When k_A responds linearly to [NaOH], as in Figure 2, and $k_3[B] \gg k_2$ (as at high [NaOH]), eq 1 simplifies to: $k_A = k_1k_3[B]/k_{-1}$. At 0.1 M NaOH, k_A is 14.5 times greater for pyrrolidine than for piperidine. If k_1 is 1.5 times greater, as it is with **1a**, k_3/k_{-1} must be an order of magnitude larger for the pyrrolidine than for the piperidine reaction.

Mechanism of Base Catalysis. We now inquire as to what significance the much higher k_3/k_{-1} ratios for pyrrolidine than for piperidine reactions have with respect to whether proton transfer or nucleofuge detachment is rate limiting. This ratio might be greater either because k_3 were larger or k_{-1} were smaller. Some guidance as to how k_{-1} varies with the identity of the amine is provided by entries in Table IV for reactions of **4**; k_{-1} for pyrrolidine is about two-thirds that for piperidine. If the same modest difference in k_{-1} parameters also obtains for reactions of **1a** and **1b**, the main cause of the big difference in k_3/k_{-1} ratios must be a difference in the magnitude of k_3.

On the hypothesis of rate-limiting proton transfer, k_3 pertains to proton removal by base from intermediates of type ZH (Scheme I). Bernasconi, Muller, and Schmid[32] present persuasive arguments that in the system of Scheme II the corresponding step should occur at encounter-controlled rate, and they assigned the k_{3p} values listed in Table IV on the basis. If proton transfer is rate limiting in the reactions we have studied, the k_3 parameter for piperidine would have to be much lower than for pyrrolidine, at least an order of magnitude below the encounter-controlled rate. We know of no precedent for such a difference.[34] Reconciliation of our results with the hypothesis of rate-limiting proton transfer is thus awkward.

On the hypothesis of rate-limiting nucleofuge detachment, k_3 represents the product of K_{ZH} (the acid dissociation constant of ZH) and k_4 (rate constant for conversion of Z^- to $ArNR_2$), divided by K_w (the ionization constant of water). If the K_{ZH}'s for the two amines reacting with the same substrate are about the same, as has been estimated for **4** in 30% dimethyl sulfoxide/70% water,[32] the difference in the k_3/k_{-1} ratios for reactions of pyrrolidine and piperidine must stem from a difference in k_4 values. This rate constant concerns nucleofuge detachment from Z^-.

We must then ask if there is any other evidence that a change from a pyrrolidino to a piperidino group in an intermediate of type Z^- can markedly decelerate the expulsion of the nucleofugal group. Indeed there is, as presented in an accompanying paper.[18] In the reactions of these two amines with 2,4-dinitro-1-naphthyl ethyl ether in dimethyl sulfoxide, the nucleofuge detachment step is about 11 000 times faster with pyrrolidine than with piperidine.

These considerations do not warrant the conclusion that the mechanism of rate-limiting proton transfer must be rejected for the reactions of **1a** and **1b** with piperidine in aqueous dioxane media. The argument involves too many assumptions based on analogy. However, the argument for the rate-limiting proton transfer mechanism[12-14] also involves assumptions based on analogy. What can be said is that the present results cast doubt on the rate-limiting proton transfer interpretation.

It would be desirable to have further evidence concerning these questions.[35]

Acknowledgment. This investigation was supported in part by Public Health Service Grant No. GM 14647 from the National Institute of General Medical Sciences. We thank Professor C. F. Bernasconi for criticism of a draft copy of the manuscript.

(34) However, we call attention to observations of M. R. Crampton and B. Gibson, privately communicated, that proton transfer from **4** (R_2NH^+– being piperidinio) to piperidine in Me_2SO solution is much slower than from the butylamine analog of **4** to butylamine.

(35) After the initial submission of this paper for publication, we learned that a similar difference between pyrrolidine and piperidine has been observed in respect to their aminodemethoxylation reactions with 2-methoxy-3-nitrothiophene: Consiglio, G.; Arnone, C.; Noto, R.; Spinelli, D. Abstracts, XII Convegno Nazionale di Chimica Organica; Società Chimica Italiana: Ancona, Sept, 1980; p 205.

Kinetics of Reactions of Cyclic Secondary Amines with 2,4-Dinitro-1-naphthyl Ethyl Ether in Dimethyl Sulfoxide Solution. Spectacular Difference between the Behavior of Pyrrolidine and Piperidine

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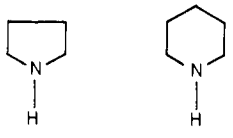
Abstract: The reactions named in the title, which form *N*-(2,4-dinitro-1-naphthyl) derivatives of these heterocyclic amines, occur in two distinct stages. In stage I, the spectrum of a σ-adduct intermediate develops at a rate which is measurable in a stopped flow apparatus; in stage II, it decays at a slower and easily measurable rate. The kinetics of both stage I and stage II have been studied. Pyrrolidine and piperidine are similar in their stage I behavior, but reactivity in stage II is about 11 000 times greater in the pyrrolidine system. This huge difference between systems apparently so similar is judged to arise from steric interactions forced by differences in conformation between the amino moieties in the intermediate σ adducts as they release the nucleofuge. It calls into question the rate-limiting proton transfer interpretation of base catalysis in analogous aminodephenoxylation reactions in protic solvents.

Remarkably different are the reactions of pyrrolidine and piperidine with 2,4-dinitrophenyl phenyl ether (DNPE) in 10% dioxane/90% water. Whereas the former is insensitive to catalysis by NaOH,[3] the latter is accelerated strongly and in curvilinear fashion that provides much evidence of mechanism.[4]



pyrrolidine piperidine

(1) On leave from Gunma University, Kiryu, Japan, 1970–71, under support of a fellowship from the Japanese Ministry of Education.
(2) On sabbatical leave from Chico State College, 1969–1970; deceased Novement 26, 1974.
(3) Bunnett, J. F.; Hermann, D. H. *Biochemistry* **1970**, *9*, 816.
(4) Bunnett, J. F.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1965**, *87*, 5209.

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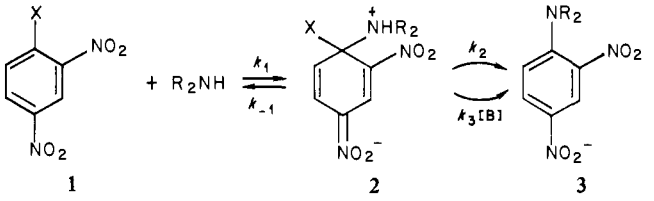
Scheme I



Base catalysis in such reactions is often discussed[5-7] with attention to the representation in Scheme I. If the chemical flux from intermediate **2** to product **3** is much greater than back to reactant **1**, base catalysis is not observed, for the initial attack of amine on **1** is not catalyzed by base. On the other hand, if $k_{-1} \gg (k_2 + \sum_i k_3^i[B_i])$, and if $k_2 < \sum_i k_3^i[B_i]$, base catalysis may be observed.

The fact that the piperidine reaction with DNPE is susceptible to catalysis by bases while the pyrrolidine reaction is not implies that the seemingly minor change from a cyclic secondary amine with five ring atoms to one with six profoundly affects the relative magnitudes of k_{-1}, k_2, and k_3. However, the kinetic data from 10% dioxane/90% water give no insight as to which rate coefficients change, or by how much.

Rate measurements on the same reactions in 60% dioxane/40% water, as affected by NaOH, are more helpful. In that solvent, both the pyrrolidine and the piperidine reactions with DNPE respond to catalysis by NaOH, in curvilinear fashion such that k_1 and the rate coefficient ratios, k_3/k_{-1} and k_2/k_{-1}, can be estimated.[8,9] The two amines differ about 14-fold in their k_3/k_{-1} ratios. However, the data do not tell whether the higher k_3/k_{-1} ratio for pyrrolidine stems from a higher k_3 or a lower k_{-1} value.

In order better to understand the differences between pyrrolidine and piperidine in systems of this type, we chose to investigate their reactions with 2,4-dinitro-1-naphthyl ethyl ether (**5**) in dimethyl sulfoxide solution. Orvik and Bunnett[10] were able, in a study of the reactions of **5** with *n*-butylamine and *tert*-butylamine in that solvent, to observe separately the formation and the further reaction of an intermediate corresponding to **2** in Scheme I and thereby to evaluate rate coefficients for several component steps. Their work involved mainly photometric measurements. Their interpretations have subsequently been confirmed by the technique of flow NMR.[11] We patterned our experiments on those of Orvik and Bunnett.

The reaction steps involved in the case of a secondary amine are shown in Scheme II. With a primary amine, the substitution product corresponding to **8** can react as a Brønsted acid with another amine molecule,[10] but **8** is unable to do that. However, **8** can act as a Lewis acid with another amine molecule to form a Jackson–Meisenheimer adduct.[12] That process has been studied separately;[12] fortunately, it is not fast enough in either the pyrrolidine or the piperidine case to interfere with rate measurements on reaction 3.

Results

The reactions of pyrrolidine and piperidine with **5** in Me_2SO occur in two steps easily recognizable by the rise and fall of absorption maximally at 522 nm attributed to intermediates of type **7**. Stage I is rapid, necessitating use of stopped flow techniques in order to measure reaction rates. Stage II is slower by a 1000-fold or more, and leads to products characterized as **8** by their UV absorption spectra. In the case of piperidine, the structure of **8b** is also indicated by NMR data.[13]

Scheme II

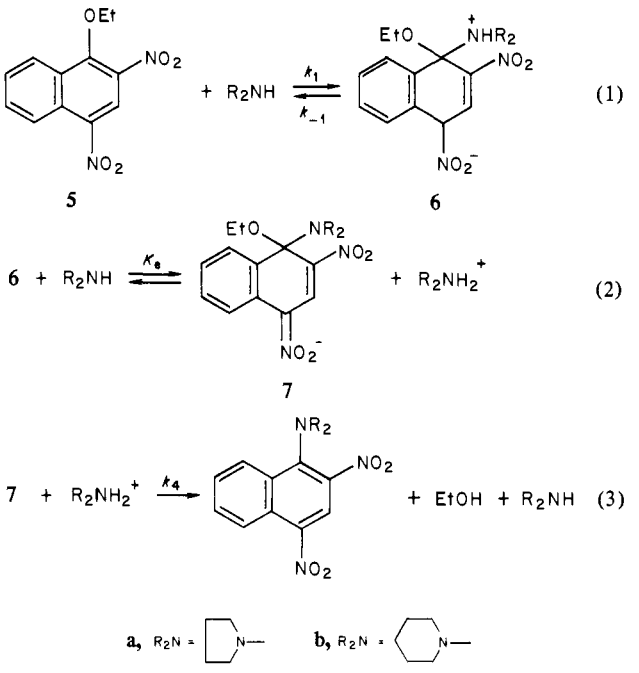


Table I. Reaction of 5 with Pyrrolidine in Dimethyl Sulfoxide: Stage I Kinetics[a]

$[C_4H_8NH]$, M	k_ψ, s^{-1}
6.0×10^{-2}	48.3 ± 0.8
10.6×10^{-2}	69.0 ± 1.6
12.1×10^{-2}	82.8 ± 1.5
13.6×10^{-2}	95.8 ± 1.6
15.1×10^{-2}	99.8 ± 2.4

[a] Temperature 25.0 °C; $[5]_0$ 1.0×10^{-5} M; $[C_4H_8NH_2^+Cl^-]$ 5.2×10^{-3} M.

The stage I equilibrium constant can be measured under appropriate conditions. From it and stage I rate data, it is evident that stage I involves measurably slow attack of amine on **5** to form **6**, followed by rapid proton transfer equilibrium reaction 2. Reversion of **6** to **5** occurs significantly and must be taken into account.

For the reaction of piperidine, the behavior described was observable after the amine had been submitted to a special purification process to remove traces of pyridine. When traces of an amine believed to be pyridine were present, the end spectrum was one characteristic of reaction of **5** with a primary amine. The impurity was observed by GLC and UV, and its absence from purified piperidine was confirmed by these techniques. The chemical nature of the complication was not investigated.

Stage I Kinetics, with Pyrrolidine. Under the conditions studied, reaction occurs rapidly to establish equilibrium between **5** and **7** according to eq 1 and 2, Scheme II. Accordingly the pseudo-first-order rate constant for the attainment of equilibrium (k_ψ) is the sum of those for the forward and reverse reactions, and eq 4 applies.

$$k_\psi = k_1[R_2NH] + \frac{k_{-1}[R_2NH_2^+]}{K_e[R_2NH]} \quad (4)$$

Multiplying each side by $[R_2NH]$,

$$k_\psi[R_2NH] = k_1[R_2NH]^2 + (k_{-1}/K_e)[R_2NH_2^+] \quad (5)$$

Our kinetic measurements on stage I are reported in Table I. In accordance with eq 5, as shown in Figure 1, a plot of $k_\psi[R_2NH]$ against $[R_2NH]^2$, at constant pyrrolidinium chloride concentration, is linear. The slope, k_1, is $6.5 \pm 0.3 \times 10^2$ M^{-1} s^{-1} (at 25.0 °C).

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Table II. Reaction of 5 with Pyrrolidine in Dimethyl Sulfoxide: Stage II Kinetics and Stage I Equilibrium[a]

$[5]_o$, M × 10^5	$[C_4H_8NH]$, M	$[C_4H_8NH_2^+Cl^-]$, M × 10^3	[salt[b]], M	A_i[c]	10^2k_{obsd}, s^{-1}	K_i, M^{-1}, from A_i[d]	K_i, M^{-1}, from stage II kinetics
			Part A				
2.53	0.00975	5.12	nil	0.054	0.486	4.6	3.5
2.53	0.0195	5.12	nil	0.127	0.127	3.1	3.7
2.53	0.0292	5.12	nil	0.293	2.90	4.3	3.4
2.53	0.0390	5.12	nil	0.370	4.03	4.0	3.4
2.53	0.0585	5.12	nil	0.519	5.50	4.7	3.3
2.53	0.0780	5.12	nil	0.576	6.40	4.5	3.4
2.53	0.0975	5.12	nil	0.609	6.92	4.3	3.4
2.61	0.099	nil	nil	0.712	0.33		
2.53	0.130	nil	nil	0.676	0.69		
			Part B[e]				
2.53	0.0700	5.12	nil	0.560	6.24	6.5	3.7
2.53	0.100	5.12	nil	0.611	7.06		
2.53	0.210	5.12	nil	0.647	7.75		
2.53	0.280	5.12	nil	0.648	7.89		
2.53	0.320	5.12	nil	0.647	7.95		
2.53	0.401	5.12	nil	0.649	8.01		
2.53	0.481	5.12	nil	0.650	8.00		
2.53	0.561	5.12	nil	0.650	7.99		
2.53	0.641	5.12	nil	0.651	8.01		
			Part C				
2.52	0.0237	1.12	0.010	0.505	0.873	5.6	2.0
2.52	0.0237	2.24	0.0087	0.416	1.40	6.3	2.7
2.44	0.0237	3.36	0.0078	0.338	1.69	6.3	2.8
2.44	0.0237	5.60	0.0056	0.279	2.09	7.3	3.1
2.44	0.0237	7.83	0.0034	0.186	2.28	5.5	3.2
2.44	0.0237	11.2	nil	0.147	2.65	5.7	3.6
2.52	0.0237	nil	0.0112	0.688	0.064		

[a] Temperature: 25.0 °C. [b] *N,N*-Dimethylpyrrolidinium chloride. [c] Stage II initial absorbance at 523 nm. [d] Reckoned on basis that ϵ for 7 is 2.71 × 10^4, except 2.57 × 10^4 for the first experiment in part B. [e] Experiments in part B were performed at Gunma University by Mr. Takao Shiobara, all in duplicate with k_{obsd} values differing by <2%.

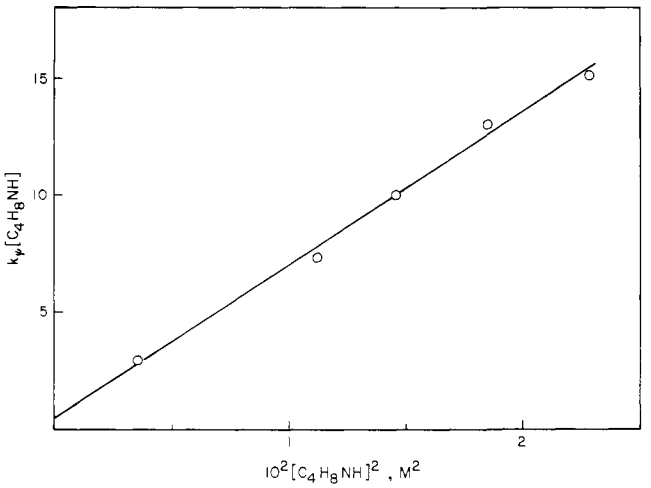


Figure 1. Stage I reaction of pyrrolidine with **5**. Plot of rate data from Table I according to eq 5.

From the intercept, one reckons (imprecisely)k_{-1}/K_e to be 8 ± 9 × 10^1 s^{-1}.

Stage I Equilibrium, with Pyrrolidine. Evaluation of the equilibrium constant, K_i, for stage I overall is both of independent interest and necessary for treatment of the stage II kinetics. In terms of algebraic principle, one could evaluate K_i from the stage I kinetics; $K_i = (k_1/k_{-1})K_e$. From the kinetic parameters reported above, K_i = 8 M^{-1}, uncertain by one standard deviation between 3.6 and ∞; this is an imprecise estimate.

One may also evaluate K_i from the stage II initial absorbance. Very early in a stage II rate measurement, the stage I equilibrium is established. Extrapolation of stage II absorbance measurements back to zero time should therefore allow K_i to be evaluated. Actually the time of mixing of reagents is not exactly the proper stage II zero time, for a little time is required to establish the stage I equilibrium. However the delay (a few tenths of a second) is very small on the time scale for stage II. In Table II, the stage II initial absorbance is tabulated as A_i, and the K_i values reckoned from it are listed for those experiments appropriate from such reckoning. The mean K_i value, of those tabulated, is 5.2 ± 1.2 M^{-1}.

K_i may also be evaluated from stage II kinetic data, as discussed below. We consider the mean K_i of kinetic origin from part A, Table II, to be the best estimate available from the present work: K_i = 3.44 ± 0.11 M^{-1}. From this K_i value and k_1 as evaluated above, k_{-1}/K_e = 1.89 ± 0.14 × 10^2 s^{-1}.

Stage II Kinetics, with Pyrrolidine. Under most conditions stage I is a mobile equilibrium, on the time scale of stage II, splitting the substrate substantially between forms **5** and **7**. After Orvik and Bunnett,[10] the stage II pseudo-first-order rate constant, k_{obsd}, depends on amine and amine hydrochloride concentrations as shown in eq 6.

$$k_{obsd} = \frac{k_4K_i[R_2NH]^2[R_2NH_2^+]}{K_i[R_2NH]^2 + [R_2NH_2^+]} \quad (6)$$

When the first term in the denominator of eq 6 greatly exceeds the second, that is, when the stage I equilibrium lies almost entirely on the side of **7**, eq 6 simplifies to eq 7.

$$k_{obsd} = k_4[R_2NH_2^+] \quad (7)$$

Our stage II kinetic data are set forth in Table II. The k_{obsd} values for all runs in parts A and B with pyrrolidine hydrochloride concentration 5.12 × 10^{-3} M are plotted against pyrrolidine concentration in Figure 2. It is noteworthy that a plateau is attained at high amine concentrations, as called for by eq 7 when the concentration of the amine conjugate acid is constant. From the plateau k_{obsd} value, k_4 is calculated by eq 7 to be 15.6 M^{-1} s^{-1}.

Once k_4 has been evaluated, eq 6 can be utilized to calculate K_i from stage II kinetic data. The values so obtained, from experiments appropriate to that purpose, are listed in the far-

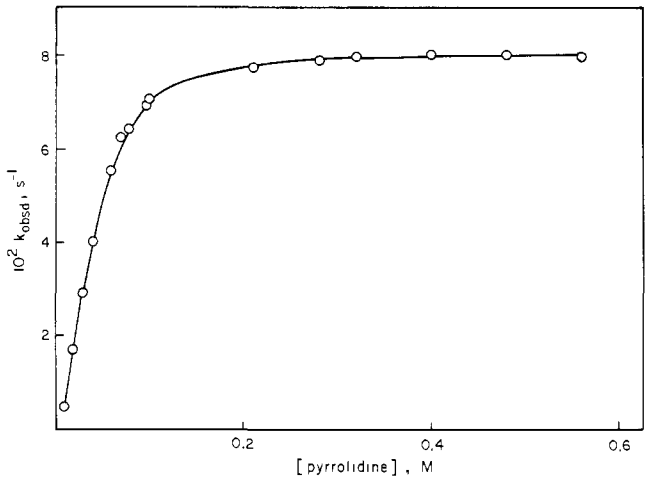


Figure 2. Stage II reaction of pyrrolidine with **5**. Plot of the observed pseudo-first-order rate constant at constant pyrrolidinium chloride concentration against pyrrolidine concentration. Data from Table II.

Table III. Reaction of 5 with Piperidine in Dimethyl Sulfoxide: Stage I Kinetics[a]

$[C_5H_{10}NH]$, M	k_ψ, s^{-1}
0.039	25.2
0.055	28.8
0.069	29.3
0.099	31.0
0.129	36.7

[a] Temperature 25.0 °C; [5] 7.9×10^{-6} M; $[C_5H_{10}NH_2^+Cl^-]$ 5.0×10^{-3} M; each k_ψ is the average of concurring duplicate determinations.

right-hand column of Table II. The K_i values reckoned in this way vary more or less randomly in part A, but in part C they increase as pyrrolidinium chloride takes the place of *N,N*-dimethylpyrrolidinium chloride. This variation is probably to be ascribed to a mild specific salt effect on one of the equilibria or on the kinetic process.[14] We take the mean K_i value from part A, namely, 3.44 M^{-1}, as the best K_i of this origin, appropriate to the conditions under which it was determined.

Equation 6 is converted into eq 8 by rearranging and taking

$$\log k_{obsd} + \log (K_i[R_2NH]^2 + [R_2NH_2^+]) = \log k_4K_i + 2 \log [R_2NH] + \log [R_2NH_2^+] \quad (8)$$

logarithms. To probe the validity of eq 6, we plotted the quantity on the left side of eq 8, taking K_i to be 3.44 M^{-1}, against the logarithm of pyrrolidine concentration. For the data of part A, Table II, the plot (not shown) was linear with slope 1.99 by linear regression analysis. Similarly, for the data of part C, Table II, using the same K_i value, we obtained a linear plot of the sum of the left side of eq 8 vs. log $[C_4H_8NH_2^+Cl^-]$. The linear regression slope was 1.08. These correlations are in nearly perfect agreement with eq 8.

Using K_i = 3.44 and k_4 = 15.6 M^{-1} s^{-1}, we calculated k_{obsd} for each experiment in Table II by means of eq 6. The calculated values were in good agreement with the experimental values, but agreement was even better when k_4 = 15.7 M^{-1} s^{-1} was employed. In the latter case, the calculated and observed values for parts A and B differ mostly by 1% or less. Deviations are somewhat greater for part C, probably in large part because of specificity of salt effects[14] as mentioned above. We consider 15.7 M^{-1} s^{-1} to be the best evaluation of k_4.

Stage I Kinetics, with Piperidine. Our data for the rate of attainment of equilibrium appear in Table III. The plot (not shown) according to eq 5 is a straight line similar to that in Figure 1. The slope represents k_1 and is $2.4 \pm 0.1 \times 10^2$ M^{-1} s^{-1}; k_{-1}/K_e is reckoned from the intercept to be $1.54 \pm 0.18 \times 10^2$ s^{-1}.

Table IV. Reaction of 5 with Piperidine in Dimethyl Sulfoxide: Stage II Kinetics and Stage I Equilibrium[a]

$[C_5H_{10}NH]$, M	$[C_5H_{10}NH_2^+Cl^-]$, M	[salt[b]], M	A_i[c]	$10^5 k_{obsd}$, s^{-1}	K_i,[d] M^{-1}
		Part A			
0.125	0.08	nil	0.119	2.53	1.58
0.200	0.08	nil	0.218	5.03	1.52
0.350	0.08	nil	0.363	8.56	1.68
0.500	0.08	nil	0.476	9.23	*e*
0.650	0.08	nil	0.485	10.3	*e*
0.800	0.08	nil	0.493	10.4	*e*
0.951	0.08	nil	0.516	10.3	*e*
		Part B			
0.402	0.0272	0.0299	0.466	3.41	*e*
0.402	0.0383	0.0199	0.457	4.58	*e*
0.402	0.0460	0.0119	0.423	6.06	1.50
0.402	0.0517	0.0064	0.414	6.53	1.48
0.402	0.0587	nil	0.399	7.63	1.39

[a] Temperature: 25 °C; $[5]_0$ 2.48×10^{-5} M; each k_{obsd} is the average of concurring duplicate determinations. [b] *N,N*-Dimethylpiperidinium chloride. [c] Stage II initial absorbance. [d] Reckoned from A_i on the basis that *e* for 7 is 2.03×10^4. [e] Data not appropriate to calculate K_i.

Table V. Rate and Equilibrium Constants for Component Steps of the Reactions of Amines with 5 in Dimethyl Sulfoxide Solution at 25 °C

		amine			
reaction	parameter	pyrrolidine	piperidine	*n*-$BuNH_2$[a]	*t*-$BuNH_2$[a]
$5 \rightarrow 6$	k_1, M^{-1} s^{-1}	6.5×10^2	2.4×10^2	31.8	0.51
$5 \rightleftarrows 7$	K_i, M^{-1}	3.44	1.55	5.4×10^2	0.074
$7 \rightarrow 5$	k_{-1}/K_e, s^{-1}	1.89×10^2	1.54×10^2	5.9×10^{-2}	4.9
$7 \rightarrow 8$	k_4, M^{-1} s^{-1}	15.7	1.40×10^{-3}	10.1	0.42

[a] From ref 10.

Stage I Equilibrium, with Piperidine. Equilibrium constant K_i was evaluated in two ways. From kinetics as just mentioned, $K_i = k_1K_e/k_{-1} = 1.55 \pm 0.25$ M^{-1}. From absorbance measurements during stage II kinetic experiments, extrapolated to time "zero", K_i is calculated to be 1.52 M^{-1}. The agreement between the two methods is excellent.

Stage II Kinetics, with Piperidine. Two sets of experiments were performed, and the data obtained are presented in Table IV. Stage II reaction is relatively slow with piperidine.

For the experiments in part A, the piperidinium chloride concentration was constant at 0.08 M, and the piperidine concentration was varied. The plot of k_{obsd} vs. [piperidine] resembles that in Figure 2. The fact that the last three experiments in part A, at the highest amine concentrations, all gave substantially the same rate constant indicates that at high piperidine concentration the stage I equilibrium is essentially wholly on the side of **7**, and that the transformation of **7** into **8** is kinetically independent of piperidine concentration, consistent with Scheme II. Division of k_{obsd} from the last three experiments in part A by $[C_5H_{10}NH_2Cl]$ provides an evaluation of k_4 as 1.29×10^{-3} M^{-1} s^{-1}.

If the model of Scheme II is correct, the data of Table IV should conform to eq 6 or 8. When the data of part A are plotted according to eq 8, the quantity on the left (calculated on the basis that K_i = 1.55 M^{-1}) being plotted against log $[C_5H_{10}NH]$, a straight line of slope 2.03 is obtained, in good agreement with slope 2.00 called for by eq 8. When the data of part B are appropriately plotted, the quantity on the left of eq 8 against log $[C_5H_{10}NH_2Cl]$, a linear plot of slope 1.19 results. The deviation from slope 1.00 is perhaps to be ascribed to imperfect compensation of salt effects upon replacement of one electrolyte by another.[14]

When eq 8 is used to compute k_{obsd} values, a better fit is obtained when $k_4 = 1.40 \times 10^{-3}$ M^{-1} s^{-1} is used rather than the value reckoned from the last three experiments of part A, Table

(14) Specific kinetic effects of amine hydrochlorides have been noted by Bernasconi, Muller, and Schmid[15] in their studies of the kinetics of attachment of amines to 1,3,5-trinitrobenzenes to form σ adducts, and the reverse processes.

(15) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.

IV, together with K_i = 1.55 M^{-1}. Most deviations of calculated from experimental k_{obsd} are ± 3% for part A, but again they are somewhat larger for part B.

Best Values of Constants. In Table V, we gather together the various rate and equilibrium constants that we have evaluated for pyrrolidine and piperidine reactions with **5**. For comparison purposes we include the corresponding values determined by Orvik and Bunnett[10] for the reactions of *n*-butylamine and *tert*-butylamine with **5**.

Discussion

Mechanism in General. Our data are compatible with the mechanism of Scheme II in several respects. Reaction solutions at the completion of stage II reaction have UV spectra that match those of authentic **8a** or **8b**. Formation of the transient intermediate identified as **7** is first order in amine, but the equilibrium expression for conversion of **5** into **7** calls for the involvement of two amine molecules as reactants and one substituted ammonium ion as a byproduct. These facts show that the transient intermediate is **7** rather than **6**, and that formation of **7** occurs stepwise via **6**. Transformation of **7** into substitution product **8** is first order in substituted ammonium ion and zero order in amine, and thus is general acid catalyzed.

Furthermore, NMR studies by Sekiguchi and co-workers[13] confirm that the transient intermediate from **5** and piperidine in $(CD_3)_2SO$ solution has structure **7b**.

Comparison of Reactivities in Stage I. The rate constants for nucleophilic attack at C-1 of **5**, namely, the k_1 values, are high and similar for the two heterocyclic amines; see Table V. Pyrrolidine is more reactive than piperidine by a factor of 2.7. *n*-Butylamine is an order of magnitude less reactive, and *tert*-butylamine lags two orders of magnitude behind its straight-chain isomer. This order of amine reactivity resembles the order of overall rate constants observed for S_NAr reactions in which formation of the σ-adduct intermediate is rate determining.[16] The superior reactivity of the secondary amines over *n*-butylamine probably stems from favorable ion-induced dipole interactions in the transition state between the (partially) positively charged amine nitrogen and the polarizable alkyl moieties attached to it. The same factor is held responsible for the greater gas-phase basicity of secondary amines.[17]

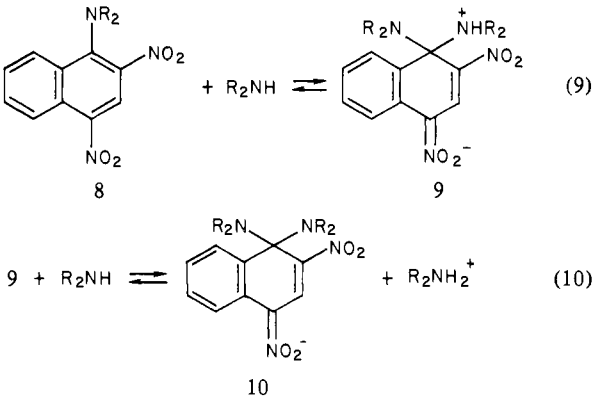
Incidentally, the pyrrolidine/piperidine reactivity ratio in nucleophilic attack, expressed as k_1, measured in the present work (2.7) is similar to that in reactions of these amines with 1,3,5-trinitrobenzene in 30% dimethyl sulfoxide/70% water[15] (2.2) or with the same trinitrobenzene in 10% dioxane/90% water[15] (2.7), or with DNPE in 60% dioxane/40% water[8] (1.6).

The overall stage I equilibrium constant, K_i, is highest for *n*-$BuNH_2$, about 100-fold less and similar for pyrrolidine and piperidine, and nearly 100-fold lower yet for *t*-$BuNH_2$. These differences probably reflect steric crowding in adducts of structure **7**, which are severe for *t*-$BuNH_2$, considerable for piperidine, a little less for pyrrolidine, and substantially less for *n*-$BuNH_2$.

The k_{-1}/K_e values are of course determined by the k_1 and K_i values already mentioned. It is interesting that they are very similar for pyrrolidine and piperidine and higher even than for *t*-$BuNH_2$. The effect that lowers the Gibbs free energy of the transition state in the forward direction for the secondary amines, suggested to be ion-induced dipole interactions, necessarily also lowers it in the reverse direction.

Stage II Reactivity: A Big Difference between the Pyrrolidine and Piperidine Systems. In stage II, a substituted ammonium ion catalyzes the expulsion of ethoxide ion from σ-complex intermediate **7**, and the rate constant is symbolized k_4. With respect to the k_4 value for the *n*-$BuNH_2$ system, k_4 for pyrrolidine is a little higher and k_4 for piperidine is much lower. For the pyrrolidine system, k_4 is about 11 000 times greater than for piperidine. This corresponds to $\Delta\Delta G^{\ddagger}$ of 5.5 kcal/mol. In view of the similarity of these two amines in their stage I behavior, it is probable that this huge stage II reactivity difference is mainly due to a difference in transition state free energies, that for the piperidine system being much higher.

Scheme III



Two important questions immediately arise: what is the cause of this major difference in stage II reactivity, and what implications does it have in regard to our understanding of the mechanism of S_NAr reactions involving amine reagents, especially the nucleofuge expulsion steps?

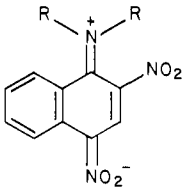
Why Do Pyrrolidine and Piperidine Differ So Greatly? These two cyclic amines are very similar in properties such as their pK_a values,[18] their rates of nucleophilic attack on aromatic carbon sites (vide supra), and electron delocalization between pyrrolidino or piperidino groups and unsaturated systems to which they are attached.[19] It is therefore inconceivable that the reason for their differing stage II behavior is a difference in polar effects. It must be of steric or stereoelectronic origin.

Step 3, Scheme II, involves the amine conjugate acid as well as amino σ-adduct **7**. A priori, either amino moiety, or some sort of interaction between the two, might be the source of the remarkable difference between the two systems. However, it has been observed[12] that pyrrolidine is also remarkably more reactive than piperidine in adding to the corresponding 2,4-dinitro-1-naphthylamine (**8**) to form a diamino σ adduct of type **10**; see Scheme III. Step 9, forward, is rate determining for the formation of **10**. Step 9 does not involve general acid-base catalysis, and therefore it is improbable that the size or conformation of the ammonium moiety in the transition state for step 3 is the feature so greatly sensitive to the difference between pyrrolidine and piperidine. We therefore conclude that some steric, stereoelectronic, or conformational effect concerning the carbon-bound amino moiety in the transition state for step 3 is the source of the huge difference in stage II reactivity.[20]

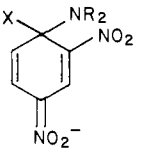
We presume that the unshared electron pair on the amino nitrogen of **7** plays a significant role in expulsion of the ethoxy group, somewhat as electron pairs on remaining amino, hydroxy, and alkoxy groups do in nucleofuge detachment from the tetrahedral intermediates involved in the hydrolysis of imidates.[21] That implies that the unshared electron pair on nitrogen must be anti-periplanar with respect to the rupturing C–O bond in the

(16) Miller, J. "Aromatic Nucleophilic Substitution"; Elsevier Publishing Co.: Amsterdam, 1968; p 206.
(17) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 6561.
(18) Albert, A.; Serjeant, E. P. "Ionization Constants of Acids and Bases"; Methuen & Co.: London, 1962; p 141.
(19) Schwotzer, W.; von Philipsborn, W. *Helv. Chim. Acta*, **1977**, *60*, 1501.
(20) We acknowledge that two amino moieties are also present in the transition state for step 9, these being the attacking amine and the one originally present in **8**, and that by coincidence the similar very large differences in behavior of the two cyclic amines in steps 3 and 9 might relate to the general acid moiety in step 3 and the nucleophile moiety in step 9. That is, however, unlikely because the nature of involvement of these two amine moieties is so different in the two steps. In contrast, the amino moieties that are carbon bound in **7** and **8** should have similar characteristics in the two transition states inasmuch as step 9 resembles the microscopic reverse of step 3.
(21) Deslongchamps, P. *Pure Appl. Chem.* **1975**, *43*, 351. Deslongchamps, P.; Cheriyan, U. O.; Pradere, J.-P.; Soucy, P.; Taillefer, R. J. *Nouv. J. Chim.* **1979**, *3*, 343.

transition state. It also implies that the amino moiety approaches the largely coplanar geometry of structure **11**, which is a canonical form of **8**.



11a, $R_2N = C_4H_8N$
b, $R_2N = C_5H_{10}N$



12

For **7b**, two prominent types of conformation with the unshared electron pair on nitrogen anti-periplanar to the C–O bond have the aryl moiety equatorial or axial with respect to the piperidine ring. Inasmuch as for both *N*-alkyl- and *N*-arylpiperidines the conformation with N substituent equatorial is greatly preferred, by about 2–3 kcal/mol for *N*-methylpiperidine,[22] the aryl-moiety-equatorial conformation for **7b** is likely to predominate.

The conformation of the carbon-bound amino moiety in the transition state for step 3 should be intermediate between its conformations in **7** and in **11**. Examination of Dreiding models for **7a**, **7b** (in the aryl-equatorial conformation), **11a**, and **11b** reveals that in both **7b** and **11b** the equatorial hydrogens at the 2′ and 6′ positions of the piperidine moiety protrude laterally,[23] toward the 2-nitro group and the 8-hydrogen, more than do the 2′- and 5′-hydrogens of the pyrrolidine moiety in **7a** and **11a**. Also, the axial 2′- and 6′-hydrogens of **7b** protrude more toward the ethoxy moiety. We suppose the 11 000-fold difference in reaction rates to stem from additional steric compressions in the piperidine transition state involving these protruding hydrogen atoms. If that is the correct explanation, we are impressed that the consequences of such interaction are so great.

The aryl-axial conformation for **7b** implies substantial crowding, especially against the alkoxy group and probably also against the ammonium moiety that must approach the ethoxy group in the step 3 transition state. If there were some reason, not apparent to us at this writing, why this transition state would require a quasi-axial situation for the aryl moiety, the great difference in stage II reeactivity between the pyrrolidine and piperidine reactions would seem an obvious consequence.

Broader Implications in Regard to Reaction Mechanisms. As discussed by Bunnett and Cartaño,[8] there are two alternative interpretations for base catalysis of the conversion of intermediates such as **2** to **3**; see Scheme I. Both interpretations postulate the conjugate base of **2**, of structure **12**, to be an intermediate. One interpretation[24-27] holds that the rate-limiting step, when X is a good leaving group such as phenoxy, is proton removal from **2** by the base, and that X then rapidly detaches from **12** as X^-. An alternative interpretation[4,9] is that **2** and **12** exist in acid–base equilibrium with each other, and that the rate-limiting step is detachment of the nucleofuge from **12**. For reactions that are general base catalyzed, as many are, the latter mechanism would imply general acid catalysis of the separation of X from **12**.

Each of these interpretations is supported by strong experimental evidence involving systems atypical with respect to common substitution reactions in solvents such as methanol or aqueous dioxane. General acid catalysis of slow nucleofuge detachment is demonstrated by experiments such as we presently report, but dimethyl sulfoxide is a solvent with characteristics much different from methanol or aqueous dioxane. Rate-limiting proton removal from species analogous to **2** is shown by relaxation kinetic studies on the reversible formation of anionic σ adducts of the Jackson–Meisenheimer type and on certain Smiles rearrangements.[24-27] These are valid and interesting systems but certainly different from common reactions such as that of piperidine with DNPE in aqueous dioxane. It has been argued plausibly that the observed general base catalysis of this archetypical reaction involves rate-limiting proton transfer.[24,26,27]

Kinetic measurements by Bunnett and Cartaño[8] show that in 60% dioxane/40% water, the reaction of DNPE with pyrrolidine, as catalyzed by hydroxide ion, is characterized by a k_3/k_{-1} ratio (see Scheme I) about 14 times larger than for the corresponding reaction with piperidine. If the k_{-1} values for the two amines are about the same, as is suggested by measurements on analogous systems,[15] it would seem curious that the rates of deprotonation of the two intermediates of type **2** by hydroxide ion should be so different. On the alternative hypothesis of rate-limiting nucleofuge detachment, it would also seem curious that the rates of phenoxide ion detachment from the two intermediates of type **12** should be much different. However, the present work shows that the rate of nucleofuge detachment from **7** (Scheme II), an analog of **12**, is four orders of magnitude greater when the amino moiety is derived from pyrrolidine rather than piperidine. Certainly the present results encourage interpretation of the k_3/k_{-1} ratios of Bunnett and Cartaño[8] in terms of rate-limiting nucleofuge departure.

One must, however, beware of arguments based strongly on considerations of analogy. Both the argument for rate-limiting proton transfer and that for rate-limiting nucleofuge expulsion, insofar as applied to the reaction of DNPE with piperidine in aqueous dioxane, invoke analogies. We conclude that evidence to compel either conclusion in respect to that archetypical reaction is lacking at present.

Experimental Section

Materials. Dimethyl sulfoxide was stored over calcium hydride and distilled at reduced pressure just before use. 2,4-Dinitro-1-naphthyl ethyl ether (**5**), mp 91–92 °C, was prepared as previously described.[10] Pyrrolidine was purified by heating it at reflux over sodium for 5 h and then distilling it, taking the fraction of bp 85–86 °C. Piperidine was first heated at reflux over sodium and distilled; the distillate was combined, with stirring and cooling, with enough concentrated aqueous HCl to neutralize about three-fourths of it; volatile substances were removed by evaporation at reduced pressure; the residue was treated with excess concentrated NaOH in water; NaCl was removed by filtration; the piperidine was taken into diethyl ether; the extract was dried over anhydrous $MgSO_4$; the ether was removed; and the piperidine distilling at 104–105 °C was collected.[28] Piperidinium chloride, mp 250–251 °C, was prepared as earlier described.[9] Pyrrolidinium chloride was prepared by combining pyrrolidine with excess concentrated aqueous HCl, removing volatile substances under reduced pressure, crystallizing three times from acetone, washing with diethyl ether, and drying overnight under vacuum at 70–80 °C. The dried salt is very hygroscopic, necessitating storage in a desiccator and precluding melting point determination. *N*-(2,4-Dinitro-1-naphthyl)piperidine (**8b**), mp 136–137 °C, was prepared as elsewhere described.[29]

N-(2,4-Dinitro-1-naphthyl)pyrrolidine (**8a**), mp 208–209 °C with decomposition, was prepared by reaction of 1-chloro-2,4-dinitronaphthalene with pyrrolidine in Me_2SO, and recrystallized from ethanol. Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.65; H, 4.73; N, 14.83.

N,N-Dimethylpyrrolidinium iodide, mp 248–250 °C with decomposition, was prepared by reaction of methyl iodide with *N*-methylpyrrolidine (Aldrich) in ethanol, and crystallized from ethanol. Anal. Calcd for $C_6H_{14}IN$: C, 31.73; H, 6.21; N, 6.17. Found: C, 31.66; H, 6.20; N, 6.03.

N,N-Dimethylpyrrolidinium chloride was prepared by stirring an aqueous solution of the iodide salt with AgCl, filtering off the silver salts,

(22) Lambert, J. B.; Featherman, S. I. *Chem. Rev.* **1975**, *75*, 611. Eliel, E. L.; Kandasamy, D.; Yen, C.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698.

(23) The conformation of **11b** is similar to that of cyclohexanone; cf. Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill Book Co.: New York, 1962; p 240.

(24) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.

(25) Cf. also Knipe, A. C.; Sridhar, N.; Lound-Keast, J. *Tetrahedron Lett.* **1979**, 2541.

(26) Bernasconi, C. F.; Hoyos de Rossi, R.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090.

(27) Bernasconi, C. F. *Chimia* **1980**, *34*, 1.

(28) This purification scheme was suggested to us by Professor Earl M. Evleth, Jr. It is designed to remove pyridine, which is less basic than piperidine.

(29) Sekiguchi, S.; Tsutsumi, K.; Shizuka, H.; Matsui, K.; Itagaki, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1521.

removing the solvent under reduced pressure, and crystallizing from 25% ethanol/75% acetone. The chloride salt did not melt below 350 °C. That used in the kinetic experiments was contaminated with about 10% of the corresponding iodide.

N,N-Dimethylpiperidinium chloride[30] was similarly prepared. Anal. Calcd for $C_7H_{16}ClN$: Cl, 23.7. Found: Cl, 23.2.

Spectral Characteristics and Changes. For **8a** in Me_2SO, λ_{max} 439 nm, ϵ 1.90×10^4 M^{-1} cm^{-1}. For **8b** in Me_2SO, λ_{max} 422 nm, ϵ 7.8×10^3 M^{-1} cm^{-1}. Upon combining **5** with pyrrolidine in Me_2SO in the absence of pyrrolidinium chloride, within 30 s a strong spectrum with λ_{max} 523 nm (ϵ 2.71×10^4 M^{-1} cm^{-1}) and 364 nm (with shoulder at 354 nm), attributed to **7a** had appeared; it slowly diminished with concomitant growing in of absorption at λ_{max} 439 nm attributed to **8a**. Upon combining **5** with purified piperidine in Me_2SO, within 1 min a strong spectrum with λ_{max} 522 nm (ϵ 2.03×10^4 M^{-1} cm^{-1}) and 367 nm (with shoulder at 357 nm) attributed to **7b** had appeared; in the absence of piperidinium chloride, this spectrum scarcely changed during 45 h, but in the presence of piperidinium chloride it slowly was superseded by a spectrum with λ_{max} 422 nm attributed to **8b**.

Kinetic procedures were the same as used by Orvik and Bunnett.[10]

Acknowledgment. This research was supported in part by the National Science Foundation. We thank Mr. Takao Shiobara of the Department of Synthetic Chemistry, Gunma University, for assistance with some experiments concerning the reaction of **5** with pyrrolidine, and Professor C. F. Bernasconi for criticism of a draft of this paper.

(30) Schmid, K.; von Philipsborn, W.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1956**, *39*, 394.

Reactions of Secondary Amines with Their *N*-(2,4-Dinitro-1-naphthyl) Derivatives To Form Jackson–Meisenheimer Adducts. Substantial Difference in Reaction Rates between Pyrrolidine and Piperidine

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Received November 10, 1980

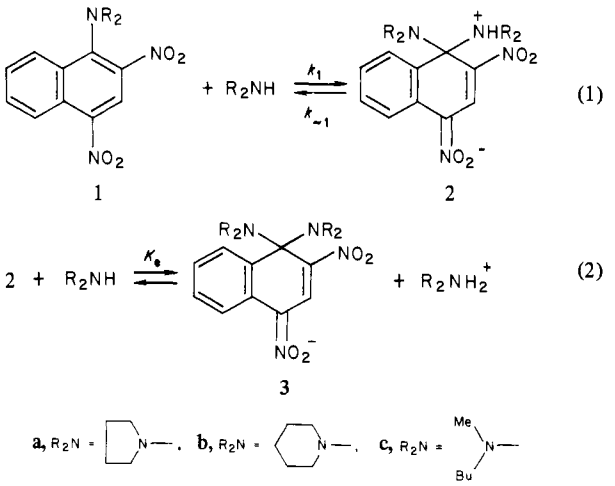
Abstract: Pyrrolidine, piperidine, and butylmethylamine react with their respective *N*-(2,4-dinitro-1-naphthyl) derivatives to form σ adducts as though the respective amide ions had attached at the 1 position. These reactions occur in dimethyl sulfoxide solution and proceed to a state of equilibrium. For the pyrrolidine and butylmethylamine reactions, equilibrium constants as well as rate constants both forward and reverse have been measured. Although two amine molecules are required to form the σ adduct, one to supply an amino moiety and the other to receive a proton, the forward reaction is only first order in amine; therefore, amine attack is not base catalyzed. Piperidine reacts so much slower than pyrrolidine, roughly $^1/_{400}$th as fast, that rate and equilibrium measurements were inconvenient. The low reactivity of the piperidine system is ascribed to stereoelectronic/conformational/steric problems in the piperidino moiety of *N*-(2,4-dinitro-1-naphthyl)piperidine as it enters the transition state.

Continuing our investigations[2,3] of pyrrolidine vis-à-vis piperidine as they take part in component steps of aromatic nucleophilic substitution by the S_NAr mechanism, we have studied the reactions of these two amines as well as that of butylmethylamine with the corresponding 2,4-dinitro-1-naphthylamines. The reactions involved are shown in Scheme I. The solvent was dimethyl sulfoxide.

The overall stoichiometry, shown in eq 3, involves two molecules of amine and forms, besides Jackson–Meisenheimer adduct **3**, a dialkylammonium ion. This stoichiometry has previously been observed for analogous processes.[4-7]

The mechanism of Scheme I involves rate-limiting step 1, not catalyzed either by base (forward) or acid (reverse), and rapid

Scheme I



proton-transfer equilibrium 2. A conceivable alternative mechanism would merge steps 1 and 2, so that eq 3 would become a

$$1 + 2R_2NH \rightleftarrows 3 + R_2NH_2^+ \quad (3)$$

(1) On leave from Gunma University, Kiryu, Japan, 1970–71, under support of a fellowship from the Japanese Ministry of Education.
(2) Bunnett, J. F.; Cartaño, A. V. *J. Am. Chem. Soc.*, preceding in this issue.
(3) Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *J. Am. Chem. Soc.*, preceding paper in this issue.
(4) Crampton, M. R.; Gold, V. *J. Chem. Soc. B* **1967**, 23.
(5) Bernasconi, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 129.
(6) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.
(7) Buncel, E.; Eggiman, W. *J. Am. Chem. Soc.* **1977**, *99*, 5958.

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