J. Am. Chem. Soc. **1989**, *111*, 5880-5886

Changes of Selectivity in the Reactions of Substituted 4-Nitrobenzyl Sulfonates with Nucleophilic Reagents[1]

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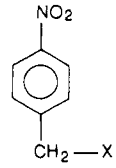
Abstract: The selectivities for anionic nucleophilic reagents are larger for reaction with 4-nitrobenzyl mesylate than with the corresponding triflate. Selectivities were determined over a range of rate constants of $\sim 10^4$ for nucleophiles and $\sim 10^5$ for 4-nitrobenzyl sulfonates in 20:80 CH_3CN/HOH (v:v) at 25 °C, ionic strength 0.5 M ($NaClO_4$). The slope of a correlation of log (k_N/k_{HOH}) for the two compounds is 1.12. Larger increases in selectivity of up to 11-fold were observed with more basic nucleophiles. The size of the additional increase is roughly proportional to the basicity of the nucleophile, and it is suggested that reaction of the partially desolvated species may contribute to these differences. The results are described by a positive interaction coefficient $p_{xy} = \partial s'/\partial \log k_{HOH} = \partial s_{lg}/\partial \log k_{nuc} = 0.026$. No significant change in selectivity of *p*-nitrobenzyl tosylate, nosylate, and triflate toward substituted anilines was observed over a 5–6-fold range of amine reactivity. The values of $\beta_{nuc} = 0.31$ and 0.26 for the reactions of substituted anilines and aliphatic amines, respectively, with 4-nitrobenzyl tosylate do not differ significantly (70:30 EtOH/HOH (v:v), 25 °C). The tosylate anion is a stronger nucleophile than water toward 4-nitrobenzyl triflate. It is concluded that S_N2 substitution reactions do follow the Hammond postulate, or "Bema Hapothle", but that the small magnitude of the changes in selectivity requires the examination of a large range of reactivity for both the nucleophile and the substrate.

The question of whether changes in structure-reactivity parameters and in the structure of the transition state occur in bimolecular substitution reactions at carbon is, to put it mildly, highly controversial. Reaction coordinate profiles, energy surfaces, and other theoretical approaches have suggested that selectivity should increase with decreasing reactivity of the leaving group or nucleophile, as described by the hypotheses of Bell, Marcus, Hammond, Polanyi, Thornton, Leffler, and others[3,4] or the Bema Hapothle,[5] while the configuration mixing model and other treatments have concluded that the opposite result is expected[6,7] and have questioned the interpretation of structure-reactivity parameters as measures of transition-state structure.[8,9] Several experimental studies have shown increases in selectivity with decreasing reactivity,[10-13] in agreement with the former hypothesis, while other studies have shown the opposite.[14,15] Arnett and Bordwell and their co-workers have reported experiments that show no changes in selectivity with changing reactivity of the nucleophile and leaving group and have concluded, forcefully, that such changes are of little or no significance.[16,17]

We report here an experimental approach to these problems based on an examination of the selectivity of a series of anionic nucleophilic reagents toward the *p*-nitrobenzyl sulfonates **1a–d**,



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X = a, $—O_3SPhCH_3$, *p*-toluenesulfonate (tosylate);
b, $—O_3SPhNO_2$, *p*-nitrobenzenesulfonate (nosylate);
c, $—O_3SCH_3$, methylsulfonate (mesylate);
d, $—O_3SCF_3$, trifluoromethylsulfonate (triflate)

which differ in reactivity over a range of $\sim 10^5$. This reaction series was chosen for six reasons. (1) To study a reaction series in which there is a large difference in reactivity of the nucleophiles and the substrates but no change in the chemical structure of the leaving group at the site of bond cleavage. (2) To avoid polar substituents on the nucleophiles that might give rise to electrostatic interactions with substituents on the leaving group and cause changes in structure-reactivity coefficients that are unrelated to changes in transition-state structure. (3) To examine a reaction series in which reactivity and selectivity are determined directly, without a requirement for the use or interpretation of structure-reactivity parameters. (4) To determine whether changes in selectivity, for a given reactivity, are different for different classes of nucleophiles. (5) To examine substrates that are known to undergo bimolecular nucleophilic substitution at a convenient rate and give products that are convenient to analyze. Many studies of S_N2 substitution have been carried out with substituted benzyl compounds; the *p*-nitrobenzyl derivatives fit structure-reactivity correlations defined by other benzyl compounds and have a high selectivity toward nucleophiles.[18] (6) To take advantage of the fact that changes in the slope of structure-reactivity

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(1) This research was supported in part by grants from the National Institutes of Health (GM20888) and the National Science Foundation (PCM-8117816).

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correlations that arise from different substituents in the nucleophile and the leaving group are easier to determine and to interpret than changes in the slope of a correlation with structure-reactivity parameters that causes curvature in a single correlation.[19] Furthermore, energy-contour diagrams for these reactions suggest that changes are likely to be larger for cross-coefficients that describe interactions between the nucleophile and leaving group than for direct coefficients that give rise to curvature in correlations of log k against a property of the nucleophile or leaving group.[4,5,20a]

The results show that there is an increase in selectivity with decreasing reactivity of the benzyl sulfonate. The increase is small but well beyond experimental uncertainty; the largest increase is 11-fold. The failure to detect this increase in some previous studies arises from the requirement that a large range of reactivity must be examined for both the nucleophile and the leaving group in order to detect the change in selectivity. Electrostatic interactions between substituents on the nucleophile and the substrate also may mask small changes in selectivity.[20b]

Experimental Section

Materials. Reagent grade inorganic salts and absolute ethanol were used without further purification. Acetonitrile (Fisher Reagent Grade) was dried for 24 h over 4A, 8–12 mesh molecular sieves, distilled, and stored over molecular sieves.

Water was glass distilled. Anilines were recrystallized or distilled under reduced pressure; other amines were commerical preparations and were used without further purification. 4-Nitrobenzyl bromide was recrystallized from ethanol (mp 98–99.5 °C; lit. 99–100 °C[21]) and was shown to be >99% pure by HPLC.

4-Nitrobenzenesulfonic acid was prepared by refluxing 2.0 g of 4-nitrobenzenesulfonyl chloride in 100 mL of water for 2 h or until it was dissolved, and the hot solution was filtered. The water was removed by evaporation under reduced pressure, and the yellow solid was dried under vacuum (mp 109–111 °C; lit. 109–111 °C[21]).

Silver 4-nitrobenzenesulfonate was prepared from 0.5 g (2.5×10^{-3} mol) of 4-nitrobenzenesulfonic acid and 0.6 g (2.6×10^{-3} mol) of silver(*I*) oxide in 13 mL of dry acetonitrile. After stirring for 1 h in the dark the solution was gravity filtered, the acetonitrile was removed under reduced pressure, and the yellow solid was dried under vacuum.

4-Nitrobenzyl tosylate was prepared according to a published procedure[22] with the following modifications. After neutralization with aqueous sulfuric acid, the aqueous solution was extracted twice with 50-mL portions of ethyl ether. The combined ether layers were washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the product was recrystallized from anhydrous ethyl ether (mp 98–99 °C; lit. 105–105.5 °C); it was shown to be >99% pure by HPLC analysis.

4-Nitrobenzyl nosylate was prepared by the addition of 0.53 g (2.5×10^{-3} mol) of 4-nitrobenzyl bromide in 7 mL of dry acetonitrile to 0.76 g (2.5×10^{-3} mol) of silver 4-nitrobenzene sulfonate in 5 mL of dry acetonitrile at 0 °C in the dark. The solution was stirred at room temperature for 18 h, refluxed for 4 h, and filtered while hot to remove any silver bromide. The acetonitrile was removed under reduced pressure, and the beige solid was triturated twice with ethyl ether to give a product that was >98% pure by HPLC analysis, mp 167–170 °C.

4-Nitrobenzyl triflate was prepared by the addition of 0.6 g (2.3×10^{-3} mol) of silver triflate to 1.0 g (4.6×10^{-3} mol) of 4-nitrobenzyl bromide in 35 mL of carbon tetrachloride with stirring in a flask that was protected from light and moisture. After 8 h an additional 0.8 g of silver triflate was added, and the solution was stirred for 16 h. The solution was vacuum filtered through a fritted filter and washed with 20 mL of CCl_4. The resulting solution of 4-nitrobenzyl triflate was shown to be >95% pure by HPLC analysis after quenching aliquots in water, methanol, ethanol, or trifluoroethanol and analyzing for the appropriate 4-nitrobenzyl ether or alcohol. The CCl_4 solution was stored in a desiccator in a freezer. The triflate was shown to be stable for more than a month under these conditions. For each experiment ~1 mL of the solution was evaporated under reduced pressure, and the amber oil was used immediately.

4-Nitrobenzyl mesylate was prepared by the addition of 2.2 g (1.4×10^{-2} mol) of 4-nitrobenzyl alcohol to 1.8 g (1.6×10^{-2} mol) of methanesulfonyl chloride in 15 mL of dry pyridine at −10 °C with stirring. After stirring for 30 min at −10 °C, 30 mL of 5 N H_2SO_4 was added, and the solution was cooled to 0 °C. The crystalline product was collected by filtration and washed with cold water. Recrystallization from chloroform–low boiling petroleum ether gave a pale beige solid that was >99% pure by HPLC analysis, mp 102–104 °C.

Product Analysis and Kinetics. Reaction products were analyzed by high-pressure liquid chromatography (HPLC) with a Waters Associates Reverse Phase 5 μm NOVA-PAK C_{18} column in a radial compression module. Separation of the components of the reaction mixture was accomplished by gradient elution with 40:60 to 52:48 (v:v) CH_3CN/HOH mixtures. For the reaction of trifluoroethylamine with 4-nitrobenzyl tosylate the components of the reaction mixture were separated by isocratic elution with a mobile phase of 40:60 (v/v) HOH/MeOH. Peak areas were obtained by electronic integration of their UV absorbance at 277 nm with a Waters Model 730 data module. It was shown that all products had the same extinction coefficient at 277 nm under the conditions of the experiments.

Solutions of the sodium salt of the nucleophile and of $NaClO_4$, 0.5 M in 80:20 (v:v) HOH/CH_3CN, were prepared by dissolving the salts in 50 mL of water in a 100-mL volumetric flask. To this was added 20 mL of acetonitrile, and the flask was filled to volume with water.

The rate constant ratios k_N/k_{HOH} were determined by HPLC product analysis; k_N is the second-order rate constant for reaction with a nucleophile, and k_{HOH} is the pseudo-first-order rate constant for reaction with water. For the reaction of 4-nitrobenzyl mesylate with nucleophiles, known volumes of a 0.5 M solution of the nucleophile and a 0.5 M solution of $NaClO_4$ were placed in a 4-mL HPLC sample vial to give 0.08–0.5 M nucleophile in a total volume of 3 mL. To this was added 10 μL of a freshly prepared solution of $\sim 6.5 \times 10^{-2}$ M 4-nitrobenzyl mesylate in acetonitrile. The vial was closed with a Teflon-sealed cap, shaken, and placed in a constant temperature bath at 25 ± 0.2 °C. After an appropriate time the samples were analyzed by HPLC as described above. It was shown that all products were stable during the time of the experiment.

The ratio k_N/k_{HOH} for 4-nitrobenzyl triflate as a substrate was determined similarly, by rapidly injecting 10 μL of a solution of 4-nitrobenzyl triflate in acetonitrile with a Hamilton CR-700-20 constant rate syringe into 3 mL of a solution of the nucleophile that was being mixed on a vortex mixer. The reactions were carried out at room temperature, 25 ± 1 °C, and the products were analyzed by HPLC. The solution of 4-nitrobenzyl triflate was prepared shortly before use by dissolving 10 μL of 4-nitrobenzyl triflate in 1.0 mL of acetonitrile and was kept at 0 °C to prevent decomposition. A sample of 4-nitrobenzyl triflate in acetonitrile that stood in acetonitrile for 1 h at room temperature and was quenched with water gave >90% *N*-4-nitrobenzylacetamide [NMR ($CDCl_3$) δ 8.2 (d, 9 H_z, 2 H), 7.5 (d, 9 H_z, 2 H), 6.4 (b, 1 H_z), 4.5 (d, 6 H_z, 2 H), and 2.1 (s, 3 H)].[23] No reaction with acetonitrile was found after 30 min at 0 °C. It was shown that 4-nitrobenzyl tosylate did not decompose significantly over the time required for its analysis by HPLC in the reaction of 4-nitrobenzyl triflate with tosylate anion.

The ratio k_N/k_{HOH} was obtained from plots of [R–N]/[R–OH] against [N⁻] according to eq 1. Five concentrations of the nucleophile were used for each analysis, and the individual points followed eq 1 within ±5%, with rare exceptions. Replicate determinations showed good agreement. Several of the determinations with highly reactive nucleophiles, which were present in low concentrations, were confirmed by measuring product ratios in the presence of the nucleophile and azide, which is also a reactive nucleophile. These experiments gave no indication of systematic errors from local depletion of the concentration of strong nucleophiles during mixing.

$$[\text{R–N}]/[\text{R–OH}] = k_N[\text{N}^-]/k_{HOH} \qquad (1)$$

The pseudo-first-order rate constant, k_{HOH}, for solvolysis of $\sim 2 \times 10^{-3}$ M 4-nitrobenzyl mesylate in 80:20 HOH/CH_3CN (v:v) was determined by HPLC analysis of mesylate disappearance at 13 times over 3 half-lives. The only observed product was the alcohol.

The pseudo-first-order rate constant for solvolysis of 4-nitrobenzyl triflate in 80:20 HOH/CH_3CN (v:v) was obtained by adding 10 μL of a freshly prepared solution of 4-nitrobenzyl triflate in acetonitrile (kept at 0 °C) with a Hamilton CR-700-20 constant rate syringe to 1.5 mL

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Table I. Nucleophilic Selectivities, k_N/k_{HOH}, for Reactions of Anionic Nucleophiles with 4-Nitrobenzyl Mesylate and Triflate in 20:80 CH_3CN/H_2O (v:v) at 25 °C and Ionic Strength 0.5 M ($NaClO_4$)

nucleophile	k_N/k_{HOH}, M^{-1}, for leaving group $-OSO_2CH_3$	$-OSO_2CF_3$
I^-	260	100
Br^-	36	18
Cl^-	7	3.7
F^-	0.22	0.094
NO_3^-	0.47	0.44
CH_3COO^-	5.4	1.6
N_3^-	630	160
SCN^-	330	100
HO^-	30	2.7
$(CF_3)_2CHO^-$	29	6
CH_3CONHO^-	1200	120
HOH	0.023[a]	0.023[a]
$CH_3C_6H_4SO_3^-$		0.19

[a] Corrected to a standard state of 1 M, for comparison.

of 0.5 M $NaClO_4$ in 80:20 HOH/CH_3CN (v:v) that was being mixed rapidly on a vortex mixer. The reaction was then quenched by forcefully injecting 1.5 mL of 7.0 M aqueous NaI into the reaction mixture after 1, 2, 3, 4, and 5 s. The solution was then analyzed by HPLC. It was shown that 3.5 M NaI quantitatively converts 4-nitrobenzyl triflate to 4-nitrobenzyl iodide. A 4-point semilogarithmic plot of the fraction of 4-nitrobenzyl iodide against time gave a first-order rate constant of 1.3 s^{-1}.

Selectivities, k_{amine}/k_{EtOH}, for 4-nitrobenzyl tosylate, nosylate, and triflate in 70:30 EtOH/HOH (v:v) were determined similarly. Aliquots from the reaction of 0.008–0.05 M amine with ~9 × 10^{-5} M tosylate at 25 ± 0.2 °C were analyzed by HPLC at appropriate times. The nosylate was analyzed similarly, except that the reaction was initiated by the addition of 10 μL of ~0.028 M substrate in acetonitrile to 3.0 mL of solution. Reactions of the triflate were initiated with the constant rate syringe and a vortex mixer at room temperature, as described above.

Values of k_{amine}/k_{EtOH} were obtained as described for the anionic nucleophiles, with at least five concentrations of amine in the range 0.005–0.05 M. These results and the observed value of k_{EtOH}/k_{HOH} were used to calculate k_{amine}/k_{HOH}. This ratio could not be measured directly in some reactions because of interference by unreacted amine with the alcohol peak on HPLC analysis.

Determination of Amine pK_a. Measurements of pH were made at 25 ± 0.1 °C with an Orion Research Model 701A pH meter, a glass combination electrode containing saturated potassium chloride, and a thermostated cell holder. The meter was standardized at pH 7.0 and 4.0 with standard aqueous buffers, and the pH of 0.01 M HCl in 70:30 EtOH/HOH (v:v) was recorded. A 0.05 M solution of amine was neutralized with 0.05 M HCl and titrated with 0.05 M NaOH, all in 70:30 $EtOH/H_2O$ (v:v). The pH was calculated from the apparent pH according to eq 2, which was obtained from the observed pH readings of

$$pH = pH_{app} - 0.38 \qquad (2)$$

0.001, 0.01, 0.03, and 0.05 M HCl in water and in 70:30 EtOH/HOH. The pH meter was readjusted for drift, if necessary, and a correction for the amount of HCl required to maintain the pH was made for 3-nitroaniline.[24] Plots of log [amine]/[amine H^+] had slopes of 1.0.

Results

Pseudo-first-order rate constants of k_{HOH} = 2.0 × 10^{-5} and 1.3 s^{-1} for the reactions of *p*-nitrobenzyl mesylate and triflate, respectively, in 20:80 CH_3CN/H_2O (v:v) and ionic strength 0.5 M ($NaClO_4$) at 25 °C were determined as described in the Experimental Section. Rate constant ratios for the reactions with anionic nucleophiles and water, k_N/k_{HOH}, were determined by product analysis with HPLC and eq 1; they are reported in Table I.

Rate constant ratios, k_{amine}/k_{HOH}, for the reactions of substituted anilines and aliphatic amines with *p*-nitrobenzyl tosylate, nosylate, and triflate in 70:30 EtOH/HOH (v:v) at 25 °C were determined by product analysis as described in the Experimental Section and are reported in Table II. Typical data, for the reactions of 4-nitrobenzyl nosylate with substituted anilines, are shown in Figure 1.

Table II. Nucleophilic Selectivities, k_{Amine}/k_{EtOH}, for Reactions of Amines with 4-Nitrobenzyl Sulfonates in 70:30 EtOH/HOH (v:v) at 25 °C

amine	pK_a[a]	$10^{-2}(k_{Amine}/k_{EtOH})$, M^{-1}, for leaving group X^- OTs	ONs	OTf	OTs/OTf[b]
4-methylaniline	4.34	13	13		
aniline	3.83	9.2	6.8	3.0	3.1
4-chloroaniline	3.00	5.4	4.6	2.0	2.7
3-chloroaniline	2.61	3.9	2.9	1.5	2.6
3-nitroaniline	1.40	1.6	1.5	0.60	2.7
ethylamine	9.73	3.7			
methoxyethylamine	8.62	2.8			
cyanoethylamine	6.88	0.95			
trifluoroethylamine	4.60	0.23			

[a] In 70:30 EtOH/HOH (v:v) at 25 °C and ionic strength 0.025 M. [b] $(k_{amine}/k_{EtOH})_{OTs}/(k_{amine}/k_{EtOH})_{OTf}$.

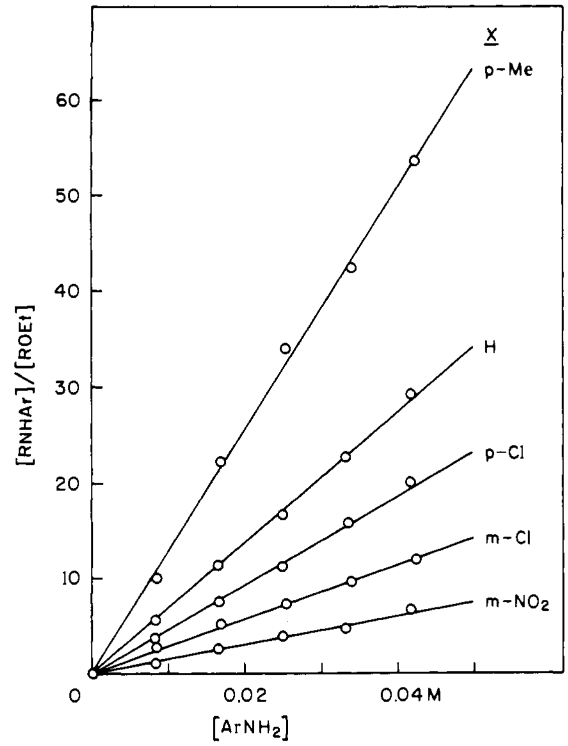

Figure 1. Product yields from the reactions of 4-nitrobenzyl nosylate with substituted anilines in 70:30 EtOH/HOH (v:v) at 25 °C.

The ratio k_{tos}/k_{HOH} = 0.19 M^{-1} for reaction with 4-nitrobenzyl triflate (Table I) shows that the tosylate anion is eight times more reactive than water when equal molarities of the two nucleophiles are compared. Kohnstam et al. have shown previously that nucleophilic reactivity toward 4-phenoxybenzyl chloride decreases in the order Cl^- > F^- > NO_3^- > $PhSO_3^-$.[25]

Discussion

Figure 2 shows that the selectivity of 4-nitrobenzyl mesylate toward nucleophilic reagents, log(k_N/k_{HOH}), is significantly larger than that of 4-nitrobenzyl triflate. The lower line has a slope of 1.0, and the slope of the solid line through the rate constants for reaction with weakly basic nucleophiles is 1.12. Larger increases in selectivity are observed for more basic nucleophiles (open squares). The increases in selectivity range up to a factor of 11. These increases in selectivity are observed with a decrease in reactivity by a factor of 8 × 10^4 for the solvolysis of the mesylate compared with the triflate. The range of reactivity of the series

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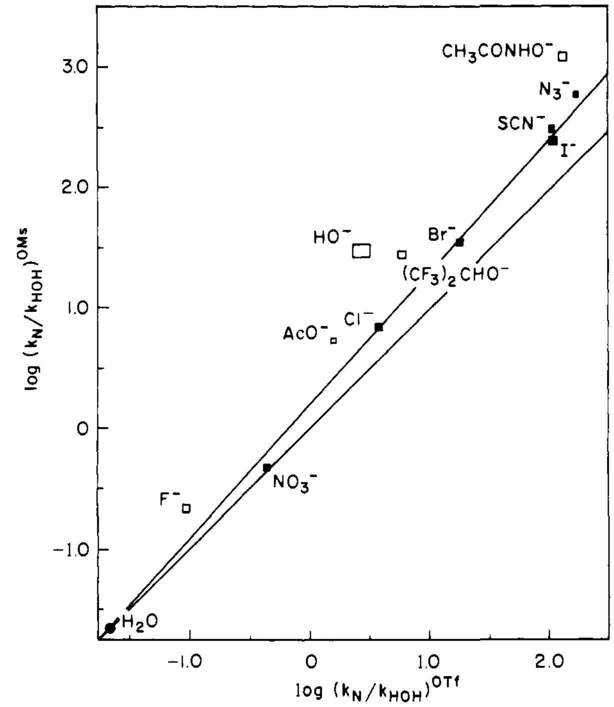

Figure 2. Selectivities $\log(k_N/k_{HOH})$, for reactions of 4-nitrobenzyl mesylate and triflate with anionic nucleophiles in 20:80 CH_3CN/HOH (v:v) at 25 °C. The sizes of the squares correspond to the estimated error of the selectivities. The open squares are the selectivities of basic nucleophiles.

of nucleophiles for a given substrate is $\sim 10^4$.

Clearer evidence for these conclusions is provided by the logarithmic plot in Figure 3 of the selectivity of the different nucleophilic reagents against their reactivity toward 4-nitrobenzyl mesylate. If there were no increase in selectivity, all of the points would fall on the lower line of zero slope. The selectivity is greatest for the most basic nucleophiles, shown by the open circles. There is an increase in selectivity with increasing reactivity of the weakly basic nucleophiles (closed circles) and for the basic nucleophiles, with the exception of hydroxide ion. The selectivities and reactivities are plotted as the k_N/k_{HOH} ratios that were determined experimentally by product analysis; the rate constants for water are corrected to a standard state of 1.0 M in Figures 1 and 2 for comparison with the other reagents. The slope of the solid line is 0.12; a line drawn through the point for NO_3^-, instead of water, has a slope of 0.16.

Swain–Scott correlations with rate constants for the reactions of methyl iodide in water[26] give slopes of $s = 0.67$ for 4-nitrobenzyl mesylate and 0.61 for the triflate (not shown). These correlations confirm the increase in selectivity of about 10% for the less reactive substrate; they also show that these compounds exhibit the expected behavior for S_N2 substitution reactions and are approximately two-thirds as selective toward nucleophiles as is the reference compound.

The large increases in selectivity for the more basic nucleophilic reagents, shown as the open circles in Figures 2 and 3, mean that the selectivity of these nucleophiles corresponds to that expected for stronger nucleophiles. This increase in selectivity actually causes a reversal of the relative reactivities of azide and acetohydroxamate ions, the two most reactive nucleophiles that were examined. The hydroxamate, which is an "α-effect" compound, is more reactive than azide with the more selective mesylate compound (Table I).

Part, but probably not all, of this increase in selectivity could arise from reaction of partially desolvated nucleophile (eq 3). A basic nucleophile is expected to be strongly solvated in water and may undergo partial desolvation, with the equilibrium constant K_D. The desolvated species represents only a small fraction of the total nucleophile concentration and has a correspondingly larger rate constant.[27] This notion is consistent with the large increases, by factors of up to 10^9, in the reactivity of basic anions in aprotic compared with hydroxylic solvents[28] and with limiting rate constants for the diffusion-controlled reactions of acetate and trifluoroethoxide ions with 1-phenylethyl carbocations that are about 10-fold smaller than those for azide ion, which is believed to be less strongly solvated.[29] It is also consistent with the correlation in Figure 4, which shows that the deviation increases with increasing basicity of the nucleophile, with a slope of 0.05. Solvation is expected to become stronger with increasing basicity of the anion. Furthermore, the deviation is larger for hydroxide than for acetohydroxamate ion, although the hydroxamate is more reactive. However, the values of K_D that are required to account for the entire change in selectivity from an extrapolation of the line in Figure 3 are very small, in the range $10^{-2.2}$–$10^{-5.9}$; a value of $K_d = 0.02$ has been suggested for base-catalyzed proton removal from thiazolium cations by hydroxide ion.[30] This suggests that fluoride and basic oxygen anions may have an intrinsically larger tendency than other nucleophiles to undergo an increase in selectivity with increasing reactivity, in addition to a requirement for partial desolvation.

$$RO^-(HOH)_n \underset{}{\overset{K_D}{\rightleftharpoons}} RO^-(HOH)_{n-x} + xH_2O \xrightleftharpoons{ArCH_2X} \ddagger \quad (3)$$

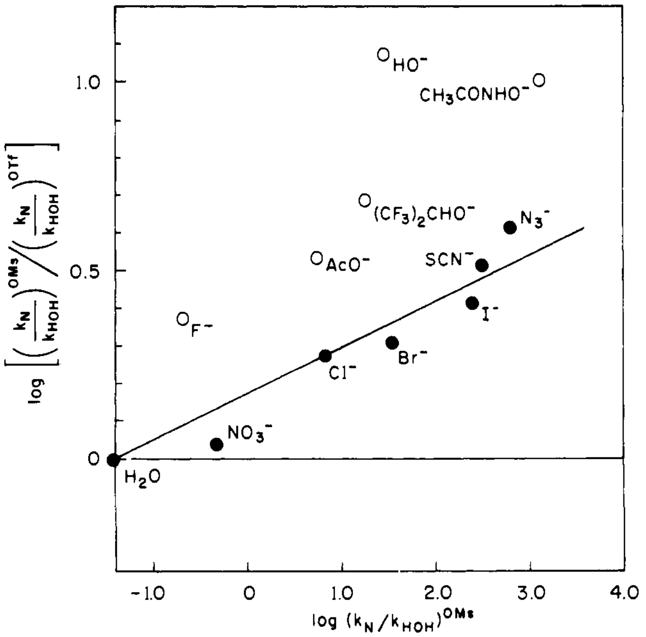

Figure 3. The dependence of the selectivity ratio for reactions of 4-nitrobenzyl mesylate and triflate with anionic nucleophiles on the reactivity of the nucleophile, in 20:80 CH_3CN/HOH (v:v) at 25 °C. The open circles refer to basic nucleophiles.

It is useful to describe the change in selectivity directly by the p_{xy} cofficient of eq 4, which does not require the use of indirect

$$p_{xy} = \frac{\partial s'}{-\partial \log k_{HOH}} = \frac{\partial s_{lg}}{-\partial \log k_{nuc}} \qquad (4)$$

measures of reactivity such as n or pK_a. In eq 4 $s'$is the selectivity from log k for the reactions of 4-nitrobenzyl sulfonates with

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different nucleophilic reagents, k_{HOH} is a measure of the reactivity of the substrate, s_{lg} is the sensitivity of log k_{HOH} to the structure of the leaving group, and k_{nuc} is the rate constant for reaction of a nucleophile with 4-nitrobenzyl triflate.[5] The value of p_{xy} for the reactions with weakly basic nucleophiles is $0.12/4.9 = 0.024$. This result is virtually identical with a value of $p_{xy} = 0.11/4.16 = 0.026$ for the reactions of methyl tosylate and methyl triflate with substituted benzenethiolate anions in sulfolane[11] (the values of log k_{nuc} are for the reactions with PhS^-). It is about one-third as large as the p_{xy} coefficient of 0.080 for the reaction of substituted pyridines with phosphorylated pyridines[20] (this p_{xy} coefficient is also defined in terms of log k according to eq 4, with values of log k_{nuc} for the reactions with pyridine, rather than in terms of pK_{nuc} and β_{nuc}[20]).

These are classical Hammond, or Polanyi, or "Bema Hapothle" effects.[3-5] They can be described empirically by energy contour diagrams in which the x and y axes are defined by the amount of bond breaking and bond formation, which may be estimated from the sensitivity to the nature of the leaving group and the nucleophile, s_{lg} and s', respectively.[4,5,31,32] A change to a poorer leaving group, such as from triflate to mesylate, raises the energy of the right side of the diagram. The position of the transition state at a saddle point is then expected to move in the direction along the reaction coordinate toward the position of higher energy on the right side of the diagram and to move perpendicular to the reaction coordinate away from the position of higher energy. There is a tendency of these movements to cancel with respect to movement along the x coordinate for bond breaking, so that the change in s_{lg} is expected to be less than the change in s'.[5,31,32] These are the same changes that are described by Thornton's reacting bond rules.[4] This behavior has been observed for reactions of phosphorylated pyridines.[20]

The rate constants for reactions of substituted anilines with 4-nitrobenzyl tosylate and triflate, as measured by the ratio $k_{\mathrm{amine}}/k_{\mathrm{EtOH}}$ (Table II), show a small increase in selectivity with decreasing reactivity that is consistent with the value of $p_{xy} = 0.024$, but the range of reactivity of 5–6-fold for different nucleophiles that was examined is not large enough to determine a reliable p_{xy} coefficient.

Other Reactions. Previous studies have shown increases, decreases, or no change in selectivity with increasing reactivity of the nucleophile with different leaving groups for bimolecular substitution at saturated carbon.

Berg et al. observed an increase in selectivity for the reactions of pyridines with 2-substituents of increasing size and methyl iodide compared with methyl fluorosulfonate, which is 10^4 more reactive.[10] The increased steric hindrance for reactions with the less reactive compound provides rather direct evidence for a tighter transition state with this compound. Le Noble and co-workers observed increasingly negative volumes of activation with increasing bulk of the substituents in the reaction of 2,6-dialkylpyridines with methyl iodide that are consistent with a later transition state for the slower, more hindered reactions; they reached the same conclusion from an increase in the chloride isotope effect in the corresponding reactions with methyl chloride.[33] Increases in ρ_{lg} in the series 0.74, 0.90, and 1.39 for the reactions of substituted methyl arylsulfonates with decreasing reactivity of the nucleophile in the series PhO^-, MeO^-, and MeOH, respectively, were reported by Buncel and Chuaqui,[13] and Kevill has shown that the sensitivity of allyl sulfonates toward the nucleophilicity of the solvent, l, increases with decreasing reactivity of the leaving group; there is a progressive increase in l from 0.86 to 1.07 with increasing leaving group basicity.[13] Lee et al. have recently shown an increase in β_{nuc} from 0.65 to 0.75 with decreasing leaving group ability for the reactions of substituted anilines with phenacyl benzylsulfonates over a range of reactivity of only ~10-fold.[34]

Large changes in selectivity are well-known with changes in the *nature* of the leaving atom, but they do not necessarily correlate with changes in reactivity. For example, nucleophilic substitution at secondary carbon, with 1-(4-nitrophenyl)-2-propyl-X, follows Swain–Scott correlations with $s = 0.27$, 0.34, and 0.43 for the tosylate, bromide, and iodide, respectively, but the reactivity toward most nucleophiles decreases in the order tosylate > iodide > bromide.[35] Similarly, Ballistreri et al. observed an increase in the ratio $k_{\mathrm{RI}}/k_{\mathrm{RCl}}$ from 64 to 147 with increasing basicity of the nucleophile in the reaction of substituted anilines with benzyl halides in ethanol.[18b]

On the other hand, Arnett and Reich observed a linear structure-reactivity correlation for the reaction of methyl iodide with a series of nucleophilic reagents in acetonitrile and found no change in the slopes of correlations of log k, for the alkylation of substituted pyridines by different reagents, against the pK_a values of the pyridines over a range of ~10^9 in reactivity.[16] Bordwell and Hughes found no effect of substitution in the leaving group on the selectivity for reactions of fluorenide anions with *N*-benzyl-*N*,*N*-dimethylanilinium ions over a range of reactivity of ~20-fold for different leaving groups,[17] and Ando et al. found no difference in the nitrogen isotope effect for the reaction of *N*,*N*-dimethyl-4-methylaniline with a series of benzyl sulfonates substituted in the leaving group, over a 12-fold range of reactivity.[36]

Finally, the opposite behavior has been observed in several studies. Lee et al. observed an increase in ρ_{lg} from 1.35 to 1.57 with increasing basicity of the aniline in reactions with substituted benzyl arylsulfonates in methanol–acetonitrile and a similar result with 2-phenylethyl sulfonates[15] which correspond to a negative p_{xy} coefficient. An increased sensitivity to electron-donating substituents on arylthiolate anions with better leaving groups was reported by Westaway and Ali for the reaction with substituted *N*-benzyldimethylanilinium ions in dimethylformamide[14] and was attributed to an electrostatic interaction.

There are explanations for some, but not all, of these differences in behavior. (1) This work and the earlier measurements of Lewis and Vanderpool[11] show that the changes in selectivity are small for ordinary substitution reactions on carbon with changes in the nucleophile and leaving group, so that it is necessary to examine a range of reactivities of at least 10^4–10^5 for variation of *both* the nucleophile and the leaving group[11] in order to detect differences in selectivity. (2) It is difficult to establish and to interpret the existence of curvature in a structure-reactivity correlation; changes in cross coefficients such as p_{xy} are easier to determine and are expected to be larger than changes in direct coefficients, such as $p_x = -\partial\beta_{\mathrm{nuc}}/\partial pK_{\mathrm{nuc}}$.[4,5,19,20a] (3) It is necessary to compare closely related reactions under the same experimental conditions. Thus, it is difficult to draw a conclusion from correlations of pK values of pyridines in water with rate constants for the alkylation of pyridines by different alkylating agents that were measured in different solvents.[16]

The increases in selectivity with increasing reactivity[14,15] are consistent with predictions of the configuration mixing model of Pross and Shaik[6] and with an important contribution of polarization and change transfer in a molecular orbital model of Lee et al.[7,15] These workers have suggested that an electron-withdrawing substituent that stabilizes the development of negative charge on the leaving group, for example, will not only stabilize the transition state in which this negative charge is partially developed but will also increase the *rate of change* of transition-state stability with increasing electron withdrawal. It will increase the extent to which the transition state resembles the structure with negative charge on the leaving group; it will increase the contribution of this structure to the structure of the transition state.[6] The theory also includes changes in the position of the transition state along the reaction coordinate corresponding to

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normal Hammond effects,[9,37,38] so that it is consistent with either experimental result.

Electrostatic Interactions. The possibility should also be considered that "anti-Hammond" effects from variation of the nucleophile and leaving group may represent simple electrostatic effects from dipole–dipole or charge–dipole interactions, which do not require a change in the structure of the transition state.[5,14-16,39] For example, the transition state may be stabilized by an electrostatic interaction between an electron-withdrawing substituent on the leaving group and an electron-donating substituent on the nucleophile. This will increase the rate constant and, therefore, increase the value of β_{nuc} or s for reactions with this more reactive leaving group, which corresponds to an "anti-Hammond" effect or a negative p_{xy} coefficient. Several of the reaction series in which negative p_{xy} coefficients or no changes in structure-reactivity parameters were observed were carried out by varying polar substituents in the reactants that might be expected to give electrostatic effects of this kind.[14,15,17]

Bordwell and Hughes have recently reported an increase in β_{nuc} with increasing σ for substituents on the benzyl group in the reactions of substituted fluorenide anions with substituted benzyl-*N*,*N*-dimethylanilinium ions in Me_2SO. This change in β_{nuc} corresponds to a positive $p_{xy'}$ coefficient (eq 5), which describes an interaction between substituents on the nucleophile and on the central carbon atom that is undergoing substitution. It was suggested that this change arises from an electrostatic interaction between the negative charge of the anion and the polar substituent on the benzyl group, rather than from a change in transition-state structure.[17]

$$p_{xy'} = \partial\beta_{nuc}/\partial\sigma = \partial\rho/\partial pK_{nuc} \qquad (5)$$

The observation that ρ is larger and often changes from negative to positive for reactions of substituted benzyl compounds with anionic compared with uncharged nucleophiles is consistent with an electrostatic interaction between an anionic nucleophile and the substituent that increases ρ.[14,15,17,30,18b,40-42] However, this charge–dipole interaction will give an increased value of ρ that is constant; it does not explain the *change* in ρ with changing substituents on the nucleophile that is described by the $p_{xy'}$ coefficient. The observation that ρ for reactions with substituted benzyl compounds increases with electron-donating substituents on the nucleophile for reactions with substituted (uncharged) anilines also shows that the change in ρ does not arise from a charge–dipole interaction.[18b,42]

If there were a significant dipole–dipole interaction between substituents on the benzyl group and polar substituents on the nucleophile, it could give a positive $p_{xy'}$ coefficient because the interaction is different for different nucleophiles. However, the energy of a simple dipole–dipole interaction is proportional to cos θ, and the polar substituent on the benzyl group is approximately perpendicular to that on the nucleophile,[43] so that any such dipole–dipole interaction is expected to be small. It is conceivable that polarization by substituents could induce a favorable electrostatic interaction between partial charges on the substrate and the nucleophile, in spite of this unfavorable geometry.[14]

If any such interaction between substituents on the nucleophile and the central carbon atom is significant, an electrostatic interaction between substituents on the leaving group and the nucleophile is expected to be of comparable or greater significance, in spite of the additional atom that separates the substituents, because of the more favorable geometry for colinear compared with perpendicular dipole–dipole interactions.[43] This corresponds to a negative p_{xy} coefficient, as described above. We must conclude, therefore, that if electrostatic effects are significant and the observed p_{xy} coefficient is zero, this result requires that there is a fortuitous cancellation of a negative p_{xy} coefficient from the electrostatic effect and a positive p_{xy} coefficient from a change in transition-state structure. In other words, there is an increase in selectivity ($\partial\beta_{nuc}$) with a less reactive leaving group (∂pK_{lg}), which is masked by an electrostatic interaction.

The unfavorable geometry for a dipole–dipole interaction between substituents on the nucleophile and the benzyl group and the observed changes in secondary deuterium isotope effects on the benzylic carbon atom with changing benzyl substituents[40a,41] support the conclusion that the observed changes in the effects of substituents on the nucleophile and benzyl group do represent changes in transition-state structure.

Rothenberg et al. have shown that interactions between polar substituents on the benzene ring and on substituted aliphatic alcohols are responsible for changes in the equilibrium constants, K_{AB}, for interconversion of ring-substituted 1-phenylethyl ethers with different alcohols (eq 6).[39] These interactions correspond

$$ArCH(CH_3)OCH_2X + HOCH_2Y \overset{K_{AB}}{\rightleftharpoons} ArCH(CH_3)OCH_2Y + HOCH_2X \qquad (6)$$

to a *negative* p_{xy} coefficient of −0.10 that can be attributed to a simple electrostatic interaction in a ground-state reaction at equilibrium. The magnitude of this interaction is consistent with the τ value of 0.013 that describes the Hine coefficient for the formation of hydrogen bonds between substituted phenolate ions and protonated aliphatic amines in aqueous solution.[44] The formation of hydrogen bonds is also believed to arise largely or entirely from an electrostatic interaction.[45]

These results suggest, although they do not prove, that negative p_{xy} coefficients for correlations of reaction rates can arise from simple electrostatic interactions. The uncertainty arises from the possibility that there may be significant covalent contributions to hydrogen bonding and that the negative p_{xy} coefficient in the 1-phenylethyl ether series could reflect changes in ground-state structure that arise from interactions between electron-donating and electron-withdrawing substituents. Kirby and co-workers have shown that an electron-donating group at the β-position increases the C–O bond length,[46] which corresponds to the behavior that is expected from double bond–no bond resonance.

Finally, we wish to comment on an earlier conclusion of Young and Jencks that the reactivity-selectivity principle (RSP) should be abandoned as a general principle,[31] which has sometimes been misinterpreted. The emphasis in this conclusion is on the word *general*. It is unreasonable to expect that the RSP should be manifested in all reaction series. It may not be detected because the reaction series that was examined covers too small a range of reactivity, because of cancellation of parallel and perpendicular movements of the reaction coordinate, because of sharp curvatures of the reaction surface, because of electrostatic interactions that counteract it, or because it does not occur.[4,5,17,39] However, it is equally unreasonable to conclude that changes in transition-state structure do not occur. There is no reason to believe that all transition states in chemistry must have exactly the same structure for a given class of reaction, and there are numerous examples of changes in structure-reactivity parameters and isotope effects within reaction series.[47] It is unlikely that none of these changes arise from changes in transition-state structure. We suggest,

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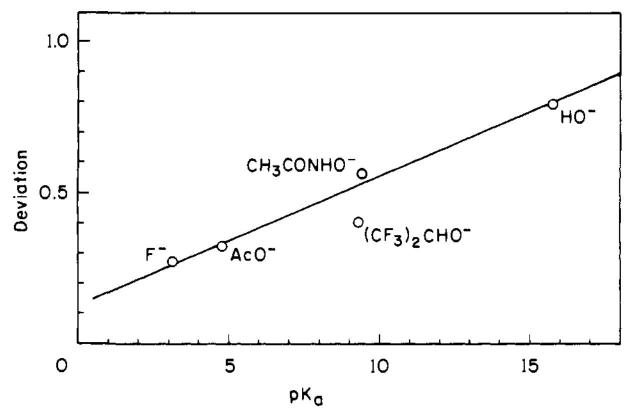

Figure 4. The dependence of the deviations in the selectivities of basic nucleophiles, from the correlation in Figure 2, on the basicity of the nucleophile.

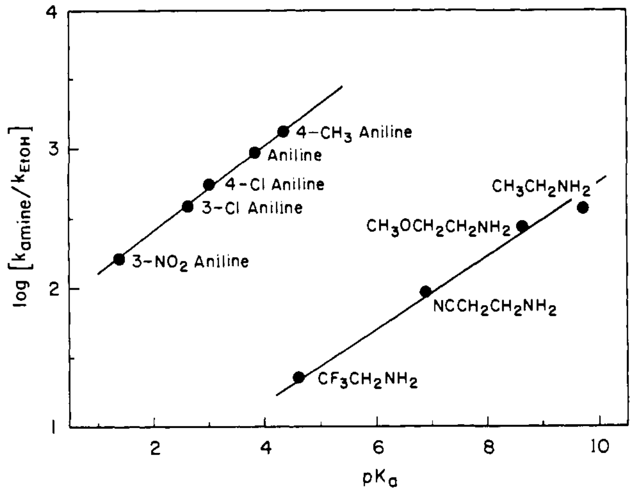

Figure 5. Brønsted-type plots for the reactivities of substituted anilines and aliphatic amines with 4-nitrobenzyl tosylate in 70:30 EtOH/HOH (v:v) at 25 °C.

therefore, that it is time to terminate the debate as to *whether* or not the RSP exists. The problem is to identify, characterize, and interpret the changes that are observed in the hope that these will provide a better understanding of the nature of chemical reactions and their transition states.

Values of β_{nuc} for Displacement by Amines. The dependence on amine basicity of the rate constants for S_N2 displacement on 4-nitrobenzyl tosylate is shown in the Bronsted-type plots of Figure 5. The slopes of the two lines do not differ significantly; the values of β_{nuc} are 0.31 for the substituted anilines and 0.26 for the aliphatic amines. This conclusion is different from that of an earlier study, in which values of $\beta_{nuc} = 0.62$ for anilines and 0.20 for aliphatic amines were reported.[48] The reason for the difference in results is not clear, but the earlier results[48] were obtained from a comparison of rate constants in methanol with pK_a values in water, and the slope for anilines was heavily weighted by the rate constant for *p*-nitroaniline.

The very similar values of β_{nuc} for reactions of aliphatic amines and anilines provide no evidence for a different transition-state structure for these two classes of amines, which might arise from resonance in the aniline series[49] for example. However, the absolute values of the rate constants are nearly two orders of magnitude larger for the anilines compared with the aliphatic amines, for a given basicity. The reactivity of phenoxide ion for nucleophilic substitution at carbon is also unusually large compared with that of the more basic methoxide ion,[13] and benzenethiolate anion is 10^2–10^4 more reactive than methanethiolate anion in nucleophilic aromatic substitution with iodonitrobenzenes in methanol.[50] Stabilization of the transition state by interaction with the aromatic ring of phenoxide and arylthiolate anions could conceivably represent an interaction similar to the stabilization from the electron pair at the α position of α-effect nucleophiles in substitution at carbon.[51]

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Silylative Decarbonylation: A New Route to Arylsilanes[1]

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Abstract: A new synthetic procedure for the preparation of aromatic chlorosilanes via the palladium-catalyzed reaction of methylchlorodisilanes and aromatic acid chloride is described. The silylative decarbonylation process is solventless, can utilize low metal catalyst loadings (500–1000 ppm Pd), is carried out under moderate conditions (145 °C), and selectively gives aromatic chlorosilanes in good yield, generally 60–85%. The procedure is tolerant of a variety of aromatic substituents, for example, alkyl, halo, nitro, cyano, imide, acid anhydride, etc., and the synthesis of several new substituted aromatic chlorosilanes containing benzoyl chloride and phthalic anhydride moieties is described. Chloromethyldisilane starting reagents are available from the direct reaction of methyl chloride and silicon, making this methodology an attractive synthetic route to functionalized aromatic chlorosilanes.

Aromatic chlorosilanes are employed in a wide variety of applications in the silicone industry.[2] While some arylsilanes can be prepared in the laboratory by utilizing aryl Grignard type reactions with chlorosilanes (within the usual constraints of substituents which can tolerate such a method), only two synthetic procedures are currently practiced industrially: the direct reaction of chlorobenzene with silicon to yield primarily diphenyldichlorosilane (Rochow process)[3] and the boron trichloride catalyzed reaction between methyldichlorosilane and benzene to give methylphenyldichlorosilane (Barry process).[4,5] There are undesirable

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