

Aromatic Substitution Reactions of Amines with Ring-Substituted 1-Phenyl-2,2,2-trifluoroethyl Carbocations

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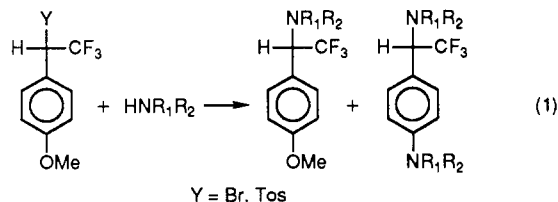
Abstract: 4-MeOArCH(CF₃)Br in 20% acetonitrile in water reacts with Me₂NH to form 4-MeOArCH(CF₃)NMe₂ and 4-Me₂NArCH(CF₃)NMe₂, with MeO(CH₂)₂NH₂ to form 4-MeOArCH(CF₃)NH(CH₂)₂OMe and 4-MeO-(CH₂)₂NArCH(CF₃)NH(CH₂)₂OMe, and with a mixture of MeO(CH₂)₂NH₂ and Me₂NH to form all the above-mentioned products plus 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe and 4-MeO(CH₂)₂NArCH(CF₃)NMe₂. Evidence is presented that the aromatic substitution products of these reactions are formed by a four-step mechanism through the following three reaction intermediates. (1) 4-MeOArCH(CF₃)⁺: 4-MeOArCH(CF₃)Br ionizes to 4-MeOArCH(CF₃)⁺, which is trapped by azide ion and solvent with a partition rate constant ratio of $k_{az}/k_s = 50 \text{ M}^{-1}$. 4-Me₂NArCH(CF₃)NMe₂ is formed by a mechanism that includes Me₂NH capture of 4-MeOArCH(CF₃)⁺ as a step, rather than by direct addition of Me₂NH to 4-MeOArCH(CF₃)Br. (2) C-4 amine adduct to 4-MeOArCH(CF₃)⁺: The carbocation 4-MeOArCH(CF₃)⁺ undergoes aromatic substitution by amines to form 4-R₁R₂NArCH(CF₃)⁺. By analogy with the mechanisms for related aromatic substitution reactions, it is proposed that the C-4 amine adduct to 4-MeOArCH(CF₃)⁺ is an intermediate of this reaction. (3) 4-R₁R₂NArCH(CF₃)⁺: The reaction of 4-MeOArCH(CF₃)Br with Me₂NH and N₃⁻ gives 4-Me₂NArCH(CF₃)N₃ from the capture of 4-Me₂NArCH(CF₃)⁺ by N₃⁻. The same product ratio 4-Me₂NArCH(CF₃)NMe₂/4-Me₂NArCH(CF₃)N₃ is observed from the reaction of 4-MeOArCH(CF₃)Br, 4-MeOArCH(CF₃)Tos, and 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) at a number of [Me₂NH]/[N₃⁻] ratios. This is classical evidence that each compound reacts through 4-Me₂NArCH(CF₃)⁺, which has been shown to form as an intermediate of the solvolysis reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate).^{5b} The reaction of 4-MeOArCH(CF₃)⁺ in the presence of MeO(CH₂)₂NH₂ gives 4-MeO(CH₂)₂NArCH(CF₃)⁺, which is trapped by Me₂NH and MeO(CH₂)₂NH₂ with the same rate constant ratio observed for the trapping of the intermediate generated in the S_N1 reaction of 4-MeO-(CH₂)₂NArCH(CF₃)N₃. The reaction of 4-MeSArCH(CF₃)Br in the presence of Me₂NH gives 4-Me₂NArCH(CF₃)NMe₂, presumably by a mechanism similar to that for the reaction of 4-MeOArCH(CF₃)Br in the presence of Me₂NH. Factors that favor nucleophilic aromatic substitution reactions at α -benzyl carbocations are discussed.

A great deal of effort has been directed toward measuring and rationalizing the effect of strongly electron-withdrawing α -substituents (e.g., cyano,¹ carbonyl,² or trifluoromethyl³⁻⁷) on the mechanism for nucleophilic substitution at saturated carbon and on the rate and equilibrium constants for carbocation formation. For the reaction of 4-XArCH(R)Y ($\sigma_X^+ \leq -0.32$), an α -CF₃ for α -CH₃ substitution causes a 10⁵–10⁹-fold decrease in the rate constant for solvolysis by rate-determining formation of a carbocation intermediate,^{3f} a comparable decrease in the stability of the carbocation relative to the neutral precursor,⁵ but little or no change in the carbocation reactivity as measured by the rate constant for its capture by solvent or acetate anion.⁵

These are interesting results, because carbocation reactivity generally shows a marked sensitivity to changing thermodynamic stability.⁸⁻¹⁰ It was proposed that the failure to observe the

destabilizing α -CF₃ inductive effect at the transition state for the capture of XArCH(CF₃)⁺ by nucleophiles was due to a second stabilizing effect of the CF₃ group, which offsets the inductive effect and increases the barrier to capture, thereby conferring an exceptional kinetic stability to these carbocations. Evidence was presented that XArCH(CF₃)⁺ carbocations are also very highly stabilized by resonance electron delocalization from the aromatic ring and that the unusually large barrier to nucleophile capture of XArCH(CF₃)⁺ is due, at least in part, to the relatively large extent of the loss of this resonance stabilization at the transition state for carbocation capture by solvent or the acetate anion.⁵

I report here a further unusual effect of the extensive electron delocalization from the aromatic ring on the reactivity of 4-MeOArCH(CF₃)⁺. The reaction of 4-MeOArCH(CF₃)Br in the presence of MeO(CH₂)₂NH₂ or Me₂NH gives the expected aliphatic substitution product 4-MeOArCH(CF₃)NR₁R₂ and also an aromatic substitution product R₁R₂NArCH(CF₃)NR₁R₂ (eq 1). Amine addition to the C-4 ring position of 4-MeOArCH-



(CF₃)⁺ is a step in the mechanism that leads to formation of aromatic substitution products. Apparently, the electron delocalization at 4-MeOArCH(CF₃)⁺ is so extensive that the C- α and the C-4 ring positions exhibit comparable reactivities with amine nucleophiles.

Aromatic substitution reactions at highly electron-deficient carbocations were first reported by Tidwell and co-workers, who found that the ethanolysis of 4-MeOArC(CF₃)₂Tos gives a 1:1 ratio of the aliphatic substitution product 4-MeOArC(CF₃)₂OEt

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and the aromatic substitution product 4-EtOArC(CF₃)₂OEt.³⁸

These reactions are remarkable because, formally, they correspond to displacement of a poor alkoxide leaving group from a substrate lacking highly electron-withdrawing substituents to activate the aromatic ring for nucleophilic attack. The ionization of 4-MeOArC(CF₃)₂Tos or 4-MeOArCH(CF₃)X to carbocations unmasks highly electron-withdrawing substituents (C(CF₃)₂⁺ or CH(CF₃)⁺) at positions para to the 4-methoxy group. These substituents so strongly activate the C-4 carbon that its chemical reactivity with nucleophilic reagents approaches the reactivity of C-α.

I present here the results of a detailed study of the mechanism for aromatic substitution reactions by amines at 4-MeOArCH(CF₃)Y, which strongly support the following 4-step reaction mechanism: (1) substrate ionization to form 4-MeOArCH(CF₃)⁺; (2) reaction between the amine and the carbocation to form a C-4 ring adduct; (3) breakdown of the C-4 adduct with expulsion of methoxide or methanol to form 4-R₁R₂NArCH(CF₃)⁺; (4) capture of 4-R₁R₂NArCH(CF₃)⁺ by a second molecule of amine to form the product.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Commercially available organic chemicals used for syntheses were reagent grade and were not further purified. Trifluoroethanol, Gold Label from Aldrich; methanol and acetonitrile, HPLC grade; and Me₂NH, a 40% aqueous solution from Aldrich were used without purification. Methoxyethylamine, Gold Label from Aldrich, was distilled. The water used for 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:^{5b} 4-MeOArCH(CF₃)Br, 4-MeOArCH(CF₃)Tos, 4-MeSArCH(CF₃)Br, and 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate).

The azide adduct 4-Me₂NArCH(CF₃)N₃ was synthesized by the reaction of 60 mg of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) with a 0.01 M solution of NaN₃ in 50 mL of 80/20 (v/v) trifluoroethanol/water. After the solution was stirred for 3 h at room temperature, the trifluoroethanol was removed under reduced pressure, and the products were extracted into ether. The ether was washed with saturated sodium bicarbonate, dried over MgSO₄, and removed in vacuo to give a brown oil of greater than 95% purity by HPLC; IR (liquid film) 2115 cm⁻¹ (N₃); ¹H NMR (CDCl₃, 200 MHz) δ 2.99 (s, 6 H, CH₃), 4.79 (q, 1 H, J = 7 Hz, CH), 6.72, 7.28 (A₂B₂, 4 H, J = 8 Hz, Ar); exact mass calcd for C₁₀H₁₁F₃N₄, 244.0937; found, 244.0935.

Product and Kinetic Analyses. Published methods were used for the HPLC analysis of the products of the reactions of 4-Me₂NArCHCF₃ derivatives and 4-MeOArCH(CF₃) derivatives and for measurement of the pseudo-first-order rate constants for the reaction of 4-MeOArCH(CF₃)Tos and 4-MeOArCH(CF₃)Br.^{5b} The experiments in 20% acetonitrile in water were at a constant ionic strength of 0.80 maintained with NaClO₄.

The reactions of 4-Me₂NArCH(CF₃)N₃ and 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) in 20% acetonitrile in water (I = 0.8, NaClO₄) were monitored by HPLC. The reaction of the latter compound was fast (t_{1/2} ~ 1 min) compared to the time required to inject a sample onto the HPLC column. Therefore, aliquots were withdrawn from the reaction mixture and quenched using a procedure that allows the relative concentrations of reactant and products present at the time of quenching to be determined by HPLC analysis. Different procedures were used for reactions in the absence and presence of Me₂NH.

(a) The reaction was run in the presence of 5 mM sodium azide to ensure a quantitative yield of the azide adduct by azide ion trapping of 4-Me₂NArCH(CF₃)⁺. At fixed reaction times, 1.0-mL aliquots were withdrawn and quenched into 0.25 mL of 40% Me₂NH in water in order to rapidly and quantitatively convert the unreacted substrate to 4-Me₂NArCH(CF₃)OH by Me₂NH addition to the 3,5-dinitrobenzoate group. The yields of the azide adduct and alcohol were then determined by HPLC analysis; the yields are proportional to the concentration of the azide adduct and unreacted substrate, respectively, present in the solution at the time of quenching. The pseudo-first-order rate constant, k_{obsd}, for the substrate reaction was calculated as the slope of a semilogarithmic plot of the decrease in the HPLC peak area for 4-Me₂NArCH(CF₃)OH with time.

(b) For the reaction in the presence of 0.08 M ([B]/[BH⁺] = 1) Me₂NH, 1.0-mL aliquots were withdrawn and mixed with 0.25 mL of 5.0 M NaN₃, and after the reaction of the remaining substrate, the products were determined by HPLC. Since the S_N1 reaction of 4-

Me₂NArCH(CF₃)(3,5-dinitrobenzoate), which occurs prior to "quenching", gives 4-Me₂NArCH(CF₃)NMe₂ and the S_N1 reaction after the addition of NaN₃ gives 4-Me₂NArCH(CF₃)N₃, the yield of 4-Me₂NArCH(CF₃)N₃ is proportional to the concentration of substrate remaining at the time of quenching. The reaction also gives a 50% yield of 4-Me₂NArCH(CF₃)OH from bimolecular addition of Me₂NH to the 3,5-dinitrobenzoate group; however, this pathway does not interfere with the determination of k_{obsd} for the disappearance of substrate, which was calculated as the slope of a semilogarithmic plot of the decrease in the HPLC peak area for 4-Me₂NArCH(CF₃)N₃ with time.

Characterization of Reaction Products. **Reaction of 1-(4-(Dimethylamino)phenyl)-2,2,2-trifluoroethyl Derivatives.** The products of the reaction of N₃⁻, Me₂NH, and MeO(CH₂)₂NH₂ with 4-Me₂NArCH(CF₃) derivatives were separated by HPLC and identified as the respective nucleophile adducts by showing that their formation was accompanied by a decrease in the yield of the other products of the reaction.^{5b}

Products from the Reaction of 4-MeOArCH(CF₃)Br and 4-MeSArCH(CF₃)Br in the Presence of Amines or the Presence of Amines and Azide. The products of the nucleophile reactions were initially identified on an analytical scale by the HPLC analysis of the products from the reaction of 0.1–1 mM substrate in 20% acetonitrile in water (I = 0.80, NaClO₄). The material for spectral analyses was obtained by the following general procedure. 4-MeOArCH(CF₃)Br (100–200 μL) was mixed with 200 mL of an aqueous solution of the amine and a small amount of HClO₄, which was added to minimize the possible formation of products by an HO⁻-catalyzed elimination of F⁻. After reaction overnight, the amine was removed in vacuo and the remaining aqueous solution extracted with ether. The ether was washed with saturated NaCl, dried with MgSO₄, and carefully removed by evaporation. The products were then dissolved in 2 mL of 80% methanol in water and separated by HPLC over a semipreparative C-18 chromatography column, eluting with solutions of methanol/water.

The specific conditions for the individual synthesis are given below:

(1) 200 μL of 4-MeOArCH(CF₃)Br, 200 mL of a 40% solution of dimethylamine in water, and 0.2 mL of concentrated HClO₄ were mixed and set overnight at 45 °C; (2) 120 μL of 4-MeOArCH(CF₃)Br, 200 mL of 65/35 (v/v) water/methoxyethylamine, and 0.2 mL of concentrated HClO₄ were mixed and set overnight at room temperature; (3) 100 μL of 4-MeOArCH(CF₃)Br and 100 mL of 60/40 (v/v) water/methoxyethylamine containing 0.05 M NaN₃ were set overnight at room temperature; (4) 50 μL of 4-MeSArCH(CF₃)Br and 40 mL of 50/50 (v/v) water/methoxyethylamine were set overnight at 50 °C.

(1a) *N,N*-Dimethyl-1-(4-methoxyphenyl)-2,2,2-trifluoroethylamine. Oil; UV (water) λ_{max} 271 nm (ε₂₇₁ 1100, ε₂₈₀ 630, ε₂₅₄ 440 M⁻¹ cm⁻¹); ¹H NMR (CDCl₃, 200 MHz) δ 2.33 (s, 6 H, N(CH₃)₂), 3.83 (s, 3 H, OCH₃), 3.91 (q, 1 H, J = 9 Hz, CH), 6.94, 7.29 (A₂B₂, 4 H, J = 8 Hz, C₆H₄); exact mass calcd for C₁₁H₁₄F₃NO, 233.1028; found, 233.1025. Anal. (C₁₁H₁₄F₃NO) C, H.

(1b) *N,N*-Dimethyl-1-(4-dimethylamino)phenyl)-2,2,2-trifluoroethylamine. Oil; UV (water) λ_{max} 255 nm (ε₂₅₅ 14 000, ε₂₅₄ 14 000, ε₂₈₀ 3200 M⁻¹ cm⁻¹); ¹H NMR (CDCl₃, 200 MHz) δ 2.32 (s, 6 H, CHNMe₂), 2.98 (s, 6 H, ArN(CH₃)₂), 3.86 (q, 1 H, J = 9 Hz, CH), 6.71, 7.29 (A₂B₂, 4 H, J = 8 Hz, C₆H₄); exact mass calcd for C₁₂H₁₇F₃N₂, 246.1344; found, 246.1344. Anal. (C₁₂H₁₇F₃N₂) C, H.

(2a) *N*-(Methoxyethyl)-1-(4-((methoxyethyl)amino)phenyl)-2,2,2-trifluoroethylamine. Oil, UV (water) λ_{max} 248 nm (ε₂₄₈ 14 000, ε₂₅₄ 12 000, ε₂₈₀ 1500 M⁻¹ cm⁻¹); ¹H NMR (CDCl₃, 400 MHz) δ 2.73 (br t, 2 H, CH₂NHCH), 3.29 (br t, 2 H, CH₂NHAr), 3.32, 3.39 (2 s, 6 H, OCH₃), 3.46 (m, 2 H, CH₂CH₂NHCH), 3.61 (br t, 2 H, CH₂CH₂NHAr), 4.02 (q, J = 7 Hz, CH), 6.62, 7.20, (A₂B₂, 4 H, C₆H₄); exact mass calcd for C₁₄H₂₁F₃N₂O₂, 306.1555; found, 306.1565. Anal. (C₁₄H₂₁F₃N₂O₂) C, H, N.

(2b) *N*-(Methoxyethyl)-1-(4-methoxyphenyl)-2,2,2-trifluoroethylamine. Oil, UV (water) λ_{max} 271 nm (ε₂₇₁ 1100, ε₂₅₄ 420, ε₂₈₀ 700 M⁻¹ cm⁻¹); ¹H NMR (CDCl₃, 400 MHz) δ 2.72 (br t, 2 H, CH₂N), 3.33 (s, 3 H, CH₃OCH₂), 3.47 (m, 2 H, CH₂O), 3.82 (s, 3 H, CH₃OAr), 4.10 (q, J = 9 Hz, 1 H, CH), 6.91, 7.33, (A₂B₂, 4 H, J = 7 Hz, C₆H₄); exact mass calcd for C₁₂H₁₆F₃NO₂, 263.1133; found, 263.1132. Anal. (C₁₂H₁₆F₃NO₂) C, H, N.

(3) 1-(4-((Methoxyethyl)amino)phenyl)-2,2,2-trifluoroethyl Azide. Oil, UV (water) λ_{max} 253 nm; ¹H NMR (CDCl₃, 400 MHz) δ 3.24 (br t, 2 H, CH₂NH), 3.33 (s, 3 H, CH₃O), 3.55, (br t, 2 H, MeOCH₂), 4.71 (q, J = 7 Hz, 1 H, CH), 6.57, 7.15 (A₂B₂, 4 H, J = 9 Hz); exact mass, calcd for C₁₁H₁₃F₃N₄O, 274.1041; found, 274.1042.

(4) *N*-(Methoxyethyl)-1-(4-(thiomethyl)phenyl)-2,2,2-trifluoroethylamine. Oil, UV (water) λ_{max} 256 nm (ε₂₅₆ 15 000, ε₂₅₄ 14 500 M⁻¹ cm⁻¹); ¹H NMR (CDCl₃, 200 MHz) δ 2.49 (s, 3 H, SCH₃), 2.72 (m, 2 H, CH₂N), 3.33 (s, 3 H, OCH₃), 3.48 (m, 2 H, CH₂O), 4.12 (q, 1 H, J = 7 Hz, CH), 7.3 (m, 4 H, C₆H₄); exact mass calcd for C₁₂H₁₆F₃NOS, 279.0904; found, 279.0905.

Reaction of 1-(4-Methoxyphenyl)-2,2,2-Trifluoroethyl Bromide in the Presence of a Mixture of Dimethylamine and Methoxyethylamine. HPLC analysis of the products from the reaction in 20% acetonitrile in water ($I = 0.80$, NaClO_4) shows a total of four product peaks from the amine reactions, which elute at the same position as the products from the reaction of 4-MeOArCH(CF₃)Br in the presence of the individual amines: 4-MeOArCH(CF₃)NMe₂, 4-MeOArCH(CF₃)NH(CH₂)₂OMe, 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe, and 4-Me₂NArCH(CF₃)NMe₂. However, the relative peak areas for the products eluting at the positions of 4-MeOArCH(CF₃)NMe₂ and 4-MeOArCH(CF₃)NH(CH₂)₂OMe are up to 30-fold larger than observed for the substrate reaction in the presence of only Me₂NH or MeO(CH₂)₂NH₂, showing that each of these peaks contains a second product from the combined reaction of the two amines. This is confirmed by the UV spectra for these peaks, which are aniline-like at neutral pH ($\lambda_{\text{max}} \sim 250$ nm) and anisole-like in acid ($\lambda_{\text{max}} \sim 270$ nm), where the aniline ring is protonated.

The two new compounds were identified as 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂ (coeluting with 4-MeOArCH(CF₃)NH(CH₂)₂OMe) and 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe (coeluting with 4-MeOArCH(CF₃)NMe₂) by comparison of their HPLC retention times with standards prepared by the nucleophilic substitution reactions of 4-MeO(CH₂)₂NHArCH(CF₃)N₃ or 4-Me₂NArCH(CF₃)N₃ with the appropriate amine.

The peak areas were determined in an experiment in which the total concentration of Me₂NH and MeO(CH₂)₂NH₂ was held constant at 0.80 M and the ratio [Me₂NH]/[MeO(CH₂)₂NH₂] varied. The relative contributions of 4-MeOArCH(CF₃)NMe₂ or 4-MeOArCH(CF₃)NH(CH₂)₂OMe ([area]_{aniline}) to the total peak area for the anisole/aniline mixtures were calculated by using eq 2, where [area]_{ROH} is the observed

$$[\text{area}]_{\text{aniline}} = [\text{area}]_{\text{ROH}} [\text{R}_1\text{R}_2\text{NH}] (k_{\text{C-}\alpha}/k_s) \quad (2)$$

peak area for the water adduct (4-MeOArCH(CF₃)OH) and $k_{\text{C-}\alpha}/k_s$ (M⁻¹) is the rate constant ratio for 4-MeOArCH(CF₃)⁺ partitioning between C- α capture by water and amine, calculated from the product ratio observed for the reaction in the presence of 0.80 M single amine. It is assumed that $k_{\text{C-}\alpha}/k_s$ does not change for the reaction with the mixtures of two amines. General base catalysis of solvent addition by the two amines, which might cause the observed value of k_s to change,¹¹ is at best only a minor reaction (in preparation), and the apparent catalysis by 0.80 M dimethylamine is only slightly greater than by 0.80 M methoxyethylamine. No attempt was made to correct for differences in general base catalysis by the two amines, because the corrections would have been small relative to the experimental error in the peak areas for the mixture of aniline and anisole derivatives.

The value of [area]_{aniline} for 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe or 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂ was calculated as the difference between the total peak area for the mixture and [area]_{aniline}. The aniline derivatives constitute between 50% and 97% of the area of the mixture, depending on [Me₂NH]/[MeO(CH₂)₂NH₂].

Calculation of Nucleophilic Selectivities. Rate constant ratios for nucleophile reactions with XArCH(CF₃)⁺ were calculated by one of two methods.

(1) The rate constant ratios were calculated from product ratios using eq 3 where [area]_{RNU1}/[area]_{RNU2} is the ratio of the integrated peak areas from HPLC analysis, $\epsilon_{\text{RNU2}}/\epsilon_{\text{RNU1}}$ is the ratio of the extinction coefficients for the two products, and [Nu2]/[Nu1] is the ratio of the concentrations of the two nucleophiles.

$$k_{\text{Nu1}}/k_{\text{Nu2}} = \frac{\epsilon_{\text{RNU2}}[\text{area}]_{\text{RNU1}}[\text{Nu2}]}{\epsilon_{\text{RNU1}}[\text{area}]_{\text{RNU2}}[\text{Nu1}]} \quad (3)$$

The extinction coefficient ratios for products with the same phenyl ring substituent were determined as described previously.^{5b} The ratios are 1.0, except for 4-Me₂NArCH(CF₃)N₃, which shows a 20% smaller ϵ_{254} than the amine adducts 4-Me₂NArCH(CF₃)NMe₂ and 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe.

When the ring substituents at two products were different, $\epsilon_{\text{RNU2}}/\epsilon_{\text{RNU1}}$ was calculated from the extinction coefficients listed under the spectral data for the respective compounds. The value of ϵ_{254} for 4-MeSArCH(CF₃)NMe₂ was not determined and is assumed to have the value of 14 500 M⁻¹ cm⁻¹ for 4-MeSArCH(CF₃)NH(CH₂)₂OMe. The errors in these rate constant ratios are estimated to be roughly $\pm 20\%$ because of a $\pm 10\%$ error in the product ratio from HPLC and a $\pm 10\%$ error in the extinction coefficient ratio.

(2) Nucleophilic selectivities for the partitioning of 4-R₁R₂NArCH(CF₃)⁺ between reaction with amines and azide were calculated from the

Table I. Rate Constant Ratios for the Partitioning of XArCH(CF₃)⁺ between the Formation of Aliphatic and Aromatic Substitution Adducts to Amine Nucleophiles^a

amine	$k_{\text{C-}\alpha}/k_{\text{C-4}}^b$	
	4-MeOArCH(CF ₃) ⁺	4-MeSArCH(CF ₃) ⁺
Me ₂ NH	1	2.5
MeO(CH ₂) ₂ NH ₂	1.5	~ 100

^a For reaction in 20% acetonitrile in water at room temperature (22 \pm 2 $^\circ\text{C}$) and constant ionic strength of 0.80, maintained with NaClO₄.

^b The ratio of the concentrations of the C- α (4-XArCH(CF₃)NR₁R₂) and C-4 (4-R₁R₂NArCH(CF₃)NR₁R₂) adducts. The ratios were calculated from HPLC data by using eq 3.

slope of a plot of f_{RNU1} against $\{f_{\text{RNU1}}([\text{Nu2}]/[\text{Nu1}])\}$ (eq 4),¹² where f_{RNU1} is the fractional yield of the nucleophile adduct determined by HPLC analysis.

$$f_{\text{RNU1}} = 1 - (k_{\text{Nu2}}/k_{\text{Nu1}})f_{\text{RNU1}}([\text{Nu2}]/[\text{Nu1}]) \quad (4)$$

Values of $k_{\text{amine}}/k_{\text{HOH}}$ for the capture of 4-MeSArCH(CF₃)⁺ by Me₂NH and MeO(CH₂)₂NH₂ decrease up to 30% as the concentration of [R₁R₂NH] is increased from 0.08 to 0.40 M. The decrease may be due to general base catalysis of the water reaction¹¹ or to a more complicated solvent effect. The limiting $k_{\text{amine}}/k_{\text{HOH}}$ value at [R₁R₂NH] = 0 M was obtained by a short extrapolation of a plot of $k_{\text{amine}}/k_{\text{HOH}}$ against [R₁R₂NH]. The extrapolated values are within 10% of the value measured at the lowest amine concentration.

Results

In 50:50 (v:v) water:trifluoroethanol and 40% methanol in water, XArCH(CF₃) derivatives ($\sigma_x^+ \leq -0.32$) react with solvent and added nucleophiles by an S_N1 mechanism through the carbocation intermediates XArCH(CF₃)⁺.^{5b} The same mechanism was observed for the reaction in 20% acetonitrile in water ($I = 0.80$, NaClO_4); 4-MeSArCH(CF₃)Br and 4-MeOArCH(CF₃)Br undergo reactions zero order in [N₃⁻] with values of $k_{\text{obsd}} = 5.5 \times 10^{-4}$ and 2.7×10^{-3} s⁻¹, respectively. Good yields of the azide adduct were obtained from both substrates, which were quantified by HPLC analyses. The product ratios gave rate constant ratios k_{az}/k_s of 205 and 50 M⁻¹, respectively, for the partitioning of 4-MeSArCH(CF₃)⁺ and 4-MeOArCH(CF₃)⁺ between capture by solvent and azide ion. There was a small decrease in k_{az}/k_s from the respective values of 400 and 95 M⁻¹ observed in 50:50 (v:v) water:trifluoroethanol.^{5b} This solvent effect is similar to that reported previously for the partitioning of XArCH(CH₃)⁺.⁹

The k_{obsd} value for the reaction of 4-MeOArCH(CF₃)Br in 20% acetonitrile in water ($I = 0.80$, NaClO_4) decreases to 1.2×10^{-3} s⁻¹ as [Me₂NH] ([B]/[BH⁺] = 1) is increased to 0.80 M. The decrease is due to the decreasing solvent polarity and the large sensitivity of the rate constants for S_N1 solvolysis to this change.^{3f,13}

The pseudo-first-order rate constant, k_{obsd} , for the S_N1 reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) at 25 $^\circ\text{C}$ in 20% acetonitrile in water ($I = 0.80$, NaClO_4) and in the presence of 5 mM NaN₃ is 0.93×10^{-2} s⁻¹. The reaction gave a quantitative yield of the azide adduct 4-NMe₂NArCH(CF₃)N₃. The pseudo-first-order rate constant increased to 1.9×10^{-2} s⁻¹ for the substrate reaction in the presence of 0.08 M dimethylamine ([B]/[BH⁺] = 1). This reaction gave a 50% yield of the alcohol 4-Me₂NArCH(CF₃)OH and a 50% yield of the amine adduct 4-Me₂NArCH(CF₃)NMe₂. These results show that there is a reaction first order in [Me₂NH] that produces 4-Me₂NArCH(CF₃)OH. The reaction is probably bimolecular addition of dimethylamine to the dinitrobenzoate group.

Two nucleophile adducts were isolated from the reaction of 4-MeOArCH(CF₃)Br in the presence of Me₂NH, which were identified as 4-Me₂NArCH(CF₃)NMe₂ and 4-MeOArCH(CF₃)NMe₂ by NMR, UV, and mass spectroscopic analyses. The product rate constant ratio $k_{\text{DMA}}/k'_{\text{DMA}}$ (Table I) for the reaction of 4-MeOArCH(CF₃)Br to give aliphatic (k_{DMA}) and aromatic (k'_{DMA}) substitution products was calculated by using eq 3. It

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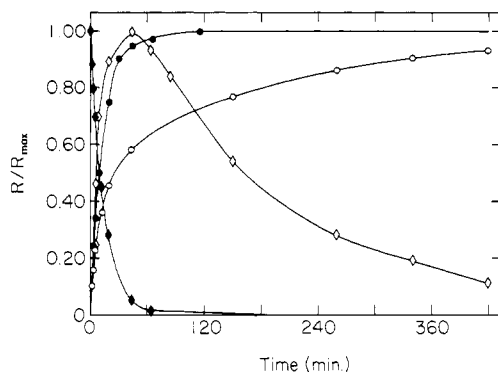


Figure 1. Change in substrate and product concentration with time for the reaction of 4-MeOArCH(CF₃)Br at 25 °C with 0.76 M dimethylamine ([B]/[BH⁺] = 1.0) and 0.04 M NaN₃ (*I* = 0.80, NaClO₄). The yields are reported as *R/R*_{max}, where *R* is the HPLC peak area of the reactant or product isolated at the given time from a constant volume of the reaction mixture and *R*_{max} is the maximum peak area observed during the course of the reaction: (♦) 4-MeOArCH(CF₃)Br, (●) 4-MeOArCH(CF₃)OH, (○) 4-Me₂NArCH(CF₃)NMe₂, (◇) 4-Me₂NArCH(CF₃)N₃.

will be shown in the Discussion section that $k_{\text{DMA}}/k'_{\text{DMA}}$ is the rate constant ratio for partitioning of 4-MeOArCH(CF₃)⁺ between trapping by dimethylamine at the C-α and the C-4 ring positions.

There is no evidence that any of the reactions of Me₂NH are general or specific acid or base catalyzed at pHs close to the p*K*_a for Me₂NH. The product yields from the reaction of 4-MeOArCH(CF₃)Br at two different Me₂NH buffer ratios ([B]/[BH⁺] = 1, 9) depend only on the concentration of the basic form of the amine and not on the pH or the concentration of the conjugate acid.

The reaction of 4-MeOArCH(CF₃)Br in the presence of MeO(CH₂)₂NH₂ gave 4-MeOArCH(CF₃)NH(CH₂)₂OMe and 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe, and the reaction of 4-MeSArCH(CF₃)Br in the presence of Me₂NH gave 4-Me₂NArCH(CF₃)NMe₂ and 4-MeSArCH(CF₃)NMe₂. Partition rate constant ratios for the formation of aliphatic and aromatic substitution products from XArCH(CF₃)⁺ are reported in Table I.

I previously reported that 4-MeSArCH(CF₃)NH(CH₂)₂OMe is the only product isolated from the reaction of 4-MeSArCH(CF₃)Br in the presence of MeO(CH₂)₂NH₂.⁶ When this experiment was repeated at a higher substrate concentration, a second peak was observed with ca. 1% of the area of the major product (4-MeSArCH(CF₃)NH(CH₂)₂OMe) and the same HPLC retention time as 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe. The rate constant ratio $k_{\text{MEA}}/k'_{\text{MEA}}$ listed in Table I for the reaction of 4-MeSArCH(CF₃)⁺ is calculated assuming that this minor peak is the aromatic substitution product. It is possible that the reactions of other amines with 4-MeSArCH(CF₃)⁺ may have also given low yields of aromatic substitution products. The occurrence of aromatic substitution reactions complicates, but does not change, the conclusions drawn in the previous study⁶ of the reactions of amines with 4-MeSArCH(CF₃)⁺ (manuscript in preparation).

The large difference in the extinction coefficients of aniline and anisole derivatives at 254 nm ($\epsilon(\text{Me}_2\text{NArCH}(\text{CF}_3)\text{NMe}_2)/\epsilon(4\text{-MeOArCH}(\text{CF}_3)\text{NMe}_2) = 32$) makes it possible to detect, by HPLC analysis at this wavelength, much lower yields of aromatic substitution adducts than is possible when the products are monitored at 280 nm. No aromatic substitution adducts were detected at 280 nm from the reaction of CF₃CH₂NH₂ with 4-MeOArCH(CF₃)Br.⁶ When this experiment was repeated in the present work and the products monitored at 254 nm, a second product peak was detected with an area 1.2-fold greater than that for 4-MeOArCH(CF₃)NHCH₂CF₃. This product was not characterized, but by analogy with the reactions of 4-MeOArCH(CF₃)Br with Me₂NH and MeO(CH₂)₂NH₂, it is probably the aniline derivative CF₃CH₂NHArCH(CF₃)NHC-H₂CF₃.

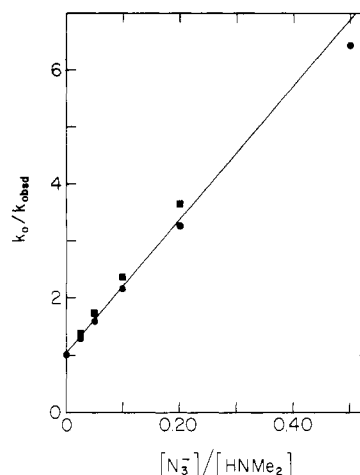


Figure 2. Effect of changing $[\text{N}_3^-]/[\text{Me}_2\text{NH}]$ on the rate constant ratio k_0/k_{obsd} for the reaction of 4-Me₂NArCH(CF₃)N₃, where k_0 is the observed rate constant at $[\text{N}_3^-] = 0.0$ M. The azide adduct is generated in situ, and the decrease in its concentration with time is followed by HPLC. The squares are for the reaction of 4-Me₂NArCH(CF₃)N₃ generated in situ from the reaction between 4-MeOArCH(CF₃)Br, 0.76 M dimethylamine ([B]/[BH⁺] = 1.0), and increasing concentrations of NaN₃ (*I* = 0.80, NaClO₄). The circles are for the reaction of 4-Me₂NArCH(CF₃)N₃ generated in situ from the reaction between 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate), 0.08 M dimethylamine ([B]/[BH⁺] = 1.0), and increasing concentrations of NaN₃ (*I* = 0.80, NaClO₄). The k_0 values were determined using chemically synthesized 4-Me₂NArCH(CF₃)N₃.

The reaction of 4-MeOArCH(CF₃)Br was studied in the presence of amine plus N₃⁻, because it was reasoned that if the aromatic substitution products R₁R₂NHArCH(CF₃)NHR₁R₂ form by amine capture of R₁R₂NHArCH(CF₃)⁺, then it should be possible to trap this carbocation with azide ion.

This prediction is confirmed in Figure 1, which shows the time course for the reaction of 4-MeOArCH(CF₃)Br at 25 °C in the presence of 0.76 M dimethylamine ([B]/[BH⁺] = 1.0) plus 0.04 M NaN₃ (*I* = 0.80, NaClO₄). All of the products from the reaction of 4-MeOArCH(CF₃)Br with the individual nucleophiles are observed, plus a new product (◇, Figure 1) which reaches a maximum level after about 45 min of reaction and then slowly reacts to form 4-Me₂NArCH(CF₃)NMe₂ (○, Figure 1). No attempt was made to isolate and characterize the unstable product because of its low yield.^{14a} It was identified as 4-Me₂NArCH(CF₃)N₃ by a comparison of its HPLC retention time and chemical reactivity with that of a standard prepared by the reaction of azide anion with 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate).

Figure 2 compares the chemical reactivity of the product of the reaction of 4-MeOArCH(CF₃)Br in the presence 0.76 M Me₂NH, ([B]/[BH⁺] = 1.0) and increasing $[\text{N}_3^-]$ (■) with the reactivity of 4-Me₂NArCH(CF₃)N₃ formed in situ from the reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) in the presence of 0.08 M Me₂NH ([B]/[BH⁺] = 1) and increasing $[\text{N}_3^-]$ (●). Note that 4-Me₂NArCH(CF₃)N₃ is much less reactive than either 4-MeOArCH(CF₃)Br or 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate).

The values for k_0 in Figure 2 (k_{obsd} at $[\text{N}_3^-] = 0$ M), measured with chemically synthesized 4-NMe₂ArCH(CF₃)N₃, are $2.3 \times 10^{-4} \text{ s}^{-1}$ under the reaction conditions used to generate 4-Me₂NArCH(CF₃)N₃ from 4-MeOArCH(CF₃)Br (0.76 M

(14) (a) At azide ion concentrations that trap a significant fraction of 4-Me₂NArCH(CF₃)⁺, only a small amount of the carbocation is formed from the reaction of 4-MeOArCH(CF₃)⁺, because azide ion is very effective at trapping 4-MeOArCH(CF₃)⁺, a precursor to 4-Me₂NArCH(CF₃)⁺. Therefore, it is not possible to obtain good yields of 4-Me₂NArCH(CF₃)N₃. (b) The yield of 4-MeO(CH₂)₂NHArCH(CF₃)N₃ in this experiment is much better than the yield of 4-Me₂NArCH(CF₃)N₃ from the reaction of 4-MeOArCH(CF₃)Br in the presence of Me₂NH and N₃⁻, because the efficiency of N₃⁻ trapping of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ in the presence of MeO(CH₂)₂NH₂ ($k_{\text{az}}/k_{\text{MEA}} = 90$, Table II) is better than for N₃⁻ trapping of 4-Me₂NArCH(CF₃)⁺ in the presence of Me₂NH ($k_{\text{az}}/k_{\text{DMA}} = 11$, Table II).

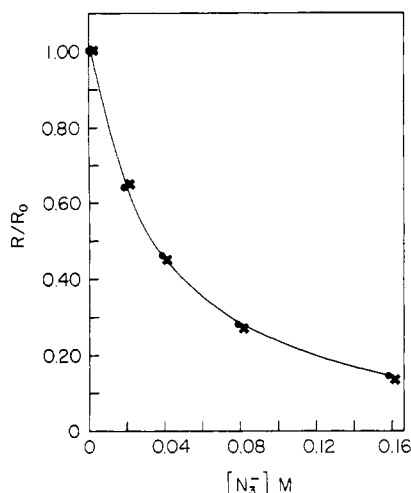
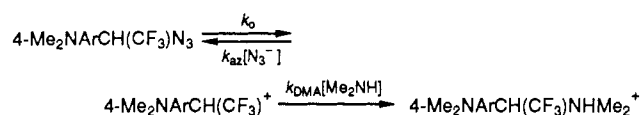


Figure 3. Effect of increasing $[N_3^-]$ on the yield of aliphatic and aromatic substitution products from the reaction of 4-MeOArCH(CF₃)Br with 0.76 M Me₂NH ($[B]/[BH^+] = 1.0$). The yields are reported as R/R_0 , where R is the HPLC peak area of products isolated from a constant volume of the reaction mixture and R_0 is the yield at $[N_3^-] = 0.0$ M; (●) aliphatic substitution products 4-MeOArCH(CF₃)NMe₂ and 4-MeOArCH(CF₃)OH; (×) aromatic substitution products 4-Me₂NArCH(CF₃)NMe₂ and 4-Me₂NArCH(CF₃)N₃.

Scheme 1



Me₂NH, $[B]/[BH^+] = 1.0$, and $3.3 \times 10^{-4} \text{ s}^{-1}$ under the reaction conditions used to generate 4-Me₂NArCH(CF₃)N₃ from 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) (0.08 M Me₂NH, $[B]/[BH^+] = 1$). Different [Me₂NH]'s were used in the two sets of experiments, because a large concentration was required to generate measurable amounts of 4-Me₂NArCH(CF₃)N₃ from 4-MeOArCH(CF₃)Br, while a lower concentration was used in the reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) in order to reduce Me₂NH addition to the 3,5-dinitrobenzoate group to an acceptable level (50% of reaction products, see above). The reaction of chemically synthesized 4-Me₂NArCH(CF₃)N₃ gave 4-Me₂NArCH(CF₃)NMe₂ as the only detectable product, showing that dimethylamine-catalyzed addition of water to 4-Me₂NArCH(CF₃)⁺ is not a significant reaction.

The data in Figure 2 show a good fit to eq 5, which is derived for a reaction (Scheme 1) that shows an azide common-ion effect. The k_0/k_{obsd} values obtained at the same $[N_3^-]/[\text{Me}_2\text{NH}]$ are the same for the two sets of data within an experimental error of $\pm 10\%$, and all of the data show a reasonable fit to a single line with slope $k_{\text{az}}/k_{\text{DMA}} = 12.0$ (eq 5). It is concluded, therefore,

$$k_0/k_{\text{obsd}} = 1 + (k_{\text{az}}/k_{\text{DMA}})([N_3^-]/[\text{HMe}_2]) \quad (5)$$

that Me₂NArCH(CF₃)N₃ is the unstable product formed from the reaction of 4-MeOArCH(CF₃)Br in the presence of dimethylamine and azide ion.

Figure 3 shows the effect of increasing [NaN₃] on the yield of aliphatic substitution products [4-MeOArCH(CF₃)OH + 4-MeOArCH(CF₃)N₃] (●) and aromatic substitution products [4-Me₂NArCH(CF₃)NMe₂ + 4-Me₂NArCH(CF₃)N₃] (×) from the reaction of 4-MeOArCH(CF₃)Br in the presence of 0.76 M Me₂NH ($[B]/[BH^+] = 1.0$).

The reaction of 4-MeOArCH(CF₃)Tos in the presence of Me₂NH and/or N₃⁻ produces all of the products observed from the reaction of 4-MeOArCH(CF₃)Br, plus an additional minor product. The area for this product peak (A_{254} , nm) observed for the reaction of 4-MeOArCH(CF₃)Tos in the presence of 0.80 M dimethylamine ($[B]/[BH^+] = 1.0$) is 12% of the total area of all product peaks. This minor product was not identified.

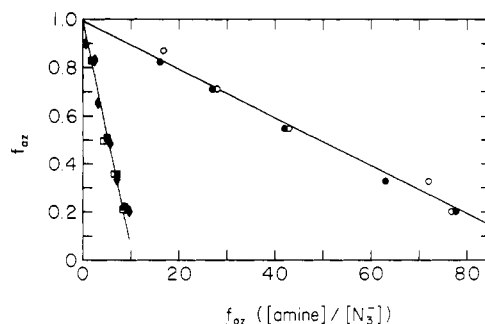


Figure 4. Dependence of the fraction of 4-Me₂NArCH(CF₃)⁺ or 4-MeO(CH₂)₂NHArCH(CF₃)⁺ trapped by azide anion (f_{az}) on $[\text{amine}]/[N_3^-]$ for the reaction in 20% acetonitrile in water ($I = 0.80$, NaClO₄). The steeper line is for 4-Me₂NArCH(CF₃)⁺ partitioning between capture by N₃⁻ and Me₂NH: (■) 4-Me₂NArCH(CF₃)⁺ generated by the reaction of 4-MeOArCH(CF₃)Br with 0.76 M [Me₂NH] ($[B]/[BH^+] = 1.0$); (□) 4-Me₂NArCH(CF₃)⁺ generated by the reaction of 4-MeOArCH(CF₃)Tos with 0.76 M [Me₂NH] ($[B]/[BH^+] = 1.0$); (◆) 4-Me₂NArCH(CF₃)⁺ generated directly from the reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) in the presence of 0.08 M Me₂NH ($[B]/[BH^+] = 1.0$). The more shallow line is for 4-MeO(CH₂)₂NHArCH(CF₃)⁺ partitioning between capture by N₃⁻ and MeO(CH₂)₂NH₂: (○) 4-MeO(CH₂)₂NHArCH(CF₃)⁺ generated by the reaction of 4-MeOArCH(CF₃)Br with 0.38 M methoxyethylamine; (●) 4-MeO(CH₂)₂NHArCH(CF₃)⁺ generated by the reaction of 4-MeOArCH(CF₃)Br with 0.19 M methoxyethylamine.

If the reaction of 4-MeOArCH(CF₃)Br or 4-MeOArCH(CF₃)Tos in the presence of Me₂NH produces 4-Me₂NArCH(CF₃)⁺, then the further reactions of this intermediate must give the same products as the S_N1 reactions of nucleophiles with 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate), which ionizes directly to form 4-Me₂NArCH(CF₃)⁺.^{5b} Figure 4 compares the yield of 4-Me₂NArCH(CF₃)N₃ expressed as f_{az} , the fraction of the products from the trapping of 4-Me₂NArCH(CF₃)⁺ (4-Me₂NArCH(CF₃)N₃ plus 4-Me₂NArCH(CF₃)NMe₂), for the reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate) (◆), 4-MeOArCH(CF₃)Br (■), and 4-MeOArCH(CF₃)Tos (□) in the presence of azide ion and Me₂NH. The f_{az} values for these reactions were determined after a 10-min reaction time, before there is significant breakdown of 4-Me₂NArCH(CF₃)N₃. The yield of 4-Me₂NArCH(CF₃)OH is not included in the calculation of f_{az} for the reaction of 4-Me₂NArCH(CF₃)(3,5-dinitrobenzoate), because the alcohol is not a product of the trapping of 4-Me₂NArCH(CF₃)⁺ but rather forms by a bimolecular reaction of the substrate with Me₂NH (see above).

The data in Figure 4 for the reaction of all three substrates show a good fit to eq 4 and define a single line with a slope $k_{\text{DMA}}/k_{\text{az}} = 1/11.0$, as required if the reaction of each substrate proceeds through the common intermediate 4-Me₂NArCH(CF₃)⁺. There is good agreement between $k_{\text{az}}/k_{\text{DMA}} = 11$ from Figure 4 and the value of 12 obtained from the analysis of the azide common-ion effect on the reaction of 4-Me₂NArCH(CF₃)N₃ (Scheme 1 and Figure 2).

The reaction of 4-MeOArCH(CF₃)Br with a mixture of MeO(CH₂)₂NH₂ and N₃⁻ gives 4-MeO(CH₂)₂NHArCH(CF₃)N₃, the product of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ capture by N₃⁻.^{14b} At 25 °C, in 20% acetonitrile in water containing 0.08 M MeO(CH₂)₂NH₂ (free base, $I = 0.80$, NaClO₄), 4-MeO(CH₂)₂NHArCH(CF₃)N₃ is converted to 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe with a pseudo-first-order rate constant $k_{\text{obsd}} = 7.3 \times 10^{-5} \text{ s}^{-1}$.

The yield of 4-MeO(CH₂)₂NHArCH(CF₃)N₃ from the reaction of 4-MeOArCH(CF₃)Br (f_{az}) is plotted against $f_{\text{az}} - ([\text{MEA}]/[N_3^-])$ in Figure 4, where f_{az} is the yield expressed as the fraction of the products from the trapping of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ (4-MeO(CH₂)₂NHArCH(CF₃)N₃ plus 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe). The reactions were in unbuffered solutions of 0.19 M MeO(CH₂)₂NH₂ (●) or 0.38 M MeO(CH₂)₂NH₂ (○). The slope of the line in Figure 4 is $k_{\text{MEA}}/k_{\text{az}} = 1/90$ (eq 4), where $k_{\text{MEA}}/k_{\text{az}}$ is the rate constant

ratio for the partitioning of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ between capture by N₃⁻ and MeO(CH₂)₂NH₂.

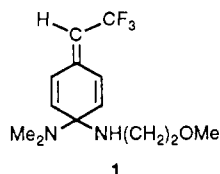
The reaction of 4-MeOArCH(CF₃)Br with unbuffered mixtures of Me₂NH and MeO(CH₂)₂NH₂ gives 4-Me₂NArCH(CF₃)⁺ and 4-MeO(CH₂)₂NHArCH(CF₃)⁺, which are trapped by the amines to produce two compounds, 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe and 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂, not formed from reactions in the presence of the individual amines.

Rate constant ratios for the partitioning of 4-Me₂NArCH(CF₃)⁺ and 4-MeO(CH₂)₂NHArCH(CF₃)⁺ between capture by Me₂NH and MeO(CH₂)₂NH₂ were calculated from the product yields from the reaction of 4-MeOArCH(CF₃)Br in the presence of dimethylamine and methoxyethylamine at a fixed total amine concentration of 0.80 M and changing [MeO(CH₂)₂NH₂]/[Me₂NH] (Figure 5). In Figure 5, *f*_{DMA} is the yield of the dimethylamine adduct expressed as either the fraction of the products from the trapping of 4-Me₂NArCH(CF₃)⁺ (Figure 5A, ▲) or from the trapping of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ (Figure 5B, ●).

Also shown in Figure 5 are data for Me₂NH and MeO(CH₂)₂NH₂ trapping of 4-Me₂NArCH(CF₃)⁺ (Figure 5A, Δ) and 4-MeO(CH₂)₂NHArCH(CF₃)⁺ (Figure 5B, ○) generated directly by the reactions of 4-Me₂NArCH(CF₃)N₃ and 4-MeO(CH₂)₂NHArCH(CF₃)N₃, respectively. These reactions were also carried out in unbuffered solutions at a constant total amine concentration of 0.80 M.

The data for the open and closed symbols in Figure 5A show a good fit to a single line, consistent with the conclusion that the reaction of Me₂NH with 4-MeOArCH(CF₃)Br gives the same intermediate (4-Me₂NArCH(CF₃)⁺) that forms in the direct solvolysis reaction of 4-Me₂ArCH(CF₃)N₃. A rate constant ratio *k*_{DMA}/*k*_{MEA} = 6.6 (eq 4) is calculated from the slope of the line in Figure 5A. While the fit of the two sets of data in Figure 5B is not as good as in Figure 5A, Figure 5B also supports the conclusion that the two substrates react through a common intermediate (4-MeO(CH₂)₂NHArCH(CF₃)⁺). The slopes of the lines through the solid and open symbols give *k*_{DMA}/*k*_{MEA} values of 8.2 and 6.5, respectively, and the slope of the line through all of the points gives *k*_{DMA}/*k*_{MEA} = 7.4. It is unlikely that the difference in the slopes of the lines for the two sets of data is significant. Product rate constant ratios are normally accurate to ±10%; however, the error in the closed symbols is larger because of the indirect method used to estimate the yield of 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂ from the reaction of 4-MeOArCH(CF₃)Br (see Experimental Section).

The interconversions of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ and 4-Me₂NArCH(CF₃)⁺ (generated from reaction of the respective azide derivatives) by aromatic substitution of methoxyethylamine or dimethylamine are not important reactions in unbuffered solutions containing the two amines. The only detectable products of the reaction of 4-Me₂NArCH(CF₃)⁺ with MeO(CH₂)₂NH₂ and the reaction of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ with Me₂NH are 4-Me₂NArCH(CF₃)NH(CH₂)₂OMe and 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂, respectively. A mixture of 4-MeO(CH₂)₂NHArCH(CF₃)NMe₂ and 4-Me₂NArCH(CF₃)NMe₂ would have been isolated if Me₂NH had been added to the C-4 ring position of 4-MeO(CH₂)₂NHArCH(CF₃)⁺ to form the ring adduct **1**, provided the breakdown of **1** favors the formation of



4-Me₂NArCH(CF₃)⁺ instead of regeneration of the more unstable carbocation 4-MeO(CH₂)₂NHArCH(CF₃)⁺.¹⁵ If **1** were to form

(15) The rate constant for the reaction of an azide derivative to form 4-Me₂NArCH(CF₃)⁺ is 4-fold larger than for the reaction to form 4-MeO(CH₂)₂NHArCH(CF₃)⁺, showing that there is a modest difference in the stabilities of the two carbocations.

Table II. Dimensionless Ratios of Second-Order Rate Constants for Nucleophile Addition to XArCH(CF₃)⁺ in 20% Acetonitrile in Water^a

	nucleophile		
	HOH	Me ₂ NH	MeO(CH ₂) ₂ NH ₂
4-MeOArCH(CF ₃) ⁺			
<i>k</i> _{az} / <i>k</i> _{C-α} ^b	2200 ^c	70 ^d	50 ^e
<i>k</i> _{az} / <i>k</i> _{C-4} ^f	<i>g</i>	70 ^h	75 ^h
<i>k</i> _{az} /(<i>k</i> _{C-α} + <i>k</i> _{C-4})	<i>g</i>	35	30
4-MeSArCH(CF ₃) ⁺			
<i>k</i> _{az} / <i>k</i> _{C-α} ^b	9300 ^c	60 ⁱ	50 ^j
<i>k</i> _{az} / <i>k</i> _{C-4} ^f	<i>g</i>	160 ^h	~5000 ^h
<i>k</i> _{az} /(<i>k</i> _{C-α} + <i>k</i> _{C-4})	<i>g</i>	45	50
4-MeO(CH ₂) ₂ NHArCH(CF ₃) ⁺ ^o			
<i>k</i> _{az} / <i>k</i> _{amine} ^b		12 ^k	90 ^l
4-Me ₂ NArCH(CF ₃) ⁺ ^o			
<i>k</i> _{az} / <i>k</i> _{amine} ^b		11.0 ^m	70 ⁿ

^a At room temperature (22 ± 2 °C) and constant ionic strength of 0.80, maintained with NaClO₄. ^b The rate constant ratio for carbocation partitioning between azide and nucleophile addition at C-α. ^c Average of values obtained for the reaction of the respective bromide at five different azide concentrations. ^d The average of values obtained at 0.02 M NaN₃ and two dimethylamine concentrations (0.36 and 0.72 M, [B]/[BH⁺] = 1). ^e The average of values obtained at 0.016 M NaN₃ and five different [MeO(CH₂)₂NH₂] (free base) between 0.16 and 0.80 M. ^f The rate constant ratio for carbocation partitioning between the addition of azide at C-α and the addition of nucleophile at the C-4 ring position. ^g No product from the nucleophile addition reaction to the C-4 ring carbon was observed. ^h Calculated from *k*_{az}/*k*_{C-α} (this table) and *k*_{C-α}/*k*_{C-4} in Table I. ⁱ Calculated from the value for *k*_{az}/*k*_{HOH} for the water reaction (this table) and *k*_{C-α}/*k*_{HOH} = 150, which is the *y* intercept of a plot of *k*_{C-α}/*k*_{HOH} against [Me₂NH], for the reaction at five different [Me₂NH] from 0.16 to 0.80 M ([B]/[BH⁺] = 1). ^j Calculated from the value for *k*_{az}/*k*_{HOH} for the water reaction (this table) and *k*_{C-α}/*k*_{HOH} = 180, which is the *y* intercept of a plot of *k*_{C-α}/*k*_{HOH} against [MeO(CH₂)₂NH₂], for the reaction at five different [MeO(CH₂)₂NH₂] from 0.16 to 0.80 M ([B]/[BH⁺] = 1.0). ^k Calculated from *k*_{az}/*k*_{MEA} = 90 (this table) and *k*_{DMA}/*k*_{MEA} = 7.4 (the slope of the line in Figure 5B). ^l The slope of the line (open and closed circles) in Figure 4. ^m The slope of the line (diamonds, open and closed squares) in Figure 4. ⁿ Calculated from *k*_{az}/*k*_{DMA} = 11 (this table) and *k*_{DMA}/*k*_{MEA} = 6.6 (the slope of the line in Figure 5A). ^o No products from the reaction of water, or the reaction of amines at the C-4 ring position, were observed for this carbocation.

Table III. Estimated Rate Constants for the Reactions of Amines with XArCH(CF₃)⁺ in 20% Acetonitrile in Water^{a,b}

	nucleophile		
	HOH, M ⁻¹ s ⁻¹	Me ₂ NH, M ⁻¹ s ⁻¹	MeO(CH ₂) ₂ NH ₂ , M ⁻¹ s ⁻¹
4-MeOArCH(CF ₃) ⁺			
<i>k</i> _{C-α} ^c	2.3 × 10 ⁶	7 × 10 ⁷	1.0 × 10 ⁸
<i>k</i> _{C-4} ^d		7 × 10 ⁷	6.7 × 10 ⁷
4-MeSArCH(CF ₃) ⁺			
<i>k</i> _{C-α} ^c	5.4 × 10 ⁵	8 × 10 ⁷	1.0 × 10 ⁸
<i>k</i> _{C-4} ^d		3.1 × 10 ⁷	~1.0 × 10 ⁶

^a At room temperature (22 ± 2 °C) and constant ionic strength of 0.80, maintained with NaClO₄. ^b The rate constants were calculated from the azide selectivities reported in Table II and a value of 5 × 10⁹ M⁻¹ s⁻¹ for *k*_{az}.¹⁶ ^c Rate constant for the addition of the nucleophile to the benzylic carbon. ^d Rate constant for the addition of the nucleophile to the C-4 ring carbon.

and for some reason breakdown preferentially to 4-MeO(CH₂)₂NHArCH(CF₃)⁺, then 4-MeO(CH₂)₂NHArCH(CF₃)NH(CH₂)₂OMe would have been isolated from the reaction between 4-Me₂NArCH(CF₃)⁺ and MeO(CH₂)₂NH₂.

Table II summarizes the product rate constant ratios determined in these experiments for the reactions of XArCH(CF₃)⁺ with solvent and added nucleophiles. Data are given for nucleophile addition at the C-α and the C-4 ring positions in cases where both reactions were observed.

Scheme II

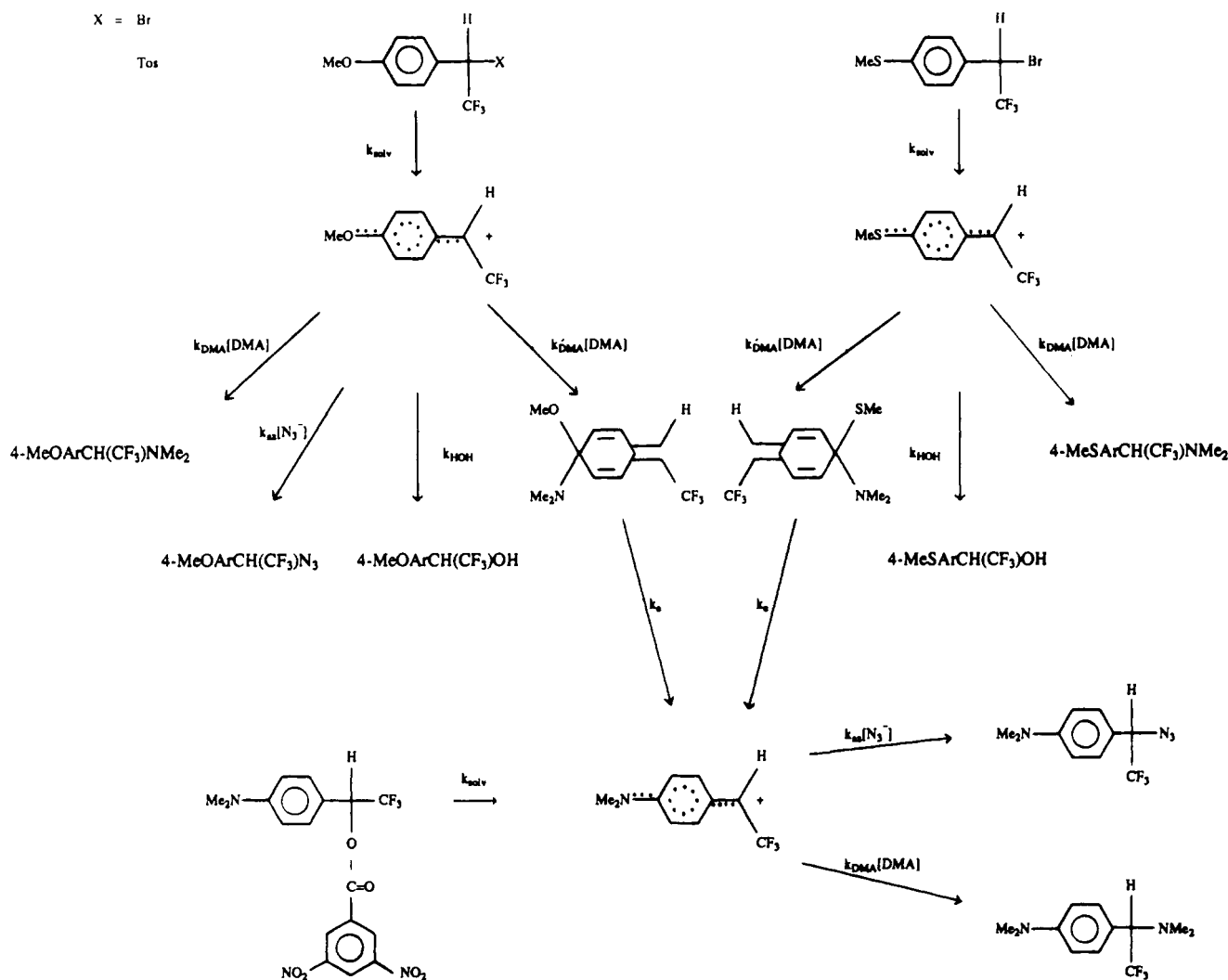


Table III lists estimated second-order rate constants for the amine reactions with $4\text{-MeOArCH(CF}_3\text{)}^+$ and $4\text{-MeSArCH(CF}_3\text{)}^+$. These values were calculated from the experimental rate constant ratios $k_{\text{az}}/k_{\text{Nu}}$ (Table II) and an estimated value of $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the diffusion-limited rate constant k_{az} .^{5,16}

Discussion

The Aromatic Substitution Reaction of Dimethylamine with $4\text{-MeOArCH(CF}_3\text{)X}$. There are a total of four bonds to carbon made or broken in the conversion of $4\text{-MeOArCH(CF}_3\text{)Br}$ or $4\text{-MeOArCH(CF}_3\text{)Tos}$ to $4\text{-Me}_2\text{NArCH(CF}_3\text{)NMe}_2$. The data in the Results section provide strong evidence that these reactions proceed by the mechanism in Scheme II, in which there is a separate step for each bond cleaved or made and a total of three reaction intermediates. The evidence for the formation of these intermediates is presented below.

$4\text{-MeOArCH(CF}_3\text{)}^+$. Nucleophilic substitution reactions at $4\text{-MeOArCH(CF}_3\text{)X}$ are kinetically $\text{S}_{\text{N}}1$, through a trappable $4\text{-MeOArCH(CF}_3\text{)}^+$ intermediate.⁵ The aromatic substitution product $4\text{-Me}_2\text{NArCH(CF}_3\text{)NMe}_2$ must form either by a mechanism that includes dimethylamine reaction with this carbocation or, much more improbably, by the direct reaction between Me_2NH and substrate. The latter possibility is ruled out by the data in Figure 3. In this experiment, the decrease in the yield of aromatic (X) and aliphatic (●) substitution products is com-

pared at increasing concentrations of azide anion, which is a very effective trapping reagent for $4\text{-MeOArCH(CF}_3\text{)}^+$. The observation of the same proportional decrease in the yield of the two types of adducts with increasing $[\text{N}_3^-]$ shows that all of the products form by *competitive trapping* of $4\text{-MeOArCH(CF}_3\text{)}^+$. The data in Figure 3 rule out the alternative possibility that $4\text{-Me}_2\text{NArCH(CF}_3\text{)NMe}_2$ forms by a direct reaction between Me_2NH and substrate. For this mechanism, the percent yield of aromatic substitution products would depend only on the relative rates of the $\text{S}_{\text{N}}1$ reaction of $4\text{-MeOArCH(CF}_3\text{)Br}$ and the hypothetical direct amine reaction; consequently, the yield would be independent of $[\text{N}_3^-]$, because both reaction rates are independent of $[\text{N}_3^-]$.

$4\text{-Me}_2\text{NArCH(CF}_3\text{)}^+$. A simple result which provides strong evidence that the aromatic substitution products from the reaction of $4\text{-MeOArCH(CF}_3\text{)X}$ form by the partitioning $4\text{-Me}_2\text{NArCH(CF}_3\text{)}^+$ is the observation that the reaction is through an intermediate with the same chemical reactivity as the carbocation intermediate of the solvolysis reaction of $4\text{-Me}_2\text{NArCH(CF}_3\text{)}$ derivatives. This result is shown in Figure 4, which compares the yield of $4\text{-Me}_2\text{NArCH(CF}_3\text{)N}_3$ (f_{az} , the fraction of the total yield of $4\text{-Me}_2\text{NArCH(CF}_3\text{)}$ derivatives) at increasing $[\text{Me}_2\text{NH}]/[\text{N}_3^-]$ from the reaction of $4\text{-Me}_2\text{NArCH(CF}_3\text{)(3,5-dinitrobenzoate)}$ (◆), $4\text{-MeOArCH(CF}_3\text{)Br}$ (■), and $4\text{-MeOArCH(CF}_3\text{)Tos}$ (□). All of the data in Figure 4 are fit by a single line, as required if the reaction of each substrate is through a common $4\text{-Me}_2\text{NArCH(CF}_3\text{)}^+$ intermediate (Scheme II).

C-4 Ring Adduct between Me_2NH and $4\text{-MeOArCH(CF}_3\text{)}^+$. The conversion of $4\text{-MeOArCH(CF}_3\text{)}^+$ to $4\text{-Me}_2\text{NArCH(CF}_3\text{)}^+$ may be a stepwise reaction through the intermediate formed by

(16) Footnote 45 in ref 9a. Recently, a value of $7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ was measured for the diffusion-limited reactions of azide with ring-substituted diarylmethyl carbocations. McClelland, R. A.; Kanagasabapathy, V. W.; Steenken, S. J. *Am. Chem. Soc.* **1988**, *110*, 6913-6914.

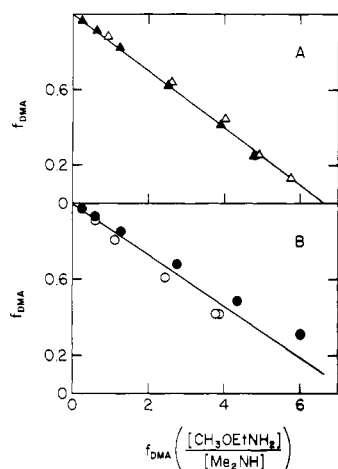
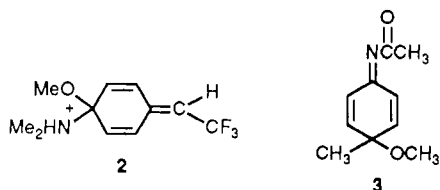


Figure 5. Dependence of the fraction of $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$ or $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)^+$ trapped by Me_2NH (f_{DMA}) on $[\text{MeO}(\text{CH}_2)_2\text{NH}_2]/[\text{Me}_2\text{NH}]$. The two carbocations were generated in 20% acetonitrile in water ($I = 0.80$, NaClO_4) either by the reaction of $4\text{-MeOArCH}(\text{CF}_3)\text{Br}$ with a mixture of Me_2NH and $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ (solid symbols) or by the solvolysis reactions of $4\text{-Me}_2\text{NArCH}(\text{CF}_3)\text{N}_3$ or $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)\text{N}_3$ (open symbols). (A) Data for the partitioning of $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$: (\blacktriangle) generated by the reaction of $4\text{-MeOArCH}(\text{CF}_3)\text{Br}$, (\triangle) generated by the reaction of $4\text{-Me}_2\text{NArCH}(\text{CF}_3)\text{N}_3$. (B) Data for the partitioning of $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)^+$: (\bullet) generated from the reaction of $4\text{-MeOArCH}(\text{CF}_3)\text{Br}$, (\circ) generated by the reaction of $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)\text{N}_3$.

Me_2NH addition to the C-4 ring carbon of $4\text{-MeOArCH}(\text{CF}_3)^+$ (k'_{DMA} , Scheme II) or a concerted reaction in which $4\text{-MeOArCH}(\text{CF}_3)^+$ is transformed directly into $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$. The arguments presented below are offered to support the stepwise pathway in Scheme II. These arguments are speculative, and further experiments are needed to prove or disprove the existence of **2**.

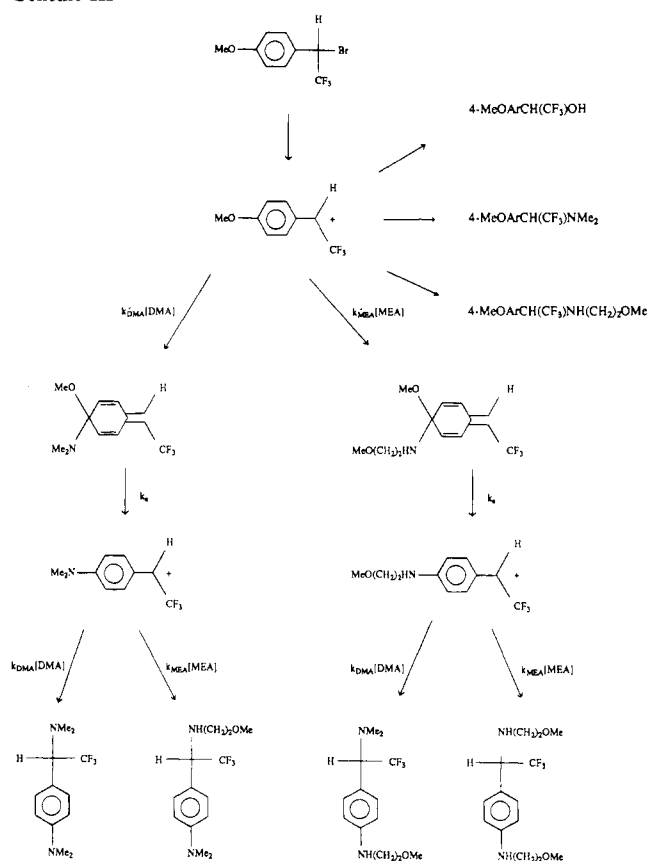
(1) The estimated net rate constant for the conversion of Me_2NH and $4\text{-MeOArCH}(\text{CF}_3)^+$ to $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$ and MeOH is $k'_{\text{DMA}} = 7 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (Table III). This is a plausible value if the reaction is stepwise and k'_{DMA} is the rate constant for the addition to the electrophilic C-4 ring carbon. It is more difficult to understand why a concerted reaction in which C-O and N-H bonds are cleaved and a C-N bond is formed in a single step should proceed at a rate only 100-fold slower than the rate of a diffusion-limited reaction.

(2) Compounds with structures similar to **2** are known to form as intermediates of aromatic substitution reactions.¹⁷⁻²³ The capture of a nitrenium ion by methanol gave **3**, which has been



isolated and characterized.¹⁷ Meisenheimer complexes have been shown to form as intermediates of aromatic substitution reactions at di- and trinitrobenzene derivatives.¹⁸⁻²³

Scheme III



In the course of the overall conversion of $4\text{-MeOArCH}(\text{CF}_3)^+$ to $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$, a proton is lost from the dimethylamine nucleophile and added to the methoxide leaving group. It remains to be determined if these proton transfer steps may be rate determining in the aromatic substitution reaction, as has been observed for the aromatic substitution reactions of nitrogen and oxygen nucleophiles at trinitrobenzene derivatives.^{18-20,22,23}

Further Aromatic Substitution Reactions. The following are further examples of aromatic substitution reactions by amines at $4\text{-MeOArCH}(\text{CF}_3)\text{X}$ and $4\text{-MeSArCH}(\text{CF}_3)\text{Br}$.

(1) The reaction of $4\text{-MeSArCH}(\text{CF}_3)\text{Br}$ in the presence of Me_2NH gives $4\text{-Me}_2\text{NArCH}(\text{CF}_3)\text{NMe}_2$. The mechanism for this reaction is probably analogous to the four-step mechanism for the formation of aromatic substitution products from the reaction of $4\text{-MeOArCH}(\text{CF}_3)\text{X}$ in the presence of Me_2NH (Scheme II).

(2) The reaction of $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ in the presence of $4\text{-MeOArCH}(\text{CF}_3)\text{Br}$ gives $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)\text{NH}(\text{CH}_2)_2\text{OMe}$, and the reaction of this substrate in the presence of a mixture of $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ and NaN_3 gives the dimethoxyethylamine adduct and $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)\text{N}_3$. This result is consistent with a mechanism for $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ reaction similar to that for the reaction of Me_2NH shown in Scheme II. A rate constant ratio $k_{\text{az}}/k_{\text{MEA}} = 90$ for the partitioning of $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)^+$ between capture by N_3^- and $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ is calculated from the slope of the line in Figure 4 (circles).

(3) The reaction of $4\text{-MeOArCH}(\text{CF}_3)\text{Br}$ in the presence of a mixture of $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ and Me_2NH gave four aromatic substitution products. This array of products is formed by the mechanism shown in Scheme III in which the amine substitution reactions of $4\text{-MeOArCH}(\text{CF}_3)^+$ produce $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$ and $4\text{-MeO}(\text{CH}_2)_2\text{NArCH}(\text{CF}_3)^+$, which in turn partition between the reaction with $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ and Me_2NH to form the final amine adducts (Scheme III). Figure 5 provides classical

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evidence for the formation of the two aminophenyl-substituted carbocations in Scheme III. The data show that the reaction between $4\text{-MeOArCH}(\text{CF}_3)^+$ and Me_2NH produces an intermediate that reacts with Me_2NH and $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ to form the same yield of products as isolated from the amine reactions with $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$ (Figure 5A) and, likewise, that the intermediate from the reaction between $\text{MeO}(\text{CH}_2)_2\text{NH}_2$ and $4\text{-MeOArCH}(\text{CF}_3)^+$ reacts with the two amines to form the same yield of products as isolated from the amine reactions with $4\text{-MeO}(\text{CH}_2)_2\text{NHArCH}(\text{CF}_3)^+$ (Figure 5B). In this experiment, $4\text{-Me}_2\text{NArCH}(\text{CF}_3)^+$ and $4\text{-MeO}(\text{CH}_2)_2\text{NHArCH}(\text{CF}_3)^+$ were generated directly by the solvolysis reactions of the respective azide derivatives.

(4) The sulfite dianion reduces $4\text{-MeSArCH}(\text{CF}_3)^+$ to $4\text{-MeSArCH}(\text{CF}_3)^-$, in a reaction that may involve the formation of an intermediate C-4 adduct between SO_3^{2-} and $4\text{-MeSArCH}(\text{CF}_3)^+$.⁷

Why Aromatic Substitution? Nucleophilic aromatic substitutions at benzyl carbocations are unusual reactions, because C- α is generally the more electrophilic center. The reversal in the electrophilic reactivities of C- α and C-4 is due mainly to the nature of the substituents the benzylic carbon. The yield of aromatic substitution products is also influenced by the nucleophilic reagent and the leaving group at the aromatic ring.

Benzylic Carbon Substituent. The relative reactivity of C- α and C-4 at $4\text{-MeOArCR}_1\text{R}_2^+$ depends on the extent of electron delocalization from the ring to C- α , which tends to decrease the reactivity of C- α and make C-4 react like an oxocarbenium ion. There is a clear trend of increasing resonance delocalization and concomitant increasing reactivity of C-4 relative to C- α with the addition of CF_3 substituents to C- α of $\text{MeOArCR}_1\text{R}_2^+$. To the best of my knowledge, C-4 ring addition to α -hydrogen- or α -alkyl-substituted benzyl carbocations has not been observed. $4\text{-MeOArCH}(\text{CF}_3)^+$, with a single CF_3 group at C- α , reacts with solvent and a number of other nucleophiles at C- α , but the reactions with amines give low to modest yields of aromatic substitution products. A second CF_3 group at C- α increases the electrophilic reactivity of C-4 further, and even the weak nucleophile ethanol adds to this center. The solvolysis of $4\text{-MeOArC}(\text{CF}_3)_2\text{Tos}$ in ethanol gives a 50:50 ratio of the aliphatic substitution product $4\text{-MeOArC}(\text{CF}_3)_2\text{OEt}$ and the aromatic substitution product $4\text{-EtOArC}(\text{CF}_3)_2\text{OEt}$.³⁸

There are many examples of how removal of alkyl or aryl substituents from a cationic center leads to increased electron delocalization to this center from the remaining substituents.²⁴⁻²⁶ One explanation for these observations is that decreasing the number of electron-donating substituents α to a carbocation decreases the competition between the remaining substituents for delocalization into the vacant p orbital, allowing for greater electron delocalization from these substituents. In addition, the large destabilizing electrostatic interaction between the positive charge and the positive end of the CF_3 dipole may act to "drive" the positive charge into the aromatic ring; this increases the effective separation and decreases the charge-dipole interaction between the two interacting centers.

A nitrenium ion results when the element α to the aromatic ring is changed from carbon to nitrogen (e.g., PhNH^+ , $2,6\text{-Me}_2\text{ArNH}^+$, and $4\text{-XArN}(\text{COCH}_3)^+$). Electron delocalization from the aromatic ring is greater at a nitrenium ion than at the corresponding carbenium ion because nitrogen is more electronegative than carbon. Consequently, these ions readily add water and other nucleophiles at the C-4 ring position.^{17,27,28}

Aromatic substitution of a 4-Cl or 4-NMe₂ ring substituent by water had been observed at triarylmethyl carbocations, when water addition to the central carbon is sterically hindered by 2,6-Me₂ substituents at a second aromatic ring.²⁹

Nucleophile. The relative yields of aromatic and aliphatic substitution products depends on the selectivity of the nucleophile between addition to the electrophilic centers at C- α and C-4 and on the tendency of the C-4 adduct to breakdown with the expulsion of ring substituent.

The weak nucleophiles water and ethanol^{3f,5} are highly selective for reaction at C- α of $4\text{-MeOArCH}(\text{CF}_3)^+$; the aliphatic substitution adducts are the only products detected from this reaction. For the reaction of ethanol, this is due to the large selectivity for C- α addition to $4\text{-MeOArCH}(\text{CF}_3)^+$ and not to the preferential expulsion of ethanol from the C-4 ring adduct, because ethanol and methanol have similar basicities and should be expelled at roughly equal rates from such an adduct.³⁸

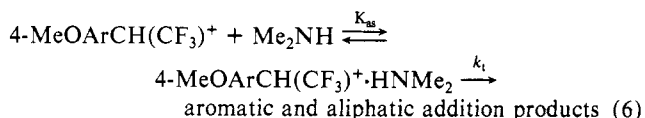
The nucleophiles acetate, iodide, and azide, which are also good leaving groups, react only at C- α of $4\text{-MeOArCH}(\text{CF}_3)^+$.⁵ It is not known whether there is also nucleophile addition at the C-4 ring carbon; however, if these reactions occur, they do not give stable products, presumably because the C-4 ring adducts preferentially expel the nucleophile to regenerate $4\text{-MeOArCH}(\text{CF}_3)^+$.

There is a decrease in selectivity, with increasing nucleophilicity, between addition to the two electrophilic centers at $4\text{-MeOArCH}(\text{CF}_3)^+$; the reaction of weakly nucleophilic solvent is highly selective for addition to C- α ,^{3f,5} while it is reported here that the strongly nucleophilic amines show only a small discrimination between reaction at C- α and C-4. The details of the explanation for this decrease in selectivity are uncertain; however, the decrease is probably directly related to the very small chemical barrier to the amine addition reactions.

(1) If there is no chemical barrier to the amine addition reaction (the barrier is smaller than that for a bond vibration), then a low selectivity will be observed which depends on the small difference in the barriers to nucleophile approach toward the two electrophilic centers.

(2) If there is a small chemical barrier to the addition of amines to the two electrophilic centers of $4\text{-MeOArCH}(\text{CF}_3)^+$, then the decrease in selectivity is due to a Hammond-type movement to a more reactant-like transition state.³⁰ This shift is not normally observed for carbocation addition reactions;^{31,32} however, it is favored as the reaction approaches the vibrational limit and the barrier to nucleophile addition disappears.³³

The rate constant k_t for dimethylamine addition to $4\text{-MeOArCH}(\text{CF}_3)^+$ is estimated to lie between 1.4×10^9 and 10^{14} s^{-1} (eq 6), consistent with a reaction that is at or slightly below the vibrational limit. The lower limit is calculated from the sum



of the second-order rate constants in Table III ($k_{\text{DMA}} + k'_{\text{DMA}} = 1.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$), $K_{\text{as}} = 0.1 \text{ M}^{-1}$ ³⁴ and $k_t = k_{\text{amine}}/K_{\text{as}}$. This value underestimates the rate of chemical bond formation, because the amine reaction is limited by the rate of cleavage of an amine-solvent hydrogen bond.⁶ The upper limit for the chemical reaction is calculated using $k_s = 1 \times 10^8 \text{ s}^{-1}$ ($[\text{H}_2\text{O}]k_{\text{HOH}}$, Table III) and $k_{\text{amine}}/k_s = 10^{5.3}$, where $10^{5.3}$ is the rate constant ratio

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for the activation-limited reaction of ethylamine with a number of more stable carbocations.³²

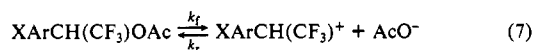
The products from the collapse of the C-4 dimethylamine adduct to 4-MeOArCH(CF₃)⁺ might depend on the relative nucleofugalities of Me₂NH and MeO⁻ or MeOH. This is unlikely because there will be a large decrease in the p*K*_a of the amine nitrogen upon bond formation to the C-4 ring carbon.³⁵ Therefore, under the present reaction conditions (pHs close to the p*K*_a of dimethylamine), the nitrogen at the C-4 ring adduct will be largely deprotonated, and the dominant effect controlling the breakdown of the adduct will be the greater push to leaving group expulsion provided by nitrogen than oxygen, which favors expulsion of MeO⁻ or MeOH. This effect is a maximum at the carbocation products and is reflected by the $\sim(5 \times 10^{11})$ -fold greater stability of 4-Me₂NArCH(CF₃)⁺ than 4-MeOArCH(CF₃)⁺ (relative to acetate esters);³⁶ there will be a proportionally smaller relative stabilization of the transition state for 4-Me₂NArCH(CF₃)⁺ formation.

Ring Substituent. The ring substituent X may influence the yield of aromatic substitution product from XArCH(CF₃)⁺ at either the addition step or the elimination step of the substitution reaction.

(1) Addition of Nucleophile to XArCH(CF₃)⁺. Aromatic substitution reactions by amines are observed at 4-MeOArCH(CF₃)⁺ and 4-MeSArCH(CF₃)⁺ but not at 4-MeO(CH₂)₂NHArCH(CF₃)⁺ and 4-Me₂NArCH(CF₃)⁺. This result

(35) The p*K*_a of the dimethylamine nitrogen at the C-4 ring adduct will be lower than at the free amine because of the effect of the electron-withdrawing 4-MeO and α-CF₃ substituents and the conjugated system of double bonds at 2.

(36) The ratio of equilibrium constants for carbocation formation from the respective acetate esters (eq 7) is estimated as $K^{\text{NMe}}/K^{\text{OMe}} = (k_t^{\text{NMe}}/k_t^{\text{OMe}})$



$k_t^{\text{OMe}}(k_t^{\text{OMe}}/k_t^{\text{NMe}}) = (6 \times 10^8)(900) = 5 \times 10^{11}$. The substituent effect on k_t ((6×10^8) -fold) is calculated from a ρ^+ value of -10 for the reaction of XArCH(CF₃)Tos^{5b} and the difference in the σ^+ values for the 4-Me₂N and 4-MeO substituents $((-1.67) - (-0.79)) = -0.88$, ref 21, pp 55-78). The substituent effect on k_t (900-fold) is the ratio of the rate constants for the capture of 4-Me₂NArCH(CF₃)⁺ and 4-MeOArCH(CF₃)⁺ by acetate ion in 50:50 (v:v) trifluoroethanol:water.^{5b}

shows that increasing cation stabilization by resonance has a complicated effect on the nucleophile selectivity between addition to C-α and the C-4 ring positions.

(2) Breakdown of the C-4 Ring Adduct. The yield of aromatic substitution products also depends on the leaving group ability of the ring substituent X. The value $k_{\text{C-}\alpha}/k_{\text{C-4}}$ for the reaction of Me₂NH with 4-MeOArCH(CF₃)⁺ is 1.5-fold smaller than for the addition of a less basic amine MeO(CH₂)₂NH₂, while there is a 40-fold difference in $k_{\text{C-}\alpha}/k_{\text{C-4}}$ for the addition of these two amines to 4-MeSArCH(CF₃)⁺ (Table I). These data can be explained if MeO is expelled more readily than MeS from the C-4 amine adduct³⁷ so that amine addition is irreversible for the reaction of 4-MeOArCH(CF₃)⁺ (C-4 adduct formation is rate limiting) and reversible for the reaction of 4-MeSArCH(CF₃)⁺ (C-4 adduct breakdown is rate limiting). When addition is rate limiting, as is proposed for the reaction of 4-MeOArCH(CF₃)⁺, $k_{\text{C-}\alpha}$ and $k_{\text{C-4}}$ will both increase with increasing amine basicity and the net change in $k_{\text{C-}\alpha}/k_{\text{C-4}}$ will be small. There is considerably greater bonding between the amine and the C-4 ring carbon in the rate-limiting transition state for the aromatic substitution reaction when the breakdown of the C-4 adduct is rate limiting, than for rate-limiting formation of the C-4 adduct. This will increase the sensitivity of the yield of aromatic substitution products to amine basicity, as is observed when comparing the reaction of 4-MeOArCH(CF₃)⁺ with the reaction of 4-MeSArCH(CF₃)⁺.

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