

and for the reverse reaction in 50:50 TFE:H₂O.³ The two values are in excellent agreement, better than might be expected in view of the difference in solvent and the probable error of the rate constants used in these calculations.

Registry No. 4-(CH₃)₂NC₆H₄C⁺HCH₃, 82414-94-6; 4-CH₃OC₆H₄C⁺HCH₃, 18207-33-5; 4-CH₃SC₆H₄C⁺HCH₃, 82414-95-7; 4-PhOC₆H₄C⁺HCH₃, 82414-96-8; 4-CH₃O-3-BrC₆H₃C⁺HCH₃, 88510-80-9; 4-CH₃O-3-O₂NC₆H₃C⁺HCH₃, 88510-81-0; 4-CH₃C₆H₄C⁺HCH₃,

31042-87-2; 4-FC₆H₄C⁺HCH₃, 31067-69-3; 3-CH₃OC₆H₄C⁺HCH₃, 82414-97-9; 3-BrC₆H₄C⁺HCH₃, 82414-98-0; 4-O₂NC₆H₄C⁺HCH₃, 82415-00-7; CH₃CH₂OH, 64-17-5; CH₃(CH₂)₃CH₂OH, 71-41-0; CH₃-OH, 67-56-1; Cl(CH₂)₃OH, 627-30-5; CH₂=CHCH₂OH, 107-18-6; HO(CH₂)₂OH, 107-21-1; CH₃O(CH₂)₂OH, 109-86-4; Cl(CH₂)₂OH, 107-07-3; NC(CH₂)₂OH, 109-78-4; HC≡CCH₂OH, 107-19-7; Cl₂CH-CH₂OH, 598-38-9; CH₃CO₂⁻, 71-50-1; HCO₂⁻, 71-47-6; CH₃OCH₂C-O₂⁻, 20758-58-1; ClCH₂CO₂⁻, 14526-03-5; F₃CCH₂O⁻, 24265-37-0; CH₃CH₂CH₂SH, 107-03-9; HOCH₂CH₂SH, 60-24-2.

Concerted Bimolecular Substitution Reactions of 1-Phenylethyl Derivatives¹

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Abstract: Substituted 1-phenylethyl derivatives with $\sigma^+ > -0.08$ exhibit bimolecular substitution reactions with azide ion in 20% acetonitrile in water. The reactions with 1-phenylethyl chlorides follow a Hammett correlation with $\rho = -2.9$, compared with $\rho = -5.6$ ($\rho^+ = 1.15$) for solvolysis. Swain-Scott correlations give values of $s = 0.46$ and 0.22 for 1-(4-nitrophenyl)ethyl chloride and tosylate, respectively; there are large positive deviations for azide ion and water and negative deviations for cyanide ion. The value of β_{nuc} is 0.09 for reactions of substituted acetates with the chloride. The reactions exhibit "synergism" between the nucleophile and leaving group that favors the bimolecular reaction with Me₂S, Br⁻ > Cl⁻ > OTs⁻ leaving groups. The bimolecular reaction with azide follows the Grunwald-Winstein Y correlation with $m = 0.8$ in methanol-water mixtures. Bimolecular reactions with less reactive nucleophiles in the series N₃⁻, CN⁻, AcO⁻, and ROH appear at progressively larger σ values, as the carbocation becomes less stable. It is concluded that these reactions are S_N2 displacements that proceed through an open, "exploded" transition state that closely resembles a carbocation. Specific salt effects are small in water but are significant in acetonitrile-water mixtures and could be mistaken for normal or induced common ion rate depressions. No evidence was obtained for nucleophilic assistance to the formation of a carbocation intermediate. Concurrent S_N1 and S_N2 pathways occur in the reactions with solvent and azide of [1-(4-methylphenyl)ethyl]dimethylsulfonium ion, 1-(4-fluorophenyl)ethyl chloride, 1-(3-methoxyphenyl)ethyl chloride, and, probably, 1-(3-nitro-4-methoxyphenyl)ethyl chloride. Crude estimates of the lifetime of the carbocation intermediate in the presence of the nucleophile are consistent with the hypothesis that the concerted reactions are enforced by the absence of a significant lifetime of the carbocation in the presence of the nucleophile and that stepwise mechanisms are followed when the intermediate has a significant lifetime; the change from a stepwise to a concerted mechanism occurs when the intermediate ceases to have a lifetime in the presence of a nucleophile.

We have briefly described evidence that bimolecular substitution reactions of 1-phenylethyl derivatives with azide ion² in a good ionizing solvent proceed through a concerted S_N2 displacement mechanism, not through reaction with an ion pair intermediate. This evidence includes large ratios of the rate constants for reaction with azide and solvent, the dependence of rate constants on the nucleophilicity of the attacking reagent and on ring substituents in the substrate, and estimates of rate constants for collapse of an ion pair intermediate, which are inconsistent with the ion pair mechanism.³ Other evidence is available that the nonlinear dependence of the rate on the concentration of azide ion that is observed for reactions of 1-phenylethyl derivatives under some conditions⁴ is not the result of a change in rate-limiting step of an ion pair mechanism.^{5,6} The lowest energy pathway for a second-order displacement reaction through a highly unstable intermediate should, in any case, be through a preassociation mechanism, which does not undergo a change in rate-limiting step with increasing nucleophile concentration.⁷

We describe here an examination of the properties of bimolecular substitution reactions of 1-phenylethyl derivatives with azide and other nucleophilic reagents. The results provide further support for the concerted reaction mechanism of substitution but show that the transition state closely resembles that expected for a monomolecular, S_N1 substitution mechanism. This supports the suggestion⁷ that classification of reaction mechanisms according to the quantitative structural properties of the transition state, in terms of "carbocation character" or "assistance", provides no sharp dividing lines between mechanisms and gives a large "borderline" region of mechanism; a more clear-cut distinction among mechanisms can be obtained by classification according to the lifetime, or lack thereof, of reaction intermediates.

Experimental Section

Materials. Inorganic salts, methanol and acetonitrile (HPLC grade), and trifluoroethanol (Gold Label grade, Aldrich Chemical Co.) were used without further purification. Mercaptoethanol and propanethiol were distilled under nitrogen. Procedures for the synthesis of solvolysis substrates were described previously.⁸

Solvolysis Reaction Procedures. Mixed trifluoroethanol:water solvents were prepared by mixing measured volumes of water (at ionic strength 1.0) and trifluoroethanol. For kinetic studies in mixed acetonitrile:water or methanol:water solvents, stock solutions of the cosolvents were prepared by diluting a measured volume of the organic solvent to a specified

(1) Supported by grants from the National Institutes of Health (GM-20888) and National Science Foundation (PCM 77-08369). Dr. Richard was supported by a grant from the National Institutes of Health (AM 07251).

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final volume with water. A single stock solution was used to prepare all of the solutions containing inorganic salts that were used in a given set of experiments. Unless otherwise stated these reactions were studied under conditions of constant ionic strength equal to the fractional water composition times 1.0. Solvolysis reactions were run at room temperature ($22 \pm 2^\circ\text{C}$) when only the product composition was to be analyzed, since the product ratios are not affected by these small changes in temperature. Rate constants for nucleophilic substitution were measured at 25°C unless indicated otherwise.

Chromatographic Analysis of Products. The conditions for HPLC separation of solvolysis reaction products and the procedures for identification of these products are described in the earlier papers in this series.^{8,9} The solvent selectivity for the reaction of 1-(4-nitrophenyl)ethyl tosylate in 50:50 TFE:H₂O and the azide selectivity for the reaction of 1-(4-nitrophenyl)ethyl chloride were obtained after reaction for ~ 10 halftimes because the trifluoroethyl ether and the azide adduct coelute with 1-(4-nitrophenyl)ethyl tosylate and 1-(4-nitrophenyl)ethyl chloride, respectively. The azide adduct formed from 1-(3-bromophenyl)ethyl chloride coelutes with 3-bromostyrene, which was also a solvolysis reaction product. In 20% acetonitrile in water 3-bromostyrene accounted for less than 5% of the total product absorbance. However for reaction in 50:50 TFE:H₂O, 3-bromostyrene formation increased to 20% of the total product absorbance. The azide selectivity in this solvent was estimated after removal of 3-bromostyrene with mercaptoethanol as described previously.⁸ The value obtained agrees within 20% with the value calculated from the fractional decrease in the amount of water adduct at increasing azide concentrations. The yield of styrene at 70°C is larger and the azide selectivity was obtained from the decrease in the amount of water adduct in the presence of 5 concentrations of azide. The azide peak areas for the reactions of 1-(4-fluorophenyl)ethyl chloride and bromide in TFE:H₂O:CH₃CH₂CH₂SH were corrected by 15–20% for the presence of 4-fluorostyrene, assuming that the same fraction of total products was styrene in the presence and absence of azide ion. The amount of O-ether formed from mercaptoethanol and 1-(3-nitro-4-methoxyphenyl)ethyl chloride in 50:50 TFE:H₂O was calculated from the observed area of the S-alkyl product and the O:S ratio of 0.11 observed in the absence of azide, because the O-ether eluted with the azide peak.

Kinetic Methods. Rate constants for the reactions of [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide and 1-(4-methylphenyl)ethyl pentafluorobenzoate with solvent and azide at 25°C in 50:50 (v/v) TFE:H₂O, ionic strength 0.5 maintained with NaClO₄, were measured by monitoring product appearance and substrate disappearance, respectively, by HPLC. Reactions of 1-(4-nitrophenyl)ethyl chloride with solvent and added nucleophiles at ionic strength 1.0 were also monitored for substrate disappearance by HPLC. First-order rate constants were obtained from semilogarithmic plots of $[\text{S}]$ or $[\text{P}_\infty] - [\text{P}_t]$ against time ($\text{S} = \text{substrate}$, $\text{P} = \text{product}$), which were typically linear for 2–3 halftimes.

The solvolysis reaction of 1-(4-nitrophenyl)ethyl chloride at 25°C in 20% acetonitrile in water and constant ionic strength of 0.8, maintained with NaClO₄, was followed by analysis of product formation (P) by HPLC for the first 5% of reaction; the rate constant, k_{solv} , was obtained from the slope of a plot of $[\text{P}]/[\text{S}]_0$ against time. Under similar conditions the rate of substrate disappearance in the presence of I^- was fast enough to allow the reaction to be followed for 1–4 halftimes at 0.025–0.20 M I^- , so that k_{obsd} values could be obtained from semilogarithmic plots as described above. Extrapolation to zero $[\text{I}^-]$ of a plot of k_{obsd} against $[\text{I}^-]$ gave a value of k_{solv} within 10% of the value obtained by measuring the initial rate of the solvolysis reaction.

Pseudo-first-order rate constants for the reactions of substituted 1-phenylethyl chlorides and bromides with solvent and azide at 25°C in water, methanol–water, or acetonitrile–water were measured spectrophotometrically at 290–300 nm by following the protonation of phenolate anion by acid that is formed from solvolysis. Typically, reactions in a volume of 3.0 mL containing 5 μL of 0.5 M phenol (90% phenolate anion in 50% acetonitrile in water) were initiated by addition of 40 μL of a solution of substrate in acetonitrile to give a final concentration of 0.5–1.5 mM (the concentration of phenolate ion was always larger than that of solvolysis products). Identical rate constants were obtained for the reaction of 1-(3-methoxyphenyl)ethyl chloride when protonation of phenolate was monitored at 290 or 300 nm. Pseudo-first-order rate constants, k_{obsd} , were obtained from the slopes of semilogarithmic plots of $(A_t - A_\infty)$ against time, which were usually linear for more than three halftimes. The fast reaction of 1-(4-methylphenyl)ethyl chloride and 1-(4-fluorophenyl)ethyl bromide, with halftimes as short as ~ 1 s, were followed for the terminal part of the reaction and gave satisfactory first-order kinetics using an end point based on ΔA for 5 halftimes + 3%

ΔA . The end point drifts over longer times, possibly because of incomplete dissolution of traces of substrate. Other end points were stable for several minutes or for longer times if argon was bubbled through the organic and aqueous solvents before mixing. Second-order rate constants, k_{az} , for the direct reaction between azide and substrate were obtained from the slopes of linear plots of k_{obsd} against $[\text{N}_3^-]$.

First-order plots for the reaction of 1-(3-methoxyphenyl)ethyl chloride in the presence of I^- gave downward curvature that was shown by HPLC analysis of reaction products at early times to be due to the formation of 1-(3-methoxyphenyl)ethyl iodide, which then reacts at a slightly faster rate than the chloride. The rate constant for the solvolysis of 1-(3-methoxyphenyl)ethyl chloride in the presence of I^- was obtained from the initial slope of a semilogarithmic plot of $(A_t - A_\infty)$ against time.

Biphasic kinetics were observed for the reactions of a number of substituted 1-phenylethyl bromides in 40% acetonitrile in water in the presence of chloride ion at constant ionic strength of 0.6 maintained with NaClO₄. The rate constant obtained from the initial slope of a semilogarithmic plot of $(A_\infty - A_t)$ is similar to that obtained for reaction of the 1-phenylethyl bromide in the absence of chloride. The rate constant obtained from the slope of this plot at long reaction times is identical, within experimental error, with the rate constant for reaction of the similarly substituted 1-phenylethyl chloride under comparable reaction conditions. Approximate values of the fraction of 1-phenylethyl chloride formed as a reaction product were estimated from a semilogarithmic plot of $(A_\infty - A_t)$ against time by extrapolating the slow phase for reaction of the 1-phenylethyl chloride to zero reaction time. The error in this extrapolation from nonlinearity at early times was estimated to be $\leq 8\%$. Formation of 1-(4-fluorophenyl)ethyl chloride from 1-(fluorophenyl)ethyl bromide under the same reaction conditions was detected by HPLC analysis of the reaction components at early times.

Results

We previously reported that the observed rate constants for the reactions of substituted 1-phenylethyl chlorides with $\sigma^+ \geq -0.08$, in 20% acetonitrile in water at 25°C and ionic strength 0.8 maintained with NaClO₄, increase with increasing azide concentration due to a reaction pathway that gives the azide product.³ The rate constants k_{solv} (s^{-1}) and k_{az} ($\text{M}^{-1} \text{s}^{-1}$) for these reactions and for the reactions of substituted 1-phenylethyl bromides are given in Table I. Plots of k_{obsd} against azide concentration are linear,³ in contrast, the reaction in ethanol at 50°C and increasing ionic strength gives plots with downward curvature.⁴ Also shown in Table I are values of k_{az}/k_s (M^{-1}) calculated from the ratio of the products from addition of azide and solvent. For the 4-methyl and 3-nitro-4-methoxy compounds these values are larger than the values of $k_{\text{az}}/k_{\text{solv}}$ from the kinetic data because the azide adduct is formed from the carbocation intermediate and there is little or no second-order reaction with azide for these substrates.⁹ For the 4-fluoro, 3-methoxy, and 3-bromo compounds the product ratios are in fair to good agreement with the values of $k_{\text{az}}/k_{\text{solv}}$ from kinetic data and show that the azide adduct formed as product is sufficient to account for the observed rate increase. The small excess of azide adduct over that predicted from kinetic data for the 4-fluoro- and 3-methoxy-substituted compounds could be caused by a small specific salt effect that decreases k_{solv} , formation of a small amount of azide adduct by reaction with a carbocation intermediate, experimental error, or a combination of these factors.

The values of k_{az}/k_s from product analysis for the reactions of the 4-fluoro and 3-methoxy 1-phenylethyl halides were found to increase $\sim 20\%$ as the azide concentration is increased from 0.16 to 0.64 M; average values are reported in Table I. The second-order plots of k_{obsd} against azide concentration do not suggest upward curvature;¹⁰ however, slight curvature would not be evident because the k_{obsd} values are only accurate to $\pm 5\%$. The increasing k_{az}/k_s values could reflect a specific salt effect that increases k_{az} or decreases k_s .

The second-order rate constant for the reaction of azide ion with 1-(4-fluorophenyl)ethyl bromide in 20% acetonitrile was calculated from the experimentally determined value for k_{solv} and the k_{az}/k_s value of 2.0 M^{-1} obtained from product analysis, because the k_{obsd} values in the presence of azide were too fast to measure conveniently. The rate constant for the fast ($t_{1/2} = 1$ s) solvolysis

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Table I. Rate Constants and Partitioning Ratios for the Reactions of Ring-Substituted 1-Phenylethyl Chlorides with Solvent and Azide in 20% Acetonitrile in Water^a

substituent	$\sigma^n + \rho^+(\sigma^+ - \sigma^n)^b$	Cl ⁻ leaving group				Br ⁻ leaving group			
		$k_{\text{solv}}, \text{s}^{-1}$	$k_{\text{az}},^c \text{M}^{-1} \text{s}^{-1}$	$k_{\text{az}}/k_{\text{solv}},^d \text{M}^{-1}$	$k_{\text{az}}/k_{\text{s}},^e \text{M}^{-1}$	$k_{\text{solv}}, \text{s}^{-1}$	$k_{\text{az}},^c \text{M}^{-1} \text{s}^{-1}$	$k_{\text{az}}/k_{\text{solv}},^d \text{M}^{-1}$	$k_{\text{az}}/k_{\text{s}},^e \text{M}^{-1}$
4-CH ₃	-0.35	$8 \pm 1 \times 10^{-1}$	$\leq 1.6 \times 10^{-1}$ ^f	≤ 0.2	1.2				
3-NO ₂ , 4-OCH ₃	-0.18	1.2×10^{-1}	$\sim 0.5 \times 10^{-1}$ ^g	~ 0.4	1.4				
4-I ⁻	-0.11	3.6×10^{-2}	$4.1 \pm 0.6 \times 10^{-2}$	1.1	1.2	3.5×10^{-1}	7×10^{-1} ^h		2.0
3-CH ₃	-0.07	2.5×10^{-2}	3.4×10^{-2}	1.4					
H	0	9.8×10^{-3}	1.8×10^{-2}	1.8					
3-OCH ₃	0.12	3.7×10^{-3}	7.2×10^{-3}	1.95		4.6×10^{-2}	1.8×10^{-1}	3.9	4.6
3-Br	0.39	7.1×10^{-5}	1.2×10^{-3}	16.9	2.4	8.5×10^{-4}	2.7×10^{-2}	32	34
4-NO ₂ ⁱ	0.79	3.4×10^{-7}	1.2×10^{-4} ^h		350				

^a At 25 °C and constant ionic strength of 0.8 maintained with NaClO₄. First-order rate constants, k_{obsd} , were measured by monitoring the disappearance of phenoxide indicator as a result of the release of acid from solvolysis, unless noted otherwise. ^b Values for σ^+ and σ^n are from Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975; pp 55-78. An ρ^+ value of 1.15 determined for the reaction of 1-phenylethyl chlorides in 80% aqueous acetone is used.²⁵ ^c Obtained from the slope of a plot of ≥ 5 values of k_{obsd} against the concentration of azide ion. ^d The ratio of the rate constants in the previous two columns. ^e Based on the relative concentrations of the products from reaction with solvent and azide. ^f The calculation of this upper limit is described in the text. ^g Based on a 20% increase in k_{obsd} as the azide concentration was increased from 0 to 0.48 M. ^h Calculated from k_{solv} (s⁻¹) and $k_{\text{az}}/k_{\text{s}}$ (M⁻¹) determined by product analysis. ⁱ Rate constants were measured by following the initial rate of product formation using HPLC.

of 1-(4-methylphenyl)ethyl chloride agrees with the value of 0.77 s⁻¹ obtained from the rate constant of 6.4×10^{-2} s⁻¹ for the reaction in 40% acetonitrile in water and a value of 12 ± 1 for the ratio of the rate constants for 1-(3-methoxyphenyl)ethyl chloride and 1-(4-fluorophenyl)ethyl chloride in the two solvents.

No increase in k_{obsd} was observed in the presence of azide ion for the reactions of 1-(4-methylphenyl)ethyl chloride in a number of mixed methanol-water and acetonitrile-water solvents, as noted previously.³ The absence of a rate increase in these solvents indicates that there is also no second-order reaction in 20% acetonitrile in water, because k_{az} is less sensitive than k_{solv} to solvent polarity (Y, see below). The upper limit for k_{az} in Table I was calculated assuming a 10% increase in k_{obsd} as the azide concentration is increased from 0-0.5 M. Values of k_{obsd} for this unstable substrate in 20% acetonitrile in water were not measured in the presence of azide because measurements of k_{solv} in this solvent showed variations of $\sim 20\%$. An upper limit of k_{az} for the reaction of 1-(3-nitro-4-methoxyphenyl)ethyl chloride was obtained from the 20% increase in k_{obsd} that was observed as the azide concentration was increased from 0 to 0.48 M. A larger increase of 50% was observed with 0.4 M azide in 50% methanol in water. The second-order rate constant for the reaction of azide with 1-(4-nitrophenyl)ethyl chloride was calculated from the value of k_{solv} , determined from the initial rate of the solvolysis reaction, and the ratio $k_{\text{az}}/k_{\text{s}} = 350 \text{ M}^{-1}$, determined from product analysis.

Nucleophilic selectivity values, based on product analysis, are reported in Table II as dimensionless ratios of second-order rate constants for the reactions of nucleophile and solvent with 1-phenylethyl chlorides or bromides in 50:50 TFE:H₂O and 20% acetonitrile in water. The data are reported as dimensionless ratios in order to facilitate comparison of nucleophilic selectivities for reactions in different solvents. Values for the reactions of 1-(3-bromophenyl)ethyl chloride, 1-(4-cyanophenyl)ethyl chloride, and 1-(4-nitrophenyl)ethyl bromide in 50:50 TFE:H₂O were determined at 70 °C. The difference in the product ratios for the 3-bromo compound at 22 ± 2 and 70 °C is not large and the increases in the product ratios for the 4-cyano and 4-nitro compounds, which were measured only at 70 °C, are larger than expected from the difference in temperature for all nucleophiles except water (Table II).

The value of $k_{\text{CN}^-}/k_{\text{s}}$ in 20% acetonitrile in water for 1-(3-bromophenyl)ethyl bromide was found to decrease by only 10% as the concentration of hydroxide ion was increased to 0.033 M. A competing reaction with hydroxide ion is also not significant for the reactions of 1-(4-fluorophenyl)ethyl and 1-(3-methoxyphenyl)ethyl chloride or bromide with cyanide ion and solvent because azide ion, a much stronger nucleophile, would give only a small reaction at concentrations comparable to those of hydroxide ion in these reactions.

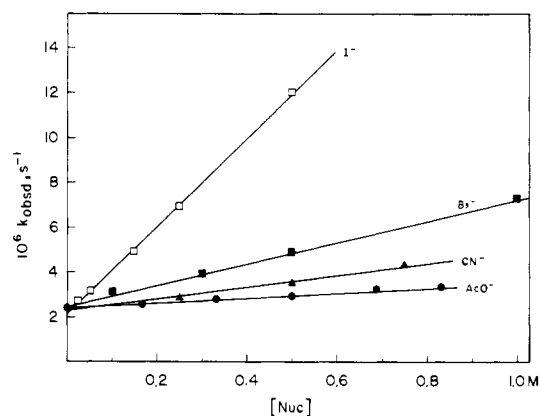


Figure 1. The dependence of k_{obsd} on the concentration of anionic nucleophiles for reactions of 1-(4-nitrophenyl)ethyl chloride in water at constant ionic strength of 1.0 maintained with NaClO₄.

A rate constant of $k_1 = 7.5 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ was measured for the reaction of 1-(4-nitrophenyl)ethyl chloride in 20% acetonitrile in water. Combining this value, the k_{solv} value in Table I, and the concentration of water gives a dimensionless ratio $k_1/k_{\text{H}_2\text{O}} = 980$, which is in good agreement with the result from product analysis in Table II.

When substituted 1-phenylethyl bromides react in 40% acetonitrile in water containing chloride ion, the corresponding 1-phenylethyl chloride accumulates during the relatively fast reaction of the bromide and then undergoes solvolysis in a slower phase. The rate constants for the slow phase were the same as those for the corresponding chloride derivative. The approximate values of $k_{\text{Cl}^-}/k_{\text{H}_2\text{O}}$ listed in Table II are based on the amount of chloride adduct formed in the fast phase, which was estimated by extrapolation as described in the Experimental Section.

The following nucleophilic selectivities were determined from product analysis for reactions of 1-(4-nitrophenyl)ethyl tosylate in 50:50 TFE:H₂O at ionic strength 0.5 and room temperature: $k_{\text{az}}/k_{\text{TFE}} = 360$, $k_{\text{AcO}^-}/k_{\text{TFE}} = 5.4$, $k_{\text{MeOH}}/k_{\text{TFE}} = 2.5$, $k_{\text{H}_2\text{O}}/k_{\text{TFE}} = 0.9$. Values of $k_{\text{az}} = 3.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{solv}} = 2.9 \times 10^{-4} \text{ s}^{-1}$ were obtained under the same conditions.

Figure 1 shows plots of k_{obsd} against the concentration of nucleophile for reactions of 1-(4-nitrophenyl)ethyl chloride in water at 25 °C and ionic strength 1.0. Table III lists nucleophilic selectivities for the reactions of 1-(4-nitrophenyl)ethyl chloride in water at ionic strength 1.0 based on product analyses and the second-order rate constants, k_{N} , obtained from the slopes in Figure 1. Also shown in Table III are nucleophilic selectivities based on product analysis for reactions of 1-(4-nitrophenyl)ethyl tosylate

Table II. Nucleophilic Selectivities Toward Ring-Substituted 1-Phenylethyl Chlorides and Bromides for Reactions in 50:50 (v:v) TFE:H₂O and 20% CH₃CN in Water^a

substituent	50:50 TFE:H ₂ O (v:v) ^d solvent							
	Cl ⁻ leaving group				Br ⁻ leaving group			
	k_{az}/k_{TFE}	k_{AcO^-}/k_{TFE}^b	k_{MeOH}/k_{TFE}^c	k_{H_2O}/k_{TFE}^d	k_{az}/k_{TFE}^e	k_{AcO^-}/k_{TFE}^b	k_{MeOH}/k_{TFE}^c	k_{H_2O}/k_{TFE}^d
3-NO ₂ , 4-OCH ₃	150 ^f	10	11	2.6				
4-CH ₃	52 ^f	4.5	7	1.3				1.4
4-F	59 ^f	3	4.6	1.6	94	3.5	5.0	1.6
3-OCH ₃	58 ^f	2	3.0	0.89	110	3	3.5	0.94
3-Br	480 ± 80 ^e	7	3.2	1.3	1180	6	3.6	1.0
	370 ^g	6.9 ^g	3.9 ^g	1.8 ^g				
4-CN	4400 ^{g,h}	28 ^g	5.4 ^g	1.6 ^g				
4-NO ₂	12 600 ^{g,i}	55 ^g	6.9 ^g	1.6 ^g				

substituent	20% CH ₃ CN in water ^j solvent			40% CH ₃ CN in water ^k solvent	
	Cl ⁻ leaving group			Br ⁻ leaving group	
	$k_{AcO^-}/k_{H_2O}^l$	$k_{CN^-}/k_{H_2O}^m$	$k_{I^-}/k_{H_2O}^n$	$k_{CN^-}/k_{H_2O}^m$	$k_{Cl^-}/k_{H_2O}^o$
4-CH ₃	4				13
4-F	2.5				11
3-OCH ₃	4	3		3.5	11
3-Br	6	3	44	5	
4-NO ₂	37	53	900		

^a For reaction at room temperature (22 ± 2 °C), except where noted otherwise, and constant ionic strength 0.5 maintained with NaClO₄. Selectivity values were calculated from the relative concentrations of reaction products. ^b Average of values for at least two acetate concentrations. ^c For reaction in 50:45:5 (v:v:v) H₂O:TFE:MeOH. ^d In 50:50 (v:v) TFE:H₂O. ^e Average of values obtained at 0.1, 0.2, and 0.3 M azide. ^f Average of at least 5 values at azide concentrations between 0.1 and 0.5 M. ^g At 70 °C. ^h Average of values obtained at 0.017 and 0.050 M azide. ⁱ Average of values obtained at 0.017, 0.033, and 0.050 M azide. ^j At 25 °C and ionic strength 0.8 (NaClO₄). ^k At 25 °C and ionic strength 0.6 (NaClO₄). ^l Average of values for at least two acetate concentrations between 0.16 and 0.80 M. ^m Average values for at least two cyanide concentrations between 0.2 and 0.8 M. ⁿ Based on product ratios obtained at early reaction times, assuming equal extinction coefficients for the chloride and iodide. ^o Approximate values from product analysis (Experimental Section).

Table III. Rate Constants and Rate Constant Ratios for Reactions of 1-(4-Nitrophenyl)ethyl Chloride and Tosylate in Water^a

nucleophile	leaving group			
	$10^6 k_N$, M ⁻¹ s ⁻¹ , ^b	Cl ⁻		OTs ⁻
		k_N/k_{solv} , M ⁻¹	(k_N/k_s) prod, ^c M ⁻¹	(k_N/k_s) prod, ^c M ⁻¹
N ₃ ⁻			130	3.4 ^d
HOCH ₂ CH ₂ S ⁻			750	5.4
I ⁻	19.7	8.2		0.82
Br ⁻	4.7	2.0		0.35
Cl ⁻				0.18
CN ⁻	2.8	1.2	0.42	0.07
AcO ⁻	1.07	0.43	0.37	0.08
F ⁻			0.05	≤ 0.04 ^e
H ₂ O	0.043 ^f		0.018 ^f	0.018 ^f

$k_{solv} = 2.4 \times 10^{-6} \text{ s}^{-1}$

^a In the presence of 1% acetonitrile at 25 °C and constant ionic strength of 1.0 maintained with NaClO₄. The reactions were followed by monitoring substrate concentration using HPLC.

^b The slope of a plot of k_{obsd} against nucleophile concentration (Figure 1). ^c Ratio of rate constants based on product analysis.

^d Identical values were obtained with 5 μM and 50 μM substrate.

^e At 0.5 M [F⁻] no fluoride adduct was detected. The selectivity value is calculated by using an upper limit of 0.02 as the fraction of total product as fluoride adduct which may have escaped detection. ^f Based on the second-order rate constant for water, $k_{solv}/55.5$.

under the same conditions. The increase in k_{obsd} for the reaction of 1-(4-nitrophenyl)ethyl chloride in the presence of cyanide ion is larger than can be accounted for by the contribution of the second-order pathway for the nucleophilic reaction of cyanide estimated from product analysis. However, the ratio k_N/k_s from product analysis was found to remain constant with increasing cyanide concentration. The increase in k_{obsd} is not caused by a reaction with hydroxide ion because k_{obsd} increases only 15% in

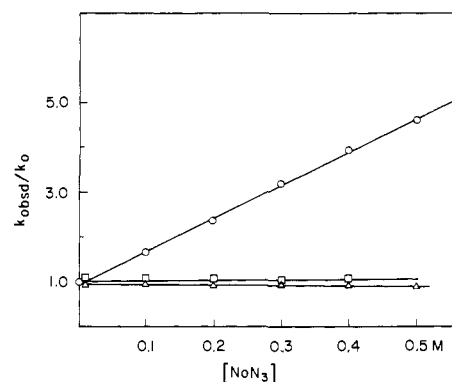


Figure 2. The effect of azide concentration on the rate constants for reactions of 1-(4-methylphenyl)ethyl chloride derivatives at 25 °C and ionic strength 0.5 (NaClO₄): (□) 1-(4-methylphenyl)ethyl chloride in 50% methanol in water; (Δ) 1-(4-methylphenyl)ethyl pentafluorobenzoate in 50:50 TFE:H₂O; (○) [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide in 50:50 TFE:H₂O.

the presence of 0.025 M [OH⁻]. These results are consistent with a specific salt effect of cyanide ion that increases both k_{solv} and k_N by 30% as the concentration of cyanide is increased from 0.25 to 0.75 M. They are not explained by an effect of cyanide on only the reaction with solvent because such an effect, with the rate constant k_B , would give a decrease in the product ratio with increasing cyanide concentration, as described by eq 1.

$$(k_N/k_s)_{obsd} = k_N/(k_{solv} + k_B[CN^-]) \quad (1)$$

Nucleophilic selectivities of substituted acetate anions toward 1-(4-nitrophenyl)ethyl chloride were determined by product analysis for reactions in water at ionic strength 1.0 maintained with NaClO₄: $k_{AcO^-}/k_s = 21$, $k_{CH_3OAcO^-}/k_s = 18$, and $k_{ClAcO^-}/k_s = 14$.

The reaction of [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide is first order with respect to azide ion, as shown in Figure

Table IV. Specific Salt Effects on the Observed Rate Constants for the Disappearance of 1-(3-Methoxyphenyl)ethyl Chloride in Water^a

[X ⁻], M	10 ² k _{obsd} , s ⁻¹					
	Cl ⁻ ^b	Br ⁻ ^b	I ⁻ ^{b,c}	AcO ⁻ ^b	N ₃ ⁻ ^b	ClO ₄ ⁻ ^d
0	3.1	3.1	3.0	3.1	3.1	2.1
0.2	3.4	3.1	2.9	2.9	3.7	2.6
0.4	3.2	3.4	2.9	2.8	4.5	3.0
0.6	3.3	3.4	2.7	2.6	5.2	3.2
0.8		3.6		2.4	5.9	
1.0		3.7		2.2		3.1

^a Containing 1% acetonitrile at 25 °C. First-order rate constants were obtained by monitoring acid release with phenolate ion as an indicator. ^b At constant ionic strength of 1.0 maintained with NaClO₄. ^c The rate constant was estimated from the initial rate of the solvolysis reaction. ^d The reaction mixtures contained only NaClO₄.

2, and gives rate constants of $k_{az} = 15 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{solv} = 1.9 \times 10^{-5} \text{ s}^{-1}$. Product analysis by HPLC showed that the entire rate increase could be accounted for by the formation of the azide adduct. Rate constant ratios are $k_{az}/k_{H_2O} = 300$ and $k_{H_2O}/k_{TFE} = 1$. 1-Phenylethylidimethylsulfonium ion has been shown previously to react with azide by displacement at the 1-carbon atom.² A value of $k_{solv} = 2.0 \times 10^{-5} \text{ s}^{-1}$ was observed for the reaction of 1-(4-methylphenyl)ethyl pentafluorobenzoate but there is a decrease in k_{obsd} of 20% as the azide concentration is increased from 0 to 0.5 M. This compound gives a small amount of azide adduct by a trapping mechanism.⁹ Azide ion has no effect on the rate of solvolysis of 1-(4-methylphenyl)ethyl chloride in 50% methanol in water (Figure 2). The solvolysis of [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide in 20% acetonitrile in water at four acetate concentrations in the range 0.32–0.80 M gives small amounts of the acetate ester with a dimensionless rate constant ratio of $k_{AcO^-}/k_{H_2O} = 5.4 \pm 1.2$.

The effect of increasing ionic strength (NaClO₄) and specific salt effects on k_{obsd} at constant ionic strength for reaction of 1-(3-methoxyphenyl)ethyl chloride at 25 °C in water are given in Table IV.

Pseudo-first-order rate constants for solvolysis and second-order rate constants for the reaction of azide ion with substituted 1-phenylethyl chlorides at constant ionic strength in a number of methanol-water solvents are reported in Table V. No k_{az} values are given for the reaction of 1-(4-methylphenyl)ethyl chloride because k_{obsd} values for this compound are independent of azide concentration. Table VI gives azide-solvent product selectivity values obtained for the same reactions in methanol-water. The ionic strength was maintained constant with NaClO₄ as the azide concentration was increased at each methanol concentration.

Table V. Effect of Increasing the Solvent Methanol Content on the Rate Constants for Reactions of Solvent, k_{solv} , and Azide, k_{az} , with Substituted 1-Phenylethyl Chlorides in Aqueous Methanol^a

% MeOH ^b	Y ^c	substituent				
		4-CH ₃		4-I ⁻		3-OCH ₃
		k_{solv}, s^{-1}	k_{solv}, s^{-1}	$k_{az}, \text{M}^{-1} \text{s}^{-1}$	k_{solv}, s^{-1}	$k_{az}, \text{M}^{-1} \text{s}^{-1}$
0	3.49				3.1×10^{-2}	3.6×10^{-2}
10	3.28				1.7×10^{-2}	2.3×10^{-2}
20	3.02				9.0×10^{-3}	16.1×10^{-3}
30	2.75		3.8×10^{-2}	3.9×10^{-2}	4.1×10^{-3}	7.7×10^{-3}
40	2.39		1.8×10^{-2}	2.0×10^{-2}	1.9×10^{-3}	4.4×10^{-3} ^d
50	1.97	1.6×10^{-1}	6.2×10^{-3}	9.3×10^{-3}	9.7×10^{-4}	19×10^{-4}
60	1.49	5.9×10^{-2}	2.3×10^{-3}	3.3×10^{-3}		
70	0.96	2.1×10^{-2}	7.4×10^{-4}	1.6×10^{-3}		
80	0.38	6.0×10^{-3}	2.3×10^{-4}	6.8×10^{-4}		
90	-0.30	1.5×10^{-3}				
III		0.90	0.94	0.75	1.02	0.80

^a Constant ionic strength with increasing [NaN₃] was maintained with NaClO₄ and was equal to the fractional water composition of the solvent (by volume) times 1.0. Azide concentrations were increased up to 0.8 of the initial [NaClO₄]. The reactions were followed by monitoring acid release with phenolate ion as an indicator. With one exception, k_{az} is the slope of a plot of 5 k_{obsd} values against the azide concentration. ^b Volume % MeOH in water. ^c The Y values are for MeOH:H₂O (v/v) solutions at zero ionic strength.³⁸ ^d Based on a 4 point plot of k_{obsd} against azide concentration.

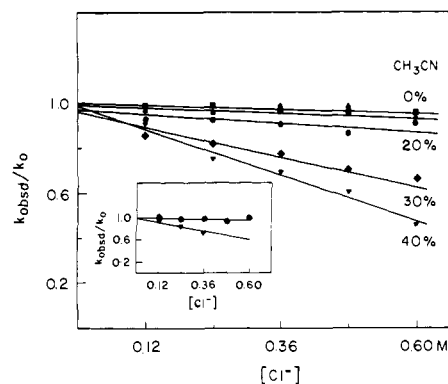


Figure 3. The solvent dependence of the specific salt effect of chloride anion on the rate constant for solvolysis of 1-(3-methoxyphenyl)ethyl chloride at 25 °C in mixed acetonitrile in water solvents at constant ionic strength of 0.6 maintained with NaClO₄. The inset is for the reaction of 1-(3-methoxyphenyl)ethyl bromide. Water (■); acetonitrile in water: 10% (▲); 20% (●); 30% (◆); 40% (▼).

The effects of increasing acetonitrile concentration on the specific bromide and chloride salt effects for the solvolysis of 1-(3-methoxyphenyl)ethyl bromide and chloride at 25 °C and constant ionic strength of 0.6, maintained with NaClO₄, are shown in Figure 3. The kinetic data are given in Table S1 (Supplementary Material).

The reactions of propanethiol with 1-(4-fluorophenyl)ethyl chloride, 1-(4-fluorophenyl)ethyl bromide, and 1-(3-nitro-4-methoxyphenyl)ethyl chloride in 90:10 TFE:H₂O and in the presence of 0.08 M azide were investigated at constant ionic strength of 0.1 maintained with NaClO₄. Figure 4 is a plot of each reaction product, as a fraction of total products, against the volume percent of propanethiol in the solvent. The data are given in Tables S2 and S3 (Supplementary Materials).

Discussion

Second-order reactions of 1-phenylethyl derivatives with azide ion, in 20% acetonitrile in water, become significant with 1-(4-fluorophenyl)ethyl chloride and are progressively more important for compounds with more electron-withdrawing substituents. The increase in the observed reaction rate is linear with increasing azide concentration up to 0.64 M at constant ionic strength in this solvent¹⁰ and accounts for ≥80% of the observed azide product (Table I). The reactions of azide ion with 1-phenylethyl chloride and 1-phenylethylidimethylsulfonium ion in 80% ethanol proceed with inversion.² Second-order reactions with other nucleophiles appear only with compounds that have more electron-withdrawing substituents, depending on the strength of the nucleophile; with 1-(4-nitrophenyl)ethyl chloride there is a linear increase in rate

Table VI. Azide Product Selectivity Ratios for the Reactions of 1-(4-Fluorophenyl)ethyl Chloride and 1-(3-Methoxyphenyl)ethyl Chloride in TFE-H₂O and MeOH-H₂O Solvents^a

% TFE (v:v)	ring substituent					
	4-F			3-OCH ₃		
	$k_{az}/k_{s,b}$ M ⁻¹	$k_{az}/k_{H_2O}^c$	k_{az}/k_{TFE}^c	$k_{az}/k_{s,b}$ M ⁻¹	$k_{az}/k_{H_2O}^c$	k_{az}/k_{TFE}^c
50	1.1	37	57	1.8	65	57
60	1.2	35	58	1.9	60	58
70				2.2	56	60
80	1.8	31	60	2.5	52	59
90	2.4	28	56	2.9	47	57

% MeOH in water	ring substituent					
	4-F ^d			3-OCH ₃ ^d		
	$k_{az}/k_{s,b}$ M ⁻¹	$k_{az}/k_{H_2O}^c$	k_{az}/k_{MeOH}^c	$k_{az}/k_{s,b}$ M ⁻¹	$k_{az}/k_{H_2O}^c$	k_{az}/k_{MeOH}^c
0				1.7	95	
10				1.8	105	40
20	1.2	71	31	2.1	118	46
30	1.3	73	34	2.2	127	51
40	1.5	77	40	2.5	144	59
50	1.7	85	48	2.9	160	72
60	2.1	104	60			
70	3.0	128	85			
80	4.1	158	115			

^a Reaction at 22 ± 2 °C. Constant ionic strength with increasing azide concentration was maintained with NaClO₄ and was equal to the fractional water composition of the solvent (by volume) times 1.0. ^b Treating the solvent reaction as a first-order rate constant. ^c Dimensionless ratio of second-order rate constants. ^d Data are from product analysis of the same experiments used to obtain the kinetic data in Table V.

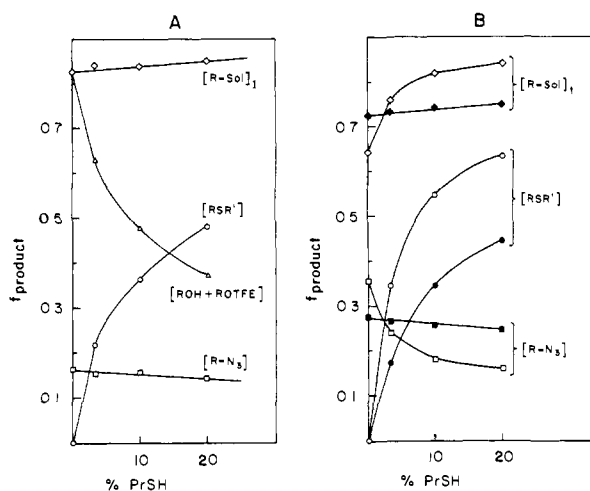


Figure 4. The effect of propanethiol on the yields of products from the reactions with azide, solvent, and thiol of 1-(4-fluorophenyl)ethyl chloride (A), 1-(4-fluorophenyl)ethyl bromide (B, closed symbols), and 1-(3-nitro-4-methoxyphenyl)ethyl chloride (B, open symbols). The reactions were carried out at 22 ± 2 °C in the presence of 0.08 M sodium azide and 0.02 M sodium perchlorate. Propanethiol was substituted for trifluoroethanol in a solvent of 90:10 TFE:H₂O (v/v).

with increasing concentration of iodide, bromide, cyanide, and acetate anions (Figure 1). Evidence has been described briefly³ supporting the conclusion that the reaction with azide ion proceeds through a preassociation concerted S_N2 displacement mechanism that "contains only one stage, in which two molecules simultaneously undergo covalency change", as defined by Ingold.¹¹

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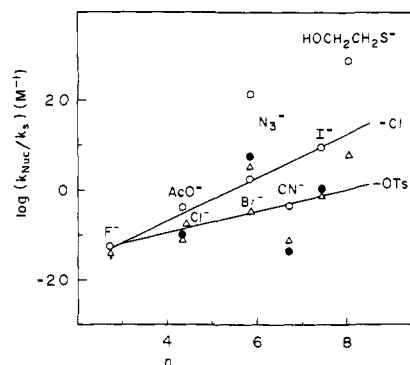


Figure 5. A Swain-Scott plot of nucleophilic selectivities against the *n* value of the nucleophile¹² for the reactions of (○) 1-(4-nitrophenyl)ethyl chloride in water at μ = 1.0 (NaClO₄), (Δ) 1-(4-nitrophenyl)ethyl tosylate in water at μ = 1.0 (NaClO₄), and (●) 1-(3-methoxyphenyl)ethyl chloride in 20% acetonitrile in water at μ = 0.8 (NaClO₄). An estimated value of *n* = 8.0 for HS⁻ is used for HOEtS⁻.¹²

However, the transition state for this reaction is open or "exploded" and has a number of properties that resemble those of a carbocation. The results described here characterize some of these properties and provide additional evidence consistent with a concerted S_N2 displacement mechanism for these reactions.

Structure-Reactivity Correlations. Nucleophilic Reactivity. The sensitivity toward the nucleophilic reactivity of the attacking reagent is smaller for displacement reactions on 1-(4-nitrophenyl)ethyl derivatives than for methyl halides, but generally larger than for displacements on methoxymethyl derivatives, which also proceed through a carbocation-like transition state. Swain-Scott correlations based on nucleophilic reactivity toward methyl iodide in methanol¹² show large deviations for azide and cyanide ions and give slopes of *s* = 0.46 and 0.22 for reactions of halide ions with 1-(4-nitrophenyl)ethyl chloride and tosylate, respectively (Figure 5). Displacement reactions on *N,N*-(methoxymethyl)-*N,N*-dimethyl-*m*-nitroanilinium ion show similar deviations and follow a correlation with *s* = 0.28;¹³ the same reactions with 2,4-dinitrophenolate ion as the leaving group have a similar slope.¹⁴ Slopes of *s* = 0.69 and 0.49 for 1-(4-nitrophenyl)ethyl chloride and tosylate, respectively, were obtained from a smaller number of nucleophilic constants based on reactions of methyl bromide in water,¹⁵ with positive deviations of 50-fold for azide and 200-fold for water. There is a similar deviation of the point for water from a two-point plot against the *N*⁺ values for azide and cyanide ions.¹⁶

Rate constants for displacement by substituted acetate ions on 1-(4-nitrophenyl)ethyl chloride (Results) show a small dependence on basicity, with β_{nuc} = 0.09, which may be compared with β_{nuc} = 0.29 and 0.23 for nucleophilic reactions of oxygen anions with methyl iodide and methyl perchlorate, respectively,¹⁷ and β_{nuc} ~ 0.05 for displacement of 2,4-dinitrophenolate anion from the methoxymethyl group.¹⁴

The large positive deviations of azide and negative deviations of cyanide ion from the Swain-Scott correlations (Figure 5) give a reactivity order of *k*_{az} >> *k*_{CN}, which is opposite to that for displacement on methyl halides but the same as for nucleophilic reactions with carbocations.^{12,16} This reflects the large amount of carbocation character of the transition state. The same deviations and reversed reactivity order are found for displacement

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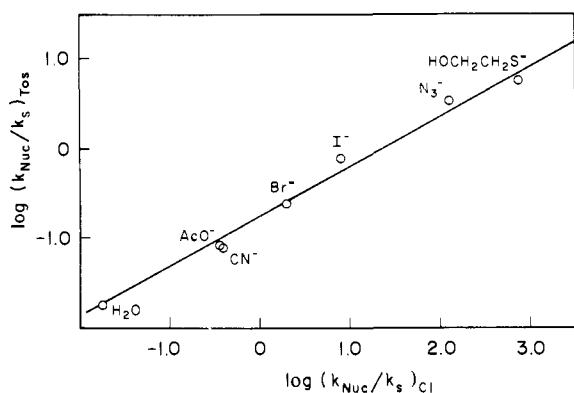


Figure 6. Comparison of nucleophilic selectivities toward 1-(4-nitrophenyl)ethyl tosylate and 1-(4-nitrophenyl)ethyl chloride for reactions in water at ionic strength 1.0 (NaClO_4).

on the methoxymethyl group.¹³ However, the larger deviations for the phenylethyl derivatives (10- to 100-fold compared with 3-fold) indicate an even larger amount of carbocation character in the transition state, according to this criterion.

Displacement reactions in the phenylethyl system show a large dependence of nucleophilic reactivity on the nature of the leaving group, or a "synergism" between the nucleophilic and nucleofugic groups.¹⁸ Figure 6 shows that there is a linear correlation of the values of $\log(k_{\text{Nuc}}/k_s)$ for the reactions with 1-(4-nitrophenyl)ethyl tosylate and chloride with a slope of 0.57, or 1.7 for $\log k_{\text{Cl}}$ against $\log k_{\text{OTs}}$. The rate constants for reactions with azide, cyanide, and thiol anions and with water, which show large deviations from Swain-Scott correlations, fit this correlation. Thus, the factors which cause deviations from the Swain-Scott correlation, such as the enhanced reactivity of azide, are affected proportionately when the leaving group is changed. The interaction between the attacking and leaving groups in the transition state supports a coupled, concerted reaction mechanism.

It is particularly significant that the rate constants for water, cyanide, and acetate fall close to the straight line of Figure 6, because these compounds are less nucleophilic than chloride ion toward 1-(4-nitrophenyl)ethyl tosylate (Table III) but are more nucleophilic than the tosylate ion.^{12,19} This behavior is consistent with a concerted $\text{S}_{\text{N}}2$ displacement reaction mechanism. It would not be expected for a stepwise reaction with an ion pair intermediate because the relative nucleophilic reactivities of the entering and leaving groups require that bond breaking would be rate limiting for all reactions of the tosylate but that bond making would be rate determining for reactions of weak nucleophiles with the chloride compound. Since there must be different amounts of bond formation to the nucleophilic reagent when bond making and bond breaking are rate determining, there should be a change in the slope of Figure 6 accompanying such a change in rate-determining step;¹³ no such change is observed.

The limited data for 1-(3-methoxyphenyl)ethyl chloride (solid symbols, Figure 5) show a smaller selectivity toward nucleophiles, similar to that of 1-(4-nitrophenyl)ethyl tosylate, and suggest that the less electron-withdrawing substituent on this substrate results in a transition state with even less bond formation and more carbocation character than for the reactions of 1-(4-nitrophenyl)ethyl chloride. This kind of change in transition state structure (corresponding to an interaction coefficient $\partial\beta_{\text{nuc}}/\partial\sigma = \partial\rho/\partial pK_{\text{nuc}}$)²⁰ is well-known for displacement reactions on substituted benzyl derivatives.¹⁹⁻²³

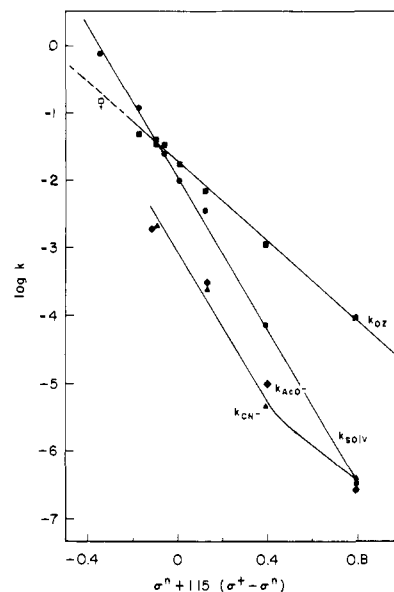


Figure 7. Hammett plots of the rate constants for reactions of ring-substituted 1-phenylethyl chlorides with nucleophiles and solvent at 25 °C in 20% acetonitrile in water at ionic strength 0.8 (NaClO_4): (●) k_{solv} (s^{-1}); (■) k_{az} ($\text{M}^{-1} \text{s}^{-1}$); (▲) k_{CN^-} ($\text{M}^{-1} \text{s}^{-1}$); (◆) k_{AcO^-} ($\text{M}^{-1} \text{s}^{-1}$). The points for CN^- and AcO^- are based on product analysis and represent upper limits for second-order rate constants, except for 1-(4-nitrophenyl)ethyl chloride.

An even more striking example of "synergism" between entering and leaving groups is seen for the reaction of azide ion with the [1-(4-methylphenyl)ethyl]dimethylsulfonium ion. Figure 2 shows that azide ion provides no nucleophilic assistance to the ionization of 1-(4-methylphenyl)ethyl chloride or pentafluorobenzoate, but reacts with the corresponding dimethylsulfonium ion through a second-order reaction with a ratio of $k_{\text{az}}/k_{\text{solv}} = 7.9 \text{ M}^{-1}$. Evidently there is a favorable interaction between the strongly nucleophilic azide ion and the "soft" dimethyl sulfide leaving group that lowers the energy of the transition state to the point that the $\text{S}_{\text{N}}2$ reaction becomes significant. It is possible that a favorable electrostatic effect contributes to this interaction, but the small ratios of $k_{\text{AcO}^-}/k_{\text{H}_2\text{O}} = 5.4$ and 4 for the reactions of acetate anion with the sulfonium ion and chloride derivatives, respectively, provide no indication of any such electrostatic effect.

The ratio $k_{\text{OTs}}/k_{\text{Cl}}$ decreases as the mechanism for solvolysis of a series of compounds changes from $\text{S}_{\text{N}}1$ to $\text{S}_{\text{N}}2$.²⁴ The data in Table III show that the ratio $k_{\text{OTs}}/k_{\text{Cl}}$ for solvolysis is larger than for the reaction with azide by a factor of $130/3.4 = 38$.

Structure-Reactivity Correlations. Aromatic Substituents. Rate constants for the solvolysis of ring-substituted 1-phenylethyl chlorides in 20% acetonitrile in water follow a Hammett correlation, modified according to Yukawa and Tsuno,²⁵ with $\rho = -5.6$ and $r^+ = 1.15$ (Figure 7). This r^+ value is based on the data of Tsuno et al. for the solvolysis of 1-phenylethyl chlorides in 80:20 acetone:water; it corresponds to $\rho^* = -6.4$ and a contribution of resonance stabilization in the transition state that is slightly larger than that for the solvolysis of cumyl chlorides.^{25,26} The ρ value is similar to values of -5.0 ,²⁵ -5.1 ,²⁷ -5.7 ,^{28,29} and -6.3 ³⁰ for related

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reactions of 1-phenylethyl derivatives and to $\rho^+ = -5.7$ reported earlier for the same reaction based on more limited data.³

The rate constants for the second-order reaction with azide ion also decrease sharply with electron-donating substituents, although the ρ value of -2.9 is less negative than that for solvolysis (Figure 7). The difference in slope, $\Delta\rho = 2.7$, provides evidence that the developing bond formation to azide ion reduces the positive charge on the central carbon atom in the transition state. An electrostatic interaction between the negative charge of azide ion and the substituent on the substrate may contribute to this difference, but the contribution is not expected to be large because a full negative charge at a similar distance from the substituent gives a ρ value of only 1.1 in the ionization of trifluoroacetophenone hydrates.³¹ Similar behavior is observed for the reactions of 1-aryl-5-hexenyl and 1-aryl-4-methoxy-1-butyl chlorides, which occur with intramolecular nucleophilic assistance from the olefin or ether groups and follow ρ^+ values of -3.9 and -3.8 , respectively; the solvolysis of compounds with a nonreactive alkyl side chain follows $\rho^+ = -6.3$.³⁰

Hammett correlations for reactions of substituted 1-phenylethyl bromides are very similar to those for the chloride, with values of $\rho = -5.6$ for solvolysis and -3.0 for the second-order reaction with azide (not shown). However, the values of k_{soln} are ~ 10 -fold larger and those of k_{az} are ~ 20 -fold larger than for reactions with the corresponding chlorides (Table I).

The observed ρ values of -2.9 and -3.0 for the reactions with azide ion are much more negative than those for most $S_{\text{N}}2$ substitution reactions. They show that there is a large development of positive charge on the 1-position of the phenylethyl group in a transition state that has relatively weak bonding to the entering and leaving groups; there is a small amount of bond formation and a large amount of bond cleavage. Bimolecular substitution reactions on alkyl substrates in which the central carbon atom is insulated from resonance stabilization show little or no effect of polar substituents.⁶ Reactions of substituted benzyl derivatives show relatively small changes in rate and follow curved or U-shaped Hammett plots that can be explained, at least in part, by additive electrostatic and resonance effects;²⁰⁻²² the same effects presumably contribute to the curved or U-shaped Hammett plots and small ρ values for substitution reactions of benzhydryl and 1-phenylethyl derivatives in nonpolar solvents.³² The electrostatic effect from interaction with an anionic nucleophile will increase in nonpolar solvents and give a larger (less negative) value of ρ . Nonpolar solvents may also cause a shift in the structure of the transition state toward less cationic character, perpendicular to the reaction coordinate. Steric hindrance by the methyl group of 1-phenylethyl derivatives³³ is expected to decrease the amount of bond formation and increase the cationic character of the transition state compared with that for substitution reactions of benzyl derivatives.

An upper limit of the rate constant for the second-order reaction of azide ion with 1-(4-methylphenyl)ethyl chloride, which shows no rate increase in the presence of azide, is shown as the open square in Figure 7; the rate constant for the reaction with 1-(3-nitro-4-methoxyphenyl)ethyl chloride is an upper limit that is based on a 20% rate increase in the presence of 0.48 M azide ion and is shown as a closed square. Both of these rate constants are consistent with an extrapolation of the correlation line for the observed second-order reactions.

Rate constants for the reaction with cyanide ion follow a

correlation line parallel to that for the solvolysis reaction in Figure 7 for most 1-phenylethyl derivatives. These rate constants are based on product analysis and are too small to give a significant increase in the observed rate constants for substrate disappearance, so that they represent upper limits of the second-order rate constants for reaction with cyanide ion. However, there is an upward break in the line for the reaction of the *p*-nitro compound, which corresponds to the appearance of a significant second-order reaction of cyanide with this compound (Figure 1). The data for acetate anion are more scattered, but the appearance of a second-order reaction with the *p*-nitro compound requires a smaller value of ρ for the second-order reaction than for solvolysis, as in the case of the azide reaction.

The difference in the ρ values for the reactions with azide and with solvent is inconsistent with several possible mechanisms for these reactions that proceed through an ion pair intermediate.

(1) An activation-limited reaction of solvent and a diffusion-controlled reaction of azide with the intermediate would give a more positive value of ρ for the solvent reaction than for the azide reaction. This behavior is observed for reactions of the free cation with solvent and azide⁸ but is the opposite of that observed for these reactions. The reaction of azide ion with any such unstable intermediate would certainly be diffusion controlled.

(2) Diffusion-controlled reactions, or other mechanisms that are not activation limited, for both solvent and azide would give the same value of ρ for both reactions. This is not observed.

(3) Most mechanisms that involve activation-limited reactions of both solvent and azide with an ion pair, with or without nucleophilic assistance to ionization, would be expected to give a similar or more positive value of ρ for the reaction with solvent than with azide. Reaction with azide, a strong nucleophile, might be expected to involve an early transition state with little bond formation and much cationic character, whereas reaction with the much less nucleophilic solvent should occur through a later transition state with more bond formation, less cationic character, and a more positive ρ . A larger value of ρ is observed for the reaction of trifluoroethanol, a weak nucleophile, than for the reactions of methanol and ethanol with 1-phenylethyl carbocations.⁹ The opposite is observed for azide; the ρ values show that there is more bond formation and less carbocation character in the reaction with azide than with solvent.

The selectivities toward solvent components, $k_{\text{MeOH}}/k_{\text{TFE}}$ and $k_{\text{H}_2\text{O}}/k_{\text{TFE}}$, show little change or increase with increasing σ for 1-phenylethyl derivatives electron-withdrawing substituents (Table II). For reaction with an ion pair a decrease in selectivity would be expected with electron-withdrawing substituents as the carbocation becomes less stable. There is such a decrease in $k_{\text{MeOH}}/k_{\text{TFE}}$ and $k_{\text{EtOH}}/k_{\text{TFE}}$ for the reactions that do proceed through a free carbocation or an ion pair.⁹ The opposite behavior is observed for compounds with electron-withdrawing substituents, with an increase in $k_{\text{MeOH}}/k_{\text{TFE}}$ from 3.0 to 6.9 (Table II). This corresponds to a more positive value of ρ for the more basic alcohol and to the interaction coefficient $\partial\beta_{\text{nuc}}/\partial\sigma = \partial\rho/\partial pK_{\text{nuc}}$. This behavior, which is characteristic of the $S_{\text{N}}2$ displacement mechanism,²⁰⁻²³ is the complement of that described above.

Salt and Solvent Effects. The solvolysis of 1-(3-methoxyphenyl)ethyl chloride in water shows a modest positive salt effect, with a rate increase of 50% when the ionic strength is increased to 0.0–1.0 with sodium perchlorate (Table IV, last column). Similar effects of 0.6 M sodium perchlorate were observed in the presence of 20–40% acetonitrile (Table S1, Supplementary Material).

Specific salt effects were examined in water and in acetonitrile–water to determine if the solvolysis reaction is subject to a common ion rate depression or an induced common ion effect.³⁴ We conclude that neither of these effects exist, in water or water–acetonitrile, but that the observed salt effects in the mixed aqueous–organic solvents could be mistakenly interpreted as ev-

(30) Mihel, I.; Orlovic, M.; Polla, E.; Borcic, S. *J. Org. Chem.* **1979**, *44*, 4086–4090. Mihel, I.; Sistik, J.; Borcic, S.; Humski, K.; Sunko, D. E. *Ibid.* **1979**, *44*, 4091–4096. Polla, E.; Borcic, S.; Sunko, D. E. *Ibid.* **1979**, *44*, 4096–4100. The ρ^+ values are based on rate constants extrapolated from data in several solvents. The different ρ^+ values suggest that the reaction with solvent occurs with little or no nucleophilic assistance, while the intramolecular reaction involves assistance. The difference presumably arises from the large decrease in the effective reaction barrier that is characteristic of many intramolecular reactions.

(31) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399–406.

(32) (a) Cecccon, A.; Papa, I.; Fava, A. *J. Am. Chem. Soc.* **1966**, *88*, 4643–4648. (b) Stein, A. R. *Tetrahedron Lett.* **1974**, 4145–4148.

(33) Reference 11, pp 428–437.

(34) Winstein, S.; Klindinst, P. E., Jr.; Robinson, G. C. *J. Am. Chem. Soc.* **1961**, *83*, 885–895. Vitullo, V. P.; Wilgis, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 880–883.

idence for such common ion effects.

Substitution of chloride for perchlorate ions in water at a constant ionic strength of 1.0 gives no specific salt effect or common ion inhibition, as shown in Table IV. Thus, specific stabilization of carbocations by perchlorate ion³⁵ is not significant for the transition state of this reaction. Substitution of 0.6 M bromide or iodide ions for perchlorate ion gives small rate increases or decreases of 10%, respectively. The rate constants for solvolysis in the presence of iodide ion were determined by measurements of initial reaction rates because substitution by iodide becomes significant at longer times. Substitution by bromide could account for the small increase in the observed first-order rate constant in the presence of bromide ion and substitution by azide accounts for the increased rate constants in the presence of azide ion, as determined by product analysis. A specific salt effect of acetate anion gives a 30% rate decrease at 1 M.

However, when the reaction was carried out in the presence of 40% acetonitrile a 30% decrease in the rate constant for solvolysis of 1-(3-methoxyphenyl)ethyl chloride, from 2.3×10^{-4} to $1.6 \times 10^{-4} \text{ s}^{-1}$, was observed upon the addition of 0.6 M sodium chloride (Table S1). There is an even larger decrease in k_{solv} , of >50%, when 0.6 M chloride is substituted for perchlorate ion at a constant ionic strength of 0.6 in 40% acetonitrile, as shown in Figure 3. A similar inhibition was observed for 1-(3-methoxyphenyl)ethyl bromide in the presence of bromide ion (Table S1). These results might be taken as evidence for common ion inhibition of solvolysis by reaction of chloride (or bromide) ion with a carbocation intermediate to regenerate the starting material. The larger effect in the presence of perchlorate ion could be taken as evidence for a perchlorate-induced common ion effect. However, the following evidence shows that the inhibition in the mixed solvent is a specific salt effect, not a common ion rate depression.

(1) There is no common ion effect in water, a good ionizing solvent, in which a carbocation intermediate would be expected to be equally or more stable and show an equal or larger common ion inhibition.

(2) Chloride ion inhibits the solvolysis of 1-(3-methoxyphenyl)ethyl bromide almost as much as the chloride, as shown in the inset to Figure 3 (28% for the chloride at 0.36 M $[\text{Cl}^-]$, Table S1).

(3) Solvolysis of the bromide compound in the presence of 0.6 M sodium chloride gave only 20% of the chloride product. Thus, capture of any carbocation intermediate by 0.6 M $[\text{Cl}^-]$ is $\leq 20\%$, which cannot account for >50% inhibition of solvolysis by chloride ion (Figure 3).

Similar negative specific salt effects on solvolysis in mixed aqueous-organic solvents have been observed previously and described in terms of a salt-induced medium effect.³⁶ The same specific salt effects in mixed solvents can cause changes in rate when buffer concentration is increased and one anion is substituted for another at constant ionic strength; these changes can be mistaken for buffer catalysis.³⁷

The larger ratios of azide to solvent reactions from analysis of products (Table VI) than from measurements of rate constants in methanol-water mixtures (Table V) are consistent with a similar negative specific salt effect on k_{solv} when perchlorate is replaced by azide ion in these solvents.

The rate constants for both solvolysis and the second-order reaction with azide increase sharply with increasing ionizing power of the solvent in methanol-water mixtures, as shown in Figure 8. The slopes of these correlations against Grunwald-Winstein Y values, m , are 0.9–1.0 for solvolysis and 0.75–0.80 for the azide reactions. These Y values are based on the solvolysis of *tert*-butyl chloride.³⁸ The conditions are not strictly comparable because the rate constants reported here were determined in the presence

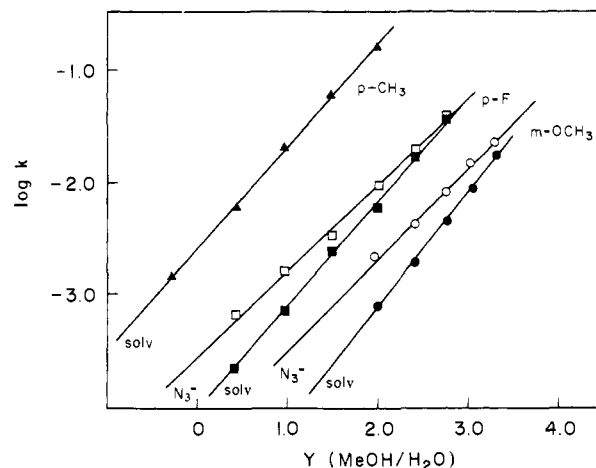


Figure 8. The dependence of k_{az} (open symbols) and k_{solv} (closed symbols) on Grunwald-Winstein Y values for methanol-water solvents³⁸ at 25 °C. The ionic strength was held constant with NaClO_4 as the concentration of azide was increased.

of sodium perchlorate in order that rate constants for the second-order reaction with azide could be determined at constant ionic strength. However, the presence of sodium perchlorate does not appear to have a significant effect because the observed m values agree with the reported value of $m = 0.91$ for the solvolysis of 1-phenylethyl chloride.³⁹ The effect of sodium perchlorate on the reaction is small, compared with the observed solvent effects, and is independent of solvent composition in acetonitrile-water mixtures (Tables IV and S1). Correlations based on Y values from the solvolysis of 1-adamantyl chloride⁴⁰ give values of $m = 0.74$ and 0.60 for solvolysis and reaction with azide of the 4-fluoro compound, respectively.

The surprisingly large values of m for the bimolecular reactions with azide anion provide further evidence for a highly polar, open transition state, with a large amount of bond cleavage and little bond formation. The reaction of an anion with an uncharged molecule would be expected to show no change or an increase in rate with decreasing solvent polarity if the charge is more dispersed in the transition state than the reactants. The observed rate decreases of 17- and 57-fold with increasing methanol concentration indicate that there is a considerable net increase in charge in the transition state.

The data provide no support for the hypothesis that nucleophilic assistance to ionization by the solvent⁴¹ is significant for any of these reactions in which ionization to an intermediate with a significant lifetime has been proved to occur.

(1) It has been pointed out previously that there is no nucleophilic assistance by solvent for the ionization of the 4-methoxy and 4-methyl compounds because there is no assistance to ionization by azide ion¹⁰ (Figure 2). If there is no assistance by a much stronger nucleophilic reagent, there is not expected to be assistance by solvent.⁴² Similarly, there is no detectable rate increase from a second-order reaction with cyanide ion for 1-phenylethyl derivatives with substituents as electron-withdrawing as 3-bromo, although the ratio $k_{\text{CN}^-}/k_{\text{solv}}$ is $10^{6.7}$ for methyl iodide in methanol.¹²

(2) A decrease in the Grunwald-Winstein m values for the 4-fluoro and 3-methoxy compounds, compared with that for the 4-methyl compound, would be expected if nucleophilic assistance to ionization were becoming significant. This decrease would

(39) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 1597–1602.

(40) Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741–5747.

(41) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67. Bordwell, F. G.; Wiley, P. F.; Mecca, T. G. *J. Am. Chem. Soc.* **1975**, *97*, 132–136.

(42) Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4821–4828.

(35) Bunton, C. A.; Huang, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 3536–3544.

(36) Grunwald, E.; Butler, A. F. *J. Am. Chem. Soc.* **1960**, *82*, 5647–5654.

Duynstee, E. F. J.; Grunwald, E.; Kaplan, M. L. *Ibid.* **1960**, *82*, 5654–5660.

(37) Salomaa, P.; Kankaanpera, A.; Lahti, M. *J. Am. Chem. Soc.* **1970**, *93*, 2084–2085.

(38) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770–2777.

reflect an increase in rate in solvents containing higher concentrations of methanol, a relatively strong nucleophile, and a decrease in ionic character of the transition state. Instead, a small increase in m is observed. This increase may represent an increase in m with increasing water content of the solvent, which has been observed previously for the solvolysis of 1-phenylethyl chloride,³⁹ because the less reactive compounds were examined in solvents with a higher water content. Plots of k_{solv} for the 4-methyl-, 4-fluoro-, and 3-methoxy-substituted compounds against k_{solv} for the unsubstituted compound³⁹ were found to give slopes of 0.96–0.97.

(3) An upward break in the selectivity ratio $k_{\text{MeOH}}/k_{\text{TfE}}$ is expected at the point at which nucleophilic assistance becomes important, because an upward break marks the onset of nucleophilic assistance for the reactions of azide, cyanide, and acetate (Table II). According to this criterion, the onset of nucleophilic assistance by solvent methanol is not observed until the 1-(4-cyanophenyl)ethyl chloride is reached (Table II), so that compounds with smaller σ values are expected to show no assistance. There is no evidence that a carbocation intermediate with a significant lifetime is formed from the 4-cyano- and 4-nitro-substituted phenylethyl chlorides, as discussed below.

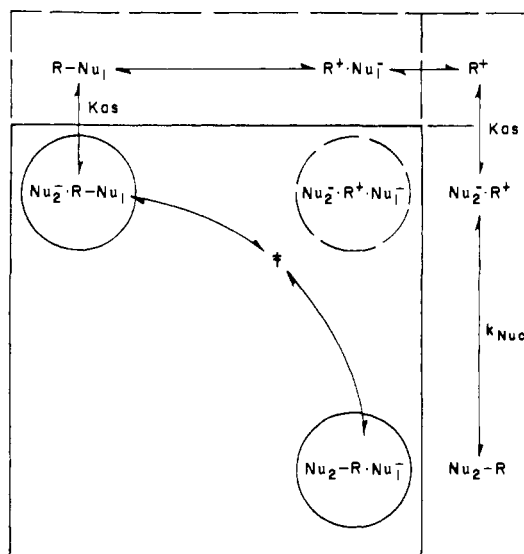
Product analysis shows that there is a decrease in $k_{\text{MeOH}}/k_{\text{TfE}}$ with increasing σ values of substituents up to the 3-methoxy compound ($\sigma = 0.39$), until limiting values of ~ 3 are reached (Table II). Similar changes occur for $k_{\text{EtOH}}/k_{\text{TfE}}$, which reaches limiting values of ~ 2 .⁹ These changes are in the opposite direction from that expected for nucleophilic assistance to ionization. The observed product ratios for these compounds may be accounted for by the selectivities for reaction with a free ion or ion pair, which may include an electrostatic interaction between the dipolar reagent and the developing carbocation.⁹

There is also no significant assistance by azide and other strong nucleophiles to the ionization of 2-(3,4-dinitrophenoxy)tetrahydropyran,¹⁴ although closely related methoxymethyl derivatives undergo bimolecular substitution reactions with a number of nucleophiles.^{13,14} Substitution of a CF_3 group for the CH_3 group of 1-phenylethyl derivatives decreases the rate constant for solvolysis by 10^5 – 10^7 and must greatly decrease the lifetimes of the carbocation intermediates. Nevertheless, the value of $\rho = -11.9$ for solvolysis of 1-aryl-2,2,2-trifluoroethyl sulfonates in ethanol is even more negative than the values for solvolysis in less nucleophilic solvents, such as $\rho \approx -6.7$ in trifluoroacetic acid. This indicates that the transition state has a large amount of carbocation character and little bond formation to the incoming group even in ethanol, a strongly nucleophilic solvent.⁴³

Concurrent $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ Mechanisms. A reaction can proceed concurrently through stepwise, monomolecular and concerted, bimolecular reaction mechanisms when the intermediate has a long lifetime in the solvent, but no lifetime when it is in contact with an added nucleophilic reagent. The bimolecular mechanism will be observed when the added reagent stabilizes the transition state; this represents a *coupled concerted mechanism*.⁷

The stepwise, dissociative mechanism of an $\text{S}_{\text{N}}1$ substitution reaction proceeds through the "wings" of Scheme I when the carbocation intermediate has a long enough lifetime to allow the leaving group, Nu_1^- , to diffuse away and the incoming group, Nu_2^- , to diffuse in before the intermediate reacts with solvent. When the cation has no lifetime in the presence of Nu_2^- the bimolecular reaction in the presence of Nu_2^- must occur by a preassociation concerted mechanism with no intermediate, inside the box of Scheme I. However, if there is no stabilization of the transition state for bond breaking by Nu_2^- , this *uncoupled concerted mechanism* will be of little significance because the association constant for formation of a random encounter complex with Nu_2^- , K_{as} , is small and most of the bond-breaking events will occur in the absence of Nu_2^- through a trapping mechanism, along the wings of Scheme I. The preassociation coupled concerted pathway inside the box becomes significant when interaction between the

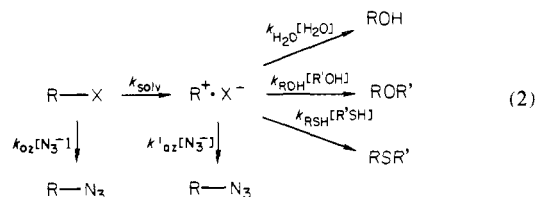
Scheme I



entering Nu_2^- , R , and the leaving Nu_1^- stabilizes the transition state of the bimolecular $\text{S}_{\text{N}}2$ reaction.⁷

Substituted 1-phenylethyl derivatives in good ionizing solvents react through the fully stepwise $\text{S}_{\text{N}}1$ mechanism along the wings of Scheme I when the carbocation is stabilized by the 4-phenoxy group or other substituents with $\sigma^+ \leq -0.5$. However, 1-(4-fluorophenyl)ethyl chloride reacts concurrently with solvent by the stepwise $\text{S}_{\text{N}}1$ mechanism, around the wings of Scheme I, and with azide ion by a concerted $\text{S}_{\text{N}}2$ mechanism, through the middle of Scheme I. A short extrapolation gives a rate constant of $k_s = 2 \times 10^{10} \text{ s}^{-1}$ for the reaction of the 1-(4-fluorophenyl)ethyl carbocation with 50:50 TFE: H_2O ,⁸ so we can conclude with some confidence that the cation has a significant lifetime in the presence of solvent. The reaction with azide occurs through concerted bimolecular substitution.³ The extrapolated first-order rate constant for reaction of the carbocation with azide within an encounter complex, k_{Nuc} in Scheme I, is 10^{17} s^{-1} , which is much larger than a bond vibration frequency and suggests that the cation does not have a significant lifetime in the presence of azide ion. This rate constant is based on a value^{35,44} of $N^+ = k_{\text{az}}/k_s = 10^6 \text{ M}^{-1}$ and a value of $K_{\text{as}} = 0.3 \text{ M}^{-1}$ for the formation of an encounter complex with azide ion.^{9,45} The N^+ ratios have little or no dependence on cation stability for carbocations that react at rate constants up to the diffusion-controlled limit.¹⁶ A concurrent stepwise reaction of azide with the cation by trapping must also exist but is too small to be detected in the presence of the fast reaction with solvent and the $\text{S}_{\text{N}}2$ reaction with azide.

The occurrence of concurrent stepwise and concerted reactions of 1-(4-fluorophenyl)ethyl chloride and bromide was tested by examining the partitioning between different reaction pathways in the presence of increasing concentrations of a nucleophile, propanethiol, that is an efficient trap for the cation intermediate.⁹ If all products were formed through the same carbocation intermediate, the addition of propanethiol would decrease the formation of all products by the same fraction (eq 2, right).



(44) Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039–7044.

(45) The value of $k_{\text{az}}/k_s = 10^6 \text{ M}^{-1}$ in 55 M water³⁵ gives $k_{\text{az}}/k_{\text{H}_2\text{O}} = 5.5 \times 10^7$. The values of k_{Nuc} were calculated from this ratio, values of $k_{\text{H}_2\text{O}}$,⁸ the relationship $k_{\text{Nuc}} = k_{\text{az}}/K_{\text{as}}$, and $K_{\text{as}} = 0.3 \text{ M}^{-1}$.

(43) Allen, A. D.; Ambidge, I. C.; Che, C.; Micheal, H.; Muir, R. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983**, *105*, 2343–2350.

However, if the azide reaction occurs through a separate, but concurrent, displacement reaction (eq 2, left), propanethiol would decrease the yield of products that are formed through the carbocation intermediate but would not decrease the yield of azide adduct formed through this separate pathway. The result, shown in Figure 4A, is that the addition of propanethiol decreases the formation of alcohol and ether from 1-(4-fluorophenyl)ethyl chloride through the carbocation intermediate but has little effect on the yield of azide product through the S_N2 pathway. A similar result was obtained with 1-(4-fluorophenyl)ethyl bromide (Figure 4B, closed symbols). In contrast, the decrease in the yield of azide adduct from 1-(3-nitro-4-methoxyphenyl)ethyl chloride upon the addition of propanethiol, indicated by the open symbols in Figure 4B, shows that with this substrate the azide adduct is formed by trapping the same carbocation intermediate that reacts with solvent and thiol. This carbocation is slightly more stable than the 4-fluoro-substituted carbocation, with an estimated rate constant for reaction with solvent of $3 \times 10^9 \text{ s}^{-1}$.⁸

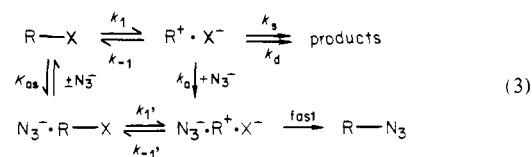
These results provide additional evidence against solvent assistance to ionization that results in reaction with the assisting solvent molecule; such a reaction would be bimolecular and would behave like the reaction with azide.

There is evidence, but not conclusive proof, for the existence of concurrent S_N1 and S_N2 reactions of 1-(3-nitro-4-methoxyphenyl)ethyl chloride with azide. In the presence of 0.48 M azide ion (at constant ionic strength) there is an increase of 20% in k_{obsd} for substrate disappearance that probably represents a second-order reaction with azide; no such increase is observed with the 4-methyl compound. A larger increase of 50% was observed in the presence of 0.4 M azide in 50% methanol in water, which is similar to the increases in $k_{\text{az}}/k_{\text{sol}}$ that are observed for other substrates that exhibit clear-cut bimolecular reactions with azide (Table V). Furthermore, the observed rate increase corresponds to the second-order rate constant for reaction with azide that is expected from the Hammett plot for the reaction with azide (Figure 7). The decrease in the yield of azide product that is shown in Figure 4 appears to level off at high propanethiol concentration, which is consistent with concurrent S_N1 and S_N2 reactions. However, this leveling could also be accounted for by a solvent effect of propanethiol; addition of 20% acetonitrile was found to give a 60% increase in the fraction of azide adduct formed from 1-(4-fluorophenyl)ethyl bromide (not shown).

1-(4-Methylphenyl)ethyl derivatives are "borderline" compounds that react, in part, through an ion pair intermediate with a significant lifetime.⁹ The mechanism of the reaction with azide depends on the leaving group: there is no second-order reaction of azide with the chloride or the pentafluorobenzoate, which give azide adduct by a trapping mechanism, but there is a large second-order reaction of azide with the dimethylsulfonium compound (Figure 2).⁹ The estimated rate constant⁴⁵ for collapse of the ion pair with azide is $k_{\text{Nuc}} = 10^{16} \text{ s}^{-1}$, which suggests that the second-order reaction with the dimethylsulfonium compound proceeds through a coupled concerted mechanism concurrently with solvolysis through a carbocation intermediate. The chloride and pentafluorobenzoate compounds, which show no second-order reaction with azide, presumably form azide adduct by an uncoupled concerted mechanism in which there is no intermediate and no stabilization of the transition state by azide if azide is present when the carbocation is formed and by a diffusion-controlled trapping mechanism when azide is not present initially. The appearance of the coupled concerted mechanism with the dimethyl sulfide leaving group appears to be an example of substrate synergism, as noted above, in which polarizable or "soft" entering and leaving groups interact favorably to stabilize the transition state for concerted displacement reactions.¹⁸ Azide is a powerful nucleophile that interacts strongly with the cationic central carbon atom in the transition state and dimethyl sulfide is probably also highly reactive, since the reaction of thiols with the carbocation is diffusion controlled.⁹

The absence of a significant bimolecular reaction of azide with the chloride and pentafluorobenzoate derivatives is of particular interest because these leaving groups might be expected to give

internal return and a bimolecular reaction through an uncoupled preassociation mechanism. If the leaving group returns faster than the intermediate reacts with solvent (k_{-1} and k_s , eq 3) many



ionization events will give no product, but if ionization occurs in the presence of azide (k_1' , eq 3) product will be formed, so that an increase in the rate of substrate disappearance is possible even if there is no nucleophilic assistance to ionization by azide. The ratio k_{-1}/k_s for chloride ion is known to be $\gg 1$ for other carbocations⁴⁶ and there is evidence for internal return of pentafluorobenzoate in this system.⁹

However, the rate and equilibrium constants for these reactions evidently do not meet the rather stringent requirements that must be satisfied in order to observe a significant rate increase by this mechanism.^{7b} With a value of $K_{\text{as}} = 0.3 \text{ M}^{-1}$ only 13% of the ionization events will take place in the presence of 0.5 M azide and with the pentafluorobenzoate leaving group about half of the remaining events will go on to products even in the absence of azide.⁹ The absence of an observed rate increase with azide even in this relatively favorable situation is further evidence against an ion pair mechanism for those reactions in which a bimolecular reaction with azide is observed.

Concurrent S_N2 reactions with azide and S_N1 reactions with solvent occur also for 1-(3-methoxyphenyl)ethyl and, probably, for 1-(3-bromophenyl)ethyl derivatives. The extrapolated rate constants for reaction of the corresponding cations with solvent are 2×10^{11} and 10^{12} s^{-1} .⁸ The second-order reaction with azide becomes more important and the $k_{\text{MeOH}}/k_{\text{TFE}}$ ratio becomes smaller and then levels off with these electron-withdrawing substituents (Tables I and II), in agreement with these assignments and the increasing reactivity of the carbocation intermediate.

It was noted above that water shows a positive deviation of ~ 200 -fold from Swain-Scott correlations of nucleophilic reactivity toward 1-(4-nitrophenyl)ethyl chloride and tosylate. This suggests that solvolysis in water occurs with little or no nucleophilic assistance. For 1-(4-nitrophenyl)ethyl chloride the second-order rate constant for reaction of water is similar to that for fluoride ion and increased rate constants are observed only with stronger nucleophiles; for the tosylate and for compounds with less electron-withdrawing substituents acetate and cyanide ions also have molar reactivities comparable to that of water (Table III, bottom of Table II). These results are consistent with the hypothesis that the reactions with weak nucleophiles occur through a dissociative mechanism with little or no assistance, possibly through an uncoupled concerted mechanism for the 4-nitro compounds, and that bimolecular substitution with nucleophilic participation becomes important with stronger nucleophiles and with strongly electron-withdrawing substituents.

The dissociative mechanism of substitution is favored when the solvent is less reactive and provides less competition to the associative mechanism, but the associative mechanism may be favored by poor ionizing solvents that inhibit the dissociative mechanism and accelerate nucleophilic attack of an ion. The second of these possibilities appears to hold for the exchange reaction of benzhydryl thiocyanates with labeled SCN^- in acetonitrile, which proceeds concurrently through a first-order dissociative mechanism with $\rho = -4.5$ and a second-order associative mechanism with ρ near zero.^{32a} Similar behavior has been observed for reactions of benzhydryl chloride with Br^- and Cl^- in dimethyl formamide.⁴⁷

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Concurrent first- and second-order substitution reactions also occur with *N*-(4-methoxybenzyl)pyridinium ions in chlorobenzene.⁴⁸

How Does the Reaction Change Its Mechanism? The change from a stepwise S_N1 to a concerted S_N2 mechanism in the 1-phenylethyl series could occur in either of two ways:

First, the transition states of coexisting stepwise and concerted mechanisms for reaction with a given nucleophile may have different energies, so that only one mechanism is usually observed. When the structure of the reactants is changed, by decreasing the stability of the carbocation for example, the relative energies of the two transition states change and the concerted rather than the stepwise mechanism is observed.

Second, only a single mechanism may exist when a given nucleophile is present at the time that bond breaking occurs. There is a *transformation* of the stepwise, S_N1 mechanism to the concerted S_N2 mechanism when the intermediate of the stepwise mechanism ceases to exist.

Nucleophilic assistance from stabilization of the transition state by the incoming reagent can, in principle, occur already with the stepwise mechanism, appear concurrently with the change from the S_N1 to the S_N2 mechanism, or develop only after the intermediate ceases to exist. In the last case there is an intermediate region with an "uncoupled concerted mechanism" in which the reaction takes place in a single step but there is no significant assistance by the incoming nucleophile.⁷

The available data are consistent with, but do not rigorously establish, the second of these pathways for the change from an S_N1 to an S_N2 mechanism in the 1-phenylethyl series. They are consistent with the hypothesis—or notion—that for substitution at carbon a stepwise mechanism will be followed when the intermediate exists and the stepwise mechanism is possible; the concerted mechanism is followed only when it is enforced by the nonexistence of the intermediate.⁷ The relevant data from this work can be summarized as follows:

(1) The bimolecular reaction of azide ion with 1-(4-nitrophenyl)ethyl chloride certainly proceeds through a concerted S_N2 mechanism that is enforced by the nonexistence of the carbocation intermediate in the presence of azide. The calculated value⁴⁵ of $k_{\text{Nuc}} = 10^{20} \text{ s}^{-1}$ for collapse of an azide-carbocation ion pair (Scheme I) is much larger than a bond vibrational frequency; it is too large to be consistent with a chemical barrier for this collapse even with a generous allowance for uncertainties in its estimation.

This rate constant and other values of k_{Nuc} given below are based on extrapolations of structure-reactivity correlations and observed rate constant ratios. These structure-reactivity correlations are characteristically linear and rate constant ratios often remain constant until limiting values due to diffusion or desolvation are reached.^{8,9,16} However, changes in selectivity do occur with highly reactive cations and structure-reactivity correlations are likely to become nonlinear as the reaction barrier approaches an insignificant value,⁹ so that these estimated "rate constants" of $\geq 10^{13} \text{ s}^{-1}$ should be viewed as rough approximations of what the rate constant would be if the barrier did not disappear. In this case the required extrapolation of $k_{\text{H}_2\text{O}}$ is by a factor of 4×10^3 using a correlation that is linear over a range of $>10^6$; the correlation used here, with $r^+ = 1.8$,⁸ is more conservative than the correlation with σ^+ used previously.¹⁰

(2) The reaction of a thiol anion and presumably of azide anion, which has essentially the same reactivity as thiol anions, with the 1-(4-(dimethylamino)phenyl)ethyl carbocation is probably diffusion controlled; it is certainly close to diffusion controlled and fits the correlation line for other diffusion-controlled reactions.¹⁰ A diffusion-controlled reaction means that collapse of the ion pair is faster than diffusional separation and occurs with a rate constant of $\sim 10^{11} \text{ s}^{-1}$ or more. The reactivity of solvent increases by a factor of 2×10^6 for the 4-methyl carbocation¹⁰ and the ratio $N^+ = k_{\text{az}}/k_s$ is independent of cation stability in the range that both reactions are activation limited.¹⁶ Since a factor of only $\sim 10^2$

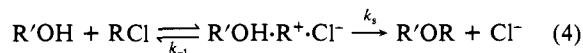
is required to increase the rate constant for collapse of the ion pair with azide to a value larger than a bond stretching frequency, it is unlikely that even the 4-methyl carbocation intermediate can exist in the presence of azide ion. This suggests that the reaction cannot occur by a stepwise mechanism if azide is present and that there is no chemical barrier even for the reactions of some carbocations that are trapped by azide ion at a diffusion-controlled rate.

(3) The extrapolated value of the rate constant for the reaction of the 1-(4-nitrophenyl)ethyl carbocation with solvent⁸ is $k_s = 10^{13} \text{ s}^{-1}$, comparable to a bond vibration frequency, and the rate constant for reaction of the carbocation with azide cannot be larger than this. The observed value of $k_{\text{az}}/k_s = 350$ (Table I), therefore, is inconsistent with a reaction that proceeds through such an intermediate.

(4) The alternative hypothesis predicts that concerted reactions with nucleophilic assistance can occur when the intermediate does have a lifetime in the presence of the nucleophile. There is no indication of any such assistance in the 1-phenylethyl system and there is no nucleophilic assistance by azide even with 1-(4-methylphenyl)ethyl chloride, which gives a cation with a calculated value of $k_{\text{Nuc}} = 10^{16} \text{ s}^{-1}$ in the presence of azide ion.⁴⁵

(5) If the appearance of the concerted reaction depends on the disappearance of the barrier for reaction of the intermediate with a nucleophile, the concerted reaction should appear later with weaker nucleophiles as σ is increased and the carbocation becomes less stable. Figure 9 shows that the increase in selectivity that results from the appearance of the nucleophilic reaction appears progressively later with increasing σ^+ as the nucleophile becomes weaker, in the sequence azide, acetate, and solvent for reactions in 50:50 TFE:H₂O. The Hammett plots in Figure 7 show that the change in slope that is characteristic of nucleophilic participation occurs with the 4-fluoro compound for azide ion and only with the 4-nitro compound for the less nucleophilic cyanide and acetate anions in 20% acetonitrile in water.

(6) The estimated rate constants for collapse of the cation-nucleophile pair suggest that the second-order reaction appears only when the rate constant for collapse in the presence of a particular nucleophile is so large that the barrier for collapse has disappeared. For azide the value of k_{Nuc} is 10^{17} s^{-1} for the 4-fluoro compound.⁴⁵ For acetate k_{Nuc} is $5 \times 10^{13} \text{ s}^{-1}$ for the 3-bromo compound, which shows an increase in selectivity toward acetate (Table II), and $3 \times 10^{14} \text{ s}^{-1}$ for the 4-nitro compound, which shows a significant second-order reaction (Figure 1). The value of k_{Nuc} for acetate was calculated from values of k_{TFE} ,⁸ an average value of $k_{\text{AcO}^-}/k_{\text{TFE}} = 60$ for the 4-CH₃O-, 4-CH₃S-, 4-PhO-, and 3-Br-4-MeO-substituted carbocations,⁹ and $K_{\text{as}} = 0.04 \text{ M}^{-1}$.⁹ For alcohols there is a small increase in $k_{\text{MeOH}}/k_{\text{TFE}}$ for 1-(4-cyanophenyl)ethyl chloride. The value of k_{Nuc} for methanol is $5 \times 10^{12} \text{ s}^{-1}$ based on an extrapolated value⁸ of $k_{\text{TFE}} = 10^{11} \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{MeOH}}/k_{\text{TFE}} = 5.4$, and $K_{\text{as}} = 0.1 \text{ M}^{-1}$. However, it is more likely that the intermediate ceases to exist because of the absence of a barrier for collapse of the carbocation-chloride ion pair (k_{-1} , eq 4). The values^{8,46} of $k_s = 6 \times 10^{12} \text{ s}^{-1}$ and $k_{\text{Cl}^-}/k_s \sim 100 \text{ M}^{-1}$



mean that k_{Nuc} for chloride ion is expected to be $\sim 10^{15} \text{ s}^{-1}$. This is consistent with the absence of an increase in $k_{\text{MeOH}}/k_{\text{TFE}}$ even for the 4-nitro compound when the leaving group is the less nucleophilic tosylate ion¹⁹ (Figure 9). It is also consistent with the conclusion that the relatively small secondary α -deuterium isotope effect for the solvolysis of 1-(4-nitrophenyl)ethyl chloride in 5% acetone-water results from an appreciable nucleophilic character for the reaction with solvent.²⁹

The proposed sequence of events for the transformation of the S_N1 to the S_N2 mechanism in the 1-phenylethyl series can be summarized as follows: When the carbocation, R⁺, has a significant lifetime it exists in a potential well and substitution occurs through the two transition states for the formation and capture of this intermediate, as shown in the reaction coordinate profile and contour diagram of Figure 10A. When the cation is mod-

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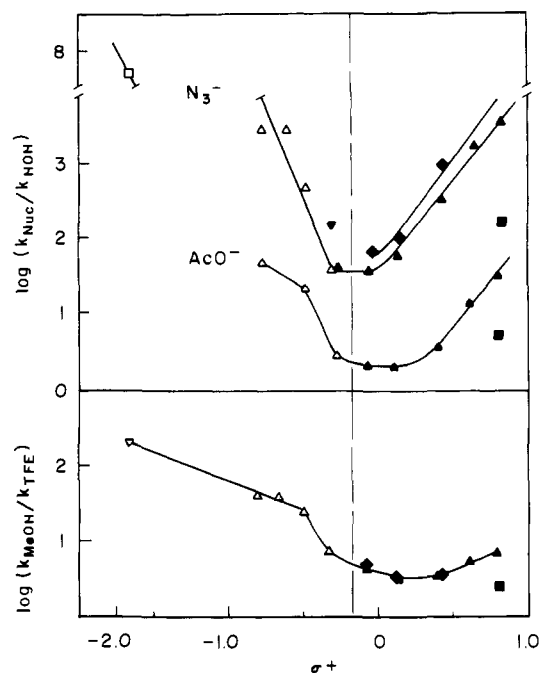


Figure 9. Nucleophilic selectivities, based on product analysis (Table II),^{8,9} for reactions of substituted 1-phenylethyl derivatives in 50:50 TFE:H₂O at ionic strength 0.5 (NaClO₄). The selectivities are plotted against the Hammett substituent constant σ^+ . Leaving groups: 3,4-dichlorobenzenethiolate (\square); water (∇); substituted benzoates (Δ); chloride (\blacktriangle); bromide (\blacklozenge); tosylate (\blacksquare); dimethyl sulfide (\blacktriangledown).

erately stable the curvature of the energy surface at the transition state is relatively sharp and there is little or no change in the position of the transition state with changing reactant structure, as is observed for carbocations that follow the N^+ scale of nucleophilic reactivity.¹⁶ As the cation becomes less stable the barriers for its collapse and their curvatures become smaller, so that changes in transition state structure and structure-reactivity parameters are observed with changing reactant structure.^{9,20,49}

In the presence of a powerful nucleophile the barrier for collapse of an unstable cation will eventually disappear and there will be only one transition state and one step along the reaction coordinate, as shown in the reaction coordinate profile and contour diagram of Figure 10B. However, there is no requirement that the transition state should immediately move downward along the y axis for bond formation to the nucleophile, so that the one-step reaction may initially show no nucleophilic assistance; i.e., it will be an uncoupled concerted reaction. The reaction of azide with 1-(4-methylphenyl)ethyl chloride is a likely candidate for this mechanism in view of the absence of nucleophilic assistance by azide, the estimated rate constant of $k_{\text{Nuc}} = 10^{16} \text{ s}^{-1}$ for reaction of the carbocation with azide that is present at the time of its formation,⁴⁵ and the occurrence of a second-order $S_{\text{N}}2$ reaction of azide with the corresponding dimethylsulfonium compound that is favored by "synergism" between the nucleophile and leaving group. In Figure 9 this interaction between the entering and leaving groups appears as the positive deviations for the reactions of the dimethylsulfonium (inverted triangle) and bromide (diamonds) derivatives with azide and the negative deviations of the tosylate derivative (squares), which has a smaller interaction than the chloride with nucleophiles. An uncoupled concerted mechanism is suggested for the reaction of methanol with 1-(3-bromophenyl)ethyl chloride by a value of $k_{\text{Nuc}} = 10^{14} \text{ s}^{-1}$ for collapse of the ion pair with chloride ion, estimated as described above for the 4-cyano compound. However, in this case it is the barrier

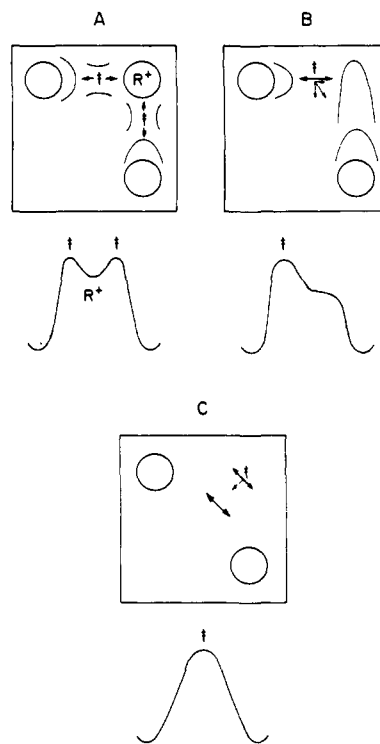


Figure 10. Reaction coordinate diagrams for substitution on carbon: (A) stepwise, $S_{\text{N}}1$ mechanism with a carbocation intermediate; (B) uncoupled concerted mechanism with no intermediate and no nucleophilic assistance; (C) coupled, concerted $S_{\text{N}}2$ displacement mechanism with varying amounts of carbocation character in the transition state.

along the x axis, for bond formation to the leaving group, that disappears.

As the cation becomes still less stable, the energy of the upper right corner of the diagram increases and the transition state for bond cleavage will tend to slide downhill toward the bottom of the diagram, perpendicular to the reaction coordinate, and to climb uphill toward the right side of the diagram, parallel to the reaction coordinate, as shown by the arrows in Figure 10B.²⁰ This shift corresponds to an increase in the amount of bond formation to the nucleophile in the transition state, so that nucleophilic assistance is observed and the reaction proceeds through a coupled concerted mechanism with an open transition state. This is the behavior that is observed for substitution reactions with 1-phenylethyl and methoxymethyl derivatives.^{13,14} The transition state closely resembles a carbocation, as shown in the upper right corner of Figure 10C.

As the cationic structure become progressively less stable in substitution reactions of benzyl, secondary alkyl, and finally primary alkyl derivatives, the energy of the upper right corner increases further and the position of the transition state slides downhill, perpendicular to the reaction coordinate, until the structure of the transition state is that for classical $S_{\text{N}}2$ substitution on a methyl halide. The great instability of the methyl carbocation provides a steep upward curvature to the side of the reaction coordinate so that there is little or no change in the structure of this transition state as the structure of the reactants is varied.^{20,49}

The overall process described here is the transformation of an energy well for the carbocation into a ridge as the carbocation becomes less stable, just as a crater can fill and become a ridge when a volcano erupts. Essentially the same process has been proposed for the conversion of a stepwise E1cB to a concerted E2 mechanism in elimination reactions.⁵⁰

Registry No. 1-(4-Methylphenyl)ethyl chloride, 2362-36-9; 1-(3-nitrophenyl)ethyl chloride, 34586-27-1; 1-(4-methoxyphenyl)ethyl chloride, 1538-89-2; 1-(4-fluorophenyl)ethyl chloride, 456-16-6; 1-(3-

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methylphenyl)ethyl chloride, 19935-78-5; 1-phenylethyl chloride, 672-65-1; 1-(3-methoxyphenyl)ethyl chloride, 58114-05-9; 1-(3-bromophenyl)ethyl chloride, 19935-76-3; 1-(4-methylphenyl)ethyl bromide, 24344-85-2; 1-(3-nitrophenyl)ethyl bromide, 29067-55-8; 1-(4-methoxyphenyl)ethyl bromide, 55214-85-2; 1-(4-fluorophenyl)ethyl bromide, 65130-46-3; 1-(3-methylphenyl)ethyl bromide, 88563-82-0; 1-phenylethyl bromide, 585-71-7; 1-(3-methoxyphenyl)ethyl bromide, 88563-83-1; 1-(3-bromophenyl)ethyl bromide, 59770-98-8; 1-(4-nitrophenyl)ethyl

chloride, 19935-75-2; 1-(4-nitrophenyl)ethyl bromide, 19935-81-0; 1-(4-nitrophenyl)ethyl tosylate, 82925-36-8; 1-(4-methylphenyl)ethyl pentafluorobenzoate, 88563-51-3; [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide, 65130-40-7.

Supplementary Material Available: Salt effects and product compositions in Tables S-1, S-2, and S-3 (4 pages). Ordering information is given on any current masthead page.

General Base Catalysis of the Addition of Hydroxylic Reagents to Unstable Carbocations and Its Disappearance¹

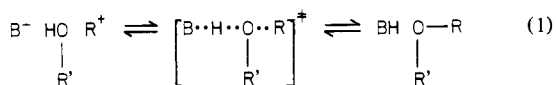
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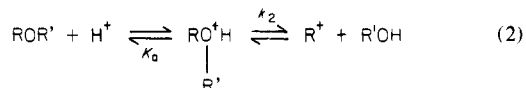
Abstract: General base catalysis of the addition of ROH is significant for 1-phenylethyl carbocations of moderate stability and is most important for weakly basic alcohols. The Brønsted slope for catalysis of the addition of trifluoroethanol to the 1-(4-methoxyphenyl)ethyl carbocation is $\beta = 0.08$. The development of positive charge on the attacking alcohol decreases with decreasing stability of the carbocation; this may be described by the interaction coefficient $p_{yy'} = \partial\beta_{nuc}/-\partial\sigma$. The positive $p_{yy'}$ coefficient and small β correspond to a small component of proton transfer in the transition state for alcohol addition; in contrast, acetate catalysis of ROH addition to more stable electrophiles exhibits a negative $p_{yy'}$ coefficient that corresponds to a large component of proton transfer and a diagonal reaction coordinate on an energy contour diagram. It is concluded that the observed catalysis involves hydrogen bonding and represents the transition region between fully concerted, coupled general acid-base catalysis and specific acid catalysis with solvation of the proton in the transition state. Catalysis disappears with less stable cations when reaction with solvent and diffusion become competitive, with $k_s \sim 10^9 \text{ s}^{-1}$, and the rate constant for base catalysis approaches a limiting value of $\sim 10^7 \text{ M}^{-2} \text{ s}^{-1}$. The absence of general base catalysis of alcohol addition corresponds to specific acid catalysis of alcohol expulsion to form an unstable carbocation in the reverse direction.

Most reactions that involve the addition or loss of water and alcohols are subject to general acid-base catalysis through the mechanism shown in eq 1. This class *n* mechanism involves



catalysis of proton transfer to or from the nucleophilic reagent, with general base catalysis of proton removal from ROH in the addition direction and general acid catalysis of proton addition in the reverse direction. Structure-reactivity correlations have provided strong evidence that a number of these reactions are concerted, with significant contributions of both heavy atom movement and proton transfer in the transition state.²⁻¹³

This type of catalysis has been observed for several reactions in which carbocations are formed or react, including the hydrolysis of acetals and ortho esters and the addition of ROH to a phthalimidium ion.^{3-5,9,10,14} However, other reactions in this group proceed with only specific acid catalysis for carbocation formation and with no catalysis of the addition of water or alcohols to the carbocation (eq 2).¹⁵ We would like to know why this change



in mechanism takes place and what is the sequence of events as one mechanism changes, or "merges", into the other. Three factors are known that can be involved in these changes:

(1) There is a progressive increase in the Brønsted coefficient α (or a decrease in β in the addition direction) as the cation becomes less stable and the alcohol becomes more basic. When α becomes 1.0 (or β becomes 0) the reaction will usually become specific acid catalyzed (or uncatalyzed in the addition direction, eq 2). These changes can be described in terms of changes in the position of the transition state and reaction coordinate on an energy

(1) Supported by grants from the National Institutes of Health (GM-20888) and National Science Foundation (PCM 77-08369). Dr. Richard was supported by a grant from the National Institutes of Health (AM 07251).

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