Desolvation-limited Reactions of Amines with the 1-(4-Methylthiophenyl)-2,2,2-trifluoroethyl Carbocation

John P. Richard

University of Kentucky, Department of Chemistry, Lexington, Kentucky, 40506-0055, U.S.A.

The rates of capture of the 1-(4-methylthiophenyl)-2,2,2-trifluoroethyl carbocation by alkylamines in a desolvation-limited reaction decrease with increasing amine pK_a, and are up to 200 times slower than diffusion-limited carbocation capture by azide.

Carbocation capture by a nucleophile in a hydroxylic solvent involves at least three steps (Scheme 1). (a) Solvent separated ion or dipole pair formation (k_d), (b) extrusion of solvent to free an electron pair for reaction with nucleophile (k_h), (c) bond formation (k_{Nu}). The barrier to k_h may make a significant, but unknown,† contribution to the overall reaction barrier.[1,2] The problem is simplified when the chemical barrier is so small that solvent-separated or contact ion pair formation is rate determining. Here the observed rate constants will depend only on the first two steps in Scheme 1 and variations in rate constants for different nucleophiles will reflect differences in k_h, because k_d for solvent-separated ion pair formation should be largely nucleophile independent.

In 20% methanol in water (μ = 0.8 M, $NaClO_4$. t = 22 ± 2 °C), 4-SMe and 4-OMe-substituted 1-phenyl-2,2,2-trifluoroethyl bromides and tosylates‡ react by an S_N1 mechanism through highly reactive, solvent equilibrated, carbocation intermediates (**1**) and (**2**).[3] Reactions in the presence of increasing $[N_3^-]$, or at a constant $[N_3^-]$ and increasing [amine] gave nucleophilic adducts§ which were separated by h.p.l.c. and quantitated spectrophotometrically.[3,4] Selectivities k_{az}/k_{amine} and k_{az}/k_{solv} were calculated from product and reactant concentration ratios, using the average of values for at least 5 different amine or azide concentrations, respectively.[3,4] The values for k_{az}/k_{solv} are 100 and 28 $dm^3\ mol^{-1}$ for (**1**) and (**2**), respectively. Amine general-base catalysis of solvent addition is weak since an increase from 0 to 0.6 M ethylamine increases the fraction of solvent adducts by only 30%, relative to the azide adduct formed in an uncatalysed reaction.[5]

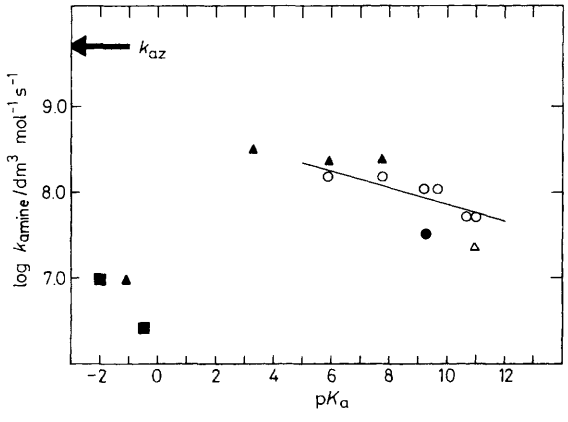
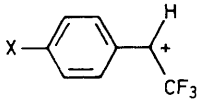


Figure 1. The Brønsted plot of second-order rate constants for 1-(4-methylthiophenyl)-2,2,2-trifluoroethyl carbocation capture by amines calculated relative to a value of 5 × 10^9 $dm^3\ mol^{-1}\ s^{-1}$ for k_{az}. ○, primary alkylamines; ethylamine (pK_a 11.0), propylamine (pK_a = 10.9),[12] methoxyethylamine (pK_a 9.2),[13] ethylene diamine (pK_a 9.7, statistically corrected),[13] ethylene diamine monocation (pK_a 7.5),[13] and trifluoroethylamine (pK_a 5.9);[12] ▲, other primary amines; hydrazine (pK_a = 7.8, statistically corrected),[13] hydroxylamine (pK_a 6.0),[13] acetylhydrazine (pK_a 3.2),[13] and hydrazine monocation (pK_a −1.1);[14] △, diethylamine (pK_a = 11.0);[13] ●, ammonia (pK_a = 9.25);[13] ■, amides; acetamide (pK_a ≪−0.5)[15] and urea (pK_a = −1.7).[16] The solid line has been drawn through points for primary alkylamines.

The azide reactions are diffusion limited; this is observed for azide addition to thermodynamically more stable 1-phenylethyl carbocations.[4] Substitution of k_{az} = 5 × 10^9 $dm^3\ mol^{-1}\ s^{-1}$ (refs. 4, 6) into k_{az}/k_{solv} gives k_{solv} values of 5 × 10^7 and 1.8 × 10^8 s^{-1}, respectively for (**1**) and (**2**). The ratio k_{az}/k_{amine} (dimensionless) for trifluoroethylamine (TFEA) reaction decreases only slightly from 34 for (**1**) to 30 for (**2**); *i.e.*, k_{az} and k_{TFEA} change little relative to one another as k_{solv} increases 4-fold. We conclude that TFEA is like azide, and captures (**1**) and (**2**) with a carbocation independent rate constant for rate-limiting ion–dipole pair formation. If TFEA reaction is limited by the rate of encounter complex formation, then so is that of the more basic amine ethylamine with k_{az}/k_{amine} = 100 for reaction of (**1**). Simple diffusion-limited rate constants should not differ by 30—100 fold.¶ Therefore a step which is slower than diffusion limits the overall rate of amine–carbocation complex formation.

The Brønsted plot in Figure 1 provides convincing evidence that the rate-limiting step is amine desolvation. The k_{amine}



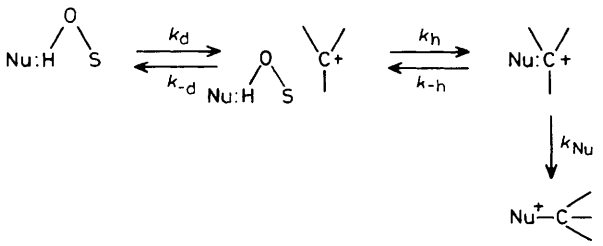
(**1**) X = SMe
(**2**) X = OMe

† Note, however, that it has been shown that azide reacts about 10 times faster than acetate in encounter-limited reactions with the 1-(4-methylphenyl)ethyl carbocation.[2]

‡ The bromides and tosylates were prepared from the corresponding phenyltrifluoroethanols using methods described previously.[3] All new compounds were characterized by ^1H n.m.r. spectroscopy, high resolution mass spectroscopy, and elemental analysis.

§ The product of the reaction between 4-(thiomethylphenyl)-2,2,2-trifluoroethyl bromide and methoxyethylamine was isolated and characterized by ^1H n.m.r. and high resolution mass spectroscopy.

¶ The rate constants for diffusion-limited proton transfer between electronegative atoms decrease by only a factor of 2—3 for each unit increase in charge of like sign at the other reactant.[17] A statistical correction of k_{az} is inappropriate because the azide reaction is diffusion limited (there is, for instance, no statistical advantage to diffusional azide reaction over that for the spherically symmetrical nucleophile I^-). Diffusional rate constants are dependent on the magnitude of the angle of attack which gives products,[18] and the diffusional azide reaction may be *ca.* 2-fold faster than for a monodentate nucleophile if non-reactive carbocation–nucleophile pairs separate faster than nucleophile rotation into a reactive configuration. Not enough is known about the behaviour of these complexes to justify a correction of k_{az} relative to k_{amine}.



Scheme 1

values, calculated from k_{az}/k_{amine} and the above value for k_{az}, decrease with increasing amine basicity ($\beta_{nuc} = -0.09$ for primary alkylamines). This is inconsistent with a diffusion-limited amine reaction, but may be readily explained by a desolvation-limited (k_h, Scheme 1) reaction, where k_h decreases as the amine–solvent hydrogen bond is strengthened by increasing amine basicity.[7,8] The low reactivity of urea and hydrazine monocation suggests that there is a change to rate determining k_{Nu} (Scheme 1) for the reaction of weakly basic nucleophiles.

Grunwald has reported that water extrusion from an amine–water–ammonium cation complex is slower than proton transfer between buffer species, through the intervening water molecule.[9,10] It is shown here that water extrusion from an amine–water–carbocation complex (k_h, Scheme 1) is markedly slower than diffusional breakdown by k_{-d}, and that carbocation reaction with the sandwiched solvent (amine catalysis of solvent addition) is not much faster than uncatalysed addition. Jencks has reported negative β_{nuc} values for phosphoryl transfer to substituted quinuclidines.[11] These reactions are much slower ($1—10^{-7}$ dm^3 mol^{-1} s^{-1}) than the reactions studied here, and are unlikely to be desolvation limited. The observed β_{nuc} was proposed to result from $\beta_{nuc} = -0.20$ for a pre-equilibrium desolvation step and a smaller positive β_{nuc} value for the chemical step.

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