Nucleophilic Attacks on Carbon–Carbon Double Bonds. 25.[1,2] Reactions of Monoamines and Diamines with 1,1-Dicyano-2-*p*-dimethylaminophenyl-2-trifluoroethoxyethylene

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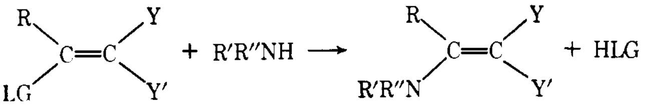
Abstract: The substitution of the trifluoroethoxy group of 1,1-dicyano-2-*p*-dimethylaminophenyl-2-trifluoroethoxyethylene (**6**) by aliphatic monoamines and diamines in acetonitrile was studied. With 1,2- and 1,3-diamines and their *N,N*-dimethyl derivatives the reactions were first order in the amine with low $\Delta H^{\ddagger}$ and high negative $\Delta S^{\ddagger}$ values. Differences between the rates of most of the diamines were small and the reactions were much faster than the uncatalyzed reaction of the monoamines. The rate equation for the monoamines contains both a first-order, noncatalyzed (k') and a second-order, amine-catalyzed (k'') term in the amine. Sterically hindered secondary amines gave a curved k_{obsd} vs. [amine] plot. Most of the k''/k' ratios followed the amine basicity and were low for hindered amines. The $\Delta H^{\ddagger}$ values were low or negative and the $\Delta S^{\ddagger}$ values were highly negative. It is suggested that the reactions initiate by an equilibrium addition of the amines to **6** to form the zwitterion **2**. With the diamines this is followed by a rate-determining intramolecular proton transfer to the free amino group of **2**. The rate-determining step for the noncatalyzed route involves an intramolecular assisted leaving-group departure by the ammonium ion while the catalyzed route involves an intermolecular deprotonation by another amine molecule. Steric effects are important in the addition and the deprotonation steps. The activation parameters and the solvent and substituent effects were discussed and alternative reaction routes were excluded.

In nucleophilic vinylic substitution via addition–elimination[3,4] the cleavage of the bond to the leaving group (LG) is usually faster than the rate of addition of the nucleophile to the double bond. Regardless of the rate-determining step, a second-order kinetics is predicted if the intermediate is formed in steady-state concentrations. Hence the usually observed second-order kinetics[3] cannot distinguish between a concerted one-step mechanism and a multistep reaction via a carbanionic intermediate. A probe used to distinguish between these alternatives is the comparison of the reactivities of systems which carry different leaving groups, since the cleavage of the C–LG bond is part of the concerted process. The similar reactivities of otherwise identical substituted vinyl chlorides and bromides argue strongly for a multistep process.[3,5,6] A consequence of this mechanism is that if the C–LG bond cleavage becomes slower while the rate of the nucleophilic attack is only slightly affected, a point may be reached when the lifetime of the intermediate may become long enough making the C–LG bond cleavage rate determining. Structural and medium changes which are likely to favor this change are better negative charge stabilizing α substituents, a dipolar aprotic solvent where the anionic leaving group is destabilized, a nucleophile whose attachment to the β carbon of the intermediate reduces the ease of the C–LG cleavage, and especially a leaving group of low nucleofugacity.

This goal was achieved in our recent work on replacement of "sluggish" leaving groups in appropriately substituted electrophilic olefins by amines in aprotic solvents (eq 1).[7-11]

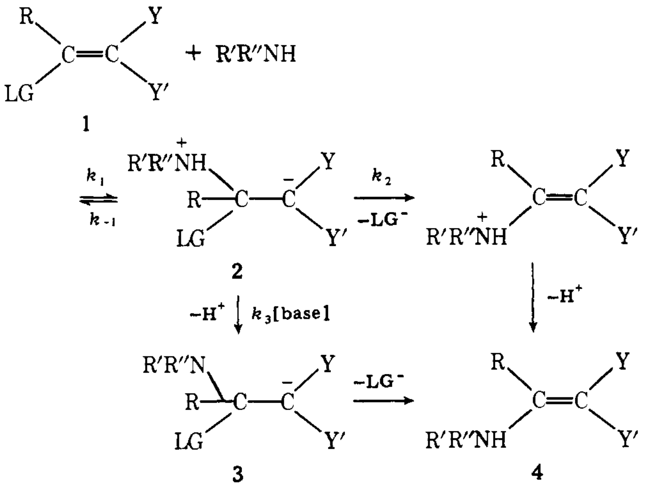


(1)

Y, Y' = electron-withdrawing groups

The details of the reaction are given in Scheme I. The intermediate formed by the initial nucleophilic attack of amine on the electrophilic olefin **1** is the zwitterion **2**, and the combination of a sluggish leaving group and the strong electron withdrawal by the ammonium moiety at C_β slows down the C–LG bond cleavage as to make it sometimes rate determining.

Scheme I



e.g., base = R'R''NH

A special feature of **2** is that formation of the final product **4** can take place by two routes: (a) A slow C–LG bond cleavage (rate constant k_2) is accompanied by a fast loss of the proton from the N-protonated **4**. (b) Slow amine-promoted deprotonation of the ammonium ion gives the carbanion **3** (rate constant k_3) from which the C–LG bond cleavage is fast.

Regardless of the detailed mechanism, the observation of an appreciable "amine-catalyzed" reaction is a strong evidence for a multistep mechanism.

The analogous reaction in nucleophilic aromatic substitution has been known for many years[12] and was extensively investigated,[12-15] but the prediction of amine catalysis in vinylic system was borne out only recently. Both a third-order catalyzed reaction, second order in the amine with rate constant k'', and a second-order uncatalyzed reaction, first order in the amine with rate constant k', were observed.[7-11] The relative importance of the two routes is usually evaluated in terms of the k''/k' ratios. Catalysis was not observed with good leaving groups such as brosylate or tosylate in system **1a**,[6] but when the electron-withdrawing ability of the α substituents increases

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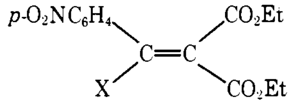
Table I. Reaction of Diamines with **6** in Acetonitrile[a]

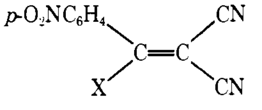
amine	in H_2O[b]		in MeCN[c]		concn range, 10^4 M[d]	k', $M^{-1}\,s^{-1}$[e]		$\Delta H^{\ddagger}$,[f] kcal mol^{-1}	$\Delta S^{\ddagger}$ (303 °C),[f] cal mol^{-1} K^{-1}
	pK_1	pK_2	pK_1	pK_2		at 30 °C	at 45 °C		
$H_2NCH_2CH_2NH_2$	9.93	6.85	18.46	13.01	2-16	5.66 ± 0.08	8.21 ± 0.05	4.1 ± 0.8	−43 ± 3
					3-10	5.13 ± 0.06[g]	6.89 ± 0.17[g]	3.1 ± 0.04[g]	−46 ± 0.1[g]
$H_2NCHMeCH_2NH_2$	10.00	7.13			2-7	2.57 ± 0.12	4.68 ± 0.12	7.0 ± 0.1	−35 ± 0.5
$H_2NCH_2CH_2CH_2NH_2$	10.30	8.29	19.70	14.98	3-10	8.80 ± 0.23	12.0 ± 0.70	3.3 ± 0.1	−45 ± 0.3
$Me_2NCH_2CH_2NH_2$	9.53	6.63			2-12	3.78 ± 0.09	6.02 ± 0.07	5.3 ± 0.1	−40 ± 0.3
$Et_2NCH_2CH_2NH_2$	10.02	7.07			2-7	5.49 ± 0.08	7.53 ± 0.11	3.4 ± 0.04	−45 ± 0.1
$Me_2NCHMeCH_2NH_2$					2-7	6.10 ± 0.07	6.97 ± 0.12	1.1 ± 0.1	−53 ± 0.2
$Me_2NCH_2CHMeNH_2$					2-7	0.88 ± 0.02	1.41 ± 0.04	5.3 ± 0.04	−43 ± 0.1
$Me_2NCH_2CH_2CH_2NH_2$	9.91	7.67			2-7	5.61 ± 0.20	8.39 ± 0.23	4.5 ± 0.05	−42 ± 0.2

[a] [**6**] = (0.5-5) × 10^{-5} M. [b] Z. Rappoport, "Handbook of Tables for Organic Compounds Identification", 3rd ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1967. [c] J. F. Coetzee, *Prog. Phys. Org. Chem.*, **4**, 45 (1967). [d] Concentration range of the amine used for establishing the second-order kinetics. [e] Average of at least four experiments. [f] The errors in the activation parameters were calculated according to R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961). [g] Reaction in tetrahydrofuran.



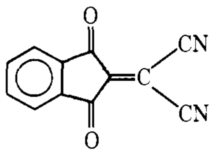
X = OTs, OBs

1a



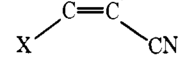
X = Cl, Br

1b

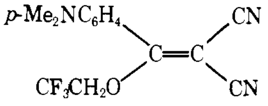


1c

as in system **1b**, catalysis is shown even with good leaving groups such as chloride and bromide, although the k''/k' ratios are low.[11] On the other hand, in reactions with **1c** with the notoriously slow cyano leaving group,[16] the third-order process is dominant and is nearly exclusive with several amines. Extensive studies of system **5**, X = Cl,[7] F,[7,8] OEt,[9] CN,[9] OAr,[17] showed that the kinetic behavior varies with the nature of the leaving group. With X = Cl, a weak catalysis was observed in acetonitrile[7a] but not in alcohols,[7b] while with X = F with anilines[7a] or with X = CN with morpholine in acetonitrile[9] only the catalyzed process was observed. With ethoxy[9] and substituted phenoxy[17] as the leaving groups both catalyzed and uncatalyzed terms were found. While it is clear that k''/k' ratios are low or zero for good leaving groups and high for sluggish leaving groups, the extent of catalysis for the latter does not follow expected measures of leaving-group ability such as the pK_a of the conjugate acid of the leaving groups. Since steric effects may be important in this respect, it seemed desirable to study a leaving group more reactive than ethoxy but less reactive than fluoride but with identical steric bulk with the former. We therefore chose for our study the trifluoroethoxy derivative of system **5**, i.e., 1,1-dicyano-2-*p*-dimethylaminophenyl-2-trifluoroethoxyethylene (**6**).



5



6

In addition there are several questions concerning the role of the "catalytic" amine molecule which were either little studied or deserve further study. Although we presented above the catalyzed process as involving a rate-determining proton transfer on the basis of evidence for systems **1c**[10] and **5**, X = F,[7,8] other alternatives are specific base-general acid catalysis, electrophilic catalysis, or bifunctional catalysis. The details of the catalysis may depend on the leaving group and have to be investigated for each system. Another question is whether an internal base may compete favorably with an external amine molecule. Furthermore, although the effects of the basicity, the steric bulk of the amine, and the polarity of the solvent on the k''/k' ratios were investigated in the past,[7-11] additional information is required for extending our understanding of these effects.

For these reasons we studied the reactions of compound **6** with amines of different electronic and steric requirements. We especially investigated the reactions of diamines where one amino group serves as the nucleophile while the other may serve as an internal catalyst in the substitution process. To our knowledge only one such system was previously studied in vinylic substitution,[8] but to our surprise substitution by diamines in nucleophilic aromatic substitution was studied only in a few cases.[18-20] The monoamines also had different basicities and steric bulk and involved primary, secondary, and tertiary amines. For comparison with previous work, acetonitrile was mostly used as the solvent.

Results

Reaction with Diamines. The reactions of **6** with 1,2-diaminoethane, 1,2- and 1,3-diaminopropane, and their mono-*N,N*-dimethyl derivatives were studied in acetonitrile under pseudo-first-order conditions. The amine concentrations were changed between 2.5- and eightfold for different amines and the concentration of **6** was changed by a factor of 2 in the reaction with each amine. All the reactions were found to be of an overall second order (rate constant k'), first order in **6** and in the amine. The reactivity differences between most of the amines were small and the statistically corrected reactivity for the terminal diamines was close to that of their mono-*N,N*-dialkyl derivatives. The reactivity differences for the substituted 1,2-diaminopropanes were larger and 2-amino-1-dimethylaminopropane was much less reactive than the other amines. The activation enthalpies were low but positive and the activation entropies were highly negative. The reaction of 1,2-diaminoethane in tetrahydrofuran was also of a second order and had kinetic parameters similar to those in acetonitrile. The data are given in Table I and examples of k' vs. [amine] plots for 1,2-diaminoethane and its mono-*N,N*-dimethyl derivative are given in Figure 1.

Reactions with Monoamines. The reactions with primary and secondary, hindered and nonhindered monoamines were conducted in acetonitrile under conditions similar to those used for the diamines. In all the systems the observed second-order rate constant k_{obsd} increased with the increase in the amine

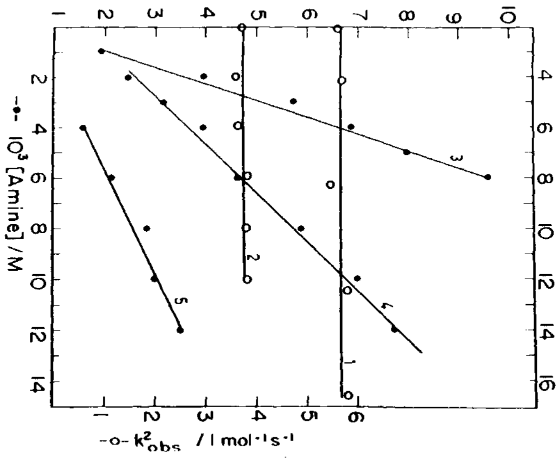


Figure 1. k_{obsd} vs. [amine] plots for the reactions of **6** in acetonitrile at 30 °C with (1) 1,2-diaminoethane; (2) *N,N*-dimethyl-1,2-diaminoethane (upper and right scales); (3) *n*-propylamine; (4) ethanolamine; (5) 2-methoxyethylamine (lower and left scales).

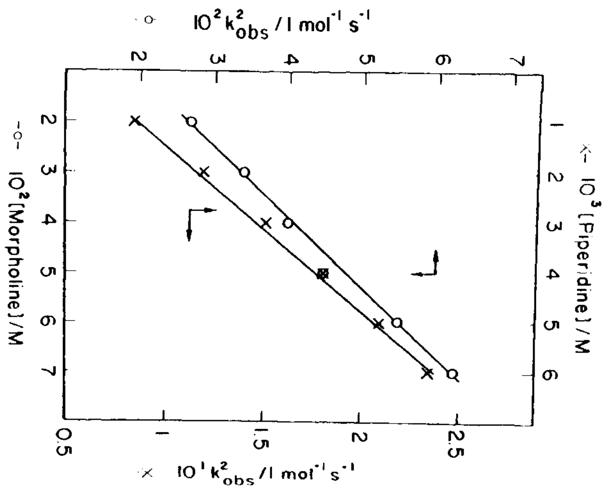


Figure 2. k_{obsd} vs. [amine] plots for the reactions of **6** with morpholine (O, lower and left scales) and piperidine (X, upper and right scales) in acetonitrile at 30 °C.

concentration. Except for the reactions of diisopropylamine and diisobutylamine at 30 °C, the rate increase was linear according to

$$k_{obsd} = k' + k''[\text{amine}] \tag{2}$$

This is demonstrated in Figure 1 for the primary amines *n*-propylamine, ethanolamine, and 2-methoxyethylamine and in Figure 2 for the secondary amines piperidine and morpholine. The least-squares intercepts, which are the "uncatalyzed" second-order rate coefficients k', and the slopes, which give the "amine-catalyzed" third-order rate coefficients k'', and their ratios are given in Table II.[21] The k''/k' ratios are high for all the systems except for *tert*-butylamine and with imidazole the relative contribution of the uncatalyzed process at 30 °C is so low that the reaction is of an overall third order.

Table II. Reactions of Amines with **6**[a]

	pK_a		concn		$10^2k'$, M^{-1} s^{-1} [e]		k'', M^{-2} s^{-1} [e]		k''/k', M^{-1}	
amine	in H_2O[b]	in MeCN[c]	range, 10^2 M[d]	solvent	at 30 °C	at 45 °C	at 30 °C	at 45 °C	at 30 °C	at 45 °C
$CH_3CH_2CH_2NH_2$	10.69	18.22	0.1-0.6	MeCN	8.7 ± 0.3	6.1 ± 0.2	147.0 ± 8.0	172.0 ± 5.0	1700	2820
$CH_3(CH_2)_3NH_2$	10.61	18.26	0.2-0.7	MeCN	19.3 ± 2.1	6.9 ± 0.2	144.0 ± 4.0	172.0 ± 5.0	746	2480
			0.1-0.6	THF	5.5 ± 0.1	1.0 ± 0.1	110.0 ± 2.0	74.2 ± 3.0	1985	7200
$(CH_3)_2CHCH_2NH_2$	10.72	17.92	0.2-1.2	MeCN	14.3 ± 1.3	3.8 ± 0.16	30.1 ± 1.7	45.1 ± 2.2	210	1190
$HOCH_2CH_2NH_2$	9.50	17.53	0.2-1.2	MeCN	16.3 ± 1.5	12.6 ± 1.9	52.2 ± 2.1	75.4 ± 3.5	320	598
$MeOCH_2CH_2NH_2$	9.61		0.2-1.0	MeCN	7.3 ± 0.2	2.7 ± 0.5	23.7 ± 2.3	37.2 ± 0.7	326	1646
$HOCH_2CH_2CH_2NH_2$	9.96		0.1-0.6	MeCN	71.1 ± 2.3	38.5 ± 7.0	133.0 ± 5.0	339.0 ± 25.0	187	880
piperidine	11.21	18.92	0.1-0.6	MeCN	5.9 ± 0.3	0.6 ± 0.07	30.1 ± 0.8	34.4 ± 0.2	514	5740
			0.5-4.0	THF	0.8 ± 0.02	0.87 ± 0.05	5.50 ± 0.08	4.53 ± 0.14	692	526
morpholine	8.33	16.61	2-7	MeCN	1.22 ± 0.18	1.26 ± 0.27	0.70 ± 0.04	0.78 ± 0.05	58	62
			2-7	THF	1.31 ± 0.07	1.32 ± 0.15	0.28 ± 0.02	0.32 ± 0.03	22	24
			1-5	Me_2SO	3.23 ± 0.5		2.55 ± 0.15		79	
Me_3CNH_2	10.68	18.14	20-60	MeCN	0.146 ± 0.01	0.0094 ± 0.0003	0.055 ± 0.001	0.0041 ± 0.0002	6.4	7.4
imidazole	6.95		10-50	MeCN	0	0.24 ± 0.01	0.05 ± 0.001	0.042 ± 0.004	∞	17
$(Me_2CHCH_2)_2NH$	10.91	17.88	5-60	MeCN	[f]	0.014 ± 0.004	[f]	0.0017 ± 0.0001	[f]	12.2
Et_3N	10.75	18.46	10-50	MeCN	0.10 ± 0.01	0.196 ± 0.018	0.35 ± 0.03	0.375 ± 0.05	3.4	1.9
Dabco[g]	8.19	18.29	5-30	MeCN	0.11 ± 0.01	0.446 ± 0.02				

[a-d] See corresponding footnotes to Table I. [e] The errors are the computed standard deviations of the intercepts and the slopes. [f] Curved k_{obsd} vs. [amine] was found at 30 °C. [g] Diazabicyclo[2.2.2]octane.

Table III. Second-Order Rate Constants for the Reaction of Hindered Amines with **6** in Acetonitrile at 30 °C[a]

$10^3[i\text{-}Bu_2NH]$, M	50	100	100[b]	200	300	400	500	600
10^5k_{obsd}/L mol^{-1} s^{-1}	21.6	32.8	33.2	52.3	65.3	75.5	82.9	86.9
$[k_{obsd}/(k_1 - k_{obsd})]/[i\text{-}Bu_2NH]$, M^{-1}	4.4	3.8	3.8	3.9	4.0	4.2	4.4	4.4
$10^3[i\text{-}Pr_2NH]$, M	50	100	200	300	400	500	500[b]	
10^5k_{obsd}/L mol^{-1} s^{-1}	66	87	150	192	205	214	208	
$[k_{obsd}/(k_1 - k_{obsd})]/[i\text{-}Pr_2NH]$, M^{-1}	5.9	4.3	5.4	6.5	6.0	5.6	5.1	

[a] [**6**] = (5.6–6.5) × 10^{-5} M. [b] [**6**] = 2.5 × 10^{-5} M.

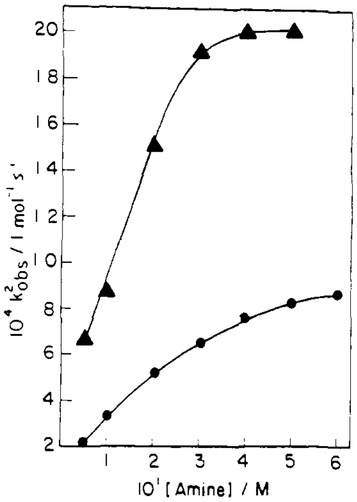


Figure 3. k_{obsd} vs. [amine] plot for the reactions of **6** with diisobutylamine (●) and diisopropylamine (▲) in acetonitrile at 30 °C.

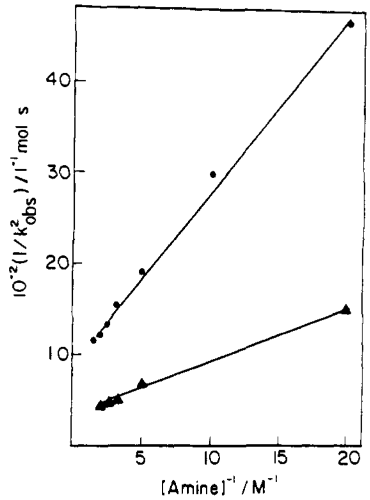


Figure 4. $1/k_{obsd}$ vs. 1/[amine] plots for the reactions of **6** with diisobutylamine (●) and diisopropylamine (▲) in acetonitrile at 30 °C.

Table IV. Kinetic Parameters for the Reaction of **6** with Sterically Hindered Amines in Acetonitrile at 30 °C

amine	k''', M s	k'''', M^2 s	10^5k_1, M^{-1} s^{-1}	$10^5\cdot k_1k_3/k_{-1}$, M^{-2} s^{-1}	k_3/k_{-1}, M^{-1}
$(Me_2CHCH_2)_2$-NH	885	195	113 ± 7	514 ± 17	4.6 ± 0.4
$(Me_2CH)_2NH$	345	58.5	290 ± 10	1710 ± 40	5.9 ± 0.4

With diisobutylamine and diisopropylamine the k_{obsd} values at 30 °C increase nonlinearly with the amine concentration (Table III). The curved dependence indicates an approach to a plateau in the k_{obsd} vs. [amine] relationship at high amine concentration (Figure 3). An inverse plot of $1/k_{obsd}$ against 1/[amine] for these two amines is linear (eq 3, Figure 4). The intercepts (k''') and the slopes (k'''') of these relationships together with their reciprocals (see Discussion section) are given in Table IV.

$$1/k_{obsd} = k''' + k''''/[\text{amine}] \qquad (3)$$

The reactions of **6** with morpholine, piperidine, and *n*-butylamine in tetrahydrofuran and that of morpholine in dimethyl sulfoxide showed a similar kinetic behavior and the data are in Tables II and V.

The activation parameters for the uncatalyzed and the catalyzed processes are given in Table V. Almost all the $\Delta H^{\ddagger}$ values for the uncatalyzed process are negative and the $\Delta S^{\ddagger}$ values are extremely highly negative. The $\Delta H^{\ddagger}$ values for the catalyzed reaction are mostly low or negative and the activation entropies are negative, but less than for the uncatalyzed process. Obviously, the errors in some of the low $\Delta H^{\ddagger}$ values and in the derived $\Delta S^{\ddagger}$ values are very high. Since the values seem unusual few experiments were repeated after 1 year with freshly distilled solvent and reagents. The results were identical within the experimental error with those given in Tables II and V.

For comparison with the reactions of the *N,N*-dimethyldiamines the stability of **6** in the presence of triethylamine, *N*-methylpiperidine, and 1,4-diazabicyclo[2.2.2]octane (Dabco) was studied. It was found that the absorption at the λ_{max} of **6** at 400 nm decreased in a pseudo-first-order reaction with a concomitant formation of a new maxima at 303 nm with triethylamine and *N*-methylpiperidine and at 515 nm with Dabco. The products were not isolated. The k_{obsd} values were approximately constant for Dabco, followed eq 2 for triethylamine (Table II), and were irreproducible for *N*-methylpiperidine.

Aromatic and heterocyclic amines such as *p*-anisidine, *p*-phenylenediamine, pyridine, 2-aminopyridine, and pyrazole were unreactive in their reaction with **6** even at [amine] ≥ 0.2 M for 5 h at 45 °C.

Discussion

The present results suggest a different reaction mechanism for the monoamines and for the diamines. Points of interest involve the nature of the uncatalyzed process for the diamines and its relationship either to the catalyzed or to the uncatalyzed process with the monoamines, the extreme values of the activation parameters, and the effects of the solvent, the leaving group, and the structure of the amine on the competition between the catalyzed and the uncatalyzed routes.

A steady-state treatment of Scheme I gives eq 4 for the observed second-order rate constant and four kinetic behaviors may be observed.

$$k_{obsd} = \frac{k_1(k_2 + k_3[\text{amine}])}{k_{-1} + k_2 + k_3[\text{amine}]} \qquad (4)$$

(a) For good leaving groups one of the forward reactions of **2** or both reactions are faster than the reverse reaction, k_2 +

Table V. Activation Parameters for the Second- and Third-Order Processes in the Reaction of **6** with Amines[a]

		"uncatalyzed" reaction		"catalyzed" reaction	
amine	solvent	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$ (30 °C), cal mol^{-1} K^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$ (30 °C), cal mol^{-1} K^{-1}
$HOCH_2CH_2NH_2$	MeCN	−4 ± 2	−76 ± 8	4 ± 1	−39 ± 3
$MeOCH_2CH_2NH_2$	MeCN	−15 ± 7	−116 ± 23	5 ± 2	−37 ± 8
$HOCH_2CH_2CH_2NH_2$	MeCN	−8 ± 1	−86 ± 3	11 ± 1	−13 ± 3
piperidine	MeCN	−30 ± 1	−164 ± 4	1 ± 1	−50 ± 2
morpholine	MeCN	0 ± 4	−69 ± 12	1 ± 1	−58 ± 5
imidazole	MeCN			−3 ± 1	−75 ± 2
$CH_3CH_2CH_2NH_2$	MeCN	−3 ± 10	−76 ± 32	1 ± 1	−46 ± 5
$CH_3(CH_2)_3NH_2$	MeCN	−14 ± 3	−108 ± 10	2 ± 1	−45 ± 3
$(CH_3)_3CNH_2$	MeCN	−13 ± 2	−116 ± 7	−11 ± 8	−107 ± 3
$(CH_3)_2CHCH_2NH_2$	MeCN	−17 ± 2	−122 ± 8	5 ± 1	−38 ± 5
Et_3N	MeCN	−8 ± 2	−98 ± 8	−16 ± 2	−21 ± 7
piperidine	THF	−1 ± 7	−68 ± 23	−3 ± 1	−67 ± 1
morpholine	THF	−1 ± 1	−70 ± 5	1 ± 1	−60 ± 5
$CH_3(CH_2)_3NH_2$	THF	−22 ± 4	−139 ± 13	−6 ± 1	−36 ± 2

[a] The errors were calculated according to R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).

k_3[amine] ≫ k_{-1}, the reaction is of an overall second order, and k_{obsd} is given by eq 5.

$$k_{obsd} = k_1 \qquad (5)$$

(b) When the uncatalyzed reaction is faster than the catalyzed reaction but slower than the reverse reaction, i.e., $k_{-1} \gg k_2 \gg k_3$[amine], k_{obsd} is composite but it is again a second-order constant (eq 6).

$$k_{obsd} = k_1k_2/k_{-1} \qquad (6)$$

(c) For a "slow" leaving group, the reversal of the zwitterion formation may be faster than its decomposition, i.e., $k_{-1} \gg k_2 + k_3$[amine]. k_{obsd} is then given by the sum of a second-order and a third-order term (eq 7), and it will increase linearly with the increase in the amine concentration. The slope/intercept ratio is k_3/k_2, i.e., the ratio of the rate constants for the catalyzed vs. the uncatalyzed process.

$$k_{obsd} = k_1k_2/k_{-1} + (k_1k_3/k_{-1})[\text{amine}] \qquad (7)$$

(d) When the rates of the reversal of the zwitterion formation and the forward reactions are similar, i.e., when $k_{-1} \sim k_2 + k_3$[amine], a curved relationship between k_{obsd} and [amine] is expected according to eq 4. This is the transition region between a linear k_{obsd} vs. [amine] relationship (eq 7) at low amine concentrations and a constant k_{obsd} (eq 5) at high [amine].

All these kinetic variants were previously observed for system **5** and related systems.[7-11]

Mechanism of the Reaction with the Diamines. Four important features characterize the reactions of the diamines: (1) The reaction is of a first order in the amine in spite of the important second-order term in the amine obtained for monoamines of similar basicity. (2) The effect of N,N-dialkylation, chiefly N,N-dimethylation, on the reaction rate is minor. (3) The reaction is at least one order of magnitude faster than the corresponding uncatalyzed counterpart in the reaction of monoamines (Table VI). (4) The $\Delta H^\ddagger$ values are low and the $\Delta S^\ddagger$ values are negative, but both terms are appreciably more positive than the values for the reactions of the monoamines.

First-order dependence on the amine is expected for cases (a) and (b) above. An unmodified variant (a) which calls for an unassisted rate-determining attack of the nucleophile on the double bond is excluded for two reasons. First, trifluoroethoxy is a leaving group of low nucleofugacity as judged both by the pK_a of trifluoroethanol in water (12.34)[22] and by the catalysis observed with the monoamines. Second, if the role of the second amine group in the diamines is that of a substituent, affecting only the nucleophilicity without any specific function, monoamines and diamines of similar basicity and steric bulk such as n-propylamine and 1,2-diaminoethane should show the same kinetic behavior, contrary to what was observed. On the other hand, if some specific feature of the structure of the diamine enhances the uncatalyzed process compared with the catalysis by an external amine molecule, the condition $k_3/k_2 \ll 1$ may be reached and it can lead to two situations. If $k_2 \gg k_{-1}$ the nucleophilic attack will be rate determining (eq 5), while if $k_{-1} \gg k_2$ situation (b) will be encountered and the rate constant will be given by eq 6.

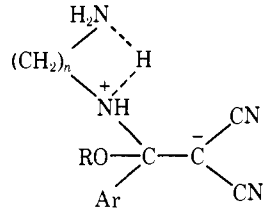
Table VI. Relative Rates for the First-Order Reaction in the Amine in Acetonitrile

X in XCH_2NH_2	rel k'[a]	X in XCH_2NH_2	rel k'[a]
CH_3CH_2	1.0	CH_2NMe_2	43
$CH_3CH_2CH_2$	2.2	CH_2NEt_2	63
$(CH_3)_2CH$	1.6	$CH_2CH_2NH_2$	51[b]
CH_2OH	1.9	$CH_2CH_2NMe_2$	64
CH_2OMe	0.8	$CH(Me)NH_2$	30
CH_2CH_2OH	8.2	$CH(Me)NMe_2$	70
CH_2NH_2	33[b]		

[a] Relative to n-propylamine. [b] Statistically corrected for the presence of two identical amino groups.

Such a feature calls for the amine molecule to operate as a bifunctional molecule. One amino group reacts as the nucleophile while the other operates as an intramolecular catalyst, replacing the external second amine molecule in the reaction of the monoamines. Similarly to the role of the intermolecular catalytic amine molecule (see below), three transition states can be suggested for the k' step of the diamines. The second amino group can serve as a base for proton expulsion from the ammonium ion moiety of **2** (transition state **7**). It can be an electrophilic catalyst, assisting in the departure of the leaving group from the zwitterion (transition state **8**). Both features can be combined in transition state **9** where the neutral amino group reacts as a bifunctional catalyst. The nitrogen deprotonates the ammonium ion concurrently with the departure of the trifluoroethoxy group which is assisted by the amino hydrogen.

Transition states **8** and **9** are excluded for several reasons. It is reasonable that the neutral amino group is a weaker acid in acetonitrile than trifluoroethanol, so that proton transfer from the nitrogen to the incipient trifluoroethoxy anion is thermodynamically unfavored[23] and hence there would be no driving force for such catalysis. This argument may not be valid



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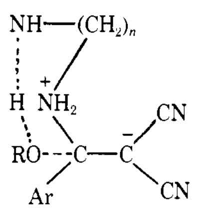

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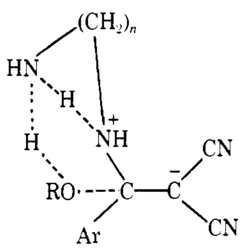

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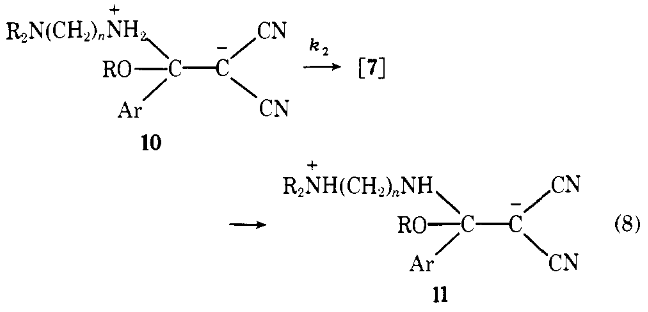
if the electrophilic assistance involves only hydrogen bonding for which there is no thermodynamic objection. A more valid objection is that electrophilic assistance by the substituted amino group is impossible for the *N,N*-dimethyl derivatives.[24] Since these derivatives show second-order behavior and gave rate constants very similar to those for the unsubstituted compounds (Tables I and VI), electrophilic assistance is also unlikely for the latter. Moreover, whereas the terminal hydroxy groups of ethanolamine and 3-aminopropanol are at least as capable of an electrophilic assistance as the terminal amino group, the kinetic behavior of these amines resembles that of the monoamines rather than that of the diamines.[25]

Transition state **7** or other base-catalyzed processes (see below) are consistent with the experimental observations. For a family of structurally related amines their carbon nucleophilicities (measured by k_1) or carbon basicities (measured by k_1/k_{-1}) are of little importance. The differences in the pK_1 values of our diamines in water are small, in line with the small reactivity range. The difference is larger in acetonitrile, where only two pK_1 values are available,[27] and again the more basic amine reacts faster.

The intramolecular proton transfer between the ammonium ion and the free amine raises two questions. If the first intermediate is the zwitterion **10**, the proton is transferred (eq 8)

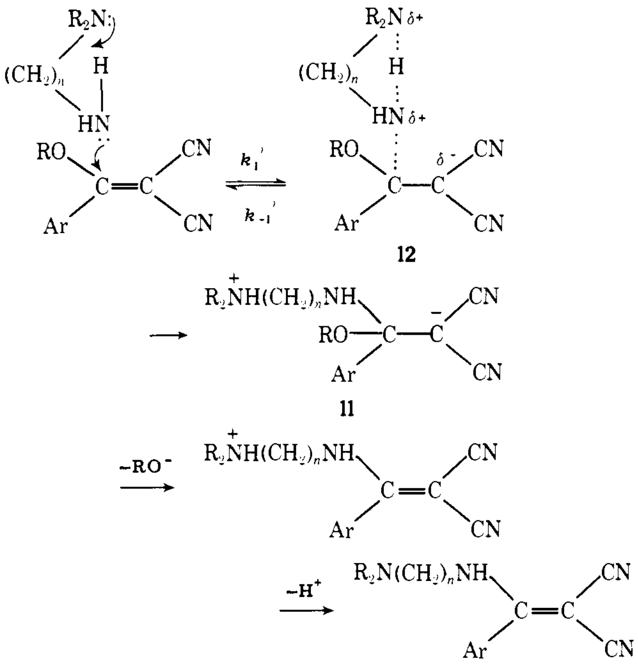


10 **11** (8)

from a weaker acid to the conjugate base of a stronger one, as judged by the much lower pK_2 values compared with the pK_1 values of the diamines. This should be regarded as a formal objection since, in contrast to intermolecular proton transfer, the relative acidities of the two reaction sites in the intramolecular case change with the extent of proton transfer. In the product **11** the relative acidities of the two nitrogens are opposite to those in **10**.

The second question is why the intramolecular proton transfer by an initially weaker base competes so favorably with the intermolecular reaction with another diamine molecule, to the exclusion of the third-order process. Apparently, the favorable enthalpy term for the intermolecular catalysis is more than compensated by an entropy term which favors the intramolecular reaction. The presence of an additional amine molecule in the transition state of the intermolecular reaction results in an entropy decrease of 10–15 eu, while transition state **7** involves in our system the stable five- and six-membered rings.

Scheme II



12 **11**

The behavior of the hydroxy amines is also consistent with transition state **7** since deprotonation of an ammonium ion by a hydroxy group is much less likely than by the more basic amine.[25]

Another explanation for the second-order process with the diamines which can be excluded is that the third-order reaction is due to a reaction of the dimer of the amine, while only the monomeric form of the diamine is available for the reaction. There is evidence for tetramers and *n*-mers of aliphatic amines,[28] but the association in CCl_4 starts to be important at 0.1 M concentrations, which are higher than our working concentrations with the diamines. Moreover, if association is kinetically important it should be more pronounced with the diamines since 1,2-diaminoethane has the highest association constant of all the amines studied in pyridine.[29] Even then, the dimer concentrations are negligible at our conditions compared with the monomer concentrations.

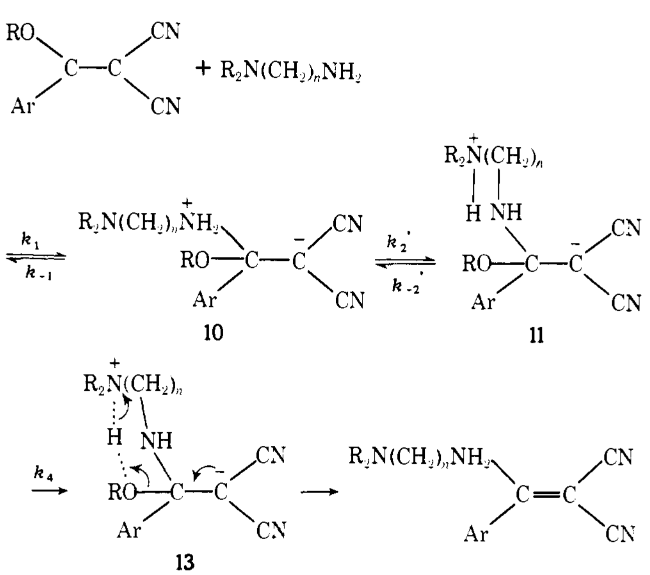
Transition state **7** may appear after the rate-determining step when eq 5 applies, or it may be the transition state for the rate-determining step (e.g., for the **10** → **11** process in eq 8) with a rate constant k_2'. The observed rate constant is then given by

$$k_{\text{obsd}} = k_1 k_2'/k_{-1} \qquad (9)$$

There are two additional alternative routes which involve a base-catalyzed step and give the same kinetics. The first one is demonstrated for a terminal diamine in Scheme II. The nucleophilic attack is concerted with the proton transfer and gives directly the rearranged zwitterion **11** via transition state **12**. This route explains the absence of the intermolecular reaction: the strength of the deprotonating base is similar to that of the monoamines, while the entropy gain of the intramolecular process is retained.

The second route, which is discussed in more detail below for the reactions of the monoamines, is the currently accepted route for base catalysis in aprotic solvents.[15] The initial nucleophilic attack is followed by a rapid equilibrium deprotonation by the neutral amino group and the rate-determining

Scheme III



step is the leaving-group expulsion catalyzed by the conjugate base of the ammonium ion (rate constant k_4). This "specific base-general acid" mechanism (SB-GA) is demonstrated in Scheme III. The observed rate constant for reaction via transition state **13** is given by eq 10.

$$k_{\text{obsd}} = k_1 k_2' k_4 / k_{-1} k_{-2}' \qquad (10)$$

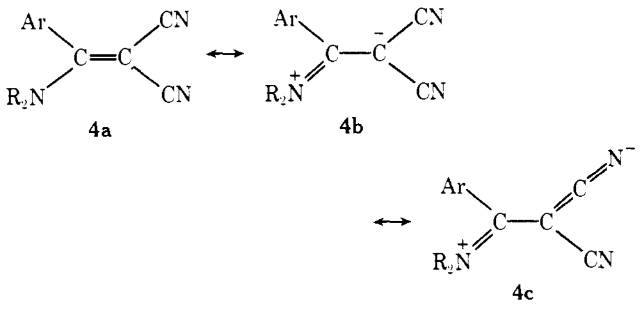
The substituent effects and the activation parameters may distinguish between several of these alternatives. The relative reactivities of the diamines differ by only one order of magnitude and most of the difference is due to the low reactivity of 2-amino-1-dimethylaminopropane. The reactivities of all the other amines change within a factor of 3.4 and, if the values for 1,2-diaminoethane and 1,3-diaminopropane are corrected for the presence of two identical amino groups, the reactivity span is only 2.4. The only clear effect within this narrow range is that an amino group on a secondary carbon is less reactive than that on a primary carbon, especially when the substituents on this carbon are bulky as in 2-amino-1-dimethylaminopropane. This effect reflects the steric hindrance in the nucleophilic attack step. Apparently, the higher basicity of the other, tertiary, amines, which should result in a higher reactivity, is counterbalanced by the steric bulk which should reduce the reactivity since the transition state is crowded. Since basicity (or acidity of the conjugate base) and steric bulk are important in the k_1 step which is common to all these routes, substituent effects cannot distinguish between the alternative mechanisms.

On the other hand, the activation parameters can exclude a rate-determining nucleophilic attack (eq 5). The activation enthalpies of 1-7 kcal mol^{-1} seem unreasonably low for a bond-formation process between two neutral species. The reactions proceed at easily measurable rates only because of the rate-reducing effect of the corresponding very negative activation entropies.

Very low activation enthalpies were found for other nucleophilic vinylic substitutions of "slow" leaving groups by amines.[7-9,17,30] These values were interpreted in terms of reaction schemes similar to Scheme I with a composite rate coefficient. The $\Delta H^{\ddagger}$ term is a sum of $\Delta H°$ for the equilibrium addition of the amine to the double bond and $\Delta H_2{}^{\ddagger}$ term for the cleavage of the C-O bond. The $\Delta H°$ term is probably negative as found for the analogous addition of tri-*n*-butylphosphine to arylidenemalononitriles

$$\mathrm{ArCH{=}C(CN)_2 + Bu_3N \rightleftharpoons ArCH(\overset{+}{P}Bu_3){-}\overset{-}{C}(CN)_2} \qquad (11)$$

where $\Delta H° = -13$ to -21 kcal mol^{-1}.[31] The $\Delta H_2{}^{\ddagger}$ term is then positive and appreciable. The small difference between the energies of the ground state and the transition state probably reflects the stabilization of the product enamine by the contributing dipolar structures **4b**–**4c**.



The very high negative values of the activation entropies reflect the formation of a dipolar transition state from two neutral reactants. Examples for precedents of similar values for reactions of the same charge type in aprotic solvents are $\Delta S_2{}^{\ddagger} = -46$ eu for the reaction of phenacyl bromide with aniline in chloroform,[32] or $\Delta S^{\ddagger} = -43$ to -66 eu for the amine-catalyzed isomerization of ethyl α-cyano-β-*o*-methoxyphenylacrylate in benzene.[26] It is important that the $\Delta S°$ values for reaction 11 are -27 to -50 eu in methanol.[31] We note that, although the activation parameters cannot distinguish between Schemes II and III, Scheme III seems more reasonable in view of the low $\Delta H^{\ddagger}$ values.

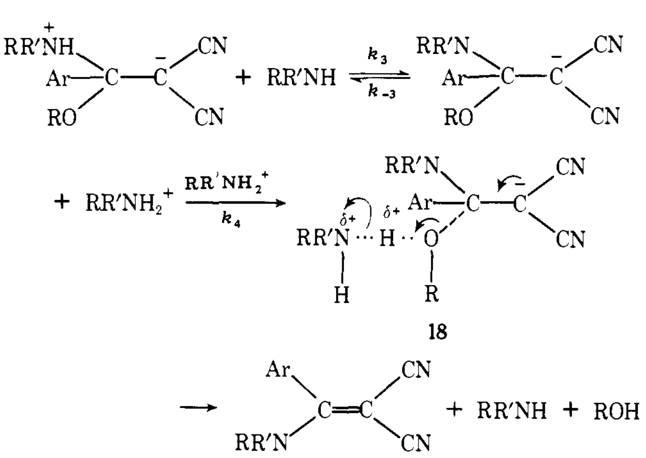
The low sensitivity to the polarity of the solvent is somewhat surprising. The reaction of 1,2-diaminoethane is only 10% faster in acetonitrile ($\epsilon = 37.5$)[33] than in tetrahydrofuran ($\epsilon = 7.6$)[34] at 30 °C and the activation parameters are the same within the combined experimental errors. It is expected that a nucleophilic attack will be much faster in the more polar solvent, thus excluding eq 5. A compensating effect of the other terms is therefore involved. Assuming that the solvent effect on the ground state is small, the observed effect requires also a small effect on the transition state. This can be consistent with a rate-determining k_2' step since the intramolecular proton transfer between two nitrogens does not involve a change in the charge on the transition state and the origin and terminus of the proton attachment are very similar. It can also be consistent with Scheme III if the extent of charge neutralization, i.e., of the proton transfer, in the transition state is low.

Mechanism of the Reaction of the Monoamines. For all the monoamines except for the highly hindered ones, a linear k_{obsd} vs. [amine] relationship is observed. Consequently, case (c), i.e., $k_{-1} \gg k_2 + k_3$[amine], is observed and the reaction follows two competing routes: an uncatalyzed route whose rate constant k' is given by k_1k_2/k_{-1} and a catalyzed route whose rate constant k'' is given by k_1k_3/k_{-1}. Hence, the k''/k' values of Table II are identical with the k_3/k_2 ratios of Scheme I and they measure the relative importance of the two routes starting from the common intermediate **2**.

The ratios observed for our system are relatively high, being in the region assigned by Bunnett and Garst[14b] in nucleophilic aromatic substitution as the region of genuine base catalysis. Several mechanisms for the base catalysis were previously suggested in nucleophilic aromatic substitution[13c] and discussed for nucleophilic vinylic substitution of systems **1c**[10] and **5**.[7-9]

As with the diamines, the important mechanisms for the catalyzed route are (1) rate-determining base-catalyzed proton

Scheme IV

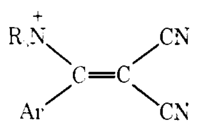


transfer, (2) specific-base-general-acid-catalyzed process, (3) electrophilically assisted route, and (4) bifunctional catalyzed process. In previous investigations[7-10] the effect of an added base was used as the main tool for distinguishing between some of these mechanisms. The rate increase of the reaction of **5**, X = F, with *p*-toluidine by added *N,N*-dimethylaniline or pyridine in acetonitrile[7a] was interpreted in terms of a slow proton-transfer step. On the other hand, the absence of rate increase by *N*-methylpiperidine for the reaction of **5**, X = OEt, with piperidine and morpholine and the relative reactivity of the two amines suggested specific base-general acid catalysis.[9] Although trifluoroethoxy is structurally similar to ethoxy, the same route need not apply for it since the pK_a of trifluoroethanol[22] is only one pK_a unit higher than that of piperidine and the driving force for the proton transfer

$$\text{incipient-}CF_3CH_2O^- + RR'NH_2^+ \rightarrow CF_3CH_2OH + RR'NH \quad (12)$$

is much lower than that for the corresponding reaction of the ethoxy leaving group.

This probe could not be used for the reaction of **6** with tertiary amines since they reacted with **6**. Although the nature of the products is unknown, it is reasonable that the first step involves formation of the vinylammonium ion **14** by nucleophilic attack on the double bond. This may be the spectroscopically observed product with Et_3N since its λ_{max} is lower than that for the enamines. In contrast, the λ_{max} of the reaction product of Dabco is higher and a subsequent reaction involving ring opening is possible. The reaction of Dabco with 1-chloro-2,4-dinitrobenzene gave initially compound **15**, while compound **16** was formed with excess amine[35a] and an analogous reaction may take place with **6**. The evidence against electrophilic assistance for leaving-group departure therefore rests on the demonstration of intramolecular base catalysis in the reaction of diamines with **6**.



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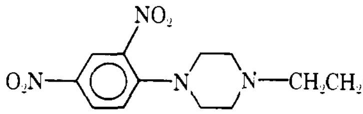

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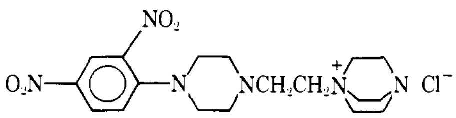

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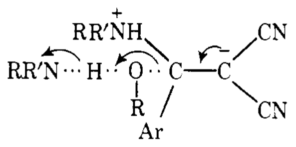


17

Electrophilic catalysis either via transition state **17** or via specific base-general acid catalysis (Scheme IV, transition state **18**) seems unlikely by comparison of the reactivities of piperidine and morpholine. Their steric bulk is identical whereas the morpholinium ion is 2.3 pK_a units more acidic in acetonitrile than piperidinium ion.[27] It is also likely that morpholine is a stronger proton donor than piperidine owing to the electron withdrawal by the oxygen.

If formation of **17** is rate determining the k''/k' ratio for morpholine, which is one of the weakest bases studied by us, should be one of the highest observed, but instead it was one of the lowest found. If formation of **18** is rate determining the k''(piperidine)/k''(morpholine) ratio, which is given by

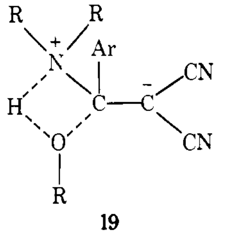
$$k''(\text{piperidine})/k''(\text{morpholine}) = [(k_1/k_{-1})(k_3/k_{-3})k_4](\text{piperidine})/[(k_1/k_{-1})(k_3/k_{-3})k_4](\text{morpholine}) \quad (12a)$$

is expected to be low. This is based on the assumption that the k_3/k_{-3} term is independent of the amine and that the higher k_1/k_{-1} term for piperidine than for morpholine, as found recently,[35b] is largely compensated by a lower k_4 for piperidine than for morpholine. However, the observed ratios of 43-44 in acetonitrile and 14-20 in tetrahydrofuran are inconsistent with this expectation. The higher reactivity of piperidine and the linearity of the k_{obsd} vs. [amine] plots for the two amines (Figure 2) are in contrast with the nonlinear relationship for morpholine and the linear relationship for piperidine in their reaction with **5**, X = OEt. The latter behavior resulted in a k''(piperidine)/k''(morpholine) < 1, which was interpreted in terms of general base-specific acid catalysis.[9]

Consequently, a rate-determining proton transfer seems the most likely route. A recent work by Bernasconi and co-workers analyzes possible mechanisms for S_NAr reactions and concludes that proton transfer may be rate determining in water.[15] Although extrapolation to acetonitrile is unjustified without corroborative evidence, it is important that a very rapid proton transfer can still be rate determining.

Uncatalyzed Route. The details of the uncatalyzed route concern the sequence of cleavage of the $^+$N-H and the C-O bonds. In contrast with the reaction in protic solvents, an initial rate-determining or preequilibrium deprotonation of the $^+$N-H bond by the solvent cannot compete effectively with deprotonation by added amine. This possibility was also ruled out for S_NAr reactions[14j] owing to the inconsistency of the observed rate constants with those calculated for such a proton transfer.

Two variants of a reaction involving a rate-determining C-O bond cleavage are possible. One is an unassisted cleavage of the C-O bond, which is unattractive since acetonitrile is not a good anion solvator. Alternatively, the C-O bond cleavage may be assisted electrophilically by the proton of the ammonium moiety (cf. transition state **19**) as suggested in the aromatic[13c] and the vinylic[9] cases. Here, the proton transfer involves an unfavorable geometry, but it has the advantage of



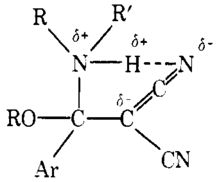
19

internal solvation of the leaving group with a consequent charge dispersal in the transition state.

Reaction via **19** should be strongly dependent on the basicity of the leaving group and it is predicted to be much more important for the more basic ethoxy than for the trifluoroethoxy leaving group. The possibility of reaction via **19** was previously raised for **5**, X = OEt.[9] This question is discussed further below.

Structural Dependence of the Rate Constants. According to Scheme I and eq 7, the uncatalyzed rate constant is a product of the carbon basicity of the nucleophile toward **6** (k_1/k_{-1}) and k_2. Since the leaving group is identical in all cases, k_2 will be affected only by changes in the electron-withdrawal ability of the ammonium ion moiety. This is related to the pK_a of the ammonium ion, and the zwitterion **2** which is derived from the more basic amine will be a weaker acid and will give a higher k_2. Hence, both terms should contribute to the increase of the overall reactivity with the increase in the carbon basicity of the amine. Indeed, the rate differences among the family of primary amines, or among the family of secondary amines, are small, and the notable exception is the low reactivity of *tert*-butylamine, which is likely to be due to a reduced carbon basicity as a result of steric effects. The similarity of the other values suggests that in the absence of severe steric effects the carbon basicities of the amines follow the hydrogen basicities of these amines which differ at most by one pK_a unit. A similar behavior was observed for a nucleophilic vinylic cis-trans isomerization.[36]

Primary amines were found to be more reactive than secondary amines. This is in contrast with the observation that in nucleophilic aromatic substitution of *p*-nitrophenyl phosphate[37] or 2,4-dinitrophenyl phenyl ether[14d] secondary amines are usually more reactive than primary amines. The difference can be ascribed to two reasons. First, although secondary amines are more basic than primary amines toward a proton, the k_1/k_{-1} term for them may be lower than for the primary ones owing to steric reasons. Second, **2** can be stabilized by intramolecular hydrogen bonding between the negatively polarized cyano group and the acidic proton (cf. structure **20**).



20

This stabilization will affect both k_{-1} and k_2. Lowering of k_{-1} will be similar for both primary and secondary amines. However, if an N-H bond cleavage is part of the rate-determining step, this hydrogen bond will have to be cleaved in the case of a secondary amine, with a corresponding increase in the activation energy and decrease in k_2. A similar increase in the activation energy does not accompany the proton transfer from the zwitterion derived from the primary amine, since the hydrogen which is not involved in the hydrogen bond can be transferred. The reactivity difference between primary and secondary amines in nucleophilic aromatic substitution was similarly explained by hydrogen bonding to an ortho nitro group.[13c]

The rate constant for the catalyzed reaction is a product of the carbon basicity of the amine and the rate constant k_3 for the proton transfer. Again, the more basic amine will react faster if carbon basicity and hydrogen basicity are parallel. The amine is involved twice in the k_3 step. A more basic amine will be a better base in the deprotonation, but the ammonium ion will be a weaker acid. Consequently, in a series of amines the two effects may compensate one another, making k_3 relatively independent of the amine basicity. The steric effects on k_3 will be more pronounced than on k_2 since two bulky amine molecules are present in the transition state. Table II shows that the k'' values are higher for the unbranched primary amines (*n*-propylamine, *n*-butylamine, 3-aminopropanol) than for the primary amines substituted either at the α carbon (isobutylamine, *tert*-butylamine) or at the β carbon (ethanolamine and methoxyethylamine). This is understood by the steric factor, and as expected the effect is at a maximum with *tert*-butylamine, for which k'' is 15 700 times lower than for *n*-butylamine. Similar behavior was shown by these two amines in nucleophilic aromatic substitution.[38] The lower values of k'' for ethanolamine and its methoxy derivative are also due to their lower basicity as compared with the other amines.

When the steric bulk of the amines is similar the basicity becomes the dominant factor. Consequently, piperidine is much more reactive than morpholine in the catalyzed process. The Brønsted β based on the pK_as of the two amines in acetonitrile is 0.7.

Similarly to the behavior of the k' values, the k'' values are also lower for secondary than for primary amines and this is true even for piperidine, which is the strongest base studied. Steric effects are apparently of great importance for the catalyzed process. The steric effects for the primary amines reduce the reactivity without altering the kinetics. In contrast, with sterically hindered secondary amines such as diisopropylamine or diisobutylamine, the kinetic form is changed and a curved k_{obsd} vs. [amine] plot is obtained. The reactivity of these amines becomes so low that much higher amine concentrations are required for obtaining conveniently measurable rates. As a result, in spite of the increase in k_{-1} which involves a reduction of the steric crowding, the condition for linearity, i.e., $k_{-1} \gg k_2 + k_3[\text{amine}]$, is no longer fulfilled and it is replaced by $k_{-1} \sim k_2 + k_3[\text{amine}]$, resulting in the curved relationship (situation (d) above). A similar behavior was observed previously when a relatively weak base (morpholine) was reacted with system **5**, X = OEt, which carries a sluggish leaving group (OEt).[9]

The appearance of the curved relationship which is predicted by eq 4 is a strong evidence for Scheme I. For a slow leaving group such as trifluoroethoxy it is reasonable that the condition $k_2 < k_3[\text{amine}]$ is fulfilled since the k_3/k_2 ratios for the other amines are high and the [amine] term is high. Equation 4 is then reduced to

$$1/k_{\text{obsd}} = 1/k_1 + (k_{-1}/k_1k_3)(1/[\text{amine}]) \qquad (13)$$

which calls for linearity between $1/k_{\text{obsd}}$ and $1/[\text{amine}]$. The observed linearity for the two amines (Figure 4) justifies both Scheme I and the assumptions involved in deriving eq 13.

These plots give rate constants which are not usually available for amine-catalyzed reactions. The reciprocal of the intercept k''' gives k_1, the rate constant for the nucleophilic attack, since at high amine concentration this rate constant is rate determining (cf. the plateau region in Figure 3), while the reciprocal of the slope k'''' gives $k_1k_3/k_{-1} = k''$ from which the k_3/k_{-1} ratio is obtained. These values are given in Table IV.

Equation 4 can be also rearranged in a different way, giving

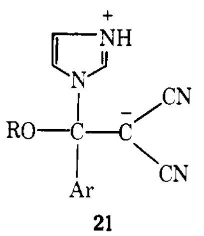
$$k_{\text{obsd}}/(k_1 - k_{\text{obsd}}) = k_2/k_{-1} + k_3[\text{amine}]/k_{-1} \qquad (14)$$

from which both k_2/k_{-1} and k_3/k_{-1} values could be obtained from the intercept and the slope of $k_{\text{obsd}}/(k_1 - k_{\text{obsd}})$ vs. [amine] when the k_1 values are obtained from eq 13. These plots (not shown) for the two amines were linear, but the intercepts were highly sensitive to small deviations of the k_{obsd} values. Nevertheless, the k_{-1}/k_2 value of $\geqslant 10$ for diisobutylamine demonstrates that the forward reaction of the intermediate is rate determining. The small values of the intercepts are demonstrated by the near constancy of the $(k_{obsd}/(k_1 - k_{obsd}))/[\text{amine}]$ values for the two amines which are given in Table III.

Since $k'''' = 1/k''$, the catalyzed reaction for the sterically hindered amines could be shown to be much slower than that of the less hindered primary amines. Although the hydrogen basicity of diisopropylamine is higher than that of isopropylamine, the catalyzed process is nearly four orders of magnitude slower, $k''(\text{PrNH}_2)/(1/k'''')(i\text{-Pr}_2\text{NH}) = 8600$. Isobutylamine and diisobutylamine have almost identical hydrogen basicities in acetonitrile but $k''(\text{Me}_2\text{CHCH}_2\text{NH}_2)/(1/k'''')((\text{Me}_2\text{CHCH}_2)_2\text{NH}) = 1770$ at 30 °C and 30 000 at 45 °C.

The k_3/k_{-1} ratios of 2-6 obtained from eq 13 and 14 resemble the ratios obtained previously for the reaction of **5**, X = OEt, with piperidine in 2-propanol and of morpholine in ethanol but are lower than the ratios for morpholine in 2-propanol (17.5) or in acetonitrile (26-30).[9] Formally, these ratios can be regarded as due to similar heterolytic processes, one involving an N-H bond cleavage assisted by an external base (amine) and the other involving a C-N bond cleavage assisted by an internal nucleophile (the carbanionic α carbon). These are the reversals of the processes measuring hydrogen nucleophilicity and carbon nucleophilicity, respectively, and it is not surprising that the deprotonation is faster.

A different type of competition is measured by the k_3/k_2 ratios. A relationship between these ratios and the basicity of the amine was found for the reaction of **5**, X = F, with aromatic amines.[7a] While most of our amines have similar pK_as, the trend is clear. Morpholine, one of the weakest bases studied, gave the lowest ratios of 60 ± 2, while piperidine, the most basic amine, gave the highest ratio of 5730. Steric effects are discernible in the low ratios of 6.4-7.4 found for *tert*-butylamine. An interesting case is the reaction of imidazole at 30 °C, which was of an overall third order, i.e., the k_3/k_2 ratio is very high. This is in contrast to the dependence on basicity discussed above, since imidazole is the weakest base studied. However, higher k_3/k_2 ratios for imidazole compared with the corresponding reactions of primary or secondary amines were found previously for its reaction with 1-halo-2,4-dinitrobenzenes.[39] In our case this may be due to the very slow reaction which required very high base concentrations, so that the condition $k_3[\text{amine}] \gg k_2$ may be obeyed. Another possibility is that imidazole reacts via its tertiary nitrogen, followed by shift of the double bond in the heterocyclic ring, giving the zwitterion **21.** If the k_2 step indeed involves an intramolecular assistance to leaving-group departure (transition state **19**), such assistance cannot be achieved in **21** since the acidic proton is not at a bonding distance to the oxygen.[39a] Consequently, k_2 will decrease and the k_3/k_2 ratio will increase. This situation is interesting since it extends the variations of transition-state structure for the "uncatalyzed" route. This route is genuinely uncatalyzed for imidazole, it is intramoleculary electrophilically catalyzed for the other monoamines, and it is intramolecularly base catalyzed for the diamines.



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Activation Parameters. The activation parameters for both the catalyzed and the uncatalyzed routes (Table V) have even more extreme values than those for the reactions with diamines. All the activation enthalpies for the uncatalyzed reaction are negative except for morpholine, where the value is zero, and the compensating $\Delta S^{\ddagger}$ values are very highly negative, being below −100 eu for six of the amines. The $\Delta H^{\ddagger}$ values for the catalyzed reactions are low or negative, with low, but not unreasonably so, compensating activation entropies. The parameters for the catalyzed reactions resemble those for other second-order processes with amines.[7,9,17,30]

Although these activation parameters, especially the low or negative $\Delta H^{\ddagger}$ values, seem exceptional, the discussion above and the additional examples below show that such behavior is the rule, rather than the exception, in the reaction of amines with electrophilic olefins in aprotic media. In the reaction of anilines with **1c** in acetonitrile the $\Delta H^{\ddagger}$ values[40] are negative for the catalyzed process with *p*-anisidine and *p*-toluidine, but positive for the less basic amines, and the $\Delta S^{\ddagger}$ values are low.[10] Low $\Delta H^{\ddagger}$ and highly negative $\Delta S^{\ddagger}$ values were found for the reactions of secondary amines with **5**, X = OEt: $\Delta H^{\ddagger} = 2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -75$ eu with piperidine in EtOH. [9]$\Delta H^{\ddagger} = 0.6$ kcal mol^{-1}, $\Delta S^{\ddagger} = -46$ eu for the catalyzed reaction of **5**, X = CN, with piperidine in acetonitrile, while for the reaction of morpholine with **5**, X = F, in acetonitrile, $\Delta H^{\ddagger} = -3.2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -55$ eu.[9] Likewise, the reaction of **5**, X = F, with *p*-anisidine in 2-propanol and *tert*-butyl alcohol gave very low $\Delta H^{\ddagger}$ and negative $\Delta S^{\ddagger}$ values for the uncatalyzed reaction but negative $\Delta H^{\ddagger}$ and highly negative $\Delta S^{\ddagger}$ values for the catalyzed process.[7b] The reactions of **5**, X = F, with anilines in acetonitrile are of a third order and $\Delta H^{\ddagger}$ values are low and positive.[7a] Negative $\Delta H^{\ddagger}$ values were also found in the reaction of cyclopentadienylidenetriphenylphosphorane with tetracyanoethylene.[41] The $\Delta H^{\ddagger}$ values are also low for related reactions which do not involve a leaving group. For the addition of pyrrolidine to *trans*-chalcone in acetonitrile the second-order process in the amine has $\Delta H^{\ddagger} = 2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -62$ eu,[42] for the addition of morpholine to acrylophenone, $\Delta H^{\ddagger} = 2.4$ kcal mol^{-1}, $\Delta S^{\ddagger} = -47$ eu in methanol,[43] and for the isomerization of *cis*-ethyl α-cyano-β-*o*-methoxyphenylacrylate by tri-*n*-butylamine in benzene $\Delta H^{\ddagger} = 2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -58$ eu.[26] An example of similar parameters in nucleophilic aromatic substitution of a sluggish leaving group is the reaction of tricarbonyl(fluorobenzene)chromium with piperidine in acetonitrile where $\Delta H^{\ddagger} = 2.1$ kcal mol^{-1} and $\Delta S^{\ddagger} = -64$ eu for the catalyzed process.[44]

In the discussion below we consider low positive, zero, and low negative $\Delta H^{\ddagger}$ values together since the errors in these terms are appreciable, especially for the uncatalyzed reaction where the rate constants k' are obtained from intercepts of linear plots at two temperatures.

Since the low $\Delta H^{\ddagger}$ values are unreasonable for a one-step substitution they serve as a strong corroboration for the multistep substitution reaction of Scheme I. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values can be analyzed as sums of the appropriate enthalpy and entropy terms for the individual steps of Scheme I (eq 15-18). In the absence of better data, the $\Delta H°$ values of −13 to −21 kcal mol^{-1} and the $\Delta S°$ values of −27 to −51 eu for the equilibrium addition of tributylphosphine of reaction 11[31] are taken as approximate values for the analogous addition of amines to **6**. Since both $\Delta H°$ and $\Delta S°$ values are negative, a low $\Delta H_2^{\ddagger}$ or $\Delta H_3^{\ddagger}$ value and a highly negative $\Delta S_2^{\ddagger}$ or $\Delta S_3^{\ddagger}$ value will lead to an overall low or negative $\Delta H^{\ddagger}$ and highly negative $\Delta S^{\ddagger}$.

$$\Delta H^{\ddagger}(\text{uncatalyzed process}) = \Delta H_1^{\ddagger} - \Delta H_{-1}^{\ddagger} + \Delta H_2^{\ddagger} = \Delta H° + \Delta H_2^{\ddagger} \quad (15)$$

$$\Delta S^{\ddagger}(\text{uncatalyzed process}) = \Delta S_1^{\ddagger} - \Delta S_{-1}^{\ddagger} + \Delta S_2^{\ddagger} = \Delta S° + \Delta S_2^{\ddagger} \quad (16)$$

$$\Delta H^{\ddagger}(\text{catalyzed process}) = \Delta H_1^{\ddagger} - \Delta H_{-1}^{\ddagger} + \Delta H_3^{\ddagger} = \Delta H° + \Delta H_3^{\ddagger} \quad (17)$$

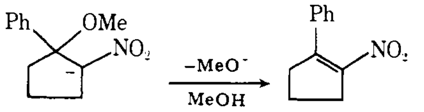
$$\Delta S^{\ddagger}(\text{catalyzed process}) = \Delta S_1^{\ddagger} - \Delta S_{-1}^{\ddagger} + \Delta S_3^{\ddagger} = \Delta S^{\circ} + \Delta S_3^{\ddagger} \quad (18)$$

The higher $\Delta H^{\ddagger}$ for the catalyzed reaction means that $\Delta H_3^{\ddagger} > \Delta H_2^{\ddagger}$. The $\Delta H''^{\ddagger} - \Delta H'^{\ddagger} = \Delta H_3^{\ddagger} - \Delta H_2^{\ddagger}$ values are positive or close to zero (31 to -2 kcal mol^{-1}) for most of the amines, except for the reaction of triethylamine, whose nature is not understood. Consequently, the plausible prediction that the catalysis is due to a favorable enthalpy of activation is not borne out. The catalysis is due to a favorable entropy of activation and $\Delta S_3^{\ddagger} - \Delta S_2^{\ddagger}$ values are indeed highly positive (11–114 eu) except for the reactions of piperidine and morpholine in THF. This result is not unreasonable. Deprotonation of an ammonium ion by a structurally similar amine should be exothermic only by a few kilocalories per mole and the activation enthalpy may be relatively high. Whereas data on the activation enthalpy for expulsion of a small anion from a zwitterion are not available, ElcB reactions of the second type, where the expulsion of a small carbanion from a larger one is thought to be rate determining,[45] were studied. The $\Delta H^{\ddagger}$ values for reactions 19, 20, and 21 are 18,[46] 24,[47] and 23[48] kcal mol^{-1}, respectively, and values of 7.3–19.4 kcal mol^{-1} were found for expulsion of OH$^-$ and OMe$^-$ from several Meisenheimer complexes.[49] The rate-retarding effect of the ammonium ion may be compensated by mesomeric electron donation by the aryl group. Consequently, the catalyzed reactions may have a higher activation enthalpy only if the above-mentioned values will be reduced. Apparently, the intramolecular assistance by the ammonium proton to the expulsion of the leaving group reduces sufficiently the $\Delta H_2^{\ddagger}$ term as to make it lower than $\Delta H_3^{\ddagger}$.

$$\mathrm{ArC(CN)_2{-}\bar{C}(CN)_2 \xrightarrow[CHCl_3]{-CN^-} ArC(CN){=}C(CN)_2} \quad (19)$$

$$(\mathrm{Ar = 3,5\text{-}Me_2\text{-}4\text{-}NH_2C_6H_2})$$

$$(t\text{-}\mathrm{Bu})_2\mathrm{C(NO_2){-}\bar{C}(Me)NO_2} \xrightarrow[\mathrm{CD_3OD}]{-\mathrm{NO_2}^-} (t\text{-}\mathrm{Bu})_2\mathrm{C{=}C(Me)NO_2} \quad (20)$$



(21)

Whereas the negative values of the activation entropies are easily understood since two charges are created from neutral species, the positive difference of $\Delta S_3^{\ddagger} - \Delta S_2^{\ddagger}$ is not obvious. The $\Delta S_3^{\ddagger}$ term includes a negative contribution due to the loss of translational and rotational entropy in the termolecular transition state. The corresponding entropy loss of the $\Delta S_2^{\ddagger}$ term should be lower, unless the intramolecular assistance to the departure of the leaving group reduces $\Delta S_2^{\ddagger}$ due to the constrained geometry in transition state **19**. The $\Delta S^{\ddagger}$ values for reactions 18–20 are 2 to -10 eu[46-48] and the loss of entropy in the four-membered ring of **19** should be appreciable. We feel that a better understanding of the differences in the activation parameters would be obtained only if data on the individual steps of closely related reactions will become available.

The overall activation energy measures differences between the ground-state and the transition-state energies. We rationalize the small difference as due to the formation of the strong σ C–N bond at the expense of the weaker π(C=C) bond. The unfavored formation of charged species is compensated, at least partially, by the strong interaction between the strong Lewis acid **6** and the amine.

Solvent Effect. All the three solvents studied are aprotic so that solvent assistance to the leaving-group expulsion is negligible. However, the change in the dielectric constant from 7.6 for THF[34] to 48 for Me$_2$SO[33] is appreciable. It is predicted that formation of the polar zwitterion will be enhanced in the more polar solvent. The solvent effect on k_2 and k_3 depends on the question whether electrophilic assistance is involved (via transition states **18** and **19**) with a consequent charge dispersal, or whether two separate ions are formed from a zwitterion in an unassisted process. Most of the reactions are accelerated in the more polar solvent. The uncatalyzed reactions of *n*-butylamine, piperidine, and morpholine at 30 °C are 3.5, 7.5, and 0.9 times faster in MeCN than in THF, and the catalyzed processes are 1.3, 5.5, and 2.5 times faster, respectively. The $k(\mathrm{Me_2SO})/k(\mathrm{THF})$ ratio for morpholine is 2.5 for k' and 8.9 for k''. These values suggest that the transition state is more polar than the ground state and at least for morpholine they fit an assisted k_2 via transition state **19.**

Ethoxy and Trifluoroethoxy as Leaving Groups. Comparison with our previous work[9] enables the comparison of the reactivities of ethoxy (compound **5**, X = OEt) and trifluoroethoxy (compound **6**) as leaving groups. This is of special interest since the steric effects of the two groups are similar and the differences will mainly reflect electronic effects. Trifluoroethoxy was found to be a much better leaving group than ethoxy in the reaction with piperidine at 30 °C: $k'(\mathrm{OCH_2CF_3})/k'(\mathrm{EtO}) = 293$, $k''(\mathrm{OCH_2CF_3})/k''(\mathrm{EtO}) = 2600$, $(k''/k')(\mathrm{OCH_2CF_3})/(k''/k')(\mathrm{EtO}) = 0.116$. The differences are much smaller with diisobutylamine: k' and k'' values for **6** at 45 °C are two to four times higher than for **5**, X = OEt, at 30 °C.

In terms of the individual rate constants both the carbon basicity toward **6** and k_3 will be higher than those toward **5**, X = OEt, with the same amine, owing to the higher electron withdrawal by the trifluoroethoxy group. On the other hand, the cleavage of the C–O bond would be easier for trifluoroethoxy. Data on leaving-group ability is scarce, but from a recent work on ElcB elimation the leaving abilities of alkoxide ions would be proportional to the acidities of the parent alcohols.[16]

Consequently, the ratio of the k' values for the two leaving groups reflects mainly the high leaving ability of trifluoroethoxy and is reasonable since trifluoroethanol is much more acidic than ethanol in water. On the other hand, the k_3 term does not involve a cleavage of the C–O bond and the rate-enhancing effect of the trifluoroethoxy group should reflect its acidifying effect on the ammonium ion moiety of the zwitterion. The high ratio of the k'' values is therefore composed from contributions in the same direction of both the k_1/k_{-1} and the k_3 terms for the trifluoroethoxy group. That the effect is more pronounced when the substituent operates via the inductive effect rather than when the bond to the substituent is cleaved is reminiscent of the effect of arenesulfonate leaving groups in vinylic substitution. The $k_{\mathrm{OBs}}/k_{\mathrm{OTs}}$ ratio is ca. 3 for the vinylic S$_\mathrm{N}$1 reaction when the C–O bond is cleaved in the rate-determining step,[50] and it is ca. 0.3 in the electrophilic addition–elimination route when a proton adds in a rate-determining step to a carbon β to the arenesulfonate group.[51]

However, the high ratio is probably due to a different reason. We suggested above that k'' for **6** measures the proton-transfer rate. It was suggested earlier that k'' for **5**, X = OEt, measures a rate-determining ammonium ion catalyzed departure of the leaving group according to Scheme IV. In this case k_3 should be replaced by k_3k_4/k_{-3} where k_4/k_{-3} is lower than unity.[9] Hence, the $k''(\mathrm{CF_3CH_2O})/k''(\mathrm{EtO})$ ratio will be larger than the $k_3(\mathrm{CF_3CH_2O})/k_3(\mathrm{EtO})$ ratio. Since the k_1/k_{-1} ratio is also included in k'' it should be concluded that our comparison of the leaving-group abilities in the catalyzed step does not measure the relative efficiency of the C–O bond cleavage of the two substituents. A similar conclusion was obtained previously when the leaving-group abilities of Cl and CN were compared in the reactions of tetracyanoethylene and tricyanovinyl chloride with aromatic amines.[30]

Experimental Section

Solvents and Materials. Dry acetonitrile was prepared as described by Rappoport and Ta-Shma.[7a] The fraction boiling at 78 °C was used. Tetrahydrofuran (Frutarom) was dried for 24 h over $CaCl_2$, filtered, refluxed over sodium for 3 h, and distilled. The distillate was refluxed for 2 h over $LiAlH_4$ and redistilled. The fraction boiling at 67 °C was used. Dimethyl sulfoxide was fractionally distilled at 3.3 mm and the fraction boiling at 40 °C was used. The amines were commercial samples which were kept over KOH and distilled twice before use. The middle fraction, corresponding to the literature boiling point, was used.

1,1-Dicyano-2-*p*-dimethylaminophenyl-2-trifluoroethoxyethylene (6). To a saturated solution of 2-chloro-1,1-dicyano-2-(*p*-dimethylaminophenyl)ethylene[52] (2.3 g, 10 mmol) in acetonitrile at 50 °C, sodium trifluoroethoxide (1.2 g, 10 mmol) in trifluoroethanol (15 mL) was added. The dark color brightened within a few minutes and the precipitate of NaCl was filtered. Water was added to the filtrate and the mixture was extracted with ether. The solvent was evaporated, giving yellow crystals of 1,1-dicyano-2-*p*-dimethylaminophenyl-2-trifluoroethoxyethylene (2.5 g, 85%). Crystallizations from aqueous methanol gave yellow powder, mp 128 °C.

Anal. Calcd for $C_{14}H_{12}N_3F_3O$: C, 56.90; H, 4.06; N, 14.30; F, 19.30. Found: C, 56.60; H, 4.24; N, 14.27; F, 19.00.

λ_{max} (MeCN): 401 nm (ϵ 23 000). ν_{max} (Nujol): 2200 (doublet, $C{\equiv}N$), 1610 ($C{=}C$) cm^{-1}. δ ($CDCl_3$): 3.1 (6 H, s, Me), 4.54 (2 H, q, CH_2), 7.12 (4 H, center of AA′BB′ q, Ar). *m/e:* 295 (M, 100%), 196 (M − OCH_2CF_3, 5%), 175 (M − Ar, 7%), 91 (tropylium, 12%).

Enamines. The enamines were prepared by adding 4–5 molar equiv of the amine to a saturated solution of 2-chloro-1,1-dicyano-2-(*p*-dimethylaminophenyl)ethylene in acetonitrile. When the color change was complete the ammonium salt was filtered and the solvent was evaporated. The products were crystallized several times from methanol–water. The analytical data are given in Table VII[21] and the spectral data in Table VIII.[21] The products from the reactions of the three unsubstituted diamines were oils and we were unable to purify them sufficiently for a good analysis by using thin layer chromatography. The products were identified by the spectral properties of the oils. The UV spectra of the isolated materials were identical with those obtained from the kinetic runs at infinity. The products from the primary amines show a hydrogen-bonded N–H at 3200–3250 cm^{-1} and a doublet at 2210–2205 cm^{-1} which is characteristic for an unsaturated dicyanomethylene group substituted by electron-donating substituents at the β position.[53]

Kinetic Procedure. The solutions for the kinetic experiments were prepared daily. The kinetics were followed as described earlier.[9] First-order rate constants were calculated by the KINDAT program.[54]

Supplementary Material Available: Table IIa summarizing all the kinetic data for the monoamines; Table VII summarizing the analytical data for the enamines; Table VIII summarizing the spectroscopic data for the enamines (7 pages). Ordering information is given on any current masthead page.

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