Catalysis of α-Hydrogen Exchange. IX. Isobutyraldehyde-2-*d* Exchange in the Presence of Amino Acids[1]

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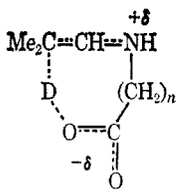
Catalysis of the deuterium exchange of isobutyraldehyde-2-*d* by glycine, β-alanine, γ-aminobutyric acid, δ-aminovaleric acid, and ε-aminocaproic acid has been studied in the presence of pyridine and acetate buffers. In all cases there appears to be catalysis due to the reversible formation of an iminium ion from the aldehyde and amino acid followed by the removal of deuterium from the iminium ion by the various bases present. In no case could bimolecular catalysis *via* the internal attack of the carboxylate anion group be established.

Previous work has provided evidence that the dedeuteration of isobutyraldehyde-2-*d* in the presence of buffered solutions of primary amine salts involves the rate-controlling attack of the buffer base (B^-) on the N-isobutylidenealkylammonium ion to give an enamine.[3-6] We have now studied the catalytic activity

$$Me_2CDCHO + RNH_3^+ \rightleftharpoons Me_2CDCH{=}NHR^+$$
$$Me_2CDCH{=}NHR^+ + B^- \longrightarrow BD + Me_2C{=}CHNHR$$

of several ω-amino-*n*-alkanoic acids, species in which a primary amine salt and a basic group are both present in the same molecule, in order to learn whether bifunctional catalysis would occur. The transition state in such a bifunctionally catalyzed reaction would have the form shown below.



Results

The dedeuteration of isobutyraldehyde-2-*d* was followed by nmr measurements. Catalysis by glycine, β-alanine, γ-aminobutyric acid, δ-aminovaleric acid, and ε-aminocaproic acid was studied in the presence of pyridine buffers and, except in the case of glycine, acetate buffers. Within any given run the reaction obeys the first-order rate equation (eq 1) where k_p is the

$$-d[AD]/dt = k_p[AD] \quad (1)$$

pseudo-first-order rate constant and AD is the deuterated aldehyde. We have assumed that the dedeuteration takes place *via* rate-controlling attack of the various bases present on isobutyraldehyde-2-*d* and the two different iminium ions that it can form on reaction with an amino acid. In addition, we have considered the possibility of removal of deuterium (with the rate constant k_i') by the internal carboxy group in the species $Me_2CDCH{=}\overset{+}{N}H(CH_2)_nCO_2^-$ (*i.e.*, eq 2) where

$$-d[AD]/dt = \sum_j (k_{B_j}[AD] + k_{B_j}'[HImD] + k_{B_j}''[HImDH^+]) + k_i'[HImD] \quad (2)$$

$HImD = Me_2CDCH{=}\overset{+}{N}H(CH_2)_nCO_2^-$ and $HImDH^+ = Me_2CDCH{=}\overset{+}{N}H(CH_2)_nCO_2H$. Combining the equilibrium constant for the formation of imine (ImD^-)

$$K = \frac{[ImD^-]}{[AD][Z^-]}$$

$$K_1 = \frac{[H^+][Z^-]}{[HZ]}$$

$$K_{Im} = \frac{[H^+][ImD^-]}{[HImD]}$$

$$K_c = \frac{[H^+][HImD]}{[HImDH^+]}$$

from the amino acid anion (Z^-) and various acidity constants with eq 1 and 2, we obtain eq 3.

$$k_p = \sum_j \left(k_{B_j} + \frac{k_{B_j}'KK_1[HZ]}{K_{Im}} + \frac{k_{B_j}''KK_1[H^+][HZ]}{K_cK_{Im}}\right) + \frac{k_i'KK_1[HZ]}{K_{Im}} \quad (3)$$

Since values of k_{B_j} are known for several bases, k_p may be "corrected" by substracting these known contributions to the total reaction rate. Thus we define k_{cor} by eq 4 where B is the buffer base, pyridine, or acetate ion. In all cases studied the term $k_h[OH^-]$ was less than 1% as large as $k_B[B]$. Since attack by hydroxide ions thus contributed negligibly to exchange *via* the free aldehyde, we assumed that dedeuteration of the iminium ions *via* attack by hydroxide ions was also negligible. We also neglected basic catalysis by the amino acid anion Z^-. Catalysis by the small amount of free RNH_2 in equilibrium with other RNH_3^+ species (of acidity comparable to that of HZ) is negligible at the pH's at which the present runs were made.[4,6] Significant catalysis by the carboxylate anion group of Z^- is even less plausible. According to earlier work, an acetate ion is more than 2800 times as reactive as a water molecule in removing deuterium from the N-methyliminium ion derived from isobutyraldehyde-2-*d* (and pyridine is even more reactive).[4,5] We assumed that the relative reactivities toward $Me_2CDCH{=}\overset{+}{N}H$-

$$k_{cor} = k_p - k_h[OH^-] - k_w[H_2O] - k_B[B] \quad (4)$$

(1) (a) This investigation was supported in part by Public Health Service Grants 06829MCB and AM10378 from the National Institute of Arthritis and Metabolic Diseases. (b) For the preceding paper in this series, see J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

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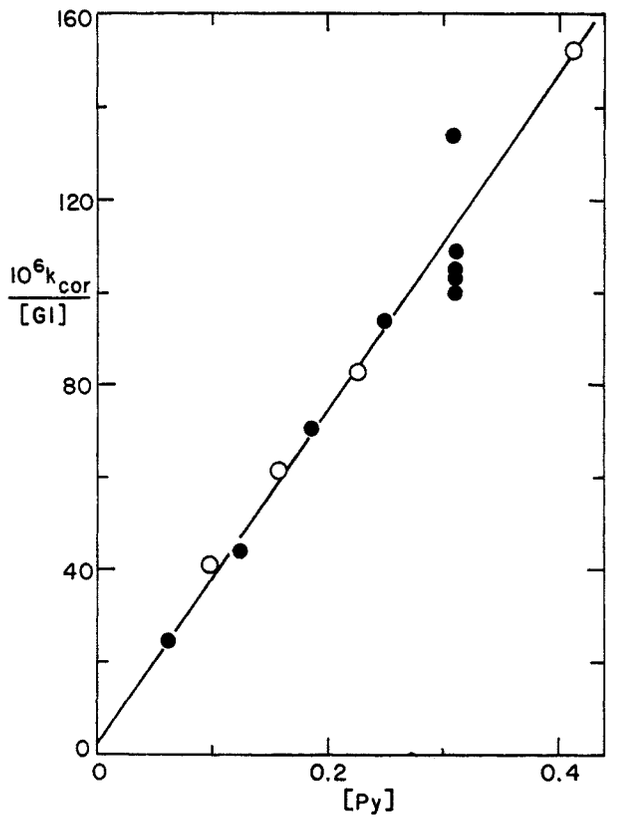

Figure 1.—Plot of $10^6 k_{cor}$/[glycine] *vs.* pyridine concentration: solid circles, at pH 5.20; open circles, at pH's 4.58, 4.82, 5.02, and 5.40 (in order of increasing [Py]).

$(CH_2)_nCO_2H$'s are similar and therefore neglected the k_w'' term. With the neglect of these terms, eq 3 and 4 may be combined to give eq 5.

$$k_{cor} = k_{hz}[HZ] + (k_{hz}'[HZ] + k_B'[B] + k_w'[H_2O] + k_i') \times \frac{KK_1[HZ]}{K_{Im}} + (k_{hz}''[HZ] + k_B''[B]) \frac{KK_1[H^+][HZ]}{K_eK_{Im}} \quad (5)$$

Division by [HZ], rearrangement, and collection of terms gives eq 6.

$$k_{cor}/[HZ] = C + C_b[B] + C_{bh}[B][H^+] + C_{hz}[HZ] + C_{hzh}[HZ][H^+] \quad (6)$$

$$C = k_{hz} + R(k_i' + k_w'[H_2O])$$
$$C_b = Rk_B'$$
$$C_{hz} = Rk_{hz}'$$
$$R = KK_1/K_{Im}$$
$$C_{bh} = Rk_B''/K_e$$
$$C_{hzh} = Rk_{hz}''/K_e$$

Data on the dedeuteration of isobutyraldehyde-2-*d* in the presence of glycine and pyridine buffers are shown in Table I. The importance of the last two terms in eq 6 may be measured by the extent to which $k_{cor}/[HZ]$ (in this case, $k_{cor}/[Gl]$) increases with increasing amino acid concentration at constant concentrations of buffer and hydrogen ion. From the first five entries in Table I there is seen to be no clearly observable increase of this type. Thus we conclude that the last two terms in eq 6 are negligible in this case. Figure 1 contains a plot of all the values of $k_{cor}/[Gl]$ in Table I *vs.* the pyridine concentration. The fact that the best straight line through these points passes within the experimental error of the origin shows that the first term in eq 6 is negligible, and the fact that the four points at pH's other than 5.20 are about as close to the line as the nine points at pH 5.20 are shows that the C_{bh} term is also negligible. The slope of the line, $36 \times 10^{-5}\ M^{-2}\ sec^{-1}$, is equal to C_b, which we shall denote C_{Py} in this case.

It is not surprising that basic catalysis by glycine is negligible in the presence of significant amounts of pyridine. Pyridine removes deuterium from isobutyraldehyde-2-*d* nine times as rapidly as acetate ion does,[7] and the carboxylate anion group of an acetate ion[8] is more than 100 times as basic as that of the zwitterion form of glycine.[9] Catalysis by the other amino acids was studied in the presence of both acetate and pyridine buffers. Basic catalysis by these amino acids, which are 15 to 100 times as basic as glycine, should contribute more to the reactions carried out using acetate buffers than to those in which pyridine buffers were used. Kinetic data obtained using acetate buffers with β-alanine, γ-aminobutyric acid, and δ-aminovaleric acid are listed in Tables II, III, and IV, respectively. For

TABLE I
DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF GLYCINE AND PYRIDINE BUFFERS AT 35°[a]

Concentration, *M*			$10^6 k_p$,	$10^6 k_{cor}$,	$10^6 k_{cor}$/[Gl],
Py	PyH^+	Gl	sec^{-1}	sec^{-1}	$M^{-1}\ sec^{-1}$
0.310	0.233	0.085	13.9	11.4	134
0.310	0.233	0.170	19.5	17.0	100
0.310	0.233	0.255	28.8	26.3	103
0.310	0.233	0.340	39.7	37.2	109
0.310	0.233	0.425	47.0	44.5	105
0.062	0.047	0.425	11.1	10.6	24.9
0.124	0.093	0.425	19.7	18.7	44.0
0.186	0.140	0.425	31.5	30.0	70.6
0.248	0.186	0.425	42.0	40.0	94.1
0.097[b]	0.306	0.425	18.3	17.5	41.2
0.157[c]	0.286	0.425	27.5	26.2	61.6
0.226[d]	0.262	0.425	37.0	35.2	82.8
0.414[e]	0.196	0.425	67.7	64.4	152

[a] Initial concentration of Me_2CDCHO = 0.319 *M*. The pH is 5.20 in all runs except where stated otherwise. [b] pH 5.48. [c] pH 4.82. [d] pH 5.02. [e] pH 5.40.

TABLE II
DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF β-ALANINE AND ACETATE BUFFERS AT 35°[a]

Concentration, *M*			[βA],	$10^6 k_p$,	$10^6 k_{cor}/[\beta A]$, $M^{-1}\ sec^{-1}$	
AcO^-	HOAc	pH	*M*	sec^{-1}	Found	Calcd
0.511	0.093	5.21	0.504	22.2	43.0	43.2
0.285	0.048	5.25	0.505	15.0	29.2	29.6
0.057	0.007	5.40	0.511	7.99	15.5	16.0
0.508	0.095	5.20	0.342	15.0	42.5	40.9
0.506	0.097	5.19	0.256	10.5	39.2	39.6
0.546	0.457	4.55	0.469	31.4	65.0	64.5
0.533	0.470	4.53	0.317	20.3	62.6	61.5
0.525	0.478	4.52	0.237	14.2	58.2	59.8
0.317	0.236	4.60	0.473	20.8	43.3	42.3
0.073	0.030	4.87	0.492	9.04	18.2	19.1
0.520	0.183	4.93	0.495	23.2	45.9	48.5
0.514	0.188	4.91	0.336	15.0	43.3	46.0
0.511	0.192	4.90	0.251	12.2	46.6	44.7
0.294	0.094	4.97	0.496	18.2	36.2	32.8
0.061	0.012	5.19	0.504	8.97	17.7	16.7

[a] Initial concentration of Me_2CDCHO = 0.079 *M*.

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(9) E. J. King, *J. Amer. Chem. Soc.*, **67**, 2178 (1945).

TABLE III

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF γ-AMINOBUTYRIC ACID AND ACETATE BUFFERS AT 35°[a]

Concentration, *M*			[γAB],	10^6k_p,	$10^6k_{cor}/[\gamma AB]$, M^{-1} sec^{-1}	
AcO⁻	HOAc	pH	*M*	sec^{-1}	Found	Calcd
0.088	0.006	5.62	0.479	14.3	29.7	30.9
0.033	0.001	5.85	0.483	13.4	27.7	26.4
0.526	0.077	5.31	0.465	33.3	70.6	63.8
0.520	0.083	5.27	0.330	23.4	69.6[b]	56.2
0.516	0.087	5.25	0.246	13.2	51.6	51.4
0.599	0.404	4.65	0.392	42.7	108	105
0.358	0.195	4.74	0.408	29.4	71.5	73.1
0.085	0.018	5.16	0.456	17.0	37.2	35.7
0.576	0.427	4.61	0.274	26.6	95.5	94.7
0.562	0.441	4.58	0.208	19.3	90.2	88.6
0.547	0.156	5.02	0.444	34.3	76.3	74.7
0.315	0.073	5.11	0.451	23.8	52.2	53.8
0.067	0.006	5.50	0.474	13.8	28.9	30.4
0.537	0.166	4.98	0.313	21.1	65.9	66.3
0.530	0.173	4.96	0.240	14.1	56.7	61.4

[a] Initial concentration of Me_2CDCHO = 0.068 *M*. [b] This value was omitted from the least-squares treatment since its deviation was more than four times the average deviation of the other values.

TABLE IV

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF δ-AMINOVALERIC ACID AND ACETATE BUFFERS AT 35°[a]

Concentration, *M*			[δAV],	10^6k_p,	$10^6k_{cor}/[\delta AV]$, M^{-1} sec^{-1}	
AcO⁻	HOAc	pH	*M*	sec^{-1}	Found	Calcd.
0.520	0.084	5.27	0.142	6.15	39.9[b]	48.3
0.292	0.041	5.33	0.145	4.62	30.1	31.6
0.059	0.004	5.64	0.153	2.30	14.7	14.5
0.540	0.063	5.41	0.410	29.6	71.2	67.3
0.531	0.072	5.34	0.266	15.0	54.5	57.3
0.564	0.439	4.58	0.098	8.69	84.4	85.8
0.333	0.220	4.66	0.104	5.82	53.5	53.2
0.081	0.022	5.03	0.131	2.52	18.8	19.3
0.534	0.169	4.98	0.128	8.17	60.4	57.9
0.305	0.083	5.04	0.132	4.84	34.8	37.2
0.065	0.008	5.39	0.147	2.32	15.4	15.7
0.644	0.358	4.73	0.306	34.6	112	109
0.606	0.397	4.66	0.191	18.4	94.3	96.7
0.573	0.130	5.12	0.377	31.5	82.2	78.0
0.555	0.148	5.05	0.242	18.3	73.6	67.5

[a] Initial concentration of Me_2CDCHO = 0.068 *M*. [b] This value was omitted from the least-squares treatment since its deviation was more than four times the average deviation of the other values.

each of these amino acids, the five constants in eq 6 were evaluated by the method of least-squares.[10a] The values obtained included small negative values of *C* for γ-aminobutyric acid and δ-aminovaleric acid. Since such values are meaningless, these least-squares treatments were repeated with the values of *C* set at zero. The values of C_{hz}, C_{hzh}, C_{Ac}, and C_{Ach} (the latter two constants are C_b and C_{bh} for the case where the buffer base is acetate ion) obtained were capable of reproducing the values of $k_{cor}/[HZ]$ used with average deviations of 3.5 and 3.8%, respectively.[10b] In the case of β-alanine, a small positive value of *C* was obtained, which, with the other constants obtained, was capable of reproducing the $k_{cor}/[HZ]$ values with an average deviation of 3.5%. It cannot be claimed that this value of *C* is really significant, however, since the constants obtained when *C* was set equal to zero were capable of reproducing $k_{cor}/[HZ]$ with an average deviation of 4.0%.

In the case of ε-aminocaproic acid, for which results are listed in Table V, not enough measurements were made to permit the reliable determination of C_{Ach} and C_{hzh}. Judging from the results obtained for the other amino acids, the C_{Ach} and C_{hzh} terms in eq 6 should never comprise more than about 10% of the overall reaction rate in any of the runs listed in Table V. Therefore it was assumed that the ratios C_{Ac}/C_{Ach} and C_{hz}/C_{hzh} have the same value for ε-aminocaproic acid as for δ-aminovaleric acid. With this assumption and the neglect of *C*, values of C_{Ac} and C_{hz} were calculated by the method of least squares. From these values and the values of C_{Ach} and C_{hzh} that may be calculated from them, the values of $k_{cor}/[\epsilon AC]$ in Table V may be calculated with an average deviation of 1.3%. Thus, with this amino acid too, *C* is negligible.

TABLE V

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF ε-AMINOCAPROIC ACID AND ACETATE BUFFERS AT 35°[a]

Concentration, *M*			[εAC],	10^6k_p,	$10^6k_{cor}/[\epsilon AC]$, M^{-1} sec^{-1}	
AcO⁻	HOAc	pH	*M*	sec^{-1}	Found	Calcd
0.547	0.056	5.47	0.428	33.1	76.3	76.5
0.062	0.001	6.11	0.458	18.8	40.8	40.1
0.338	0.025	5.60	0.460	29.4	63.1	62.6
0.119	0.004	5.91	0.472	21.3	44.8	45.8

[a] Initial concentration of Me_2CDCHO = 0.080 *M*.

The values of the kinetics constants in eq 6 for the various amino acids studied in the presence of acetate buffers are listed in Table VI. Also listed are values of

TABLE VI

CATALYSIS OF THE DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* BY ω-AMINOALKANOIC ACIDS IN THE PRESENCE OF ACETATE AND PYRIDINE BUFFERS AT 35°

Amino acid	pK_2	10^6C, M^{-1} sec^{-1}	10^5C_{Ac}, M^{-2} sec^{-1}	C_{Ach}, M^{-3} sec^{-1}	10^5C_{hz}, M^{-2} sec^{-1}	C_{hzh}, M^{-3} sec^{-1}	10^5C_{Py}[a] M^{-2} sec^{-1}
β-Alanine	3.54	6[b]	5.05	1.39	1.22	0.31	37
γ-Aminobutyric acid	4.05	0[c]	5.80	2.17	4.69	2.57	44
δ-Aminovaleric acid	4.40	0[c]	5.64	2.59	6.15	3.92	34
ε-Aminocaproic acid	4.51	0[d]	5.86	2.69[e]	7.56	4.82[e]	38

[a] For glycine, C_{Py}, the only constant that could be determined, was 36 × 10^{-5}. [b] This value may not be significantly different from zero. [c] A least-squares treatment gave a negative value for this constant. It was then assumed to be zero. [d] Assumed. [e] Probably relatively unreliable.

pK_2, where K_2 is defined as shown below. The C_{Ach}

$$K_2 = \frac{[H^+][HZ]}{[HZH^+]}$$

and C_{hzh} values (especially for ε-aminocaproic acid) are probably less reliable than the C_{Ac} and C_{hz} values, since the C_{Ac} and C_{hz} terms contributed more to the overall rates of reaction.

(10) (a) In all the least-squares treatments, it was the sum of the squares of the *percentage* deviations that was minimized. (b) Since the computer calculations were made using more significant figures than listed in the present paper, the average deviations obtained may be slightly different from those that would be calculated from the figures given here.

Experiments using pyridine buffers had been carried out on all the amino acids and the reactions found to be dominated by processes involving pyridine. Only then was the reaction studied in the presence of acetate buffers, whose diminished catalytic activity permits the first, fourth, and fifth terms in eq 6 to be evaluated more reliably. Since C, C_{hz}, and C_{hzh} can therefore not be determined reliably in the presence of pyridine buffers, we have used the constants obtained with acetate buffers in a new corrected constant, k_{cor}', which is defined as in eq 7. With this definition and the nota-

$$k_{cor}' = k_{cor}/[HZ] - C - C_{hz}[HZ] - C_{hzh}[HZ][H^+] \quad (7)$$

tion C_{Py} and C_{Pyh} for C_b and C_{bh} in the present case, where the base is pyridine, eq 6 becomes eq 8.

$$k_{cor}' = C_{Py}[Py] + C_{Pyh}[Py][H^+] \quad (8)$$

The results obtained using pyridine buffers are listed in Tables VII–X. Since pyridine is more basic than acetate ions these runs were, on the average, carried out in more basic solutions than those in which acetate buffers were used. Perhaps because of this the second term in eq 8 proved to be too small to be clearly detectable. If this term contributed significantly to the overall reaction rate, a plot of k_{cor}' *vs.* the concentration of pyridine should show the points run at high acidity to be above the best straight line through all the points and the points at low acidity below this line. As the sample plot of the data obtained in the presence of γ-aminobutyric acid (Figure 2) shows, this is not observed. Hence we have neglected the second term in eq 8 and assumed that the slope of the best straight line in plots like Figure 2 is equal to C_{Py}. The resultant values of C_{Py} are listed in Table VI.

TABLE VII

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF PYRIDINE BUFFERS AND β-ALANINE AT 35°[a]

Concentration, *M*						
Py	PyH^+	pH	[βA], *M*	10^6k_p, sec^{-1}	$10^6k_{cor}/[\beta A]$, M^{-1} sec^{-1}	$10^6k_{cor}'$, M^{-1} sec^{-1}
0.311	0.232	5.21	0.068	10.4	116	109
0.313	0.230	5.22	0.135	20.0	130	122
0.314	0.229	5.22	0.203	27.5	123	114
0.316	0.227	5.22	0.270	38.5	133	123
0.317	0.226	5.23	0.338	46.5	130	119
0.068	0.041	5.30	0.339	11.9	33.3	22.7
0.130	0.087	5.25	0.339	19.7	55.2	44.5
0.192	0.134	5.24	0.339	29.0	81.1	70.4
0.255	0.179	5.23	0.338	36.3	102	91
0.119	0.284	4.70	0.323	19.2	56.3	44.4
0.172	0.271	4.88	0.330	25.7	73.6	62.3
0.236	0.252	5.05	0.335	35.5	100	89
0.418	0.192	5.42	0.341	58.0	160	149

[a] Initial concentration of Me_2CDCHO = 0.319 *M*.

TABLE VIII

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF PYRIDINE BUFFERS AND γ-AMINOBUTYRIC ACID AT 35°[a]

Concentration, *M*						
Py	PyH^+	pH	[γAB], *M*	10^6k_p, sec^{-1}	$10^6k_{cor}/[\gamma AB]$, M^{-1} sec^{-1}	$10^6k_{cor}'$, M^{-1} sec^{-1}
0.315	0.228	5.22	0.081	14.4	147	142
0.320	0.223	5.24	0.161	28.0	158	148
0.324	0.219	5.25	0.242	40.9	158	143
0.329	0.214	5.27	0.323	57.6	170	150
0.333	0.210	5.28	0.405	65.2	154	130
0.077	0.032	5.46	0.413	25.2	59.6	36.5
0.143	0.075	5.36	0.409	36.7	86.8	63.0
0.207	0.119	5.32	0.407	46.0	109	85
0.270	0.164	5.30	0.406	61.3	146	122
0.152	0.251	4.86	0.373	35.7	92.5	62.1
0.199	0.244	4.99	0.386	44.7	112	83
0.257	0.231	5.13	0.397	58.5	142	116
0.429	0.181	5.45	0.413	88.8	207	184

[a] Initial concentration of Me_2CDCHO = 0.319 *M*.

TABLE IX

DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF PYRIDINE BUFFERS AND δ-AMINOVALERIC ACID AT 35°

Concentration, *M*							
AD[a]	Py	PyH^+	pH	[δAV], *M*	10^6k_p, sec^{-1}	$10^6k_{cor}/[\delta AV]$, M^{-1} sec^{-1}	$10^6k_{cor}'$, M^{-1} sec^{-1}
0.319	0.781	0.185	5.71	0.185	54.8	263	250
0.290	0.680	0.201	5.61	0.201	54.8	246	232
0.266	0.596	0.213	5.53	0.213	50.7	216	200
0.246	0.526	0.223	5.45	0.223	40.8	164	147
0.228	0.465	0.231	5.38	0.231	39.3	154	136
0.213	0.412	0.238	5.32	0.238	35.9	137	118
0.213	0.526	0.124	5.71	0.124	25.5	172	164
0.266	0.654	0.155	5.71	0.155	40.5	228	217

[a] Initial concentration of Me_2CDCHO.

TABLE X

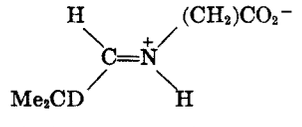
DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-*d* IN THE PRESENCE OF PYRIDINE BUFFERS AND ε-AMINOCAPROIC ACID AT 35°[a]

Concentration, *M*						
Py	PyH^+	pH	[εAC], *M*	10^6k_p, sec^{-1}	$10^6k_{cor}/[\epsilon AC]$, M^{-1} sec^{-1}	$10^6k_{cor}'$, M^{-1} sec^{-1}
0.360	0.065	5.83	0.042	7.83	118	114
0.361	0.062	5.84	0.086	15.6	148	141
0.363	0.060	5.86	0.129	22.8	154	143
0.366	0.058	5.88	0.174	27.0	138	124
0.368	0.056	5.90	0.217	36.5	155	137
0.078	0.0070	6.12	0.220	9.73	41	24
0.152	0.018	6.01	0.219	14.3	60	42
0.225	0.030	5.95	0.218	23.3	99	81
0.296	0.043	5.92	0.218	30.7	130	112

[a] Initial concentration of Me_2CDCHO = 0.319 *M*.

Discussion

The most significant result of this study is the observation that no detectable amount of bifunctional catalysis occurs. Thus, even in the exchange reactions carried out in the presence of acetate buffers, where the reactions are largely due to the attack of carboxylate anions on iminium ions, the carboxylate anion group in the iminium ion did not attack internally. By analogy to various imines derived from isobutyraldehyde, which exist so largely in the *trans* form that none of the *cis* isomer could be detected,[11] it seems probable that the imines, and hence the iminium ions, derived from isobutyraldehyde-2-*d* and amino acids exist very largely in the *trans* form which is shown below. From ex-



(11) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89**, 2669 (1967).

amination of molecular models it appears that none of the amino acids which we have used contain enough carbon atoms between the amino group and the carboxy group to permit internal dedeuteration by the carboxy group in a *trans* iminium ion. The stereochemistry of the intramolecular dedeuteration of iminium ions will be discussed in more detail in connection with cases in which it occurs.[1b]

Although not enough variations in the concentrations of various species were made to establish kinetic eq 6 unequivocally, the validity of the equation is supported not only by the good agreement with the rate data obtained but also by the plausibility of certain trends in the kinetic constants. For example, the relative rates at which acetate ions and a given amino acid dedeuterate the iminium ions derived from the amino acid should be about the same for the carboxy form as for the carboxylate–anion form of the iminium ion; that is, the ratios of k_{Ac}'/k_{hz}' and k_{Ac}''/k_{hz}'' should be of about the same magnitude. The values of the ratios, which are equal to C_{Ac}/C_{hz} and C_{Ach}/C_{hzh}, respectively, are shown in Table XI. For each amino acid the two ratios are within the experimental uncertainty of each other.

TABLE XI
RELATIVE RATE CONSTANTS FOR DEDEUTERATION BY AMINO ACIDS AND ACETATE IONS

Amino acid	k_{Ac}'/k_{hz}'	k_{Ac}''/k_{hz}''
β-Alanine	4.1	4.5
γ-Aminobutyric acid	1.2	0.9
δ-Aminovaleric acid	0.9	0.7
ε-Aminocaproic acid	0.8	0.6

Experimental Section

Materials.—Isobutyraldehyde-2-*d* was prepared as described previously. The glycine was an Eastman White Label product and the other amino acids were the best grades available from CalBiochem Co. (A grade β-alanine and γ-aminobutyric acid and C grade δ-aminovaleric acid hydrochloride and ε-aminocaproic acid).

p*K* Determinations.—A Radiometer PHM-26 pH meter was used in the titration of 0.1 *M* solutions of the amino acids and 0.5 *M* sodium chloride with 0.5 *M* hydrochloric acid. The p*K* values were calculated from the pH of the solutions at the half-equivalence point. The values obtained were quite near those that would be expected from reported measurements on β-alanine,[12] γ-aminobutyric acid,[13] δ-aminovaleric acid,[14] and ε-aminocaproic acid,[15] when allowance is made for differences in temperature and ionic strength.

Kinetics.—Kinetic runs in the presence of pyridine buffers were carried out by nmr measurements directly on the reaction solutions.[7] Those in the presence of acetate buffers were carried out by nmr analysis of chloroform extracts.[7] In the pyridine runs, the pH of the reaction solutions was measured. In the acetate runs the pH of the solutions was calculated from the p*K*'s of acetic acid[16] and the amino acid, both at ionic strength 0.5 *M*. In the acetate runs in which less than 0.5 *M* sodium acetate had been added, enough sodium chloride was added to bring the ionic strength to 0.5 *M*.

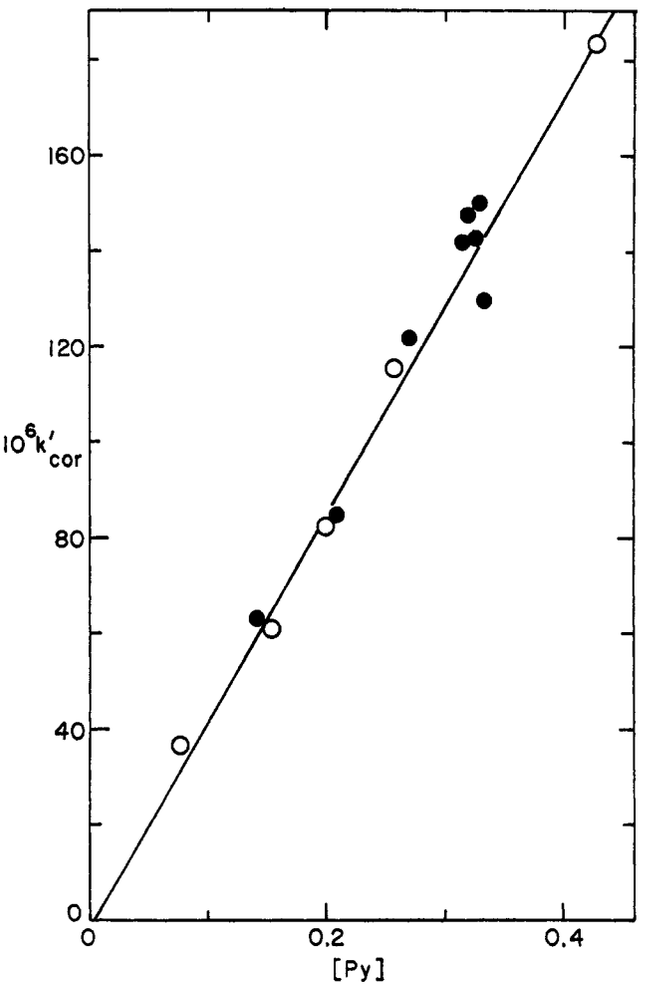


Figure 2.—Plot of $10^6k'_{cor}$ in the presence of γ-aminobutyric acid *vs.* pyridine concentration: solid circles, at pH 5.29 ± 0.07; open circles, at pH's 5.46, 4.86, 4.99, 5.13, and 5.45 in order of increasing pyridine concentration.

Registry No.—Isobutyraldehyde-2-*d*, 4303-51-9; glycine, 56-40-6; β-alanine, 107-95-9; γ-aminobutyric acid, 56-12-2; δ-aminovaleric acid, 660-88-8; ε-aminocaproic acid, 60-32-2.

(12) M. May and W. A. Felsing, *J. Amer. Chem. Soc.*, **73**, 406 (1951).
(13) E. J. King, *ibid.*, **76**, 1006 (1954).
(14) E. L. Duggan and C. L. A. Schmidt, *Arch. Biochem.*, **1**, 453 (1943).
(15) E. R. B. Smith and P. K. Smith, *J. Biol. Chem.*, **146**, 187 (1942).
(16) 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.