 = \rho_H \cdot \log(S/S_0)_1 \qquad (2)$$

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

The first two equations indicated that an antihydrophobic cosolvent, such as ethanol, increases the water solubility of a hydrophobic substrate by changing the free energy of solution in proportion to the amount of hydrophobic surface that the solute contains (eq 1). The constant ρ_H is the ratio of the hydrophobic surface areas for two solutes of similar types, and the free energy relationship means that the solubilities of the two solutes in water (S_0) relative to their solubilities in the presence of the cosolvent (S) obey the relationship of eq 2.

We had confirmed this by comparing the solubilities of benzamide and of *N*-phenylbenzamide in water at 25 °C with and without the addition of 10% or 20% v/v 1,4-butanediol (BD) cosolvent.[1] The values of ρ_H were 2.0 and 1.95 for the two measurements comparing two phenyl groups with one. We have further confirmed eqs 1 and 2 by comparing the solubilities of benzaldehyde and benzil. The value of ρ_H is 1.9 with 10% BD and 2.0 with 20% BD. Also, comparing the water solubilities of *trans*-stilbene oxide and benzamide, using 10% v/v *tert*-butyl alcohol as cosolvent, the value of ρ_H is 2.03 (10% cosolvent) and 1.95 (20% cosolvent). In all these comparisons the two phenyl groups are nonoverlapping. We had seen previously that benzoin has a ρ_H of 1.5 when compared with benzaldehyde, since the two phenyl groups can partially overlap.[1] We now see that ρ_H for *cis*-stilbene oxide compared with benzamide is 1.6 ± 0.1, again because of partial overlap of the phenyls.

The third equation relates the rate effect of antihydrophobic cosolvents in water to their effect on the water solubility of the reactants. The value of h reflects the fraction of reactant hydrophobic surface that becomes solvent inaccessible in the transition state. Although this equation will be correct only if there are no other major effects of the antihydrophobic cosolvents on the transition state energies, and this may not be true in all cases, our treatment did give sensible pictures for the transition states of some Diels−Alder reactions and the benzoin condensation. Thus we have explored the use of such antihydrophobic cosolvent effects to probe displacement reactions. The results are listed in Table 1.

We had reported that the rate of the displacement reaction on sodium iodoacetate by hydroxylamine is unchanged when 20% v/v ethanol is added and that the displacement on sodium chloroacetate by sodium thiomethoxide even increases a little in rate when 20% ethanol was added.[1] By contrast, the displacement reaction of *N*-methylaniline (**1**) with sodium 4-(chloromethyl)benzoate (**2**) was *slowed* by 10% or 20% added ethanol. In the transition state for a direct displacement reaction (Figure 1) some overlap of the two phenyl groups is expected, consistent with our explanation that some hydrophobic surface loses contact with the solvent in the transition state.

Table 1. Relative Second-Order Rate Constants for Some Displacement Reactions in Water and with Added Ethanol at 25 °C

nucleophile	electrophile	% EtOH v/v	$k_0/k^{a,b}$
$H_2N{-}OH$	$I{-}CH_2{-}CO_2Na$	20	1.00
$CH_3S{-}Na$	$Cl{-}CH_2{-}CO_2Na$	10	0.97
$CH_3S{-}Na$	$Cl{-}CH_2{-}CO_2Na$	20	0.88
Ph−NHMe **1**	4-chloromethylbenzoate Na^+ **2**	10	1.26
Ph−NHMe **1**		20	1.59
PhS^- **3**	$PhCH_2Cl$	10	1.09
PhS^- **3**	$PhCH_2Cl$	20	1.08
3	**2**	10	0.98
3	**2**	20	0.97
3	*p*-nitrobenzyl chloride **7**	20	0.72
3	*m*-nitrobenzyl chloride **8**	20	0.64
PhO^- **4**	**2**	20	0.95
4	**7**	20	0.57
dimethylPhO^- **5**	**2**	10	1.28
dimethylPhO^- **5**	**2**	20	1.65
5	**7**	20	0.35
dimethylPhS^- **6**	**2**	20	0.97
6	7	20	0.58

[a] The rate constant in water over the rate constant in the mixed solvent. [b] ±5% or better.

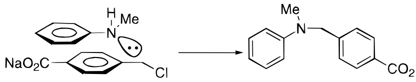

Figure 1. Displacement reaction of *N*-methylaniline (**1**) with 4-chloromethylbenzoate ion (**2**), whose transition state has some shielding of one face of the benzene ring of each reactant.

However, we had seen that there was no rate effect of added ethanol on the displacement reaction of sodium thiophenoxide (**3**) with **2**.[1] This clearly indicates that the phenyl group of **3** does not overlap that of **2** in the transition state. We now find (Table 1) that this is also true in the displacement on **2** by sodium phenoxide (**4**). We considered that the contrast with the overlapping geometry in the *N*-methylaniline (**1**) displacement might reflect the required use of nitrogen electrons that are part of the π system in **1**, but the preferred use of non-π electrons in the case of **4**. To test this, we examined the displacement on **2** by 2,6-dimethylphenoxide ion (**5**), in which the methyl groups block such a non-π in-plane approach. Now we find significant slowing of the reaction by 10% and 20% ethanol, consistent with partial shielding from solvent of the two phenyl rings in the transition state that uses the π electrons for displacement. Thus the unhindered phenoxide nucleophile **4** is apparently using a direct displacement mechanism, but with a geometry (Figure 2) in which there is no overlap of the phenyl groups.

This change in mechanistic detail is not seen in the sulfur series. Displacement on **2** by 2,6-dimethylthiophenoxide (**6**) shows no rate effect of ethanol cosolvent, behaving just like the unsubstituted **3**. Molecular mechanics calculations[3,4] indicate that the methyl groups in **6** should prevent direct non-π

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(1) Breslow, R.; Connors, R. *J. Am. Chem. Soc.* **1995**, *117*, 6601−6602.
(2) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923−9924.
(3) Using Macromodel (ref 4), we calculated the energy of 2,6-dimethylanisole and of 2,6-dimethylthioanisole as the methyl on oxygen or sulfur was brought through the ring plane by rotation of the phenyl−O (or S) bond. The barrier was larger (5.7 kcal/mol) in the sulfur case than in the oxygen case (1.4 kcal/mol), since the smaller C−S−C angle more than compensated for the longer C−S bond lengths.
(4) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. *MacroModel, v 3.5*; Department of Chemistry, Columbia University: New York, NY 10027.

S0002-7863(96)00868-2 CCC: $12.00

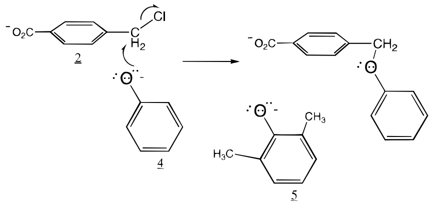

Figure 2. Mechanism of displacement by phenoxide ion (**4**) on 4-chloromethylbenzoate ion (**2**), in which attack by oxygen in-plane unshared electrons is preferred so as to avoid breaking up the π conjugation. This leads to a transition state geometry in which no shielding of the phenyl surfaces occurs. By contrast, displacement on **2** by the 2,6-dimethylphenoxide ion **5** must use the π oxygen electrons, and now there is some shielding of one face of each reactant in the transition state.

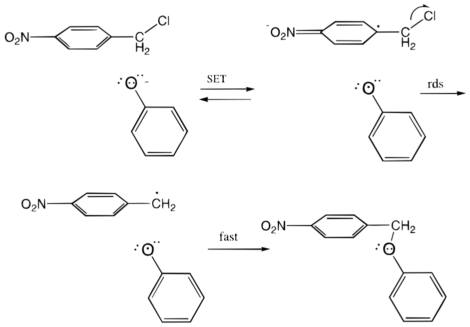

Figure 3. Single-electron-transfer displacement mechanism in which the transition state has no shielding of the phenyl surfaces. A similar process is invoked for thiophenoxide anions with and without 2,6-dimethyl substituents. A radical chain process is excluded by the fact that radical trapping agents do not affect the rates.

displacement, just as they did in **5**. Thus yet another mechanism is operating in the sulfur series.

It seemed likely that a single-electron-transfer (SET) process was involved.[5−11] To favor this we switched to a new substrate, 4-nitrobenzyl chloride (**7**). The kinetic effects of added ethanol were striking. Now (Table 1) the displacement by thiophenoxide ion **3** was *faster* with the added cosolvent. The effect was larger with **6**, and in the phenoxide series there were even larger accelerations. The transition states cannot have more exposed hydrophobic surface than the unassociated starting materials, which this result seems to indicate, but the surfaces can still be fully exposed and more hydrophobic. This is what we propose in the mechanism of Figure 3.

In the transition state of this mechanism, the anionic phenoxide or thiophenoxide starting ions, with delocalized charge making the rings less hydrophobic, have become neutral *more* hydrophobic radicals.[12] The negative charge is mainly in the nitro group, partly in the developing chloride ion, neither of which was a significantly hydrophobic segment of the substrate to start. Thus there has been a net increase in hydrophobicity in the transition state compared with the reactants. This explains the increased rate when ethanol is added. This mechanism probably also operates in the reaction of the thiophenoxides **3** and **6** with substrate **2**, but in that case there is no nitro group to take up most of the negative charge in the substrate anion radical, so there is no net increase in hydrophobicity in the transition state.

An alternate mechanism for the nitro substrate **7** would have the nucleophiles add to the benzene ring para to the nitro group and then move to the benzylic position. However, we find almost the same behavior (Table 1) with the *m*-nitrobenzyl chloride **8**, which cannot use the latter mechanism but can perfectly well use the SET mechanism. Another alternative to the mechanism of Figure 3 would be an $S_{RN}1$ radical chain process.[13] However, we find that the rates of reaction of the thiophenoxides **3** and **6** with **7** (and of **3** with **2**) are unaffected by the addition of 0.2 equiv of *p*-dinitrobenzene, of di-*tert*-butylnitroxyl, or of 4-carboxy-2,2,6,6-tetramethylpiperidinoxyl, all of which will block radical chains. Thus our evidence seems best explained by the scheme of Figure 3.

These examples further illustrate the power of the use of antihydrophobic cosolvents in aqueous reactions. Remarkable mechanistic differences have been detected for nominally similar reactions. It will be interesting to see whether the qualitative information provided by this tool is useful in other mechanistic areas and whether the quantitative conclusions embodied in our equations are indeed reliable guides to the detailed structures of transition states.

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Supporting Information Available: The experimental method for rate determination, evidence on the products of the reactions, and the methods to obtain solubility data (2 pages). See any current masthead page for ordering and Internet access instructions.

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