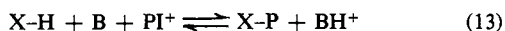


occurs more or less simultaneously with C-O bond formation or cleavage (eq 13, X = RO⁻). The compar-



able mechanism for protonated amines (X = R₂NH⁻) would require proton removal from an amine cation during attack and proton addition to a protonated amine during amine expulsion and is not observed, presumably because there are no free electron pairs on the

nitrogen atom to make such a mechanism feasible. The equilibrium proton transfer mechanism (specific acid catalysis of adduct breakdown) is favored for free amines (X = R₂N⁻) as a consequence of the much larger basicity of nitrogen than of oxygen, and it is apparent that an extrapolation of the dependence of α on pK (Figure 3) from the pK_a values of 12-16 for alcohols to 30-35 for amines predicts an α value of 1.0 for amines.

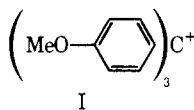
Reactions of the Tri-*p*-anisylmethyl Cation with Primary and Secondary Amines¹

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Abstract: The tri-*p*-anisylmethyl cation, R⁺, reacts with aliphatic primary and secondary amines to give derivatives of tri-*p*-anisylmethylamine. Amine nucleophilicity decreases with increasing bulk of substituents and with decreasing basicity, but the decrease is relatively small when the amine contains -I groups such as aryl, amino, or alkoxy. The reaction order is first with respect to most amines, and in these reactions there is no general base catalysis. Typical second-order rate constants are: MeNH₂, 6.3 × 10⁴; PhCH₂NH₂, 4.7 × 10⁴; *t*-BuNH₂, 54; H₂NNH₂, 3.2 × 10⁶ l. mol⁻¹ sec⁻¹. The reaction with pyrrolidine and 2-methylpyrrolidine is general base catalyzed, because the initially formed ammonium ion can lose R⁺, or a hydrogen ion to a general base, at similar rates. The rate constant for the initial attack of pyrrolidine upon R⁺ is 6.4 × 10⁶ l. mol⁻¹ sec⁻¹. Tri-*p*-anisylmethylamine decomposes readily in dilute acid. Kinetic salt effects upon the reaction of R⁺ with ammonia can be explained in terms of salt effects upon the activity coefficient of ammonia.

The reactivity of trivalent carbocations toward nucleophiles has been extensively studied. Much of the work has been done using triphenylmethyl dye cations (e.g., Crystal Violet and Malachite Green) which react relatively slowly with nucleophiles,²⁻⁵ but more reactive cations have been studied by several groups.⁶⁻¹¹ Ritchie has suggested that general base catalysis may be kinetically important in reactions of the less reactive cations with water;¹² but general base catalysis has not as yet been observed in reactions of the tri-*p*-anisylmethyl cation (R⁺, I),^{7-9,11} and the small deute-



(1) Support of this work by the National Science Foundation is gratefully acknowledged.

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(6) R. A. Diefenbach, K. Sano, and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 4747 (1966).

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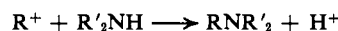
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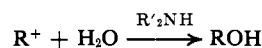
rium kinetic solvent isotope effect suggests that slow proton transfers are not important for attack of water.⁷ Consistently the reaction of R⁺ in the presence of tertiary amines is much slower than with primary amines.

Our present work was intended to test this point further by using sterically hindered amines, and also to differentiate between two reaction paths by product examination.

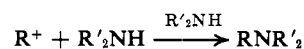
Nucleophilic attack



General base catalysis of water reaction



General base catalysis of amine reaction



In two cases, reaction with pyrrolidine and its 2-methyl derivative, we found evidence for general base catalysis of amine attack, but it seems that it is not important in most reactions of I.

Experimental Section

Materials. The amines were generally commercial samples and most of them were purified by distillation. Methylamine, dimethylamine, and trimethylamine were purified as their hydrochlorides using extraction with CHCl₃ followed by recrystallization.¹³ 2-Methylpyrrolidine was prepared from 5-methyl-2-pyr-

(13) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc., Ser. A*, 177, 499 (1941).

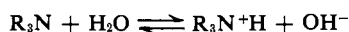
rolidinone (Aldrich) by reduction with LiAlH_4 .¹⁴ It was distilled, bp 96° (lit.¹⁵ bp 96°). The nmr spectrum was consistent with the structure.

Tri-*p*-anisylmethylamine and its *N*-*n*-propyl, *N*-*n*-hexyl, and *N*-pyrrolidine derivatives were prepared by treating tri-*p*-anisylmethyl chloride (Aldrich) first with HCl gas in dry benzene and then with excess amine.¹⁶ The volatiles were removed and the product was extracted into Et_2O , and the solution was washed with cold dilute NaOH and dried (Na_2SO_4). Tri-*p*-anisylmethylamine could be recrystallized (Et_2O -petroleum ether), mp 105–106° (Anal. Calcd: C, 75.7; H, 6.6; N, 4.0. Found: C, 75.6; H, 6.9; N, 3.8). The other amines could not be crystallized, but they all gave nmr spectra in CDCl_3 or CCl_4 (Varian T-60), which were consistent with their structure. They were unstable in acid.

Kinetics. The reactions were followed at 25.0° using a Durrum-Gibson stopped-flow spectrophotometer. The carbocation, R^+ , in dilute HCl (usually 0.1 *M*) was in one syringe, and ammonia or the reagent amine was in the other.¹¹ With most of the amines, we used an excess of amine over acid, but in some experiments we used 0.1 *M* NaOH to neutralize the acid, so that the second syringe contained NaOH + amine. Both methods were used with some amines and good agreement was obtained. Because of the possibility that the syringes delivered slightly different volumes, we exchanged solutions and syringes for every amine studied, and found no significant differences in rate constants. The maximum amine concentrations were usually <0.05 *M*, except for very unreactive amines.

The first-order rate constants, k_{ψ} , sec^{-1} , were calculated in the usual way.

Treatment of the Rate Enhancement by Amines. When HCl was neutralized with an excess of amine, the reaction solution contained the alkylammonium hydrochloride (typically 0.05 *M*) and the excess of amine, whereas if HCl was neutralized with 1 equiv of NaOH the solution contained NaCl plus amine, and hydroxide ion formed in the equilibrium



Part of any rate enhancement could therefore be caused by nucleophilic attack of OH^- upon R^+ .

The concentration of hydroxide ion was calculated for the reaction conditions using *pK* values from the literature corrected for the ionic strength, usually 0.05, using the Davies equation.¹⁷ The literature K_B was multiplied by a factor of 1.7, when thermodynamic values were available.

The contributions of the reactions of R^+ with both water and hydroxide ion were subtracted from the observed rate constants, and, where necessary, the amine concentration was corrected for formation of the hydrochloride, and it is the corrected concentrations and rate constants (k_{corr}) which are used in the discussion of the results. The corrections were for the most part small except for amines which were very weak nucleophiles (Me_3N) or were strongly basic such as pyrrolidine ($\text{p}K_A = 11.27$).

This general procedure appears to be satisfactory, because good agreement was obtained between rate constants calculated using both procedures. It was also found that addition of Me_3N to *sec*-butylamine did not markedly increase the reaction rate.

Products. The reactions of R^+ were first order with respect to amine (except for pyrrolidine and 2-methylpyrrolidine), and therefore most of the amines must have been acting either as nucleophiles or as general base catalysts for the attack of water on R^+ . In order to eliminate this second possibility, we used thin-layer chromatography to demonstrate amine formation, for reaction with ammonia and several amines. Eastman Kodak Chromatogram 6060 silica gel sheets were pretreated with 7.5% Nujol in hexane, and dried at room temperature.¹⁸ The sample was spotted in ether and acetone-water was used for development. The spots were detected using uv light, or by treatment with HCl gas. In our initial experiments, the spots were very smeared, probably because the

amine decomposed on the plates, but this problem disappeared if small amounts of Me_3N were added to the pretreatment and development solutions. The amines were identified by comparing their R_f values with those of authentic material (Table I). Tri-*p*-

Table I. R_f Values of the Tri-*p*-anisylmethylamines

Amine	Acetone vol % ^a	
	65	70
<i>n</i> - $\text{C}_3\text{H}_7\text{NHR}$	0.207	0.535
cyclo- $\text{C}_4\text{H}_8\text{NR}$	0.115	0.349
<i>n</i> - $\text{C}_6\text{H}_{13}\text{NHR}$	~0	0.233
ROH	0.736	~1.0

^a Acetone- H_2O .

anisylmethanol was always present because the concentrations of HCl used in preparing the reaction mixture were insufficient to convert ROH wholly into R^+ .

In another series of experiments ROH was dissolved in 0.5 *M* HCl and the solution was added to 0.55 *M* NaOH containing 10^{-2} *M* amine. The nmr spectra of the *N*-alkyl residues of the products extracted into Et_2O were identical with those of authentic specimens prepared by reaction of R^+ with the amines in dry C_6H_6 . The spots obtained after chromatography (tlc) were dissolved in 6 *M* HCl to convert both ROH and the tri-*p*-anisylmethylamines into R^+ . In 0.5 *M* HCl ROH is 81.5% ionized to R^+ and the percentages of amines in the reaction products separated by tlc were for *n*-propylamine 79% and for *n*-hexylamine and pyrrolidine 80%.

Results

Reactions of Primary Amines. There is a linear relation between k_{corr} and concentration of ammonia or primary amines (cf. ref 7 and 9) as shown in Figures 1 and 2 for reactive and unreactive amines. Figure 1 shows the rate constants corrected for reaction of water and hydroxide ions using an excess of amine over HCl. Figure 2 shows that the same corrected first-order rate constants are obtained when HCl is neutralized by NaOH or excess amine, and in the following discussion, we will assume that the effect of 0.05 *M* NaCl or amine hydrochloride formed by neutralization is small and can be neglected. This figure also gives the rate constants in high concentrations of two very unreactive amines. Figure 3 shows that the rate of reaction of R^+ with *n*-hexylamine is unaffected by added hydroxide ion, and by changes in the concentration of NaCl.

Steric effects are only important when the crowding is large (Table II). For example, cyclohexylamines, irrespective of their conformation, are only slightly less reactive than *n*-hexylamine, but they are slightly more reactive than isopropylamine and *sec*-butylamine (Table II). Ammonia is considerably less nucleophilic toward R^+ , and less basic, than the *n*-alkylamines. This relatively low nucleophilicity of ammonia also appears in its complexing with boranes,¹⁹ and these differences have been interpreted in terms of solvation, angle strain, and electronic effects of alkyl groups.^{19,20}

Where comparisons can be made (for ammonia and ethylamine) our second-order rate constants agree reasonably well with those of other workers.^{7,9}

Somewhat surprisingly, benzylamine is almost as reactive as the *n*-alkylamines, although it is less basic (cf. the behavior of ammonia). There is considerable evidence for interactions between carbocations and

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(19) H. C. Brown, *J. Amer. Chem. Soc.*, **66**, 435 (1944).

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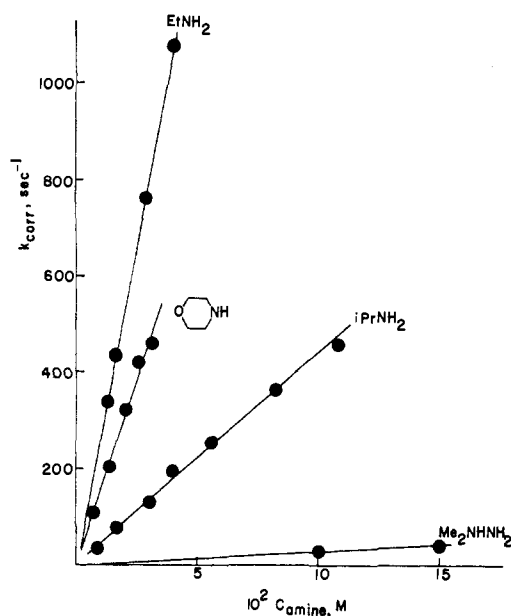
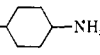
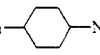


Figure 1. Variation of corrected first-order rate constants with amine concentration in the presence of 0.05 M amine hydrochloride.

Table II. Second-Order Rate Constants for Reactions of Ammonia and Primary Amines

Amine	k , l. mol ⁻¹ sec ⁻¹ ^a	pK _a ^b
NH ₃	1.6×10^3	9.21
CH ₃ NH ₂	63×10^3	10.62, 10.66
C ₂ H ₅ NH ₂	25×10^3	10.63
<i>n</i> -C ₃ H ₇ NH ₂	50×10^3	10.53, 10.71
<i>n</i> -C ₄ H ₉ NH ₂	48×10^3	10.59, 10.77
<i>n</i> -C ₅ H ₁₁ NH ₂	44×10^3	
<i>n</i> -C ₆ H ₁₃ NH ₂	50×10^3	
<i>n</i> -C ₈ H ₁₇ NH ₂	45×10^3	10.65
<i>i</i> -C ₃ H ₇ NH ₂	4.3×10^3	10.63
<i>s</i> -C ₄ H ₉ NH ₂	3.8×10^3	10.56
<i>i</i> -C ₄ H ₉ NH ₂	60×10^3	
<i>t</i> -C ₄ H ₉ NH ₂	0.05×10^3	10.55, 10.83
cyclo-C ₃ H ₉ NH ₂	11×10^3	10.64
cyclo-C ₆ H ₁₁ NH ₂	9×10^3	10.64
<i>cis-t</i> -Bu-  -NH ₂	12×10^3	
<i>trans-t</i> -Bu-  -NH ₂	15×10^3	
PhCH ₂ NH ₂	47×10^3	9.33, 9.58
O ₂ -CCH ₂ NH ₂	52×10^3 ^c	9.6

^a All reaction solutions contained 0.05 M chloride from neutralization of HCl with amine or OH⁻. ^b Values from H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957); E. A. Brandt and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, New York, N. Y., 1955; R. M. C. Dawson, D. C. Elliott, W. H. Elliott, and K. M. Jones, "Data for Biochemical Research," Clarendon Press, Oxford, 1959. ^c At pH 10.7 in 0.05 M carbonate buffer + 0.05 M NaCl.

aromatic groups, and such interactions may increase the reactivity of benzylamine toward R⁺.²¹

Rate enhancements which have been ascribed to hydrophobic interactions have been observed for attack of long chain *n*-alkylamines on carbonyl carbon,²² but we observed no such rate increase up to *n*-octylamine

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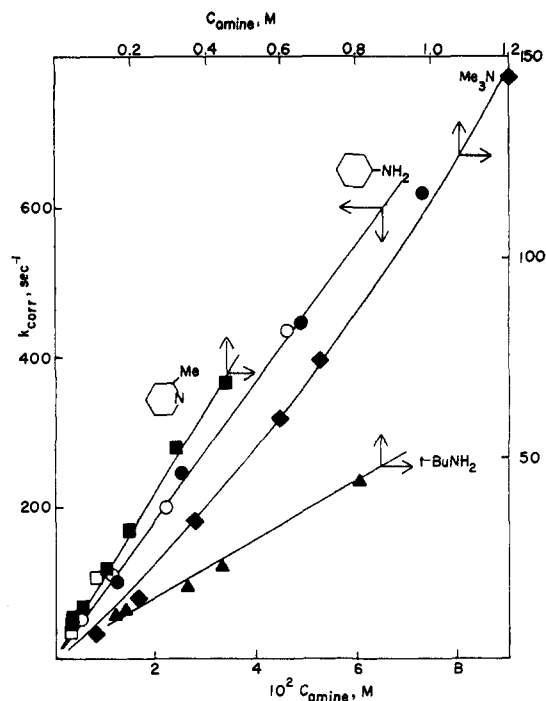


Figure 2. Variation of corrected first-order rate constants with amine concentration: (solid points) HCl neutralized by amine; (open points) HCl neutralized by 0.05 M OH⁻.

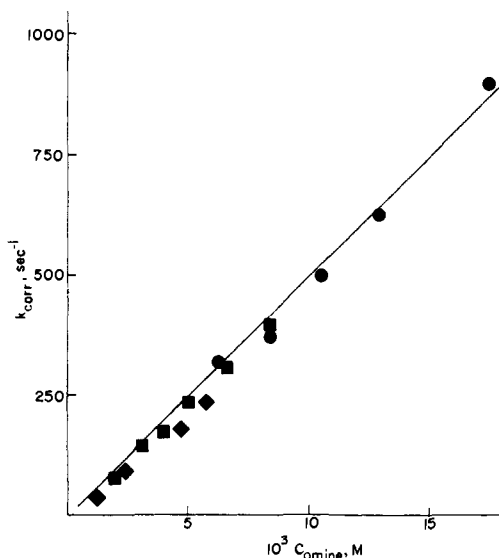


Figure 3. Reaction of R⁺ with *n*-hexylamine: (■) 0.5×10^{-3} M NaOH, 0.05 M NaCl; (●) 10^{-3} M NaOH, 0.1 M NaCl; (◆) 10^{-2} M NaOH, 0.1 M NaCl.

suggesting that these rate enhancements depend upon "twinning" of long alkyl groups in both the amine and the substrate.

Several lines of evidence confirm the absence of general base catalysis in most of these reactions. (i) The reaction is first order with respect to amine and amines are formed. (ii) The rate constants are the same whether the acid is neutralized by amine or by hydroxide ion, provided that allowance is made for nucleophilic attack of hydroxide ion present in equilibrium with the amine (Figure 2), and added NaOH has no effect (Figure 3). (iii) The second-order rate constant for reaction of *sec*-butylamine is independent

Table III. Effect of Trimethylamine on the Reaction of R⁺ with *sec*-Butylamine

$10^2 C_{\text{BuNH}_2}$, <i>M</i>	$C_{\text{Me}_3\text{N}}$, <i>M</i>	k_{ψ} , sec ⁻¹	k_{corr}^a	$10^{-3} k_{\text{corr}} /$ C_{BuNH_2}
2.5		117	104	4.2
2.5	0.1	135	94	3.8
2.5	0.2	159	100	4.1
2.5	0.4	197	107	4.3
2.5	0.8	269	113	4.5
5.0		211	198	4.0
5.0	0.1	246	205	4.1
5.0	0.2	269	210	4.2
5.0	0.4	287	197	4.0
5.0	0.8	390	234	4.7

^a Corrected for reactions due to OH⁻, H₂O, and Me₃N.

of added trimethylamine (Table III). The slight increase of rate constant at high concentrations of trimethylamine (Figure 2) could be a medium effect (*cf.* ref 9). (iv) At low concentrations of trimethylamine and *tert*-butylamine, the increase in the overall first-order rate constant, k_{ψ} , is caused largely by the generation of hydroxide ion, as shown in Table IV.

Table IV. Rate Constants in the Presence of Low Concentrations of Weakly Nucleophilic Amines^a

Amine	$10^2 C_{\text{amine}}$	k_{ψ} , sec ⁻¹	k_{corr} , sec ⁻¹ ^b
<i>t</i> -BuNH ₂	1.2	15	0
<i>t</i> -BuNH ₂	7.0	24.6	5
<i>t</i> -BuNH ₂	8.5	25.3	5
Me ₃ N	0.45	13.8	0
Me ₃ N	3.5	15.9	1
Me ₃ N	5.7	17.5	2
Me ₃ N	8.3	20.0	5










^a At 25.0° in 0.05 *M* alkylammonium chloride. ^b Corrected for reaction of H₂O and OH⁻.

Reactions of Secondary and Tertiary Amines. The reactivities and basicities of methyl and dimethylamine toward the tri-*p*-anisylmethyl cation, R⁺, are very similar (Tables II and V); both should be influenced by factors such as hydrogen bonding to a forming ammonium ion, inductive effects of the methyl group, and steric effects.^{19,20}

The reactivity of cyclic secondary amines toward R⁺ is generally very similar to that of dimethylamine, except that a heterocyclic electronegative atom such as oxygen reduces the reactivity of, for example, morpholine, but the effect is very much less than would be expected in terms of the decreased basicity. A similar but smaller effect is shown by a heterocyclic nitrogen atom (Table V). Therefore the inductive effect which sharply reduces basicity has little effect upon nucleophilicity toward R⁺, possibly because of favorable interactions between the unshared electrons of the heterocyclic oxygen or nitrogen atom and the carbocation in which the positive charge is delocalized into the aryl groups.

The reactions of pyrrolidine and its 2-methyl derivative with R⁺ are special cases and are discussed in detail in a separate section. (The second-order rate constants in Table V for the pyrrolidines are for the initial step of attack of the amine on R⁺, and are obtained in

Table V. Second-Order Rate Constants for Reactions of Secondary and Tertiary Amines

Amine	k , l. mol ⁻¹ sec ⁻¹ ^a	pK _a ^b
(CH ₃) ₂ NH	79 × 10 ³	10.69, 10.71
(CH ₃) ₃ N	Very slow	9.76
	640 × 10 ³	11.27
	60 × 10 ³	11.12, 11.22
	15 × 10 ³	8.33, 8.36
	60 × 10 ³	9.83
	820 × 10 ³ ^c	10.6
	74 × 10 ³	~10.4 ^d
	0.18 × 10 ³	10.99 ^e
	8 × 10 ³	4.23 ^f
	0.56 × 10 ³	6.95

^a Reaction solutions contained 0.05 *M* chloride from neutralization of HCl with amine or OH⁻. ^b Values from H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957); R. M. C. Dawson, D. C. Elliott, W. H. Elliott and K. M. Jones, "Data for Biochemical Research," Clarendon Press, Oxford, 1959. ^c At pH 11.7 with 0.05 *M* phosphate buffer and 0.05 *M* NaCl. ^d For 2-ethylpyrrolidine pK_a = 10.43. ^e H. C. Brown in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955. ^f G. Baddeley, J. Chadwick, and H. T. Taylor, *J. Chem. Soc.*, 448 (1956).

the presence of sufficient base to make the ensuing loss of a hydrogen ion very fast.) The reaction with R⁺ is very fast, and although pyrrolidine is much more nucleophilic, it is not more basic than piperidine. This difference can be related to the different conformations of five- and six-membered rings. Indoline is relatively unreactive compared with the purely aliphatic amines, but its reactivity is higher than expected in view of its low basicity, as for benzylamine.

The low reactivity of 2-methylpiperidine can be ascribed to steric hindrance by the methyl group. However, the carboxylate group in the 2 position of proline does not reduce nucleophilicity (Table V).

Imidazole is much less basic than the other amines in this group but nonetheless is not especially unreactive, as might be expected in view of its high nucleophilicity in other reactions.²³

Reactions of Amino Acids. Both glycine and proline were examined at pH's well above their pK_a values, and their kinetic behavior and reactivities are very similar to those of the corresponding primary and secondary amines (Tables II and V) and the carboxylate group has no special catalytic effect, suggesting that intramo-

(23) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, Chapter 1.

lecular general base catalysis and electrostatic effects are unimportant.²⁴

Reactions of Hydrazines. Hydrazine is considerably more reactive toward cations than would be expected from its low basicity, relative to primary alkylamines (Tables II and VI). This α effect has been observed in

Table VI. Second-Order Rate Constants for Reactions of Hydrazines

Hydrazine	k , l. mol ⁻¹ sec ⁻¹	pK _a ^a
H ₂ NNH ₂ ^b	320 × 10 ³	8.07, 8.10
CH ₃ NHNHCH ₃ ^b	22 × 10 ³	7.52
(CH ₃) ₂ NNH ₂ ^c	0.21 × 10 ³	7.21

^a R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958). ^b In presence of 2.5 × 10⁻³ M OH⁻ and 0.05 M NaCl, k is corrected for reaction of OH⁻ and H₂O. ^c Reaction run with no added OH⁻ in presence of 0.05 M (CH₃)₂NN⁺H₃Cl⁻.

reactions with the relatively stable triphenylmethyl dyestuff cations, and possible explanations have been discussed.²⁵ The lower reactivity of 1,2-dimethylhydrazine is probably caused by a mild steric hindrance, and the low reactivity of 1,1-dimethylhydrazine by a more powerful steric hindrance.

The value of N₊ for hydrazine is 5.60 and for ethylamine, it is 4.88.²⁶ Using these values and a first-order rate constant of 12 sec⁻¹ at 25° for the reaction of the tri-*p*-anisylmethyl cation with water,¹¹ the predicted second-order rate constants for reaction with R⁺ are 5 × 10⁶ l. mol⁻¹ sec⁻¹ for hydrazine, as compared with 3 × 10⁵ l. mol⁻¹ sec⁻¹ (Table VI) and 9 × 10⁵ l. mol⁻¹ sec⁻¹ for ethylamine, as compared with 2.5 × 10⁴ l. mol⁻¹ sec⁻¹ (Table II). These observations, and others (*cf.* ref 4), show that water is consistently more reactive toward R⁺ than predicted by the N₊ values. Ritchie has suggested that general base catalysis may be responsible for some of these differences.¹²

Reaction with Ammonia and Kinetic Salt Effects. Ammonia reacts readily with the tri-*p*-anisylmethyl cation in a second-order reaction, and proton loss from the ammonium ion appears to be fast (*cf.*, ref 7 and 9).



The second-order rate constant for the forward reaction is given in Table II. The reaction is reversible in dilute acid, but we were unable to follow the acid-catalyzed decomposition of tri-*p*-anisylmethylamine kinetically, because in solutions which are sufficiently acidic for tri-*p*-anisylmethanol to give appreciable amounts of its carbocation, R⁺, the spectrophotometrically observable process is simply the relatively slow equilibration of this cation, so that the observed first-order rate constant is given by $k_f + k_b$, which is 91 sec⁻¹ in 1 M hydrochloric acid,¹¹ and which is, therefore, a minimum value for the first-order rate constant for formation of R⁺ from the amine in 1 M HCl.

Added salts affect the reaction of ammonia with the tri-*p*-anisylmethyl cation, R⁺ (Table VII). This table

(24) B. Holmquist and T. C. Bruce, *J. Amer. Chem. Soc.*, **91**, 2982 (1969), and references cited therein.

(25) See ref 5 for a general discussion of α effects.

(26) It is suggested that the N₊ nucleophilicity scale, which is based largely on reactions with relatively stable carbocations, is related to the energy of desolvation of nucleophiles.^{3b, 4}

Table VII. Salt Effects upon the Reaction with Ammonia^a

Salt	C _s , M	k _{corr} , sec ⁻¹	k ^s _{corr} /k ⁰ _{corr}	f _{NH₃} ^b	f _{R⁺} /f _x [±]
		40.4			
LiCl	0.5	44.3	1.10	0.99	1.11
LiCl	1.0	40.5	0.99	0.96	1.03
LiCl	2.0	31.4	0.77	0.89	0.87
NaCl	0.5	42.6	1.05	1.04	1.01
NaCl	1.0	43.7	1.08	1.08	1.01
NaCl	2.0	47.6	1.18	1.17	1.01
KCl	0.5	45.3	1.12	1.04	1.08
KCl	0.75	46.4	1.14	1.07	1.07
KCl	1.0	50.6	1.25	1.10	1.14
KCl	1.5	53.6	1.31	1.15	1.14
CsCl	0.25	36.0	0.89		
CsCl	0.5	40.5	1.00		
Me ₄ NCl	0.5	45.8	1.14		
Me ₄ NCl	1.0	51.5	1.27		
Me ₄ NCl	2.0	66.5	1.64		
NaBr	0.5	40.3	1.00	1.01	0.99
NaBr	1.0	39.2	0.97	1.03	0.95
NaBr	2.0	46.0	1.14	1.06	1.08
NaNO ₃	0.5	39.5	0.98	1.04	0.96
NaNO ₃	1.0	42.0	1.04	1.07	0.98
NaNO ₃	2.0	45.8	1.13	1.16	0.97
LiClO ₄	0.25	41.2	1.01	0.99	1.02
LiClO ₄	0.5	40.0	0.97	0.94	1.03
LiClO ₄	1.0	36.4	0.89	0.89	1.00
LiClO ₄	2.0	29.4	0.72	0.76	0.95
NaClO ₄	0.5	43.8	1.07	1.00	1.07
NaClO ₄	1.0	43.0	1.05	1.00	1.05
NaClO ₄	2.0	40.2	0.98	1.00	0.98

^a At 25.0° with 0.0257 M NH₃ and 0.025 M NH₄Cl. ^b These values are interpolated from existing data.²⁷

gives the first-order rate constants corrected for the reaction with water, *i.e.*

$$k_{\text{corr}} = k_{\psi} - k^s_{\text{H}_2\text{O}}$$

where $k^s_{\text{H}_2\text{O}}$ is the rate constant in the aqueous salt solution.

The salt effect can be treated using the Brønsted-Bjerrum rate equation

$$k^s_{\text{corr}} = k^0_{\text{corr}} f_{\text{NH}_3} f_{\text{R}^+} / f^{\pm}$$

where the superscripts s and 0 refer to reaction in the presence and absence of added salt.

The overall kinetic salt effects (Table VII) are generally smaller than those found for the water reaction, and they can be accounted for almost completely in terms of the salt effects upon the activity coefficient of ammonia because the values of f_{R^+}/f^{\pm} are almost independent of the electrolyte, for those salts for which the activity coefficient of ammonia is known.²⁷ The largest kinetic salt effect is with tetramethylammonium chloride, whose effect upon f_{NH_3} is not known, but this positive kinetic salt effect is similar to those observed for reactions of R⁺ with water and anionic nucleophiles, where it has been suggested that bulky tetraalkylammonium ions have some special effect, probably upon the water structure.^{9,11}

The negative salt effects of perchlorates upon nucleophilic attack have been interpreted in terms of interactions with the tri-*p*-anisylmethyl cation which stabilized it relative to the transition state.¹¹ The kinetic results for reaction with ammonia (Table VII) show

(27) R. Abegg and H. Riesenfeld, *Z. Phys. Chem.*, **40**, 84 (1902); R. A. Durst, P. G. Schmitt, and I. Feldman, *J. Phys. Chem.*, **70**, 2058 (1966); M. Randall and C. F. Fairlen, *Chem. Rev.*, **4**, 271 (1927).

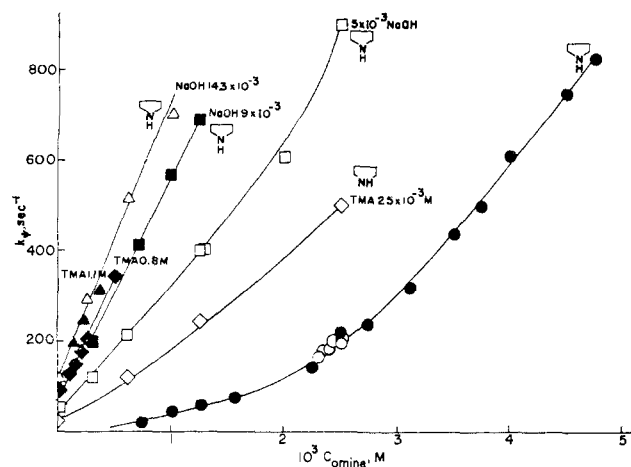


Figure 4. Variation of observed rate constant with stoichiometric concentration of pyrrolidine in presence of 0.05 M NaCl: (●○) (see text); (□) 5×10^{-3} M NaOH; (■) 9×10^{-3} M NaOH; (△) 14.3×10^{-3} M NaOH; (◇) 2.5×10^{-3} M Me₃N; (◆) 0.8 M Me₃N; (▲) 1.1 M Me₃N.

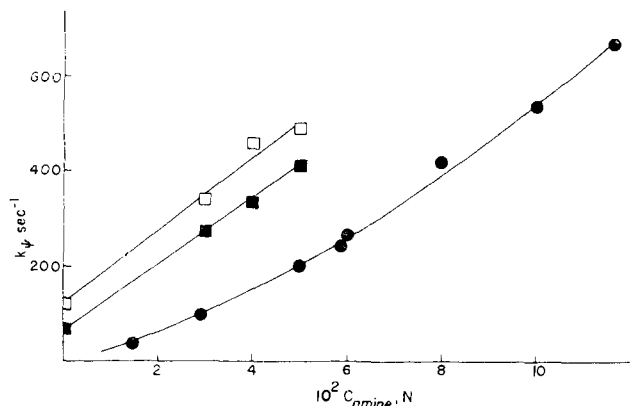


Figure 5. Variations of observed rate constant with stoichiometric concentration of 2-methylpyrrolidine: (●) in presence of 0.05 M NaCl; (■) 8×10^{-3} M NaOH; (□) 15×10^{-3} M NaOH.

that in this system any ground-state stabilization of R⁺ must be reflected in the transition state, suggesting that the transition state must have considerable carbocationic character, *i.e.*, there is not a high degree of charge transfer to nitrogen in its formation. (Indicator measurements show that perchlorate ions stabilize carbocations relative to ammonium ions.²⁸) We did not examine the salt effects upon reaction between R⁺ and amines, because of the absence of information on salt effects upon the activity coefficients of the amines.

Reactions with Pyrrolidines. The kinetic forms of the reactions of pyrrolidine (Figure 4) and its 2-methyl derivative (Figure 5) differ from those shown by all the other amines, and there is curvature even when allowance is made for the contribution of the reaction of R⁺ with hydroxide ion in equilibrium with pyrrolidine²⁹ (Figure 6). In Figures 4 and 5, we show the variation of the observed rate constant, k_p , with stoichiometric amine concentration in the absence of added base, and the rate enhancement obtained on the addition of either hydroxide ion or trimethylamine. These

(28) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

(29) For Figure 6 this amine concentration is corrected for the formation of ammonium and hydroxide ions.

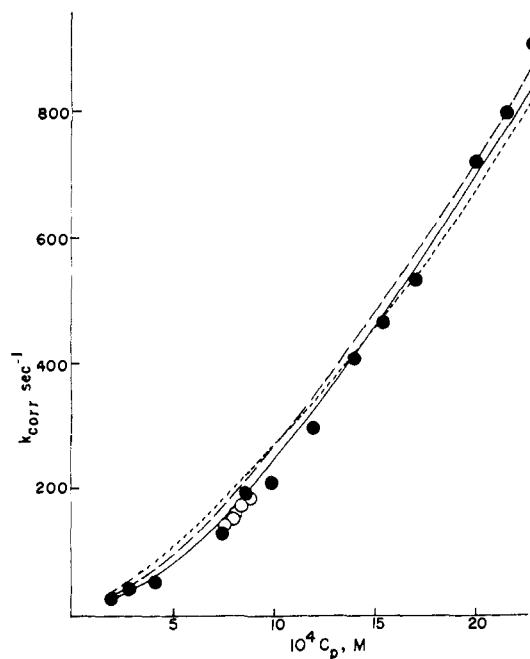
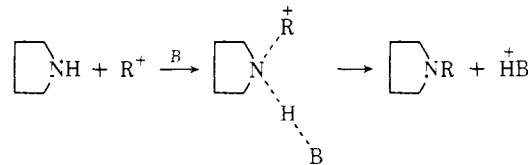


Figure 6. Variation of corrected rate constants with the actual concentration of pyrrolidine. The solid and open points were determined at different times, and the lines are calculated (see text).

results show that the curvature of these plots decreases as base is added, and that limiting linear plots of k_p against pyrrolidine concentration are reached with *ca.* 10^{-2} M hydroxide ion or 1 M trimethylamine. Additional rate constants were obtained at other concentrations of added base than shown in Figure 4, but these data were not used in the kinetic analysis, and are omitted in the interest of clarity. Figure 4 also illustrates a test which we made of the reproducibility of the data for the reaction with pyrrolidine in the absence of excess trimethylamine or sodium hydroxide. The open circles (Figure 4) were obtained with different solutions of the reagents and with a 2-week time interval between their determination and that of the data represented by the solid circles. The points in Figure 6 represent the variation of k_{corr} with the actual concentration of pyrrolidine, corrected for the formation of hydroxide ion in equilibrium with pyrrolidine. The simplest explanation of this kinetic form is that the reaction is general base catalyzed. The reaction could



in principle be concerted and termolecular, but this possibility is eliminated by the observation of a limiting second-order rate constant at high concentrations of either hydroxide ion or trimethylamine (Figures 4 and 5). (The base, B, could be water, pyrrolidine, or an added amine or hydroxide ion.)

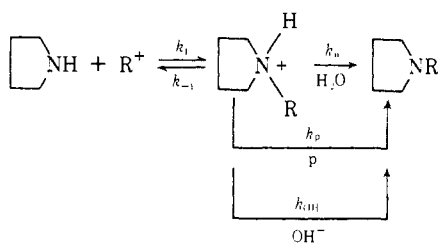
We considered another explanation of the curvature of plots of rate constant against the stoichiometric concentration of pyrrolidines (Figures 4 and 5). The



actual concentration of pyrrolidine will be less than the stoichiometric concentration, and added hydroxide ion or trimethylamine in relatively high concentration suppresses protonation of pyrrolidine. On this hypothesis, the actual concentration of pyrrolidine in a reaction mixture will be given approximately by $(6.4 \times 10^5)/k_{\text{corr}}$. (The value of 6.4×10^5 is the second-order rate constant for reaction of pyrrolidine in the presence of relatively large amounts of added hydroxide ion or Me_3N , Figure 4.) However, the value of K_B for pyrrolidine calculated on this approach varies from $2-2.6 \times 10^{-2}$ for 1-1.5 mM total pyrrolidine to 0.9×10^{-2} for 5 mM total pyrrolidine, whereas $K_B = 3.2 \times 10^{-3}$ (corrected for 0.05 ionic strength using the Davis equation).^{17,30} We therefore conclude that the curvature of the plots of k_p against total pyrrolidine concentration and the rate enhancement by added hydroxide ion or trimethylamine must be caused by general base catalysis. (We did not make this test with 2-methylpyrrolidine because its $\text{p}K$ is not known.)

The concentrations of hydroxide ion and amine were calculated for each stoichiometric concentration of amine, and the observed first-order rate constants were corrected for the reactions of water and hydroxide ion with R^+ , using rate constants determined earlier¹¹ (12 sec^{-1} for H_2O and $8200 \text{ l. mol}^{-1} \text{ sec}^{-1}$ for OH^-), giving the corrected values (k_{corr}) in Figure 6.

A stepwise general base catalyzed reaction can be formulated as



(where p represents pyrrolidine) and

$$k_{\text{corr}}/C_p = \frac{k_1(k_w/k_{-1} + C_{\text{OH}}k_{\text{OH}}/k_{-1} + C_p k_p/k_{-1})}{1 + k_w/k_{-1} + C_{\text{OH}}k_{\text{OH}}/k_{-1} + C_p k_p/k_{-1}} \quad (1)$$

where C_{OH} and C_p are actual concentrations.

The value of k_1 is calculated from k_{corr} at high concentrations of added base (Figure 4) where

$$k_1 = k_{\text{corr}}/C_p = 6.4 \times 10^5 \text{ l. mol}^{-1} \text{ sec}^{-1}$$

Calculation of the other kinetic parameters in eq 1 is more difficult. First, we tried to calculate k_p/k_{-1} by carrying out the reaction with an excess of pyrrolidine over HCl , but this approach failed because pyrrolidine is so reactive that its concentration had to be very low, and we could not use it as buffer. This problem of neutralization is much less serious if the acid is neutralized by hydroxide ion, which is a much poorer nucleophile than pyrrolidine toward R^+ .

The approach was to calculate an approximate value of k_w/k_{-1} by extrapolating k_{corr}/C_p to zero, so that

$$(k_{\text{corr}}/C_p)_{C_p \rightarrow 0} = \frac{k_1(k_w/k_{-1})}{1 + k_w/k_{-1}}$$

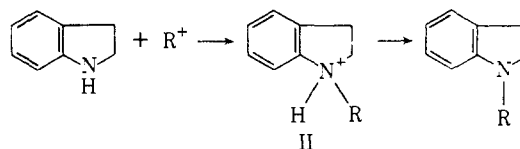
(30) The thermodynamic $\text{p}K_B$ of pyrrolidine is 11.27.³¹

(31) S. Searles, M. Tamres, F. Block, and L. A. Quantemna, *J. Amer. Chem. Soc.*, **78**, 4917 (1956).

There is considerable uncertainty in these values of k_w/k_{-1} simply because at low pyrrolidine concentrations, the rate constant is not much greater than that for the reactions of R^+ with water and hydroxide ion, but $k_w/k_{-1} < 0.2$. We then chose arbitrary values for k_p/k_{-1} and k_{OH}/k_{-1} and calculated values of k_{corr} , taking $k_1 = 6.4 \times 10^5 \text{ l. mol}^{-1} \text{ sec}^{-1}$, and $k_w/k_{-1} < 0.2$.

The form of the curve can be fitted reasonably well to various combinations of k_w/k_{-1} , k_p/k_{-1} , and k_{OH}/k_{-1} , as can be seen from the calculated lines in Figure 6, where the lines are calculated using various values of k_w/k_{-1} , k_p/k_{-1} , and k_{OH}/k_{-1} , i.e., 0.05, 500, 50 (solid line); or 0.05, 500, 100 (— —); or 0.1, 250, 200 (----), respectively. We cannot decide the best values from the data, because we have three kinetic parameters, and there are uncertainties in the concentrations of hydroxide ion and pyrrolidine using existing equilibrium constants and in the rate constants, especially at low reagent concentrations where the contribution of the spontaneous reaction is relatively large and at higher reagent concentrations where the reaction is very fast. However, the evidence suggests that both k_p/k_{-1} and k_{OH}/k_{-1} are within an order of magnitude of 10^2 , and that $k_p > k_{\text{OH}}$, despite the greater basicity of hydroxide ion over pyrrolidine. There is extensive evidence that hydroxide ion is often kinetically a relatively ineffective base, and the efficiency of amines in abstracting hydrogen ions from ammonium ions and their derivatives has been noted.³²

Indoline is a derivative of pyrrolidine and its reaction with R^+ might be expected to be general base catalyzed, but its reaction is first order with respect to amine, in part because of the low concentration of indoline necessitated by its low solubility, but the first formed ammonium ion (II) should be relatively acidic, because



of electron withdrawal by the aromatic group, and therefore readily go forward to products. Indoline is not much less reactive than 2-methylpyrrolidine, although it should be less basic (*cf.* the behavior of benzylamine).

The nucleophilicity of proline is very high (Table V), but there is no curvature in plots of rate constant against amine concentration, but loss of the hydrogen ion should not be slow in the presence of a neighboring carboxylate ion, and the reaction was carried out in phosphate buffer.

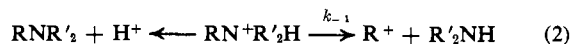
Decomposition of the Ammonium Ion. With most amines, the hydrogen ion is lost much more readily than R^+ , but with pyrrolidine we can estimate the relative rates of loss, and make approximate estimates of the values of k_{-1} , k_w , and k_{OH} .

Proton loss from ammonium and methylammonium ions to hydroxide ion is diffusion controlled,³³ with second-order rate constants in the range $2-4 \times 10^{10} \text{ l. mol}^{-1} \text{ sec}^{-1}$, and for transfer to the amine, either directly or through a water molecule, the second-order rate constants are in the range $1-10 \times 10^8 \text{ l. mol}^{-1} \text{ sec}^{-1}$.

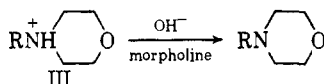
(32) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8818, 8828 (1972), and references cited therein.

(33) E. F. Caldin, "Fast Reactions in Solution," Wiley, New York, N. Y., 1964, Chapters 4 and 11.

For reactions of R^+ with most amines, proton loss from the ammonium ion must be faster than the back reaction (eq 2) where R'_2NH is a simple primary or secondary amine. In making our estimates, we will use morpholine, $pK_A = 8.3$, whose reaction with R^+ is second order. For its reaction with R^+ the lowest concentration of free amine was $7 \times 10^{-3} M$ and the pH was approximately 8.3. We can therefore calculate approximate rate constants for loss of a proton to OH^- ($10^{10} \times 5 \times 10^{-6} \text{ sec}^{-1}$) and to morpholine ($10^8 \times 7 \times 10^{-3}$) in the reaction³⁴



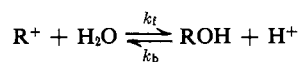
dary amine. For its reaction with R^+ the lowest concentration of free amine was $7 \times 10^{-3} M$ and the pH was approximately 8.3. We can therefore calculate approximate rate constants for loss of a proton to OH^- ($10^{10} \times 5 \times 10^{-6} \text{ sec}^{-1}$) and to morpholine ($10^8 \times 7 \times 10^{-3}$) in the reaction³⁴



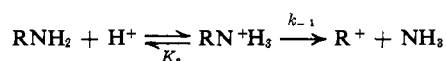
so that the overall first-order rate constant for proton loss must have been of the order of 10^6 sec^{-1} , and k_{-1} must have been considerably smaller than this number because of the absence of general base catalysis. (This calculation assumes that the rate of proton loss from III will be similar to that from a trimethylammonium ion.³³)

We can also place a lower limit upon the value of k_{-1} by noting that the observable slow step in the reaction of tri-*p*-anisylmethylamine with acid is the equilibration of R^+ and ROH, even in 1 *M* acid.

For the equilibrium¹¹



$k_t = 12 \text{ sec}^{-1}$ and $k_b = 79 \text{ l. mol}^{-1} \text{ sec}^{-1}$. Therefore in 1 *M* strong acid the first-order rate constant for the overall reaction



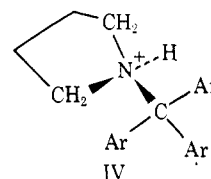
must be much greater than 91 sec^{-1} , and because the amine is protonated in 1 *M* acid

$$k_{-1} \gg 91 \text{ sec}^{-1}$$

Although there are great uncertainties in these values

(34) Assuming second-order rate constants of 10^{10} and $10^8 \text{ l. mol}^{-1} \text{ sec}^{-1}$ for proton loss to OH^- and amine, respectively.³³

of k_{-1} , it seems that $10^6 \gg k_{-1} \gg 10^2$. It remains to consider the unusual behavior of pyrrolidine and 2-methylpyrrolidine in requiring assistance from a general base for their reaction with R^+ . The nitrogen atom in IV is relatively congested so that its decomposition to



R^+ and the amine should be sterically accelerated, and at the same time proton loss to a base should be hindered.³⁵

The present observations, and others,^{7,9,11} suggest that general base catalysis of reaction of the tri-*p*-anisylmethyl cation with nucleophiles is observed only in special cases, *cf.* ref 12. A problem in examining reactions of the more stable carbocations with nucleophiles is that the products of nucleophilic addition are often unstable in water,³ so that this reaction might not be detected, and the basic nucleophiles might then catalyze the slower water reaction. Formate or acetate ions could attack R^+ to give unstable esters, and both azide and phenoxide ions give addition products which have a short life.^{7,11,21}

For those amines whose reaction with R^+ is not general base catalyzed the effect of structural changes upon reaction rate will be complex and not necessarily related to basicity in solution which is strongly dependent upon hydrogen bonding to the ammonium ion. Alkyl substitution on nitrogen does not reduce amine nucleophilicity in water, unless the alkyl group is so bulky as to sterically hinder reaction. The evidence from gas phase basicities and proton affinities is that polarizable alkyl groups assist amine protonation,³⁷ and this effect could be present in reactions with R^+ , and it could be hard to separate from the easier desolvation of the bulkier amines (*cf.* ref 4).

(35) For discussion of the geometry of the transition state for loss of a hydrogen ion, see ref 36.

(36) L. L. Ingraham, *Biochim. Biophys. Acta*, **279**, 8 (1972).

(37) J. I. Brauman, J. M. Riveros, and L. K. Blair, *J. Amer. Chem. Soc.*, **93**, 3914 (1971); D. H. Aue, H. M. Webb, and M. T. Bowers, *ibid.*, **94**, 4726 (1972).