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Differing Behavior of Pyrrolidine and Piperidine as Nucleophiles toward 2,4-Dinitrophenyl and 2,4-Dinitro-6-methylphenyl Phenyl Ethers[1]

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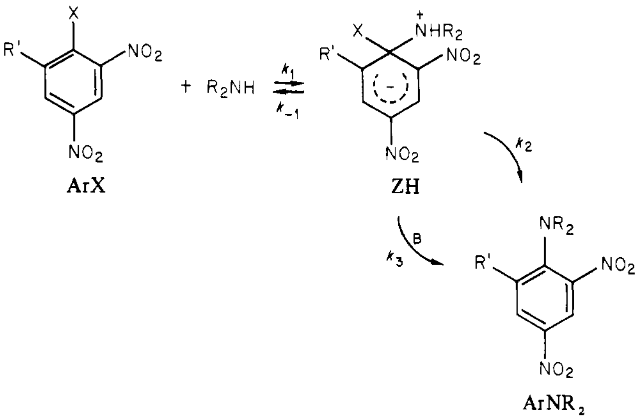
Abstract: Kinetics of the hydroxydephenoxylation reactions of the two title ethers with NaOH and of their aminodephenoxylation reactions with pyrrolidine and piperidine have been determined. The solvent was 60% dioxane/40% water. The 6-methyl group retards reactions with all three nucleophiles. The four aminodephenoxylation reactions are all catalyzed by NaOH, but the pattern of catalysis varies as the amine is changed and as a 6-methyl group is introduced. The data are consistent with the S_NAr mechanism. Quantitative dissection of the rate data reveals that the rate of base-catalyzed transformation of the intermediate σ adduct to products is an order of magnitude faster, relative to the rate of reversion to reactants, for pyrrolidine than for piperidine reactions. As to the mechanism of base catalysis, these results are more consistent with rate-limiting nucleofuge detachment from the conjugate base of the σ adduct than with rate-limiting proton transfer from the σ adduct to base.

Some of the most important evidence for the S_NAr mechanism of aromatic nucleophilic substitution comes from studies of base catalysis of reactions involving amine nucleophiles. Since the original discovery[2] of this effect in 1958, it has been extensively studied by numerous scientists.[3-18] The representation of the reaction in Scheme I has been found to be generally useful.[19]

Scheme I



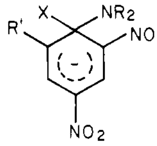
The base-catalysis phenomenon is variable in incidence. Whether or not base catalysis can be observed depends on the identity of the amine, the nucleofugal group, the base, and the solvent. Base catalysis is more often observed with secondary than with primary amines, with poorer leaving groups, and in less polar solvents. Studies directed at understanding these effects give attention to quantitative aspects of the phenomenon, usually with reference to the kinetic expression of eq 1, which is appropriate

$$k_A = \frac{k_1k_2 + k_1k_3[B]}{k_{-1} + k_2 + k_3[B]} \qquad (1)$$

to the mechanism of Scheme I if the σ-adduct intermediate (ZH) does not accumulate to an appreciable extent. In eq 1, k_A is a rate "constant" of second-order type, obtained by dividing the pseudo-first-order rate constant, k_ψ, by amine concentration.

According to eq 1, the reaction is not catalyzed by base if $(k_2 + k_3[B]) \gg k_{-1}$ or if $k_{-1} > k_2$ but $k_2 \gg k_3[B]$. k_A is linearly dependent on base concentration if $k_{-1} \gg (k_2 + k_3[B])$. If k_2 is relatively small and $k_{-1} \approx k_3[B]$ within the experimental range of base concentrations, k_A depends on base concentration in curvilinear fashion: linear dependence at low [B] changes to a plateau at which k_A is independent of base at high [B]. In such a case one can use eq 1 to evaluate k_1 as well as the rate coefficient ratios: k_3/k_{-1}, k_2/k_{-1}, and k_3/k_2. Much attention has been given to the ways in which these values depend on the structural and environmental factors mentioned above.

For the most part, *general* base catalysis prevails. Two interpretations of it are currently advocated. One is that the base abstracts the ammonium proton from the σ-adduct intermediate (ZH) in Scheme I in a rate-limiting step, to form deprotonated intermediate Z^- from which the nucleofuge rapidly detaches.[12-14]



Z^-

The other is that ZH and Z^- are in reversible acid-base equilibrium and that the rate-limiting step is general acid catalyzed detachment of the nucleofuge from Z^-.[3,4,8] The latter is sometimes called the SB-GA (specific base-general acid) mechanism. However, when the base is hydroxide ion in a water-containing medium, as in the present study, it is better characterized as a mechanism of rate-limiting nucleofuge detachment.

Each of these alternative interpretations is supported by strong experimental evidence. The mechanism of rate-limiting nucleofuge detachment has been observed straightforwardly for reactions of 2,4-dinitro-1-naphthyl ethyl ether with four amines in dimethyl

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[19] The phenomenon is by no means restricted to 1-substituted-2,4-dinitrobenzene substrates; such are shown in Scheme I because they are involved in the present work.

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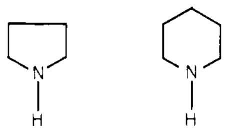
sulfoxide solution. In that type of system, the deprotonated σ adduct of type Z^- has a sufficient lifetime so that it can be characterized by its UV and NMR spectra,[20-22] and conventional kinetic studies can be performed on its conversion to ultimate substitution product.[8,18] The kinetics show nucleofuge detachment to be first order in the conjugate acid of the amine, consistent with general acid catalysis of the detachment of the ethoxy group.

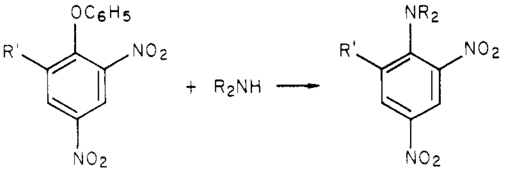
The mechanism of rate-limiting proton transfer is indicated by sophisticated relaxation kinetic measurements on two types of systems: the reversible addition of nucleophiles to substrates such as 2,4,6-trinitroanisole to form anionic σ adducts of the Jackson–Meisenheimer type, and reversible substitutive rearrangements of the Smiles rearrangement type.[13,14] Four types of observations are cited in support of the mechanism of rate-limiting proton transfer and against the SB–GA mechanism: (i) lack of evidence for general acid catalysis of alkoxide ion detachment from anionic σ adducts; (ii) measurement of rates of alkoxide and phenoxide ion detachment coupled with "suitable extrapolation" which leads to the conclusion that phenoxide ion detachment from deprotonated intermediates of type Z^- should occur at rates much faster than reprotonation to ZH; (iii) estimates of pK_{ZH} which indicate the probable rate constant for protonation of Z^-, just alluded to; and (iv) measurement of amine detachment rates, from which the conclusion is drawn that reversion of ZH to reactants should be very fast. From these observations it was concluded that base catalysis involves rate-limiting deprotonation of ZH when the leaving group is a good one, such as phenoxy, although nucleofuge detachment is probably rate limiting with poor leaving groups (e.g., methoxy).[12-14] These observations and conclusions pertain to reactions in water or other protic solvents.

It happens that each of these two contrary interpretations is supported by experimental evidence concerning systems atypical with respect to common substitutions in solvents such as water, methanol, or aqueous dioxane. The reversible formation of a Jackson-Meisenheimer complex is not a typical substitution reaction, nor is a reversible Smiles rearrangement. In the latter case there are special entropic effects as well as possibly special steric or stereoelectronic features. The solvent characteristics of dimethyl sulfoxide are hugely different from those of common protic solvents. Accordingly, it is uncertain which of the two alternative base catalysis mechanisms actually applies in common cases, such as the reaction of Scheme I in an aqueous dioxane solvent.

Piperidine/Pyrrolidine Dichotomy. It is a remarkable fact that the reaction of piperidine with 2,4-dinitrophenyl phenyl ether (**1a**) in 10% dioxane/90% water is strikingly catalyzed by NaOH[4] whereas the reaction of pyrrolidine with the same substrate in the same solvent is insensitive to base catalysis.[9] Such differences have often been observed between secondary and primary amines,[7,10] but for two amines so similar in structure to behave so differently is curious. We undertook to study them more extensively. We now report kinetic study of the reactions of these two amines with **1a** and with its 6-methyl analog, **1b**, in 60% dioxane/40% water solution. The latter provides a probe of the effect of extra steric bulk in the vicinity of the reaction site. We note that the reaction of **1a** with piperidine in the chosen solvent was earlier studied, but at a higher ionic strength than presently employed.[3]



pyrrolidine piperidine



1a, R' = H
b, R' = CH_3

2a, R' = H; $NR_2 = NC_4H_8$
b, R' = H; $NR_2 = NC_5H_{10}$
c, R' = CH_3; $NR_2 = NC_4H_8$
d, R' = CH_3; $NR_2 = NC_5H_{10}$

$+ C_6H_5OH$ (2)

Experimental Section

Materials. Pyrrolidine and piperidine were purified by refluxing with sodium for 24 h and were then distilled, the fractions distilling at 88.0 and 104.5 °C, respectively, being collected. These amines were stored over Linde molecular sieves under nitrogen gas in dark bottles. 1,4-Dioxane was purified and stored as described elsewhere.[4] Piperidinium chloride and 2,4-dinitrophenyl phenyl ether (**1a**) were prepared after Bunnett and Garst.[3] Pyrrolidinium chloride was prepared by passing hydrogen chloride gas into the purified amine, removing absorbed water on the rotary evaporator, and recrystallizing from absolute ethanol; this very hygroscopic material was stored in a desiccator over phosphorus pentoxide. *N*-(2,4-Dinitrophenyl)pyrrolidine (**2a**), mp 103.0 °C (lit.[9] 103 °C), and *N*-(2,4-dinitrophenyl)piperidine (**2b**), mp 92.0–92.5 °C (lit.[23] 92 °C), were prepared by reactions of the amines with 1-chloro-2,4-dinitrobenzene and crystallized from 85% ethanol. *N*-(2,4-Dinitro-6-methylphenyl)piperidine (**2d**), mp 88.5 °C (lit.[24] 88–89 °C), was prepared by reaction of piperidine with 2-chloro-3,5-dinitrotoluene (prepared analogously to 4-chloro-3,5-dinitrotoluene[25]) and purified by chromatography on alumina with acetone elution. *N*-(2,4-Dinitro-6-methylphenyl)pyrrolidine (**2c**), mp 61.0 °C, was similarly prepared; ^1H NMR (CCl_4) δ 2.02 (m, 4 H), 2.44 (s, 3 H), 3.27 (m, 4 H), 8.10 (m, 1 H), 8.25 (m, 1 H). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.97; H, 5.30; N, 16.17 (Micro-Tech Laboratories, Skokie, Ill.). 2,4-Dinitro-6-methylphenyl phenyl ether (**1b**) was prepared by the reaction of phenol with 2,4-dinitro-6-methylphenyl *p*-toluenesulfonate in dry pyridine during 30 min at reflux, and recrystallized from 85% ethanol; fine yellow crystals, mp 108.5 °C. Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68; N, 10.22. Found:[26] C, 57.55; H, 3.62; N, 10.23.

Kinetic Measurements. For reactions with amines, the general procedure described by Bunnett and Bernasconi[4] was employed. The "quenching solution" was prepared by mixing 10 mL of concentrated phosphoric acid with 500 mL of 95% ethanol and 500 mL of distilled water. In most cases the Guggenheim method[27] was used to determine the pseudo-first-order rate constant,[28] and good first order behavior was observed. The pseudo-first-order rate constant (k_ψ) so measured represented the sum of aminodephenoxylation (k_A*) and hydroxydephenoxylation (k_{OH}*) components. The magnitude of the latter was reckoned from the measured second-order rate constant (k_{OH}) for reaction of **1a** or **1b** with NaOH and the prevailing NaOH concentration. Subtraction of k_{OH}* from k_ψ gave k_A*, which was then divided by amine concentration to get k_A. As can be seen in Tables II and III, hydroxydephenoxylation was a small component of the overall rate process, 20% at most, in reactions of **1a** but a much larger factor, as high as 68%, in reactions of **1b**.

The sampling and quenching procedure was also used in measuring the rate of the hydroxydepyrrolidinylation reaction of **2c** with NaOH.

The reaction of **1a** with NaOH was conducted in a Gilford 2000 kinetics spectrophotometer with automatic monitoring of absorbance. The reaction of **1b** with NaOH was followed by taking samples, the absorbance of which was measured without quenching.

Solutions of the dinitroarylamines in 60% dioxane/40% water were quenched in the same fashion as kinetic samples and their absorbances were measured. The molar absorptivity coefficients (ϵ) so measured are: for **2a**, 19 800 M^{-1} cm^{-1} at 383 nm; for **2b**, 16 300 M^{-1} cm^{-1} at 390 nm;

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Table I. Kinetics of Reactions of 2,4-Dinitrophenyl Phenyl Ether (1a) and 2,4-Dinitro-6-methylphenyl Phenyl Ether (1b) with Sodium Hydroxide in 60% Dioxane/40% Water at 30.0 °C[a]

substrate	[NaOH], M	$10^4k_{OH}^*$, s^{-1}	10^4k_{OH}, M^{-1} s^{-1}
1a[b]	0.0201	0.242	12.0
	0.0401	0.477	11.9
	0.0602	0.762	12.7
		mean value	12.2 ± 0.4
1b[c]	0.0563	0.402	7.13
	0.0750	0.531	7.08
	0.0938	0.679	7.24
		mean value	7.15 ± 0.08

[a] Ionic strength maintained at 0.1 M by addition of NaCl as required. [b] $[1a]_0$ 2.0×10^{-4} M. [c] $[1b]_0$ 1.0×10^{-4} M.

Table II. Kinetics of Reactions of Pyrrolidine with Ethers 1a and 1b at Various Sodium Hydroxide Concentrations in 60% Dioxane/40% Water at 30.0 °C

substrate	[NaOH],[a] M	10^4k_ψ, s^{-1}	$10^4k_A^*$,[b] s^{-1}	10^3k_A, M^{-1} s^{-1} exptl	10^3k_A, M^{-1} s^{-1} calcd[c]
1a[d]	*e*	3.70	3.70	18.5	-
	nil	3.16	3.16	15.8	15.5
	0.0050	6.70	6.64	33.2	33.4
	0.0100	8.42	8.30	41.5	42.4
	0.0201	10.8	10.5	52.7	51.3
	0.0301	11.7	11.4	56.8	55.7
	0.0501	12.1	11.5	57.4	60.2
	0.0602	13.0	12.3	61.3	61.4
	0.0802	13.8	12.8	64.0	63.1
1b[f]	*e*	0.10	0.10	0.20	
	nil	0.11	0.11	0.22	
	0.0193	0.53	0.39	0.78	
	0.0297	0.97	0.76	1.52	
	0.0396	1.15	0.87	1.74	
	0.0495	1.53	1.18	2.36	
	0.0593	1.79	1.37	2.74	
	0.0692	2.02	1.53	3.06	
	0.0791	2.50	1.93	3.86	
	0.0890	2.84	2.20	4.40	
	0.0989	3.11	2.40	4.80	

[a] Ionic strength maintained at 0.1 M by addition of NaCl as required. [b] k_A^* represents k_ψ less k_{OH}^*, reckoned from k_{OH} (Table I) and [NaOH]. [c] Calculated from k_1, k_3^{OH}/k_{-1}, and k_2/k_{-1} in Table IV, by means of eq 1. [d] $[1a]_0$ 2.0×10^{-4} M; $[C_4H_8NH]$ 0.020 M. [e] Pyrrolidinium chloride 0.025 M, instead of Na NaOH. [f] $[1b]_0$ 5.0×10^{-4} M; $[C_4H_8NH]$ 0.050 M.

Table III. Kinetics of Reactions of Piperidine with Ethers 1a and 1b at Various Sodium Hydroxide Concentrations in 60% Dioxane/40% Water at 30.0 °C

substrate	[NaOH],[a] M	10^4k_ψ, s^{-1}	$10^4k_A^*$,[b] s^{-1}	10^3k_A, M^{-1} s^{-1} exptl	10^3k_A, M^{-1} s^{-1} calcd[c]
1a[d,e]	*f*	2.78	2.78	2.78	
	nil	2.88	2.88	2.88	2.19
1a[d,g]	0.010	1.21	1.09	5.45	5.55
	0.020	1.73	1.49	7.45	8.40
	0.030	2.48	2.11	10.6	10.8
	0.040	3.05	2.56	12.8	13.0
	0.050	3.64	3.03	15.2	14.8
	0.060	4.00	3.27	16.4	16.5
	0.070	4.48	3.63	18.2	18.0
	0.080	4.68	3.70	18.5	19.3
	0.090	5.36	4.26	21.3	20.5
1b[e,h]	*i*	0.018	0.018	0.018	
	f	0.019	0.019	0.019	
	nil	0.027	0.027	0.027	
	0.010	0.137	0.065	0.065	
	0.020	0.267	0.124	0.124	
	0.030	0.325	0.110	0.110	
	0.040	0.436	0.150	0.150	
	0.050	0.510	0.152	0.152	
	0.060	0.646	0.216	0.216	
	0.070	0.729	0.228	0.228	
	0.080	0.852	0.280	0.280	
	0.090	0.982	0.338	0.338	
	0.100	1.044	0.329	0.329	

[a-c] See Table II. [d] $[1a]_0$ 2×10^{-4} M. [e] $[C_5H_{10}NH]$ 0.100 M. [f] $[C_5H_{10}NH_2Cl]$ 0.025 M, instead of NaOH. [g] $[C_5H_{10}NH]$ 0.020 M. [h] $[1b]_0$ 1.0×10^{-3} M. [i] $[C_5H_{10}NH_2Cl]$ 0.050 M, instead of NaOH.

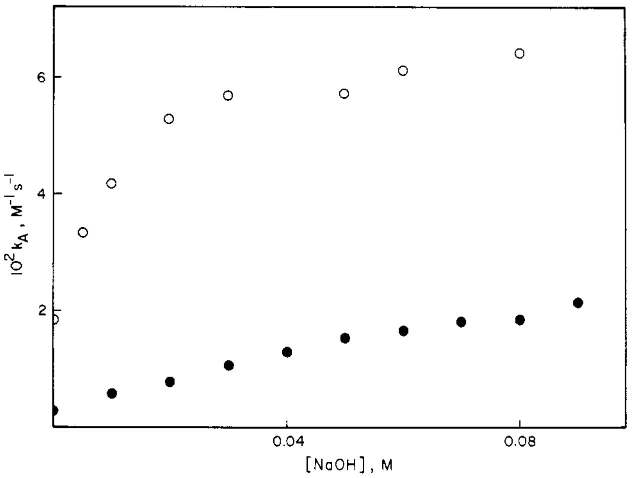

Figure 1. Reactions of **1a** with pyrrolidine (open circles) and piperidine (filled circles); variation of the second-order-type rate coefficient, k_A, with NaOH concentration is shown. Data from Tables II and III.

for **2c**, 16 000 M^{-1} cm^{-1} at 385 nm; and for **2d**, 15 580 M^{-1} cm^{-1} at 390 nm.

Results

Reactions with NaOH. Ethers **1a** and **1b** reacted straightforwardly with NaOH, as reported in Table I. These reactions were second order, first order in each reactant. The measured second-order rate constant, k_{OH}, for reaction of **1a** with NaOH at ionic strength 0.1 M is within the range of "not very precise" previous estimates[3] for the same solvent at ionic strength 0.2 M.

The pseudo-first-order rate constant (k_ψ) for reaction of amine **2c** with 0.1 M NaOH in 60% dioxane/40% water was 2.90×10^{-6} s^{-1}. On the assumption that hydroxydepyrrolidinylation is second order, k_{OH} is 2.90×10^{-5} M^{-1} s^{-1}.

Reactions with Pyrrolidine and Piperidine. Reactions of ethers **1a** and **1b** with both amines were conducted, some in the absence of NaOH, most at various NaOH concentrations. Our data are presented in Tables II and III.

It is noteworthy that all four reactions respond to catalysis by NaOH. However, the form of acceleration varies from case to case. The reaction of **1a** with pyrrolidine, which is insensitive to catalysis by NaOH in 10% dioxane/90% water,[9] is in 60% dioxane/40% water steeply accelerated at low NaOH concentrations but soon reaches a plateau; see Figure 1. The reaction of **1a** with piperidine also gives a curvilinear plot of k_A vs. [NaOH], as shown too in Figure 1, but the curvature is much less pronounced and no semblance of plateau is attained.

The reactions of **1b** with both amines respond linearly to catalysis by NaOH, as shown in Figure 2.

In all cases pyrrolidine is more reactive than piperidine at a chosen NaOH concentration, and **1a** is more reactive than **1b**. The decelerating effect of the 6-methyl group of **1b** is evidently a manifestation of steric hindrance, an effect which has been seen before in similar cases.[24,29,30]

The data in Tables II and III concerning the variation of k_A with [NaOH] for reactions of **1a** were fit to eq 1 by means of curve-fitting analysis, the sum of the squares of deviations of calculated from experimental k_A values being minimized.[31] The

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Table IV. Rate Coefficients for Component Steps of the Reactions of Pyrrolidine and Piperidine with 1a, 1b, and 3[a]

substrate	solvent[b]	rate coefficient or ratio	pyrrolidine	piperidine	ref
1a	10% dioxane	k_1, $M^{-1}\ s^{-1}$	4.6×10^{-2}	3.1×10^{-2}	4, 9
		k_3^{OH}/k_{-1}, M^{-1}		1.4×10^{2}	
		k_2/k_{-1}		7.0×10^{-2} [c]	
		k_3^{OH}/k_2, M^{-1}		2.0×10^{3} [d]	
1a	60% dioxane[e]	k_1, $M^{-1}\ s^{-1}$	6.9×10^{-2}	4.3×10^{-2}	this work
		k_3^{OH}/k_{-1}, M^{-1}	1.3×10^{2}	9.4	
		k_2/k_{-1} [f]	0.29	5.3×10^{-2}	
		k_3^{OH}/k_2, M^{-1} [f]	4.5×10^{2} [d]	1.8×10^{2} [d]	
1a	60% dioxane[g]	k_1, $M^{-1}\ s^{-1}$		3.5×10^{-2}	3
		k_3^{OH}/k_{-1}, M^{-1}		12.2	
		k_2/k_{-1}		3×10^{-2} [h]	
		k_3^{OH}/k_2, M^{-1}		3.7×10^{2} [d]	
1b	60% dioxane	k_3^{OH}/k_2, M^{-1}	*i*	1.1×10^{2}	this work
3	10% dioxane[j]	k_1, $M^{-1}\ s^{-1}$	8.1×10^{3}	3.0×10^{3}	32
		k_{-1}, s^{-1}	1.5×10^{6}	2.1×10^{6}	
		k_{3p}^{OH}, $M^{-1}\ s^{-1}$	5×10^{9}	5×10^{9}	
		k_{3p}^{OH}/k_{-1}, M^{-1}	3.4×10^{3}	2.4×10^{3}	
3	30% Me_2SO[k]	k_1, $M^{-1}\ s^{-1}$	9.0×10^{3}	4.1×10^{3}	32
		k_{-1}, s^{-1}	6.2×10^{5}	1.0×10^{6}	
		k_{3p}^{OH}, $M^{-1}\ s^{-1}$	5×10^{8}	5×10^{8}	
		k_{3p}^{OH}/k_{-1}, M^{-1}	8.1×10^{2}	5.0×10^{2}	

[a] Temperature 29.4 or 30.0 °C except as noted. [b] The rest of the solvent is water. [c] If the amine catalysis component is removed, $k_2/k_{-1} = 2 \times 10^{-2}$. [d] Not corrected for amine catalysis contribution to k_2. [e] Ionic strength 0.1 M. [f] Ratios involving k_2 are reckoned from a single datum. [g] Ionic strength 0.2 M. [h] If the amine catalysis component is removed, $k_2/k_{-1} = 1.0 \times 10^{-2}$. [i] Cannot be ascertained from the data; see text. [j] 25 °C. [k] 20 °C.

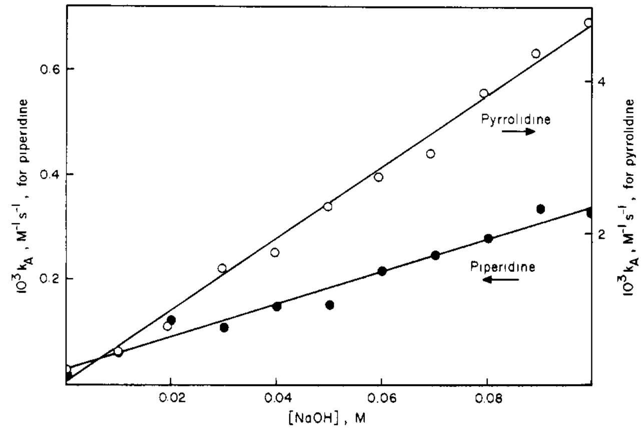


Figure 2. Reactions of **1b** with pyrrolidine (open circles) and piperidine (filled circles); variation of the second-order-type rate coefficient, k_A, with NaOH concentration is shown. Data from Tables II and III.

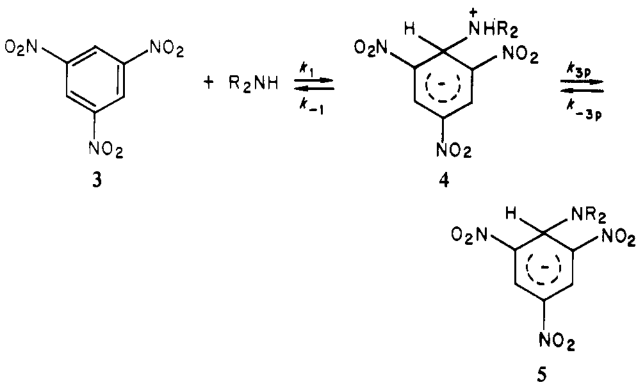
resulting estimates of k_1, k_3^{OH}/k_{-1}, k_2/k_{-1}, and k_3^{OH}/k_2 are reported in Table IV, together with relevant data from other studies. (k_3^{OH} represents k_3 in respect to hydroxide ion base; k_3^{amine}, representing k_3 in respect to amine base, is a constant contribution within each set of experiments performed, and is subsumed within k_2.) In respect to k_{-1}, k_2, and k_3^{OH}, the data do not enable evaluation of the rate constants as such, but only of the ratios reported. The uncertainty of the k_1 estimates is small (about 2%), of the k_3^{OH}/k_{-1} estimates considerable (about 17%), and of the k_2/k_{-1} estimates large (about 40%). From these estimates as listed in Table IV, k_A was calculated at each [NaOH] concentration studied experimentally. In Table II and III, the calculated k_A values are listed alongside those determined experimentally.

When k_A responds linearly to change in NaOH concentration, as for the reactions of **1b** with the two amines (Figure 2), dissection of k_A into its component rate coefficients can be performed only to the extent of estimating k_3/k_2 from the slope/intercept ratio. One employs the simplified version of eq 1 for the case $k_{-1} \gg (k_2 + k_3[B])$.

Discussion

Comparison of Pyrrolidine and Piperidine. The data assembled in Table IV concern mainly the reactions of **1a** with the two amines, from the present work and similar studies under other conditions of solvent or ionic strength, and reactions of 1,3,5-trinitrobenzene with the two amines[32] as depicted in Scheme II.

Scheme II



Let us first compare the two amines in nucleophilic attack, with rate constant k_1. The two amines are very similar, but throughout pyrrolidine is a little more reactive than piperidine, by factors about 1.5 for **1a** and 2.5 for **3**.

We next examine nucleofuge detachment rate constants, k_{-1}, which are available in Table IV only for reactions of **4**. In two solvents, k_{-1} is about 50% greater for piperidine than for pyrrolidine. Again the two amines are very similar in their behavior.

However, the two amines differ substantially in the k_3^{OH}/k_{-1} rate ratios for reaction with **1a** in 60% dioxane/40% water, the ratio for pyrrolidine being 14 times greater than for piperidine.[33] A major difference in the same direction is implied by the fact that NaOH does not observably catalyze the reaction of **1a** with pyrrolidine in 10% dioxane/90% water[9] while its reaction with piperidine in that solvent is clearly base catalyzed.[4]

A substantial difference in k_3^{OH}/k_{-1} values is also implied by the higher reactivity of **1b** with pyrrolidine than with piperidine.

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

(33) A referee has suggested that the piperidine data in Figure 1 conform to a straight line just as well as to the curve defined by the kinetic parameters listed in Table IV fit into eq 1. The fit to a straight line is actually not as good, but the suggestion nevertheless merits consideration. If the data did define a straight line, the implication would be that k_3^{OH}/k_{-1} were *less* than 9.4 as listed in Table IV. In that event, the k_3^{OH}/k_{-1} ratio for pyrrolidine would exceed that for piperidine by *more* than 14-fold. In other words, linearity in the piperidine plot in Figure 1 would serve to magnify the difference in behavior which is our chief present interest.

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.

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[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; Societă 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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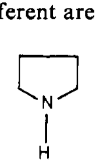
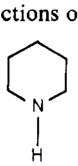
Abstract: The reactions named in the title, which form *N*-(2,4-dinitro-1-naphthyl) derivatives of these heterocyclic amines, occur in two distinct stages. In stage I, the spectrum of a σ-adduct intermediate develops at a rate which is measurable in a stopped flow apparatus; in stage II, it decays at 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

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[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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