Lifetimes of Imidinium Ions in Aqueous Solution

Kevin N. Dalby[1] and William P. Jencks*

Contribution from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254-9110

Received February 26, 1997[⊗]

Abstract: Imidinium ions, $ArN=CNR_2^+$, were generated in aqueous solution from the solvolysis of fluoro and chloro formamidines at pH 9.3 and 25 °C. Rate constants for the hydration of five imidinium ions were determined from a kinetic analysis of their trapping by thiolacetate anion, CH_3COS^-, in the presence of a pool of competing fluoride anion, and a rate constant of $k_{AcS^-} = 5 \times 10^9$ M^{-1} s^{-1} for diffusion-controlled trapping of the carbocations with thiolacetate anion. The rate constants, k_s, for hydration of the imidinium ions, $XArN=CNC_4H_8O^+$ are 3.6×10^5, 5.8×10^5, 1.5×10^6, 1.6×10^6, and 1.8×10^6 s^{-1} for X = H, 4-Cl, 3-CN, 4-CN, and 3-NO$_2$, respectively. In a similar experiment a rate constant of $k_s = 3.3 \times 10^7$ s^{-1} was obtained for hydration of the imidinium ion 4-NO$_2$-ArN=CNCH$_3$(OCH$_3$)$^+$, by using azide anion to trap the cation and a rate constant of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for diffusion-controlled trapping of the imidinium ion with azide ion. The partitioning rate constant ratio k_{AcS^-}/k_s for 4-ClArN=CNC$_4$H$_8$O$^+$ decreases by approximately 6-fold in 45% v/v glycerol/water in contrast to k_{az}/k_s, which remains almost constant, showing that thiolacetate, but not azide anion, combines with the imidinium ion at a diffusion-limited rate. The reactivity of the imidinium ions deviate from behavior predicted by the N_+ scale in a manner that may be explained by a difference in the selectivity of the cation when compared to the more stable N_+ carbocations.

Introduction

Relatively little is known about the properties of sp-hybridized carbocations in aqueous solution[2] which are expected to be significantly more reactive toward solvent and solute molecules than sp^2-hybridized carbocations, of which considerably more is known.[3] Ritchie's extensive study of the combination of several relatively stable sp^2-hybridized carbocations ($k_s < 10^2$ s^{-1}) with a number of nucleophilic reagents, in several solvents, led to the development of the N_+ scale of chemical reactivity.[4,5] Although this scale was later shown to fail for a series of activation limited reactions of 1-phenylethyl carbocations[6] (with alcohols), triarylmethyl and diarylmethyl carbocations[7] (with alkyl amines) and 1-phenyl-2,2,2-trifluoroethyl carbocations[8] (with alkyl amines, alcohols, and alkyl carboxylate anions) it still provides, in many cases, a useful point of reference. A number of unstable carbocations ($k_s > 10^7$ s^{-1}) have been examined by utilizing the diffusion-controlled combination of azide or thiolate anions with the carbocation as a "clock" by which to estimate the lifetime of the carbocation in aqueous solution.[6,9,10] These studies have described a broad correlation between the breakdown of the N_+ scale and the attainment of a diffusion-limited rate constant for the addition of nucleophiles

to the carbocations[6,9] and have shown how the change from a stepwise to a concerted mechanism for substitution can be predicted from the effect of substituents on the lifetime of the carbocation.[9a,11]

In this paper we report the use of thiolacetate anion and (in one case) azide anion as diffusion-controlled trapping reagents[12,13] to estimate the rate constants for the reactions of several sp-hybridized imidinium ions (ArN=CNR$_2^+$) with solvent and fluoride anion, as a function of carbocation structure and an extensive investigation of the reactivity of the imidinium ion 4-ClArN=CN(C$_4$H$_8$O)$^+$, **3**$^+$, with a series of nucleophiles. We report that thiolacetate anion and 2-hydroxyethane thiolate anion combine with **3**$^+$ at the approximate diffusion-controlled limit of $k_{AcS^-} \approx k_{HOC_2H_4S^-} = 5 \times 10^9$ M^{-1} s^{-1}, while azide anion, cyanide anion, thioglycolate dianion, bisulfite dianion, and several other nucleophiles do not. Combinations of the rate constants for reaction of the carbocations with fluoride ion and for solvolysis of the fluoroformamidines provide estimates of the equilibrium constants for carbocation formation, and a picture of the development and distribution of positive charge as the transition state is approached from both directions.

Results

Solvolysis and Common Ion Inhibition. The rate constants for hydrolysis of the fluoroformamidines, **1-F**−**11-F** and the chloroformamidine **12-Cl**[14] (Table 1) were determined at pH

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1997.

(1) Present address: College of Pharmacy, The University of Texas at Austin, Division of Medicinal Chemistry, Austin, TX 78712-1074.

(2) (a) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109,* 3160. (b) Song, B. D.; Jencks, W. P. *Ibid.* **1989**, *111*, 8470.

(3) Richard, J. P. *Tetrahedron* **1994**, *51,* 1535.

(4) Ritchie, C. D.; Virtanen, P. O. I. *J. Am.Chem. Soc.* **1972**, *94,* 4966.

(5) (a) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348. (b) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

(6) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.

(7) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1992**, *114,* 1816.

(8) Richard, J. P.; Amyes, T. L.; Vontor, T. *J. Am. Chem. Soc.* **1992**, *114,* 5626.

(9) (a) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4691. (b) Richard, J. P.; Jencks, W. P. *Ibid.* **1982**, *104,* 4689.

(10) (a) Fishbein, J. C.; McClelland, R. A. *J. Am. Chem. Soc.* **1987**, *109,* 2824. (b) Amyes, T. A.; Jencks, W. P. *Ibid.* **1988**, *110*, 3677. (c) Amyes, T. L.; Jencks, W. P. *Ibid.* **1989**, *111*, 7888. (d) Nagorski, R. W.; Brown, R. S. *Ibid.* **1992**, *114*, 7773. (e) Eldin, S.; Jencks, W. P. *Ibid.* **1995**, *117*, 4851. (f) Eldin, S.; Digits, J. A.; Huang, S.; Jencks, W. P. *Ibid.* **1995**, *117*, 6631.
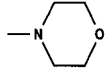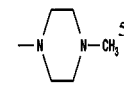
(11) (a) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789. (b) Richard, J. P.; Jencks, W. P. *Ibid.* **1984**, *106*, 1383. (c) Amyes, T. L.; Jencks, W. P. *Ibid.* **1989**, *111*, 7900. (d) Amyes, T. L.; Richard, J. P. *Ibid.* **1990**, *112*, 9507. (e) Banait, N. S.; Jencks, W. P. *Ibid.* **1991**, *113*, 7951. (f) Eldin, S.; Jencks, W. P. *Ibid.* **1995**, *117*, 9415.

(12) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113,* 1009.

(13) McClelland, R. A.; Cozenns, F. L.; Steenken, S. Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1717.

(14) The hydrolysis of **12-F** was too slow to study conveniently, and therefore the chloroformamidine was used.

Table 1. Rate Constants, k_{solv}, for the Solvolysis of Haloformamidines, $ArN{=}C(X)NR_2$, and Estimated Rate Constants, k_s, for the Hydration and Rate Constant Ratios for the Addition of Anions to Imidinium Ions, $ArN{=}CNR_2^+$

	R	−NR$_2$	k_{solv}	$\dfrac{k_{az}}{k_s}$ [e]	$\dfrac{k_{AcS}}{k_s}$ [e]	$\dfrac{k_F}{k_s}$ [g]	$\dfrac{k_{Cl}}{k_s}$ [i]	k_s
			s^{-1}	M^{-1}	M^{-1}	M^{-1}	M^{-1}	s^{-1}
X = F [a]								
1-F	C$_6$H$_5$	(morpholino)	3.43×10^{-3}	3800	14000	14.9	—	3.6×10^5 [j]
2-F	4-F-C$_6$H$_4$		3.00×10^{-3}	—	—	—	—	—
3-F	4-Cl-C$_6$H$_4$		1.37×10^{-3}	2400	8600	15.7	—	5.8×10^5 [j]
4-F	3-Cl-C$_6$H$_4$		4.52×10^{-4}	—	—	—	—	—
5-F	3-CN-C$_6$H$_4$		2.00×10^{-4}	1300	3330	15.2	—	1.5×10^6 [j]
6-F	4-CN-C$_6$H$_4$		1.22×10^{-4}	1300	3200	15.0	—	1.6×10^6 [j]
7-F	3-NO$_2$-C$_6$H$_4$		1.33×10^{-4}	1100	2800	16.2	—	1.8×10^6 [j]
8-F	4-NO$_2$-C$_6$H$_4$		5.10×10^{-5}	—[f]	—	19.1	—	$\sim 3.2 \times 10^6$ [k]
9-F	C$_6$H$_5$	(pyrrolidino)	4.45×10^{-2}	4000	—	18.2	—	$\sim 3.1 \times 10^5$ [l]
10-F	C$_6$H$_5$	(4-methylpiperazino)	5.62×10^{-3} [c]	5600	—	25.8	—	$\sim 2.0 \times 10^5$ [l]
11-F	C$_6$H$_5$	N(OCH$_3$)CH$_3$	2.18×10^{-5}	—[f]	—	4	—	$\sim 3.4 \times 10^6$ [m]
X = Cl [b]								
12-Cl	4-NO$_2$-C$_6$H$_4$	N(OCH$_3$)CH$_3$	2.6×10^{-1} [d]	170	—	—[h]	27	3.1×10^7 [n]

[a] 25 °C at pH 9.3 (DABCO, 60% base, 30 mM) and ionic strength 1.0 M (KCl). pK_a values of anilines: **1-F**, 4.58; **2-F**, 4.52; **3-F**, 3.81; **4-F**, 3.32; **5-F**, 2.75; **6-F**, 1.74; **7-F**, 2.45; **8-F**, 1.11 and secondary amines **1-F**−**8-F**, 8.36; **9-F**, 11.22, **10-F**, 9.82, **11-F** and **12-Cl**, 4.75 from Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology*, 2nd ed. Sober, H. A., Ed.; CRC Press: Cleveland, 1970; pp J150−189. [b] 25 °C at pH 9.3 (DABCO, 60% base, 30 mM) and ionic strength 1.0 M (NaClO$_4$). [c] At pH 9.3 **10-F** is not protonated. [d] Obtained, from the intercept at [Cl$^-$] = 0 M, of a plot of $1/k_{obs}$ against [Cl$^-$] for common ion inhibition by Cl$^-$ of the solvolysis of **12-Cl**. [e] Calculated by combining k_X/k_s and k_{nuc}/k_X. k_{nuc}/k_X is obtained from the linear least squares fit of a plot of $k_{solv}/(k_{solv} - k_{obs})$ against [nuc] for the disappearance of the haloformamidine in the presence of 0.2 M KF, according to $k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_X[X^-] + k_{nuc}[nuc]/k_X[X^-]$. [f] At pH 9.3 **8-F** and **11-F** undergo a bimolecular reaction with azide ion that precludes the determination of k_{az}/k_s in the presence of fluoride ion. [g] Obtained from a linear fit to a plot of $1/k_{obs}$ against [F$^-$], (0−0.2 M) for common ion inhibition by F$^-$ of the solvolysis of the fluoroformamidine. [h] No effect of 0−0.5 M F$^-$ on k_{obs} was detected for the solvolysis of **12-Cl** in the presence of 0.5 M chloride ion. [i] Obtained from a linear fit to a plot of $1/k_{obs}$ against [Cl$^-$] (0.1−0.8 M) according to eq 3. [j] Obtained by combining k_{AcS^-}/k_s with a rate constant of $k_{AcS^-} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled combination of the thiolate ion with the cation. [k] Obtained by extrapolation of a correlation of log k_s of the imidinium ions in Table 1 against the pK_a of the aniline; $\beta_{dg}^{ArN} = -0.26$. [l] Obtained from a linear correlation of [log $k_{AcS}/k_s = 1.36 \times$ log $k_{az}/k_s - 0.71$] and by combining the extrapolated value of k_{AcS^-}/k_s, that is obtained, with the rate constant of $k_{AcS^-} = 5 \times 10^9$ M^{-1} s^{-1} for diffusion-controlled combination of the thiolate ion with the cation. [m] Obtained assuming that the sensitivity to the 4-NO$_2$ substituent is the same when comparing k_s for **12**$^+$ and **8**$^+$ to **1**$^+$ and **11**$^+$ respectively. [n] Obtained by combining k_{az}/k_s with the rate constant of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled combination of the azide ion with the cation.

9.3.[15] The large dependence of the rate on the leaving group and on the pK_a of both electron-donating nitrogen atoms, $\beta_{dg}^{ArN} = +0.51$ and $\beta_{dg}^{RN} = +0.54$[16] is consistent with a large amount of C−X bond cleavage in the transition state of an S_N1

(15) Below pH 4 compounds **1-F** and **3-F** have been shown to hydrolyze through an alternative pathway in which the transition state for the hydrolysis contains an extra proton (K. N. Dalby and W. P. Jencks, unpublished results). The mechanism for this process is believed to involve the hydrolysis of the fluoroformamidinium ion and is not significant above pH 8 for any of the compounds studied. At pH 9.3 the solvolysis of the compounds studied is pH independent. A reaction of **3-F** with hydroxide ion becomes significant at 0.01 M hydroxide ion.
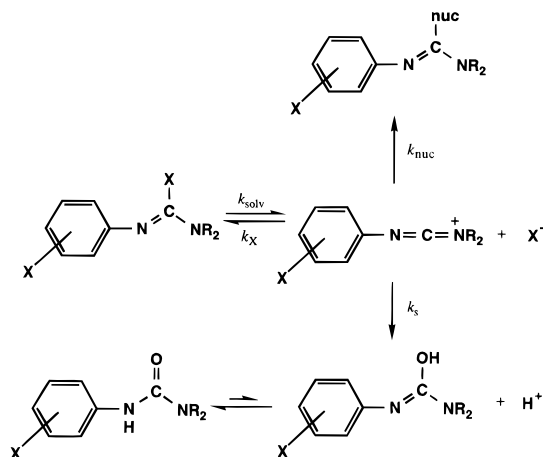
(16) Values of k_{solv} for **12-F** may be estimated to be 3.8×10^{-7} s^{-1} from the value of k_{solv} for **11-F** and $\rho = -2.26$ for the solvolysis of **1-F**−**8-F** (Table 1). This gives a value of 5.3×10^5 for k_{Cl}/k_F. The terms β_{dg}^{ArN} and β_{dg}^{RN} are Brønsted type correlations for the dependence of rate constants on the pK of the parent primary aniline or secondary amine, respectively.

$(D_N + A_N)$[17] reaction mechanism (Scheme 1). At pH 9.3 the solvolysis is first order and the formation of adducts with azide anion (0−0.1 M), acetate anion (0−1.0 M), thiolacetate anion (0−50 mM), and 2-hydroxyethanethiolate anion (0−2 mM) from **3-F** are all zero order. The product of the reaction is almost exclusively the substitution product at the higher concentration given in the parentheses. This shows that the nucleophiles react with an intermediate after the rate-limiting step.

Increasing the ionic strength of the medium from 0.01−1.0 M with several salts results in a small increase in rate (6−14%) and the addition of organic solvents results in a decrease in k_{solv} for **3-F** (Table 2). These results are consistent with a transition state that is more polar than the ground state and

(17) Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343.

Lifetimes of Imidinium Ions in Aqueous Solution

J. Am. Chem. Soc., Vol. 119, No. 31, 1997 7273

Scheme 1

Table 2. Effects of Salts, Organic Solvents, and Ionic Strength on the Rates of Solvolysis of **3-F**[a]

salt or solvent	concentration, M	$10^3 k_{obs}$, s^{-1}
methanol[b]	20% v/v	0.48
glycerol[b]	20% v/v	0.87
	45% v/v	0.40
DABCO 20% base	0.25	1.1
glycine 80% base[c]	0.25	1.3
trifluoroethylamine[b]	0.18	1.14
NMe$_4$Br[b]	0.25	0.77
NaBr	0.5	1.45
	1.0	1.50
NaCl	0.5	1.44
	1.0	1.53
NaClO$_4$	0.01	1.36
	0.5	1.39
	1.0	1.44
NaN$_3$[b]	0.05	1.41
	0.15	1.41
	0.30	1.39
KOAc	1.0	1.32
K$_2$CO$_3$	0.33	1.31
K$_2$SO$_4$	0.33	1.25
K$_2$PO$_4$H	0.33	1.28
NaOH[c]	1.0	2.98
KOH[c]	1.0	2.98
NaCN[c]	1.0	3.53

[a] 25 °C at pH 9.3, 30 mM DABCO, 60% base. [b] Maintained at 1 M ionic strength with KCl. [c] No DABCO buffer added.

suggest that solvation of the developing fluoride ion may be significant in the transition state (Table 2). Divalent anions at 0.33 M, such as sulfate, carbonate, and hydrogen phosphate cause a small (<10%) decrease in k_{solv} compared to KCl (μ = 1.0 M). A 10% decrease in rate was observed with 1 M acetate, while 1 M bromide caused a 5% increase. These results are in broad agreement with the results of a similar study of the effects of solvents and salts on the stability of a series of 1-phenylethyl carbocations, that include a much wider range of carbocation stability, in which it was concluded that stabilization/destabilization effects of solvents and non-nucleophilic salts are small.[18] The addition of 1 M hydroxide or cyanide ions increases the rate of disappearance of **3-F** by 2.2 and 2.6 fold, respectively. The hydroxide reaction represents a bimolecular reaction with **3-F** that was observed for most of the fluoroformamidines in Table 1. The reaction mechanism with cyanide anion has not been determined conclusively.

Figure 1 shows that k_{obs} for the solvolysis of **3-F** at pH 9.3 in 30 mM DABCO (1,4-diazabicyclo[2.2.2.]octane) buffer, 60%
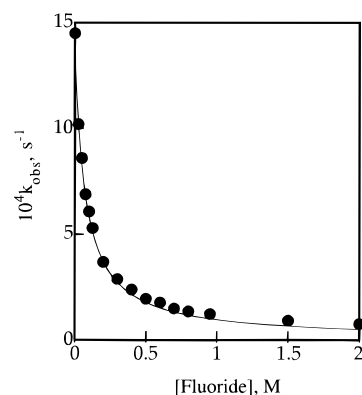
Figure 1. Common ion inhibition by fluoride ion of the hydrolysis of **3-F** at 25 °C, pH 9.3 (DABCO, 30 mM, 60% base), and ionic strength 2.0 M (KCl) in H$_2$O. The line through the diagram is the fit to the reciprocal plot over the range 0–0.2 M [F$^-$] in H$_2$O according to $1/k_{obs}$ = k_F[F$^-$]/$k_{solv}k_s$ + $1/k_{solv}$, with k_{solv}= 1.45×10^{-3} s^{-1} and k_F/k_s = 14.5 M^{-1}.

base, decreases by 95% as the concentration of fluoride ion is increased from 0 to 2 M. At high concentrations of fluoride ion k_{obs} is significantly greater than predicted for simple common ion inhibition. The most likely reason for this is that fluoride ion accelerates the hydration of **3$^+$** by general base catalysis,[19] which has been shown to be significant for the hydration of several carbocations of varying stability.[20,21] The value of k_{obs} for the solvolysis of **12-Cl** at pH 9.3 in DABCO buffer, 30 mM 60% FB decreases by 96% as the concentration of chloride ion is increased in the range 0–0.8 M.

Values of partitioning rate constant ratios k_F/k_s for **1-F**, **3-F**, **5-F**, **6-F**, **7-F**, **9-F**, **10-F**, and **11-F** (Table 1) were determined over the concentration range 0–0.2 M F$^-$. In all cases a reciprocal plot of $1/k_{obs}$ against [F$^-$] was linear over this range, consistent with common ion inhibition of the hydration of the free imidinium ion intermediate. The reactions were generally buffered with DABCO buffer (60% base, 30 mM) which had only a minimal effect on values of k_F/k_s (<5%) for several substrates.[22]

Trapping the Cations with Azide Ion. Imidinium ions were generated in equilibrium with the haloformamidine in the presence of halide ion. Figure 2 shows that k_{obs} for the solvolysis of **3-F** in the presence of 0.083 M (●) or 0.20 M (□) fluoride ion at pH 9.3 in 30 mM DABCO buffer, 60% base, increases sharply (from 40% of k_{solv} with 0.083 M fluoride or 24% of k_{solv} with 0.2 M fluoride) to the limiting value of k_{solv} over the range 0–50 mM of added azide ion. These data are

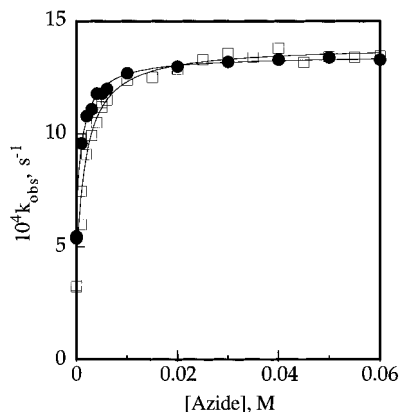(18) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361.

(19) The value of k_{obs} for the solvolysis of **3-F** at 2.0 M KF is greater than the value predicted from the reciprocal plot over the range 0–0.2 M [F$^-$] in H$_2$O according to $1/k_{obs}$ = k_F[F$^-$]/$k_{solv}k_s$ + $1/k_{solv}$, with k_{solv}= 1.45 × 10^{-3} s^{-1} and k_F/k_s = 14.5 M^{-1} (Figure 1). A good fit to the data over the range 0–2.0 M fluoride ion is obtained by nonlinear regression using the following expression, k_{obs} = $k_{solv}(k_s$ + k_B[F$^-$])/(k_s + (k_F + k_B)[F$^-$]), which includes a term for general base catalysis of the hydrolysis of the cation by fluoride anion, k_B[F$^-$]. The value obtained for k_B, k_B= 0.28 k_s, indicates that below 0.2 M fluoride ion k_s > 18 × k_B[F$^-$] and the expression reduces to k_{obs} ≈ $k_{solv}k_s$/(k_s + k_F[F$^-$]). Within this range a reciprocal plot of $1/k_{obs}$ against [F$^-$] is linear for all the fluoroformamidines studied.

(20) Kandanarachchi, P.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 5592.

(21) (a) Ritchie, C. D.; Wright, D. J.; Huang D.-S.; Kamego, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 1163. (b) Young, P. R.; Jencks, W. P. *Ibid.* **1977**, *99*, 8238. (c) Gandler, J. *Ibid.* **1985**, *107*, 8218.

(22) The ratio k_F/k_s for **3-F** was found to decrease slightly as the concentration of DABCO buffer was increased, in proportion to the concentration of the acid form of the buffer. A possible reason for the decrease in k_F/k_s is participation of the buffer in a competing process such as general base catalysis of the hydrolysis of the protonated form of **3-F**. Tetramethylammonium bromide has no significant effect on k_F/k_s (Table 2), suggesting that the decrease in k_F/k_s is not a salt effect.

Figure 2. Dependence of k_{obs} for the disappearance of **3-F** on the concentration of azide anion in the presence of 0.083 M (●) or 0.20 M (□) KF at 25 °C and ionic strength 1.0 M (KCl), at pH 9.3 (DABCO, 30 mM, 60% base). The line through the data corresponds to $k_{obs} = (k_{solv}k_s + k_{solv}k_{az}[az])/(k_F[F^-] + k_s + k_{az}[az])$. Values of $k_{az}/k_F = 127$ or 153, determined in 0.083 M (●) or 0.20 M (□) KF, respectively, were obtained from plots of $k_{solv}/(k_{solv} - k_{obs})$ against [azide] according to $k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_F[F^-] + k_{az}[az]/k_F[F^-]$. Values of $k_{solv} = 1.4 \times 10^{-3}$ s^{-1} and $k_F/k_s = 15.7$ M^{-1} were obtained from a reciprocal fit of $1/k_{obs}$ against [F$^-$] for common ion inhibition of the hydrolysis of **3-F** by 0–0.2 M KF.

representative and are consistent with the change in partitioning of the cation **3$^+$** between the solvent, the pool of fluoride anion and azide anion, as the concentration of azide is increased (Scheme 1).

Values of k_{az}/k_F for **1$^+$**, **3$^+$**, **5$^+$**, **6$^+$**, **7$^+$**, **9$^+$**, and **10$^+$** were obtained from linear fits to plots of $k_{solv}/(k_{solv} - k_{obs})$ against [azide] (see Experimental Section, eq 2) and were used to calculate values of k_{az}/k_s, that are presented in Table 1, by combining the ratios k_{az}/k_F and k_F/k_s. **8-F** and **11-F** both exhibit a strong bimolecular reaction with azide ion under the reaction conditions, which competes too strongly with the dissociative pathway for k_{az}/k_s to be determined. Values of k_{obs} for the solvolysis of **12-Cl** in the presence of 0.5 M chloride ion at pH 9.3 in 30 mM DABCO buffer, 60% base, at ionic strength 1.0 M (NaClO$_4$), increase from 7% of k_{solv} to within 87% of the limiting value of k_{solv} over the range 0–0.5 M of added azide anion (data not shown). The ratio k_{az}/k_{Cl} may be obtained in the same manner as described above. No effect of 0–0.5 M fluoride ion on k_{obs} for the solvolysis of **12-Cl** in the presence of 0.5 M chloride ion was observed, possibly because the strong hydration of fluoride ion decreases the rate constant for trapping of **12$^+$**.

Trapping with Other Nucleophiles. Several other nucleophiles were found to trap **3$^+$** and form stable adducts in the presence of 0.2 M fluoride anion (Figure 3 and Table 3). Figure 3 shows that in the presence of 0.2 M fluoride anion thiocyanide has no effect on k_{obs} for the solvolysis of **3-F**; however, the thiolate anions, thiolacetate anion, and 2-hydroxyethanethiolate anion are very effective at trapping **3$^+$**, indeed more effective than azide ion. Acetohydroxamate and cyanide anions were found to be as effective as azide anion for trapping **3$^+$**, while bisulfite dianion and hydroxide ion were found to be slightly less reactive. The trapping of **3$^+$** by a series of substituted acetate anions is dependent on the basicity of the acetate ($\beta_{nuc} = 0.39$, Figure 4). There is some uncertainty about the value for trifluoroacetate as the observed rate increase upon addition of 0.25 M TFA is only 15%. The value in Table 3 may be an underestimate, explaining its 2-fold deviation from the Brønsted correlation through the more basic acetates. The primary amines trifluoroethylamine, ethanolamine, and ethylamine exhibit a dependence on the basicity of the amine of $\beta_{nuc} = 0.27$ (Figure
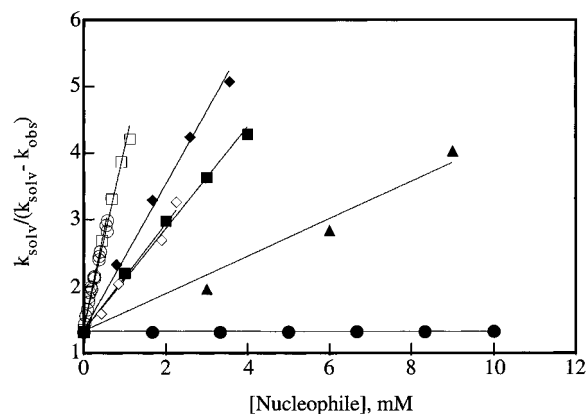

Figure 3. Dependence of $k_{solv}/(k_{solv} - k_{obs})$ on the concentration of nucleophiles for reactions of **3-F** in the presence of 0.2 M KF at 25 °C and ionic strength 1.0 M (KCl), at pH 9.3 (DABCO, 30 mM, 60% base). The lines correspond to the fit of $k_{solv}/(k_{solv} - k_{obs})$ against the concentration of 2-hydroxyethanethiolate anion, $k_{HOC_2H_4S^-}/k_s = 9300$ M^{-1} (○), thiolacetate anion, $k_{AcS^-}/k_s = 8600$ M^{-1} (□), cyanide anion $k_{CN^-}/k_s = 3500$ M^{-1} (◆), acetohydroxamate anion, $k_{AH}/k_s = 2500$ M^{-1} (◇), azide anion, $k_{az}/k_s = 2400$ M^{-1} (■), bisulfite dianion, $k_{SO_3^{2-}}/k_s = 880$ M^{-1} (▲), and thiocyanide, k_{SCN}/k_s not detectable (●) according to $k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_F[F^-] + k_{nuc}[nuc]/k_F[F^-]$ (Table 4).

Table 3. Ratios of k_{nuc}/k_F and Estimated Rate Constants, k_{nuc}, for the Addition of Nucleophiles to **3$^+$** [a]

nucleophile	pK_a[c]	N_+[d]	concn range, mM	k_{nuc}/k_F[f]	k_{nuc},[l] M^{-1} s^{-1}
water	−1.7	0.73	(55.5 M)	0.0011	1.1×10^4
trifluoroacetate	0.23		0–250	0.11	9.9×10^5
trichloroacetate	0.65		0–215	0.31	2.8×10^6
thiocyanide	0.85		0–10	−	−
difluoroacetate	1.24		0–120	1.1	9.9×10^6
cyanoacetate	2.43		0–50	3.6	3.2×10^7
fluoride	3.17		0–200	1[g]	9.2×10^6
methoxyacetate	3.53		0–60	8.9	8.1×10^7
thiolacetate	3.62		0–1	550	5.0×10^9
azide	4.72	7.54	0–100	150	1.4×10^9
acetate	4.76		0–40	13	1.2×10^8
trifluoroethylamine	5.70	3.45	0–100	0.31[h]	2.8×10^6
bisulfite	7.21	8.01	0–10	56	5.1×10^8
acetohydroxamate	9.40		0–2[e]	100	9.3×10^8
cyanide	9.40	4.12	0–4[e]	220	2.0×10^9
ethanolamine	9.50		0–70[e]	3.5[h]	3.2×10^7
2-hydroxyethanethiolate	9.54	8.87	0–2[e]	590	5.4×10^9
thioglycolate	10.25	9.09	0–0.4[e]	190[i]	1.7×10^9
ethylamine	10.6	5.28	0–4[e]	6.4[h]	5.8×10^7
hydroxide[b]	15.7	4.75	0–40	57	5.2×10^8

[a] Experimental conditions: pH 9.3 (DABCO, 30 mM, 60% base), 0.2 M [F$^-$] at 25 °C and ionic strength 1.0 M (KCl). [b] No DABCO buffer present. [c] From Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology*, 2nd ed.; Sober, H. A., Ed.; CRC Press: Cleveland, 1970. [d] From reference 5b. [e] Determined from the pK_a of the nucleophile and the pH of the solution. [f] Calculated from the linear least squares fit of $k_{solv}/(k_{solv} - k_{obs})$ against [nuc] according to $k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_F[F^-] + k_{nuc}[nuc]/k_F[F^-]$ for the solvolysis of **3-F** in the presence of 0.2 M KF. [g] Obtained from a fit of $1/k_{obs}$ against [F$^-$] for common ion inhibition of **3-F** by 0–0.2 M F$^-$. [h] A correction of 1.5×10^{-3} [amine] was added to the values of k_{obs} to allow for a solvent effect of the added amine on k_{solv} which was measured in the absence of F$^-$. [i] A correction of $0.134 \times$ [thioglycolate dianion] was deducted from k_{obs} for the disappearance of **3-F**, to take account of a competing reaction of thioglycolate dianion with the protonated form of **3-F** (see footnote 24). [l] Obtained by combining k_{nuc}/k_s with the rate constant for the hydrolysis of **3$^+$**, k_s, in Table 1.

4). At pH 9.3 ethylamine and ethanolamine are predominantly protonated and therefore the concentration of the free amine that may be attained is low, before large corrections have to be made for solvent effects (Table 3, footnote h). DABCO buffer (0.27 M, 80% base) has no noticable effect on the ratio k_F/k_s for common ion inhibition of the solvolysis of **3-F** (data not
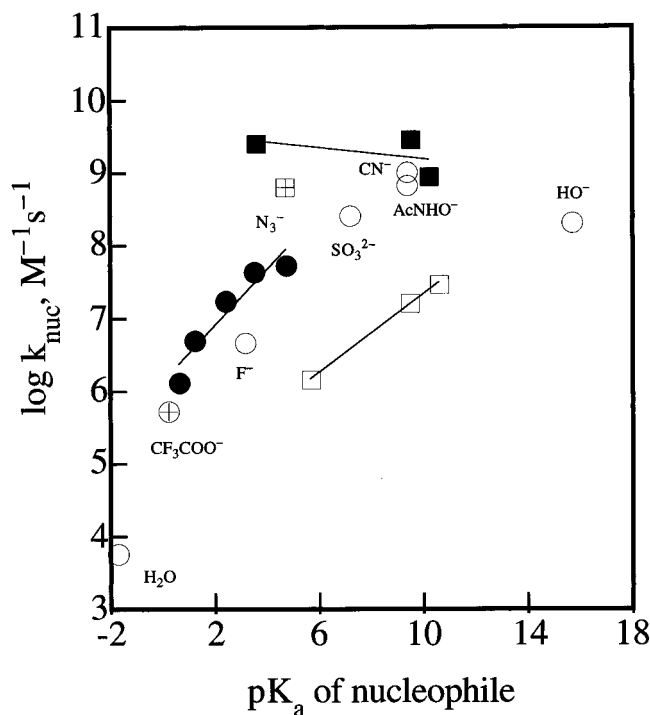
Figure 4. The dependence of log k_{nuc} on the pK_a of the nucleophile for the addition to **3$^+$** of substituted acetate ions ($\beta_{nuc} = +0.39$, ●), primary amines ($\beta_{nuc} = +0.27$, □), thiolate anions ($\beta_{nuc} = \sim0$, ■), azide anion (box with cross), and several other nucleophiles, as indicated (Table 4) in the presence of 0.2 M KF at 25 °C and ionic strength 1.0 M (KCl) at pH 9.3 (DABCO, 30 mM, 60% base).

shown), suggesting that general base catalysis of the hydration of the cation by DABCO is not significant and that general base catalysis does not make a significant contribution to the ratios k_{nuc}/k_F, obtained for the primary amines. The ratios of $k_{AcS}-/k_F$ for **1$^+$**, **5$^+$**, **6$^+$**, and **7$^+$** were obtained by the same method (Table 1).

The following criteria show that the ratios k_{nuc}/k_s in Tables 1 and 4 and k_{nuc}/k_F in Table 3 represent true partitioning rate constant ratios for the reaction of the nucleophiles, fluoride ion and water with the imidinium ions **1$^+$–12$^+$**.

1. The adducts formed by the trapping of the cations with added nucleophiles are stable for >10 half lives under the conditions of the experiment.[23]

2. Within the range 0–0.2 M fluoride ion the change in k_{obs} is accurately described by common ion depression, and the inhibition of the common ion effect by added nucleophiles is accurately described by eqs 1 and 2 (see Experimental Section).

3. The ratio of the azide and urea products, **3-az** and **3=O**, formed in 1 M sodium perchlorate, $k_{az}/k_s = 2560$ M^{-1}, obtained by analyzing the final absorbances of the reactions at different concentrations of azide ion (data not shown), agrees with the ratio of $k_{az}/k_s = 2400$ M^{-1} that was obtained from the effect of added azide ion on the observed rate constant for solvolysis of **3-F** in the presence of 0.2 M fluoride ion at ionic strength 1.0 M (KCl) (Figure 2).

4. The value of k_{solv} is not affected by the addition of 0–0.3 M azide ion, 0–0.008 M thiolacetate ion, or 0–005 M 2-hydroxyethanethiolate ion, in the absence of fluoride ion, with any of the fluoroformamidines in Table 1. Limiting values of k_{obs} at high concentrations of nucleophile in the presence of 0.2 M fluoride ion are in excellent agreement with values of k_{solv} that were obtained in the absence of added nucleophile.

This indicates that there is no significant salt effect on k_{solv} by the fluoride ion or added nucleophiles at the concentrations used.[24]

5. The partitioning experiments in Figure 2 for **3-F** were carried out in the presence of two different concentrations of fluoride ion. The ratios k_{az}/k_s obtained from these experiments are within the confidence limits (15%) of the experiments[25] and are in the opposite order to what would be expected if fluoride anion catalyzes hydration of the imidinium ion significantly.

6. The absence of a solvent deuterium isotope effect on the rate of addition of acetate ion to **3-F** at pH 9.3 over the range 0–0.1 M acetate in the presence of 0.2 M fluoride ion (data not shown) indicates that acetate-catalyzed hydration of the cation **3$^+$** is not significant over the concentration range 0–40 mM. This suggests that general base catalysis by nucleophiles that are weaker bases than acetate, such as azide and thiolacetate, does not contribute to k_s. General base catalysis of the hydrolysis of the cations is not significant for any of the nucleophiles studied, because the rate constants for the addition of the nucleophiles are several orders of magnitude greater than the rate constant for the addition of water (Table 3). However, the failure to obtain complete inhibition of the reaction at high [F$^-$] (Figure 1) could represent general base catalysis of hydration by F$^-$, which would have a solvent isotope effect.

Thiolacetate, 2-hydroxyethanethiolate, and cyanide anions are more efficient at trapping **3$^+$** than azide anion (Figure 4). Although thiolate ions generally react faster with stable sp^2-hybridized cations than azide anion,[26] the reverse is true for the 1-(4-methoxyphenyl)ethyl cation in 50:50 (v:v) TFE:H$_2$O, for which the ratio of the diffusion-limited rate constants $k_{C_3H_7S}$-/k_{az} is 0.55.[6] The larger reactivity of azide ion is presumably a statistical or steric effect.

The imidinium ions exhibit a selectivity of $k_{RS}-/k_{az} = 3-4$ which may be explained by the following possibilities:

1. A preassociation mechanism through the lower pathway in Scheme 2 could account for the differences in reactivity if noncovalent interactions of the carbocations with thiolate and cyanide ions, K_{assoc}, are more favorable than with azide ion. This mechanism follows a sequence of steps in which noncovalent association of the nucleophile with the fluoroformamidine, K_{assoc}, is followed by R–F bond cleavage, k'_{solv}, and addition of the nucleophile, k'_{Nu} (Scheme 2). However, the inhibition by fluoride ion of both the solvolysis and the substitution by azide ion of **3-F** strongly indicates a mechanism through the free carbocation **3$^+$**.

2. Azide ion may not react at a diffusion-controlled rate with the carbocations **1$^+$–11$^+$** and therefore the ratio, $k_{RS}-/k_{az}$, may reflect the diffusion-limited reaction of the thiolate ions with the carbocations and a small activation barrier for the combination of the carbocations with azide ion.

3. It is possible that imidinium ions display a different selectivity toward sp-hybridized cations and that the thiolate

(23) The final product of trapping by 2-hydroxyethanethiolate, presumably the C–O adduct, is stable.

(24) Generally the value of k_{obs} was found to be within 5% of k_{solv} at high concentrations of the nucleophiles, where measured, and eq 1 describes the changes in k_{obs} satisfactorily. However, for acetohydroxamate anion at >10 mM, a competing reaction of the nucleophile with the protonated form of **3-F** is significant; therefore, the concentration was limited to 2 mM. For the same reason thioglycolate dianion was limited to 0.4 mM (data not shown), although in this case a correction was made for a significant reaction with the protonated form of **3-F** (see footnote i, Table 3). The inital S–C adduct upon addition of the 2-hydroxyethanethiolate anion rearranges, presumably to the O–C adduct, with a rate constant, k_r, that is similar to the rate constant for the solvolysis, k_{solv}, of **3-F** at pH 9.3 and becomes partially rate limiting when $k_{obs} \sim k_{solv}$. The concentration of 2-hydroxyethanethiolate anion was therefore kept below 2 mM, in order to maintain first order kinetics.

(25) The values of k_{az}/k_s were found to be 2400 M^{-1} and 2000 M^{-1} in the presence of 0.2 M and 0.083 M fluoride ion, respectively.

(26) Ritchie, C. D.; Gandler, J. *J. Am. Chem. Soc.* **1970,** *101,* 7318.

Table 4.   The Effect of the Viscosogens Methanol and Glycerol on the Rate Constant Ratios k_{nuc}/k_s for Addition to 3^+ [a]

	$\eta/\eta°$ [b]	solvent molarity	$k_{HOC_2H_4S^-}/k_s$,[c,d] M^{-1}	k_{AcS^-}/k_s,[c] M^{-1}	k_{az}/k_s,[c] M^{-1}	k_F^-/k_s,[f] M^{-1}	k_{AcO^-}/k_s,[c] M^{-1}
H$_2$O	1	55	9300	8600	2400	15.7	200
20% v/v MeOH	1.5	49				17.4	
20% v/v Glyc	2	47	7400		2000	16.8	
45% v/v Glyc	6	37	<1500[e]	1400	1900	18.5	260

[a] Experimental conditions: pH 9.3 (DABCO, 30 mM, 60% base), 0.2 M KF at 25 °C and ionic strength 1.0 M (KCl). [b] From *Handbook of Chemistry and Physics*; Weast, R. C., Ed.; CRC Press Inc.: Boca Raton, FL, 1979. [c] Calculated by combining k_X/k_s and k_{nuc}/k_X. k_{nuc}/k_X was obtained from the linear least squares fit of a plot of $k_{solv}/(k_{solv} - k_{obs})$ against [nuc] for the disappearance of the haloformamidine in the presence of 0.2 M KF, according to $k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_X[X^-] + k_{nuc}[nuc]/k_X[X^-]$. Values of $k_{solv} = 1.4 \times 10^{-3}$ s^{-1} and $k_F/k_s = 15.7$ M^{-1} in H$_2$O, $k_{solv} = 8.7 \times 10^{-4}$ s^{-1} and $k_F/k_s = 16.8$ M^{-1} in 20% v/v glycerol, and $k_{solv} = 4.0 \times 10^{-4}$ s^{-1} and $k_F/k_s = 18.5$ M^{-1} in 45% v/v glycerol were obtained independently from plots of $1/k_{obs}$ against fluoride ion concentration for common ion inhibition of the solvolysis of **3-F** by 0–0.2 M fluoride ion. [d] The concentration of 2-hydroxyethanethiolate anion was calculated from the pH of the solution and the pK_a = 9.54 of the thiol that had been determined using the method of Jencks and Salveson (*J. Am. Chem. Soc.* **1971**, *93*, 4433.). The apparent pK_a value is 9.53 in water, 20% glycerol, and 45% glycerol. [e] An upper limit as >50% of the observed rate constant can be attributed to another underlying reaction, that is probably the reaction of the protonated form of **3-F** with the thiolate anion (see footnote 27). [f] Obtained from a plot of $1/k_{obs}$ against fluoride ion concentration for common ion inhibition of **3-F** by 0–0.2 M fluoride ion.
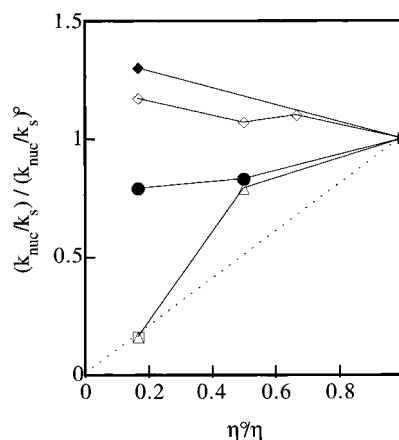
Scheme 2
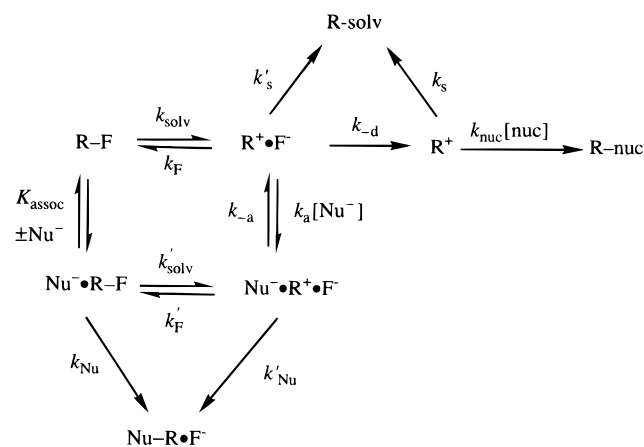
anions and azide anion are combining with the carbocation below the diffusion-controlled rate.

To examine these possibilities, we attempted to measure the effect of solvent viscosity on the ratios k_{az}/k_s, k_{AcS^-}/k_s, $k_{HOC_2H_4S^-}/k_s$, k_{AcO^-}/k_s, and k_F/k_s by using methanol and glycerol as viscosogens. If the rate constant k_{nuc} represents diffusion-controlled combination with the imidinium ion, the ratio k_{nuc}/k_s will be inversely proportional to the viscosity, because, in ideal cirumstances, k_s will be unaffected by the addition of viscosogens, while k_{nuc} will decrease in proportion to the increase in viscosity. The analysis in 20% methanol was complicated, because k_{obs} for the disappearance of **3-F** does not reach a limiting value of k_{solv} in this solvent mixture, but continues to increase with the concentration of azide or thiolate anion, making the analysis unreliable for these anions in this solvent mix. This is probably due to an underlying reaction with the protonated form of **3-F**,[27] that becomes apparent upon the addition of a significant amount of organic solvent, that retards k_{solv}. Similar effects were seen for 2-hydroxyethanethiolate anion in 45% glycerol, where it was only possible to estimate an upper limit for the ratio $k_{HOC_2H_4S^-}/k_F$ (data not shown). The ratio, k_F/k_s, was determined by common ion inhibition of the solvolysis of **3-F** in the mixed solvents. The effects of several nucleophiles were examined with the results that are summarized in Table 4.

The values of k_{AcS^-}/k_s and $k_{HOC_2H_4S^-}/k_s$ decrease by 6 and >4-fold,[28] respectively, in 45% v/v glycerol, compared with

Figure 5.   The dependence of $(k_{nuc}/k_s)/(k_{nuc}/k_s)°$ on $\eta°/\eta$ for the addition to 3^+ of thiolacetate ion (△), 2-hydroxyethanethiolate anion (□), azide anion (●), acetate anion (◆) and fluoride anion (◇) in H$_2$O ($\eta°/\eta = 1$), 20% methanol ($\eta°/\eta = 0.67$, 20% glycerol ($\eta°/\eta = 0.5$), and 45% glycerol ($\eta°/\eta = 0.17$) at 25 °C and ionic strength 1.0 M (KCl) at pH 9.3 (DABCO, 30 mM, 60% base) in the presence of 0.2 M KF (Table 3). The dashed line corresponds to the ideal situation, a slope of 1.0.

water (Figure 5). This is consistent with retardation of the rate of diffusion-controlled combination of these anions with 3^+ with increasing viscosity. However, k_{az}/k_s decreases by only 1.3 fold in 45% glycerol, suggesting that the addition of azide ion to 3^+ is activation limited. The value of k_{AcS^-}/k_s is decreased slightly in 20% glycerol ($\eta/\eta° = 2$), while the ratios k_{AcO^-}/k_s and k_F/k_s both increase slightly upon the addition of the cosolvent, suggesting that there may be a small solvent effect on the ratios that results in an overestimate of k_{AcS^-}/k_s in this solvent mixture. The 1.3-fold reduction of k_{az}/k_s in 45% glycerol where $k_{az} \sim k_{AcS^-}$ suggests that the combination of azide with 3^+ may also approach the diffusion-controlled limit in this solvent mixture.

Estimation of Cation Lifetimes. The selectivities of k_{AcS^-}/k_s for the imidinium ions 1^+, 3^+, 5^+, 6^+, and 7^+ (Table 1) were combined with the rate constant $k_{AcS^-} = 5 \times 10^9$ M^{-1} s^{-1} for diffusion-limited reaction with the cation to give the rate constants, k_s, for hydration of the cations. The rate constant for hydration of 12^+ was obtained from the ratio k_{az}/k_s in Table 1 and the rate constant of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for combination of the cation with azide anion. The small value of $k_{az}/k_{Cl} = 6$ and $k_{az}/k_s = 170$ M^{-1} is consistent with the assumption that the

---

(27) Several nucleophiles were found to react with the protonated form of **3-F** with significant rates at pH values above its pK_a (unpublished results). For instance, the second-order rate constant for the addition of azide ion is $k_{az-3FH^+} = 1.2 \times 10^3$ M^{-1} s^{-1} and for 2-hydroxyethanethiol anion $k_{HOC_2H_4S^- -3FH^+} = 3.1 \times 10^5$ M^{-1} s^{-1}. In the presence of organic cosolvents and fluoride ion these reactions could become significant at pH 9.3.

(28) It is not possible to quantify the effect of changing solvent from water to 45% glycerol on $k_{HOC_2H_4S^-}/k_s$ because of a competing reaction in the more viscous solvent that accounts for all of the observed rate constant (data not shown). An estimate of an upper limit for $k_{HOC_2H_4S^-}/k_s$ in 45% glycerol indicates that it has been significantly (>4-fold) depressed in 45% glycerol.

addition of azide anion to 12^+ is diffusion-controlled.[12] Values of k_s were estimated for 9^+ and 10^+ by extrapolation of a correlation of log k_{AcS^-}/k_s against log k_{az}/k_s from the data in Table 1.[29] A value of $k_s = 3.2 \times 10^6$ s^{-1} for 8^+ was obtained from an extrapolation of the values of k_s in Table 1 with $\beta_{dg}^{ArN} = -0.26$. A value of $k_s \sim 3.7 \times 10^6$ s^{-1} was estimated for the hydration of 11^+, assuming that the 8.8-fold difference in k_s between 1^+ and 8^+ is a good approximation to the difference between the values of k_s for 11^+ and 12^+. The rate constant $k_s = 3.1 \times 10^7$ s^{-1} for the hydration of 12^+, calculated from the ratio k_{az}/k_s in Table 1, is in good agreement with the value of $k_s > 1.7 \times 10^7$ s^{-1} obtained from the estimate of k_s for 8^+ and $\beta_{dg}^{RN} \sim -0.20$.

Discussion

Lifetimes of the Imidinium Ions. The imidinium ions, $(ArN=CNR_2^+)$ that we have examined fall within a range of reactivity of $k_s = 3 \times 10^5 - 10^7$ s^{-1}, which overlaps that of the more reactive triarylcarbocations[12] and falls within the range covered by a series of 1-phenyl-2,2,2-trifluoroethyl carbocations, $XArCH(CF_3)^+$.[8] A comparison of the reactivity of the imidinium ions described in Table 1 with a series of iminium ions recently studied in this laboratory[10e,f] shows that they are slightly more stable in water than iminium ions of similar structure. For example, an estimated rate constant of $k_s = 2.4 \times 10^6$ s^{-1} [30a] for the hydration of the iminium ion, $OC_4H_8NCH_2^+$, is only
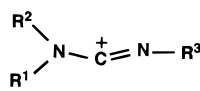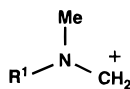
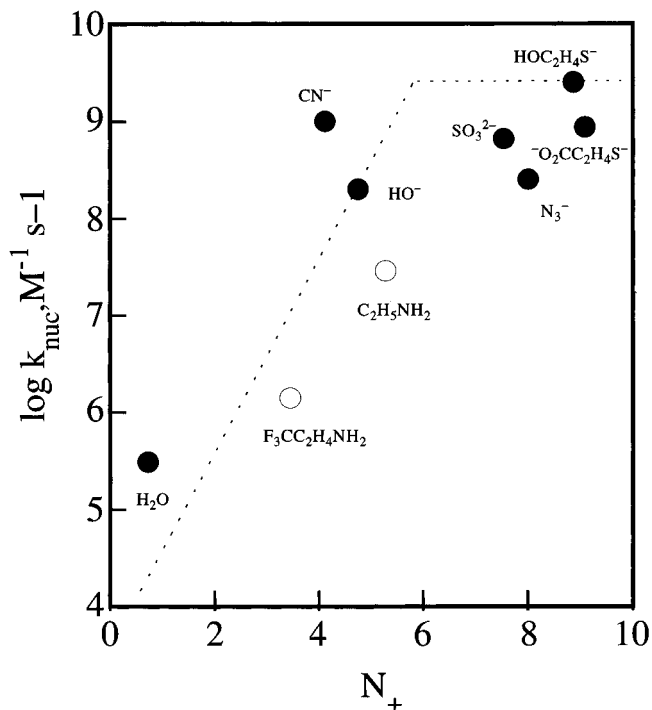4-fold greater than $k_s = 5.8 \times 10^5$ s^{-1} for the hydration of the imidinium ion I^+ in Table 1.[30b] The small effect of the second nitrogen atom may be due, in part, to an inductive effect of the sp^2-hybridized nitrogen atom of the imidinium ion, that outweighs the increased delocalization of positive charge and to the difference in the hybridization state of the cationic centers.

Selectivity of 3^+ toward Nucleophiles. The solvolysis of the fluoroformamidines (Table 1) is persuasive evidence that the imidinium ions are sufficiently stable to become diffusionally equilibrated, before they react with solute molecules or water. The rate constant ratios k_{az}/k_s for the imidinium ions in Table 1, in the range 150 to 5600 M^{-1}, are within the range expected for a diffusion-controlled reaction of azide anion with an sp^2-hybridized carbocation, based on the N_+ scale;[5,31] however, the small effect of viscosogens on k_{az}/k_s shown in Figure 5 suggests that the addition of azide anion to 3^+ is not diffusion limited. The decrease in the partitioning rate constant ratios for the reactions of thiolacetate and 2-hydroxyethanethiolate anions with 3^+ in the presence of viscosogens suggests that the rate constants for the addition of these thiolate anions to 3^+ are at least partially diffusion-controlled.[32a] We estimate that k_{az} is $\sim 3-6$-fold below the diffusion-controlled limit for the addition of azide ion to carbocations, but there is some uncertainty in this estimate,

Figure 6. The dependence of log k_{nuc} on the N_+ value of the nucleophile for the addition to 3^+ of several nucleophiles. The dashed line corresponds to a correlation of 1.0 to the N_+ scale, arbitrarily chosen to pass through hydroxide ion. The line is drawn with a slope of zero at the diffusional limit, $k_{nuc} = 5 \times 10^9$ M^{-1} s^{-1}. The rate constant for H$_2$O is in units of s^{-1}, by convention. It would fall close to the dashed line for a standard state of 1 M.

because it is possible that the limit for k_{az} may be ~ 2-fold higher than that for k_{RS^-}.[32b] The nonlimiting reactivity of azide anion observed is consistent with an analysis of the rate constants for the addition of azide ion to a series of triarylmethyl carbocations, in which it was concluded that carbocations with a rate constant for hydration of $k_s < 10^6$ s^{-1} may not react with azide anion at the diffusion-controlled limit.[12]

Table 3 summarizes the second-order rate constants for addition of nucleophilic reagents to the carbocation 3^+, based on the value of $k_{AcS^-} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled combination of thiolacetate anion with 3^+. It is clear from Figures 4 and 6 that the rate constants for most of the reactions of nucleophiles with 3^+ fall below the diffusion-controlled limit for the reaction of thiolacetate anion. The rate constants for azide and cyanide ions and thioglycolate dianion fall 3.6-, 2.5-, and 3-fold below this limit, respectively. The dashed line in Figure 6 shows the expected behavior for cation−nucleophile combinations that follow the N_+ correlation with a slope of unity before leveling off at the diffusion-controlled limit. This behavior is not observed for the addition of nucleophiles to 3^+, which follow a pattern of reactivity that is similar to that for the trityl cation (Ph$_3$C$^+$), which has a lifetime

(29) A linear plot of log k_{AcS^-}/k_s against log k_{az}/k_s has a slope of 1.36. Extrapolation to log $k_{az}/k_s = 3.6$ and 3.75 for 9^+ and 10^+ gives values of $k_{AcS^-}/k_s = 1.6 \times 10^4$ and 2.5×10^4, respectively.

(30) (a) Obtained from the rate constant of $k_s = 1.8 \times 10^7$ s^{-1} for hydration of the iminium ion II (R1 = CF$_3$CH$_2$)[10f] and the Brønsted slope of $\beta_{dg} = -0.35$, from the rate constants for hydration of a series of aryliminium ions.[10e] (b) Obtained from the value of k_s for 1^+ and $\beta_{dg}^{RN} < -0.20$.

(31) The N_+ value for azide anion is 7.5.[5b] This scale predicts a difference in reactivity toward a carbocation of of $\sim 10^7$ between azide anion and water.

(32) (a) It is possible that the reactions are not fully diffusion-limited in H$_2$O, which would explain why the reduction of k_{AcS^-}/k_s in 20% glycerol is smaller than expected; however, it should be noted that the values of k_{AcO^-}/k_s and k_F/k_s are both slightly larger in 20% glycerol than in water, suggesting that a solvent effect may be significant. The 1.3-fold decrease of k_{az}/k_s in 45% glycerol may occur because the addition of azide anion to 3^+ is partially diffusion-controlled in this solvent. (b) A value of $k_{az}/k_{C_3H_7S^-} = 1.8$ was observed[6] for reactions of the 1-(4-methoxyphenyl)ethyl carbocation in 50/50 (v/v) TFE/H$_2$O. We do not know how this limit varies with different carbocations or thiolate anions. If this value reflects the general difference between azide ion and thiolate anions, due to a statistical effect, the deviation of the rate constants for the addition of azide ion to the imidinium ions will be approximately 6-fold below the value of 5×10 M^{-1} s^{-1},[12] and the rate constants reported in Table 1 will be overestimates by a factor of approximately 2-fold.

similar to that for 3^+ in water.[33] A crude correlation through the points gives a slope of ~0.4, which is similar to that for the correlation found by McClelland for the addition of nucleophiles to the trityl cation.[33]

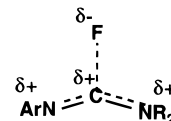Some of the deviations from the N_+ scale for the reactions of 3^+ and Ph_3C^+ with nucleophiles are probably the result of a smaller selectivity of the cations toward nucleophiles, compared with the selectivity of the relatively stable cations upon which the N_+ scale is based. Although the very existence of the N_+ scale implies that there is little change in selectivity between moderately stable cations of varying stability, the behavior of 3^+ and Ph_3C^+ [33] suggests that more reactive cations can display less selectivity toward nucleophiles. Other work supports this conclusion, for example 1-phenylethyl carbocations exhibit large changes in selectivity in their activation-limited reactions with alcohol, as the reactivity of the cation increases,[6] while similar effects of selectivity are observed for the reactions of 1-phenyl-2,2,2-trifluoroethyl carbocations with alkyl carboxylate ions and alkyl amines,[8] and for triarylmethyl and diarylmethyl carbocations with amines.[7] These effects may be the result of a relatively small curvature of the reaction barrier, compared with that for more stable carbocations; this allows the position of the transition state to shift along the reaction coordinate with changing reactivity of the reactants.[34]

The 1.4-fold decrease in k_{AcS}^-/k_{az} for the series of cations 1^+ to 7^+ (Table 1), in which the reactivity toward water decreases 5-fold across the series, is probably due to an increase in k_{az} that is activation limited, in contrast to k_{AcS}^-, which is diffusion-limited and independent of cation stability. The 5-fold decrease in k_{az}/k_s for the series of cations, 7^+ to 10^+ (Table 1), in which the reactivity toward water decreases 10-fold across the series means that as the imidinium ion becomes more unstable its reactivity toward water increases more than toward azide anion; this is consistent with a Hammond type effect.

Solvation Effects. There is no evidence that a kinetically significant desolvation step is required for the reactions of azide or cyanide anions with carbocations in hydroxylic solvents. On the contrary, the rate constants for addition of azide and thiophenolate anions to aryldiazonium ions in methanol range up to a diffusion-controlled limit of $~10^{10}$ M^{-1} s^{-1} and then level off sharply,[35] and the rate constant for the addition of azide ion to a series of triarylmethyl carbocations also increases with carbocation reactivity up to the diffusion-controlled limit of k_{az} $~ 5 \times 10^9$ M^{-1} s^{-1}.[12] For both systems desolvation of the nucleophile appears to play a minor role. While we cannot exclude the possibility that solvation or desolvation requirements of azide anion or the transition state may be significant for the addition of azide anion to 3^+, the simplest explanation for the nonlimiting rate constant is that covalent bond formation is rate limiting in this process, which is probably the case also for cyanide anion which is generally less reactive toward carbocations than azide anion.

Transition State Structures. Second-order rate constants for the reactions of substituted arylimidinium ions with fluoride anion, k_F, and first-order rate constants for the solvolysis of arylfluoroformamidines, k_{solv}, are summarized in Table 1. Brønsted type correlations for log k_{solv} give values of β_{dg}^{ArN} = +0.51 and β_{dg}^{RN} = +0.54, and for log k_F give β_{dg}^{ArN} = −0.26 and β_{dg}^{RN} ~ −0.10 (Scheme 3).

(33) McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1986**, *108,* 7023.

(34) (a) Hughes, E. D.; Ingold, C. K.; Shapiro, U. G. *J. Chem. Soc.* **1936**, 225. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77,* 334. (c) Thornton, E. R. *Ibid.* **1967**, *89,* 2915.

(35) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94,* 1589.

Scheme 3

The equilibrium constants for carbocation formation from the fluoroformamidines are given by $K_{eq} = k_{solv}/k_F$ and range from ~8×10^{-9} M^{-1} for **9-F** to ~8×10^{-13} M^{-1} for **8-F**. Brønsted type correlations for the equilibrium constants, K_{eq}, give β_{eq}^{ArN} = +0.77 and $\beta_{eq}^{RN} > +0.61$.[36] Comparison of the values of β_{dg}^{ArN} and β_{dg}^{RN} for k_{solv} and for K_{eq} is consistent with a transition state that is ~66% of the way toward the carbocation with respect to charge development, as measured by the effect of substituents on the aniline and <83% with respect to the amine. The similar relative contributions from the two nitrogen atoms indicate that reorientation and rehybridization of the two nitrogen atoms have developed to a similar extent at the transition state. Values of $\beta_{dg}^{ArN} = -0.26$ and $\beta_{dg}^{RN} < -0.20$ for the rate constant for the addition of water to the imidinium ion, k_{H_2O}, indicate that the degree of charge development on the two nitrogen atoms is similar in the transition states for the addition of water. The Brønsted correlation of $\beta_{nuc} = 0.39$ for the combination of substituted acetates with 3^+ suggests that bond formation is approximately 40% complete in the transition state for the addition of substituted acetate anions, assuming that β_{eq} is ~1.0. This is consistent with the values of 66% and <83% for the solvolysis of the haloformamidines; i.e. there is approximately 70% bond cleavage at the transition state.

Summary. Fluoroformamidines may react through a stepwise dissociative pathway with a sp-hybridized carbocation intermediate that is diffusionally equilibrated with respect to trapping by solutes present in solution. Of several nucleophiles examined, only thiolacetate and 2-hydroxyethanethiolate anions react with the series of carbocations $ArN=C(C_4H_8O)^+$ at the diffusional limit with a rate constant of ~5×10^9 M^{-1} s^{-1}. Azide, cyanide, thioglycolate, acetohydroxamate, and bisulfite ions react less rapidly. The negative deviations from extrapolations of reactivities of the carbocations, at least with some of the nucleophiles, based on N_+ parameters, probably reflect a decrease in selectivity of the more reactive carbocations, although desolvation of the nucleophile may be important for thioglycolate dianion.

Experimental Section

Materials. Unless stated otherwise organic reagents were used without further purification. Inorganic buffers and salts were reagent grade. Acetonitrile and dioxane were spectroscopic grade and were stored over 4 Å molecular sieves under nitrogen. Potassium hydroxide and hydrochloric acid were purchased from Fluka as 1 M solutions. Potassium salts of carboxylic acids and amine hydrochlorides were recrystallized from aqueous ethanol. DABCO was recrystallized as the free base from hexane. Trifluoroethanol was gold label and was stored over 4 Å molecular sieves. Aliphatic thiols were distilled under nitrogen or purchased as salts. The 99.99% isotopically pure D_2O used in this study was obtained from Cambridge Isotopes, and DCl (99.99% isotopically pure) and KOD (98+% isotopically pure) from Aldrich, were titrated against a standard before use. Amine hydrochlorides were neutralized with KOH before adding to solutions buffered with DABCO. Millipore water was used throughout.

(36) The value of β_{dg}^{RN} is an upper limit based on extrapolated values of k_{AcS}^-/k_s for reaction with the carbocations assuming that k_{AcS}^- for reaction with the carbocations is at the diffusion-controlled limit of 5×10^9 M^{-1} s^{-1} (see Table 1). The variation in the structure of the amine substituents also suggests that this value should be treated with caution.

Synthetic Methods. Toluene and ethers were dried over sodium wire and stored under nitrogen. The haloformamidines used in this study were prepared in the following general manner from the corresponding aniline:

Formanilides. The aniline was refluxed overnight in formic acid (88% v/v), and the hot solution was filtered and allowed to cool to room temperature. Formic acid was removed by distillation under reduced pressure, and the crude product was either recrystallized from aqueous ethanol to give the formanilide (>90%) or used without further purification in the next step.

Arylcarbonimidoyl Dichlorides. These were prepared following a modification of the protocol of Hegarty.[37] The formanilide (usually about 3−5 g), 1 equiv of sulfuryl chloride, and thionyl chloride (*ca.* 20 mL) in a two-necked round-bottom flask fitted with a reflux condensor were stirred overnight at room temperature. Less soluble formanilides were warmed until they dissolved, and the solution was stirred overnight at room temperature. The solvent was removed under reduced pressure with a rotary evaporator to give the imidoyl dichloride as a crude oil, which was distilled (Kugelrohr, pressure < 0.1 mmHg) to give the dichloride as a viscous clear oil, which occasionally solidified on storage at −20 °C. The yields were generally *ca.* 70%. Electron-donating groups on the aromatic ring reduce the yields significantly and produce more polymeric material, as has been noted previously.[38]

***N,N*-Dialkyl-*N′*-arylchloroformamidines.** These were generally prepared following a modification of the protocol of Hegarty.[37] Two equivalents of the amine (0.1 M in toluene) were added to a solution of the dichloride in anhydrous toluene at 0 °C. The solution was stirred at room temperature for 10 min and then filtered. The solvent was removed, and the residue was distilled (Kugelrohr, pressure < 0.1 mmHg) to give the purified imidoyl chloride (>70%) as an oil that solidified on storage.

***N*-Methyl-*N*-methoxy-*N′*-arylchloroformamidine.** To a solution of the dichloride in anhydrous toluene was added 1 equiv of *N*-methyl-*N*-methoxyamine hydrochloride and 2 equiv of triethylamine (0.1 M in toluene) at 0 °C. The product was isolated as above to give the imidoyl chloride as a yellow solid. *N*-Methyl-*N*-methoxy-*N′*-(4-nitrophenyl)chloroformamidine **12-Cl**: yellow oil; δ_H(400 MHz; CDCl$_3$) 8.21 (2H, d, *J* = 9 Hz, Ar), 7.00 (2H, d, *J* = 9 Hz, Ar), 3.81 (3H, s), 3.30 (3H, s).

***N,N*-Dialkyl-*N′*-arylfluoroformamidines.** The *N,N*-dialkyl-*N′*-arylchloroformamidines were added to a saturated solution of potassium fluoride in anhydrous trifluoroethanol and stirred for several hours. The solvent was removed, and the residue was dissolved in chloroform and chromatographed rapidly (SiO$_2$, hexane−ethyl acetate, 50/50 v/v). The isolated products were distilled (Kugelrohr, pressure < 0.1 mmHg) to give the following *N,N*-dialkyl-*N′*-arylfluoroformamidines with >90% yield, as solids that were scraped off the inside of the receiving flask: *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-phenylfluoroformamidine, **1-F**: white solid; *m/z* 209 (100%, MH$^+$), 189 (5%, M − F) and 77 (4%, C$_6$H$_5$)(Found: MH$^+$, 209.1093. C$_{11}$H$_{14}$FN$_2$O requires MH, 209.1090). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(4-fluorophenyl)fluoroformamidine, **2-F**: white solid; *m/z* 225 (100%, MH$^+$), 181 (30%, MH − CH$_2$OCH$_2$) and 137 (40%, M − C$_4$H$_9$NO)(Found: MH$^+$, 225.0825. C$_{11}$H$_{13}$FN$_2$O requires MH, 225.0839). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(4-chlorophenyl)fluoroformamidine, **3-F**: white solid; δ_H(400 MHz; CDCl$_3$) 7.27 (2H, m), 7.18 (2H, m), 3.75 (4H, m), 3.50 (4H, m); *m/z* 243 (100%, MH$^+$), 223 (3%, M − F)(Found: MH$^+$, 243.0690. C$_{11}$H$_{13}$ClFN$_2$O requires MH, 243.0700). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(3-cyanophenyl)fluoroformamidine, **5-F**: white solid; δ_H(400 MHz; CDCl$_3$) 7.32 (2H, m), 7.27 (2H, m), 3.78 (4H, t, *J* = 3 Hz), 3.50 (4H, t, *J* = 3 Hz); *m/z* 234 (100%, MH$^+$), 88.1 (95%, C$_7$H$_4$ or C$_4$H$_{10}$NO)(Found: MH$^+$, 234.1047. C$_{12}$H$_{13}$FN$_3$O requires MH, 234.1043). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(4-cyanophenyl)fluoroformamidine, **6-F**: white solid; δ_H-(400 MHz; CDCl$_3$) 7.55 (2H, d, *J* = 6 Hz), 7.05 (2H, d, *J* = 6 Hz), 3.77 (4H, t, *J* = 3 Hz), 3.52 (4H, t, *J* = 3 Hz); *m/z* 232 (100%, MH$^+$), 144 (80%, M − C$_4$H$_9$NO), 88.1 (100%, C$_4$H$_{10}$NO)(Found: MH$^+$, 232.0902. C$_{12}$H$_{13}$FNO requires MH, 232.0886). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(3-nitrophenyl)fluoroformamidine, **7-F**: yellow solid;

δ_H(400 MHz; CDCl$_3$) 7.9 (1H, d, *J* = 7 Hz), 7.85 (1H, s), 7.4 (1H, t, *J* = 8 Hz), 7.3 (1H, d, *J* = 7 Hz), 3.75 (4H, t, *J* = 3 Hz), 3.55 (4H, t, *J* = 3 Hz); *m/z* 254 (100%, MH$^+$), 234 (2%, MH − F), 224 (25%, MH − CH$_2$O), 181 (43%, M − C$_4$H$_6$O), 88.1 (40%, C$_4$H$_{10}$NO)(Found: MH$^+$, 254.0948. C$_{11}$H$_{13}$FN$_3$O$_3$ requires MH, 254.0941). *N,N*-(3-Oxapentane-1,5-diyl)-*N′*-(4-nitrophenyl)fluoroformamidine, **8-F**: yellow solid; δ_H(400 MHz; CDCl$_3$) 8.14 (2H, d, *J* = 9 Hz), 7.08 (2H, d, *J* = 9 Hz), 3.78 (2H, t, *J* = 4.5 Hz), 3.55 (2H, t, *J* = 4.5 Hz); *m/z* 254 (100%, MH$^+$), 234 (1%, M − CH$_2$OCH$_2$) and 209 (1%, M − F)(Found: MH$^+$, 254.0940. C$_{11}$H$_{13}$FN$_3$O$_3$ requires MH, 254.0941). *N*-(Butane-1,5-diyl)-*N′*-phenylfluoroformamidine, **9-F**: white solid; δ_H-(400 MHz; CDCl$_3$) 7.27−7.22 (3H, m), 6.98 (2H, m), 3.43 (4H, s), 1.63 (6H, s). *N,N*-(3-Azapentane-1,5-diyl)-*N′*-phenyl-*N″*-methylfluoroformamidine, **10-F**: white solid; δ_H(400 MHz; CDCl$_3$) δ 7.4−7.2 (2H, m), 7.1−6.9 (3H, m), 3.5 (4H, t, *J* = 3 Hz), 2.5 (4H, t, *J* = 3 Hz), 2.35 (3H, s); *m/z* 221 (100%, MH$^+$), 202 (70%, MH − F), 164 (15%, M − C$_3$H$_7$N), 83 (20%, C$_5$H$_9$N), 70 (65%, C$_4$H$_8$N)(Found: MH$^+$, 222.1386. C$_{12}$H$_{17}$FN$_3$ requires MH, 222.1406). *N*-Methyl-*N*-methoxy-*N′*-phenylfluoroformamidine, **11-F**: clear oil; δ_H(400 MHz; CDCl$_3$) 7.3 (2H, t, *J* = 8 Hz, Ar), 7.1 (1H, t, *J* = 8 Hz, Ar), 7.05 (2H, d, *J* = 8 Hz, Ar), 3.75 (3H, s), 3.15 (3H, s); *m/z* 181 (100%, MH$^+$), 166 (10%, M − CH$_3$), 151 (1%, M − OCH$_3$), 119 (7%, M − HNCH$_3$(OCH$_3$)), 61 (55%, HNCH$_3$(OCH$_3$)), 77 (2%, C$_6$H$_5$)(Found: MH$^+$, 181.096. C$_9$H$_{12}$FN$_2$O requires MH, 181.0777). **4-F** was prepared by adding a solution of **4-Cl** in acetonitrile to an equal volume of aqueous 0.1 M potassium fluoride and then adding 2 μL of the resulting solution to the reaction mixture. The changes in the UV spectra upon hydrolysis of the compounds that were used for kinetic analysis were all very similar and were consistant with hydrolysis to the urea.

Kinetic Methods. The fluorides were stored at −20 °C for periods of weeks without any noticable decomposition. The chlorides were unstable after prolonged storage, as noted previously.[38] Reaction solutions at ionic strength 1.0 M, maintained with KCl, were prepared in quartz cuvettes and equilibrated to 25 °C before the addition of *ca.* 5 μL of a 0.03 M stock solution of the substrate in acetonitrile or dioxane. The products and substrates of the various reactions studied had largely overlapping ultraviolet spectra. Most reactions exhibited a shift in the ultraviolet spectrum to longer wavelength which enabled a change in absorbance of typically 0.4 to be monitored at the concentration of 5×10^{-5} M, that was generally used. Biphasic kinetics were observed if the substrate was not completely dissolved, and these runs were discarded. The reactions were followed with a Cary 1E UV-visible spectrophotometer, a Perkin-Elmer Lamda 4B UV/vis spectrophotometer, or a Milton Roy Company spectronic 1001. The buffer concentration was ≥100 times the substrate concentration, so that pseudo-first-order conditions were maintained. Standard conditions were 25 °C at ionic strength 1.0, maintained with potassium chloride. When thiolates were used, argon gas was bubbled through the reaction cells prior to addition of reagents. All pH measurements were made under the conditions of the kinetic experiments using an Orion Research Digital pH meter with a 611 Corning semimicro combination electrode. The pD of solutions in D$_2$O was measured using the same electrode that had been standardized against (protium) standard buffers and was taken to be 0.4 above the reading of the pH meter.[39] The absorbance was measured at set intervals (more than ten points per half life) and recorded either on a printer connected to the spectrophotometer or on a computer. The data were analyzed with a Gateway 2000 4SX-33 computer using Sigma Plot. Reactions were generally followed for >5 half lives and an end point was taken after >10 half lives. Rate constants were obtained from semilogarithamic plots of $(A_t − A_\infty)$ against time. These were linear for more than five half-lives, and, where duplicated, the rate constants were generally within 5%.

Rate constant ratios k_{nuc}/k_X for the reactions of nucleophiles with the haloformamidines were determined from a plot of $k_{solv}/(k_{solv} − k_{obs})$ against [nuc], obtained in the presence of a constant concentration of a common halide anion, X$^-$, according to eq 2 which is obtained simply by rearrangement of eq 1. Values of k_X/k_s and k_{solv} were determined by common ion inhibition in the absence of the nucleophile using eq 3.[40]

(37) Hegarty, A. F.; Cronin, J. D.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 429.

(38) Kühle, E. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 647.

(39) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188.

(40) See Royer R. E.; Daub, G. H.; Vander Jagt, D. L. *J. Org. Chem.* **1979**, *44*, 3196, for a similar approach.

$$k_{obs} = \frac{k_{solv}k_s + k_{solv}k_{nuc}[\text{nuc}]}{k_X[X^-] + k_s + k_{nuc}[\text{nuc}]} = \frac{k_{solv}(1 + (k_{nuc}[\text{nuc}]/k_s))}{(k_X/k_s)[X^-] + 1 + (k_{nuc}[\text{nuc}]/k_s)}$$

(1)

$$k_{solv}/(k_{solv} - k_{obs}) = 1 + k_s/k_X[X^-] + k_{nuc}[\text{nuc}]/k_X[X^-]$$ (2)

$$\frac{1}{k_{obs}} = \frac{k_X[X^-]}{k_{solv}k_s} + \frac{1}{k_{solv}}$$ (3)

Product Analysis. *Hydrolysis* of the series of imidoyl fluorides in Table 1 over the full pH range gave ultraviolet spectra that were identical to those of the products of hydrolysis of the corresponding chlorides, the urea. For example, **3-F** and **3-Cl** both gave *N,N*-(3-oxapentane-1,5-diyl)-*N'*-(4-chlorophenyl)urea, δ_H(400 MHz; CDCl$_3$) 7.25−7.15 (4H, m), 3.75 (4H, t, *J* = 3 Hz), 3.45 (4H, t, *J* = 3 Hz). The product of hydrolysis of **8-F** below pH 11 is the corresponding urea. However, above pH 11 an unidentified yellow product (λ_{max} = 440 nm) is formed that is not derived from the stable urea.

Addition of Azide. **3-F** (10 mg, 4 × 10^{-5} mol) was dissolved in CD$_3$CN, and an equal volume of aqueous 1.0 M NaN$_3$ was added. After 2 h the solution was extracted with chloroform, the solvent was removed *in vacuo*, and the residue was chromatographed (SiO$_2$, hexane−ethyl acetate, 1:1, v/v) to give *N,N*-(3-oxapentane-1,5-diyl)-*N'*-(4-chlorophenyl)azidoformamidine: δ_H(400 MHz; CDCl$_3$) 7.7−7.3 (4H, m), 3.75 (4H, t, *J* = 3 Hz), 3.25 (4H, t, *J* = 3 Hz). The ultraviolet spectrum of the product is identical to the that of the product obtained when **3-F** was added to a 1 mM solution of NaN$_3$ (pH = 9.3, DABCO buffer, 30 mM, 60% base) and is consistent with the substitution of azide anion for fluoride anion. The changes in the ultraviolet spectra of the series of fluoroformamidines in Table 1 were all consistent with formation of the azido products, which were stable to hydrolysis for >24 h at 25 °C and ionic strength 1.0 M (KCl). The products of azide addition to **8-F** and **11-F** were not stable above pH 11.

Addition of Acetate to 3-F. At pH > 6 acetate anion adds to **3-F** to give an adduct *N,N*-(3-oxapentane-1,5-diyl)-*N'*-(4-chlorophenyl)-acetoxyformamidine; δ_H(400 MHz; CDCl$_3$) 7.4 (2H, d, *J* = 6 Hz), 7.23 (2H, d, *J* = 6 Hz), 3.62 (4H, m), 3.52 (4H, m), 2.1 (3H, s). There is a single isosbestic point at 228 nm in the ultraviolet spectrum. The addition of other acetates give a similar change in the ultraviolet spectrum that is consistent with substitution of the acetate for fluoride.

Addition of Thiolate Anions. Thiolate anions substitute for fluoride under the experimental conditions and give a characteristic increase in the ultraviolet spectrum at ~300 nm. 2-Hydroxyethanethiolate anion adds to **3-F** and **3-Cl** at sulfur and then rearranges to the ether with a decrease in absorbance at 300 nm. *N,N*-(3-Oxapentane-1,5-diyl)-*N'*-4-chlorophenyl(2-mercaptoethoxy)formamidine; δ_H (400 MHz; CDCl$_3$) 7.3, (4H, m, Ar), 3.9 (2H, t, *J* = 3 Hz), 3.75 (4H, t, *J* = 3 Hz), 3.45 (4H, t, *J* = 3 Hz), 2.9 (2H, t, *J* = 3 Hz).

Addition of Other Nucleophiles. Several other substitutions were examined: the addition of cyanide ion and acetohydroxamate ion displayed unique isosbestic points at 268 and 247 nm, respectively. The product of the reaction of **3-F** with several primary amines was not identified because a considerable amount of the urea is formed from hydrolysis of the imidinium ion under the reaction conditions. The product of the reaction with bisulfite was assumed to be the bisulfite adduct.