its well-established value, 1.36×10^{-3},[24] lends confidence in it. Two, quite different, values of K_{HA} for fluoroacetic acid have been previously reported, neither obviously flawed. The present redetermination is in good agreement with that of Bell and Kuhn,[25] shown in Table I. The Bell and Kuhn value would also improve the fit of fluoroacetic acid in the Kresge and Chiang correlation.[7] No precise value of K_{HA} could be found for difluoroacetic acid. Judging by success in the other two cases, the value presently reported should not be uncertain by more than its imprecision, ±8%.

Experimental Section

Allylmercuric iodide was prepared as previously.[2] All inorganic reagents were of analytical reagent quality and were used without further purification. Aqueous inorganic acids and bases were made up and standardized in the usual ways.[26] Acetic, formic, and oxalic acid were also of analytical reagent quality. The identity and purity of the latter was further verified by titration. The former two were used as supplied. Fluoroacetic and difluoroacetic acids were purchased from K and K Laboratories. They were distilled under vacuum and fractions of narrow boiling range were used. Their identity was verified by C and H analysis of their sodium salts. The same procedures were used for chloroacetic acid, which was purchased from Eastman Kodak Co. Cyanoacetic acid was purchased from Aldrich Chemical Co., and used as supplied. Its identity was verified by C and H analysis of its sodium salt. Glycine was purchased from Eastman Kodak Co. Its identity and purity were verified by titration with base in the presence of excess formaldehyde.

Rate Measurements. Most of the rate measurements were made by the techniques previously described.[2] However, in the case of oxalic acid, the buffer solutions were too strongly absorbing to permit this, so aliquots were withdrawn periodically, the allylmercuric iodide was extracted from the buffer with isooctane, and its optical density determined. For a pseudo-first-order reaction, such as the present one, it is not necessary that the allylmercuric iodide be quantitatively extracted, nor that the mercuric iodide or buffer be quantitatively excluded. It is only necessary that the amounts of each substance extracted be proportional to its concentration in the reaction mixture, and that the changes in optical densities produced be reliably measurable.[9] These conditions are reasonably met in the present case. Although there is more scatter from eq 1 in these experiments than in those not involving the extraction, there is no discernible systematic deviation.

Spectra and Optical Densities. Continuous spectra were obtained as needed, with a Beckman DK-2 spectrophotometer. Most optical density measurements at a single wavelength were made on a Beckman DU spectrophotometer, but a few were made on the DK-2 spectrophotometer, set so as to record optical density as a function of time at a single wavelength. The temperature in the cell compartments of both instruments was controlled by pumping water of known temperature through their jackets. Direct measurements in the cells verified that these did not vary by more than 0.1° from the temperature of the water bath.

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[24] G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. Ltd., London, 1961, p 293.

[25] R. P. Bell and A. T. Kuhn, *Trans. Faraday Soc.*, **59**, 1789 (1963).

[26] I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The MacMillan Co., New York, N. Y., 1943.

Catalysis of α-Hydrogen Exchange. III. Exchange of Isobutyraldehyde-2-*d* in the Presence of Methylammonium Ions[1]

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Abstract: The kinetics of the dedeuteration of isobutyraldehyde-2-*d* in the presence of methylammonium chloride have been investigated using 2,6-lutidine–2,6-lutidinium chloride buffers and sodium acetate–acetic acid buffers. The results obtained are consistent with the view that much of the dedeuteration is due to the rate-controlling attack of the various bases present on the iminium ion, $\mathrm{Me_2CDCH{=}NHMe^+}$. The acidity constant of the 2,6-lutidinium ion is found to be decreased to the same extent by added methylammonium chloride or sodium chloride but increased by added 2,6-lutidine or 2,6-lutidinium chloride. Specific medium effects of this type are blamed for differences between the values for certain kinetic constants determined in aqueous solutions with different buffers present.

In the presence of several tenths molar methylamine and methylammonium ions, conditions under which isobutyraldehyde exists largely in the form of its N-methylimine, the deuterium exchange of isobutyraldehyde-2-*d* is largely due to a term in the kinetic equation that may be written[1b]

$$k[\mathrm{Me_2CDCH{=}NMe}][\mathrm{MeNH_3^+}]$$

or alternatively

$$k'[\mathrm{Me_2CDCH{=}NHMe^+}][\mathrm{MeNH_2}]$$

Inasmuch as the exchange reaction is much too slow for a proton transfer from methylammonium ions to the imine to be the rate-controlling step, it seems highly probable that the rate-controlling step is the removal of deuterium from the iminium ion by the attack of methylamine.

In a number of reactions of aldehydes and ketones, the salts of primary and secondary amines have been found to be catalysts under conditions where not more than a very small fraction of the carbonyl compound is present as the imine or iminium ion. To learn more

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[1] (a) This investigation was supported in part by Public Health Service Research Grant AM 06829 MCB from the National Institute of Arthritis and Metabolic Diseases. (b) For the preceding paper in this series see J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).

[2] (a) The Ohio State University; (b) U. S. Public Health Service Predoctoral Fellow, 1965–1967; (c) U. S. Public Health Service Postdoctoral Fellow, 1965–1966.

about the mechanisms of such reactions we have studied the effect of methylammonium salts on the rate of deuterium exchange of isobutyraldehyde-2-*d* in solutions that are sufficiently acidic that very little free methylamine is present. Since the imine is much less basic than methylamine, the fraction of the aldehyde present as the imine in these solutions is very much smaller than in the more basic solutions used previously.[1b] In fact we have not been able to detect any imine or iminium ions in such solutions by direct measurements.

The first kinetic studies were carried out in the presence of 2,6-lutidine buffers. 2,6-Lutidine was chosen because steric hindrance should tend to minimize its entering into the reaction[3] in any way other than controlling the pH of the solution. This should make reactions involving the bases water, hydroxide ion, and methylamine more easily observable. In order to interpret the results it was necessary to have a value for the ionization constant of 2,6-lutidine under the conditions used.

Results

The Ionization Constant of 2,6-Lutidine. We have determined the acidity constant for 2,6-lutidinium ions by measurements with a pH meter equipped with a glass electrode and a calomel reference electrode. In so doing, the observed pH values have been taken as $-\log [H^+]$. The procedure introduces an error, of course, because of varying liquid junction potentials, ion activity coefficients, and factors that make the glass electrode an imperfect substitute for a hydrogen electrode. However, the use of this method for the determination of the acidity constant of methylammonium ions at 35° and an ionic strength of 0.5 *M* gave a value of p*K* (10.447)[1b] that is within the probable uncertainty of the value obtained by extrapolation of the results obtained in the careful and detailed measurements of Everett and Wynne-Jones at ionic strengths from 0.05 to 0.20 *M*.[4] Values obtained in the presence of various concentrations of 2,6-lutidine (26L), 2,6-lutidinium chloride (26LHCl), sodium chloride, and methylammonium chloride are listed in Table I. In the experiments in which methylammonium ions were present no attention had to be given to their acidity since in no case should as much as 0.05% of the methylammonium ions be transformed to methylamine. All the experiments refer to cases in which the titration of lutidine solutions by hydrochloric acid was between 30 and 70% complete, so as to minimize uncertainties in concentrations and effects of possible impurities that are the largest near the beginning and end of a titration. Comparison of experiments 1 and 2, which were carried out in dilute solution, with experiments 3–12, in which the ionic strength was 0.440 *M* and 89–93% due to sodium chloride or methylammonium chloride, shows that the latter two salts increase the value of pK_{26LH} to about the same extent. The results of experiments 15 and 21, in which the ionic strength is also 0.440 *M*, show that increased concentrations of 2,6-lutidine and 2,6-lutidinium ions decrease pK_{26LH}. Comparison of experiments 16 and 19 shows that at essentially constant 2,6-lutidine concentration, pK_{26LH} decreases with increasing concentrations of 2,6-lutidinium chloride. However, increasing concentrations of 2,6-lutidine also decrease pK_{26LH} as shown in experiments 19–24, where pK_{26LH} decreases in spite of decreasing 2,6-lutidinium chloride concentrations. Further examination of the data suggests that increasing concentrations of 2,6-lutidine and 2,6-lutidinium ions have about the same effect on pK_{26LH}, and that this effect is a fairly linear function of the concentration. The analogous conclusion concerning the effect of sodium chloride and methylammonium chloride suggests the correlation of the data in Table I by an equation of the form

$$pK_{26LH} = pK^0_{26LH} + a([NaCl] + [MeNH_3Cl]) + b([26L] + [26LHCl]) \quad (1)$$

The following optimum values for the disposable parameters in eq 1 were calculated from the data in Table I by the method of least squares: $pK^0_{26LH} = 6.608$, $a = 0.357$, $b = -0.290$. With these parameters, the data in Table I may be reproduced with an average deviation of 0.007, which is within the average experimental uncertainty.

Table I. The Acidity Constant of 2,6-Lutidinium Ions in Water at 35°

Expt	[26L], *M*	[26LHCl], *M*	[NaCl], *M*	[MeNH$_3$Cl], *M*	pK_{26LH}
1	0.0016	0.0016	0.000	0.000	6.625
2	0.0049	0.0049	0.000	0.000	6.588
3	0.0209	0.0491	0.391	0.000	6.736
4	0.0215	0.0502	0.000	0.390	6.723
5	0.0301	0.0452	0.395	0.000	6.727
6	0.0309	0.0463	0.000	0.393	6.720
7	0.0406	0.0407	0.399	0.000	6.732
8	0.0418	0.0417	0.000	0.398	6.722
9	0.0530	0.0354	0.404	0.000	6.741
10	0.0546	0.0364	0.000	0.402	6.724
11	0.0678	0.0291	0.411	0.000	6.740
12	0.0700	0.0300	0.000	0.410	6.717
13	0.108	0.252	0.211	0.000	6.577
14	0.155	0.233	0.210	0.000	6.571
15	0.161	0.230	0.209	0.000	6.571
16	0.210	0.210	0.208	0.000	6.560
17	0.275	0.183	0.206	0.000	6.544
18	0.352	0.151	0.203	0.000	6.520
19	0.218	0.509	0.000	0.000	6.407
20	0.313	0.470	0.000	0.000	6.381
21	0.385	0.440	0.000	0.000	6.371
22	0.424	0.424	0.000	0.000	6.365
23	0.556	0.370	0.000	0.000	6.344
24	0.713	0.306	0.000	0.000	6.314

Exchange in the Presence of 2,6-Lutidine Buffers. The kinetics of the loss of deuterium from isobutyraldehyde-2-*d* in the presence of methylammonium chloride and 2,6-lutidine–2,6-lutidinium chloride buffers in aqueous solutions at 35.0° were studied by nmr measurements using the techniques employed previously.[1b] Inasmuch as the concentrations of the various possible catalysts do not change within a given run, rate constants (k_p) were calculated from the first-order rate equation

$$-(d[AD]/dt) = k_p[AD] \quad (2)$$

where [AD] is the concentration of deuterated aldehyde (both hydrated and unhydrated). The first-order rate constants obtained are listed in Table II. In the last 22

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[3] J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).

[4] D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (London), **A177**, 499 (1941).

Table II. Deuterium Exchange of Me_2CDCHO in the Presence of $MeNH_3Cl$ and 2,6-Lutidine–2,6-Lutidinium Chloride Buffers at 35°[a]

Run no.	[26L], M	[26LH$^+$], M	[$MeNH_3Cl$], M	[IB$^-$], M	[NaCl], M	10^8k_p, sec^{-1}	10^8k_{cor}, sec^{-1}	$\frac{10^8k_{cor}}{[MeNH_3^+]}$, M^{-1} sec^{-1}
1	0.0427	0.0314	0.425	<0.001	0.000	103	99	233
2	0.0855	0.0627	0.425	<0.001	0.000	124	119	280
3	0.128	0.0941	0.425	<0.001	0.000	136	130	306
4	0.171	0.126	0.425	<0.001	0.000	155	148	348
5	0.214	0.157	0.425	<0.001	0.000	163	154	362
6	0.214	0.157	0.340	<0.001	0.000	122	114	335
7	0.214	0.157	0.255	<0.001	0.000	84.3	75.9	298
8	0.214	0.157	0.170	<0.001	0.000	55.7	47.3	278
9	0.214	0.157	0.086	<0.001	0.000	30.7	22.3	259
10	0.118	0.206	0.425	<0.001	0.000	94.9	89.5	211
11	0.170	0.046	0.425	<0.001	0.000	260	251	591
12	0.0453	0.0113	0.102	0.0010	0.330	36.0	29.6	290
13	0.0914	0.0218	0.102	0.0012	0.320	42.5	34.7	340
14	0.0917	0.0215	0.102	0.0009	0.320	45.2	37.5	368
15	0.138	0.0321	0.102	0.0012	0.310	49.9	40.8	400
16	0.138	0.0319	0.102	0.0010	0.310	49.0	40.0	392
17	0.137	0.0323	0.102	0.0014	0.310	42.2	33.1	325
18	0.184	0.0421	0.102	0.0009	0.300	55.2	45.1	442
19	0.184	0.0421	0.102	0.0009	0.300	60.5	50.4	494
20	0.231	0.0524	0.102	0.0009	0.290	56.6	45.5	446
21	0.184	0.0420	0.409	0.0008	0.000	359	348	851
22	0.184	0.0420	0.307	0.0008	0.100	224	213	694
23	0.184	0.0422	0.205	0.0010	0.200	148	137	668
24	0.184	0.0422	0.051	0.0010	0.350	30.3	20.4	400
25	0.00886	0.0505	0.100	0.0005	0.290	5.59	3.15	31.5
26	0.0182	0.100	0.100	0.0005	0.220	6.63	3.93	39.3
27	0.0276	0.150	0.100	0.0004	0.190	10.15	7.25	72.5
28	0.0370	0.200	0.100	0.0004	0.140	9.44	6.29	62.9
29	0.0461	0.251	0.100	0.0007	0.089	10.63	7.06	70.6
30	0.0372	0.200	0.240	0.0002	0.000	18.8	15.6	65.0
31	0.0372	0.200	0.200	0.0002	0.040	15.4	12.3	61.5
32	0.0367	0.201	0.150	0.0007	0.089	15.5	12.0	80.0
33	0.0365	0.201	0.050	0.0009	0.190	5.60	2.39	47.8

[a] Initial concentrations of isobutyraldehyde-2-*d*, 0.319 M in runs 1–11 and 0.100 M in runs 12–33.

experiments sodium chloride was added as necessary to keep the ionic strength at 0.44 M. In the first 11 experiments, the ionic strength was merely that due to the methylammonium chloride and 2,6-lutidinium chloride present and varied within the range 0.41 ± 0.17 M.

In the study of the reaction in the presence of methylamine buffers,[1b] the possibility was considered that some of the exchange is due to attack of bases on the aldehyde, some to attack of bases on the imine, and some to attack of bases on the iminium ion. The amount of reaction due to attack on the imine was too small to detect.[1b] In the present case, the ratio of imine to aldehyde can be seen by direct measurements to be much smaller and the ratio of imine to iminium ions must be much smaller since hydrogen ion concentration is greater by 10^3- to 10^4-fold. Hence reaction *via* attack of bases on the imine has been assumed to be negligible. If equilibrium between the aldehyde and iminium ions is established at a rate that is rapid compared to the deuterium exchange, the rate equation for the exchange will contain a term corresponding to the attack of each of the bases in the solution on the aldehyde and on the iminium ion. However, since attack of the imine on these reactants could not be detected in the previous study where the imine concentration was relatively high, we have neglected it in the present case. From the magnitude of the catalysis constant for the exchange of aldehyde in the presence of strong acid,[3] exchange due to hydrogen ion catalysis may be seen to be negligible in the present case. Inasmuch as catalysis by an acetate buffer has been found to be essentially entirely due to the acetate ions present and not to the acetic acid,[3] it is assumed that with lutidine–lutidinium ions and methylamine–methylammonium ions, where the basic components of the pairs are more basic than acetate ions and the acidic components less acidic than acetic acid, only the basic components will act catalytically. On the basis of these assumptions the following kinetic equation is expected

$$\begin{aligned} d[AD]/dt = {} & (k_{26L}[26L] + k_m[MeNH_2] + k_{ib}[IB^-] + \\ & k_h[OH^-] + k_w[H_2O])[AD] + (k'_{26L}[26L] + \\ & k_m'[MeNH_2] + k'_{ib}[IB^-] + k_h'[OH^-] + \\ & k_w'[H_2O])[HImD^+] \end{aligned} \quad (3)$$

where [IB$^-$] is the concentration of isobutyrate ions (unavoidably present because of oxidation of the aldehyde), $HImD^+$ is the iminium ion $Me_2CDCH{=}N\text{-}HMe^+$, the rate constants denoted k refer to attack on the aldehyde, and those denoted k' refer to attack on the iminium ion.

If K is the equilibrium constant for the formation of imine from isobutyraldehyde and methylamine, which will be assumed to be the same for isobutyraldehyde-2-*d* as for isobutyraldehyde itself

$$K = \frac{[ImH]}{[AH][MeNH_2]} = \frac{[ImD]}{[AD][MeNH_2]} \quad (4)$$

and K_{MH^+} and K_{IH^+} are the acidity constants of the methylammonium ion and the iminium ion, respectively, then

$$[\mathrm{HImD^+}] = (KK_{\mathrm{MH}}/K_{\mathrm{IH}})[\mathrm{AD}][\mathrm{MeNH_3^+}] \quad (5)$$

Substitution of eq 5 into eq 3 and combination with eq 2 yields

$$k_{\mathrm{p}} = k_{26\mathrm{L}}[26\mathrm{L}] + k_{\mathrm{m}}[\mathrm{MeNH_2}] + k_{\mathrm{ib}}[\mathrm{IB^-}] + k_{\mathrm{h}}[\mathrm{OH^-}] + k_{\mathrm{w}}[\mathrm{H_2O}] + (KK_{\mathrm{MH}}/K_{\mathrm{IH}})(k'_{26\mathrm{L}}[26\mathrm{L}] + k_{\mathrm{m}}'[\mathrm{MeNH_2}] + k'_{\mathrm{ib}}[\mathrm{IB^-}] + k_{\mathrm{h}}'[\mathrm{OH^-}] + k_{\mathrm{w}}'[\mathrm{H_2O}])[\mathrm{MeNH_3^+}] \quad (6)$$

Values of $K_{26\mathrm{L}}$, k_{h}, and k_{w} are available from earlier work.[3] The estimate of k_{ib} (1.0×10^{-6} M^{-1} sec^{-1}) made previously[3] was used, giving a correction that never amounts to as much as 1% of the total reaction rate. The value of $k'_{\mathrm{ib}}KK_{\mathrm{MH}}/K_{\mathrm{IH}}$ was estimated using the value of $k'_{\mathrm{OAc}}KK_{\mathrm{MH}}/K_{\mathrm{IH}}$ (4.2×10^{-5} M^{-2} sec^{-1}), whose determination is described later in this paper, and the assumption that $k'_{\mathrm{ib}}/k'_{\mathrm{OAc}}$ is equal to $k_{\mathrm{ib}}/k_{\mathrm{OAc}}$. The isobutyrate ion would be expected to be so similar to the acetate ion in its catalytic activity that the value (4.7×10^{-5} M^{-2} sec^{-1}) calculated in this way should not be greatly in error. Furthermore, the fact that the k'_{ib} term never comprises more than 4% of the total reaction rate makes the exact value used of decreased significance. In the first 11 runs that were made, it was merely shown that the isobutyrate concentration was below 0.001 M, and therefore no values for k_{ib} and k'_{ib} terms may be calculated. In these runs, however, the determined limit on the isobutyrate concentration does guarantee that the combined k_{ib} and k'_{ib} terms will not contribute as much as 2% to the over-all reaction rate. These k and k' values were used to obtain a corrected first-order rate constant.

$$k_{\mathrm{cor}} = k_{\mathrm{p}} - k_{26\mathrm{L}}[26\mathrm{L}] - k_{\mathrm{h}}[\mathrm{OH^-}] - k_{\mathrm{w}}[\mathrm{H_2O}] - k_{\mathrm{ib}}[\mathrm{IB^-}] - (k'_{\mathrm{ib}}KK_{\mathrm{MH}}/K_{\mathrm{IH}})[\mathrm{IB^-}][\mathrm{MeNH_3^+}] \quad (7)$$

Combination of eq 6 and 7 and replacement of $[\mathrm{MeNH_2}]$ by $K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]/[\mathrm{H^+}]$ yields

$$k_{\mathrm{cor}} = \frac{k_{\mathrm{m}}K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]}{[\mathrm{H^+}]} + \frac{KK_{\mathrm{MH}}}{K_{\mathrm{IH}}}\left(k'_{26\mathrm{L}}[26\mathrm{L}] + \frac{k_{\mathrm{m}}'K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]}{[\mathrm{H^+}]} + k_{\mathrm{h}}'[\mathrm{OH^-}] + k_{\mathrm{w}}'[\mathrm{H_2O}]\right)[\mathrm{MeNH_3^+}] \quad (8)$$

Dividing by $[\mathrm{MeNH_3^+}]$ and replacing $[\mathrm{OH^-}]$ by $rK_{\mathrm{w}}/K_{26\mathrm{LH}}$ and $[\mathrm{H^+}]$ by $K_{26\mathrm{LH}}/r$, where r is the buffer ratio $[26\mathrm{L}]/[26\mathrm{LH^+}]$ and K_{w} is the ion product constant of water, gives the following relation

$$\frac{k_{\mathrm{cor}}}{[\mathrm{MeNH_3^+}]} = \frac{k_{\mathrm{w}}'KK_{\mathrm{MH}}[\mathrm{H_2O}]}{K_{\mathrm{IH}}} + K_{\mathrm{MH}}\left(k_{\mathrm{m}} + \frac{k_{\mathrm{h}}'KK_{\mathrm{w}}}{K_{\mathrm{IH}}}\right)\frac{r}{K_{26\mathrm{LH}}} + \frac{k_{\mathrm{m}}'KK^2_{\mathrm{MH}}[\mathrm{MeNH_3^+}]r}{K_{\mathrm{IH}}\,K_{26\mathrm{LH}}} + \frac{k'_{26\mathrm{L}}KK_{\mathrm{MH}}}{K_{\mathrm{IH}}}[26\mathrm{L}] \quad (9)$$

If the values of k_{w}', k_{m}, k_{h}', k_{m}', $k'_{26\mathrm{L}}$, K, K_{MH}, K_{IH}, and K_{w} remain constant over the range of conditions under which the kinetic experiments were conducted, eq 9 may be written in the following form

$$\frac{k_{\mathrm{cor}}}{[\mathrm{MeNH_3^+}]} = C_1 + C_2\frac{r}{K_{26\mathrm{LH}}} + C_3\frac{[\mathrm{MeNH_3^+}]r}{K_{26\mathrm{LH}}} + C_4[26\mathrm{L}] \quad (10)$$

Table III. Deuterium Exchange of $\mathrm{Me_2CDCHO}$ in the Presence of $\mathrm{MeNH_3Cl}$ and NaOAc–HOAc Buffers at 35°[a]

[NaOAc], M	[HOAc], M	[Me-NH$_3^+$], M	10^8k_{p}, sec^{-1}	10^8k_{cor}, sec^{-1}	10^8 (k_{cor}/[MeNH$_3^+$]), M^{-1} sec^{-1}
0.200	0.084	0.300	268	249	829
0.200	0.084	0.300	263	244	812
0.148	0.213	0.352	232	217	617
0.148	0.213	0.340	262	247	727
0.148	0.213	0.340	231	216	636
0.148	0.213	0.255	173	158	620
0.148	0.213	0.170	144[b]	129	760
0.148	0.213	0.170	142	127	748
0.148	0.213	0.170	130	115	678
0.148	0.052	0.170	129	114	672
0.125	0.050	0.340	196	183	539
0.097	0.311	0.340	163	153	449
0.088	0.036	0.412	161	152	368
0.088	0.036	0.200	94[b]	85	424
0.088	0.036	0.200	92	83	414
0.050	0.050	0.450	122	116	257
0.050	0.050	0.450	106[c]	100	222
0.030	0.030	0.480	103	99	205
0.030	0.030	0.470	102	98	208
0.030	0.030	0.470	81[c]	77	164
0.010	0.010	0.490	45	42	87
0.010	0.010	0.490	37[c]	34	70

[a] Initial concentration of isobutyraldehyde-2-*d* 0.319 M in all runs. Sodium chloride added as necessary to keep the ionic strength at 0.500 except where noted. [b] No sodium chloride added. [c] 0.001 M in the disodium salt of ethylenediaminetetraacetic acid.

Of the various rate constants that are to remain constant, only k_{h}' refers to a reaction between two ions. Of the equilibrium constants that are to remain constant, only K_{w} refers to an equilibrium in which there is a change in the number of ions. Therefore, according to the simplest form of the Debye–Hückel equation, the only rate and equilibrium constants that should vary with ionic strength are k_{h}', which should decrease with increasing ionic strength, and K_{w}, which should increase with increasing ionic strength (to exactly the same extent that k_{h}' should decrease). Since in the only term in which these constants appear (C_2) they appear as a product, the values of C_1, C_2, C_3, and C_4 in eq 10 would not vary with the nature and concentration of added salts if the simplest form of the Debye–Hückel equation were applicable. The measurements of $K_{26\mathrm{LH}}$ already described show that for an equilibrium involving no change in the number of ions a change in ionic strength may produce a change in K whose direction as well as magnitude depends on the nature of the salt responsible for the ionic strength. However, we cannot measure K_{MH} or K_{w} in the presence of appreciable concentrations of 2,6-lutidinium ions, and direct measurement of salt effects on K_{IH} and the various rate constants seems even less feasible. Therefore eq 10 seems to be the best approximation available.

Optimum values for the constants in eq 10 were obtained from the data in Table II by the method of least squares,[5] using values of $K_{26\mathrm{LH}}$ calculated from eq 1, with the following results: $C_1 = 1.47 \times 10^{-7}$ M^{-1} sec^{-1}, $C_2 = 6.25 \times 10^{-14}$ sec^{-1}, $C_3 = 4.61 \times 10^{-13}$ M^{-1} sec^{-1}, and $C_4 = 9.74 \times 10^{-6}$ M^{-2} sec^{-1}. From these values and the appropriate values of $K_{26\mathrm{LH}}$, the various known k's, etc., the values of k_{p} in Table II

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[5] In this least-squares calculation the sum of the squares of the percentage deviations was minimized, not the sum of the squares of the absolute deviations from $k_{\mathrm{cor}}/[\mathrm{MeNH_3^+}]$.

may be calculated with an average deviation of 6.2% and a maximum deviation of 21.5%.

Exchange in the Presence of Acetate Buffers. In Table III are the results of kinetic studies of the loss of deuterium from isobutyraldehyde-2-*d* in the presence of methylammonium chloride and sodium acetate–acetic acid buffers. Comparison of various pairs of runs in which the same concentrations of reagents were used shows that in the present experiments, as in the 2,6-lutidine studies, the experimental uncertainty in the first-order rate constants obtained is on the order of 10%. In three runs the reaction solutions were made 0.001 *M* in the disodium salt of ethylenediaminetetraacetic acid (EDTA) in order to learn whether the variations in rate constants observed may have been due to trace amounts of metal ions present as impurities in the system. The rate constants obtained in these runs were lower than those in similar runs in which no EDTA was present, but by no more than the combined experimental uncertainties.[6]

No corrections were made for the small amounts of isobutyric acid present in the isobutyraldehyde used. It is assumed that isobutyric acid, like acetic acid (which is slightly stronger), would not catalyze the reaction significantly. Transformation of isobutyric acid to isobutyrate ions by reaction with acetate ions would merely replace one basic catalyst by another whose efficiency would be expected to be very little different.

In the acetate buffers, where the hydrogen ion concentration is about 100 times as high as in the 2,6-lutidine buffers, the concentrations of free methylamine and hydroxide ions are greatly reduced. Furthermore, these bases must now compete with acetate ions, which are more effective catalysts than 2,6-lutidine. For these reasons, the C_2 term, due to the attack of methylamine on aldehyde and hydroxide ions on iminium ion, and the C_3 term, due to attack of methylamine on iminium ion, are relatively small. From the values of C_2 and C_3 obtained in the previous sections it may be calculated that the C_2 term will never contribute as much as 0.15% and the C_3 term will never contribute as much as 0.4% to any of the reaction rate, described in Table III.[7] Thus, even if specific salt effects cause C_2 and C_3 to be several times as large in the presence of acetate buffers as in the presence of 2,6-lutidine buffers, the C_2 and C_3 terms will be smaller than the experimental uncertainties in the rate constants. With the neglect of these two terms, the kinetic equation for exchange in the presence of acetate buffers analogous to eq 10 for 2,6-lutidine buffers is

$$\frac{k_{\text{cor}}}{[\text{MeNH}_3^+]} = C_1 + \frac{k'_{\text{AcO}}KK_{\text{MH}}}{K_{\text{IH}}}[\text{AcO}^-] \qquad (11)$$

Correction for reaction due to the attack of hydroxide ions on aldehyde would never amount to more than 0.01% of the total reaction. For this reason the k_h term was neglected and k_{cor} defined

$$k_{\text{cor}} = k_p - k_{\text{AcO}}[\text{AcO}^-] - k_w[\text{H}_2\text{O}] \qquad (12)$$

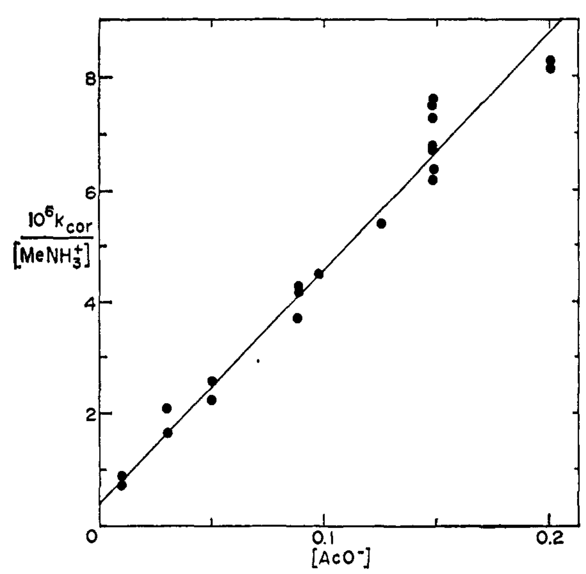

Figure 1. Plot of the $10^6k_{\text{cor}}/[\text{MeNH}_3^+]$ values from Table III *vs.* [AcO⁻].

Using this equation, values of $k_{\text{cor}}/[\text{MeNH}_3^+]$ were calculated and plotted against the acetate ion concentration as shown in Figure 1. From the best straight line (determined by the method of least squares[5]) through the points, the following values were obtained : $C_1 = 3.9 \times 10^{-7}\ M^{-1}\ \text{sec}^{-1}$, $(k'_{\text{AcO}}KK_{\text{MH}}/K_{\text{IH}}) = 4.20 \times 10^{-5}\ M^{-2}\ \text{sec}^{-1}$. However, since the intercept is so near the origin, the value of C_1 obtained is not very reliable.

Discussion

The value of C_1 obtained from measurements using acetate buffers is more than twice as large as that obtained using 2,6-lutidine buffers. Part of this difference may be due to specific salt effects, but it is likely that there are also rather large experimental errors. The C_1 value obtained from the experiments with 2,6-lutidine buffers deviates no more from the intercept of the line in Figure 1 than several of the experimental points deviate from the line. The C_1 value obtained in the acetate experiments, on the other hand, is larger than two of the values of $k_{\text{cor}}/[\text{MeNH}_3^+]$ listed in Table II and almost as large as a third. For this reason if one neglected specific medium effects and chose one of the two values as the more reliable, it would be the one determined in the presence of 2,6-lutidine buffers.

The equivalence of eq 9 and 10 defines C_2 as

$$C_2 = K_{\text{MH}}\left(k_m + \frac{k_h'KK_w}{K_{\text{IH}}}\right)$$

In a previous investigation in which methylamine–methylammonium ion buffers were used, the following value was reported.[1b]

$$\frac{k_m}{K} + \frac{k_h'K_w}{K_{\text{IH}}} = 3.0 \times 10^{-5}\ \text{sec}^{-1}$$

Multiplication of the equation by K (90.7 M^{-1}) and by K_{MH} ($3.57 \times 10^{-11}\ M$) gives

$$K_{\text{MH}}\left(k_m + \frac{k_h'KK_w}{K_{\text{IH}}}\right) = 9.7 \times 10^{-14}\ \text{sec}^{-1} = C_2$$

in comparison to the value 6.25×10^{-14} found in the

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(6) The possibility of metal ion catalysis is currently being investigated in more detail.

(7) The ionization constant for acetic acid at an ionic strength of 0.5 needed for this calculation was that determined in the presence of sodium chloride[8] ($3.3 \times 10^{-5}\ M$).

(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, p 676.

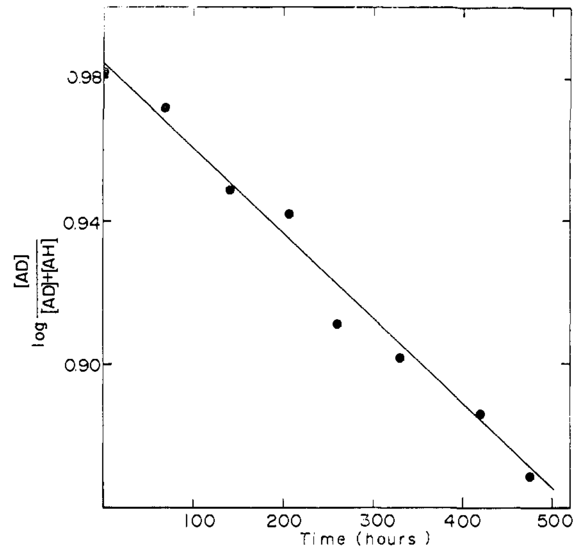

Figure 2. Kinetic plot for run 32, Table II.

present case. Similarly,

$$C_3 = k_m'KK^2_{MH}/K_{IH}$$

It was previously reported[1b,9] that

$$k_m'K_{MH}/K_{IH} = 30.6 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$$

Multiplication by KK_{MH} gives

$$\frac{k_m'KK^2_{MH}}{K_{IH}} = 9.9 \times 10^{-13}\ M^{-1}\ \text{sec}^{-1} = C_3$$

This value is more than twice as large as that ($4.6 \times 10^{-13}\ M^{-1}\ \text{sec}^{-1}$) obtained in the presence of 2,6-lutidine buffers.

The fact that smaller values of C_1, C_2, and C_3 are obtained in the presence of 2,6-lutidine buffers than in the presence of methylamine buffers and acetate buffers may be due in part simply to experimental errors. Errors in the way that the rate of reaction in the presence of 2,6-lutidine buffers has been divided into C_1, C_2, C_3, and C_4 components could cause some of the values to be too high and some to be too low. The fact that the values of C_1, C_2, and C_3 are all considerably smaller than those obtained in the absence of 2,6-lutidine buffers suggests that experimental error is not the only factor of importance. It might be suggested that the reaction mechanism in the presence of 2,6-lutidine buffers has changed, *e.g.*, perhaps imine formation has become the rate-controlling step. However, this suggestion would require that the nature of the rate-controlling step change once between pH's around 10, where the methylamine buffer experiments were run, and pH's around 7, where the 2,6-lutidine buffer experiments were run, and then change again between pH's around 7 and pH's around 5, where the acetate buffer experiments were run. It seems more plausible that C_1, C_2, and C_3 are all decreased by a medium effect due to the 2,6-lutidine and 2,6-lutidinium ions present. More specifically, it may be suggested that the intermediate iminium ion, which, like the 2,6-lutidinium ion, has its acidic proton attached to a moderately hindered sp^2-hybridized nitrogen atom, becomes more acidic as the concentration of 2,6-lutidine and 2,6-lutidinium ions increase. If K_{IH} is thus increased to the same extent that we have found K_{26LH} to be, it would be increased by as much as 60% in some of the runs described in Table II, relative to its value in the presence of enough sodium chloride and/or methylammonium chloride to yield the same ionic strength. Since K_{IH} appears in the denominator in C_1, C_2, and C_3, such an effect provides a qualitative explanation and goes far toward providing a quantitative explanation of the discrepancies observed between C values determined in different ways. It is not to be implied, however, that other equilibrium and rate constants are immune to specific medium effects under the conditions of our experiments.

For the reasons described in the preceding paragraph it is felt that the present results are consistent with the hypothesis that much of the loss of deuterium from isobutyraldehyde-2-*d* in the reactions described in this paper is due to the rate-controlling attack of bases on the N-methyliminium ion derived from isobutyraldehyde. Thus, the reaction mechanism in the present case, where the reaction solutions were so acidic that the aldehyde was essentially all present as aldehyde or aldehyde hydrate, appears to be essentially the same as in the study in which methylamine buffers were used, and the aldehyde was largely present in the form of its N-methylimine.

Additional evidence in support of the hypothesized reaction mechanism could be adduced from the relative magnitudes of the various k and k' values that have been obtained. However, discussion of this evidence will be postponed until the publication of a study in which a variety of different buffers were used.

Experimental Section[10]

p*k* Measurements. A Beckman Research pH Meter, Model 101900, was used to determine the pH of solutions whose contents are shown in Table I. A constant-temperature bath kept the solutions at 35 ± 0.5°. Inasmuch as the concentrations of both hydrogen and hydroxide ions were very small compared to the concentrations of lutidine and lutidinium ions, the concentrations of these buffer components could be calculated from the amounts of lutidine weighed out and the volume of acid of known strength added without correction for hydrogen and hydroxide ion concentrations.

Kinetic Measurements. The kinetics of the loss of deuterium from isobutyraldehyde-2-*d* were studied by techniques of the type used previously.[1b,3] Kinetic points were analyzed by extracting the acidified solutions with chloroform and measuring the isotopic content of the extracted isobutyraldehyde, using nmr spectroscopy. In the first 11 runs of Table II, which includes none of the slowest runs, kinetic points were taken in stoppered nmr tubes. In the other runs points were sealed individually in 5-ml glass ampoules, which were broken for extraction and analysis. The last 15 runs of Table II were carried out in the dark by covering the sample with metal foil or by adding black ink to the constant-temperature bath. In the runs carried out in the presence of acetate buffers, volumetric flasks were used as reaction vessels and samples withdrawn by pipet.

In all cases the extent of oxidation of isobutyraldehyde to isobutyric acid was followed by acidimetric titrations. In all cases there were significant amounts of isobutyric acid in the aldehyde used as reactant but no significant amounts of acid were formed by oxidation during the exchange reaction.

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(9) The existence of specific salt effects was noted in this case, where the values of k_{cor} obtained in the presence of methylammonium perchlorate were 10–15% larger than those obtained in the presence of methylammonium chloride at essentially the same ionic strength (~0.5). The number given above was obtained by using both the chloride and perchlorate data.

(10) All nmr measurements were made using Varian Model A-60 instruments.

About eight points were taken for each kinetic run. The rate constant was calculated from the slope of the best straight line, as determined by the method of least squares, through a plot of log [AD]/([AD] + [AH]) *vs.* time. If a single point deviated from the best straight line through the other points by four or more times the average deviation of the other points it was discarded. In no case were two points discarded from the same run. Altogether about ten points were discarded.

Runs 25–33 were particularly slow and were followed to only about 10% completion; even this required about a month. Most of the other runs were carried to about 50% reaction. A kinetic plot for run 32, Table II, one of the poorest runs, is shown in Figure 2.

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Carbonyl Oxygen Exchange in General Base Catalyzed Ester Hydrolysis[1a]

Myron L. Bender and Henry d'A. Heck[1b]

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received October 22, 1966*

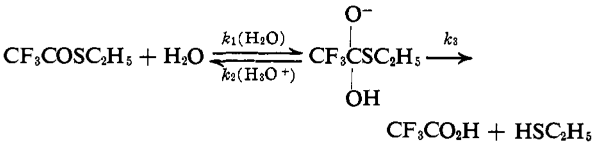
Abstract: The general base catalyzed hydrolyses of ethyl trifluorothiolacetate-O^{18} in 40% v/v tetrahydrofuran and of ethyl trifluoroacetate-*carbonyl*-O^{18} in 25% v/v acetonitrile are accompanied by carbonyl oxygen exchange with the solvent. The extent of oxygen exchange in the thiol ester experiments was quantitatively predicted from the hydrolysis kinetics, which were recently determined by Fedor and Bruice, and was consistent with an unsymmetrical partitioning of an addition intermediate. With the oxygen ester, partitioning of the intermediate is symmetrical since the partitioning is pH independent. The amount of oxygen exchange observed with the latter compound decreased significantly in the presence of deuterium oxide solvent. Temperature studies with both esters indicate that the activation energies are identical for breakdown of the intermediate to reactants or to products. The deacylations (hydrolyses) of cinnamoyl-α-chymotrypsin-*cinnamoyl-carbonyl*-O^{18} and *p*-nitrobenzoyl-α-chymotrypsin-*p-nitrobenzoyl-carbonyl*-O^{18} at neutral pH are not accompanied by carbonyl oxygen exchange with the solvent. However, in the alkaline hydrolysis of O-cinnamoyl-N-acetylserinamide-*cinnamoyl-carbonyl*-O^{18}, a model for an acyl-α-chymotrypsin intermediate, oxygen exchange takes place.

The hydrolysis of carboxylic esters often occurs simultaneously with carbonyl oxygen exchange with water.[2] Such exchange is strong evidence for the formation of a tetracovalent addition intermediate in the reaction, and provides the principal experimental justification for the two-step mechanism in ester hydrolysis.

It is well recognized, however, that oxygen exchange alone cannot prove that an intermediate lies on the reaction path. It is possible, for example, that ester hydrolysis proceeds *via* an SN2 type of substitution reaction, while oxygen exchange occurs through an addition mechanism which does not lead to the hydrolytic products.[3] Since carbonyl oxygen exchange reactions have been used widely in studies of reaction mechanism,[2] it would be of considerable interest to ascertain in a specific reaction whether the tetrahedral intermediate required for oxygen exchange is actually on the hydrolytic pathway.

Several kinetic arguments have been advanced recently requiring the presence of an intermediate on the pathway of an ester hydrolysis. Thus, the use of carbonyl oxygen exchange as a criterion for intermediate formation in ester hydrolysis can be tested by determining the amount of oxygen exchange in an ester hydrolysis which can be shown by independent kinetic evidence to involve an intermediate (presumably a tetrahedral addition compound). If the amount of exchange is in agreement with that which would be predicted from the kinetic experiments, one can conclude that the intermediate in which oxygen exchange occurs is the same intermediate which is observed kinetically.

The system chosen for investigation was ethyl trifluorothiolacetate-O^{18}. The kinetics of hydrolysis of the thiol ester have been thoroughly examined by Fedor and Bruice.[4] These authors presented strong evidence that the mechanism of hydrolysis is that outlined in eq 1. This mechanism involves a general base catalyzed attack of water at the carbonyl carbon of the thiol ester, forming a tetrahedral intermediate which decomposes spontaneously to products but reverts to reactants by acid catalysis.



$$CF_3COSC_2H_5 + H_2O \underset{k_2(H_3O^+)}{\overset{k_1(H_2O)}{\rightleftharpoons}} CF_3\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}SC_2H_5 \xrightarrow{k_3} CF_3CO_2H + HSC_2H_5 \quad (1)$$

By assuming a steady-state condition for the intermediate, the authors derived eq 2 for the hydrolytic rate constant, and showed, in accordance with eq 2,

$$k_h = k_1k_3/(k_2a_H + k_3) \quad (2)$$

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[1] (a) Taken from the Ph.D. dissertation of H. Heck, Northwestern University, 1967. Support of this work by a grant from the National Institutes of Health is gratefully acknowledged. (b) Predoctoral Fellow of the National Science Foundation.

[2] Oxygen exchange reactions of organic and organometallic compounds are reviewed by D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, 123 (1965).

[3] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, New York, N. Y., 1948, p 117.

[4] L. R. Fedor and T. C. Bruice, *J. Am. Chem. Soc.*, 87, 4138 (1965).