Antihydrophobic Evidence for the Single Electron Transfer Mechanism of Nucleophilic Substitution

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SET mechanisms have been implicated in nucleophilic substitution reactions that were previously thought of as having classical S_N2 mechanisms.[1] Evidence for the radical nature of these substitutions has been accumulated through theoretical considerations[2] and experimentally. Radical intermediates in nucleophilic substitution reactions have been observed by ESR,[3] radical traps,[4,5] and by the use of cyclizable radical probes.[5] Strong evidence for the SET mechanism is racemization of compounds previously believed to react by an S_N2 mechanism[6] and reactions at norbornyl bridgehead carbons.[7] We now report that antihydrophobic effects support the SET mechanism in a system for which previous evidence was lacking.

We have described the use of antihydrophobic cosolvents such as ethanol added to water solutions as a novel method to probe transition-state structures.[8−11] The idea is that such additives will lower the free energies of reactants and transition states by solvating hydrophobic surfaces. If less hydrophobic surface is exposed in the transition state than in the reactants, the antihydrophobic cosolvent will slow the reaction by such preferential solvation of the reactants.

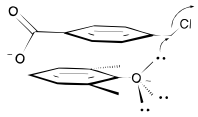
In amounts of 10 or 20 vol % (3.5 or 7 mol %), cosolvents such as ethanol had negligible rate effects on reactions in which no large hydrophobic surfaces were part of the reactants, but they significantly slowed Diels−Alder reactions that proceed through transition states with overlapping hydrophobic surfaces.[9] The rates of the benzoin condensation[10] and of some displacement reactions involving phenyl derivatives were also slowed.[8] Reactions of *p*-carboxybenzyl chloride with *N*-methylaniline, **1**, and with the 2,6-dimethylphenoxide ion were both slowed by a factor of 0.6-fold in water when 7 mol % ethanol was present (therefore, the rate change is unrelated to the charge of the nucleophile). As shown in Scheme 1, we proposed that there is an overlap of the hydrophobic surface areas in the transition state for these compounds. We argued that the reaction of simple phenoxide ion with *p*-carboxybenzyl chloride has a different geometry (Scheme 2), since added 7 mol % ethanol causes no rate decrease but instead a slight rate increase. Thiophenoxide ion as the nucleophile also showed a few percent increase with added ethanol, but this was not changed when the 2,6-dimethylthiophenoxide ion was studied.

In nucleophilic displacements on *p*-nitrobenzyl chloride,[8] reactions which with good electron-donor nucleophiles are proposed to proceed through a SET mechanism,[12] the rates of the reactions of thiophenoxide ion, **2**, 2,6-dimethylthiophenoxide ion, **3**, phenoxide ion, and 2,6-dimethylphenoxide ion were all strongly increased by the addition of 7 mol % ethanol. We proposed that the conversion of a thiophenoxide ion to a neutral thiophenoxy radical in the SET mechanism would increase its hydrophobicity[13] and that this would not be overcome by decreased hydrophobicity elsewhere (Scheme 3). Thus, the TS free energy is lowered by antihydrophobic additives more than is the free energy of the reactants, and the additives speed up the reactions.

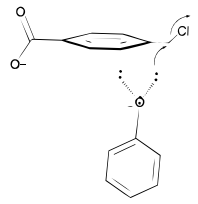
If our interpretations are correct, our antihydrophobic effects are useful evidence for the different mechanisms, indicating occlusion of hydrophobic surface area in some S_N2 substitutions on *p*-carboxybenzyl chloride and reaction by a SET mechanism for *p*-nitrobenzyl chloride. To extend the studies, we have examined another case in which the SET mechanism occurs and contrasted it with an analogous case that uses the direct S_N2 mechanism.

E-4-(Iodomethyl)-cyclohexanecarboxylic acid, **4**, was synthesized from the commercially available aminomethyl derivative by reaction with 2,4,6-triphenylpyrilium iodide to form the

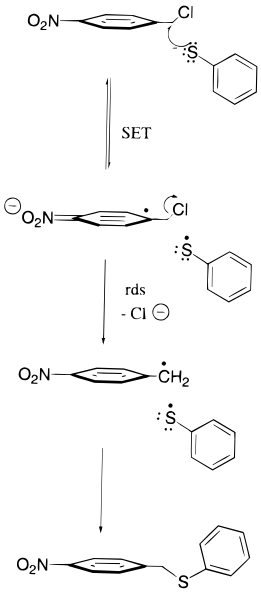
Scheme 1



Scheme 2



Scheme 3



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(13) This proposed increase in hydrophobicity of a thiophenoxy radical compared with that of a thiophenoxide ion is consistent with open shell Hartree−Fock 6-31G** calculations on a hydrophobicity model by Kevin Groves using continuum solvent SCRF via Jaguar 3.0 (to be published elsewhere).

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Table 1. Rate Constants for Displacement Reactions[a]

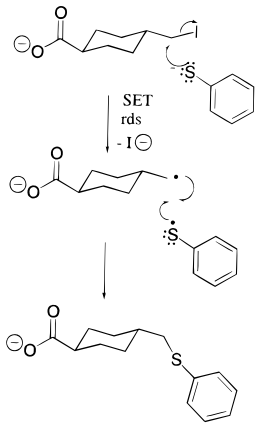
		k_{H2O}	$k_{20\%EtOH}$	$k_{20\%EtOH}/k_{H2O}$
4	**1**	.00146	.00163	1.12
4	**2**	.306	.534	1.75
4	**3**	.300	.527	1.76
5	**2**	.069	.072	1.04
5	**3**	.049	.053	1.08

[a] Average of triplicate initial rate constants in M^{-1} min^{-1} at 30 °C (< 4% error), as monitored by HPLC assay for the reaction product.

corresponding pyridinium salt and then by pyrolysis, following the method of Katritzky.[14,15] The rates of its displacement reactions with *N*-methylaniline, **1,** thiophenoxide ion, **2**, and 2,6-dimethylthiophenoxide, **3**, were determined at 30 °C in water and in water with 7 mol % ethanol by monitoring the formation of authenticated product using automated HPLC. *N*-methylaniline, **1**, showed only a 12% increase in rate with added cosolvent (Table 1), a small effect as expected for a classical S_N2 mechanism without hydrophobic overlap of surfaces in the transition state (such overlap, or a SET mechanism that decreased the hydrophobicity of the aniline nucleophile by converting it to a cation radical, should have led to a *decrease* in the rate with the added ethanol). The results with thiophenoxides **2** and **3** were quite different, a 75% rate increase in the reactions with 7 mol % ethanol vs that of the reactions in pure water (Table 1), consistent with a SET mechanism (Scheme 4).[16] The rates of the reactions are the same (within error) for both the hindered 2,6-dimethylthiophenoxide, **3**, and the unhindered thiophenoxide, **2**, indicating that there are no steric constraints to the reaction. This finding also supports the SET mechanism with its loose transition state compared with the classical S_N2 mechanism with its larger steric requirements.

We also examined displacements on the analogous *E*-4-(methylsulfoxymethyl)-cyclohexanecarboxylate, **5**, chosen because the carbon-mesylate bond is too strong to undergo easy one electron reduction and no evidence for a SET mechanism has been seen in related cases.[17] We found only small increases in the rate of the reaction of mesylate **5** with the thiophenoxides upon addition of 7 mol % ethanol, a 4% increase in the rate for thiophenoxide, **2**, and an 8% increase for that of 2,6-dimethylthiophenoxide, **3**, consistent with a classical S_N2 mechanism without hydrophobic overlap. As expected for this mechanism, the rate with the unhindered thiophenoxide, **2**, is 40% faster than with the hindered dimethylated nucleophile **3**. Adding 4.2 M LiCl to the water solvent in the reaction of 2,6-dimethylthiophenoxide, **3**, with the iodide **4** caused no rate effect, but doubled the reaction rate with the mesylate **5**. This further supports a change in mechanism upon going from the iodide to the mesylate substrate. As one more piece of evidence, the iodide **4** was more reactive than the mesylate **5** in displacements by the thiophenoxides (Table 1), but in direct displacement reactions of methyl derivatives with *N*-methylaniline and with phenoxide ion, we have found (unpublished work) that methyl mesylate is more reactive than methyl iodide. The higher reactivity of **4** over **5** with thiophenoxides in the data of Table 1 apparently reflects the kinetic advantage of the SET mechanism.

Scheme 4



Of course, the quantitative studies of such antihydrophobic effects are in their infancy and must be validated further. Furthermore, some charge neutralization of phenoxide or thiophenoxide ions could also occur in simple direct displacement reactions if they had late transition states in which the nucleophilic charge was partially erased. Such an effect may account for the 4% and 8% rate increases in the reactions of **5** with **2** and **3**. Thus, an increase in hydrophobicity of a thiophenoxide or phenoxide ion nucleophile at the transition state is not alone sufficient to establish a SET mechanism. However, our data taken all together support the conclusion that displacement on a primary iodide, but not a mesylate, by thiophenoxide ions uses the SET mechanism. Our results also help validate the use of the rate effects of antihydrophobic agents in water solution as supporting evidence for such a mechanism.

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Supporting Information Available: Synthetic procedures, spectroscopic data for new compounds, and experimental procedures (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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