Yields of 2,5-diphenyloxazole (**1a**) and 2,5-di(4-biphenylyl)oxazole (**4f**) greater than 90% were obtained from compounds **2a** and **3f**, respectively. The other amido ketones gave yields of the oxazoles ranging from 61 to 79% with the exception of **3c**, which gave only a trace of product.

An attempt to condense 1,2-dibenzoylhydrazine (**5**) to 2,5-diphenyloxadiazole (**6**) with anhydrous hydrofluoric acid failed (Scheme I, eq 3). In initial experiments only benzoic acid was isolated. The experiment was repeated with the exclusion of moisture following the addition of the hydrofluoric acid; this precaution did prevent cleavage to benzoic acid but only the starting material **5** was recovered. The use of phosphorus oxychloride gave a 55% yield of **6** from **5**.

Experimental Section[6]

General Procedure.—The *N*-aroyl-α-amino ketone was dissolved in anhydrous hydrofluoric acid (10 ml of acid/1 g of ketone) in a polyethylene beaker, and the resulting solution was allowed to evaporate to dryness. The dry, crystalline material obtained was slurried in saturated aqueous sodium bicarbonate to destroy any hydrogen fluoride salts which may have formed. The product was then extracted into benzene; this benzene extract was washed with water, dried (Na_2SO_4), and chromatographed on neutral Woelm alumina. The solvent was removed *in vacuo* from the eluate and the crude product obtained was crystallized from cyclohexane or benzene–cyclohexane except for **4f**, which was recrystallized from dimethylformamide.

Registry No.—**1a**, 92-71-7; **1b**, 2549-31-7; **2a**, 4190-14-1; **2b**, 16735-29-8; **3a**, 37611-22-6; **3b**, 37611-23-7; **3d**, 37611-24-8; **3e**, 37611-25-9; **3f**, 37061-76-0; **4a**, 37611-27-1; **4b**, 14492-02-5; **4d**, 22397-43-9; **4e**, 37610-63-2; **4f**, 2083-09-2; hydrofluoric acid, 7664-39-3.

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[6] All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point bath and in all cases were identical with those reported in the literature.

Hydrogen–Deuterium Exchange of *N*-Methylpyridinium Ion in Methanol Containing Amines. Identity of the Catalyzing Base

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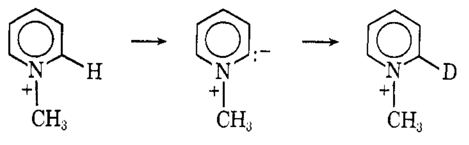
An attractive and useful solvent–base mixture for the study of hydrogen exchange reactions of weak carbon acids is found in alcohol–amines. Although a number of deprotonation studies have been carried out using such nonaqueous mixtures, the identity of the catalyzing base or bases has seldom been established.[1-4] Not only may the more abundant amine base catalyze the deprotonation reaction, but also the less abundant and more reactive alkoxide ion may serve as a catalyst. This ion is formed by the solvolysis reaction given in eq 1 where Am represents an amine. Without knowing

$$\mathrm{Am} + \mathrm{CH_3OD} \overset{K_b}{\rightleftharpoons} \mathrm{AmD^+} + \mathrm{CH_3O^-} \qquad (1)$$

the identity of the catalyst(s), the significance of comparisons involving the reactivities of various carbon acids in such mixtures is obscured.

We here provide clear and unambiguous evidence concerning the identity of the base catalyst in the H–D exchange reaction of *N*-methylpyridinium ion (I) at the 2,6-positions in methanol-*O*-*d* containing amines. Considerable evidence is available to establish that the mechanism of hydrogen exchange of this substrate involves base-catalyzed deprotonation to give an ylide which then captures a deuteron from the solvent to give product, eq 2.[5,6] Exchange at only the 2 position is shown although the equivalent 6 position reacts as well.



I

(2)

Results and Discussion

Two amine bases in CH_3OD were used to catalyze H–D exchange of I at 75.0°. They are morpholine (pK_a[7] in H_2O at 25° is 8.3) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (pK_a[8] in H_2O at 25° is 8.8). In both cases the rate of H–D exchange increased with increasing amine concentration and the more basic amine, DABCO, was the more effective. However, a tenfold change in the concentration of morpholine resulted in only a 3.1-fold change in the value of the pseudo-first-order rate constant, k_ψ. Similarly, a sevenfold change in DABCO concentration gave rise to a 3.0-fold change in k_ψ. If the amine were the sole catalyst, then the magnitude of the change in k_ψ would be the same as the magnitude of the change in the amine concentration, *i.e.*, the reaction rate would be first order in amine. This clearly is not the case. Methoxide ion resulting from the solvolysis reaction involving the amine (eq 1) must be acting as a catalyst.

Consider now the rate expression for H–D exchange given by eq 3 which includes terms for catalysis by both

$$k_\psi[\mathrm{CH}] = k_{\mathrm{MeO}}[\mathrm{CH}][\mathrm{CH_3O^-}] + k_{\mathrm{Am}}[\mathrm{CH}][\mathrm{Am}] \qquad (3)$$

methoxide ion and amine. In this equation k_{MeO} and k_{Am} are second-order rate constants for methoxide ion and amine catalysts and [CH] is the concentration of H at positions 2 and 6 as indicated by nmr. If the reaction mixture contains substrate and amine as in the experi-

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[1] I. F. Tupitsyn, N. N. Zatsepina, and A. V. Kirova, *Org. Reactiv.* (*USSR*), **5**, 626 (1968); N. N. Zatsepina, Yu. L. Kaminsky, and I. F. Tupitsyn, *ibid.*, **4**, 433 (1967); K. W. Ratts, R. K. Howe, and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 6115 (1969).

[2] For an authentic example of an amine-catalyzed deprotonation of a carbon acid in methanol, see F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970).

[3] It has been established that ethoxide ion is the catalyst for H–D exchange at position 2 of a thiazolium ion in ethanol containing an acetic acid–acetate ion buffer.[4]

[4] J. Crosby and G. E. Lienhard, *J. Amer. Chem. Soc.*, **92**, 5707 (1970).

[5] J. A. Zoltewicz and L. S. Helmick, *ibid.*, **92**, 7547 (1970).

[6] J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *ibid.*, **90**, 5939 (1968).

[7] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, Washington, D. C., 1965.

[8] J. Hine, J. C. Kaufmann, and M. S. Cholod, *J. Amer. Chem. Soc.*, **94**, 4590 (1972).

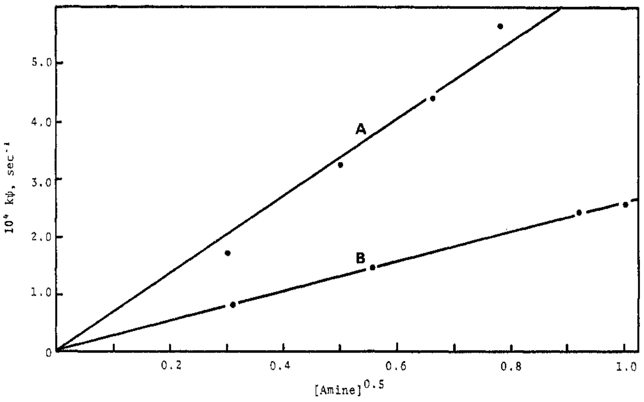

Figure 1.—Plot of the pseudo-first-order rate constants for H–D exchange at the 2,6 positions of *N*-methylpyridinium iodide in CH_3OD at 75.0° *vs.* the square root of the amine concentration. Line A refers to DABCO and B to morpholine bases.

ments just described, the methoxide ion concentration resulting from solvolysis (eq 1) is given by $K_b{}^{0.5}[Am]^{0.5}$; *i.e.*, $[CH_3O^-] = [AmD^+]$. Substituting into rate eq 3 and eliminating the concentration of substrate gives eq 4. According to eq 4, if methoxide ion alone catalyzes

$$k_\psi = k_{MeO}K_b{}^{0.5}[Am]^{0.5} + k_{Am}[Am] \qquad (4)$$

the reaction, then a plot of k_ψ *vs.* $[Am]^{0.5}$ will be linear, having slope $k_{MeO}K_b{}^{0.5}$ and intercept $k_{Am}[Am] = 0$. If both methoxide ion and the amine significantly catalyze the reaction, then such a plot will be curved and will have a zero intercept. Figure 1 shows such a plot for I undergoing H–D exchange in the presence of morpholine and DABCO. The plots are *linear* and have a zero intercept. The scatter in line A in is keeping with the ~10% uncertainty often found in kinetic nmr experiments.[5] These results clearly show that only methoxide ion and not the amine catalyzes the reaction. The observed rate increases with increasing amine concentration are due to increases in methoxide ion concentration resulting from the solvolysis of the amine according to eq 1.[9]

A critical test of this conclusion was made in two additional experiments. These involve reactions similar to the above except that DABCO along with its conjugate acid were employed. In the first, part of the amine was neutralized with methanesulfonic acid and, in the second, partial neutralization employed hydrochloric acid. Now, in the presence of the added acid the methoxide ion concentration is reduced by a factor of about 10^4.[11] This large reduction in methoxide ion concentration while maintaining the concentration of free amine at its usual levels greatly enhances the possibility of detecting amine catalysis. After 6000–7000 min no more than 20% H–D exchange occurred. This time period is equivalent to 300–350 half-lives in the absence of added acid. Without a doubt, catalysis by DABCO acting directly on substrate is insignificant.

The conclusions from the above experiments are clear and unmistakable. They establish that H–D exchange of I at its 2,6 positions in methanol–amine mixtures kinetically is specific base (lyate ion) and not general base catalyzed. This is consistent with our earlier conclusion involving H–D exchange of I in aqueous solutions.[5] Here too only lyate ion catalysis is significant.

It is likely that the above conclusions concerning catalyst identity will carry over to hydrogen exchange reactions of a large number of other carbon acids. The conclusions will apply directly to the large number of heterocyclic compounds now known to undergo exchange in aqueous solutions by specific and not by general base catalyzed reactions.[13]

Experimental Section

Materials.—DABCO (Aldrich Chemical Co.) was recrystallized before use. Morpholine was distilled from KOH pellets. CH_3OD was purchased from Thompson-Packard, Inc.

Kinetic Runs.—*N*-Methylpyridinium iodide and amine were weighed into a 1-ml volumetric flask and then diluted to mark with CH_3OD. An aliquot was sealed in an nmr tube, and a time zero spectrum was obtained on a Varian A-60A spectrometer. The sample was heated in a constant temperature bath; following this, a spectrum was obtained on the cooled sample. This cycle of heating and cooling was repeated so that about ten points were obtained over 2–4 half-lives. The sample then was heated for at least 10 half-lives to obtain an "infinity" value. The area of the 3,5 positions were employed as the area standard, since they are known to be considerable less reactive than the 2,6 positions.[5,6] Linear plots were constructed as described earlier.[14] Concentrations are corrected for a 6.3% expansion of methanol on heating.[15] The substrate concentration generally was about 0.5 *M;* amine concentrations were in the range 0.1–1.0 *M* and are given in Figure 1.

To check the stability of the substrate control runs were carried out. Two samples were prepared as indicated above except that CH_3OH was used in place of CH_3OD and *tert*-butyl alcohol was added as internal standard. The mixtures, each containing one amine, were heated at 75.0° and occasionally examined. After 3995 min of heating, the area of the 2,6 protons relative to that of the internal standard had not changed, indicating no decomposition. This heating period corresponds to more than 50 half-lives for hydrogen exchange. Substrate and amine concentrations were 0.5 *M*.

The reactivity of *N*-methylpyridinium iodide was examined in buffers consisting of DABCO and its conjugate acid. In sample "A," methanesulfonic acid was employed; the concentration of free DABCO was 0.70 *M* and its conjugate acid was 0.48 *M*. After heating this sample at 75.0° for 6790 min, the area of the 2,6 protons decreased by 20%. Sample "B" was prepared using concentrated hydrochloric acid. The free DABCO concentration was 0.59 *M* and its conjugate acid, 0.76 *M*. After heating at 75.0° for 6330 min the area of the 2,6 protons decreased by 8%. Substrate concentrations were 0.6 *M*.

Registry No.—*N*-Methylpyridinium iodide, 930-73-4.

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[9] The pK_a values for our two amines in methanol are not likely to be very different from those for aqueous solutions.[10] The K_a ratio is 3 for aqueous and 6 for methanol solutions. The latter value was calculated using the slopes obtained from the plot in Figure 1.

[10] C. D. Ritchie and P. D. Heffley, *J. Amer. Chem. Soc.*, **87**, 5402 (1965); R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter IV.

[11] This value is based on the pK_a value for an aqueous solution of DABCO[8] and the ion product[12] for CH_3OH, both at 25°.

[12] J. Koskikallio, *Suom. Kemistilehti B*, **30**, 111 (1957).

[13] This assumes the existence of valid Brønsted relationships which include lyate ion with $\beta \sim 1$.

[14] J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

[15] J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Vol. 1, Elsevier, Amsterdam, 1950, p 303.