Amine Catalysis of Elimination of Hydrogen Chloride from 9-Fluorenylmethyl Chloride

Thomas A. Spencer,* Martha C. R. Kendall, and I. David Reingold

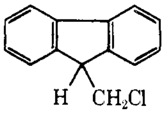
Contribution from the Department of Chemistry, Dartmouth College,
Hanover, New Hampshire 03755. *Received June 2, 1971*

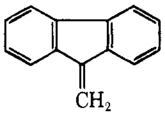
Abstract: In order to establish the relative effectiveness of a variety of amines as catalysts for direct abstraction of a proton from a carbon acid with pK_a ~20, in the absence of possible competing nucleophilic catalysis *via* amine–carbonyl condensation, a kinetic study of amine-catalyzed elimination of hydrogen chloride from 9-fluorenylmethyl chloride (**1**) to form dibenzofulvene (**2**) in aqueous solution has been made. General base catalysis is observed, as expected, and the data clearly define three distinct Brønsted relationships with $\beta = 0.5$ for primary, secondary, and tertiary amines. Negative deviations from the Brønsted lines are observed for the sterically hindered triethylamine and *N*-methylmorpholine, and for imidazole and *N*-methylimidazole.

During the last decade several extensive kinetic studies of amine catalysis of carbonyl compound reactions have appeared.[1–6] This burst of activity in an area long important in laboratory organic synthesis was largely inspired by a desire to gain understanding in model systems of the important roles amines play as general bases and as nucleophiles in enzymic reactions.[7] However, much still remains to be elucidated about such processes, particularly the details of nucleophilic catalysis *via* enamine formation by primary and secondary amines. In this and the following paper[8] we continue our efforts[9,10] to gain insight into these and other aspects of amine catalysis.

In order to provide as reliable a foundation as possible for the detection and study of nucleophilic catalysis by amines we decided first to study a closely related reaction in which such catalysis would be impossible, one in which an amine could function as catalyst only by direct proton abstraction.[11] Such an evaluation of the catalytic effectiveness as general bases of amines to be used subsequently in a reaction where nucleophilic catalysis could occur was considered important because steric hindrance and other factors often make accurate prediction of such effectiveness by use of the Brønsted catalysis law difficult.[12]

The conversion of 9-fluorenylmethyl chloride (**1**) to dibenzofulvene (**2**) seemed to be well suited for such a study. Hydroxide ion catalysis of this reaction has been briefly noted by More O'Ferrall in his detailed study of the elimination of water from 9-fluorenylmethanol.[13] It is evident from his data and discussion that base-catalyzed elimination of hydrogen chloride from **1** would involve irreversible C_9 proton removal in the rate-limiting step, and that monitoring formation of **2** would therefore provide a means of assessing the effectiveness of amines as general bases. Furthermore, compound **1** has a C_9 acidity which corresponds reasonably closely to that of a typical carbonyl compound (pK_a ~ 20),[14] presumably enhancing its value as a model system. Finally, **1** appears to have a minimum of steric hindrance to abstraction of the C_9 proton.


1


2

The amines used as catalysts for **1** → **2** in this study were selected to provide a broad range of pK_a values in each class of amine (primary, secondary, and tertiary), and on the basis of certain specific criteria concerning propensity for enamine formation which will be discussed below.

Results

The reaction of *ca.* 5×10^{-5} *M* solutions of 9-fluorenylmethyl chloride (**1**) in 9:1 water–ethanol at 25° in the presence of a large excess of catalyst was monitored by the increase in ultraviolet absorption at 254 mμ corresponding to the formation of dibenzofulvene (**2**). It was assumed that **2** was the product on the basis of the criteria discussed by More O'Ferrall,[13] and isolation was not attempted. As More O'Ferrall has noted, **2** is a reactive substance in dilute aqueous solution, and Carpino[15] has recently reported reaction of **2** with itself and with morpholine. Yet it was possible to obtain linear pseudo-first-order kinetic plots for up to 75–80%

---

(1) L. P. Koshechkina, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **35**, 55 (1969), and previous papers in this series.

(2) M. L. Bender and A. Williams, *J. Amer. Chem. Soc.*, **88**, 2502 (1966).

(3) G. E. Lienhard and T-C. Wang, *ibid.*, **90**, 3781 (1968).

(4) J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970), and previous papers in this series.

(5) R. C. Cavestri and L. R. Fedor, *J. Amer. Chem. Soc.*, **92**, 4610 (1970), and previous papers in this series.

(6) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

(7) See W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 3, especially pp 217–229, and Chapter 2, especially pp 116–146, for a review and specific references.

(8) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Amer. Chem. Soc.*, **94**, 1254 (1972).

(9) T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Lett.*, 3889 (1965).

(10) T. A. Spencer and L. D. Eisenhauer, *J. Org. Chem.*, **35**, 2632 (1970).

(11) Spencer and Eisenhauer[10] report a study in dioxane solution with a similar aim, but of less scope and precision.

(12) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter X, especially pp 175–178, provides a general discussion of deviations from the Brønsted relationship; see also reference 7, pp 175–182.

(13) R. A. More O'Ferrall and S. Slae, *J. Chem. Soc. B*, 260 (1970).

(14) (a) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **87**, 382 (1965), give the pK_a of fluorene as 20.5; (b) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940), give the pK_a of acetone as 20.0; (c) R. P. Bell and P. W. Smith, *J. Chem. Soc. B*, 241 (1966), give the pK_a of cyclohexanone as 16.7.

(15) L. A. Carpino and G. Y. Han, *J. Amer. Chem. Soc.*, **92**, 5748 (1970).

Table I. Rate Constants for the Reaction of Amines and Hydroxide Ion with 9-Fluorenylmethyl Chloride (**1**) to Form Dibenzofulvene (**2**) in 9:1 Water–Ethanol at 25°

Catalyst	pK_a	k_{AM} or k_{OH} (M^{-1} sec^{-1})	pH range	[Catalyst] (total amine concn) (M)	No. of runs
Hydroxide Ion	15.7	0.87	7.42–11.03	10^{-3}–10^{-7}	12
Pyrrolidine	11.32[b]	0.22	8.55–9.11	0.99–0.06	16
Piperidine	11.22[c]	0.13	8.59–9.25	0.50–0.03	16
Hexamethylenimine	11.10[b]	0.19	7.13–9.52	0.60–0.006	28
Quinuclidine	10.95[d]	0.43	9.26–9.45	0.50–0.03	12
Triethylamine	10.75[e]	3.1×10^{-2}	9.34–10.49	0.25–0.005	20
n-Butylamine	10.61[e]	9.4×10^{-3}	9.86–9.96	1.03–0.07	16
Piperazine	9.82[f]	5.0×10^{-2}	8.21–8.61	0.35–0.005	12
Trimethylamine	9.76[c]	7.9×10^{-2}	8.16–9.68	0.38–0.001	36[l]
Allylamine	9.49[c]	2.3×10^{-3}	8.72–8.83	0.50–0.03	8
DABCO[a]	8.7[g]	4.2×10^{-2}	8.53–8.70	0.10–0.001	12
Morpholine	8.36[c]	5.2×10^{-3}	7.64–8.60	0.40–0.01	44
Ethyl glycinate	7.73[h]	3.1×10^{-4}	7.95–8.11	0.50–0.06	8
N-Methylmorpholine	7.41[c]	3.7×10^{-3}	6.99–7.17	0.50–0.03	8
N-Methylimidazole	7.06[i]	6.8×10^{-5}	7.27–7.35	0.15–0.01	8
Imidazole	6.95[j]	6.1×10^{-5}	6.97–7.83	0.50–0.03	24
Cyanomethylamine	5.34[k]	7.1×10^{-6}–1.4×10^{-5}	5.52–5.59	0.50–0.17	8

[a] 1,4-Diazabicyclo[2.2.2]octane. [b] H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956). [c] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957). [d] C. A. Grob, A. Kaiser, and E. Renk, *Chem. Ind.* (*London*), 598 (1957). [e] N. A. Lange, "Handbook of Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, pp 1203–1204. [f] J. Bjerrum, "Stability Constants," Chemical Society, London, 1957, Part I, p 21. [g] The Merck Index, 8th ed, Merck & Co., Inc., Rahway, N. J., 1968, p 1072. [h] O. H. Emerson and P. L. Kirk, *J. Biol. Chem.*, **87**, 597 (1930). [i] Determined in this study by the half-neutralization method. [j] T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1958). [k] G. W. Stevenson and D. Williamson, *ibid.*, **80**, 5943 (1958). [l] Plus four runs in deuterium oxide.

formation of **2** in almost all cases. Greatest difficulty was encountered with the weakest base used, cyanomethylamine, and there is substantial uncertainty in the catalytic constant for that amine. In all cases where the pH dependence of amine catalysis was studied, the rate of formation of **2** was proportional to free amine concentration, as illustrated in Figure 1 for trimethylamine. The formation of **2** is governed by eq 1.

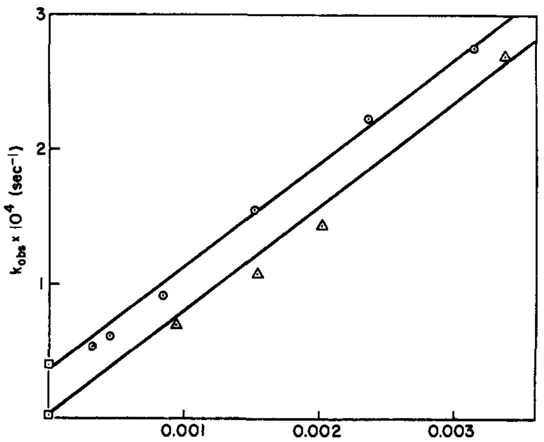


Figure 1. Plot of pseudo-first-order rate constants, k_{obsd}, for the reaction of **1** to give **2** *vs.* concentration of free trimethylamine at pH 9.68 (○) and at pH 8.42 (△). The intercepts (□) are calculated values of $k_{OH}(OH^-)$ at the respective pH values.

$$d\mathbf{2}/dt = (k_{OH}[OH^-] + k_{AM}[AM])(\mathbf{1}) \qquad (1)$$

In Table I are listed the values of k_{OH} and k_{AM} calculated from the absorbance data as described in the Experimental Section. In Figure 2 the catalytic constants for all the amines are plotted against their base strengths. The points fall so as to suggest three distinct Brønsted relationships for primary, secondary, and tertiary amines, each with $\beta = 0.5$. Negative deviations are observed for triethylamine, *N*-methylmorpholine (slight), imidazole, and *N*-methylimidazole. In an attempt to gain insight into the origin of the ineffectiveness of the latter two unhindered aromatic amines, the effect of added imidazole on morpholine catalysis of **1** → **2** was determined and was found to be negligible.

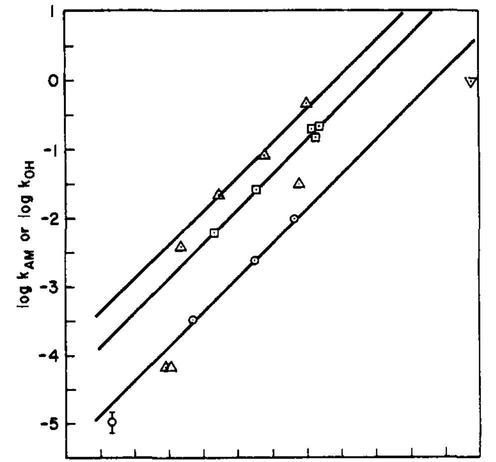


Figure 2. Brønsted plot of the logarithm of the second-order rate constants from Table I for the reaction of primary (○), secondary (□), and tertiary (△) amines, and hydroxide ion (▽), with **1** to give **2** *vs.* pK_a's of their conjugate acids. The slope of the lines is $\beta = 0.50$. (The points for the diamines piperazine and DABCO have been corrected according to the relationship given by Jencks, ref 7, p 173).

The conversion **1** → **2** was also run in deuterium oxide with trimethylamine as catalyst, and a linear pseudo-first-order plot was obtained. The nmr spectrum of unreacted **1** recovered at ~20% conversion to **2** from a large-scale run in 1:2 deuterium oxide–dioxane with morpholine as catalyst showed no detectable diminution of the C_9 proton absorption resulting from isotopic exchange.

Discussion

The observation of general base catalysis supports the assumption that the conversion **1** → **2** involves C_9 proton abstraction in the rate-limiting step, because a preequilibrium ElcB mechanism ($k_{-1} \gg k_2$ in eq 2), as observed by More O'Ferrall[13] in the case of 9-fluorenylmethanol, should show specific hydroxide ion catalysis.[16] The observation that the conversion **1** → **2** in deuterium oxide gave a linear pseudo-first-order plot confirms that if the scheme given in eq 2 applies, k_{-1}

$$\mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{1}^- \xrightarrow{k_2} \mathbf{2} \qquad (2)$$

cannot be comparable to k_2, or the incorporation of deuterium at C_9 in **1** would cause a downward curvature of the pseudo-first-order plot. Such rate diminution in D_2O has been observed by More O'Ferrall[13] and by us[17] in reactions proceeding by way of discrete carbanion intermediates which partition relatively equally to starting material and product. Final evidence of the irreversibility of proton abstraction from **1** was the failure to observe deuterium incorporation in unreacted **1** isolated after partial conversion to **2**. This finding excludes the unlikely but kinetically equivalent explanation for the observed amine catalysis that the slow step is ammonium salt catalyzed conversion to **2** of $\mathbf{1}^-$, formed in a very rapidly established preequilibrium (*i.e.*, specific base–general acid catalysis), where

$$k_{\mathrm{AM}}[\mathrm{AM}](\mathbf{1}) = k_2[\mathrm{AMH}^+](\mathbf{1}^-)$$

The subtle question of whether this type of elimination reaction always, sometimes, or ever involves a discrete carbanion intermediate which exclusively goes on to product in a fast step, or occurs with concerted departure of the leaving group (E2 mechanism), has been considered by Fedor[5] and recently discussed by More O'Ferrall[18] and Bordwell.[19] The results reported in this paper do not provide any new insight into this matter.

The pattern of three parallel Brønsted relationships for tertiary, secondary, and primary amines as decreasingly effective general bases shown in Figure 2 has precedent in analogous findings in the base-catalyzed decomposition of nitramide.[20] Such a distinction among classes of amines has also been made by Hine[21] in amine-catalyzed dedeuteriation of isobutyraldehyde-*2-d*. On the other hand, Bender[2] has represented his results for general base catalysis of the enolization of acetone by all classes of amines with a single Brønsted line. The appropriateness of using three distinct lines in the present work seems very clear. Bell[12] has interpreted such observations as being a result of the fact that the equilibrium basicity depends more on the relative ability of different classes of ammonium salts to be stabilized by solvation in water than does the stability of the transition state for the general base catalyzed process in question. Thus, for example, primary amines, whose ammonium salts are relatively well solvated, are less effective kinetically than would be predicted on the basis of their $\mathrm{p}K_\mathrm{a}$'s.

The relative ineffectiveness of hydroxide ion as a general base, evident in Figure 2 for the conversion **1** → **2**, has often been noted before,[2,22] although Fedor[23] has presented a Brønsted plot for a tertiary amine catalyzed process which shows hydroxide ion falling very close to the line.

The three secondary amines pyrrolidine, piperidine, and hexamethylenimine all fall approximately on the appropriate Brønsted line, confirming our previous conclusion[9,10] that observation of unusual catalytic effectiveness for pyrrolidine and a correlative distinct minimum for piperidine among these amines is indicative of nucleophilic catalysis. The minor differences observed in this work among the three are in accord with the effects of the geometries of the different sized rings as discussed by Edwards[24] for pyrrolidine and piperidine.

The pronounced negative deviation from the tertiary amine Brønsted line by triethylamine (as well as the smaller deviation by *N*-methylmorpholine) can be readily ascribed to steric hindrance, which has been well documented for reactions involving rate-limiting proton abstraction from carbon.[23,25–27]

The finding that imidazole and *N*-methylimidazole are *ca.* 50-fold less effective as catalysts than predicted by the Brønsted plot for tertiary amines[28] is consistent with Hine's observation[26] of a similar ineffectiveness of unhindered aromatic amines in the dedeuteration of isobutyraldehyde-*2-d*. However, in the study described in the following paper,[8] imidazole and *N*-methylimidazole have catalytic constants falling close to the tertiary amine Brønsted line. We are not able to offer a satisfying explanation of the ineffectiveness of the imidazoles in the present study,[29] nor can we satisfactorily explain

---

[16] L. R. Fedor, *J. Amer. Chem. Soc.*, **91**, 908 (1969).

[17] Unpublished observation by G. T. Sinner.

[18] R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970).

[19] F. G. Bordwell, M. M. Vestling, and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5950 (1970).

[20] R. P. Bell and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1288 (1949); R. P. Bell and G. L. Wilson, *Trans. Faraday Soc.*, 46, 407 (1950).

[21] J. Hine and J. Mulders, *J. Org. Chem.*, 32, 2200 (1967).

[22] J. Hine, K. G. Hampton, and B. C. Menon, *J. Amer. Chem. Soc.*, **89**, 2664 (1967).

[23] L. R. Fedor, *ibid.*, **89**, 4479 (1967).

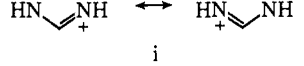
[24] H. J. Brass, J. O. Edwards, and M. J. Biallas, *ibid.*, **92**, 4675 (1970).

[25] J. Weinstock, R. G. Pearson, and F. G. Bordwell, *ibid.*, **78**, 3473 (1956).

[26] J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, **87**, 5050 (1965).

[27] C. D. Gutsche, D. Redmore, R. S. Buriks, K. Nowotny, H. Grassner, and C. W. Armbruster, *ibid.*, **89**, 1235 (1967), and references therein.

[28] Imidazole is classified as a tertiary amine because: (a) it seems eminently reasonable to assume that protonation of the heterocycle will occur at the tertiary nitrogen to give the symmetrical imidazolium ion i



i

which maintains an undisrupted aromatic sextet, and (b) the catalytic behavior of imidazole is essentially identical with that of *N*-methylimidazole. The question of whether imidazole can function as a secondary amine is considered in more detail in the following paper.[8]

[29] Hine[26] likewise offered no explanation for the ineffectiveness of the unhindered aromatic amines (pyridines and *N*-methylimidazole) in his study. The use of pyridines as catalysts in the present study to confirm the relevance of aromatic character to the observed negative deviation from the Brønsted plot would obviously be desirable, but presents substantial experimental problems owing to the large ultraviolet absorption of pyridines at 254 mμ.

the discrepancy between the findings in this and the following paper. An attempt was made to gain insight into the latter question by exploring the unlikely possibility that 9-fluorenylmethyl chloride complexes with imidazoles[30] in a manner which retards its conversion to **2**. The fact that varying concentrations of imidazole had no effect at all on morpholine-catalyzed conversions of **1** to **2** rules out such an explanation.

Aside from this anomalous behavior of the imidazoles, however, the results appear to satisfy the aim of this study: development of a reliable index of the effectiveness of a selected group of amines as general bases for proton abstraction from a carbon acid with pK_a ~20. In the following paper[8] a three-tiered Brønsted plot is useful as a guide in probing for nucleophilic catalysis of elimination of acetic acid from a β-acetoxy ketone.

Experimental Section

9-Fluorenylmethyl Chloride (1). According to the procedure of Von and Wagner,[31] fluorene was converted to 9-formylfluorene, which was reduced with sodium borohydride to afford 9-fluorenylmethanol, mp 99–100° (lit.[32] mp 102–103°; lit.[33] 99.5–100°; lit.[34] mp 107°). According to the procedure of Wawzonek and Dufek,[35] 9-fluorenylmethanol was converted to **1**, mp 67–68° (lit.[35] 66.5–67.5°).

9-Fluorenylmethyl acetate was prepared from 9-fluorenylmethanol by the method of Bavin and Dewar[36] and was initially tried in place of **1** as a substrate. However, for reasons which remain obscure and unexplored, the acetoxy compound underwent conversion to **2** only to a small extent (~20% reaction) before absorption at 254 mμ stopped increasing and decreased slowly.

Other Reagents. Available amine hydrochlorides were purchased from Aldrich Chemical Co., Inc., and were purified by recrystallization from 1-propanol–methanol or ether. The other amines were purchased from Aldrich and purified by distillation from barium oxide. In the cases of *N*-methylmorpholine, hexamethylenimine, and trimethylamine, the amine hydrochlorides were prepared by bubbling hydrogen chloride through a hexane solution of the amine and were recrystallized. Standard buffer solutions were purchased from A. H. Thomas Co.

Apparatus. A Unicam SP 800B spectrophotometer equipped with an automatic cell changer timed by a Cary 1116100 program timer was used to obtain data for four kinetic runs simultaneously. The most rapid reactions were timed with a Lab-chron 1401 timer. The temperature in the cuvettes was maintained at 25.0 ± 0.1° by circulating water controlled by a P.V. Tamson bath through the cuvette housing. pH measurements were made on a Radiometer Model 26 pH meter equipped with a GK2302C combination electrode.

Kinetics. The conversion of **1** to **2** was monitored at 254 mμ[37] using *ca.* 5×10^{-5} *M* solutions of **1** in 1:9 ethanol–water, the minimum amount of ethanol necessary to maintain complete solution throughout. Substrate solutions were added by syringe to the amine buffer catalysts in the cuvettes. Four amine buffer concentrations, prepared by dilution from a stock solution and adjusted to the desired pH by addition of hydrochloric acid or potassium hydroxide solution, were run simultaneously. All runs were made against reference solutions of equal amine buffer concentration, lacking only **1**. pH determinations were made immediately at the conclusion of each set of runs, and at the beginning of the run as well if there was any reason (*e.g.*, low buffer concentration) to suspect that the pH would change during the reaction. Experiments made to test the effect of changing ionic strength showed a negligible effect, so that although ionic strength was adjusted to $\mu = 0.4$ with potassium chloride in some runs, others had greater or lesser ionic strength depending on buffer concentrations. Values of A_∞ were determined experimentally by adding excess hydroxide ion to cause rapid conversion to **2**. Repetition of these A_∞ measurements was made frequently on the same solution of **1** and gave values which checked within 2%.

As mentioned above, More O'Ferrall[13] and Carpino[15] have reported that the product dibenzofulvene (**2**) reacts with itself and with morpholine. However, such potential complications did not cause great difficulty in obtaining reasonable rate data, and we did not find it necessary to use extremely dilute solutions in 10-cm cells to prevent precipitation of a dibenzofulvene self-condensation product, as More O'Ferrall did.[13] Confirmation that we were indeed able to obtain reliable kinetic data for the conversion of **1** to **2** was obtained from reactions monitored by repetitive wavelength scans. Tight isosbestic points were obtained for more than three half-lives at several wavelengths using either hydroxide ion or DABCO as catalyst. The uncertainty in the data for cyanomethylamine may have been caused as much by decomposition of the catalyst as by instability of **2**.

One set of runs was made in the presence of two amine buffers, as described in the Discussion. Rates of formation of **2** were determined for eight solutions containing 0.1 *M* imidazole buffer plus morpholine buffer ranging from 0.027 *M* to 0.408 *M* at pH 8.5. No effect was observed on the previously determined catalytic constant for morpholine.

Treatment of Data. Absorbance readings (A_t) were converted by computer to $\ln (1/[1 - (A_t - A_0)/(A_\infty - A_0)])$, where A_0 is the significant initial absorbance at 254 mμ of **1** obtained by extrapolation of the first few absorbance readings to zero time, and A_∞ is the final absorbance reading obtained for a given solution of **1** after rapid conversion to **2** by treatment with hydroxide ion. Pseudo-first-order rate constants (k_{obsd}) were obtained either graphically or by a computer-determined least-squares slope of a plot of $\ln (1/[1 - (A_t - A_0)/(A_\infty - A_0)])$ *vs.* time (sec). Second-order rate constants (k_{OH}, k_{AM}) were derived graphically as the slope of a plot of k_{obsd} *vs.* free amine concentration ([AM]). The latter was calculated by multiplying the measured total buffer concentration by $K_a/(K_a + a_H)$, where K_a is the ionization constant of the ammonium salt under consideration in water at 25°, and a_H is the hydrogen ion activity as measured by pH meter at *ca.* 25°. Within a set of buffer dilutions the pH tended to vary slightly. The values of k_{obsd} used to determine a given k_{AM} were all corrected to the pH of the highest buffer concentration by use of the expression $k_{\text{obsd corr}} = k_{\text{obsd}} + k_{\text{OH}}([\text{OH}^-]_{\text{ref}} - [\text{OH}^-]_{\text{obsd}})$, where $[\text{OH}^-]_{\text{ref}}$ is the hydroxide ion concentration at the pH of the highest buffer concentration.

Determination of Extent of Deuterium Incorporation in Unreacted 1 at 20% Conversion to 2. A solution of 0.217 g (1.0 mmol) of **1** in 23 ml of dioxane (dried by chromatography on Brinkmann activity 1 alumina and stored over 4Å Molecular Sieves) and 17 ml of deuterium oxide (Diaprep, Inc., 99.8% isotopic purity) was mixed with a solution of 0.420 g (4.8 mmol) of morpholine in 15 ml of dioxane and 5 ml of deuterium oxide containing enough hydrogen chloride to bring the pH to 8.2. The increase in absorbance of the resulting solution was monitored until it corresponded to 20% formation of **2**, which required 50 min. The reaction mixture was extracted with three 90-ml portions of cold ether, and the ether layers were dried over magnesium sulfate, filtered, and evaporated to afford 0.203 g of oily product. On standing this product deposited a white solid with mp > 100°, perhaps the product of the reaction of morpholine with **2**.[15] Extraction of a portion of this crude product mixture with a small amount of hexane gave *ca.* 0.08 g of oily material which in $CDCl_3$ displayed an nmr spectrum identical with that of pure **1**. In particular, the distinctive A_2B spectrum of the C_9 and chloromethyl group protons[38] was completely unchanged.

Acknowledgment. The authors are grateful for the financial support of PHS Grant AM 11815 from the

---

(30) S. Hatem, *C. R. Acad. Sci.*, 252, 2958 (1961), has reported the formation of complexes between various substituted fluorenes and benzimidazoles, although the evidence given for complexation between imidazole itself and fluorenes is questionable.

(31) I. Von and E. C. Wagner, *J. Org. Chem.*, 9, 155 (1944).

(32) E. Ghera and Y. Sprinzak, *J. Amer. Chem. Soc.*, 82, 4945 (1960).

(33) W. G. Brown and B. Bluestein, *ibid.*, 62, 3256 (1940).

(34) E. J. Greenhow, D. McNeil, and E. N. White, *J. Chem. Soc.*, 986 (1952).

(35) S. Wawzonek and E. Dufek, *J. Amer. Chem. Soc.*, 78, 3530 (1956).

(36) P. M. G. Bavin and M. J. S. Dewar, *J. Chem. Soc.*, 4477 (1955).

(37) More O'Ferrall and Slae[13] report the absorption maximum of **2** to be 255 mμ and did their kinetic measurements at that wavelength.

(38) The resonance pattern of these three protons at δ 3.8–4.4 ppm corresponds very closely to the theoretical spectrum calculated for a $J/\nu_0\delta$ ratio of 0.204 provided by J. W. Emsley, J. Feeney, and L. H. Sutcliffe in "High Resolution Nuclear Magnetic Resonance Spectroscopy," Volume 1, Pergamon Press, Oxford, 1965, p 327. We thank Professor G. W. Gribble for calling this to our attention.

National Institute of Arthritis and Metabolic Diseases, which permitted purchase of the Unicam spectrophotometer and provided funds temporarily to pursue the research; they are also grateful for an NSF Undergraduate Research Participation award to I. D. R. They also thank Professor R. L. Cleland for the generous loan of a constant temperature water circulator, and D. J. Hupe for valuable discussions.

Amine Catalysis of Elimination from a β-Acetoxy Ketone. A Study of Catalysis *via* Iminium Ion Formation

Donald J. Hupe, Martha C. R. Kendall, and Thomas A. Spencer*

Contribution from the Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755. *Received June 2, 1971*

Abstract: A kinetic study of the elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-decalone-2 (**1**) to form 10-methyl-$\Delta^{1,9}$-octalone-2 (**2**) in aqueous solution has been made using hydroxide ion, hydronium ion, acetate ion, and a variety of amines as catalysts. General base catalysis is observed, defining distinct Brønsted lines with $\beta \cong 0.6$ for primary, secondary, and tertiary amines. A mechanism for this elimination reaction involving rate-determining proton abstraction is confirmed by observation of a large primary kinetic isotope effect when the elimination is performed on **1** appropriately labeled with deuterium. With primary amines having $pK_a < 8$, covalent catalysis by amines is also found, involving terms proportional to protonated amine and proportional to protonated amine times free amine. The bell-shaped pH–rate profiles observed as a consequence of the latter term have been completely analyzed into the component general base and covalent catalysis terms. All evidence, including a primary kinetic isotope effect, is consistent with rate-limiting abstraction of an α-proton from an iminium ion by a general base in the bimolecular covalent catalysis. A Brønsted β of $\sim$0.5 has been determined for this proton abstraction. Temperature-dependence studies indicate that the bimolecular catalysis has a large negative $\Delta S^{\ddagger}$ (-35 eu), but a relatively small $\Delta H^{\ddagger}$ (10 kcal/mol). It is estimated that conversion of a carbonyl compound to a cyanomethyliminium ion increases the rate of α-proton abstraction by a given general base by $\sim 10^6$. This nucleophilic catalysis is discussed as a model for certain enzymic processes and compared with previous related studies. Evidence is presented which is inconsistent with previously postulated analogous catalysis involving iminium ion formation by imidazole.

Despite several recent studies[1-6] of amine catalysis of carbonyl compound reactions, there still remain many incompletely understood aspects of this biologically important[7] type of process, particularly with respect to the details of covalent catalysis *via* iminium ion formation by primary and secondary amines. In the preceding paper,[8] a study of general base catalysis by amines of the elimination of hydrogen chloride from 9-fluorenylmethyl chloride was made in order to establish a background against which to search for catalysis involving amines as nucleophiles. In this paper, amine-catalyzed elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-decalone-2 (**1**) has been investigated and has, as hoped, provided an opportunity to evaluate and study catalysis involving amine-carbonyl condensation.

Proposals of such covalent catalysis by amines, which were first advanced for the decarboxylation of β-keto acids[9] and the dealdolization of diacetone alcohol,[10] have been extended, with impressive if sometimes ambiguous[1] evidence, to aldehyde and ketone enolization in model systems,[2,4] and to reactions catalyzed by aldolases[11] and decarboxylases.[12] Of particular relevance to the β-elimination reaction studied in the present research are Abeles' investigation of the enzymic conversion of 2-keto-3-deoxy-L-arabonate to α-ketoglutarates emialdehyde,[13] Fedor's studies of general base catalyzed β-eliminations in model systems very similar to ours,[5] and Hine's recent finding of intramolecular bifunctional catalysis involving iminium ion formation.[4]

The particular β-acetoxy ketone (**1**) chosen as a substrate for the study described herein, while less readily prepared than other possibilities, has the distinct advantage of undergoing elimination essentially quantitatively to the chromophoric and stable enone **2**. It was also chosen because it is the same type of substance we have previously used to study the stereochemistry and mechanism of intramolecular aldol condensations[14] and ketol dehydrations.[15] The catalysts employed were

---

(1) L. P. Koshechkina, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **35**, 55 (1969), and previous papers in this series.

(2) M. L. Bender and A. Williams, *J. Amer. Chem. Soc.*, **88**, 2502 (1966).

(3) G. E. Lienhard and T-C. Wang, *ibid.*, **90**, 3781 (1968).

(4) J. Hine, M. S. Cholod, and J. H. Jensen, *ibid.*, **93**, 2321 (1971), and previous papers in this series.

(5) L. R. Fedor and W. R. Glave, *ibid.*, **93**, 985 (1971), and previous papers in this series.

(6) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

(7) See W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, especially Chapters 2 and 3 for a review and specific references.

(8) T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, **94**, 1250 (1972).

(9) K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

(10) F. H. Westheimer, *Ann. N. Y. Acad. Sci.*, **39**, 401 (1940).

(11) J. C. Speck, Jr., P. T. Rowley, and B. L. Horecker, *J. Amer. Chem. Soc.*, **85**, 1012 (1963).

(12) F. H. Westheimer, *Proc. Chem. Soc.*, 253 (1963).

(13) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, 242, 2751 (1967).

(14) T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 3785 (1963); T. A. Spencer, H. S. Neel, D. C. Ward, and K. L. Williamson, *J. Org. Chem.*, **31**, 434 (1966).