Reactions of Ring-Substituted 1-Phenyl-2,2,2-trifluoroethyl Carbocations with Nucleophilic Reagents: A Bridge between Carbocations Which Follow the Reactivity-Selectivity "Principle" and the N_+ Scale

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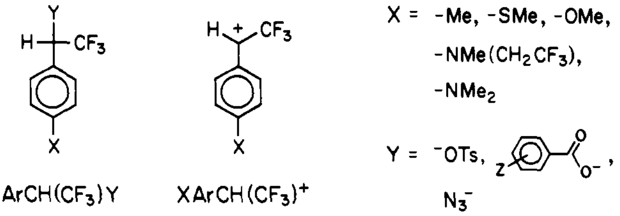
Abstract: The effect of changing carbocation reactivity on nucleophile selectivity has been determined for the reactions of ring-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations, $XArCH(CF_3)^+$, with amines, alcohols, and carboxylate ions. Rate constants, k_s, for the capture of $XArCH(CF_3)^+$ by 50/50 (v/v) trifluoroethanol/water range from 1×10^{10} s^{-1} for 4-$MeArCH(CF_3)^+$ to ≤ 200 s^{-1} for 4-$Me_2NArCH(CF_3)^+$. $\beta_{nuc} = 0.29$ was determined for the reaction of alkylamines with 4-$Me_2NArCH(CF_3)^+$. β_{nuc} for reaction of RCO_2^- decreases from 0.35 for 4-$Me_2NArCH(CF_3)^+$ to 0.05 for 4-$MeOArCH(CF_3)^+$. This decrease is due, at least in part, to a Hammond effect on the location of the reaction transition state along the reaction coordinate. β_{nuc} for reaction of alcohols decreases from 0.48 for 4-$Me_2NArCH(CF_3)^+$ to 0.09 for 4-$MeArCH(CF_3)^+$. The plot of log (k_{EtOH}/k_{TFE}) for capture of $XArCH(CF_3)^+$ by ethanol and trifluoroethanol against log k_s has a shallow negative slope for the more stable $XArCH(CF_3)^+$, which steepens with destabilization of the carbocation. This change in slope is due, in part, to a change in the magnitude of the Hammond effect, which corresponds to a third-derivative structure-reactivity effect, $p^*_{yyy'} = \partial p_{yy'}/-\partial\sigma > 0$. There is considerable overlap between the reactivities of the most unstable triarylmethyl carbocations and the most stable $XArCH(CF_3)^+$, and there are also marked similarities in the reactivity-selectivity behavior of these species in the region of this overlap. Models are considered to explain the spectrum of reactivity-selectivity behavior that is observed on moving from very unreactive to very reactive carbocations.

Carbocation-anion combination reactions are among the simplest in organic chemistry, and the study of these has been closely linked to the development of models to explain structure-reactivity effects on organic reactions.[1-3] A key conceptual advance was the recognition that comparisons between the reactions of different carbocations are facilitated by reporting rate data as ratios, or selectivities [log (k_{Nu1}/k_{Nu2})], for partitioning of the electrophile between capture by different nucleophilic reagents. It has been shown that nucleophile selectivities for the capture of some triarylmethyl carbocations[4-7] and substituted phenyltropylium ions[8] are independent of carbocation reactivity and follow the N_+ equation (eq 1).[3] However, the selectivities of nucleophiles toward

$$\log (k_{Nu}/k_0) = N_+ \qquad (1)$$

the unsubstituted triarylmethyl carbocation do not follow the N_+ equation,[9] and the selectivities of alkylamines toward ring-substituted trityl carbocations,[10] of alkyl alcohols toward ring-substituted 1-phenylethyl carbocations ($XArCH(CH_3)^+$),[11] and of halide ions toward $XArC(CF_3)_2^+$ [12] decrease with increasing carbocation reactivity. One of the unsolved problems of physical organic chemistry is the explanation for the differences in these reactivity-selectivity phenomena.

Chart I



This paper reports a study of the reaction of nucleophilic reagents with ring-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations, $XArCH(CF_3)^+$, which are generated as intermediates of the stepwise solvolysis reactions of the corresponding neutral derivatives $XArCH(CF_3)Y$ (Chart I). These substrates are very stable thermodynamically[13] relative to $XArCH(CF_3)^+$, the carbocation intermediates of solvolysis; but the carbocation intermediates are exceptionally stable in a kinetic sense, as measured by the rate constants k_s for their capture by solvent.[14] As a consequence, nucleophile adducts to $XArCH(CF_3)^+$ are much more stable than the corresponding adducts to "normal" carbocations of the same kinetic reactivity (e.g., $XArCH(CH_3)^+$). This allows the extension of these studies to weakly basic nucleophiles which react with "normal" carbocations to form *unstable* adducts. For example, 4-$Me_2NArCH(CH_3)^+$ and 4-$Me_2NArCH(CF_3)^+$ have similar reactivities toward nucleophilic reagents.[14] It was impossible in earlier work to determine the reactivity of acetate ion toward 4-$Me_2NArCH(CH_3)^+$ because the acetate adduct is unstable to isolation by reverse-phase HPLC,[15] but 4-$Me_2NArCH(CF_3)OAc$ is stable to our chromatography conditions.

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(15) The estimated rate constant for solvolysis of 4-$Me_2NArCH(CH_3)OAc$ in 30% ethanol in water at 25 °C is 2.1 s^{-1}: Hill, E. A.; Gross, M. L.; Stasiewicz, M.; Mannion, M. *J. Am. Chem. Soc.* **1969**, *91*, 7381-7392.

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These experiments have been designed to test two proposals that attempt to reconcile the constant selectivity observed for reactions of the relatively stable carbocations which obey the N_+ equation, and the decreasing selectivity with increasing carbocation reactivity that is observed for the reactions of more unstable carbocations.

(1) The reactions of carbocations with neutral alcohols, but not anionic nucleophiles, are catalyzed by proton transfer from the nucleophile to a general base catalyst.[7,16-20] The requirement for the coupling of a proton-transfer step to carbon–nucleophile bond formation for the reactions of neutral nucleophiles may lead to different reactivity–selectivity behavior than that for the more simple addition reactions of anions.[7,16] We report here a comparison of the reaction of alcohols and carboxylate ions (RCO_2^-) with $XArCH(CF_3)^+$. The data show that the increase in nucleophile selectivity with decreasing carbocation reactivity is similar for the reactions of both the neutral and the anionic nucleophiles.

(2) We report data for the reactions of alkyl alcohols with $XArCH(CF_3)^+$ which is consistent with the proposal that there is a relationship between reactivity–selectivity behavior for carbocation capture and carbocation reactivity. $XArCH(CF_3)^+$ with weakly to moderately strongly electron-donating substituents X are captured by alcohols with rate constants which approach the diffusion limit. These carbocations show sharp changes in alcohol selectivity with changing carbocation reactivity. $XArCH(CF_3)^+$ with strongly electron-donating tertiary-amino substituents have lifetimes which approach those for carbocations which follow the N_+ scale. These carbocations show very small changes in alcohol selectivity with changing carbocation reactivity, as though they were electrophiles which followed the N_+ equation. Models are considered to explain the change, with changing carbocation reactivity, from electrophile-independent to electrophile-dependent nucleophile selectivities.[21,22]

Experimental Section

Materials. Reagent grade inorganic salts and reagent grade organic chemicals used for syntheses, trifluoroethanol (Aldrich), methanol and acetonitrile (HPLC grade, Fisher), and dimethylamine (a 40% aqueous solution from Aldrich) were used without purification. Other amines were purified by recrystallization or by distillation. The water used for product and kinetic studies was distilled and then passed through a Milli-Q water purification system.

Syntheses of Substrates. The following substrates were synthesized by published procedures: $4\text{-}MeArCH(CF_3)OTs$,[13] $4\text{-}MeSArCH(CF_3)OTs$,[14] $4\text{-}MeSArCH(CF_3)Br$,[14] $4\text{-}MeOArCH(CF_3)OTs$,[13] $4\text{-}MeOArCH(CF_3)Br$,[14] $4\text{-}Me_2NArCH(CF_3)$(3,5-dinitrobenzoate),[14] $4\text{-}Me_2NArCH(CF_3)$(4-nitrobenzoate),[14] and $4\text{-}Me_2NArCH(CF_3)N_3$.[23]

1-(4-(*N*-Methyl-*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethanol. *p*-Amino-2,2,2-trifluoroacetophenone was prepared by reaction of *p*-fluoro-2,2,2-trifluoroacetophenone[24] with NH_3 in DMSO at 135 °C for 24 h.[25] Trifluoroacetylation of the product with trifluoroacetic anhydride[26] followed by reduction with $LiAlH_4$[27] gave 1-(4-(*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethanol, which was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate. Reductive methylation of the aniline nitrogen of this alcohol by reaction with formaldehyde in formic acid[28] gave the title alcohol, which was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate.

3,5-Dinitrobenzoate and Pentafluorobenzoate Esters of 1-(4-(*N*-Methyl-*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethanol. These esters were prepared from the title alcohol and the respective benzoic acid using 4-pyrrolidinopyridine as the catalyst for dehydration by *N*,*N*-dicyclohexylcarbodiimide[29] and were purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate.

1-(4-(*N*-(2,2,2-Trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethanol: oil, bp 68–69 °C (31 mmHg); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.77 (2 H, dq, J = 7, 9 Hz, CH_2), 4.60 (1 H, t, J = 9 Hz, NH), 4.90 (1 H, q, J = 7 Hz, CH), 6.68, 7.29 (4 H, A_2B_2, J = 8 Hz, C_6H_4); exact mass calcd for $C_{10}H_9F_6NO$ 273.0589, found 273.0588.

1-(4-(*N*-Methyl-*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethanol: oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.06 (3 H, s, CH_3), 3.86 (2 H, q, J = 9 Hz, CH_2), 4.92 (1 H, q, J = 7 Hz, CH), 6.79, 7.35 (4 H, A_2B_2, J = 9 Hz, C_6H_4); exact mass calcd for $C_{11}H_{11}F_6NO$ 287.0746, found 287.0745. Anal. ($C_{11}H_{11}F_6NO$) C, H.

1-(4-(*N*-Methyl-*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethyl pentafluorobenzoate: solid, mp 57–58 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.08 (3 H, s, CH_3), 3.90 (2 H, q, J = 8 Hz, CH_2), 6.26 (1 H, q, J = 8 Hz, CH), 6.82, 7.41 (4 H, A_2B_2, J = 9 Hz, C_6H_4); exact mass calcd for $C_{18}H_{10}F_{11}NO_2$ 481.0536, found 481.0535. Anal. ($C_{18}H_{10}F_{11}NO_2$) C, H.

1-(4-(*N*-Methyl-*N*-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethyl 3,5-dinitrobenzoate: solid, mp 54–55 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.10 (3 H, s, CH_3), 3.90 (2 H, q, J = 7 Hz, CH_2), 6.34 (1 H, q, J = 7 Hz, CH), 6.84, 7.47 (4 H, A_2B_2, J = 9 Hz, C_6H_4), 9.19, (2 H, d, J = 2 Hz, $Ar(NO_2)_2$), 9.28 (1 H, t, J = 2 Hz, $Ar(NO_2)_2$); exact mass calcd for $C_{18}H_{13}F_6N_3O_6$ 481.0709, found 481.0710. Anal. ($C_{18}H_{13}F_6N_3O_6$) C, H.

Methods. HPLC Analyses. Reaction products were separated by HPLC as described previously[14b,30] and were detected by the UV absorbance of the respective aromatic rings at the following wavelengths: $4\text{-}Me(CF_3CH_2)NArCH(CF_3)Y$, 253 nm; $4\text{-}Me_2NArCH(CF_3)Y$, $4\text{-}MeSArCH(CF_3)Y$, and $4\text{-}MeArCH(CF_3)Y$, 254 nm; $4\text{-}MeOArCH(CF_3)Y$, 271 nm. The nucleophile adducts of $XArCH(CF_3)^+$ were identified as described in previous work.[14b] The product ratios determined by HPLC analysis are reproducible to ±10%.

Kinetic Analyses. The reaction of $4\text{-}Me(CF_3CH_2)NArCH(CF_3)$(3,5-dinitrobenzoate) was studied at 25 °C in 20% acetonitrile in water (I = 0.80, $NaClO_4$) containing 1 or 2 mM sodium azide, 1.25 mM acetate buffer (95% free base), and ca. 10^{-5} M $4\text{-}Me_2NArCH(CF_3)OH$ as an internal standard for HPLC analyses. The reaction was initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the reaction mixture, to give a final substrate concentration of 1.2×10^{-5} M. The disappearance of substrate was then followed by HPLC. Pseudo-first-order rate constants, k_{obsd}, were obtained from the slopes of linear semilogarithmic plots of reaction progress against time, which covered 3 or more half-times for the reaction.

Procedures for Product Studies. Product studies were performed at room temperature (22 ± 2 °C). The reactions were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the reaction mixture, to give a final substrate concentration of $\sim$1 mM for the reaction of $4\text{-}MeArCH(CF_3)OTs$, 5×10^{-4} M for the reactions of $4\text{-}MeOArCH(CF_3)Y$, and 1×10^{-4} M for the reactions of $4\text{-}MeSArCH(CF_3)Y$, $4\text{-}Me_2NArCH(CF_3)Y$, and $4\text{-}Me(CF_3CH_2)NArCH(CF_3)Y$. A substrate concentration of 5×10^{-6} M was used for determination of the values k_{az}/k_{AcO} for the reactions of $4\text{-}Me_2NArCH(CF_3)Y$ and $4\text{-}Me(CF_3CH_2)NArCH(CF_3)Y$, in order to maintain the substrate concentration in ≥10-fold excess over $[N_3^-]$.

Solutions of alkyl alcohols were prepared by mixing 1 M aqueous $NaClO_4$ with an equal volume of a mixture of alcohol/trifluoroethanol to give a final solvent of $X/(50 - X)/50$ (v/v/v) alcohol/trifluoroethanol/water. Product studies were performed using 2.00 mL of this solution, to which 3 or 5 μL of 1.00 M $HClO_4$ was added for studies on the reactions of $4\text{-}Me_2NArCH(CF_3)Y$ and $4\text{-}Me(CF_3CH_2)NArCH(CF_3)Y$. Direct injection of solutions containing $4\text{-}Me_2NArCH(CF_3)Y$ onto the HPLC column gave broad peaks because of the presence of a mixture of the basic and N-protonated forms of reactants and products. These reactions were allowed to proceed for >10 half-times, and the perchloric acid was then neutralized with 2 equiv of NaOH prior to analysis of products by HPLC. The alcohol adducts were shown to be stable to the reaction conditions by determination of product ratios over extended periods of time.

Solutions for studies of the reactions of alkanecarboxylate ions were prepared by mixing an aqueous solution of the sodium salt of the car-

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Table I. Nucleophile Selectivities for Reactions of 4-Me(R)NArCH(CF_3)$^+$[a]

solvent	R	k_{AcO}/k_s, M^{-1}	k_{az}/k_{AcO}[b]	k_{az}/k_s,[c] M^{-1}	k_s,[d] s^{-1}
20% acetonitrile in water[e]	CH_3[g]	80[i]	48 000[l]	3.8×10^6	$\leq 1.3 \times 10^3$,[p] ($\leq 3 \times 10^2$)
	CH_2CF_3[h]	22.5[j]	6200[m]	1.4×10^5	3.3×10^4
50/50 (v/v) CF_3CH_2OH/H_2O[f]	CH_3[g]	220[k]	27 500[n]	6.3×10^6	$\leq 8 \times 10^2$[p] ($\leq 2 \times 10^2$)
	CH_2CF_3[h]	65[k]	3800[o]	2.5×10^5	2.0×10^4

[a] At 22 ± 2 °C. [b] Dimensionless. [c] $(k_{az}/k_{AcO})(k_{AcO}/k_s)$. [d] Calculated from k_{az}/k_s and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} (see text). [e] $I = 0.80$ ($NaClO_4$). [f] $I = 0.50$ ($NaClO_4$). [g] For reaction of 4-Me_2NArCH(CF_3)(3,5-dinitrobenzoate). [h] For reaction of 4-Me(CF_3CH_2)NArCH(CF_3)(pentafluorobenzoate). [i] Determined at [AcO^-] = 0.05 M, [B^-]/[BH] = 19. [j] Determined at [AcO^-] = 0.063 M, [B^-]/[BH] = 19. [k] Average of determinations at 3–5 values of [AcO^-] (see Table III). [l] Average of determinations at [AcO^-] = 0.71 M ([B^-]/[BH] = 19) and five values of [N_3^-] between 0.05 and 0.15 mM. [m] Average of determinations at [AcO^-] = 0.475 M ([B^-]/[BH] = 19) and five values of [N_3^-] between 0.50 and 6.7 mM. [n] Reference 14b. [o] Average of determinations at [AcO^-] = 0.50 M ([B^-]/[BH] = 9) and five values of [N_3^-] between 0.2 and 1.0 mM. [p] Using values of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} or 1.25×10^9 M^{-1} s^{-1} (see text).

Table II. Nucleophile Selectivities for Reactions of Ring-Substituted 1-Phenyl-2,2,2-trifluoroethyl Derivatives, XArCH(CF_3)Y, with Alkyl Alcohols[a]

		k_{ROH}/k_{TFE}[b] for X shown				
alcohol	pK_a[c]	4-Me_2N[d]	4-Me(CF_3CH_2)N[e]	4-MeS[f,k]	4-MeO[f,k]	4-Me[g,k]
MeOH		450[h–j]	395[h–j]	100	80	3.8
EtOH	11.0	330[h]	270[h]	71	55	3.1
MeO(CH_2)$_2$OH	9.7	60[l]	62[l]	20	17	
Cl(CH_2)$_2$OH	8.8	25[l]	24[l]	15	12.5	1.81
HC≡CCH_2OH		22[l]	25[l]	16.2	14.5	2.9
NC(CH_2)$_2$OH	8.0	9.5[k]	9.4[k]	6.9	6.4	1.3
Cl_2CHCH_2OH	7.1	4.2[k]	4.2[k]	3.7	3.5	1.4
H_2O[m]		8.9	8.0	4.0	3.8	1.4
k_s (s^{-1})[n]		≤ 800,[o] (≤ 200)	2×10^4	1.2×10^7	5×10^7	1×10^{10}[p]
β_{nuc}[q]		0.48	0.46	0.34	0.32	0.09

[a] At 22 ± 2 °C and $I = 0.50$ ($NaClO_4$). [b] Dimensionless. [c] The pK_a for the corresponding substituted alkylammonium ion: ref 20. [d] Y = 3,5-dinitrobenzoate, in solutions containing 1.5 mM $HClO_4$. [e] Y = pentafluorobenzoate, in solutions containg 1.5 mM $HClO_4$. [f] Y = Br. [g] Y = OTs. [h] For reaction in 0.25/49.75/50 (v/v/v) alcohol/trifluoroethanol/water. [i] Identical ratios were determined for reactions in 0.25/49.75/50 and 5/45/50 (v/v/v) alcohol/trifluoroethanol/water. [j] Identical ratios were determined for reactions at [$HClO_4$] = 1.5 and 2.5 mM. [k] For reaction in 5/45/50 (v/v/v) alcohol/trifluoroethanol/water. [l] For reaction in 2.5/47.5/50 (v/v/v) alcohol/trifluoroethanol/water. [m] For reaction in 50/50 (v/v) trifluoroethanol/water. [n] The pseudo-first-order rate constant for capture of the carbocation by 50/50 (v/v) trifluoroethanol/water, calculated from the product rate constant ratio k_{az}/k_s (M^{-1}, Table I or ref 14b) and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion (see text). [o] Using values of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} or 1.25×10^9 M^{-1} s^{-1} (see text). [p] Reference 32. [q] The slope of the Brønsted plot (Figure 4).

boxylate ion ($I = 1.0$, $NaClO_4$) with an equal volume of trifluoroethanol. The stability of the carboxylate adducts, XArCH(CF_3)O_2CR, was determined by monitoring the decrease in the ratio of the yields of the carboxylate and solvent adducts with time. The most reactive adducts, XArCH(CF_3)O_2CCHCl_2, were stable for at least 5 min in the presence of 0.05 M dichloroacetate anion.

Solutions of alkylamines were prepared by mixing aqueous solutions of the basic form of the amine ($I = 1.0$, $NaClO_4$) with acetonitrile to give a final solvent of 20% acetonitrile in water. Reaction mixtures were prepared to a volume of 2.00 mL by replacing the reference amine (either 0.80 M 2,2,2-trifluoroethylamine or 0.80 M 2-methoxyethylamine) with increasing volumes of a second amine. NaOH (20 μL, 1.0 M) was added to solutions that contained amines with $pK_a > 10$, in order to insure that effectively none of the amine is protonated by solvent.

Calculation of Nucleophile Selectivities. The nucleophile selectivities for the reactions of XArCH(CF_3)Y were calculated from the ratios of the areas of the product peaks determined by HPLC analyses, according to eq 2. Equation 2 holds when the two nucleophile adducts have the same extinction coefficients at the wavelength used for the HPLC analyses. The extinction coefficient ratios for the various nucleophile

$$k_{Nu1}/k_{Nu2} = (\text{area})_{RNu1}[Nu_2]/(\text{area})_{RNu2}[Nu_1] \qquad (2)$$

adducts were determined as described in previous work[14b] and in every case were found to be equal to 1.0. We were unable to determine the relative extinction coefficients for the alcohol adducts of 4-MeArCH(CF_3)$^+$, and these extinction coefficient ratios were assumed to be 1.0.[14b]

Results

In 20% acetonitrile in water ($I = 0.80$, $NaClO_4$) the reaction of 4-Me(CF_3CH_2)NArCH(CF_3)(3,5-dinitrobenzoate) with 1 mM NaN_3 gives a quantitative yield of the azide adduct. There is no change at 25 °C in the pseudo-first-order rate constant $k_{obsd} = 3.3 \times 10^{-5}$ s^{-1} when the concentration of azide ion is increased from 1 to 2 mM.

Nucleophile selectivities, determined from product ratios, for the reaction of 4-Me_2NArCH(CF_3)Y (Y = 3,5-dinitrobenzoate) and 4-Me(CF_3CH_2)NArCH(CF_3)Y (Y = pentafluorobenzoate) with azide and acetate ions in mixed aqueous/organic solvents are given in Table I. It was shown in earlier work that nucleophile selectivities for the reactions of 4-Me_2NArCH(CF_3)Y, 4-MeSArCH(CF_3)Y, and 4-MeOArCH(CF_3)Y are independent of the leaving group Y.[14b]

Nucleophile selectivities, k_{ROH}/k_{TFE}, for the reaction of XArCH(CF_3)Y in a solvent of $X/(50 - X)/50$ alcohol/trifluoroethanol/water ($I = 0.50$, $NaClO_4$) are reported in Table II. The percent composition of the alcohol nucleophile was between $X = 5\%$ and $X = 0.25\%$, depending upon the relative reactivities of the alcohol and trifluoroethanol toward XArCH(CF_3)Y. It was shown that this small change in solvent has no detectable effect on the value of k_{MeOH}/k_{TFE} (Table II). The addition of dilute acid to unbuffered reaction mixtures causes an increase in the observed product selectivity k_{ROH}/k_{TFE} for reactions of 4-Me_2NArCH(CF_3)Y and 4-Me(CF_3CH_2)NArCH(CF_3)Y, due to protonation of the highly reactive nucleophile trifluoroethoxide ion. Identical values of k_{MeOH}/k_{TFE} were observed for reactions of 4-Me_2NArCH(CF_3)Y and 4-Me(CF_3CH_2)NArCH(CF_3)Y at [$HClO_4$] = 1.50 and 2.50 mM (Table II), which shows that the reaction of trifluoroethoxide ion is not significant in these weakly acidic solutions.

Nucleophile selectivities k_{RCOO}/k_{TFE} and k_{RCOO}/k_{HOH} were determined from product yields for the reactions of 4-MeOArCH(CF_3)Y and 4-MeSArCH(CF_3)Y with alkanecarboxylate ions in 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$). The values of k_{RCOO}/k_{TFE} (not reported) decrease for the reactions of 4-MeSArCH(CF_3)Y and 4-MeOArCH(CF_3)Y by as much as 30% when [RCO_2^-] is increased from 0.045 to 0.23 M. Smaller changes (≤20%) in the ratio k_{RCOO}/k_{HOH} are also observed. Table III lists the selectivities k_{RCOO}/k_{HOH} determined for reactions of XArCH(CF_3)Y in the presence of low concentrations of carboxylate ions where the ratios are effectively independent of [RCO_2^-]. The yields of the acetate adduct from the reactions of 4-Me_2NArCH(CF_3)Y, 4-Me(CF_3CH_2)NArCH-

Table III. Nucleophile Selectivities for Reactions of Ring-Substituted 1-Phenyl-2,2,2-trifluoroethyl Derivatives, $XArCH(CF_3)Y$, with Carboxylate Anions in 50/50 (v/v) Trifluoroethanol/Water[a]

$XArCH(CF_3)Y$	carboxylate anion (pK_a)[b]	$[B^-]/[BH]$	range of buffer concns,[c] M	k_{RCOO}/k_{HOH}[d]
4-$Me_2NArCH(CF_3)$(3,5-dinitrobenzoate)	$CH_3CO_2^-$ (4.8)	0.25	0.025–0.100	6200[e]
$\beta_{nuc} = 0.35$[f]		1.0	0.005–0.050	5900[e]
	$CH_3OCH_2CO_2^-$ (3.5)	9.0	0.010–0.050	3000[e]
	$ClCH_2CO_2^-$ (2.9)	9.0	0.010–0.050	1660[e]
	$NCCH_2CO_2^-$ (2.4)	9.0	0.010–0.050	800[e]
4-$Me(CF_3CH_2)NArCH(CF_3)$(pentafluorobenzoate)	$CH_3CO_2^-$	9.0	0.010–0.050	1900[e]
$\beta_{nuc} = 0.18$[f]		1.0	0.010–0.050	1970[e]
	$CH_3OCH_2CO_2^-$	9.0	0.010–0.050	1200[e]
	$ClCH_2CO_2^-$	9.0	0.010–0.050	920[e]
	$NCCH_2CO_2^-$	9.0	0.010–0.050	670[e]
	$Cl_2CHCO_2^-$ (1.3)	99	0.010–0.050	470[e]
4-$MeSArCH(CF_3)OTs$	$CH_3CO_2^-$	9.0	0.05–0.25	150[g]
$\beta_{nuc} = 0.04$[f]		1.0	0.05–0.25	140[g]
	$CH_3OCH_2CO_2^-$	9.0	0.05–0.25	95[g]
	$ClCH_2CO_2^-$	9.0	0.05–0.25	100[g]
	$NCCH_2CO_2^-$	9.0	0.10–0.50	76[g]
	$Cl_2CHCO_2^-$	99	0.05	110[g]
4-$MeOArCH(CF_3)OTs$	$CH_3CO_2^-$	9.0	0.10–0.50	93[g]
$\beta_{nuc} = 0.05$[f]	$CH_3OCH_2CO_2^-$	9.0	0.10–0.50	71[g]
	$ClCH_2CO_2^-$	9.0	0.05–0.20	59[g]
	$NCCH_2CO_2^-$	9.0	0.10–0.50	39[g]
	$Cl_2CHCO_2^-$	99	0.05	75[g]

[a] At 22 ± 2 °C and $I = 0.50$ ($NaClO_4$). [b] Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. 1, pp 305–351. [c] The ratios k_{RCOO}/k_{HOH} were determined at five different buffer concentrations. [d] Dimensionless. [e] Average of ratios at five different concentrations of carboxylate ions. [f] The slope of the Brønsted plot (Figure 2). [g] The value observed at the lowest concentration of carboxylate ion. There is a ≤20% decrease in k_{RCOO}/k_{HOH} with increasing buffer concentration.

Table IV. Nucleophile Selectivities for Reaction of 1-(4-(Dimethylamino)phenyl)-2,2,2-trifluoroethyl Azide with Amines in 20% Acetonitrile in Water[a]

amine	pK_a	amine concn range, M	ref[f] nucleophile	TFEA concn range, M	k_{amine}/k_{MEA}[i]	k_{amine}/k_{TFEA}[j]
ethylamine	11.0[b]	0.040–0.20	TFEA[g]	0.60–0.76		25
propylamine	10.5[c]	0.040–0.20	TFEA	0.60–0.76		24
ethylenediamine	10.2[b]	0.040–0.20	TFEA	0.60–0.76		22
glycine	9.6[c]	0.040–0.16	TFEA	0.64–0.76		14
2-methoxyethylamine	9.7[b]	0.020–0.32	TFEA	0.48–0.78		15
ethanolamine	9.8[d]	0.020–0.16	TFEA	0.64–0.78		13
taurine	8.7[c]	0.040–0.16	TFEA	0.64–0.76		8.6
2,2,2-trifluoroethylamine	5.9[b]					1.0
2-cyanoethylamine	5.6[e]	0.080–0.40	TFEA	0.40–0.72		0.58
dimethylamine	10.0[c]	0.080–0.40	MEA[h]	0.40–0.72	6.6	100[k]
piperidine	11.4[b]	0.020–0.20	MEA	0.60–0.78	8.0	120[k]
piperazine	10.1[b]	0.020–0.20	MEA	0.60–0.78	4.2	63[k]
morpholine	8.8[b]	0.040–0.20	MEA	0.60–0.76	1.6	24[k]
hydrazine	8.2[b]	0.020–0.20	MEA	0.60–0.78	4.9	73[k]
hydroxylamine	6.2[b]	0.040–0.20	MEA	0.60–0.76	0.95	14[k]
methoxylamine	4.6[b]	0.040–0.20	TFEA	0.60–0.76		3.1[k]
semicarbazide	3.6[b]	0.040–0.16	TFEA	0.64–0.76		1.9[k]

[a] At 25 °C and $I = 0.80$ ($NaClO_4$). [b] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. [c] Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. 1, pp 305–351. [d] Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638–2645. [e] Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572–580. [f] The second nucleophile present in the solution, against which the reactivity of the amine was referenced. [g] TFEA = 2,2,2-trifluoroethylamine. [h] MEA = 2-methoxyethylamine. [i] The average of the product rate constant ratios determined for reactions at five different [amine]/[MEA] ratios. [j] The average of the product rate constant ratios determined for reactions at five different [amine]/[TFEA] ratios. [k] $k_{amine}/k_{TFEA} = (k_{amine}/k_{MEA})(k_{MEA}/k_{TFEA})$.

$(CF_3)Y$, and 4-$MeSArCH(CF_3)Y$ in buffered solutions at increasing fractions of acetic acid were proportional to the concentration of acetate ion, which shows that acetic acid is unreactive as a nucleophile (Table III).

The reaction of 4-$Me_2NArCH(CF_3)N_3$ with amines in 20% acetonitrile in water gave the amine nitrogen adduct as the sole detectable product (>99% yield) under the reaction conditions described in Table IV. Product rate constant ratios k_{amine}/k_{TFEA} (TFEA = 2,2,2-trifluoroethylamine) determined for the reaction of 4-$Me_2NArCH(CF_3)N_3$ with amines in 20% acetonitrile in water ($I = 0.80$, $NaClO_4$) are given in Table IV. These selectivities were determined either directly from the product yields for a reaction in the presence of TFEA and the second amine or as the product of experimentally determined rate constant ratios $(k_{amine}/k_{MEA})(k_{MEA}/k_{TFEA})$ where MEA = 2-methoxyethylamine.

Discussion

Reaction Intermediates and Their Lifetimes. In 50/50 (v/v) trifluoroethanol/water, $XArCH(CF_3)Y$ ($\sigma_x^+ \leq -0.32$) react by a $D_N + A_N$ (S_N1)[31] mechanism.[14] Therefore, the rate constant ratios reported in Tables I–IV for the reactions of $XArCH(CF_3)Y$ are for partitioning of the carbocation reaction intermediates. Rate constants for the capture of $XArCH(CF_3)^+$ by the solvent 50/50 (v/v) trifluoroethanol/water, estimated from the product rate constant ratios k_{az}/k_s (M^{-1}) and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion,[14,30] range from $k_s \approx 1 \times 10^{10}$ s^{-1} for 4-$MeArCH(CF_3)^+$[32] to $k_s \leq 800$ s^{-1} for 4-

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[31] Commission on Physical Organic Chemistry, IUPAC. *Pure Appl. Chem.* **1989**, *61*, 23–56. Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343–349.

$Me_2NArCH(CF_3)^+$[33] (Table II). For $\sigma_x^+ \leq -0.62$, it is the liberated carbocation $XArCH(CF_3)^+$, not a carbocation–leaving group ion pair, that is captured by solvent and other nucleophiles. This is because the rate of irreversible separation of the ion pair to free ions ($k_{-d} \approx 10^{10}$ s^{-1})[11] is so fast that its capture by solvent ($k_s \leq 5 \times 10^7$ s^{-1}, Table II)[34] or by dilute nucleophiles (<0.1 M) does not effectively compete with this process.

Caution must be exercised in the calculation of absolute rate constants for k_s from k_{az}/k_s and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[35] A limiting ratio of $k_{az}/k_s \sim 0.7$ M^{-1} [51] is observed when the reactions of a carbocation with both azide ion and solvent are faster than diffusion. Values for k_s can be determined once k_{az}/k_s begins to increase above 0.7 M^{-1}. Now the use of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reactions of N_3^- will give k_s to well within a factor of 2 of the true value.[35] The rate constant k_{az} for the reactions of triarylmethyl carbocations remains at the diffusion limit as k_{az}/k_s increases to a value of 10^4 M^{-1} and then *it begins to slowly decrease*;[35b] but k_{az} is still within 2-fold of the diffusional value when $k_{az}/k_s \approx 10^5$ M^{-1}. Therefore, the ratio of $k_{az}/k_s = 1.4 \times 10^5$ M^{-1} (Table I) for the capture of $4\text{-}Me(CF_3CH_2)NArCH(CF_3)^+$ suggests that k_{az} for this carbocation may be slightly below the diffusion limit, so that the value of k_s may be 2-fold smaller than that listed in Tables I and II.

A very large ratio of $k_{az}/k_s = 6 \times 10^6$ M^{-1} was determined for the reaction of $4\text{-}Me_2NArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water.[14b] The following observations show that k_{az} for this reaction is *below* the value of 5×10^9 M^{-1} s^{-1} for a diffusion-limited reaction.

(1) A value of $k_{az} = 1.6 \times 10^7$ M^{-1} s^{-1} has been determined for the reaction of $4\text{-}Me_2NArCH(CH_3)^+$ in 50/50 trifluoroethanol/water.[36] This is probably close to the value of k_{az} for the capture of $4\text{-}Me_2NArCH(CF_3)^+$, because $XArCH(CH_3)^+$ and $XArCH(CF_3)^+$ with the same substituent X (X = 4-Me, 4-MeO, or 4-MeS) have similar rate constants for reaction with nucleophilic reagents.[14b]

(2) There is a remarkable *decrease* in selectivity from $k_{az}/k_{DMA} = 45$ (DMA = dimethylamine) for trapping of $4\text{-}MeSArCH(CF_3)^+$ to $k_{az}/k_{DMA} = 11$ for the capture of $4\text{-}Me_2NArCH(CF_3)^+$, a much less reactive carbocation.[23] The reactions of N_3^- and dimethylamine with $4\text{-}MeSArCH(CF_3)^+$ are limited by the rate of formation of the carbocation–nucleophile encounter complexes.[37] The decrease in k_{az}/k_{DMA} is not due to an increase in k_{DMA} for $4\text{-}Me_2NArCH(CF_3)^+$, because the latter is much less reactive than $4\text{-}MeSArCH(CF_3)^+$ toward a wide range of nucleophilic reagents. Therefore, the 4-fold-lower value of k_{az}/k_{DMA} for $4\text{-}Me_2NArCH(CF_3)^+$ than for $4\text{-}MeSArCH(CF_3)^+$ requires that k_{az} for the former be a *minimum* of 4-fold smaller than the diffusional value. Table I reports upper limits of k_s for the capture of $4\text{-}Me_2NArCH(CF_3)^+$ using $k_{az} \leq 1.25 \times 10^9$ M^{-1} s^{-1}.

N-Methyl-N-(2,2,2-trifluoroethyl)amino Substituent Effects. 1-(4-(N-Methyl-N-(2,2,2-trifluoroethyl)amino)phenyl)-2,2,2-trifluoroethyl derivatives were prepared as precursors to $4\text{-}Me(CF_3CH_2)NArCH(CF_3)^+$. To the best of our knowledge this is the first use of the N-methyl-N-(2,2,2-trifluoroethyl)amino group as a carbocation-stabilizing substituent. The N-trifluoroethyl for N-methyl substitution causes a 280-fold decrease in the rate constant for ionization of $4\text{-}Me(R)NArCH(CF_3)$(dinitrobenzoate) in 20% acetonitrile in water, from 9.3×10^{-3} s^{-1} for R = Me[23] to 3.3×10^{-5} s^{-1} for R = CF_3CH_2. This substituent effect can be combined with $\sigma^+ = -1.69$ for $4\text{-}Me_2N$[38] and $\rho = -10$ for ionization of $XArCH(CF_3)Y$[13,14b] to give an *approximate* value of $\sigma^+ = -1.45$ for the $4\text{-}Me(CF_3CH_2)N$ substituent.

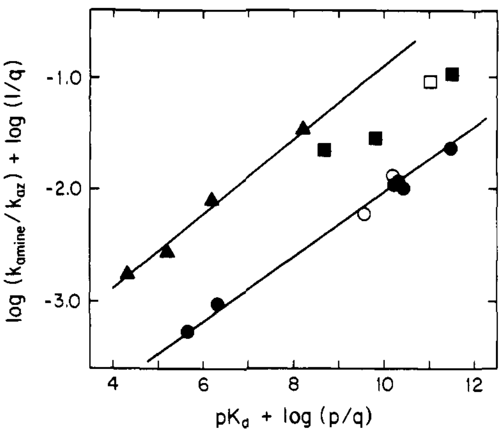
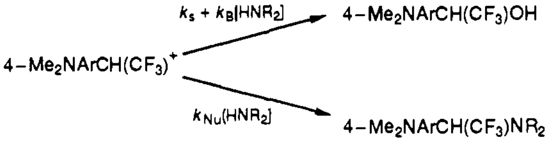


Figure 1. Brønsted plots of k_{amine}/k_{az} for the partitioning of $4\text{-}Me_2NArCH(CF_3)^+$ in 20% acetonitrile in water at $I = 0.80$ ($NaClO_4$). The rate constants for the reactions of the amines and the amine pK_as have been statistically corrected for the number of equivalent basic sites (q) at the amine free base and the number of equivalent acidic sites (p) at the conjugate acid: ●, neutral primary alkyl amines; ○, primary amines with a formal charge of 1−; ■, cyclic secondary amines; □, dimethylamine; ▲, α-effect amines.

Scheme I



Reactions of Amine Nucleophiles. $4\text{-}Me_2NArCH(CF_3)^+$ is trapped very effectively by primary and secondary amines. It was not possible to determine here if the addition of solvent to $4\text{-}Me_2NArCH(CF_3)^+$ is catalyzed by amine bases because the solvent is too weakly nucleophilic to compete with significant concentrations of amine nucleophiles. The water adduct ($4\text{-}Me_2NArCH(CF_3)OH$) was not detected for the experiments reported in Table IV. This shows that the yield of the water adduct was <1%, so that $k_{Nu} \gg k_B$ (Scheme I). General base catalysis by tertiary amines of the addition of water to triarylmethyl carbocations is observed experimentally,[16-18] when the amine adduct is formed reversibly and is thermodynamically unstable so that this adduct does not accumulate.

Figure 1 shows Brønsted plots of the selectivities k_{amine}/k_{az} of amines toward $4\text{-}Me_2NArCH(CF_3)^+$. The ratios k_{amine}/k_{az} were calculated from the data in Table IV and $k_{DMA}/k_{az} = 0.091$.[23] Data for neutral primary alkyl amines (●) and amines with a net charge of 1− (glycine and taurine, ○) are fit by a single straight line with slope $\beta_{nuc} = 0.29$, which shows that electrostatic interactions between negatively charged amines and $4\text{-}Me_2NArCH(CF_3)^+$ provide little stabilization of the transition state for the amine reaction.

A second correlation line, ca. 1 log unit above the line for primary amines and with slope $\beta_{nuc} = 0.33$, is observed for α-effect amine nucleophiles (▲). The reactivities of secondary amines (■) are intermediate between those of α-effect and primary alkylamines of the same pK_a. The high reactivity of α-effect amines toward carbocations was observed in earlier work where both rate and equilibrium constants for the formation of amine adducts were measured.[5,39a] The adducts of malachite green with α-effect

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[32] Footnote 36 in ref 14b.

[33] Footnote 35 in ref 14b.

[34] The rate constants, k_s, in Table II are for the capture of free carbocations. However, it has been shown that the presence of an internal sulfonate ion has little or no effect upon the reactivity of a carbocation in a carbocation–sulfonate ion pair: Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039–7044. There is also evidence that the $4\text{-}MeOArCH(CF_3)^+ \cdot Br^-$ ion pair is only 2–6-fold less reactive toward water than the free ion: Richard, J. P. *J. Org. Chem.* **1992**, *57*, 625–629.

[35] (a) There is a relatively small uncertainty in the value for k_{az} for the capture of carbocations in diffusion-limited reactions with azide ion. It has been shown by direct experiment that $k_{az} = 5 \times 10^9$ and 7×10^9 M^{-1} s^{-1}, respectively for the diffusion-limited reactions of triarylmethyl and diarylmethyl carbocations generated by laser flash photolysis of the corresponding acetates or phenyl ethers in 1/2 (v/v) acetonitrile/water.[35b] (b) McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913–6914; **1991**, *113*, 1009–1014.

[36] Couzens, F. L. Ph.D. Thesis, University of Toronto, 1992.

[37] Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1768–1769.

[38] Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; pp 58–65.

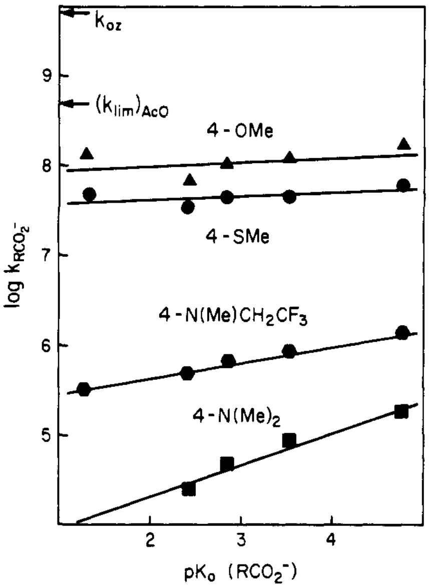

Figure 2. Brønsted plots of estimated rate constants k_{RCOO} for the reactions of carboxylate ions with $XArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water at $I = 0.50$ ($NaClO_4$). The arrows on the graph indicate the logarithmic values for the limiting rate constants $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion, and $k_{AcO} = 5 \times 10^8$ M^{-1} s^{-1} for the encounter-limited reaction of acetate ion.[11] The rate constants for the reactions of $4\text{-}Me_2NArCH(CF_3)^+$ are upper limits calculated for $k_{az} \leq 5 \times 10^9$ M^{-1} s^{-1}.

amines were found to be more stable, relative to malachite green, than the adducts with primary amines of the same pK_a, and it was shown that roughly 40% of this stabilization is expressed at the transition state for the amine addition reaction.[39a] The explanation(s) for the high basicity of α-effect nucleophiles toward sp^2-hybridized carbon is not understood.[39b]

Plots (not shown) of log (k_{amine}/k_{TFEA}) (Table IV) against the N_+ value of the amine,[3] against log k_{amine} for the reaction of amines with malachite green,[5] and against log k_{amine} for reaction of the unsubstituted trityl carbocation[9] are linear with slopes of 0.70, 0.70, and 3.1, respectively. These slopes show that the selectivity of $4\text{-}Me_2NArCH(CF_3)^+$ toward amines is greater than that of Ph_3C^+, but less than the selectivity of malachite green and other electrophiles whose selectivities toward nucleophiles are correlated by the N_+ scale.

The selectivity of $4\text{-}Me_2NArCH(CF_3)^+$ toward amine nucleophiles is in line with the chemical reactivity of this carbocation, which lies between the reactivity of malachite green and that of the trityl carbocation.[40] That is, the combination of the 4-(dimethylamino)phenyl and CF_3 groups at the methyl carbocation (CH_3^+) gives a carbocation with a lower reactivity and selectivity than that obtained from the substitution of three phenyl groups. We find the power of the (dimethylamino)phenyl group as a carbocation-stabilizing substituent to be notable and surprising.

Reactions of Carboxylate Anions. Figure 2 shows Brønsted plots for the reaction of carboxylate ions with $XArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water. Absolute rate constants, k_{RCOO}, were calculated from the values of k_{RCOO}/k_{HOH}, in Table III, and k_{HOH}.[14b,41] The values of k_{RCOO} for $4\text{-}Me_2NArCH(CF_3)^+$ are upper limits (see above). The Brønsted β_{nuc} values, determined as the slopes of the lines in Figure 2, are listed in Table III. Figure 2 shows small, but experimentally significant, positive deviations in k_{RCOO} for the reactions of $Cl_2CHCO_2^-$ with $4\text{-}MeSArCH(CF_3)^+$ and $4\text{-}MeOArCH(CF_3)^+$. We are unable to explain these deviations.

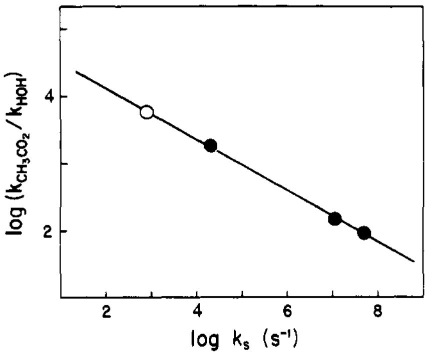

Figure 3. A plot of log (k_{AcO}/k_{HOH}) for the partitioning of $XArCH(CF_3)^+$ between reaction with acetate ion and water against log k_s (s^{-1}) for the pseudo-first-order reaction of the carbocations with 50/50 (v/v) trifluoroethanol/water. The value of k_s for the reaction of $4\text{-}Me_2NArCH(CF_3)^+$ (○) is an upper limit calculated for $k_{az} \leq 5 \times 10^9$ M^{-1} s^{-1}.

In aqueous trifluoroethanol, $4\text{-}MeOArCH(CF_3)^+$ and $4\text{-}MeOArCH(CH_3)^+$ show similar reactivities toward acetate ion, with $k_{AcO} = 1.6 \times 10^8$ and 7.6×10^7 M^{-1} s^{-1}, respectively. The small decrease in k_{AcO}/k_{TFE} and the nearly constant ratios k_{AcO}/k_{HOH} with increasing [AcO$^-$] observed for the reactions of $4\text{-}MeSArCH(CF_3)^+$ and $4\text{-}MeOArCH(CF_3)^+$ (see Results) are consistent with weak catalysis by acetate ion of the addition of trifluoroethanol, and little or no catalysis of the addition of water.[11,19,20]

The increasing values of β_{nuc} (Figure 2) and of k_{AcO}/k_{HOH} (Table III) with decreasing carbocation reactivity arise from a Hammond-type shift to transition states with increasing amounts of carbon–nucleophile bond formation.[1] These changes cannot be explained by an increase in the rate constant for the reaction of the weaker nucleophile (water or weakly basic RCOO$^-$) relative to a limiting rate constant for an encounter-limited reaction of the more strongly nucleophilic reagent (acetate ion)[11,42] because the reactions of acetate ion are not limited by the rate of formation of an [acetate–carbocation] encounter complex.

(1) The rate constant $k_{AcO} = 1.6 \times 10^8$ M^{-1} s^{-1} for the reaction of acetate ion with $4\text{-}MeOArCH(CF_3)^+$ is 3-fold smaller than the limiting rate constant of $k_{AcO} = 5 \times 10^8$ M^{-1} s^{-1} for the encounter-limited reactions of acetate ion with $XArCH(CH_3)^+$.[11]

(2) The rate constant k_{AcO} decreases with changes in the reactants that should cause a decrease in reactivity, such as a decrease in the pK_a of RCO$_2^-$ or an increase in carbocation stability (Figure 2). Constant values of k_{RCOO} with changing substrate reactivity would have been obtained for encounter-limited reactions.

(3) There is a linear relationship between log (k_{AcO}/k_{HOH}) and log k_s (s^{-1}) for the reactions of $XArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water (Figure 3). A downward break in this plot would have been observed at large values of log k_s if the rate constant k_{AcO} had become encounter-limited.[11]

Reactions of Alcohols. Combination of the rate constant ratios k_{ROH}/k_{TFE} (Table III) with values of k_{TFE}[14b,41] gives the absolute rate constants k_{ROH} for the reaction of alcohols with $XArCH(CF_3)^+$ (Figure 4).

A positive charge develops on the oxygen nucleophile at the transition state for the addition reactions of alcohols. Good correlations ($r > 0.99$) are obtained for Brønsted plots (Figure 4) of log k_{ROH} against the pK_a of the amine for which the substituent at the amino group is the same as that at the hydroxyl group of the alcohol. This is because the reference reaction for

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[39] (a) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 6592–6597. (b) Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313–319.

[40] The upper limit of $k_s \leq 200$ s^{-1} for the capture of $4\text{-}Me_2NArCH(CF_3)^+$ by 50/50 (v/v) trifluoroethanol/water is close to the value of $k_s = 90$ s^{-1} for the reaction of the bis(4-methoxyphenyl)trityl carbocation with 1/2 (v/v) acetonitrile/water. The difference in solvents for the two reactions should not have a large effect on the relative values of k_s (McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966–3972).[30]

[41] Values of $k_{HOH} = 700$ M^{-1} s^{-1} and $k_{TFE} = 90$ M^{-1} s^{-1} for the reaction of $4\text{-}Me(CF_3CH_2)NArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water were calculated from $k_s = 2.0 \times 10^4$ s^{-1} (Table I), $k_{HOH}/k_{TFE} = 8.0$ (Table II), and $[H_2O]/[TFE] = 27.8/6.94 = 4.0$.

[42] Kemp, D. S.; Casey, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6670–6680. Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082–6095.

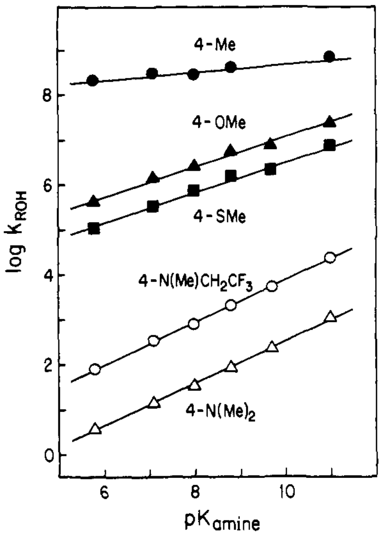

Figure 4. Brønsted plots of estimated rate constants k_{ROH} for the reactions of alcohols with $XArCH(CF_3)^+$ in 50/50 (v/v) trifluoroethanol/water. The reference reaction is protonation of an alkylamine in which the substituent at the amino group is the same as that at the hydroxyl group of the alcohol nucleophile. The rate constants for the reaction of $4\text{-}Me_2NArCH(CF_3)^+$ are upper limits calculated for $k_{az} \leq 5 \times 10^9$ M^{-1} s^{-1}.

protonation of the amine also places a positive charge on the amine base. Poorer correlations (not shown) are obtained for Brønsted plots of log k_{ROH} using protonation of the alkoxide ion as the reference reaction.[43] The values of log k_{HOH} show large negative deviations from these correlations, which shows that water has an abnormally low reactivity for a nucleophile with a pK_a of 15.7. Possible explanations for this negative deviation have been discussed in an earlier study of the reactions of $XArCH(CH_3)^+$.[11]

Plots of log (k_{ROH}/k_{TFE}) (where R $\neq$ H) for the reaction of $XArCH(CF_3)^+$ against log (k_{ROH}/k_{TFE}) for the reaction of $XArCH(CH_3)^+$ (not shown) are linear ($r \geq 0.995$) with slopes of 1.16 (X = Me_2N), 1.30 (X = MeS), and 1.16 (X = MeO). This shows that the selectivity of $XArCH(CF_3)^+$ toward alkyl alcohols is slightly larger than that of $XArCH(CH_3)^+$ for the same substituent X. It is surprising that $XArCH(CF_3)^+$ should be even slightly more selective for reactions with alkyl alcohols than the thermodynamically more stable carbocations $XArCH(CH_3)^+$. We conclude that the relative selectivity toward nucleophiles of carbocations of similar structure is not determined solely by the thermodynamic stability of the carbocation.

The values of log (k_{HOH}/k_{TFE}) for the reactions of $XArCH(CF_3)^+$ are larger than those for $XArCH(CH_3)^+$, and this is manifested as positive deviations from the above correlations.[44] Water reacts with $XArCH(R)^+$ [R = CH_3,[11] CF_3 (this work)] as though it, like trifluoroethanol, were a weakly basic alcohol of $pK_a \sim 13$. The larger ratios k_{HOH}/k_{TFE} for the reactions of $XArCH(CF_3)^+$ than for the reactions of $XArCH(CH_3)^+$ are consistent with destabilization of the transition state for the reaction of trifluoroethanol with $XArCH(CF_3)^+$ by electrostatic interactions between the two CF_3 groups. However, there is no similar destabilizing interaction for the reaction of water, because the hydrogen substituent at water is neither strongly electron-donating nor strongly electron-withdrawing.

Figure 5 shows the changes in the selectivity k_{EtOH}/k_{TFE} for the capture of $XArCH(CF_3)^+$ as the carbocation reactivity is decreased from 1×10^{10} s^{-1} for $4\text{-}MeArCH(CF_3)^+$ to $k_s \leq 200$ s^{-1} for the capture of $4\text{-}Me_2NArCH(CF_3)^+$. This plot is curved and may be divided into three regions which represent three different types of effects of changing carbocation reactivity on carbocation selectivity.

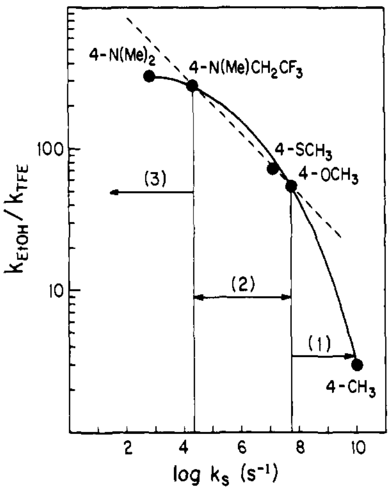

Figure 5. A logarithmic plot of the selectivities k_{EtOH}/k_{TFE} (Table II) for the partitioning of $XArCH(CF_3)^+$ against the pseudo-first-order rate constant k_s (s^{-1}) for the capture of $XArCH(CF_3)^+$ by 50/50 (v/v) trifluoroethanol/water. The dashed line shows the selectivities expected for a constant change in log (k_{EtOH}/k_{TFE}) with changing carbocation reactivity (log k_s).

Region 1: There is an extremely sharp 20-fold increase in k_{EtOH}/k_{TFE} with a 200-fold increase in k_s on moving from $4\text{-}MeArCH(CF_3)^+$ to $4\text{-}MeOArCH(CF_3)^+$. This sharp increase in selectivity is due, in part, to the decrease in k_{TFE} relative to the almost constant value of k_{EtOH} for the diffusion-limited reaction of ethanol.[11]

Region 2: There is a shallower 5-fold increase in k_{EtOH}/k_{TFE} for a 2500-fold decrease in k_s on moving from $4\text{-}MeOArCH(CF_3)^+$ to $4\text{-}Me(CF_3CH_2)NArCH(CF_3)^+$ (dashed line, Figure 5). The reactions of ethanol and trifluoroethanol with these carbocations are slower than diffusion (Figure 4), so that the increase in selectivity must be due to a shift to transition states with increasing amounts of carbon–nucleophile bond formation. The increase in selectivity is unrelated to the requirement for proton transfer from the nucleophile, because similar increases in selectivity are observed for the reactions of carboxylate anions with $XArCH(CF_3)^+$ of decreasing reactivity (Figure 3).

Region 3: The increase in carbocation selectivity with decreasing carbocation reactivity does not follow the dashed line in Figure 5, but rather a downward break is observed for the reactions of very stable carbocations. This is represented by the very small (20%) increase in k_{EtOH}/k_{TFE} for a more than 25-fold decrease in k_s (the decrease in k_s is $\geq$100-fold using $k_{az} \leq 1.25 \times 10^9$ M^{-1} s^{-1} for the reaction of $4\text{-}Me_2NArCH(CF_3)^+$, see above) on moving from $4\text{-}Me(CF_3CH_2)NArCH(CF_3)^+$ to $4\text{-}Me_2NArCH(CF_3)^+$.

Regions 1 and 2 were also observed in an earlier study of the reactions of $XArCH(CH_3)^+$, but the additional downward break in region 3 was not detected for the more limited set of ring substituents X.[11]

If the increase in carbocation selectivity across region 2 of Figure 5 arises from a Hammond effect, then the downward break on moving to region 3 must be due to a decrease in the magnitude of the Hammond effect for the reactions of $XArCH(CF_3)^+$ of decreasing reactivity. This *change in the change* of the nucleophile selectivity corresponds to a third-derivative structure–reactivity effect.[20,21,45]

Reactivity–Selectivity Effects on Carbocation–Nucleophile Combination Reactions. The data for the reaction of alkyl alcohols with $XArCH(CF_3)^+$ shown in Figure 5 establish a bridge between sharply changing nucleophile selectivities for the reactions of highly unstable carbocations (regions 1 and 2) and constant nucleophile selectivities for the reactions of relatively stable carbocations

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[43] The slopes of the plots of log k_{ROH} for the reaction of $XArCH(CF_3)^+$ against the pK_a of ROH are 0.67, 0.65, 0.48, 0.45, and 0.12, respectively, for X = $4\text{-}Me_2N$, $4\text{-}Me(CF_3CH_2)N$, 4-MeS, 4-MeO, and 4-Me.

[44] The positive deviations of the values of log (k_{ROH}/k_{TFE}) for the reactions of $XArCH(CF_3)^+$ are 0.44, 0.35, and 0.27 log units, respectively, for X = $4\text{-}Me_2N$, 4-MeS, and 4-MeO.

[45] Jencks, W. P. *Bull. Soc. Chim. Fr.* **1988**, 218–224.

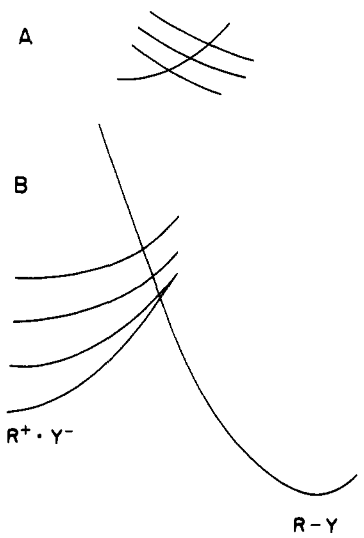

Figure 6. (A) A reaction coordinate with shallow curvature for a reaction with a relatively large second-derivative structure–reactivity coefficient $p_{yy'}$. (B) A series of reaction coordinates which show increasingly steeper curvature with increasing carbocation stability.

(region 3). A similar bridge has been established for the reactions of ring-substituted diaryl- and triarylmethyl carbocations with alkylamines, viz., the increase from small, or inverse (amine reactivity *decreases* with increasing basicity), amine selectivities toward highly unstable carbocations,[10] to constant selectivities toward stable carbocations which follow the N_+ equation (eq 1).[3-5] Figures 2 and 3 and the data in Table III show that the selectivity of carboxylate ions toward $XArCH(CF_3)^+$ increases with decreasing carbocation reactivity. Presumably, the selectivities would have approached limiting values if it had been possible to study electrophiles that are less reactive than $4\text{-}Me_2NArCH(CF_3)^+$.

The studies of the reactions of alcohol and amine nucleophiles with carbocations show that there is a change from sharply increasing nucleophile selectivities with decreasing carbocation reactivity, to constant selectivity with decreasing reactivity on moving from very rapid addition reactions ($k_{Nu} \sim 10^3\text{–}10^9$ M^{-1} s^{-1}) to slower reactions.

Reactivity–selectivity relationships and the changes in them that occur on moving from stable to unstable carbocations can be described by first-, second-, and third-derivative structure–reactivity terms. The selectivity of nucleophiles toward a carbocation is the first-derivative structure–reactivity term, $\beta_{nuc} = \partial \log k/\partial\, pK_{nuc}$. An increase in β_{nuc} with decreasing carbocation reactivity may be expressed as the second-derivative structure–reactivity term $p_{yy'} = \partial^2 \log k/(-\partial pK_{nuc}\, \partial\sigma) = \partial\beta_{nuc}/-\partial\sigma > 0$, but a constant value of β_{nuc} with decreasing carbocation reactivity is described by $p_{yy'} \sim 0$.[46] The change from $p_{yy'} > 0$ to $p_{yy'} \sim 0$ with decreasing carbocation reactivity corresponds to a third-derivative structure–reactivity effect, which can be expressed as the term $p^*_{yyy'} = \partial p_{yy'}/-\partial\sigma < 0$.[20]

First-derivative structure–reactivity terms are used to locate the position of the transition state on a two-dimensional reaction coordinate diagram, and second-derivative effects are used to describe the tendency of the location of the transition state to shift on these diagrams in response to changes in the thermodynamic driving force for the reaction. The size of a second-derivative effect depends on the curvature of the reaction energy surface in the region of the transition state. For very reactive carbocations the curvature in the region of the reaction transition state will be shallow so that large shifts in the position of the transition state may be observed with changing thermodynamic driving force for the reaction (Figure 6A). This Hammond-type movement of the reaction transition state corresponds to a value of $p_{yy'} > 0$. However, the value of $p_{yy'} = \partial\beta_{nuc}/-\partial\sigma$ cannot remain constant indefinitely with increasing carbocation reactivity, because β_{nuc} cannot exceed 1.0.[20] Therefore, $p_{yy'}$ *must* decrease as β_{nuc} approaches the limiting value of 1.0. The data for carbocation–nucleophile combination reactions show that β_{nuc} for the reactions of amines[5,10,39a] and alcohols (Figure 5) in fact levels off at values that are considerably smaller than 1.0.

Scheme II

$$Nu^x{\cdot}HOS \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} Nu^x{\cdot}{}^+(R)HCArX \xrightarrow{k_c} Nu^{x+1}\text{–}(R)HCArX$$

The change from $p_{yy'} > 0$ to $p_{yy'} \sim 0$ with decreasing carbocation reactivity is consistent with a change from a (one-dimensional) reaction coordinate with shallow curvature in the region of the reaction transition state (upper curve, Figure 6B), to reaction coordinates with increasingly steep curvature. The increasingly sharp curvature will lead to a decrease in the tendency of the reaction transition state to shift with changes in carbocation stability, as illustrated by the lower curves in Figure 6B.

It is expected that the curvature in the region of the reaction transition state should become increasingly sharp on moving from weakly resonance-stabilized carbocations that react rapidly through early transition states, to strongly resonance-stabilized carbocations that react through more product-like transition states. To a crude first approximation, the slope ($\partial G/\partial R\text{–}X$) of a linear reaction coordinate that runs from the carbocation and nucleophile reactants to the transition state is proportional to $f_{res}/f_{R\text{-}X}$, where f_{res} is the fraction of the total resonance stabilization of the carbocation which is lost on moving to the reaction transition state, and $f_{R\text{-}X}$ is the fractional progress toward the formation of a full carbocation–nucleophile (R–X) bond. The value of $f_{res}/f_{R\text{-}X}$ will be equal to 1.0 for reactions that proceed through early transition states, but it will increase to values of greater than 1.0 as $f_{R\text{-}X}$ increases, because the loss of resonance stabilization at a carbocation is not linear with reaction progress.[30,46-48] For example, the value of f_{res} for $f_{R\text{-}X} = 0.5$ would be 0.5 for a linear correlation. This assumes a planar configuration for the reaction transition state so that the full remaining resonance stabilization can be expressed. However, movement away from sp^2 hybridization at the reaction transition state inhibits the full expression of this resonance interaction so that $f_{res} > 0.50$.[30,48]

The increasingly sharper curvature with decreasing carbocation reactivity for the reaction coordinates in Figure 6B corresponds to an increase in the Marcus intrinsic barrier for the carbocation addition reaction.[22] The increase *must* be observed for reactions which show a decrease in $p_{yy'}$, because $p_{yy'}$ is inversely proportional to the Marcus intrinsic barrier.[49]

The Effect of Nucleophile Solvation on Nucleophile Selectivity. Scheme II shows the carbocation–nucleophile combination reaction as a two-step process: (1) k_d for formation of a reactive carbocation–nucleophile encounter complex and (2) k_c for collapse of this complex to give products. The increasing chemical reactivity with increasing basicity of amine (Figure 1) and carboxylate ion nucleophiles (Figure 2) toward $XArCH(CF_3)^+$ shows that carbon–nucleophile bond formation is the rate-determining step for these reactions. Therefore, $k_c \ll k_{-d}$, so that $k_{obsd} = K_d k_c$, where $K_d = k_d/k_{-d}$ (Scheme II).

Equation 3 gives the relationship between the observed value of β_{nuc} [$(\beta_{nuc})_{obsd}$] and the values of β_{nuc} for K_d (β_d) and k_c [$(\beta_{nuc})_c$] (Scheme II). The formation of the encounter complex [$Nu^x{\cdot}{}^+(R)HCArX$] from free reactants must be accompanied by the cleavage of a solvent–nucleophile hydrogen bond in order to free

$$(\beta_{nuc})_{obsd} = \beta_d + (\beta_{nuc})_c \tag{3}$$

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(46) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960.

(47) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897–1903.

(48) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888–7900.

(49) The second-derivative structure–reactivity term $p_{yy'}$ is equal to the second derivative of the Marcus equation:

$$p_{yy'} = 2.3RT\partial^2\Delta G^*/\partial\Delta G^{\circ 2} = 2.3RT/8\Lambda \tag{4}$$

where the intrinsic barrier Λ is the activation barrier to the reaction in the absence of a thermodynamic driving force (ΔG^* when $\Delta G^\circ = 0$).

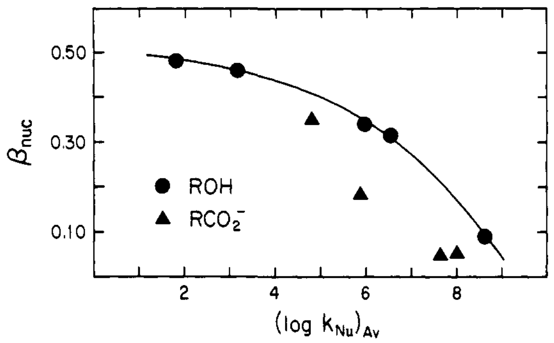

Figure 7. A plot of β_{nuc} for the reactions of alkyl alcohols (●) and carboxylate ions (▲) with $XArCH(CF_3)^+$ against log $(k_{Nu})_{av}$, the arithmetic average of the largest and smallest rate constants of the respective Brønsted correlations.

an electron pair at the nucleophile for reaction with the carbocation. Therefore, β_d will be negative for strongly solvated nucleophiles because increasing the basicity of the nucleophile will lead to a decrease in K_d, due to an increase in the strength of the solvent–nucleophile hydrogen bond.[50] The following show that $\beta_d < 0$ for the addition of amines to carbocations, so that $(\beta_{nuc})_{obsd} = 0.29$ for the addition of amines to $4\text{-}Me_2NArCH(CF_3)^+$ must be substantially smaller than $(\beta_{nuc})_c$ (eq 3).

(1) The value of $(\beta_{nuc})_{obsd} = -0.08$ for the reaction of amine nucleophiles with $4\text{-}MeSArCH(CF_3)^+$ requires $\beta_d < 0$. The reactions of amines with $4\text{-}MeSArCH(CF_3)^+$ are limited by the rate of conversion of the solvated amine to the amine–carbocation contact ion–dipole pair (k_d, Scheme II).[37]

(2) McClelland, Steenken, and co-workers have studied the reactions of amine nucleophiles with ring-substituted diaryl- and triarylmethyl carbocations. The data for these reactions can be fit to Scheme II using a value of $\beta_d = -0.2$.[10]

The limiting rate constant for the reaction of acetate ion with ring-substituted 1-phenylethyl carbocations is $k_{AcO} = 5 \times 10^8$ M^{-1} s^{-1}.[11] This is 10-fold slower than that expected for a diffusion-controlled reaction. Therefore, the rate of these reactions is limited by some step other than diffusional encounter, which probably corresponds to cleavage of a carboxylate–solvent hydrogen bond.[11]

Figure 7 shows a plot of β_{nuc} against $(\log k_{Nu})_{av}$ for the reactions of carboxylate ions and alkyl alcohols with $XArCH(CF_3)^+$, where $(\log k_{Nu})_{av}$ is the arithmetic average of the largest and smallest values of log k_{Nu} for the respective Brønsted correlations. This plot shows that the selectivity for the reactions of carboxylate ions is lower than that for the reactions of alcohols of the same reactivity. This difference in $(\beta_{nuc})_{obsd}$ for carboxylate ions and alcohols is probably due, at least in part, to a more negative value of β_d for the more strongly solvated carboxylate ions.

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Effects of Dehydroalanine on Peptide Conformations

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Abstract: The conformational preferences of dehydroalanine were examined through a combined approach of X-ray diffraction, NMR spectroscopy, and molecular modeling. Monte Carlo simulated annealing was used in conjunction with X-ray diffraction data and semiempirical quantum mechanical calculations to determine appropriate parameters for modeling dehydroalanine with the DISCOVER consistent valence force field. The two molecules in the asymmetric unit of *N*-acetyldehydroalanine *N*′-methylamide were simulated in the crystalline environment using these optimized parameters. The rms deviations between simulation and experimental data for heavy atom bond lengths, bond angles, and torsions were 0.021 Å, 1.9°, and 8.7°, respectively. The dehydroalanine-containing ring A fragment of nisin and two analogs with either L- or D-alanine substituted for dehydroalanine were synthesized and examined by NMR spectroscopy. Using distance geometry followed by conformational energy minimization with our optimized parameters, families of conformations were determined for each molecule which satisfied the observed backbone NOE, $J_{\alpha N}$ coupling constants, and temperature coefficients. Dehydroalanine adopted a roughly planar conformation, with trans orientations for the ϕ and ψ torsions, and induced an inverse γ-turn in the preceding residue. Similar effects have been observed for linear, dehydroalanine-containing peptides in solution and as crystals, suggesting that dehydroalanine exerts a powerful conformational influence independent of other constraints. The conformational preferences of the L- and D-Ala ring A analogs differed substantially from each other and from the ring A fragment.

Introduction

Dehydroalanine (Dha) is an α,β-unsaturated amino acid which plays a catalytic role in the active sites of some yeast[1] and bacterial[2] enzymes. It also occurs in a variety of peptide antibiotics of bacterial origin, including the "lantibiotics" nisin,[3] subtilin,[4] epidermin,[5] and gallidermin,[6] and more highly modified peptides

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