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Reactions of Substituted 1-Phenylethyl Carbocations with Alcohols and Other Nucleophilic Reagents[1]

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Abstract: Selectivities of a series of substituted 1-phenylethyl carbocations toward alcohols and other nucleophiles have been determined by product analysis. The 1-(4-(dimethylamino)phenyl)ethyl carbocation exhibits a high selectivity in its reactions with alcohols, with $k_{\mathrm{EtOH}}/k_{\mathrm{TFE}} = 140$ and $\beta_{\mathrm{nuc}} = 0.5$. The selectivity for activation-limited reactions with alcohols decreases progressively with increasing reactivity of the carbocation, in contrast to the behavior expected from the N^+ scale of reactivity. A sharper drop in selectivity for carbocations that react faster than $\sim 10^9$ s^{-1} is attributed to an approach to limiting rate constants for the more reactive alcohol. The limiting selectivity of $k_{\mathrm{EtOH}}/k_{\mathrm{TFE}} = 2$ for carbocations with $k_s \sim 10^{11}$ s^{-1} may represent reaction from a pool of solvent molecules in which there is a modest charge–dipole interaction between the alcohol and carbocation. The relatively low reactivity of water corresponds to that expected for an alcohol of p$K_a \sim 13$. This is ascribed to an imbalance between charge development and solvation of the transition state compared with H_3O^+. Substituted acetate anions react with the 1-(4-methoxyphenyl)ethyl carbocation with $\beta_{\mathrm{nuc}} = 0.13$. The selectivity decreases with increasing cation reactivity as the carboxylate ions approach limiting rate constants of $\sim 5 \times 10^8$ M^{-1} s^{-1}. This relatively low limit is attributed to a requirement for desolvation of basic oxygen anions before reaction. A dependence of solvent selectivity on the leaving group shows that the 1-(4-methylphenyl)ethyl carbocation reacts with solvent, in part, through an ion pair. Azide ion reacts from a pool that can be described by an equilibrium constant of $K_{\mathrm{as}} = 0.3$ M^{-1}. Styrene formation from this carbocation is catalyzed by a leaving carboxylate ion and by added buffers, with $\beta = 0.14$. The equilibrium constant for the formation of a reactive base–cation pair is ~ 0.04 M^{-1}. Rate constants for collapse of the ion pair, to form ester, and for proton removal, to form 4-methylstyrene, were estimated to be approximately 1.6×10^{10} s^{-1} and 6×10^7 s^{-1}, respectively. The rate constants for deprotonation and for hydration of the styrene give the acid dissociation constant of the carbocation to form 4-methylstyrene, p$K_A = -11.2$.

The reactivity of relatively stable carbocations toward nucleophilic reagents has been examined directly in some detail,[2] but studies of more reactive carbocations have been limited because of mixing problems. In this paper we describe the reactivity and selectivity of ring-substituted 1-phenylethyl carbocations toward substituted alcohols, water, and oxygen anions. The carbocations are generated from substituted 1-phenylethyl derivatives with different leaving groups and the relative rate constants for their reactions are measured from the yields of products. Absolute rate constants for these reactions may be estimated by comparison of the product ratios with the rate constants for reaction with solvent that were described in the previous paper.[3]

The results describe the changes in relative nucleophilic reactivity that occur as the carbocation becomes less stable and the rate constants approach the diffusional limit. The relatively low limiting rate constants for reactions with oxygen anions suggest that the rate is limited by a slow desolvation step. The 1-(4-methylphenyl)ethyl carbocation undergoes some reaction with solvent and deprotonation to give styrene before the leaving group diffuses away in 50:50 TFE:H_2O, so that it is possible to estimate rate constants for these reactions of ion pair intermediates.

Experimental Section

Materials. Reagent grade inorganic salts, sodium acetate, and sodium formate were used without further purification. Water was glass distilled. Alcohols, methoxyacetic acid, dichloroacetic acid, and trifluoroacetic acid were purified by distillation, except for trifluoroethanol and methoxyethanol which were Aldrich Gold Label Grade. Aliphatic thiols were distilled under nitrogen. Cyanoacetic acid and chloroacetic acid were recrystallized from benzene/acetone and chloroform, respectively. The procedures for the synthesis of the substrates used here are given in the previous paper.[3]

Solvolysis Reaction Procedure. Reaction mixtures were prepared by mixing water (ionic strength 1.0, maintained with $NaClO_4$) with an equal volume of trifluoroethanol. Reactions were run at room temperature, 22 ± 2 °C; the product ratios do not change significantly over this temperature range. Argon was bubbled through water and trifluoroethanol (separately) before they were used to prepare solutions containing thiolate anions. The concentration of thiolate anion in solutions containing excess sodium hydroxide was determined from the amount of 2-nitro-5-mercaptobenzoic acid released after addition of Ellman's reagent.[4] Solutions of trifluoroethoxide anion were prepared by mixing 1.00 M aqueous sodium hydroxide with trifluoroethanol.

The conditions used for the uncatalyzed reactions of substituted 1-phenylethyl benzoate esters with aliphatic alcohols and thiols are similar to those previously reported for reactions of the substrates in 50:50 TFE:H_2O,[3] except that some of the trifluoroethanol was replaced by an equal volume of thiol or alcohol. The ionic strength was maintained at 0.5 with $NaClO_4$ unless noted otherwise. Peak ratios for the ester and the solvent adducts were shown to be constant at early reaction times for reactions of carboxylate ions in which the ester product is unstable. Perchloric acid was used to catalyze the reactions of trifluoroethanol and an aliphatic alcohol or thiol with substituted 1-phenylethyl alcohols in a solvent containing 50% H_2O, ≥45% TFE, plus ROH or RSH. The products are unstable in perchloric acid, but constant product ratios were obtained during the first 1% of reaction.

Acid-catalyzed solvolysis reactions of 1-(4-(dimethylamino)phenyl)ethyl alcohol were initiated by the rapid injection from a syringe of organic solvent into a solution of substrate in dilute aqueous perchloric acid, to give a final substrate concentration of 1 mM. Aliquots were removed at intervals and quenched by rapid injection of 0.2 mL into a tube containing 0.01 mL of 1 M sodium carbonate. Initial experiments with poor mixing gave a burst of trifluoroethyl ether formation that increased product ratios by ~20% at 2 min reaction time; this increase was <10% with mixing by rapid injection. Only the free base of 1-(4-(dimethylamino)phenyl)ethyl alcohol reacts at the dilute acid concentrations used. The acid-catalyzed reaction of the protonated form is $\sim 10^{11}$ times slower on the basis of $\rho^+ = -4.55$ and σ^+ values of -1.67 and 0.82 for dimethylamino and trimethylammonium substituents, respectively.[3]

In all cases the observed alcohol selectivities obtained for the acid-catalyzed reactions of substituted 1-phenylethyl alcohols were found to be independent of acid concentration. The following concentrations of perchloric acid were used: 1-(4-(dimethylamino)phenyl)ethyl alcohol, 2 and 10 mM; 1-(4-methoxyphenyl)ethyl alcohol, 0.5 and 2 mM; 1-(3-

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[2] Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348-354.

[3] Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

[4] Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70-77.

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bromo-4-methoxyphenyl)ethyl alcohol, 0.0033 and 0.033 M; 1-(4-(methylthio)phenyl)ethyl alcohol, 4 mM; 1-(4-methylphenyl)ethyl alcohol, 0.0067 and 0.10 M; 1-(4-fluorophenyl)ethyl alcohol, 0.50 M; 1-(3-methoxyphenyl)ethyl alcohol, 0.5 and 1.0 M. Reaction mixtures containing >50 mM perchloric acid were neutralized with 1.0 M sodium carbonate prior to chromatographic analysis.

Product Analysis. Product analysis was accomplished by HPLC using the procedures described in the previous paper.[3] The thiol, alcohol, and carboxylate adducts were identified as the additional peak appearing on the HPLC elution profile for analysis of a reaction mixture that contained the nucleophile. These assignments were confirmed by the following observations. (1) For reactions of thiols, methanol, and carboxylate anions the ratio of peak areas for the nucleophile and solvent adducts is directly proportional to the nucleophile concentration. (2) The relative retention times of the adducts of a given nucleophile relative to the solvent adduct are similar or identical for compounds with different ring substituents. (3) The products assigned an alkyl ether structure were observed to be unstable at acid concentrations that catalyze the reaction of the parent 1-phenylethyl alcohols. (4) The products assigned the structures of 1-(4-methoxyphenyl)ethyl esters of substituted acetic acids undergo solvolysis at rates comparable to those of 1-(4-methoxyphenyl)ethyl benzoate esters. (5) In all cases, except for the reaction of mercaptoethanol, only a single product derived from the nucleophile was observed.

Mercaptoethanol gave two product peaks. The size of the smaller peak corresponded to that expected for reaction with an alcohol and the larger peak was assigned to the thioether product. The ratio of the reactivities of trifluoroethoxide and azide ions was determined from the increase in the ratio of the trifluoroethyl ether to azide adduct products from reactions in the presence of constant azide and increasing trifluoroethoxide ion concentrations. The size of the azide adduct peak was corrected by up to 50% for the presence of 4-methylstyrene, which coelutes with the azide adduct and is formed in the presence of trifluoroethoxide ion. The correction was made from analysis of 4-methylstyrene formation in reaction mixtures containing trifluoroethoxide but no azide ion, assuming that the styrene constituted identical fractions of the total solvolysis reaction products in both solutions. Catalysis of styrene formation by azide is not expected to be significant on the basis of the observed catalysis by the more basic acetate ion. The corrected values for the azide adduct gave constant trifluoroethoxide selectivity values at increasing trifluoroethoxide concentrations.

The relative reactivity of methyl thioglycolate and azide anions toward 1-(4-methoxyphenyl)ethyl 3,5-dinitrobenzoate was determined from the peak ratios for their nucleophilic adducts in the presence of an excess of sodium trifluoroethoxide, which insured complete ionization of the thiol.

In most cases ratios of rate constants for nucleophilic reactions were obtained directly from the ratios of the peak areas of the nucleophilic adducts, since substitution at C-1 by a nonabsorbing group is not expected to alter the absorbance of the product significantly. It was shown previously that for a constant ring substituent the water, trifluoroethanol, and azide adducts have identical extinction coefficients.[3]

The extinction coefficients of the solvent and *S*-mercaptoethanol adducts formed from 1-(4-methoxyphenyl)ethyl phenyl ether are essentially the same because the total area of the product peaks formed from a constant amount of substrate was found to remain constant as the thiol adduct increased from 0% to 75% of the product. Similar experiments for substrates with lower extinction coefficients gave extinction coefficient ratios for thiol and solvent adducts of 1.7 and 1.4, respectively, for the propanethiol and mercaptoethanol adducts formed from 1-(4-methylphenyl)ethyl chloride and 1.35 for the propanethiol and solvent adducts formed from 1-(fluorophenyl)ethyl chloride at the wavelengths that were monitored for product analysis.

4-Methylstyrene was identified as a product of the solvolysis of 1-(4-methylphenyl)ethyl derivatives that eluted immediately before the trifluoroethyl ether by comparison with the elution position of authentic 4-methylstyrene. The reaction product was also found to have the same relative peak areas at 250 and 263 nm and showed the same reactivity with bromine and mercaptoethanol as 4-methylstyrene.[3] Relative extinction coefficients for 4-methylstyrene and 1-(4-methylphenyl)ethyl alcohol of 120 and 35 at 250 and 263 nm, respectively, were determined from the peak areas of standard solutions.

Solutions of carboxylate salts that were adjusted in water to pH 6–7 gave solutions in 50:50 TFE:H_2O (ionic strength 0.5, maintained with $NaClO_4$) with an observed pH of <7. Catalysis of styrene formation by trifluoroethoxide ion is insignificant at this pH.

Results

Partitioning rate constant ratios, k_{ROH}/k_{TFE}, for the reaction of solvent components with substituted 1-phenylethyl chlorides and benzoates and for the acid-catalyzed reactions of 1-phenylethyl alcohols and 1-(4-methoxyphenyl)ethyl phenyl ether in 50:45:5 (v:v:v) H_2O:TFE:ROH are given in Table I. The product ratios were found to be independent of the leaving group, within ±10%, for the compounds listed in Table I. Solvent selectivities with the different leaving groups were determined for four or more alcohols, except that for the 1-(3-bromo-4-methoxyphenyl)ethyl derivatives only the reaction with methanol was studied with two leaving groups.

The observed values of k_{RCOO^-}/k_{TFE} for the reactions of the 4-methoxy-, 4-methylthio-, 4-phenoxy-, and 3-bromo-4-methoxy-substituted 1-phenylethyl derivatives were found to decrease up to 40% as the acetate concentration was increased from 0.1 to 0.5 M. This decrease may be accounted for by general base catalysis by acetate of the reaction with trifluoroethanol.[5] A smaller decrease in k_{RCOO^-}/k_{H_2O} of ~10% was observed over the same range of acetate concentration. The values of k_{RCOO^-}/k_{TFE} reported in Table II were calculated from the observed values of k_{RCOO^-}/k_{H_2O} at the lowest concentration of carboxylate ion that was examined, at which base catalysis of the water reaction is not significant, and from values of k_{H_2O}/k_{TFE} in the absence of acetate (Table I). The yield of acetate ester from reactions of 1-(4-methoxyphenyl)ethyl derivatives was found to be directly proportional to the concentration of acetate anion in buffers with $AcO^-/AcOH$ ratios of 3, 1, and 0.1, showing that the reaction with acetic acid is not significant. Identical values of k_{AcO^-}/k_{TFE} were obtained for the reactions of 1-(4-methoxyphenyl)ethyl 4-nitrobenzoate and for the acid-catalyzed reactions of the corresponding phenyl ether (Table II, footnote *d*).

General base catalysis of solvent attack is not significant for the 1-(4-methylphenyl)ethyl carbocation. No change in the ratio k_{az}/k_s, for addition of azide and solvent, was observed as the sodium acetate concentration was increased from 0 to 0.5 M.

The nucleophilic selectivities of trifluoroethoxide ion and thiols toward substituted 1-phenylethyl derivatives are given in Table III. The values for the reaction of trifluoroethoxide ion are based on the increase in the ratios of the trifluoroethyl ether:azide products in the presence of increasing concentrations of trifluoroethoxide ion. For reaction of 1-(4-methylphenyl)ethyl chloride only a 15% increase was observed in this ratio as the trifluoroethoxide concentration was increased from 0 to 0.33 M. A smaller increase was observed in this ratio for the reaction of 1-(4-fluorophenyl)ethyl chloride and the value of k_{TFE^-}/k_{TFE} in Table III for this compound is an upper limit calculated assuming a 15% increase. A value of $k_{RSH}/k_{TFE} = 130$ was obtained for reaction of CH_3OCOCH_2SH with 1-(4-methoxyphenyl)ethyl alcohol (in the presence of acid) and a k_{az}/k_{RS^-} value of 1.8 was obtained for the reaction of $CH_3OCOCH_2S^-$ with 1-(4-methoxyphenyl)ethyl 3,5-dinitrobenzoate in 50:50 (v:v) TFE:H_2O. The ratios of the rate constants for S- and O-alkylation of mercaptoethanol are 30 for 1-(4-methoxyphenyl)ethyl derivatives, 6.6 for 1-(4-methylphenyl)ethyl chloride, and 4.5 for 1-(4-fluorophenyl)ethyl chloride, assuming equal extinction coefficients for the S and O adducts of mercaptoethanol. Nucleophilic selectivities toward 1-(4-(dimethylamino)phenyl)ethyl 3,4-dichlorophenyl thioether were reported in the previous paper.[3]

The partitioning ratios in Table IV for product formation from 1-(4-methylphenyl)ethyl derivatives are different with different leaving groups, in contrast to those in Table I for compounds that give more stable carbocations. The differences in product ratios in the top two rows of Table IV of up to 40% were observed repeatedly and are well beyond the estimated error of ±5% for these experiments. However, the ratios with water and chloride ion as leaving groups do not differ significantly (see also Table I). There is also a dependence of the fraction of styrene product on the leaving group, with a 6-fold increase for pentafluorobenzoate compared with water as the leaving group (k_p/k_s, Table IV).

A plot of the increase in the fraction of 4-methylstyrene product against the concentration of substituted acetates for the reaction

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(5) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.*, last of four papers in this issue.

Table I. Solvent Selectivities, k_{ROH}/k_{TFE},[a] for the Reactions of Substituted 1-Phenylethyl Derivatives in 50:45:5 H_2O:TFE:ROH (v:v)[b]

		ring substituent; leaving group										
alcohol	pK_a[c]	4-$N(CH_3)_2$; H_2O	4-OCH_3; H_2O, PhOH, 4-NO_2-$PhCO_2^-$	4-SCH_3; H_2O, 3,5-di-NO_2-$PhCO_2^-$	4-OPh; 3,5-di-NO_2-$PhCO_2^-$	4-OCH_3, 3-Br; H_2O	4-OCH_3, 3-NO_2; Cl^-	4-CH_3; H_2O, Cl^-	4-F; H_2O, Cl^-	3-OCH_3; H_2O, Cl^-	3-Br; Cl^-	4-NO_2; $OTos^-$
CH_3CH_2OH	16.0	140	30	26	16	17	7.5	5.1	3.7	2.3	2.1	1.8
$CH_3(CH_2)_3CH_2OH$	15.9	190	43	36								
CH_3OH	15.5	220	41	36	25	24[h]	11.2	7.0	4.6	3.0	3.2	2.5
$ClCH_2CH_2CH_2OH$	15.5[d]		27	26			6.4		2.6	2.2		
$H_2C{=}CHCH_2OH$	15.5[e]	82	28									
$HOCH_2CH_2OH$	15.1[e]		21	20	13.2	14.1	8.8			2.4		2.6
$CH_3OCH_2CH_2OH$	14.8[e]	43	15	13	8.8	9.7	5.0	4.1		2.2	1.9	1.8
$ClCH_2CH_2OH$	14.3	19	9.8	9.2	6.7	7.0	4.1	3.4	2.1	2.0	1.7	1.2
$CNCH_2CH_2OH$	14.0[e]		5.1	5.1	3.7	3.9		2.4	1.9	1.3	1.2	1.1
$HC{\equiv}CCH_2OH$	13.5	24	10.7	10.3	8.2	9.4	7.7	4.5	3.6	3.0	2.4	2.1
Cl_2CHCH_2OH	12.9	4.1	3.2	3.2				1.7	1.4	1.4		
H_2O[f]	15.7	3[g]	1.9	1.7	1.5	1.8	2.6	1.5	1.8	0.82	1.2	0.9

[a] A dimensionless ratio of second-order rate constants. In all cases in which more than one leaving group was examined the ratios for different leaving groups agreed to better than ±10%. [b] At 22 ± 2 °C and constant ionic strength of 0.5 maintained with $NaClO_4$; (in 50:49.5:0.5 H_2O:TFE:ROH for 1-(4-(dimethylamino)phenyl)ethyl cation with methanol). The reactions with water and phenol leaving groups are acid-catalyzed reactions of the alcohols and phenyl ethers (see Experimental Section). [c] Unless otherwise noted, the pK_a values are taken from Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795-798. [d] Sauers, C. K.; Jencks, W. P.; Groh, S. *J. Am. Chem. Soc.* **1975**, *97*, 5546-5553. [e] Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205-1209. [f] An average value for reaction in 50:45:5 H_2O:TFE:ROH. [g] From initial product ratios obtained for the acid-catalyzed solvolysis of 1-(4-(dimethylamino)phenyl)ethyl methyl ether. [h] The same result was obtained with the pentafluorobenzoate ester.

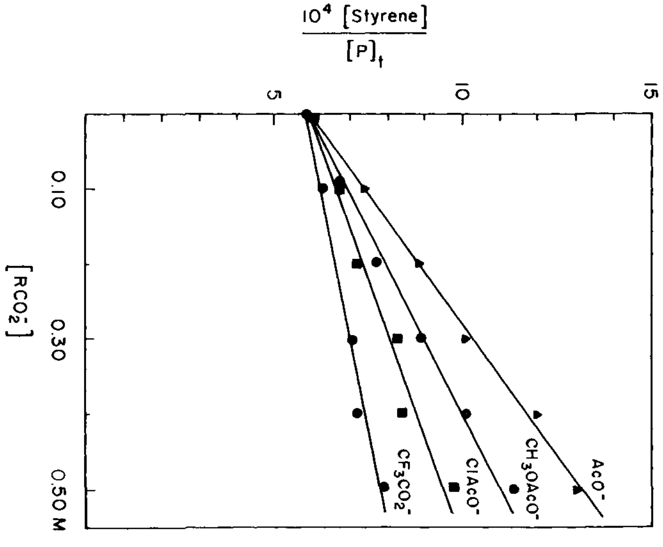

Figure 1. The increase in the fraction of 4-methylstyrene product, [styrene]/$[P]_t$, with increasing carboxylate anion concentration for the solvolysis of 1-(4-methylphenyl)ethyl chloride in 50:50 TFE:H_2O with μ = 0.5 maintained with $NaClO_4$: (▲) AcO^-; (●) CH_3OAcO^-; (■) $ClAcO^-$; (●) $CF_3CO_2^-$.

of 1-(4-methylphenyl)ethyl chloride is given in Figure 1. The plots are linear because styrene constitutes only a small fraction of the total reaction products. The slopes of these plots are equal to k_B/k_s (M^{-1}), where k_B is the rate constant for base-catalyzed elimination of 1-(4-methylphenyl)ethyl chloride and k_s is the pseudo-first-order rate constant for the nucleophilic reaction of solvent (Table V). The point for water is based on an observed yield of styrene of 0.07% in the acid-catalyzed reaction of 1-(4-methylphenyl)ethyl alcohol (Table IV). A similar yield was obtained for solvolysis of the chloride, but this is reported as an upper limit in Table IV because it was not possible to prove that the reactive starting material was free of styrene.

The observed rate constant for the hydration of 4-methylstyrene at 25 °C in 50:50 (v:v) TFE:H_2O containing 1.0 M $HClO_4$ was found to be 1.3×10^{-5} s^{-1}. Neglecting activity coefficient effects for the proton in this solvent, which are not expected to be large, the second-order rate constant for acid-catalyzed hydration is then 1.3×10^{-5} M^{-1} s^{-1}.

Discussion

Activation-Limited Reactions of Alcohols with Substituted 1-Phenylethyl Cations. The reactions of a large number of carbocations with nucleophilic reagents show little or no change in selectivity over a wide range of reactivity, as described by the N^+ scale of nucleophilic reactivity (eq 1).[2,6] In contrast, the car-

$$\log (k/k_0) = N^+ \qquad (1)$$

bocations derived from substituted 1-phenylethyl derivatives show large changes in selectivity in their activation-limited reactions with alcohols as the reactivity of the cation increases. This change in selectivity is consistent with a relatively small curvature of the reaction barrier for these rapid reactions, which permits a shift in the position of the transition state along the reaction coordinate as the barrier becomes smaller.

The 1-(4-(dimethylamino)phenyl)ethyl cation shows an exceptionally large selectivity in its reactions with alcohols. This is illustrated by the reactivity ratios of 140 for ethanol/tri-

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(6) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 1589-1594, 4966-4971.

Table II. Selectivities toward Carboxylate Anions, k_{RCOO^-}/k_{TFE},[a] for the Reactions of Substituted 1-Phenylethyl Derivatives[b]

		ring substituent; leaving group							
$RCOO^-$	pK_a[c]	4-OCH_3; 3,5-di-NO_2-$PhCO_2^-$	4-OCH_3, 3-Br; $F_5PhCO_2^-$	4-OCH_3, 3-NO_2; Cl^-	4-SCH_3; 3,5-di-NO_2-$PhCO_2^-$	4-OPh; 3,5-di-NO_2-$PhCO_2^-$	4-CH_3; Cl^-	4-F; Cl^-	3-OCH_3, Cl^-
$CH_3CO_2^-$	4.8	95[d,e]	40[e]	10[e]	80[e]	40[f,g] (32[h])	4.5[i]	3[i]	2[i]
HCO_2^-	3.8	115[f,g] (97[h])				67[f,g] (55[h])	6.5[i]		2[i]
$CH_3OCH_2CO_2^-$	3.5	65[f,g] (55[h])				26[f,g] (23[h])	4.5[i]		2[i]
$ClCH_2CO_2^-$	2.9	55[f,g]				25[f,g]	4.5[i]		2[i]

[a] Ratio of second-order rate constants. [b] In 50:50 (v:v) TFE:H_2O at 22 ± 2 °C and $\mu = 0.5$ maintained with $NaClO_4$. [c] In water.[12] [d] Average values for PhOH, 4-$NO_2PhCO_2^-$, and 3,5-di-$NO_2PhCO_2^-$ leaving groups were found to differ by less than 10% from this value. [e] Value obtained at 0.10 M NaOAc. [f] Calculated from k_{RCOO^-}/k_{H_2O}(observed) and k_{H_2O}/k_{TFE} (Table I); see text. [g] Value obtained at 0.25 M $RCOO^-$. [h] Observed value at 0.25 M $RCOO^-$. [i] Average of values at 0.25 M and 0.50 M $RCOO^-$.

Table III. Nucleophilic Selectivities, k_{Nuc}/k_{TFE},[a] toward Substituted 1-Phenylethyl Derivatives in 50:50 TFE:H_2O[b]

	ring substituent, leaving group			
nucleophile	4-OCH_3, 3,5-di-NO_2-$PhCO_2^-$	4-CH_3, Cl^-	4-F, Cl^-	3-OCH_3, Cl^-
$CF_3CH_2O^-$	690	~4	≤4	
$CH_3CH_2CH_2SH$	1700[c]	51[d]	18[d]	
HOEtSH[e]	420[f]	26[d]	10-13[d,g]	7.5[d]

[a] Dimensionless ratio of second-order rate constants. [b] In 50:50 (v:v) TFE:H_2O at room temperature and $\mu = 0.5$, maintained with $NaClO_4$. [c] Average of values obtained in experiments with 5.1 mM and 5.5 mM propanethiol. [d] In 50:45:5 (v:v:v) H_2O:TFE:RSH. [e] For reaction with the thiol group. [f] In 50:49.5:0.5 (v:v:v) H_2O:TFE:RSH. [g] The values of 13 and 10 are based on extinction coefficient ratios for the thiol and solvent adducts of 1.0 and 1.35, respectively.

Table IV. Dependence on the Leaving Group of Nucleophilic Selectivity toward 1-(4-Methylphenyl)ethyl Derivatives[a]

leaving group	H_2O[b]	Cl^-	F_5PhCOO^-	$S(CH_3)_2$
k_{MeOH}/k_{TFE}[c]	7.5	6.9	5.3	5.6
k_{H_2O}/k_{TFE}		1.3	1.0	0.95
k_{az}/k_{TFE}		52	38	d
k_p/k_{TFE} (M)[e]	0.034	≤0.028[f]	0.14	
k_p/k_s[e]	7×10^{-4}[g]	≤6×10^{-4}[f]	3.9×10^{-3}	

[a] In 50:50 (v:v) TFE:H_2O at $\mu = 0.50$, maintained with $NaClO_4$. [b] Measured in 0.0067 and 0.10 M perchloric acid. [c] For reaction in 50:45:5 (v:v:v) H_2O:TFE:MeOH. [d] The reaction with azide is second order. [e] k_p is the pseudo-first-order rate constant for the formation of 4-methylstyrene. [f] Upper limit, because it was not possible to show that the starting material was free of styrene. [g] Calculated from k_p/k_{TFE}, $k_{H_2O}/k_{TFE} = 1.3$ (row 2, this table), and $k_s = k_{TFE}[TFE] + k_{H_2O}[H_2O]$.

Table V. Base-Catalyzed Styrene Formation from 1-(4-Methylphenyl)ethyl Chloride[a]

base	pK_a[b]	$10^4 k_B/k_s$,[c] M^{-1}	k_B,[d] M^{-1} s^{-1}
$CF_3CH_2O^-$	12.4	172	6.9×10^7
AcO^-	4.8	14.3	5.8×10^6
HCO_2^-	3.8	10.8	4.4×10^6
CH_3OAcO^-	3.5	10.9	4.4×10^6
$ClAcO^-$	2.9	7.1	2.9×10^6
$CNAcO^-$	2.4	5.7	2.3×10^6
$CF_3CO_2^-$	0.2	3.6	1.4×10^6
H_2O	−1.8	0.2[e]	7×10^4[e]

[a] In 50:50 (v:v) TFE:H_2O at $\mu = 0.5$, maintained with $NaClO_4$. [b] In water.[12] [c] Ratio of 4-methylstyrene formation to solvolysis products, treating the nucleophilic reaction of solvent as a pseudo-first-order rate process. [d] Apparent rate constant for styrene formation from the carbocation based on $k_s = 4 \times 10^9$ s^{-1} for the reaction of solvent with the 1-(4-methylphenyl) carbocation.[3] [e] The solvent deprotonation reaction was treated as a second-order rate process and the water concentration of 28 M was used as the total solvent concentration (from the data in column 2, Table IV).

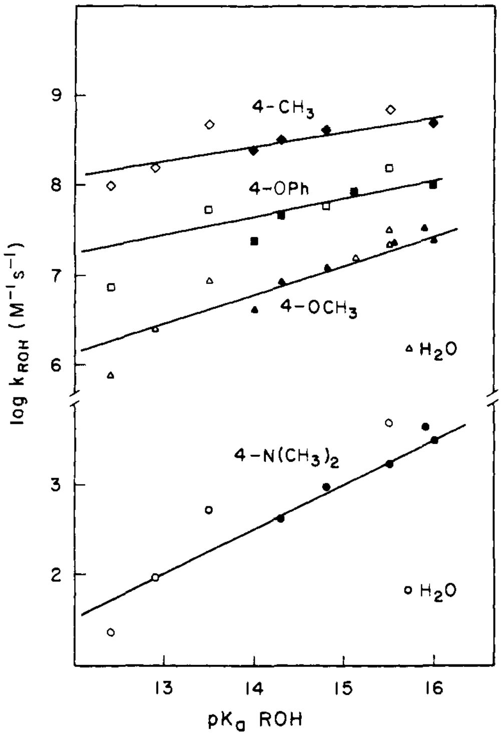

Figure 2. Estimated rate constants for the reaction of alcohols with substituted 1-phenylethyl carbocations, plotted against the pK_a of the alcohol: (◇) 1-(4-methylphenyl)ethyl carbocation; (□) 1-(4-phenoxyphenyl)ethyl carbocation; (△) 1-(4-methoxyphenyl)ethyl carbocation; (○) 1-(4-(dimethylamino)phenyl)ethyl carbocation. The solid symbols refer to alcohols with the structure XCH_2CH_2OH. The rate constants for the water reaction are shown for only two compounds.

fluoroethanol, 220 for methanol/trifluoroethanol, and 70 for methanol/water (Table I).

Absolute rate constants for reactions of 1-phenylethyl carbocations may be estimated by comparison with the reactivities of azide and thiol anions, assuming that these nucleophiles react with a diffusion-controlled rate constant of 5×10^9 M^{-1} s^{-1}.[3] The rate constants reported in this paper for reactions of carbocations were calculated from product ratios and the rate constants for reactions of solvent components in Table VII of the previous paper.[3] The absolute values are uncertain by the uncertainty of the diffusion-controlled rate constant, which is probably by a factor of 2; rate constant ratios and structure–reactivity correlations are not subject to this uncertainty.

A Brønsted-type correlation of the rate constants for reaction of a series of substituted aliphatic alcohols with the 1-(4-(dimethylamino)phenyl)ethyl cation shows a large sensitivity of the nucleophilic reactivity to the pK_a of the alcohol, with a slope of $\beta_{nuc} = 0.5$, as shown in the lower line of Figure 2. This slope is consistent with the data for most monosubstituted ethanols and dichloroethanol; methanol and propargyl alcohol show positive deviations, trifluoroethanol shows a small negative deviation, and water shows a large negative deviation. The value of $\beta_{nuc} = 0.5$

Table VI. Brønsted β_{nuc} Values for the Reactions of Substituted 1-Phenylethyl Derivatives with Alcohols, XCH_2CH_2OH and Cl_2CHCH_2OH[a]

ring substituent	leaving groups	β_{nuc}
$4\text{-}N(CH_3)_2$ [b]	H_2O	0.50
$4\text{-}OCH_3$ [b]	H_2O, PhOH $4\text{-}NO_2PhCO_2^-$	0.32
$4\text{-}OCH_3$, 3-Br[c]	H_2O $F_5PhCO_2^-$	0.22
$4\text{-}OCH_3$, $3\text{-}NO_2$ [c]	Cl^-	0.15
$4\text{-}SCH_3$ [b]	$3,5\text{-di-}NO_2PhCO_2^-$	0.30
4-OPh[c]	$3,5\text{-di-}NO_2PhCO_2^-$	0.22
$4\text{-}CH_3$ [c]	H_2O Cl^-	0.16
4-F[d]	H_2O Cl^-	0.13
$3\text{-}OCH_3$ [c]	H_2O Cl^-	0.07
3-Br[c]	Cl^-	0.05

[a] In 50:45:5 (v:v:v) H_2O:TFE:ROH at room temperature (22 ± 2 °C) and ionic strength of 0.5 maintained with $NaClO_4$. [b] For reactions of CH_3CH_2OH, $CH_3OCH_2CH_2OH$, $ClCH_2CH_2OH$, and Cl_2CHCH_2OH. [c] For reactions of CH_3CH_2OH, $CH_3OCH_2CH_2OH$, and $ClCH_2CH_2OH$. [d] For reactions of CH_3CH_2OH, $ClCH_2CH_2OH$, and Cl_2CHCH_2OH.

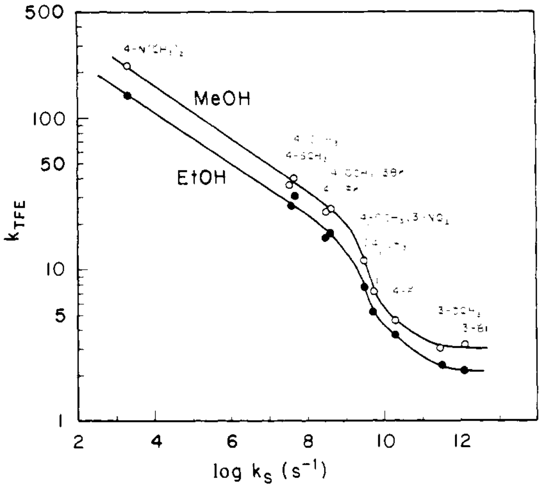

Figure 3. A logarithmic plot of the observed MeOH/TFE (○) and EtOH/TFE (●) selectivities in the solvolysis of substituted 1-phenylethyl derivatives against the absolute rate constant, k_s, for the reaction of the 1-phenylethyl carbocation with solvent, 50:50 TFE:H_2O.

implies a central transition state with a considerable amount of carbon–oxygen bond formation. The secondary α-deuterium isotope effect of 0.91 for the addition of water to the diferrocenylmethyl cation also indicates a transition state with a considerable amount of bond formation.[7]

1-Phenylethyl carbocations with less electron-donating substituents show a progressive decrease in selectivity as the carbocation becomes less stable. The values of β_{nuc} decrease to 0.32 for the 4-methoxy-substituted, 0.22 for 4-phenoxy-substituted, and 0.16 for 4-methyl-substituted 1-phenylethyl carbocations (Figure 2). A plot of log k_{ROH} for reaction of the 1-(4-(dimethylamino)phenyl)ethyl cation against log k_{ROH} for reaction of the 1-(4-methoxyphenyl)ethyl cation gives a good linear correlation with a slope of 1.42 (not shown). This shows that the decrease in selectivity with increasing reactivity is observed even for those alcohols which deviate from the Brønsted correlation. For a larger series of carbocations, which were examined with a smaller number of alcohols, the values of β_{nuc} continue to decrease as the substituents become still less electron donating (Table VI). In each case the values of β_{nuc} are based on reactivities toward monosubstituted ethanols and dichloroethanol.

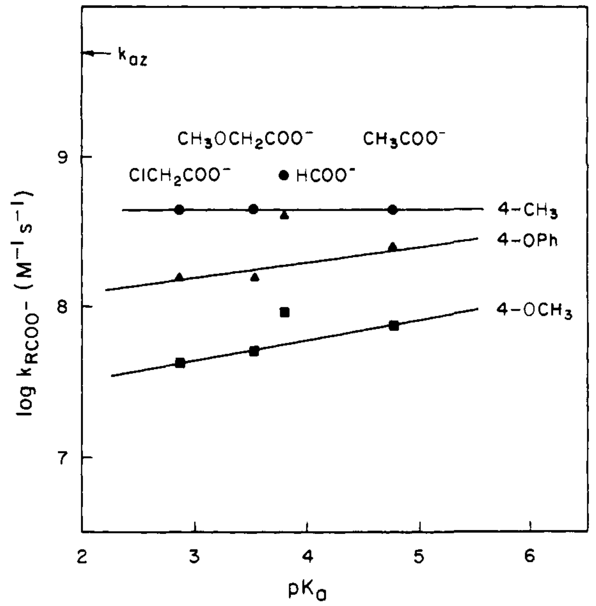

Figure 4. Estimated rate constants for the nucleophilic reactions of carboxylate anions with substituted 1-phenylethyl carbocations plotted against the pK_a of the carboxylic acid: (●) 1-(4-methylphenyl)ethyl carbocation; (▲) 1-(4-phenoxyphenyl)ethyl carbocation; (■) 1-(4-methoxyphenyl)ethyl carbocation.

The relationship between the selectivities toward alcohols, k_{MeOH}/k_{TFE} and k_{EtOH}/k_{TFE}, and the rate constants for reaction of the carbocation with solvent, k_s, is shown in the logarithmic correlation of Figure 3. For the cations with rate constants for reaction with solvent of $<10^9$ s^{-1} the reactions are certainly activation limited and there is a fairly linear decrease in log (k_{EtOH}/k_{TFE}) with increasing log k_s. In the same region there is a decrease in β_{nuc} from 0.50 to 0.22.

The ease with which the position of a transition state shifts along a reaction coordinate is expected to depend on the curvature of the energy surface in the region of the transition state. If the reaction barrier is large the curvature is expected to be sharp and there will be little tendency for the selectivity and amount of bond formation in the transition state to change with changing reactivity of the nucleophile or electrophile. However, when the barrier decreases the curvature of the surface is likely to become smaller, so that the position of the transition state, and structure–reactivity parameters that provide a measure of this position, are likely to change significantly with changing stability of the reactants.[8] This is consistent with the observed behavior for 1-phenylethyl carbocations, which exhibit a shift of the position of the transition state along (parallel to) the reaction coordinate toward the position of higher energy as the cation becomes less stable, i.e., a classical "Hammond effect".

These changes in transition state structure may be described by a structure-reactivity interaction coefficient,[9] in which ρ_{nor} =

$$p_{yy'} = 0.1 = \partial\beta_{nuc}/-\partial(\sigma^n + r^+[\sigma^+ - \sigma^n]) = \partial\rho_{nor}/-\partial pK_{nuc}$$

ρ/ρ_{equib}. A positive value of this coefficient corresponds to a small component of proton transfer in the transition state and a reaction coordinate that is close to vertical on an energy contour diagram in which the axis for proton transfer is horizontal.[5]

There is also a decrease in the value of β_{nuc} for substituted acetate anions from 0.13 to 0.11 to 0 in the reactions with 4-methoxy-, 4-phenoxy-, and 4-methyl-substituted 1-phenylethyl carbocations (Figure 4). However, these data do not permit a firm conclusion regarding changes in structure of the transition

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state for nucleophilic attack because the first decrease is small and the reaction with the 4-methyl compound may not be activation limited.

A decrease in the selectivity ratio k_{EtOH}/k_{H_2O} from 13 to 5 to 3.5 has been reported previously for 4,4′-dimethylbenzhydryl chloride as the two methyl substituents are removed.[10] A decrease in selectivity compared with that expected from the N^+ scale has also been reported for reactions with the carbocation formed from 6-(chloromethyl)benzo[a]pyrene,[11] but it is not certain how much of this change results from a change in the structure of the transition state for nucleophilic attack and how much from an approach to limiting rate constants.

Explanations are available for some of the deviations of the rate constants for particular alcohols from the Brønsted-type plots of Figure 2. The deviations for trifluoroethanol and cyanoethanol may be attributed to anomalies in the pK_a values, rather than in the rate constants, for these alcohols. This arises from the use of equilibrium constants for dissociation of alcohols to their anions for the correlation of rate constants of reactions in which the transition state has cationic character. A Brønsted plot of the rate constants for the reactions of the 1-(4-methoxyphenyl)ethyl carbocation with ethanol, methoxyethanol, cyanoethanol, and trifluoroethanol against the pK_a values of the corresponding ammonium cations gives a good fit (not shown, correlation coefficient = 0.994), no deviation for trifluoroethanol and cyanoethanol, and the same slope as Figure 2. The larger difference of 4.9 units between the pK_a of ethylammonium and trifluoroethylammonium ions compared with 3.6 units between the pK_a values of ethanol and trifluoroethanol[12] indicates that the trifluoroethyl group destabilizes a positive charge more than it stabilizes a negative charge in these systems.

The positive deviations of the rate constants for methanol and propargyl alcohol show little dependence on β_{nuc} and probably represent a steric effect resulting from relief of slightly unfavorable nonbonding interactions that arise when an sp^3 carbon atom is attached to methanol. The equilibrium constant of 1.9 for interchange of MeOH and EtOH in 1-(4-methoxyphenyl)ethyl esters[13] is larger than the ratio of $k_{MeOH}/k_{EtOH} = 1.4$ for addition to the corresponding carbocation. Similar differences in rate and equilibrium constants are found for the addition of methanol and ethanol or their anions to esters and thiol esters of acetate,[14] carbon dioxide,[15] a phthalimidium cation,[16] and pyridine carboxaldehyde;[17] the anion of propargyl alcohol also shows enhanced reactivity toward acetate esters.[14]

The behavior of water in these reactions is even more anomalous than in most other reactions. It shows a decreased reactivity compared with most alcohols that is larger for more stable carbocations and more basic alcohols; it is 70 times less reactive than methanol toward the most stable carbocation, but only about 3-fold less reactive toward unstable carbocations. However, it shows only a small change in reactivity relative to trifluoroethanol and dichloroethanol as the stability of the cation decreases (Table I). Its behavior can be summarized by the statement that it behaves like an alcohol with a pK_a of approximately 13.

The reason for this behavior is not known, but it may arise from the larger polarizability and intrinsic electron-donating power of alcohols compared with water. The basicity of alcohols in the gas phase is much larger than that of water, because of their greater polarizability, but water is more basic than alcohols in aqueous solution and in clusters of alcohols and water in the gas phase, because of the more favorable solvation energy of H_3O^+ compared with ROH_2^+.[18] The requirement for fixation and loss of entropy of several solvent molecules for this solvation is more than balanced by the large energetic advantage from the solvation of H_3O^+. However, in a transition state there is less charge development on the attacking molecule and the advantage from such solvation is smaller. This advantage may not be enough to bring about the fixation and loss of entropy of solvent molecules that is required for optimal solvation, or may provide little net advantage after the price for this ordering has been paid. Since the entropy loss from fixation of a water molecule to solvate a developing positive charge is almost constant and the advantage from solvation is variable, there is likely to be an *imbalance* between charge development and its stabilization by solvation such that the advantage from the strong solvation of H_3O^+ is not manifested proportionally in the transition state for nucleophilic attack by water. Furthermore, polarizability may be relatively more important in stabilizing transition states than products. The consequence is that water will behave like a less basic alcohol and be relatively unreactive compared with methanol and ethanol. It has been suggested that solvation also results in an imbalance in the reactions of basic alkoxide ions with esters and carbon acids, which is responsible for the small values of β and β_{nuc} for these reactions, because of a requirement for partial desolvation of the anion before nucleophilic attack.[19]

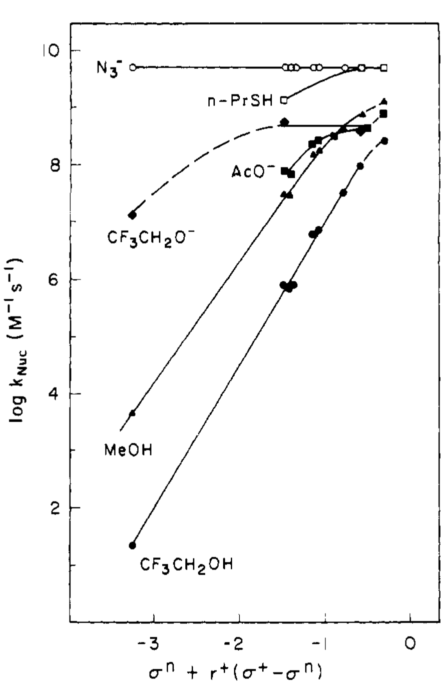

Figure 5. Estimated rate constants for reactions of nucleophiles with substituted 1-phenylethyl carbocations, plotted against the effective Hammett constant of the ring substituent with $r^+ = 2.1$: (●) trifluoroethanol; (▲) methanol; (■) acetate anion; (♦) trifluoroethoxide anion; (□) propanethiol; (○) azide.

The nucleophilic reactivity sequence for amines of Me_3N:Me_2NH:$MeNH_2$:NH_3 = 1550:700:120:1 for displacement on chloramine[20] and the larger effectiveness of tertiary compared with primary amines in some general base catalyzed reactions[21] may represent a similar influence of polarizability and imbalance between development of solvation in transition states and in the reference protonation reaction.

Approach to Limiting Rate Constants for Reactions with Solvent. As the lifetime of the 1-phenylethyl carbocation becomes shorter,

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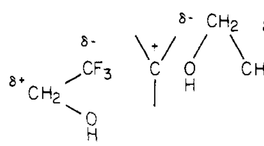
with $k_s > 10^9$ s^{-1}, there is a steeper drop in the solvent selectivity; this is followed by a leveling off to values of k_{ROH}/k_{TFE} of about 3 for methanol and 2 for ethanol when the extrapolated values of k_s are $>10^{11}$ s^{-1} (Figure 3). The steeper drop in selectivity could represent a larger change in transition state structure as the activation barrier and its curvature become still smaller or an approach to a limiting rate constant for reaction with the more nucleophilic solvent component that causes a sharper decrease in the selectivity ratio. The change in selectivity does not result from interaction with an anionic leaving group in an ion pair because it is observed with water, as well as with chloride ion, as the leaving group (Table I). It also does not represent some special resonance or polar effect because the sharp decrease is observed with increases in both σ^n and σ^r for substituents on the phenyl group.

The interpretation is clarified by comparison of the absolute rate constants for the reactions with methanol and trifluoroethanol, as shown in the modified Hammett correlation of Figure 5. The values of log k for both alcohols increase linearly with the less electron-donating substituents, although with different slopes, and the change in their ratio as the rate constants approach 10^8–10^9 s^{-1} results from an earlier and larger leveling off of the rate constants for the more nucleophilic methanol. In fact, there may be no curvature for k_{TFE} in this series of compounds because the rate constants are calculated assuming a constant, diffusion-controlled rate constant for the reaction of azide ion or thiol with the free carbocation in the reference reaction and a significant fraction of the reactions of the unstable 4-methyl- and 4-fluoro-substituted cations occurs without diffusion in an encounter complex or an ion pair, as described below. The leveling off begins at absolute values of the rate constants about an order of magnitude smaller than those for the reaction with propanethiol. We conclude that the decrease in selectivity for these unstable carbocations results from an approach to limiting rate constants that is specific for hydroxylic solvent components. This does not exclude a change in the structure of the transition state for nucleophilic attack, which also must contribute to the decrease in selectivity.

The absolute value of the limiting rate constant for reaction with solvent components cannot be determined from the data shown in Figure 5. However, it is clear that the rate begins to level off before the limiting value is reached; there is not a linear increase followed by a sharp break at the diffusion-controlled limit. The simplest explanation for this is that there is a heterogeneous collection of solvent species with different reactivities and concentrations, so that the limiting rates are reached at different cation stabilities for species with different reactivities. The reacting species are probably clusters of solvent molecules with different solvation structures around the successful nucleophile. There is evidence for an enhanced reactivity of such clusters in the reactions of alcohols with carbocations in dichloroethane.[22]

The leveling off of the selectivity ratios at $k_{MeOH}/k_{TFE} = 3$ and $k_{EtOH}/k_{TFE} = 2$ for cations with $k_s > 10^{11}$ s^{-1} (Figure 3) could represent modest nucleophilic assistance to ionization,[23] but other evidence does not provide support for significant nucleophilic participation by solvent in the formation of 1-phenylethyl carbocations that have a significant lifetime.[24] In particular, there is no assistance to the ionization of 1-(4-methylphenyl)ethyl chloride even by azide ion[25] and assistance by cyanide ion becomes significant only with the 4-cyano compound; if there is no assistance by powerful nucleophiles there is not likely to be assistance by solvent.[26] When nucleophilic assistance by the solvent does become significant, with an increase in the selectivity ratios, extrapolated rate constants predict that the carbocation intermediate no longer has a significant lifetime.[24]

We suggest that these limiting selectivities represent reaction within a pool of solvent molecules that are present at the time that the carbocation is formed,[27] with a contribution of charge–dipole interactions to the observed selectivity. The selectivity in the solvolysis of glucosyl derivatives in ethanol–trifluoroethanol mixtures, which occurs without diffusion, is too large to be accounted for by reaction within a randomly oriented pool of solvent molecules but could be accounted for by electrostatic interactions that stabilize the transition state for reaction with ethanol.[28] Charge–dipole interactions would be expected to favor the OH group of ethanol over that of trifluoroethanol in the vicinity of a developing cation (**1**). In fact, the trifluoroethanol molecule is likely to be oriented with its hydroxyl group away from the developing positive charge of the carbocation in the transition state, so that trapping does not occur unless there is time for rotation. The dielectric constants of ethanol and trifluoroethanol are almost identical,[29] and the dipole moment of trifluoroethanol, 2.03, is larger than that of ethanol, 1.65.[30] However, the CF_3 group is more electron withdrawing than the OH group so that the direction of the dipole of trifluoroethanol must be different from that of ethanol and should favor orientation of the molecule with the CF_3 group adjacent to the cation. The σ_I values for OH and CF_3 are 0.25 and 0.45, respectively, and the dipole moment of 2.28 for CF_3CH_3 is larger than the value of 1.7 for CH_3OH and CH_3CH_2OH.[31] Such an electrostatic interaction may be responsible for some of the phenomena that have been ascribed to nucleophilic assistance to ionization. It also provides a possible explanation for the slightly lower yields of thiol adduct from mercaptoethanol than from propanethiol with reactive carbocations (Table III).



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The changes in selectivity described in this section may be described in terms of changes from reactions of free ions, with a lifetime that permits diffusion and selection between solvent components, to a stepwise preassociation mechanism in which the reacting alcohol is present at the time the cation is formed, to an uncoupled concerted mechanism when the barrier for reaction disappears, but there is no nucleophilic assistance to the reaction; evidence for a coupled concerted mechanism with solvent appears only with 1-(4-cyanophenyl)ethyl chloride, when the k_{MeOH}/k_{TFE} ratio increases as solvent molecules provide increasing nucleophilic stabilization to the transition state.[24,32]

Reactions of Carboxylate and Trifluoroethoxide Anions. Nucleophilic reactions of oxygen anions reach limiting rate constants below the diffusion-controlled limit with increasing reactivity of the anion and of the carbocation. Substituted acetate anions exhibit selectivity in their activation-limited reactions with the 1-(4-methoxyphenyl)ethyl and 1-(4-phenoxyphenyl)ethyl carbocations with values of $\beta_{nuc} = 0.13$ and 0.11, respectively (Figure 4). However, for the 1-(4-methylphenyl)ethyl carbocation there is no discrimination, except for a slightly faster reaction with the smaller formate anion, and the value of β_{nuc} is zero. The absolute rate constants for the reactions of acetate ion with different carbocations (Figure 5) increase with decreasing stability of the cation and then show a similar leveling off at a limiting rate

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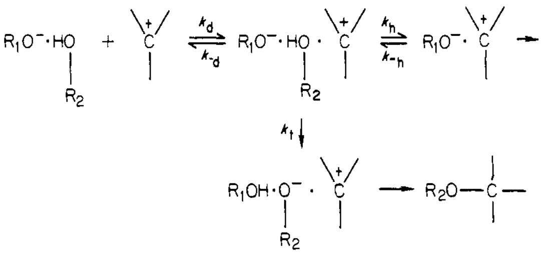
constant of approximately 5×10^8 M^{-1} s^{-1}. The value of $k = 8.7 \times 10^8$ M^{-1} s^{-1} for the 4-fluoro compound is larger, for reasons that are not clear, but this rate constant almost certainly represents reaction from a solvent pool without diffusion. The rate constant of 5×10^8 M^{-1} s^{-1} is well below the diffusion-controlled limit and is smaller than the limiting rate constants for azide anion and for the uncharged propanethiol and methanol molecules. Similar differences have been observed for nitrilium ions in water, which react with azide ion 6–7 times faster than with carboxylate anions,[33] and with 1-(4-methoxyphenyl)ethyl carbocation in 90% aqueous acetone, which can be trapped by azide ion and shows carboxylate ^{18}O scrambling but reacts considerably more slowly with added carboxylate ions.[34]

The more basic trifluoroethoxide ion shows a higher nucleophilic reactivity than acetate toward stable carbocations but reaches the same limiting rate constant as for acetate with carbocations that still show selectivity toward substituted acetates (Figure 5).

These limiting rate constants are too small to be accounted for by a less favorable steric factor for carboxylate compared with azide ions; a steric factor might decrease the rate by a factor of 2. We suggest that they are the result of strong solvation of these basic oxygen anions that provides a kinetic as well as a thermodynamic barrier to their reaction. The limiting rate constant of 4.5×10^8 M^{-1} s^{-1} for the reactions of acetate anion, which is one-tenth of that for azide anion, indicates that about 90% of the solvated acetate anions that encounter a carbocation diffuse away again without reacting. This suggests that the rate constant k_h for extrusion of a solvent molecule from the solvent-separated ion pair (eq 2) is on the order of 0.1–0.2 of that for diffusional separation, k_{-d}. Rate constants for the removal of a solvent molecule from alkoxide or carboxylate ions have not been determined, to our knowledge. However, the rate constants for breaking a hydrogen bond between aliphatic amines and a hydroxylic solvent molecule are in the range of $1-6 \times 10^{10}$ s^{-1} in water, with smaller values in other solvents, and the observation that proton transfer between oxygen anions and their conjugate acids in hydroxylic solvents occurs through 1–2 solvent molecules is consistent with a significant barrier to their desolvation.[35]



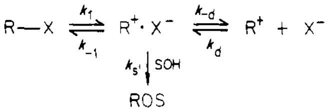
(2)

The anion of a solvent molecule can be generated next to the carbocation without diffusion of molecules simply by the transfer of a proton, through a sort of facilitated diffusion (k_t, eq 2). However, this mechanism appears to be of little, if any, significance because the limiting rate constant for reaction with trifluoroethoxide anion is the same as that for dilute acetate anion, for which this mechanism is not possible. Similarly, acetate might catalyze the reaction by removing a proton from an uncharged trifluoroethanol molecule adjacent to the carbocation (k_t, eq 2, $R_1O^- = AcO^-$), but the absence of general base catalysis of the trifluoroethanol reaction with the 1-(4-methylphenyl)ethyl cation shows that this mechanism is not significant. In both cases, proton transfer is slower than alternative mechanisms for formation of the intimate ion pair.

The faster limiting rate constants for the reactions with azide ion indicate that there is little or no kinetic barrier for desolvation of this ion. Similarly, Ritchie and co-workers have shown that the reactions of azide and benzenethiolate anions with aryldiazonium ions in methanol increase up to a diffusional limit of $\sim 10^{10}$ M^{-1} s^{-1} and then level off sharply, so that there is no kinetic barrier for their desolvation.[6] This kind of desolvation process evidently does not account for the constant selectivities of reactions that follow the N^+ scale of nucleophilic reactivity.

Heterogeneity of reacting species with different solvation provides an explanation for the different limiting rate constants that are sometimes observed in reactions that are essentially diffusion controlled. A requirement for desolvation of the nucleophile or for solvation of the transition state, as described in the previous section, can give relatively small limiting rate constants and can cause a gradual, rather than a sharp, transition to limiting rate constants.

Reactions of Ion Pairs. Ion pairs must become significant in solvolysis reactions when the carbocation becomes sufficiently unstable that it reacts with solvent (k_s', eq 3) faster than the leaving group diffuses away (k_{-d}; eq 3 does not distinguish between intimate and solvent-separated ion pairs). This is more probable in poor solvents for ions because the rate constant for diffusional encounter with the leaving group (k_d, eq 3) has little dependence on the solvent, so that an unfavorable equilibrium constant for ion-pair dissociation will give a small value of k_{-d}. We have chosen a good ionizing solvent for this work in order to minimize the importance of ion pairs because we are more interested in the chemistry and reactivity of the free reactants than in the special properties of the reactions of ion pairs. Thus, the solvolysis of 1-(4-methoxyphenyl)ethyl 4-nitrobenzoate in 70% aqueous acetone proceeds with scrambling of labeled carboxyl oxygen atoms of the leaving group in recovered starting material and with partial retention of configuration because of reactions of the ion pair,[34] but 1-(4-methoxyphenyl)ethyl derivatives in 50:50 TFE:H_2O react through the free carbocation with a lifetime of $\sim 10^{-8}$ s and no effect of the leaving group on the product distribution.[3]



$$\begin{tikzcd} R{-}X \arrow[r, shift left, "k_1"] & R^+\cdot X^- \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "k_{-d}"] \arrow[d, "k_{s'}"', "SOH"] & R^+ + X^- \arrow[l, shift left, "k_d"] \\ & ROS & \end{tikzcd}$$

(3)

Reaction through an ion pair becomes significant in 50:50 TFE:H_2O for the 1-(4-methylphenyl)ethyl carbocation, which shows a significant effect of the leaving group on the product distribution (Table IV). The increased yield of trifluoroethyl ether with the pentafluorobenzoate and dimethyl sulfide leaving groups could be the result of a favorable "hydrophobic" interaction of trifluoroethanol with the leaving group that increases its concentration near the carbocation. The increase might also arise from catalysis of trifluoroethanol attack by the pentafluorobenzoate leaving group, but the absence of such catalysis by added bases for this carbocation does not support this possibility. The 6-fold increase in styrene formation with the pentafluorobenzoate leaving group (Table IV) must also occur through an ion pair, presumably as the result of general base catalysis of proton removal by the leaving group before it diffuses away.

If the reactions of the 4-methylphenyl compound proceed through an ion pair, the reactions of all less stable carbocations must also proceed through ion pair intermediates, until the point is reached that the cation does not have a sufficient lifetime to exist as a reaction intermediate. This is consistent with the observed larger rate constants for racemization, or k_α, compared with the rate constants for solvolysis of 1-phenylethyl chloride and for the acid-catalyzed exchange of 1-phenylethyl alcohol with ^{18}O-labeled water.[27,36] The estimated value of k_s for the 1-phenylethyl carbocation in 50:50 TFE:H_2O is $\sim 10^{11}$ s^{-1}, which is comparable to the expected rate constant for diffusional separation of an ion pair or encounter pair[3] but is small enough to show that the intermediate exists.

The properties of the reactions of acetate and azide anions with 1-phenylethyl carbocations provide information regarding the expected behavior of ion pairs. The small limiting rate constant

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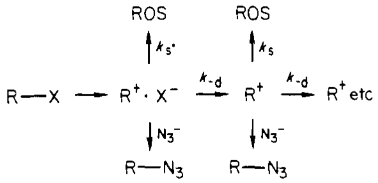
for the reaction of acetate with carbocations indicates that the solvent-separated ion pair of the carbocation and hydrated acetate undergoes diffusional separation 5–10 times faster than it extrudes solvent to form an intimate ion pair, which then collapses rapidly to give the ester (eq 2). In the reverse direction, for solvolysis, this corresponds to reversible formation of an intimate ion pair (internal return) followed by slow insertion of solvent and rapid separation; the solvent-separated ion pair gives only 10–20% return. This is consistent with the observed carboxylate ^{18}O scrambling through return from both internal and solvent-separated ion pairs during the solvolysis of 1-(4-methoxyphenyl)ethyl 4-nitrobenzoate in 70% aqueous acetone.[34] The relatively slow reaction of acetate with the 1-(4-methoxyphenyl)ethyl carbocation in 50:50 TFE:H_2O (Figure 5) suggests that the intimate ion pair of this cation is an intermediate, not a transition state.

The high yield of azide product by diffusion-controlled trapping indicates that most encounters of azide ion with the 1-(4-methylphenyl)ethyl carbocation are productive, so that $k_{-1} > k_{-d}$ (eq 3) and desolvation of the azide ion is not kinetically significant. In the reverse direction, the solvolysis of a compound with a leaving group that resembles azide will then proceed through rate-limiting diffusional separation of an ion pair when reaction of the ion pair with solvent is slower than diffusion. Whether the ion pair is a discrete intermediate or a transition state will depend on whether or not there is a significant barrier for its collapse to starting material.

The mechanism by which the azide adduct is formed from ion pairs of the 1-(4-methylphenyl)ethyl carbocation is a particularly interesting problem. This represents the "borderline" reaction for azide in this series; carbocations that are more stable than the 1-(4-methylphenyl)ethyl cation react with diffusion-controlled trapping, while compounds that would give less stable cations react with azide through a second-order, S_N2 reaction.[3,24] There is a large yield of azide product from the 1-(4-methylphenyl)ethyl cation of up to 40% under conditions in which azide causes no increase in the observed reaction rate. The yield of azide adduct corresponds[3] to a value of $k_{az}/k_s = 1.2\ M^{-1}$. This means that one azide ion reacts as fast as 40 solvent molecules, although the dependence of the product ratio on the leaving group shows that the cation reacts with solvent to a considerable extent before it diffuses out of the cage of solvent and leaving group molecules in which it was formed.

The similar product ratios for reactions with different alcohols when chloride ion or water is the leaving group (Table I) indicate that the chloride ion does not influence the reactivity of alcohols in this solvent and that internal return by chloride ion, if it occurs, does not affect the product yield. The absence of an increased rate of substrate disappearance in the presence of azide ion shows that azide does not react with a significant number of ion pairs that would otherwise undergo internal return. The uncharged propanethiol molecule has a high reactivity which is identical with that of azide ion (Table III).[37] This suggests that the reaction with propanethiol is also diffusion controlled and that the negative charge of the azide ion does not inhibit reaction with an ion pair. An intramolecular carbocation–sulfonate ion pair has been shown directly to react normally with neutral and anionic nucleophiles.[38]

If the 1-(4-methylphenyl)ethyl carbocation reacted entirely through the ion pair, without diffusion, the yields of azide and thiol adducts would be determined by the concentration of the nucleophile that is close enough to react immediately, without diffusion. The same yield of azide or thiol adduct would then be expected for trapping of the more reactive 1-(4-fluorophenyl)ethyl carbocation. The yield of azide adduct by trapping of the 1-(4-fluorophenyl)ethyl cation cannot be measured because of the S_N2 reaction with azide. However, the trapping by propanethiol, which has the same reactivity as azide ion for the 1-(4-methylphenyl)ethyl cation, is one-third as large for the 4-fluoro as for the 4-methyl compound (Table III).[3] The 1-(4-fluorophenyl)ethyl cation reacts with 1 M thiol one-third as fast as with 35 M solvent; the value of k_{RSH}/k_s is 0.32 M^{-1}. The 3-fold larger amount of trapping of the 4-methyl compound shows that at least two-thirds of the 1-(4-methylphenyl)ethyl cations can diffuse away and react with molecules outside the immediate solvent cage, so that the ratio of the rate constants for diffusion and for reaction with solvent, k_{-d}/k_s' (eq 4), is ≥ 2 for this cation.



(4)

An estimate of the ratio k_{-d}/k_s' can be obtained from the mechanism of eq 4. Since the reaction with azide ion is diffusion controlled, the cation will react very rapidly with all azide ions that are present within a certain distance before diffusion and will then partition between reaction with solvent and diffusion according to the ratio k_s'/k_{-d}. If we assume that each diffusion step places the cation in a new pool of azide and solvent molecules, the same process will be repeated until all of the cation has reacted. Defining the concentration of azide ions within reaction distance of the cation, $R^+\cdot N_3^-$, in terms of an equilibrium constant, K_{as}, the expressions for the yields of azide and solvent adducts give eq 5 for the product ratio according to this model, assuming that

$$[R\text{-}N_3]/[R\text{-}OS] = K_{as}[N_3^-](k_s + k_{-d})/k_s \qquad (5)$$

$k_s' = k_s$. At low concentrations of azide ion the fractions of reaction with azide and with solvent are given by $K_{as}[N_3^-]$ and $k_s/(k_s + k_{-d})$, respectively, in each diffusional event and it can be shown that the product ratio is given by the ratio of these two quantities at both low and high azide concentrations (eq 5). If we assume that all of the reaction of the 1-(4-fluorophenyl)ethyl carbocation with thiol occurs with the ion pair and that azide ion behaves in the same way as thiol, as suggested by the identical reactivity of the two compounds toward the 1-(4-methylphenyl)ethyl carbocation, the value of K_{as} is 0.32 M^{-1}. This may be compared with a value of $K_{as} = 0.2\ M^{-1}$ for formation of contact charge transfer complexes, which was calculated for a molecular radius of $r = 5$ Å and an average distance of $\Delta r = 0.94$ Å between neighboring molecules.[39] The observed product ratio of $[R\text{-}N_3]/[R\text{-}OS] = 1.2$ at 1 M azide for 1-(4-methylphenyl)ethyl chloride then gives a value of $k_{-d} = 2.8\ k_s$ from eq 5, which corresponds to 27% reaction of the carbocation with solvent before separation of the ion pair. Smaller fractions than this would be difficult to reconcile with the different product ratios observed with different leaving groups (Table IV).

The values of $K_{as} = k_d/k_{-d} = 0.32\ M^{-1}$ and $k_d = 5 \times 10^9\ M^{-1}\ s^{-1}$ give $k_{-d} = 1.6 \times 10^{10}\ s^{-1}$. The ratio $k_{-d}/k_s = 2.8$ then gives $k_s = 6 \times 10^9\ s^{-1}$. This value is larger than the value of $k_s = 4 \times 10^9\ s^{-1}$ that was obtained assuming that all of the reaction with azide occurs by diffusion-controlled trapping of the free ion; the difference arises from the reaction with the ion pair. The value of k_s for the 1-(4-fluorophenyl)ethyl cation is best obtained by extrapolation,[3] $k_s = 2 \times 10^{10}\ s^{-1}$.

There are obvious uncertainties in these calculations, including the choice of the model of eq 4 and the rate constant of $5 \times 10^9\ M^{-1}\ s^{-1}$ for diffusion-controlled trapping by azide ion. Nevertheless, they provide a picture of the kinds of processes that are expected to occur in an ion pair and give approximate rate constants for these processes.

Styrene Formation. The solvolysis of 1-(4-methylphenyl)ethyl derivatives gives an increased yield of styrene when the leaving group is basic or when solvolysis occurs in the presence of added buffer bases. Analogous results have been reported previously in other systems.[40] The yield of 0.4% styrene from the solvolysis

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[37] In one experiment with mercaptoethanol a similar yield of thiol adduct was obtained with chloride ion and with water as the leaving group. This shows that there is no large effect on trapping by thiol as a result of internal return by chloride ion.

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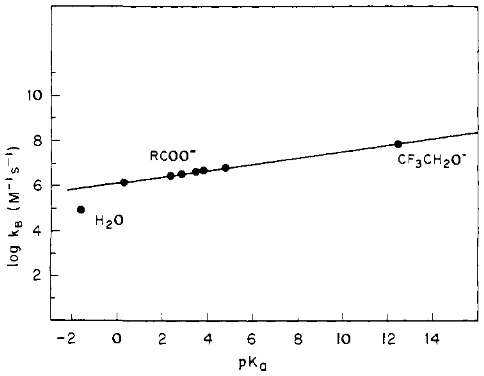


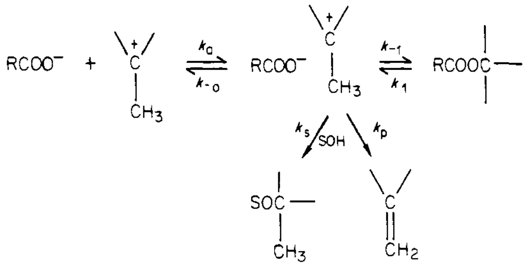
Figure 6. Brønsted plot of the estimated rate constants for 4-methylstyrene formation by deprotonation of the 1-(4-methylphenyl) carbocation by carboxylate anions and solvent in 50:50 TFE:H_2O.

of the pentafluorobenzoate ester is 6–7 times larger than with chloride ion or water as the leaving group (Table IV). The increase in the yield in the presence of added bases is larger with stronger bases, as shown in Figure 1 and Table V. The increased effectiveness with increasing basicity of the catalyst follows a Brønsted plot with a slope of $\beta = 0.14$ and a negative deviation by an order of magnitude for water, as shown in Figure 6.

The increased yield of styrene with a carboxylate leaving group and the small value of $\beta = 0.14$ for added buffer bases suggest that styrene formation occurs by base-catalyzed proton abstraction from the reactive phenylethyl carbocation. A larger value of β would be expected for proton abstraction from the weakly acidic methyl group of 1-(4-methylphenyl)ethyl chloride; the value of β for elimination from 2-(4-nitrophenyl)ethyl chloride is 0.67.[41] The low yield of styrene and the different rate constants for different added bases show that the proton abstraction is activation limited. This is confirmed by the absolute values of k_B for proton removal, estimated from the observed product ratios and values for k_s,[3] which give values of k_B that are well below the diffusion-controlled limit (Table V). The presence of a significant barrier makes it unlikely that proton abstraction by the leaving group is concerted with cleavage of the C–O bond.

Catalysis of styrene formation both by added bases and by the leaving group means that the same process can be brought about through an ion pair that is formed from two directions. It provides additional information about the properties of the ion pair because the ratio of styrene formation to other reactions is known for both directions.

Absolute values of the rate constants for the different reactions of the ion pair may be estimated from the product yields and the value of $k_s = 6 \times 10^9$ s^{-1}, according to the model of eq 6. The



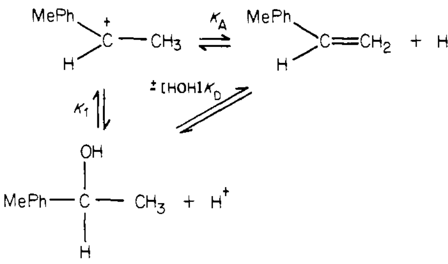
(6)

rate constant k_a in eq 6 includes the partial desolvation of the carboxylate ion described by k_h in eq 2. The observed catalysis of styrene formation in the ion pair by the leaving pentafluorobenzoate ion gives a value of $k_p/(k_s + k_{-a}) = 0.0039 - 0.0007 = 0.0032$ (Table IV). The values of $k_s = 6 \times 10^9$ s^{-1} and $k_{-a} = 1.6 \times 10^{10}$ s^{-1} (above, k_{-a} is equivalent to k_{-d} in eq 4) give k_p = 7×10^7 s^{-1}. The ratio of styrene to ester products that are formed from added carboxylate ions is equal to the ratio of proton removal to collapse of the ion pair, which gives a value of $k_B/k_{RCOO^-} = k_p/k_{-1} = 0.0044$. The value of $k_B = 2 \times 10^6$ M^{-1} s^{-1} was interpolated from the data in Table IV for a carboxylate ion of pK_a = 1.75, the pK_a of pentafluorobenzoic acid.[42] This gives a value of $k_{-1} = 1.6 \times 10^{10}$ s^{-1}.

An association constant of $K_{as} = k_a/k_{-a} = 0.04$ M^{-1} for the formation of a reactive ion pair may be obtained from k_{-a} and the yield of ester products from carboxylate anions (Table II).[43] Values of $K_{as} = 0.06$ M^{-1} and 0.08 M^{-1} for the reactions of acetate with the 4-fluoro- and 3-methoxy-substituted carbocations, respectively, are obtained from the product ratios for these cations (Tables I and II), assuming that reaction occurs before diffusion. These values are smaller than the value of $K_{as} = 0.3$ M^{-1} for the encounter complex for reaction with azide ion. Possible reasons for this difference include the requirement for desolvation of carboxylate ions, a more favorable steric factor for azide ion, and a higher reactivity of azide that leads to reaction from a large effective radius.

These calculations are subject to the same uncertainties as those described in the previous section but provide approximate values of the rate constants for the processes that occur in the ion pair. Formation of some of the styrene by proton transfer in a different ion pair, which has a geometry that does not lead to ester formation, would have the effect of decreasing the ratio k_p/k_{-1} for the reactions of eq 6 and, therefore, increasing k_{-1}. This would make collapse of the ion pair to the ester more nearly complete. The ratio of $k_{-1}/k_{-a} = 1.0$ for the model of eq 6 indicates that the ion pair with pentafluorobenzoate ion collapses and dissociates at equal rates. More basic anions will collapse faster, consistent with the conclusion that the reaction with carboxylate ions occurs with a limiting rate constant that is determined by diffusion and desolvation.

The acid dissociation constant of the 1-(4-methylphenyl)ethyl carbocation to form 4-methylstyrene, K_A in eq 7, is equal to the



(7)

ratio of the rate constants for deprotonation and for acid-catalyzed hydration of the styrene, $k_B[H_2O]/k_{-B}$. The values of $k_B[H_2O]$ and k_{-B} (Table V and Results) give values of $K_A = 7.1 \times 10^4 \times 28/1.3 \times 10^{-5} = 1.6 \times 10^{11}$ M and p$K_A = -11.2$. Evidently, the carbocation is a strong carbon acid that dissociates slowly. The small ratio of $k_p/k_s = 7 \times 10^{-4}$ (Table IV) shows that hydration is much faster than deprotonation of the cation, which confirms the conclusion that protonation is rate limiting in the hydration of 4-methylstyrene.[44] The value of $\beta = 0.14$ for proton abstraction from the carbocation to form styrene (Figure 6) corresponds to a value of $\alpha = 0.86$ for styrene protonation to give the carbocation in the reverse direction, which is consistent with the conclusion that the proton is more than half-transferred in the rate-limiting step of styrene hydration.[44]

The equilibrium constant for carbocation formation from the alcohol is given by $K_1 = K_D/K_A$ (eq 7). The value of $K_A = 1.6 \times 10^{11}$ M and a value of $K_D = 2.5\%/97.5\%$ in aqueous acid[44] gives $K_1 = 1.7 \times 10^{-13}$ M^{-1}. This may be compared with the value of $K_1 = K_{eq}/[H_2O] = 6.5 \times 10^{-12}/28$ M $= 2.3 \times 10^{-13}$ M^{-1} that was obtained from the ratio of the rate constants for acid-catalyzed dehydration of 1-(4-methylphenyl)ethyl alcohol to the carbocation

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J. Am. Chem. Soc. 1984, 106, 1383–1396

and for the reverse reaction in 50:50 TFE:H_2O.[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-$(CH_3)_2NC_6H_4C^+HCH_3$, 82414-94-6; 4-$CH_3OC_6H_4C^+HCH_3$, 18207-33-5; 4-$CH_3SC_6H_4C^+HCH_3$, 82414-95-7; 4-$PhOC_6H_4C^+HCH_3$, 82414-96-8; 4-CH_3O-3-$BrC_6H_3C^+HCH_3$, 88510-80-9; 4-CH_3O-3-$O_2NC_6H_3C^+HCH_3$, 88510-81-0; 4-$CH_3C_6H_4C^+HCH_3$, 31042-87-2; 4-$FC_6H_4C^+HCH_3$, 31067-69-3; 3-$CH_3OC_6H_4C^+HCH_3$, 82414-97-9; 3-$BrC_6H_4C^+HCH_3$, 82414-98-0; 4-$O_2NC_6H_4C^+HCH_3$, 82415-00-7; CH_3CH_2OH, 64-17-5; $CH_3(CH_2)_3CH_2OH$, 71-41-0; CH_3OH, 67-56-1; $Cl(CH_2)_3OH$, 627-30-5; $CH_2{=}CHCH_2OH$, 107-18-6; $HO(CH_2)_2OH$, 107-21-1; $CH_3O(CH_2)_2OH$, 109-86-4; $Cl(CH_2)_2OH$, 107-07-3; $NC(CH_2)_2OH$, 109-78-4; $HC{\equiv}CCH_2OH$, 107-19-7; Cl_2CHCH_2OH, 598-38-9; $CH_3CO_2^-$, 71-50-1; HCO_2^-, 71-47-6; $CH_3OCH_2CO_2^-$, 20758-58-1; $ClCH_2CO_2^-$, 14526-03-5; $F_3CCH_2O^-$, 24265-37-0; $CH_3CH_2CH_2SH$, 107-03-9; $HOCH_2CH_2SH$, 60-24-2.

Concerted Bimolecular Substitution Reactions of 1-Phenylethyl Derivatives[1]

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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 $\rho = -5.6$ ($r^+ = 1.15$) 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 Me_2S, $Br^- > Cl^- > OTs^-$ 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 N_3^-, 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 ion[2] 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 conditions[4] 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 suggestion[7] 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

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[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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