Base Catalysis of the Reaction of Piperidine with 2,4-Dinitrophenyl Phenyl Ether. Further Substantiation of the Intermediate Complex Mechanism for Aromatic Nucleophilic Substitution[1]

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Whereas most reactions of 2,4-dinitrohalobenzenes with amines are at most mildly accelerated by bases, the reaction of 2,4-dinitrophenyl phenyl ether with piperidine in 60% dioxane–40% water is strongly base catalyzed. The second-order rate coefficient, k_A, is linearly dependent on piperidine concentration. However, k_A for the NaOH-catalyzed reaction is dependent on hydroxide ion concentration in a curvilinear fashion (Figure 2). This curved plot fulfills a specific expectation from the intermediate complex mechanism as sketched in eq. 1. These observations constitute strong evidence for the mechanism and re-enforce conclusions previously drawn.

The intermediate complex mechanism for activated aromatic nucleophilic substitution reactions is indicated by several kinds of evidence.[2]   Particularly significant are the incidence and the form of base catalysis in reactions involving amine reagents.

Briefly, the facts are that reactions of nitro-activated aryl chlorides, bromides, and iodides (and certain other substrates) with primary and secondary amines are not base catalyzed[3–5] and that some reactions of fluorides are base catalyzed while others are not.   Reactions of 2,4-dinitrofluorobenzene with *n*-butylamine and aniline in alcoholic or water–dioxane solvents are not base catalyzed,[7] nor is the reaction of *p*-fluoronitrobenzene with piperidine in a wide range of polar solvents.[8] However, reactions of these aryl fluorides with amines in aromatic hydrocarbon solvents are approximately second order in amine under most conditions.[8–11]

And the reaction of 2,4-dinitrofluorobenzene with N-methylaniline in ethanol or 60% dioxane–40% water is very sensitive to catalysis by acetate or hydroxide ion; *general* base catalysis prevails.[4]

These observations find interpretation in the scheme

If no substantial concentration of intermediate complex I develops during the reaction, the following relationship obtains.[13,14]

$$k_A = \frac{k_1 k_2 + k_1 k_3[B]}{k_{-1} + k_2 + k_3[B]} \qquad (2)$$

If $(k_2 + k_3[B]) \gg k_{-1}$, eq. 2 simplifies to eq. 3.

$$k_A = k_1 \qquad (3)$$

If $k_{-1} \gg (k_2 + k_3[B])$, eq. 2 becomes eq. 4.

$$k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3[B]}{k_{-1}} \qquad (4)$$

The interpretation is as follows.   Reactions of 2,4-dinitrochloro- and -bromobenzene are insensitive to base catalysis because $k_2 \gg k_{-1}$; eq. 3 applies.   This condition also holds for many reactions of 2,4-dinitrofluorobenzene, but hydrocarbon solvents diminish the k_2/k_{-1} ratio to the point that eq. 4 becomes applicable. For the reaction of 2,4-dinitrofluorobenzene with N-methylaniline, steric compressions in the intermediate complex (I) increase k_{-1} so greatly that it exceeds k_2 and the reaction becomes sensitive to base catalysis (eq. 4).

Equation 2 predicts that, under appropriate circumstances, a nonlinear dependence of k_A on base

(1) (a) Presented in part at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 10, 1964; Abstracts, p. 45N;   (b) abstracted from the Ph.D. Thesis of R. H. Garst, Brown University, June 1964;   *Dissertation Abstr.*, 25, 4404 (1965);   (c) supported, in part, by the National Science Foundation.
(2) J. F. Bunnett, *Quart. Rev.* (London), 12, 1 (1958).
(3) J. F. Bunnett and K. M. Pruitt, *J. Elisha Mitchell Sci. Soc.*, 73, 297 (1957).
(4) J. F. Bunnett and J. J. Randall, *J. Am. Chem. Soc.*, 80, 6020 (1958).
(5) For purposes of present discussion, the mild accelerations[6] caused by bases and other species in certain reactions involving amine reagents are not designated as "base catalysis."   That designation is withheld not in ultimate rejection of the possibility they may constitute base catalysis, but because we seriously doubt whether they do.[7]   In any case, relative to the large effects of present interest, the mild accelerations of doubtful character represent small perturbations.
(6) S. D. Ross in "Progress in Physical Organic Chemistry," Vol. 1, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 31.
(7) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 87, 3875 (1965).
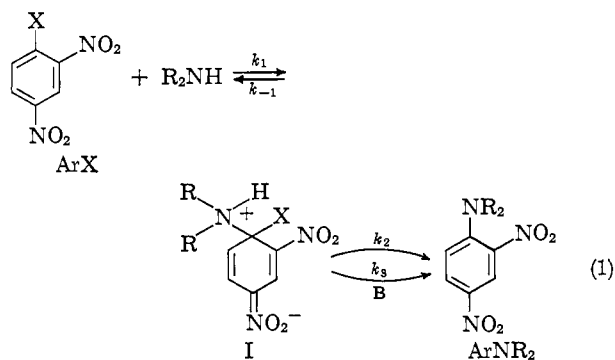(8) H. Suhr, *Ber. Bunsenges. physik. Chem.*, 67, 893 (1963).
(9) H. Zollinger and C. Bernasconi, *Tetrahedron Letters*, 1083 (1965).
(10) F. Pietra and A. Fava, *ibid.*, 1535 (1963).
(11) Inasmuch as triethylamine does not catalyze reactions of 2,4-dinitrofluorobenzene with piperidine in benzene,[10] the catalytic effect of piperidine is not simply that it acts as a base.   An attractive explana-

tion advanced by Capon and Rees[12] assigns to piperidine a dual role as both proton acceptor and donor.
(12) B. Capon and C. W. Rees, *Ann. Rept. Progr. Chem.*, 60, 278 (1964).
(13) Rate coefficients are symbolized as in footnote 13, ref. 7.
(14) A more rigorous form of eq. 2 is

$$k_A = \frac{k_1 k_2' + k_1 \Sigma k_i[B_i]}{k_{-1} + k_2' + \Sigma k_i[B_i]}$$

In eq. 2, k_2 represents the true uncatalyzed rate coefficient, k_2', plus the sum of all the $k_i[B_i]$ terms except that due to the base whose concentration is varied.

concentration should be observable. At very low base concentration, k_{-1} may greatly exceed $(k_2 + k_3[B])$, and rate may vary linearly with base concentration according to eq. 4. At very high base concentration, $k_3[B]$ may far surpass k_{-1}, and the rate may be insensitive to base concentration in accordance with eq. 3. At intermediate concentrations of base, the slope in a plot of k_A against [B] should steadily diminish. This is a specific prediction from the intermediate complex mechanism, and experimental observation of such a curvilinear dependence of rate on base concentration would be strong support for the mechanism.

For the hydroxide ion catalyzed reaction of 2,4-dinitrofluorobenzene with N-methylaniline, studied by Bunnett and Randall,[4] the plot of k_A against [OH$^-$] showed considerable scatter but an over-all tendency toward decreasing slope with increasing base concentration. (Accurate determination of aminodefluorination rates in the presence of hydroxide ion was impeded by the rapid competing hydroxydefluorination reaction.) This plot was taken to represent the curvilinear dependence predicted from the intermediate complex mechanism. However, some critics[6,15] have found the plot unconvincing. Certainly it would be desirable to observe the curvilinear dependence on base concentration in a less equivocal case.

Since both k_2 and k_3 concern steps in which the leaving group is detached from the site of substitution, they should be smaller when the leaving group is less prone to separate rapidly from carbon. With a poorer leaving group, there is more likelihood that $(k_2 + k_3[B])$ will fail greatly to exceed k_{-1} and therefore that substitutions involving amine reagents will be subject to catalysis by bases. Accordingly we investigated the reaction of piperidine with 2,4-dinitrophenyl phenyl ether to form 2,4-dinitrophenylpiperidine; phenoxy was expected to be a rather poor leaving group.

The reaction of 2,4-dinitrophenyl phenyl ether with neat piperidine was studied by Le Fevre, Saunders, and Turner.[16] They reported that 2,4-dinitrophenylpiperidine and phenol were formed. To our knowledge, no kinetic studies have been made of this reaction. Rates of reaction of piperidine with 2,4-dinitrophenyl 4-nitrophenyl ether, in methanol[17] and in 50% dioxane-50% water,[3] have been reported. In the latter solvent, addition of 0.016 M sodium hydroxide was reported[3] to accelerate 2,4-dinitrophenylpiperidine formation about 20%.

Experimental

Materials. Dioxane was purified and stored as described elsewhere.[7] Commercial piperidine was heated with sodium metal at reflux for 24 hr.; it was then distilled, and a middle cut, b.p. 104.8–105.3°, was taken; the purified piperidine was stored in a brown bottle and flushed with nitrogen, and the bottle was kept in a desiccator over sodium hydroxide. Piperidine hydrochloride was thrice recrystallized from absolute ethanol, m.p. 250.5–251°. 2,4-Dinitrophenyl phenyl ether was prepared by the method of Raiford and Colbert[18];

(15) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 390.
(16) R. J. W. Le Fevre, S. L. M. Saunders, and E. E. Turner, *J. Chem. Soc.*, 1168 (1927).
(17) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, 79, 385 (1957).
(18) L. C. Raiford and J. C. Colbert, *ibid.*, 48, 2652 (1926).

after being twice crystallized from 1:1 ethanol-acetic acid, it had m.p. 68.2–69.8°.

Kinetic Procedures. For reactions with piperidine, with or without sodium hydroxide, the photometric techniques of Bunnett and Randall were employed.[4] Rate coefficients were reckoned, and are symbolized, as indicated in ref. 7, footnote 13. Reactions with sodium hydroxide (in the absence of piperidine) were followed by conventional acid-base titration of aliquots quenched in a measured excess of standard sulfuric acid.

Results

The rate of reaction of piperidine with 2,4-dinitrophenyl phenyl ether in 60% dioxane-40% water was determined at piperidine concentrations from 0.01 to 0.30 M. Formation of 2,4-dinitrophenylpiperidine was quantitative. The initial substrate concentration was *ca.* 10^{-4} M, and pseudo-first-order kinetics were observed. The second-order rate coefficient, k_A, was found to increase sharply with piperidine concentration, as shown in Table I and Figure 1.

Table I. Kinetics of Reaction of Piperidine with 2,4-Dinitrophenyl Phenyl Ether in 60% Dioxane-40% Water at 29.4°[a]

[C$_5$H$_{10}$NH], M	[LiCl], M	$10^4 k_A^*$, sec.$^{-1}$	$10^3 k_A$, l. mole^{-1} sec.$^{-1}$
0.101	...	2.52	2.50
0.100	...	2.57	2.57
0.0100	0.10	0.0606	0.60
0.0249	0.10	0.271	1.09
0.0496	0.10	0.924	1.86
0.0500	b	0.856	1.71
0.0500	0.075[c]	0.786	1.57
0.0752	0.10	1.69	2.25
0.100	b	3.20	3.20
0.100	0.075[c]	2.82	2.82
0.101	0.10	3.01	3.01
0.150	0.10	6.52	4.37
0.200	0.10	10.6	5.33
0.250	0.10	17.5	7.03
0.301	0.10	23.0	7.64

[a] Initial concentration of 2,4-dinitrophenyl phenyl ether *ca.* 1 × 10^{-4} M. [b] Piperidine hydrochloride, 0.10 M. [c] C$_5$H$_{10}$NH$_2$Cl, 0.025 M, also present.

A linear plot such as Figure 1 may be represented by the expression: $k_A = k' + k''[B]$. Linear regression analysis of the data in Table I gives 0.47 × 10^{-3} l. mole^{-1} sec.$^{-1}$ for k' and 24.8 × 10^{-3} l.^{2} mole^{-2} sec.$^{-1}$ for k''. k''/k' is then 53 l. mole^{-1}. In mathematical form, this acceleration resembles the mild accelerations of amine reactions with 2,4-dinitrochlorobenzene caused by addition of amines or other substances.[6] The latter effects are of dubious character and may not constitute base catalysis.[7] But in *magnitude*, k''/k' in the present case is one or two orders of magnitude greater. We feel that the hugeness of the effect shown in Figure 1, coupled with the fact that hydroxide ion is even more effective (*vide infra*), warrants its identification as base catalysis.

We may next ask whether this is general base catalysis or specific lyate ion catalysis. Hydroxide ion is generated by reaction of piperidine with water: $C_5H_{10}NH + H_2O \rightleftharpoons C_5H_{10}NH_2^+ + OH^-$. In the en-

Table II. Kinetics of Reaction of Piperidine and Sodium Hydroxide with 2,4-Dinitrophenyl Phenyl Ether in 60% Dioxane–40% Water at 29.4° [a]

[NaOH], M	Salt, concn., M	$10^4 k_\psi$, sec.$^{-1}$	Yield, %	$10^4 k_A{}^*$, sec.$^{-1}$	$10^3 k_A$, l. mole^{-1} sec.$^{-1}$	$10^4 k_{OH}{}^*$, sec.$^{-1}$	$10^4 k_{OH}$, l. mole^{-1} sec.$^{-1}$
0.050	LiCl, 0.050	8.29	93.2	7.72	15.0	0.57	11
0.065	0.035	8.99	90.5	8.13	16.2	0.86	13
0.075	0.025	10.3	90.9	9.34	18.7	0.94	12
0.100	... ...	11.7	89.1	10.4	20.6	1.3	13
0.125	... ...	13.2	92.2	12.2	24.4	1.0	8
0.150	... ...	13.4	90.4	12.1	24.2	1.3	9
0.178	... ...	13.8	89.0	12.3	24.6	1.5	8
...	LiCl, 0.200	0.912[b]	100[b]	0.912	1.82		
0.010	0.190	2.45	95.2	2.34	4.68	0.12	12
0.020	0.180	4.02	94.7	3.81	7.63	0.21	10
0.035	0.165	5.75	92.7	5.23	10.5	0.52	15
0.050	0.150	7.36	93.4	6.87	13.8	0.49	10
0.075	0.125	8.73	89.5	7.82	15.6	0.92	12
0.100	0.100	11.8[c]	89.4[c]	10.5	21.0	1.3	13
0.125	0.075	12.0	88.8	10.7	21.3	1.4	11
0.150	0.050	12.8	91.5	11.7	23.5	1.1	7
0.175	0.025	13.6	87.2	11.9	23.7	1.8	10
0.200	... ...	14.4[c]	87.2[c]	12.6	25.2	1.8	9
...	NaCl, 0.200	0.817	100	0.817	1.63		
0.202	0.180	2.86	95.5	2.73	5.46	0.13	7
0.050	0.150	6.65	93.6	6.31	12.6	0.34	7
0.100	0.100	11.3	90.4	10.2	20.4	1.1	11
0.15	0.05	13.3	89.8	11.9	23.9	1.4	9
0.18	0.02	14.6	87.5	12.8	25.6	1.8	10

[a] Initial concentrations: 2,4-dinitrophenyl phenyl ether, ca. 1×10^{-4} M; piperidine, 0.050 M.   [b] Average of two runs.   [c] Average of four runs.

vironment of the experiments in Table I, excepting those in which piperidine hydrochloride was present, hydroxide ion concentration is proportional to the square root of piperidine concentration. Were the reaction specific hydroxide ion catalyzed, the slope in a plot of log $(k_A - k')$ vs. log $[C_5H_{10}NH]$ should be 0.5. The slope of the actual plot (not shown) is 0.98. It follows that the reaction is general base catalyzed. Indeed, the slope of nearly unity shows that the reaction is almost wholly catalyzed by piperidine.

With reference to eq. 4, the slope/intercept ratio of 53 l. mole^{-1} in Figure 1 represents k_3/k_2 for the piperidine-catalyzed reaction.

The effect of sodium hydroxide concentration on the reaction of piperidine with 2,4-dinitrophenyl phenyl ether was also studied. Results are set forth in Table II. In these runs, the substrate concentration was about 2×10^{-4} M throughout, and piperidine was constantly 0.05 M. Sodium hydroxide concentration was varied. In the experiments listed in the two lower parts of Table II, total electrolyte concentration was held constant at 0.2 M by addition of lithium chloride (middle part) or sodium chloride (lower part), as required. In the upper part, compensation with lithium chloride was only partial, as indicated.

Even in the presence of relatively large amounts of sodium hydroxide, the competing nucleophilic displacement involving hydroxide ion was a minor side reaction. By a standard procedure, the total pseudo-first-order rate coefficient (k_ψ) was separated into parts representing 2,4-dinitrophenylpiperidine formation $(k_A{}^*)$ and the competing reaction with hydroxide ion $(k_{OH}{}^*)$. The latter represents a small difference between large numbers and is not very precise. However, the precision in $k_A{}^*$ is high. $k_A{}^*$ and $k_{OH}{}^*$ were then transformed into second-order coefficients, k_A and k_{OH}.

As shown in Figure 2, k_A at constant total electrolyte concentration is related to [OH$^-$] in the curvilinear fashion required by eq. 2 if k_{-1} and $(k_2 + k_3[B])$ are of
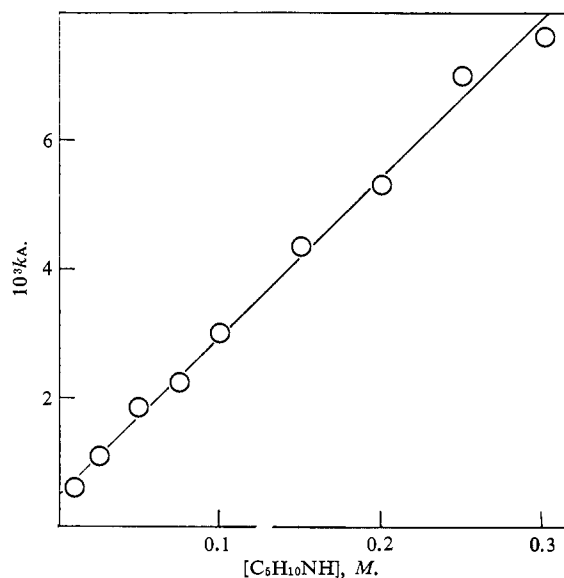

Figure 1. Second-order rate coefficient for reaction of piperidine with 2,4-dinitrophenyl phenyl ether, as a function of piperidine concentration. Data from Table I, for runs in which [LiCl] = 0.1 M.

similar magnitude. Thus, a specific prediction of the intermediate complex mechanism is fulfilled, and this is strong support for the mechanism.

Inversion of eq. 2 gives eq. 5. If $k_3[B] \gg k_2$, this

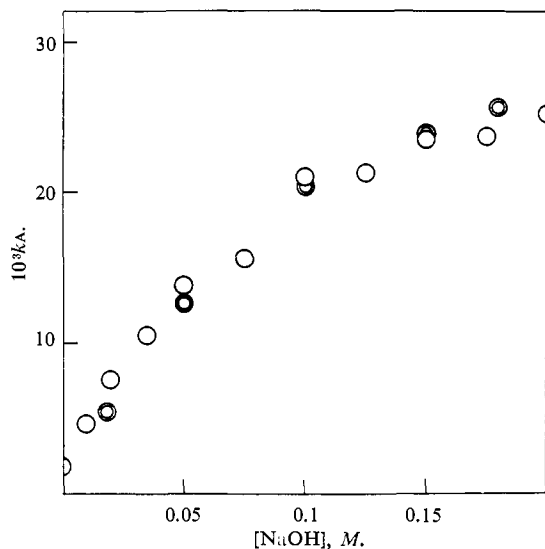$$\frac{1}{k_A} = \frac{k_{-1}}{k_1 k_2 + k_1 k_3[B]} + \frac{1}{k_1} \tag{5}$$

Figure 2. Second-order rate coefficient for reaction of piperidine with 2,4-dinitrophenyl phenyl ether to form 2,4-dinitrophenylpiperidine, as a function of sodium hydroxide concentration. Data from Table II. Total electrolyte concentration held constant at 0.2 M by compensation with LiCl (open circles) or NaCl (bull's-eyes).
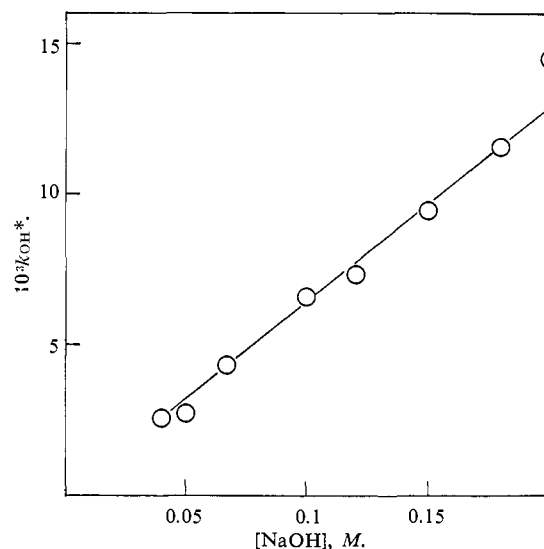

Figure 4. Pseudo-first-order rate coefficient for reaction of 2,4-dinitrofluorobenzene with sodium hydroxide in 60% dioxane, as a function of sodium hydroxide concentration. Total electrolyte concentration held at 0.2 M by compensation with NaCl. Data from Table IV, ref. 7.
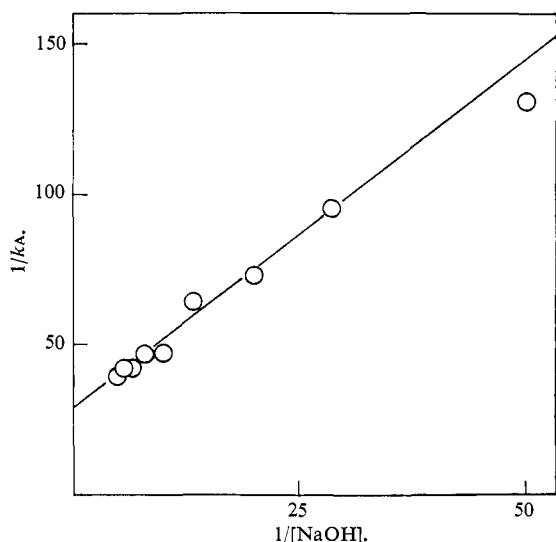

Figure 3. Reaction of 2,4-dinitrophenyl phenyl ether with piperidine in the presence of NaOH. Plot of $1/k_A$ (for LiCl-compensated runs in Table II) against $1/[NaOH]$.

simplifies to eq. 6.

$$\frac{1}{k_A} = \frac{k_{-1}}{k_1 k_3} \frac{1}{[B]} + \frac{1}{k_1} \tag{6}$$

Therefore, except at low base concentrations where simplification to eq. 6 may not be justified, a plot of $1/k_A$ vs. $1/[B]$ should be linear with slope $k_{-1}/k_1 k_3$ and intercept $1/k_1$. Data from Table II are plotted in this reciprocal manner in Figure 3.[19]

The reciprocal plot is linear, except that the last two points (for 0.01 and 0.02 M NaOH) fall below the line established by the rest.[19] At low hydroxide ion concentrations, k_2 may be comparable in magnitude to $k_3[B]$, and eq. 6 may not be valid. The deviations, toward higher rates or lower reciprocal rates, are thus consistent with eq. 5.

(19) For convenience in plotting, the 0.01 M NaOH point is omitted from Figure 3.

From the slope and intercept, k_1 is evaluated as 3.5 × 10^{-2} l. mole^{-1} sec.$^{-1}$ and k_{-1}/k_3 as 0.082 mole/l. From these values and the k_A values at 0.01 and 0.02 M sodium hydroxide, k_{-1}/k_2 is reckoned to be 30 and k_3/k_2 to be 370 l./mole. (These are all for runs at constant total electrolyte concentration with lithium chloride as compensating electrolyte.)

Before accepting this interpretation, we must inquire whether the curvature in Figure 2 might be due to activity coefficient effects. In a medium such as 60% dioxane and at a total electrolyte concentration of 0.2 M, they are surely appreciable. Conceivably the activity coefficient of hydroxide ion changes enough, as NaOH is replaced by LiCl or NaCl as an electrolyte constituent, to account for the curvature observed.

We now offer a persuasive argument and a compelling argument against this alternative interpretation. Persuasive is the fact that the rate coefficients and the form of the plot (Figure 2) were much the same whether lithium or sodium chloride was the compensating electrolyte, or whether total electrolyte concentration was allowed to vary. This indicates that salt effects, at least among the electrolytes employed, are not highly specific toward the species of present interest in 60% dioxane.

The compelling argument concerns the kinetics of reaction of 2,4-dinitrofluorobenzene with sodium hydroxide in 60% dioxane at a total electrolyte concentration of 0.2 M maintained by compensation with sodium chloride. The pseudo-first-order rate coefficient, $k_{OH}*$, is linearly related to [NaOH] through the range of conditions represented in Figure 2. The linear plot, constructed from data we have reported elsewhere,[7] is presented as Figure 4. If the curvature in Figure 2 were due to a curvilinear dependence of the activity coefficient of hydroxide ion, the plot in Figure 4 ought also to be curved. The possibility that the curvature in Figure 2 is due to change in the activity coefficient of the hydroxide ion is therefore rejected.[20]

(20) The linearity of Figure 4 and the data in ref. 7, Table IV, also imply that the partial change of electrolyte from NaOH to NaCl, at
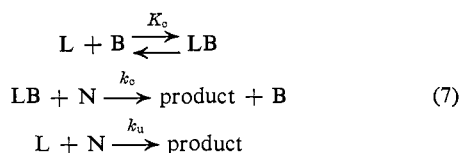
Table II also gives values for k_{OH}, the second-order rate coefficient for the hydroxydephenoxylation reaction. k_{OH} varies considerably from run to run, but there is no significant trend. The lack of precision is not unexpected, as discussed above. The average value of k_{OH} is 1.0×10^{-3} 1. mole^{-1} sec.$^{-1}$. This rate coefficient was determined independently by direct measurement, and the values obtained were similar but slightly lower.[21]

Discussion

Our results fulfill two expectations from the reaction mechanism sketched in eq. 1. The first is that base catalysis should be encountered in reactions of amines with 1-substituted-2,4-dinitrobenzenes having rather poor leaving groups. The second is that, in an appropriate case, the plot of k_A vs. base concentration should be curved as in our Figure 2. We have shown that the latter effect is not due to change in the activity coefficient of the hydroxide ion.

Can these observations be interpreted without invoking an intermediate of type I? Mathematically, the curvilinear dependence of k_A on hydroxide ion concentration and the linear dependence on piperidine concentration are consistent with schemes that do not require such an intermediate.

Let us consider a reaction between species L and N, catalyzed by B. Let us imagine that the reaction proceeds partly via complex LB, which is in rapid equilibrium with L and B, and partly by uncatalyzed reaction of L with N (eq. 7). If B is in excess, the apparent

$$L + B \underset{}{\overset{K_c}{\rightleftharpoons}} LB$$

$$LB + N \xrightarrow{k_c} product + B \qquad (7)$$

$$L + N \xrightarrow{k_u} product$$

second-order rate coefficient, k_t (first order each in L and N), depends on [B] as in eq. 8.

$$k_t = \frac{k_u + k_c K_c[B]}{1 + K_c[B]} \qquad (8)$$

In the present case, L might be either piperidine or 2,4-dinitrophenyl phenyl ether. From the reciprocal plot (Figure 3), K_c would be 12 M.

The possibility that hydroxide ion complexes with the substrate with such firmness is excluded because k_{OH} is independent of [NaOH]. Were such a complex formed, k_{OH} should decrease about threefold between 0.01 and 0.2 M sodium hydroxide.[22]

The mechanism of eq. 7, with L being piperidine, is also vitiated by several considerations. If LB were

constant total electrolyte concentration, does not change the activity coefficients or activity coefficient ratios concerning the amine, the substrate, or the transition state enough to account for the curvature in Figure 2.

(21) In 60% dioxane–40% water, with [2,4-dinitrophenyl phenyl ether]$_0$ 0.05 M, k_{OH} was 7.15×10^{-4} M^{-1} sec.$^{-1}$ when [NaOH]$_0$ was 0.05 M and [LiCl] 0.15 M, and 5.57×10^{-4} M^{-1} sec.$^{-1}$ when [NaOH]$_0$ and [LiCl] were both 0.10 M. In 50% dioxane–50% water with [substrate]$_0$ 0.02 M, k_{OH} was 4.26×10^{-4} M^{-1} sec.$^{-1}$ when [NaOH]$_0$ was 0.05 M and [LiCl] 0.15 M, and 6.63×10^{-4} M^{-1} sec.$^{-1}$ when [NaOH]$_0$ and [LiCl] were both 0.10 M.

(22) k_{OH} would diminish with increasing [NaOH] whether hydroxydephenoxylation were a reaction of free hydroxide ion and substrate, first order in each, or whether it were a reaction of the complex, first order in the complex. However, if the substrate and the complex reacted equally fast with hydroxide ion, k_{OH} would be independent of [NaOH].

piperidide ion, piperidine would have to be a much stronger acid than it is to account for the curvature in Figure 2. Also, such an interpretation for the piperidine-catalyzed reaction is inconsistent with the observed general base catalysis. If LB were an addition complex between hydroxide ion and a secondary amine, unprecedented stability would have to be attributed to it. Also, the addition complex would have to be much more reactive than piperidine with 2,4-dinitrophenyl phenyl ether but almost equal to piperidine in reactivity with 2,4-dinitrochlorobenzene. Such a reactivity pattern would be extraordinary.

For these reasons, alternative schemes of the type of eq. 7 are rejected.

A different kind of alternative is a scheme similar to eq. 1, but with the first step (both forward and reverse) base catalyzed and the second step uncatalyzed. By the usual steady-state treatment, one derives

$$k_A = \frac{k_2 \sum k_i[B_i]}{k_2 + \sum k_{-i}[B_i]} \qquad (9)$$

Here, k_i and k_{-i} pertain to the forward and reverse of the first step as catalyzed by base B_i. If $\sum k_{-i}[B] \gg k_2$, this simplifies to eq. 10. If $k_2 \gg \sum k_{-i}[B_i]$, eq. 9

$$k_A = \frac{k_2 \sum k_i}{\sum k_{-i}} \qquad (10)$$

reduces to eq. 11. Equations 10 and 11 are analogous

$$k_A = \sum k_i[B_i] \qquad (11)$$

in form to eq. 3 and 4, respectively. They can also account for a curved plot such as Figure 2, eq. 11 being obeyed at very low and eq. 10 at very high base concentration. Thus this alternative is equally acceptable to the scheme of eq. 1 insofar as observations on a single substrate are concerned.
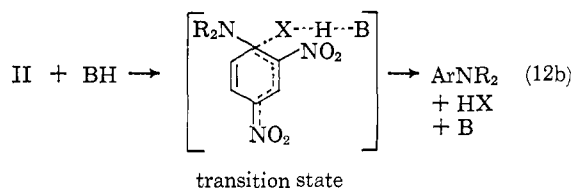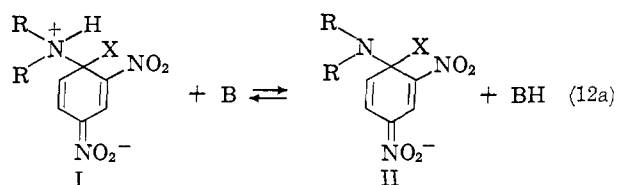
However, this alternative does not give a good account of the comparative reactivity of related substrates. Equation 9 calls for base catalysis to be evident when the leaving group is a good one (eq. 11), but not when it is a poor one (eq. 10). This is the opposite of the pattern actually observed. Also, it calls for the rates of the base-insensitive reactions to depend sharply on factors affecting the detachment of the leaving group, because of the k_2 factor in eq. 10. In fact, the reactions which are immune to base catalysis include many whose rates display little or no "element effect" with respect to the displaced group.[3,17] This alternative is also rejected.

Inasmuch as no alternative mechanism considered gives an acceptable account of the facts, the mechanism of eq. 1 is strongly indicated for aromatic nucleophilic substitution reactions involving amine reagents.

Let us consider in detail how a base may catalyze leaving group expulsion from the intermediate complex. Four possibilities come to mind. We have mentioned three in previous discussions,[4,23] and a fourth has been suggested by Capon and Rees.[12]

The most probable mechanism[23] is reversible transformation of intermediate complex I into its conjugate base (eq. 12a), followed by general acid catalyzed detachment of the leaving group (eq. 12b). This is similar to

(23) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960), footnote 27.

$$\text{I} + \text{B} \rightleftharpoons \text{II} + \text{BH} \quad (12a)$$

I   II

$$\text{II} + \text{BH} \longrightarrow [\text{transition state}] \longrightarrow \text{ArNR}_2 + \text{HX} + \text{B} \quad (12b)$$

transition state

a mechanism suggested for the aminolysis of carboxylic esters.[23]

Another possibility is that the proton removal step (eq. 12a) is rate limiting and that leaving group expulsion from II is fast. This interpretation, presented by Bunnett and Randall,[4] now seems unattractive because of the accumulation of evidence that proton transfers from rather strong acids to rather strong bases are exceedingly fast.[24] A third possibility is that proton removal and leaving group detachment are concerted, as in E2 olefin-forming eliminations.[25] A fourth is that a base which carries a proton on its basic site, such as piperidine or hydroxide ion, may assist intramolecular detachment of a proton from nitrogen and protonation of the leaving group as it departs, without BH ever separating from II.[12] This possibility is unlikely for reactions in good ionizing solvents like aqueous dioxane, but it is attractive for reactions in benzene.

Recently, Kirby and Jencks[26] have reported observations similar to those recorded in this paper. They studied reactions of amines with p-nitrophenyl phosphate in water, and in particular observed a curvilinear dependence of k_A on base concentration similar to that of our Figure 2. Their interpretation is substantially the same as ours.

In this laboratory, we have found the reaction of 2,4-dinitroanisole with piperidine, to form 2,4-dinitrophenylpiperidine, to be strongly catalyzed by sodium methoxide in methanol. Also, Mr. Claude Bernasconi has shown that in reactions of piperidine with the 2,4-dinitrophenyl ethers of a series of phenols in 10% dioxane–90% water, the incidence of base catalysis depends on the substituents present in the leaving phenoxy group. The reaction of bis(2,4-dinitrophenyl) ether is not catalyzed by bases, while that of 2,4-dinitrophenyl phenyl ether is base catalyzed, much as in 60% dioxane. These studies will be reported shortly.

Acknowledgment. We thank Dr. Kevork V. Nahabedian for discussions and counsel.

(24) M. Eigen, *Angew. Chem.*, 75, 489 (1963).
(25) J. F. Bunnett, *ibid.*, 74, 731 (1962); *Angew. Chem. Intern. Ed. Engl.*, 1, 225 (1962).

(26) A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, 87, 3217 (1965). We thank Professor Jencks for sending us a copy of their manuscript in advance of publication.

Nuclear Magnetic Resonance Spectroscopy. Conformational Properties of Cyclobutanes. Variation of Geminal Fluorine–Fluorine Chemical-Shift Differences with Temperature[1]

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The temperature dependence of the geminal fluorine–fluorine chemical-shift differences in a variety of unsymmetrically substituted cyclobutanes is interpreted in terms of a classical equilibrium between axial and equatorial conformations. With the assumption that the conformations have the same entropy, free-energy differences between the conformers are calculated and discussed. The axial conformer in monosubstituted cyclobutanes may be nearly planar. The absence of temperature effects in the spectra of a cyclobutene and a cyclobutanone indicates that these systems are statically planar. The angle of puckering of 1,1-difluoro-3-phenylcyclobutane is calculated by the dipole moment method to be about 27°.

Introduction

The nonplanar nature of cyclohexane and the resulting axial and equatorial orientation of substituents, although suggested as early as 1890, was not established until the 1920's.[3] Conformational properties have been usefully ascribed to the more flexible five- and seven-membered ring systems in terms of the pseudorotation process.[4–7] A planar representation, however, has generally been accepted for the four-membered ring systems in spite of a limited number of demon-

(3) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 553.
(4) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, 69, 2483 (1947).
(5) J. B. Hendrickson, *ibid.*, 83, 4537 (1961).
(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 248 ff.
(7) The cycloheptane system is capable of ring inversion as well.