Isobutyraldehyde and Secondary Amines.   Addition and Catalysis of Deuterium Exchange[1]

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Equilibrium constants for the addition of morpholine, piperazine, and dimethylamine to isobutyraldehyde and rate constants for catalysis of the deuterium exchange of isobutyraldehyde-2-d by these three amines and piperidine are reported.   Comparison of the results on these four secondary amines, for which a moderately satisfactory Brønsted plot may be made, with previous results shows that, when steric hindrance is minimized, tertiary amines are more effective catalysts, at a given basicity, for the reaction studied than are secondary amines, which in turn appear to be more effective than primary amines.   Although there appears to be little steric hindrance to attack by morpholine and piperidine on isobutyraldehyde-2-d, attack by their N-methyl derivatives appears to be significantly hindered.

In an earlier study, tertiary amines, like various oxygen bases, were found to act as simple basic catalysts for the deuterium exchange of isobutyraldehyde-2-d, bringing about reaction by a second-order process, first order in aldehyde and first order in base.[3] With the primary amine methylamine the reaction mechanism was more complicated.[4]   In the presence of excess amine most of the aldehyde was present in the form of its N-methylimine and most of the exchange took place *via* attack of methylamine on the N-methyliminium ion with a rate proportional to the product $[Me_2CDCH=NHMe^+][MeNH_2]$ (which is automatically proportional to $[Me_2CDCH=NMe][MeNH_3^+]$).   In other reactions in which α substituents are removed, without bonding electron pairs, from carbonyl compounds, iminium ions have also been implicated as reaction intermediates.   In at least some such cases, including decarboxylation of β-keto acids[5-7] and dealdolization of β-hydroxy ketones,[8-10] both primary and secondary amines have been found to be catalysts, but primary amines appear to be more effective catalysts than closely related secondary amines. For this reason we sought to learn whether secondary amines bring about any significant catalysis of the deuterium exchange of isobutyraldehyde-2-d *via* iminium ion formation.

Results

In order to learn whether the exchange reaction might be complicated by the formation of any significant amount of adduct of the secondary amines to the aldehyde, the absorbance of solutions with a given concentration of aldehyde and varying concentrations of dimethylamine was measured at the aldehyde maximum (at approximately 2840 A).   The results (Table I) show

TABLE I
ADDITION OF DIMETHYLAMINE TO ISOBUTYRALDEHYDE IN WATER AT 26 ± 2°

(i-PrCHO),[a,b] M	(Me₂NH),[a] M	A₂₈₄₀	[i-PrCHO-HNMe₂],[c] M	[Me₂NH],[c] M	K
0.12	0.000	1.565			
0.12	0.421	0.990	0.0441	0.361	1.61
0.12	0.842	0.695	0.0667	0.753	1.66
0.12	1.26	0.510	0.0809	1.15	1.79
0.12	1.68	0.430	0.0870	1.56	1.69
0.12	2.10	0.355	0.0928	1.97	1.73
					1.70 ± 0.05

[a] Concentration originally added. [b] Includes both free aldehyde and aldehyde hydrate. [c] Concentration present at equilibrium.

that the absorbance characteristic of the aldehyde decreases steadily with increasing concentration of amine. From these data, values for the equilibrium constant for addition were calculated.   The value used for [i-

$$K = \frac{[i\text{-PrCH(OH)NMe}_2]}{[i\text{-PrCHO}][Me_2NH]}$$

PrCHO] in this expression is the total concentration of aldehyde present including the 38% present as aldehyde hydrate[11] at the temperature (26 ± 2°) at which the measurements were made.   Corrections were made for the 1% isobutyric acid present as an impurity in the isobutyraldehyde and for the disappearance of some of the dimethylamine *via* ionization to dimethylammonium ions.   For the latter correction an ionization constant of $6 \times 10^{-4} M^{12}$ was used for dimethylamine. This is the value at 25° and 0 ionic strength.   The ionic strength in the equilibrium solution was as high as 0.04 M, but it was felt that any resulting tendency for the ionization constant to increase with increasing ionic strength might very well be compensated (or overwhelmed) by the rather large concentrations of nonpolar solutes (aldehyde and amine) present.   Since the aldehyde–amine adduct (aminol) should be more weakly basic than dimethylamine, it was assumed that only a negligible fraction of the aminol was present in a protonated form.   From the known ionization constant of the aldehyde hydrate[11] the extent of the acid–base reaction between the aldehyde hydrate and

(1) (a) Part V in the series "Catalysis of α-Hydrogen Exchange." For part IV, see J. Hine, K. G. Hampton, and B. C. Menon, *J. Am. Chem. Soc.*, **89**, 2664 (1967). (b) This investigation was supported in part by Public Health Service Research Grants AM-06829-MCB and AM 10378 from the National Institute of Arthritis and Metabolic Diseases.
(2) Author to whom inquiries should be addressed at The Ohio State University.
(3) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).
(4) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *ibid.*, **88**, 3367 (1966).
(5) E. O. Wiig, *J. Phys. Chem.*, **32**, 961 (1928).
(6) W. Franke and G. Brathuhn, *Ann.*, **487**, 1 (1931).
(7) K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934); *J. Am. Chem. Soc.*, **60**, 595 (1938); *Acta Chem. Scand.*, **8**, 710 (1954).
(8) J. G. Miller and M. Kilpatrick, *J. Am. Chem. Soc.*, **53**, 3217 (1931).
(9) F. H. Westheimer and H. Cohen, *ibid.*, **60**, 90 (1938).
(10) F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941).

(11) J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, **30**, 1184 (1965).
(12) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (London), **A177**, 499 (1941).

dimethylamine was calculated and found to be negligible.

The same technique was used for the determination of the equilibrium constants for addition of morpholine and piperazine to isobutyraldehyde, giving K values of 0.64 and 1.12 M^{-1}, respectively. When piperidine was used, however, insoluble material precipitated before the measurements were completed (at the rather high amine concentrations necessary to obtain large enough changes in the aldehyde absorption to measure accurately).

The deuterium exchange of isobutyraldehyde-2-d was studied in the presence of various secondary amine buffers. The rate of reaction was followed by nmr measurements in a manner analogous to that used previously.[3,4] Within any given run the concentrations of catalysts do not change significantly, and satisfactory first-order rate constants may be calculated from the equation

$$k_p t = 2.3 \log \frac{D_0}{D_t} \quad (1)$$

where D_0 is the fraction of deuteration of the isobutyraldehyde at zero time and D_t is the fraction at time t. Because of the formation of aminols from the aldehyde and secondary amines, not all the aldehyde is present as free aldehyde and hydrate. The free aldehyde is believed to be the only one of the three major forms of the aldehyde present that undergoes deuterium exchange directly. However, equilibrium between the free aldehyde, its hydrate, and the aminol is established so rapidly that loss of deuterium from the aldehyde serves to dedeuterate all three species. The integrated eq 1 is equivalent to the following differential form (eq 2)

$$-\frac{dD_t}{dt} = k_p(\text{Me}_2\text{CDCHO}) \quad (2)$$

where $(\text{Me}_2\text{CDCHO})$ is the total concentration of aldehyde present (in all three forms). For comparison with the data obtained in previous papers in this series and to put the data on the various runs made in the present work (in which the fraction of aldehyde present as aminol varied widely) on the same basis, we need rate constants based on the concentration of aldehyde plus aldehyde hydrate, which we shall denote [Me$_2$CDCHO]. The first-order rate constant adjusted to this basis is shown as k_p' in the following equation

$$-dD_t/dt = k_p'[\text{Me}_2\text{CDCHO}] = k_p'f_a(\text{Me}_2\text{CDCHO}) \quad (3)$$

where f_a is the fraction of aldehyde present as aldehyde plus hydrate. From eq 2 and 3 it follows that

$$k_p' = k_p/f_a \quad (4)$$

By analogy with the reaction in the presence of methylamine[4] there should be catalysis due to the attack of each of the bases in the solution on the aldehyde and on iminium ion present in equilibrium with the aldehyde (acid catalysis should be negligible under the conditions used). Thus, k_p' should fit the following equation

$$k_p' = k_h[\text{OH}^-] + k_w[\text{H}_2\text{O}] + k_{\text{R}_2\text{NH}}[\text{R}_2\text{NH}] +$$
$$k_{\text{am}}[\text{aminol}] + K_{=\text{NR}_2}[\text{R}_2\text{NH}_2^+] \sum_i k_i'[\text{B}_i] \quad (5)$$

where the k values are rate constants for attack of the various bases on the aldehyde, the k_i' values are rate constants for attack of the same bases on the iminium

ion, and $K_{=\text{NR}_2}$ is the equilibrium constant for the formation of the iminium ion from aldehyde and secondary ammonium ion.

$$K_{=\text{NR}_2} = [\text{Me}_2\text{CDCH}=\text{NR}_2^+]/[\text{Me}_2\text{CDCHO}][\text{R}_2\text{NH}_2^+] \quad (6)$$

Since the values of k_h and k_w are known, it is convenient to define k_{cor} as

$$k_{cor} = k_p' - k_h[\text{OH}^-] - k_w[\text{H}_2\text{O}] \quad (7)$$

Combining this definition with eq 5 gives

$$k_{cor} = k_{\text{R}_2\text{NH}}[\text{R}_2\text{NH}] + k_{\text{am}}[\text{aminol}] +$$
$$K_{=\text{NR}_2}[\text{R}_2\text{NH}_2^+] \sum_i k_i'[\text{B}_i] \quad (8)$$

The data obtained using morpholine buffers are listed in Table II. The hydroxide ion concentration in these

TABLE II

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-d IN AQUEOUS MORPHOLINE BUFFERS AT 35°

(R$_2$NH),[a] M	[R$_2$NH$_2^+$], M	(Me$_2$CD-CHO)$_0$,[a] M	[Aminol], M	$10^6 k_p$, sec^{-1}	$10^6 k_{cor}$, sec^{-1}
0.306	0.150	0.132	0.020	170	200
0.307	0.300	0.132	0.020	170	200
0.302	0.454	0.132	0.020	162	191
0.298	0.610	0.132	0.020	173	204
0.275	0.310	0.128	0.018	150	174
0.267	0.318	0.161	0.022	151	175
0.253	0.332	0.240	0.030	142	162
0.230	0.355	0.350	0.038	131	147
0.206	0.379	0.464	0.044	116	128
0.170	0.220	0.159	0.014	102	112
0.121	0.171	0.157	0.010	78	83
0.0711	0.123	0.154	0.0062	51	53
0.0640	0.100	0.415	0.0131	42	43
0.0567	0.111	0.415	0.0117	32	33
0.0358	0.0627	0.415	0.0074	26	26
0.0249	0.0732	0.415	0.0052	13.5	13.7
0.0206	0.0449	0.415	0.0043	16.2	16.4
0.0068	0.0260	0.415	0.0014	5.8	5.9

[a] Total concentration, without allowance for aminol formation or ionization.

runs was calculated from the ionization constant of morpholine. This in turn was calculated from the acidity constant of morpholinium ions at 25°,[13] corrected to 35° by the method of Perrin[14] (to give a pK of 8.09), and the ion product constant of water, which was assumed to vary with ionic strength in the solutions used in the same manner that it does in the presence of sodium chloride.[15] No major errors seem likely to result from this treatment because the total correction for catalysis by water and hydroxide ions never amounted to as much as 1% of the over-all reaction rate. In calculating f_a, the equilibrium constant for aminol formation determined at 26° was used in spite of the fact that the kinetics were run at a temperature 9° higher.

In the first four runs the concentrations of aldehyde and morpholine were held approximately constant and the concentration of morpholinium ions increased more than fourfold. The values of k_{cor} remained constant

(13) H. K. Hall, *J. Phys. Chem.*, **60**, 63 (1956).
(14) D. D. Perrin, *Australian J. Chem.*, **17**, 484 (1964).
(15) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 752, 754.

within the experimental uncertainty. Therefore, we may neglect the terms in eq 8 that contain the morpholinium ion concentration and get the simplified equation

$$k_{cor} = k_{R_2NH}[R_2NH] + k_{am}[aminol] \qquad (9)$$

A least-squares treatment of the data in Table II (in which the sum of the squares of the *percentage* deviations from k_{cor} was minimized) gave k_{R_2NH} and k_{am} values of 6.64×10^{-4} and 6.23×10^{-4} M^{-1} sec^{-1}, respectively. The values of k_{cor} used may be reproduced with an average deviation of 7.1% by use of these values of k_{R_2NH} and k_{am}. A least-squares treatment that neglects k_{am} and attributes the whole of k_{cor} to the k_{R_2NH} term gives a value of k_{R_2NH} of 7.56×10^{-4} M^{-1} sec^{-1}, from which the k_{cor} values of Table II may be reproduced with an average deviation of 8.8%.

The results obtained using piperazine buffers are shown in Table III. In calculating the hydroxide ion

TABLE III

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-d IN AQUEOUS PIPERAZINE BUFFERS AT 35°

(R$_2$NH),[a] M	[R$_2$NH$_2$$^+$], M	(Me$_2$CD-CHO)$_0$,[a] M	[Aminol], M	$10^5 k_p$, sec^{-1}	$10^5 k_{cor}$, sec^{-1}
0.164	0.116	0.415	0.048	360	403
0.140	0.123	0.415	0.041	307	338
0.118	0.130	0.415	0.035	268	289
0.0860	0.148	0.415	0.026	185	195
0.0820	0.184	0.100	0.0077	225	242
0.0777	0.186	0.158	0.0110	192	204
0.0685	0.193	0.251	0.0143	173	182
0.0640	0.158	0.415	0.0196	145	151
0.0543	0.205	0.335	0.0144	132	137
0.0340	0.181	0.415	0.0106	77	78
0.0101	0.181	0.415	0.0032	24	24

[a] Total concentration, without allowance for aminol formation or ionization.

concentration for use in eq 7, a procedure analogous to that used for morpholine buffers was used. A pK value for piperazinium ions of 9.58 at 35° was obtained by interpolation between the values at 30 and 40°.[16] None of the corrections for catalysis by water and hydroxide ions amounted to more than 1% of the total reaction rate.

A least-squares treatment attributing all of k_{cor} to the k_{R_2NH} term gives a value of 3.35×10^{-3} M^{-1} sec^{-1}, from which the k_{cor} values used may be reproduced with an average deviation of 2.7%. A least-squares optimumization of values of both k_{R_2NH} and k_{am} gave values of 3.09×10^{-3} and 7.26×10^{-4} M^{-1} sec^{-1}, respectively, from which the k_{cor} values could be reproduced with an average deviation of 2.5%. The fact that such good agreement may be obtained without including piperazinium ion terms in a set of experiments in which the [R$_2$NH$^+$]/[R$_2$NH] was varied from 1.0 to 26 shows that any piperazinium ion terms were probably not very significant.

Catalysis of the deuterium exchange of isobutyraldehyde-2-d was also studied in the presence of dimethylamine and piperidine buffers with the results shown in Table IV. The concentrations of hydroxide ions in the runs using dimethylamine buffers were calculated by use of the ionization constants determined by Everett

and Wynne-Jones in the presence of potassium chloride.[12] The literature log K_B values were plotted against ionic strength and values were read off the smooth curve obtained. Corrections for that part of the reaction due to water and hydroxide ions never amounted to more than 6% of the total reaction rate. Because of the relative constancy of the concentration of aldehyde used, the ratio of the concentration of dimethylamine to that of the aminol was essentially constant. For this reason the reaction rate may not be significantly subdivided into a part due to catalysis by dimethylamine and one due to catalysis by the aminol. A least-squares treatment of the data obtained in dimethylamine buffers attributing all the reaction to the dimethylamine gives a value of k_{R_2NH} of 6.83×10^{-3} M^{-1} sec^{-1}, from which the k_{cor} values used can be reproduced with an average deviation of 6.6%. Although the ratio [Me$_2$NH$_2$$^+$]/[Me$_2$NH] ranged from 10 to 57, the direction and magnitude of the deviations of the experimental k_{cor} values from those calculated using only k_{R_2NH} showed no obvious correlation with this ratio.

The concentration of hydroxide ions present in the piperidine buffers was calculated in a manner analogous to that used for morpholine buffers, using the pK_a value for the piperidinium ion at 35° (10.818).[17] However, the concentration of hydroxide ions also depends on the concentration of free piperidine, which depends on the equilibrium constant for aminol formation, which was not determined for the case of piperidine. We therefore made two alternative assumptions for the value of this equilibrium constant. The equilibrium constants for morpholine and piperazine, which are quite similar to piperidine sterically, are 0.64 and 0.56 M^{-1} per amino group, respectively. Therefore the average value 0.6 M^{-1} was used in a set of calculations on piperidine. Another set of calculations was made using the value 1.7 M^{-1}, the same value as that observed for dimethylamine, the amine whose basicity is nearest to that of piperidine. Corresponding members of the two sets of values differed from each other by only about 2%. The k_{cor} values entered in Table IV have attached plus and minus figures to cover the two different values obtained. The data obtained were not adequate to give any useful information concerning the contribution of terms containing the concentrations of aminol and piperidinium ion concentrations. Least-squares calculations attributing the entire k_{cor} value to the k_{R_2NH} term gave the value 6.4×10^{-3} M^{-1} sec^{-1} when the equilibrium constant for aminol formation was assumed to be 0.6 M^{-1} and 8.9×10^{-3} M^{-1} sec^{-1} when it was assumed to be 1.7 M^{-1}. The k_{cor} values used could be reproduced from these k_{R_2NH} values with average deviations of 3.2 and 3.0%, respectively.

Discussion

The fact that we have not been able to detect any contribution to the reactions from the [R$_2$NH$_2$$^+$] terms of eq 8 even in the presence of secondary ammonium ion concentrations as high as 0.6 M shows that secondary amines are much less capable of bringing about catalysis of the deuterium exchange of isobutyraldehyde-2-d *via* iminium ion formation than primary

(16) J. M. Pagano, D. E. Goldberg, and W. C. Fernelius, *J. Phys. Chem.*, **65**, 1062 (1961).
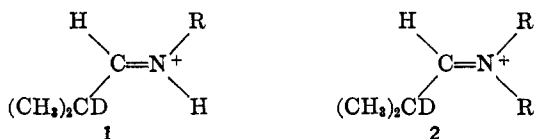
(17) R. G. Bates and V. E. Bower, *J. Res. Natl. Bur. Std.*, **57**, 153 (1956).

TABLE IV

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-d

IN AQUEOUS DIMETHYLAMINE AND PIPERIDINE BUFFERS AT 35°

Amine	(R_2NH),[a] M	$[R_2NH_2{}^+]$, M	$(Me_2CDCHO)_0$,[a] M	[Aminol], M	$10^6 k_p$, sec^{-1}	$10^6 k_{cor}$, sec^{-1}
Me₂NH	0.0150	0.116	0.260	0.0045	80	79
Me₂NH	0.0150	0.116	0.260	0.0045	79	78
Me₂NH	0.0121	0.0835	0.260	0.0037	56	54
Me₂NH	0.0104	0.119	0.254	0.0031	53	52
Me₂NH	0.0101	0.0735	0.260	0.0031	55	53
Me₂NH	0.00815	0.0635	0.260	0.0025	36	33
Me₂NH	0.00776	0.0952	0.254	0.0023	37	35
Me₂NH	0.00546	0.0723	0.254	0.0017	27	25
Me₂NH	0.00125	0.0493	0.254	0.00038	6.3	5.8
Piperidine	0.0180	0.210	0.415	~0.005	100	97 ± 1[b]
Piperidine	0.0148	0.160	0.415	~0.004	78	74 ± 1[b]
Piperidine	0.00894	0.125	0.415	~0.003	48	45 ± 1[b]

[a] Total concentration, without allowance for aminol formation or ionization.   [b] See text.

amines are. Calculations based on a study of the reaction in the presence of methylamine buffers[4] show that in the presence of 0.6 M methylammonium ions (and 0.3 M methylamine) the methylammonium ion terms in the rate equation cause the reaction to be about 17 times as fast as it would be if these terms were absent. It is believed that a contribution as large as 25% of the total reaction rate from the secondary ammonium ion terms would have been detectable in the reactions we studied. It seems plausible that at least part of the diminished efficiency of secondary ammonium ions as catalysts is due to steric hindrance. Catalysis by primary ammonium ions is probably largely due to the intermediate formation of the *trans* form of the iminium ion 1. Analogous catalysis by a secondary

ammonium ion would involve formation of the iminium ion 2, which would be destabilized by interactions between the isopropyl group from the aldehyde and an R group from the ammonium ion. Interactions of this type in the 4-methyl-2-pentenes make the *trans* isomer about 1.2 kcal/mole more stable than the *cis* isomer (according to equilibration studies at 55°).[18] Interactions in the iminium ions should be larger than in the corresponding olefins because the carbon–nitrogen double bond in an iminium ion is shorter than the carbon–carbon double bond of an olefin.[19]

Inasmuch as the data on catalysis by morpholine may be correlated almost as well when catalysis by the aminol is completely neglected as when it is considered, it is desirable to consider other arguments as to the importance of catalysis by the aminol. A study of catalysis by tertiary amines showed that catalytic constants tended to increase with increasing basicity, with Brønsted β values around 0.5 when steric factors were held constant, but that reactivity could be decreased greatly with even moderately hindered tertiary amines.[3] The catalysis constant we have obtained for

morpholine is about four times as large as the catalysis constant for N-methylmorpholine.[3] The aminol N-(α-hydroxyisobutyl)morpholine would be expected to be a weaker base than N-methylmorpholine by about 1.5 powers of 10, judging from Hall's correlation of the basicities of amines[20] and an estimate of the Taft σ^* constant for the α-hydroxyisobutyl substituent. With a Brønsted β of 0.4 this decreased basicity should make this aminol only one-fourth as reactive as N-methylmorpholine. Even if the aminol were this reactive (0.06 as reactive as morpholine) it would never contribute as much as 2% to the over-all reaction rate in any of the runs we made, but, actually, the aminol should be much less reactive than this since it is a much more hindered tertiary amine than N-methylmorpholine. For this reason we have completely neglected catalysis by the aminol derived from morpholine and have chosen the larger of the two k_{R_2NH} values for morpholine as the more nearly correct value. For analogous reasons we feel justified in our neglect of catalysis by the aminol in the case of piperidine, which is more than four times as reactive as N-methylpiperidine.

On the basis of the same type of argument we assume that addition of isobutyraldehyde to one of the NH groups of piperazine effectively eliminates the catalytic activity of that nitrogen atom. On the other nitrogen atom there should be only a small substituent effect. Hence the aminol derived from piperazine should be about half as effective a catalyst as piperazine. The least-squares treatment using both k_{am} and k_{R_2NH} gave a value for the former about one-fourth as large as the latter and therefore seems more plausible than the treatment in which k_{am} was assumed to be 0. We have adopted the value of k_{R_2NH} obtained thereby as the "best" value, although it could be argued that k_{am} should be assigned a value one-half that of k_{R_2NH} (if this were done a k_{R_2NH} value of about 2.9 × 10⁻³ would be obtained).

The N-methyl derivative of dimethylamine (trimethylamine), unlike the corresponding derivatives of morpholine and piperidine, is a *more* effective catalyst than the secondary amine (about 2.5 times as reactive). The same type of argument given in the case of morpholine may be used to show that in the case of dimethylamine the aminol is probably a poorer catalyst than

(18) A. Schriesheim and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3160 (1962).

(19) *Cf.* L. M. Trefonas, R. L. Flurry, Jr., R. Majeste, E. A. Meyers, and R. F. Copeland, *ibid.*, **88**, 2145 (1966).

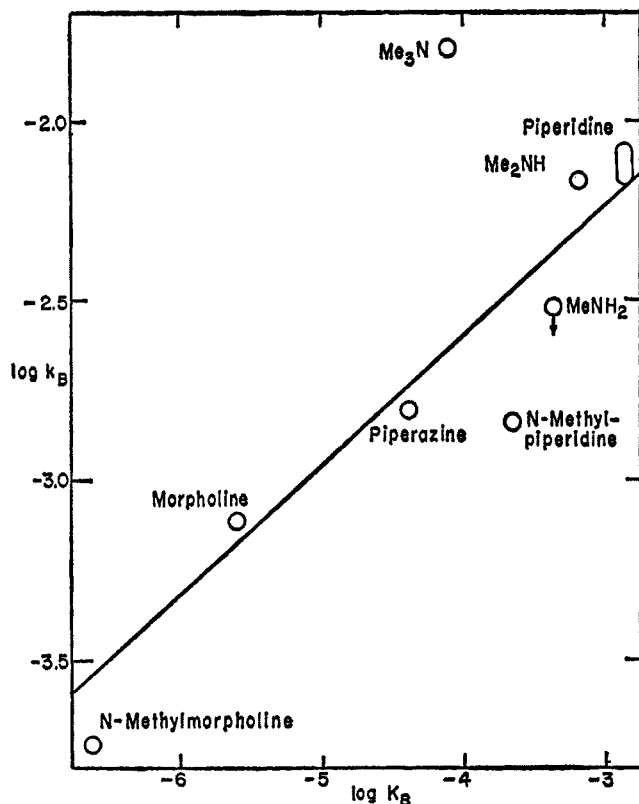(20) H. K. Hall, Jr., *ibid.*, **79**, 5441 (1957).

Figure 1.—Brønsted plot of catalysis constants for deuterium exchange of isobutyraldehyde-2-d in water at 35°. Data for piperazine are statistically corrected.

the secondary amine. From the magnitude of the steric effects previously observed with tertiary amines it seems probable that the aminol is so much poorer a catalyst that its catalytic activity may be neglected, but in the absence of a more quantitative treatment of steric effects it is difficult to be very confident about this point.

The k_{R_2NH} values taken as the best on the basis of the arguments in the preceding paragraphs are listed in Table V with the corresponding pK values (at 35° and

TABLE V

CATALYTIC AND IONIZATION CONSTANTS FOR THE SECONDARY AMINES STUDIED AND RELATED AMINES

Amine	k_B, M^{-1} sec^{-1}	pK_B
Me$_3$N	1.6×10^{-2}	4.10
Me$_2$NH	6.8×10^{-3}	3.19
MeNH$_2$	$<3.0 \times 10^{-3}$	3.37
N-Methylpiperidine	1.45×10^{-3}	3.66
Piperidine	$(7.6 \pm 1.3) \times 10^{-3}$	2.86
Piperazine	3.1×10^{-3}	4.10
N-Methylmorpholine	1.83×10^{-4}	6.61
Morpholine	7.6×10^{-4}	5.59

0 ionic strength) and analogous data for the N-methyl derivatives of the secondary amines studied[3] and for methylamine.[4] The pK values for the methylamines are due to the work of Everett and Wynne-Jones;[12] the value for N-methylmorpholine was estimated from data at 25° [13] by the method of Perrin;[14] and the value for N-methylpiperidine calculated by interpolation between values at 30 and 59.6°.[21]

(21) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5444 (1957).

A Brønsted plot of the data in Table V is shown in Figure 1. In this plot the data for piperazine have been corrected for the two identical NH groups by dividing both k_B and K_B by 2. No additional symmetry corrections were made to put the data for the primary, secondary, and tertiary amines on a common basis. Such corrections would not have changed any of the conclusions we have drawn from the data. The points for the four secondary amines studied lie fairly near a straight line, but the line in the figure was drawn through the three points for morpholine, piperazine, and piperidine, in which the amino nitrogen atoms have an essentially constant steric environment. The slope of this line (0.36) is smaller than that observed for unhindered pyridines (0.49), but perhaps by no more than the combined experimental uncertainties.

Other workers have found in several cases that tertiary amines are more effective basic catalysts at a given basicity than secondary amines, which are in turn more effective than primary amines.[22] Our results suggest that this is also true in the deuterium exchange of isobutyraldehyde-2-d if the tertiary amines have small enough steric requirements. The decrease in reactivity observed on going from trimethylamine to dimethylamine continues on going to methylamine.[23] There is evidence that the methyl groups in N-methylmorpholine and N-methylpiperidine are largely equatorial.[25a] If this is true it would, in the reactions with isobutyraldehyde-2-d, require either that the aldehyde approach the stable form of the amine from the hindered axial direction or that the amine be transformed to its less stable axial-methyl conformer before attack on the aldehyde. The latter alternative seems more plausible in view of the rather marked hindrance to attack on the aldehyde. It may be noted that trimethylamine is about 14 times as reactive as it would have to be to fall on a Brønsted line described by the points for N-methylmorpholine and N-methylpiperidine. This corresponds to an increment in the free energy of activation of 1.6 kcal/mole, which is rather near the 1.7 kcal/mole listed as the "most recommended value" for the conformational energy of a methyl group in a cyclohexane ring.[25b] In the cases of morpholine, piperazine, and piperidine, where much less energy would be required to place the amino *hydrogen* atom in the axial position, the six-membered ring amines fall near the same Brønsted line that dimethylamine does.

Experimental Section

All ultraviolet measurements were made using a 1.00-cm cell in a Carey spectrophotometer, Model 14. Kinetic runs were made by the technique described previously,[2] in which the deuterium content of the isobutyraldehyde was determined by nmr measurements directly on the reaction solution, which was in an

(22) *Cf.* R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 175–177.

(23) The value of k_B recorded for methylamine is a maximum value because a certain kinetic term could be due either to attack of methylamine on isobutyraldehyde or of hydroxide ions on the N-methyliminium ion derived from isobutyraldehyde.[24] On the basis of a linear-free-energy relationship,[24] however, the term in question is believed to be very largely due to attack of methylamine on the aldehyde.

(24) J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *J. Org. Chem.*, **32**, 2205 (1967).

(25) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1966: (a) Section 4-6b; (b) 2-2b.

nmr tube. As in the previous case, the uncertainty in the rate constants obtained is estimated to be on the order of 10%.

Catalysis of α-Hydrogen Exchange. VI. Isobutyraldehyde-2-d Exchange in the Presence of Methylammonium Ions and Various Buffers[1]
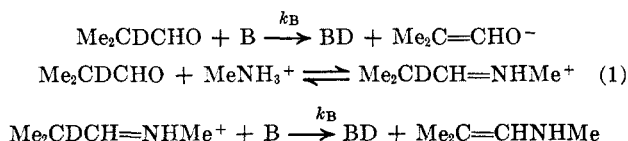
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The kinetics of the catalysis of the dedeuteration of isobutyraldehyde-2-d by methylammonium chloride were studied in the presence of pyridine, 3,4-lutidine, and N-methylmorpholine buffers. Combination of the resultant data with earlier observations shows that a Brønsted plot for the dedeuteration of the iminium ion Me₂CDCH=NHMe⁺ by various bases does not give a straight line. The deviations from linearity, some of which are attributed to steric hindrance, are quite similar to those observed in the Brønsted plot for the direct dedeuteration of isobutyraldehyde-2-d by attack of the same bases. In fact, a log–log plot of the rate constants for attack on the aldehyde vs. rate constants for attack on the iminium ion gives a close approach to a straight line. This observation supports the assumption that the rate-controlling step in the methylammonium ion catalyzed reaction is attack on the intermediate iminium ion. As expected, the iminium ion is less selective than the aldehyde in donating deuterium to bases.

The rate of loss of deuterium from isobutyraldehyde-2-d was studied in the presence of methylamine–methylammonium ion buffers, where the aldehyde exists largely in the form of its N-methylimine.[3] The major term in the kinetic equation was found to be of the form $k[\text{Me}_2\text{CDCH}{=}\text{NMe}][\text{MeNH}_3{}^+]$ or equivalently, $k'[\text{Me}_2\text{CDCH}{=}\text{NHMe}^+][\text{MeNH}_2]$, and the dedeuteration corresponding to this term was attributed to rate-controlling attack of methylamine on the iminium ion. The reaction rate was also studied in the presence of acetate buffers and 2,6-lutidine buffers, where the hydrogen ion concentration is much higher than in the case of methylamine buffers and the amount of aldehyde present as imine or iminium ion is too small to detect directly.[4] Under these conditions the observed reaction rate agreed with a kinetic equation containing several terms of the form $k[\text{Me}_2\text{CDCHO}][\text{MeNH}_3{}^+][\text{base}]$. These terms were attributed to rate-controlling attack of the various bases on N-methyliminium ions present in small concentrations in equilibrium with aldehyde and methylammonium ions, as shown in the following reaction mechanism. When the hindered

$$\text{Me}_2\text{CDCHO} + \text{B} \xrightarrow{k_\text{B}} \text{BD} + \text{Me}_2\text{C}{=}\text{CHO}^-$$

$$\text{Me}_2\text{CDCHO} + \text{MeNH}_3{}^+ \rightleftharpoons \text{Me}_2\text{CDCH}{=}\text{NHMe}^+ \quad (1)$$

$$\text{Me}_2\text{CDCH}{=}\text{NHMe}^+ + \text{B} \xrightarrow{k_\text{B}} \text{BD} + \text{Me}_2\text{C}{=}\text{CHNHMe}$$

base 2,6-lutidine and the relatively weakly basic acetate ions are used as buffer components the buffer base does not completely dominate the reaction.[4] It was therefore possible to learn something about the reactivity toward iminium ions of the much less abundant bases methylamine and hydroxide ions and the very weak base, water. Where reactivities were determined in two different ways, somewhat different results were obtained. These differences were attributed largely to specific medium effects on rate and equilibrium constants; such effects were found to be rather large in the presence of 2,6-lutidine buffers. The necessity of allowing for specific medium effects somewhat weakens the argument that kinetic terms of the form $k[\text{Me}_2\text{CDCHO}][\text{MeNH}_3{}^+][\text{base}]$ or $k'[\text{Me}_2\text{CD-CH}{=}\text{NHMe}^+][\text{base}]$ are due to the same reaction mechanism with the same rate-controlling step under all the conditions that we have studied. To obtain further evidence on this point, we have now investigated the dedeuteration of isobutyraldehyde-2-d in the presence of methylammonium ions and several additional buffers in order to compare the relative reactivity of various bases toward isobutyraldehyde and its N-methyliminium ion.

Results

If the loss of deuterium from isobutyraldehyde-2-d occurs by a process like that outlined (up to the rate-controlling steps) in mechanism 1, then the rate of reaction should follow eq 2, which is analogous to the kinetic equations used previously.[3,4] In this equation

$$-d[\text{AD}]/dt = [\text{AD}]\sum_i k_{\text{B}_i}[B_i] + [\text{HImD}^+]\sum_i k_{\text{B}_i}{}'[B_i] \quad (2)$$

AD is the deuterated aldehyde (free and hydrated), HImD⁺ is Me₂CDCH=NHMe⁺, k_{B_i} is the rate constant for the attack of the ith base (B_i) on isobutyr-

(1) (a) This investigation was supported in part by Public Health Service Research Grants AM 06829 MCB and AM 10378 from the National Institute of Arthritis and Metabolic Diseases. (b) Abstracted in part from the Ph.D. thesis of J. G. Houston, Georgia Institute of Technology, 1964. (c) For the preceding paper in this series, see J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967).

(2) (a) Author to whom inquiries should be addressed at The Ohio State University. (b) National Defense Education Act Fellow, 1960–1963.

(3) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).

(4) J. Hine, F. C. Kokesh, K. G. Hampton, and J. Mulders, *ibid.*, **89**, 1205 (1967).