Catalysis of α-Hydrogen Exchange.   I.   The Reaction of Isobutyraldehyde-2-d with Tertiary Amines and Oxygen Bases[1a]

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Isobutyraldehyde-2-d has been prepared by the reaction of isobutenyl acetate with heavy water in the presence of an acid catalyst, and the kinetics of its deuterium exchange in the presence of tertiary amines, oxygen bases, and strong acid have been studied, using n.m.r. measurements to follow the reaction. Only the basic components of the buffers used catalyze the reaction significantly. The catalysis constants for three unhindered pyridines and for seven phenoxide ions fit the Brφnsted catalysis equation satisfactorily with β values around 0.5. Pyridines with 2- and 6-substituents are less reactive than predicted by the Brφnsted equation, by more than 100-fold in the cases of 2,6-lutidine and 2,4,6-collidine. These decreases in reactivity and analogous decreases that have been observed in the reactions of pyridine and its methyl derivatives with acetone, methyl isopropyl ketone, and pinacolone are explained in terms of the commonly accepted transition state for the formation of carbanions from aldehydes and ketones, in which the carbon–hydrogen bond being broken is held almost parallel to the π orbitals of the carbonyl group. The most reactive catalysts for their basicity are the saturated tertiary amines trimethylamine and 1,4-diazabicyclo[2.2.2]octane. Other amines of this type are less reactive, probably because of steric hindrance, and, in the case of β-hydroxyamines, internal hydrogen bonds. The magnitude of the decrease in reactivity due to these effects appears to be the largest, among the amines studied, in the case of tris-2-hydroxypropylamine, whose reactivity is smaller by about 3000-fold than would be expected for an unhindered amine. The decreased reactivity of N-methylimidazole, relative to that of unhindered pyridines of similar basicity, is attributed to the fact that the molecular geometry of an imidazole changes much more on protonation than does that of a pyridine.

Introduction

The removal of the α-hydrogen atom from carbonyl compounds without its bonding electron pair is a reaction of considerable importance, being involved in such diverse processes as deuterium exchange, halogenation, racemization, epimerization, aldol condensation, elimination reactions, etc. Although the reaction has been the subject of valuable and penetrating mechanistic investigations for many years,[2a] there are still many gaps in our understanding of the subject. Aldehydes as substrates and amines as catalysts have received relatively little attention, perhaps because of their frequent incompatibility with the halogens which are commonly used in rate studies. An investigation of the action of various species as monofunctional catalysts in α-hydrogen removal reactions was also of interest in relation to a planned study of polyfunctional catalysis in such reactions.

Accordingly we have studied α-hydrogen removal from isobutyraldehyde. The reaction has been followed by n.m.r. measurements of the extent of deuterium exchange of isobutyraldehyde-2-d. Since isobutyraldehyde has only one α-hydrogen atom the reaction is not complicated by the presence of various partially deuterated species. The solubility of isobutyraldehyde in water is sufficient to permit the attainment of high enough concentrations in aqueous solution for reliable n.m.r. measurements.

In the present investigation it has been necessary to use the results of a study of the aldolization, hydration, and hydrate acidity of isobutyraldehyde.[3]

Results

Isobutyraldehyde-2-d.   At first, isobutyraldehyde-2-d was prepared by repeated base-catalyzed exchange of isobutyraldehyde with deuterium oxide. However, this method resulted in loss of much of the starting aldehyde and the use of rather large amounts of deuterium oxide; it was time consuming and gave only a slow asymptotic approach to isotopic purity. Exchange seems fundamentally a poorer method for preparing isotopically labeled compounds than a method in which the isotope is introduced into a molecule at a point where there was originally no atom of any isotope of the element in question. Reasoning from this principle, we prepared isobutyraldehyde-2-d by the reaction of deuterium oxide with isobutenyl acetate (prepared from isobutyraldehyde and acetic anhydride by the method of Bedoukian[4]) in the presence of a little deuterium sulfate.

$$(CH_3)_2C\!=\!CHOAc + D_2O \xrightarrow{\;D_2SO_4\;} (CH_3)_2CDCHO + DOAc$$
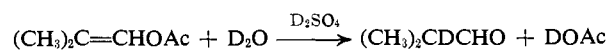
The n.m.r. spectrum of isobutyraldehyde-2-d consists of a triplet due to the methyl protons, which are split by the α-deuterium,[5] and a broad singlet due to the aldehyde proton, whose coupling constant to the α-hydrogen is much smaller, so that the expected triplet should be much harder to resolve. The chemical shifts are the same as those of the protium compound[3,7,8] and the coupling constants are about

(1) (a) Abstracted in part from the Ph.D. Thesis of James G. Houston, 1965; (b) present address: The Ohio State University, Columbus, Ohio 43210; (c) National Defense Education Act Fellow, 1960–1963.

(2) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962: (a) Section 5-2, Chapter 10, and Section 11-3; (b) Section 1-4a; (c) Section 5-3b.

(3) J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, 30, 1184 (1965).

(4) P. Z. Bedoukian, *J. Am. Chem. Soc.*, 66, 1325 (1944).

(5) Deuterium has a nuclear spin of 1.[6]

(6) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Company, Inc., New York, N. Y., 1959, p. 19.

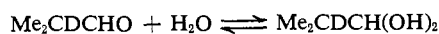(7) E. Lombardi and P. B. Sogo, *J. Chem. Phys.*, 32, 635 (1960).

(8) J. Ranft, *Ann. Physik*, 10, 1 (1962).

1/6.55 as large, in agreement with theory and with observations on other deuterium compounds.[9]

Just as in the case of isobutyraldehyde,[3,7] the n.m.r. spectrum of aqueous solutions of isobutyraldehyde-2-*d* shows a set of new peaks attributable to the hydrate.

$$Me_2CDCHO + H_2O \rightleftharpoons Me_2CDCH(OH)_2$$

The peaks due to the methyl groups and the dihydroxymethyl group are not triplets, as might be expected, but they are rather broad peaks.[10]

Kinetics of Deuterium Exchange of Isobutyraldehyde-2-d. When isobutyraldehyde-2-*d* is dissolved in water containing a basic catalyst, the n.m.r. spectrum of the solution changes until it becomes almost identical with that of a solution of the protium compound. The largest change is the decrease in the intensity of the triplet due to the methyl hydrogens of the deuterium compound, which is accompanied by the appearance and increase in intensity of the doublet due to the methyl hydrogens of the protium compound, which is centered at the same frequency as the triplet but whose splitting is much larger (6.9 compared to 1.05 c.p.s.).

The n.m.r. spectra of a number of aqueous solutions with known concentrations of isobutyraldehyde and isobutyraldehyde-2-*d* were determined. A function of the relative heights of one of the peaks for the deuterium compound and one of the peaks for the protium compound was devised so that a plot of the function against the fraction of isobutyraldehyde-2-*d* in the aldehyde mixture gave a line that was straight or nearly straight. By use of this plot the deuterium content of isobutyraldehyde in aqueous solutions could be determined from n.m.r. measurements. Although most of the n.m.r. measurements were made in this manner on the aqueous solutions in which the reaction was proceeding, a few were made by acidifying the solutions to stop the reaction, extracting the aldehyde with chloroform, and making n.m.r. measurements on the chloroform solution. Since the concentrations of catalysts are expected to remain essentially constant throughout a run, first-order rate constants are calculated from the equation

$$k = \frac{2.303}{t} \log \frac{f_0}{f_t} \tag{1}$$

where f_0 is the fraction of deuteration at zero time and f_t that at time t. Rate constants were determined from plots of log (f_0/f_t) *vs.* time (*cf.* Figure 5) and are not highly accurate. In a typical case the probable error is estimated to be about 5% and in certain unfavorable instances it may be considerably larger.

The first-order rate constants obtained by use of eq. 1 are apparent rate constants. The exchange reaction must be due to the free aldehyde in solution, not the aldehyde hydrate. However, the establishment of equilibrium between the free aldehyde and its hydrate is in all cases rapid[11,12] compared with the rate of deuterium exchange, and therefore the deuterium content of the hydrate is at all times the same (neglecting

(9) H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, 31, 1278 (1959).
(10) The doublets of the hydrate of the protium compound, in which the splitting is about 6.55 times as large, are not nearly so well resolved as those of the unhydrated aldehyde.[3]
(11) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963).
(12) J. Hine and J. G. Houston, *J. Org. Chem.*, 30, 1328 (1965).

equilibrium isotope effects) as that of the free aldehyde. Since the change in the deuterium content of both forms of the aldehyde is brought about by the reaction of only the free aldehyde, which comprises 70% of the equilibrium mixture at 35°,[3] the observed rate constants would have to be divided by 0.70 to get the true rate constants for reaction of the free aldehyde. The rate constants reported herein are the apparent rate constants, which have not been transformed to the true rate constants, at least partly to avoid introducing any error in the determination of the extent of hydration of isobutyraldehyde in water.[3] All the rate constants except two (to be considered specifically near the end of this section) were determined at 35 ± 0.2°, ordinarily in the presence of buffers.

The reaction was found to be subject to catalysis by strong acid as well as by strong and weak bases. The catalytic constant for hydrogen ions was determined by measurements in perchloric acid solution. From the value obtained (see Table II) it may be shown that hydrogen ion catalysis may be neglected in all the other runs made.

In the hydroxide ion catalyzed reaction the interpretation of the kinetics is complicated by the acidity of the hydrate. The equilibrium constant

$$K = \frac{[Me_2CHCHOHO^-]}{[Me_2CHCH(OH)_2][OH^-]} = 1.7 \ M^{-2}$$

has been determined[3] at 25° and is assumed to be little different at 35°. Although the concentration of free aldehyde is decreased slightly as some is hydrated to maintain the equilibrium that has been disturbed by transformation of some of the hydrate to its conjugate base, this decrease is negligible under the conditions used. More important, some of the hydroxide ions are used up to form another possible catalyst, the conjugate base of the aldehyde hydrate. The above equilibrium constant was used to calculate the concentrations of hydroxide ion and the conjugate base of the aldehyde hydrate. The second-order rate constants calculated by attributing all of the catalysis to hydroxide ions and none to aldehyde–hydrate anions (Table I) were poorly reproducible because of various experimental errors, but they showed no tendency to increase with increasing aldehyde concentration. This shows that most of the catalysis is due to the hydroxide ions and hence rules out the possibility that the aldehyde–hydrate anion is a *very* effective catalyst (although it may be as effective as hydroxide ion).

Table I. Kinetics of Exchange of Isobutyraldehyde-2-*d* in the Presence of Sodium Hydroxide

[Aldehyde][a]	[NaOH][a]	k_2, M^{-1} sec.$^{-1}$
0.0435	0.00908	0.035
0.0460	0.00354	0.030
0.0781	0.0125	0.029
0.0834	0.00795	0.032
0.210	0.00333	0.026
0.210	0.00782	0.031
0.210	0.0174	0.032
		Av. 0.031 ± 0.002

[a] Actual concentrations of aldehyde plus hydrate and of hydroxide ions.

In the study of certain catalysts whose buffer solutions were rather basic the observed first-order rate constants were corrected, by subtracting that part of the reaction attributed to hydroxide ions, before dividing by the catalyst concentration to obtain the catalysis constant. This correction amounts to about 33% of the reaction in the case of triethylamine and about 15% for N-methylpiperidine, tris-2-hydroxypropylamine, N-ethylbis-2-hydroxypropylamine, and N,N-diisopropylethanolamine, but is less than 6% in every other case. The corrections used for triethylamine and N-methylpiperidine and most of the small (<6%) corrections contain an uncertainty due to the fact that they are based on hydroxide ion concentrations calculated from ionization constants determined at 25°.

Since we were unable to prepare isobutyraldehyde-2-d solutions that were completely free of isobutyric acid, it was necessary to determine the acid content by titration. In all cases, except that of acetate and trimethylamine oxide, the catalyst being studied was sufficiently basic to neutralize the isobutyric acid almost quantitatively, so that the actual catalyst concentration could be obtained by subtracting the isobutyric acid concentration from the concentration of catalyst added. The n.m.r. spectrum of isobutyrate ions at fairly high concentrations overlaps that of isobutyraldehyde and therefore it was not convenient to determine the catalysis constant for this species. From examination of our data as a whole, it seems that very little error will be introduced by assuming that the catalysis constant for isobutyrate ions may be calculated from that for acetate ions by use of the Brønsted catalysis equation and a β of 0.53 (that observed for aryloxide ions). The resulting value, 1.0×10^{-6} M^{-1} sec.$^{-1}$, was used in correcting the rate constants for exchange in the presence of 2,6-lutidine, 2,4,6-collidine, and triethanolamine for that part of the reaction (26, 20, and 1%) due to isobutyrate ions. In no other case would a correction of as much as 0.5% be necessary. In runs made in the presence of acetate ions the concentration of acetate was so large and the catalytic constants and basicities of acetate and isobutyrate ions are so nearly the same that no account of the presence of isobutyric acid need be taken. In the case of trimethylamine oxide the extent to which the base was neutralized by the isobutyric acid present had to be calculated from the ionization constants of the two species.

The catalytic constant for water was so small that it was determined by extrapolation from data at higher temperatures, as follows. The first-order rate constants for the exchange reaction in the presence of 0.0048 M sodium acetate (to buffer the action of the $\sim$0.003 M isobutyric acid unavoidably present) was found to be 2.75×10^{-7} and 7.3×10^{-6} sec.$^{-1}$ at 60 and 100°, respectively. It was then assumed that the rate constant for exchange in such a reaction mixture at 35° can be obtained by use of the Arrhenius equation. From the activation energy of 20.2 kcal./mole a value of 2.3×10^{-8} sec.$^{-1}$ was obtained for the first-order rate constant at 35°. The hydrogen and hydroxide ion terms should contribute negligibly to this rate constant. Correction for reaction due to acetate and isobutyrate ions gives 1.8×10^{-8} sec.$^{-1}$, which when divided by the water concentration (55 M) gives the catalytic constant listed in Table II. The first-

order rate constants obtained in the presence of 2,6-lutidine and 2,4,6-collidine were corrected by 21 and 16% and those obtained in the presence of triethanolamine, tris-2-hydroxypropylamine, N-methylimidazole, acetate ions, 4-picoline, and p-nitrophenoxide ions by 1–6% for the contribution of water catalysis, but in no other case would this contribution be as much as 1%.

Table II. Catalysis Constants for the Deuterium Exchange of Isobutyraldehyde-2-d in Water at 35°

Catalyst	k_{cat}, M^{-1} sec.$^{-1}$	$-$Log k_{cat}[a]	$-$Log K_B[a,b]
H_3O^+	2.3×10^{-5}		
H_2O	3.3×10^{-10}	9.5	15.57[c]
OH^-	3.1×10^{-2}	1.51	-2.05^d
$CH_3CO_2^-$	8.8×10^{-7}	6.36[e]	9.57[e,f]
Me_3NO	6.0×10^{-6}	5.22	9.35[g]
p-MeC$_6$H$_4$O$^-$	2.8×10^{-3}	2.55	3.74[h]
o-MeC$_6$H$_4$O$^-$	2.2×10^{-3}	2.66	3.71[h]
$C_6H_5O^-$	1.65×10^{-3}	2.78	4.00[h]
p-ClC$_6$H$_4$O$^-$	1.25×10^{-3}	2.90	4.58[h]
m-ClC$_6$H$_4$O$^-$	6.8×10^{-4}	3.17	4.87[h]
o-ClC$_6$H$_4$O$^-$	3.3×10^{-4}	3.48	5.47[h]
m-O$_2$NC$_6$H$_4$O$^-$	2.8×10^{-4}	3.55	5.62[h]
p-O$_2$NC$_6$H$_4$O$^-$	5.1×10^{-5}	4.29	6.85[h]
3,4-Lutidine	3.2×10^{-5}	4.49	7.54[i]
4-Picoline	1.6×10^{-5}	4.80	8.02[i]
Pyridine	7.9×10^{-6}	5.10	8.78[i]
2,4-Lutidine	1.06×10^{-5}	4.97	7.37[i]
2,4,6-Collidine	7.3×10^{-7}	6.14	6.55[j]
2,6-Lutidine	2.8×10^{-7}	6.55	7.28[i]
N-Methylimidazole	1.6×10^{-5}	4.80	7.00[k]
N-Methylpyrrolidine	7.6×10^{-3}	2.12	3.54[l]
N-Methylpiperidine	1.45×10^{-3}	2.84	3.92[l]
N-Methylmorpholine	1.83×10^{-4}	3.74	6.59[k]
1,4-Diazabicyclo[2.2.2]-octane	6.5×10^{-3}	2.49[e]	5.70[e,k]
Me_3N	1.6×10^{-2}	1.80	4.20[m]
Et_2NMe	7.3×10^{-3}	2.14	3.71[n,o]
Et_3N	7.7×10^{-4}	3.11	3.35[p]
$(HOCH_2CH_2)_3N$	3.6×10^{-6}	5.44	6.23[q]
$HOCH_2CH_2NMe_2$	9.4×10^{-4}	3.03	5.00[k]
$Me_2NCH_2CH_2NMe_2$	1.4×10^{-3}	3.16[e]	5.33[e,k]
i-Pr$_2$NCH$_2$CH$_2$OH	5.0×10^{-5}	4.30	3.98[k]
$(MeCHOHCH_2)_2NEt$	1.5×10^{-5}	4.82	4.86[k]
$(MeCHOHCH_2)_3N$	6×10^{-7}	6.22	6.11[k]

[a] Including symmetry corrections[13] as noted. [b] At 25° except where otherwise noted. [c] K has been multiplied by a symmetry factor[13] of $^3/_2$. [d] K has been multiplied by a symmetry factor[13] of 2. [e] K or k has been multiplied by assymmetry factor[13] of $^1/_2$. [f] E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4939 (1951). [g] P. Nylén, *Z. anorg. allgem. Chem.*, **246**, 227 (1941). [h] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [i] R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954). [j] A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951). [k] Determined in the present investigation. [l] S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, **78**, 4917 (1956). [m] D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (London), **A177**, 499 (1941). [n] At 20°. [o] J. Hansson, *Svensk Kem. Tidskr.*, **67**, 256 (1955). [p] N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930). [q] R. G. Bates and G. Schwarzenbach, *Helv. Chim. Acta*, **37**, 1437 (1954).

Since the same value for the catalysis constant for acetate ions was obtained with a buffer ratio of 1:1 as with a buffer ratio of 7.2:1, it follows that catalysis by undissociated acetic acid does not contribute sig-

(13) As Benson has pointed out, to correct for symmetry effects the experimental values of k_{cat} and K_B should be multiplied by K_σ, the product of the symmetry numbers of the products (or transition state) divided by the product of the symmetry numbers of the reactants.[14]
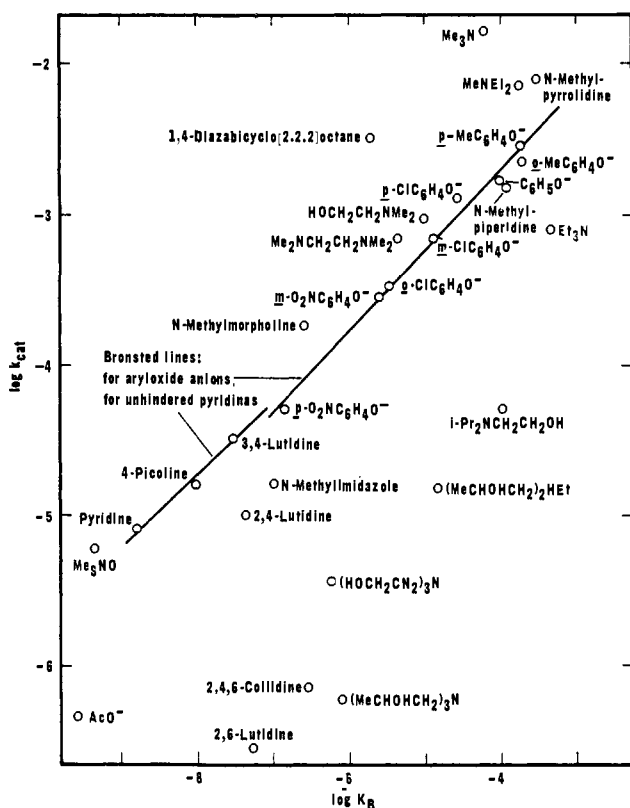(14) S. W. Benson, *J. Am. Chem. Soc.*, **80**, 5151 (1958).

Figure 1. Brønsted plot for catalysts in the base-catalyzed deuterium exchange of isobutyraldehyde-2-d in water at 35°.

Figure 2. Hammett equation plot of the catalysis constants of aryloxide ions in the deuterium exchange of isobutyraldehyde-2-d.

nificantly to the reaction. It therefore seems improbable that any other buffer's acid component whose acidity is less than that of acetic acid will contribute significantly to the over-all reaction.

The possibility that the deuterium exchange is complicated by a simultaneous aldol condensation was considered. An earlier study showed that relatively small amounts of aldolization lead to clouding of the reaction solution and separation of an organic layer.[3] When this occurred in the present investigation, the run was repeated using a lower concentration of aldehyde and/or base. The equilibrium constant for aldolization in homogeneous aqueous solution at 35° is so unfavorable that less than 10% of the aldehyde would be present as aldol even at equilibrium at the aldehyde concentration (0.21 M) most commonly used. Furthermore, except with catalysts that are relatively strongly basic but relatively unreactive, the intermediate carbanions formed should be protonated so much faster than they add to other aldehyde molecules that aldolization should not be able to compete with deuterium exchange. An estimate of the rate of protonation of the carbanions relative to their rate of combination with aldehyde, of the type used previously,[3] shows that only with triethylamine and hydroxide ion should aldolization occur to a significant extent during the deuterium exchange study.

The catalysis constants obtained are listed in Table II.

Discussion

A plot of the log k_{cat} values obtained vs. the corresponding log K_B values at zero ionic strength (at 25°, since most of the K_B values at 35° are not known)
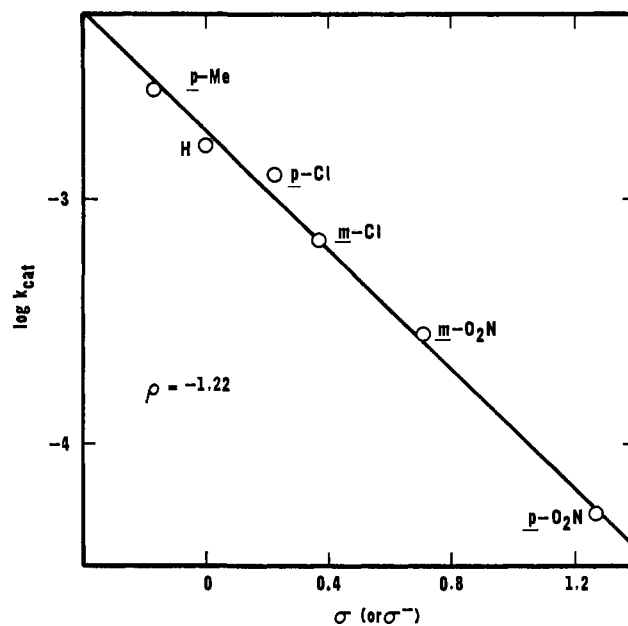
is shown in Figure 1.[13,14] There are seen to be large deviations from the Brønsted catalysis equation. For such closely related groups of compounds as pyridines lacking 2- and 6-substituents and phenoxide ions the relation holds satisfactorily, as shown by the two straight lines in Figure 1, corresponding to β-values of 0.49 and 0.53, respectively. Considering the uncertainty produced by the rather small range of pK values for the pyridines, these values may be considered equal, within the experimental error. The data on the meta- and para-substituted phenoxide ions also fit the Hammett equation satisfactorily (using σ^- for the p-nitro substituent), yielding a ρ of -1.22 as shown in Figure 2.

Although we can give no quantitative explanation for the location of all the other points in Figure 1, it seems clear that steric hindrance is important. The points for pyridines with 2- and 6-substituents lie well below the line described by the three points for pyridines without such substituents. The reactivity of 2,4-lutidine is less than one-third that to be expected of an unhindered pyridine of its basicity. The more hindered bases 2,6-lutidine and 2,4,6-collidine are less than $1/100$ as reactive as would be expected for unhindered pyridines.

There is convincing evidence that steric hindrance may decrease the reactivity of bases in reactions involving proton transfers. Some of this evidence deals with reactions in which protons appear to be removed from hydroxy groups,[15] and other examples include the removal of carbon-bound protons in elimination[16] and aromatic substitution reactions.[17] In studies more closely related to the present one, Pearson and Williams showed that in forming α-nitroethyl anions from nitroethane 2,6-lutidine is less than half as reactive as would be expected from a Brønsted plot of the data on un-

(15) Cf. R. P. Bell and M. B. Jensen, Proc. Roy. Soc. (London), A261, 38 (1961); F. Covitz and F. H. Westheimer, J. Am. Chem. Soc., 85, 1773 (1963).
(16) Cf. H. C. Brown, I. Moritani, and Y. Okamoto, ibid., 78, 2193 (1956); H. C. Brown and M. Nakagawa, ibid., 78, 2197 (1956).
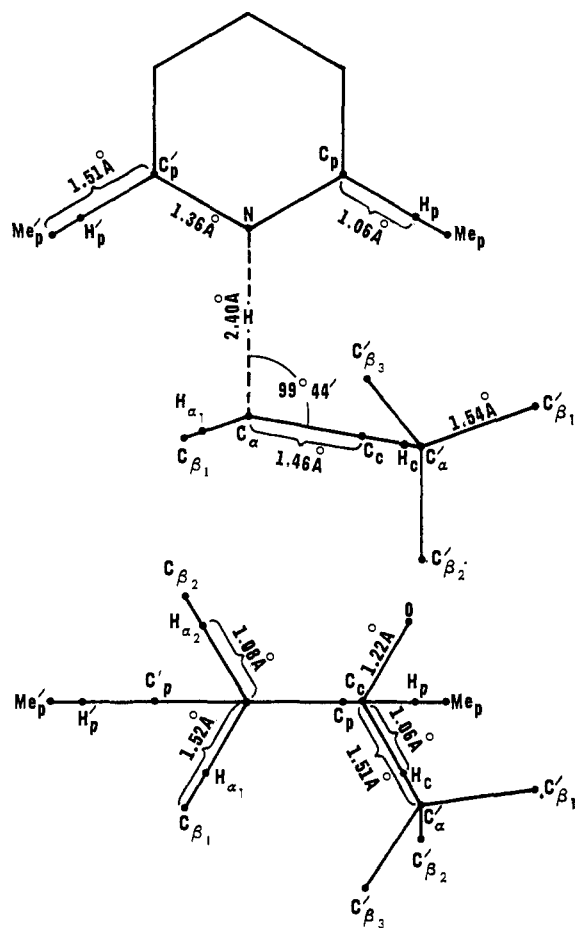(17) H. Zollinger, Helv. Chim. Acta, 38, 1623 (1955).

Figure 3. Two views of a model of the transition state for the reaction of pyridine or 2,6-lutidine with acetone, isobutyraldehyde, or one conformer of pinacolone.

ured by the deviations from the Brønsted lines for unhindered pyridines ($\Delta \log k$). On going from acetone to methyl isopropyl ketone to pinacolone (methyl t-butyl ketone), $\Delta \log k$ for 2,6-lutidine increased (in absolute magnitude) from 0.84 to 1.01 to 1.38. Because of a belief that the commonly accepted transition state for carbanion formation by a ketone, in which the bond between the α-carbon atom and the reacting hydrogen atom is held roughly parallel to the π-orbital of the carbonyl carbon atom, would not explain the increasing steric hindrance observed on going from acetone to methyl isopropyl ketone to pinacolone, Feather and Gold suggested a transition state of the following type, in which *all of the atoms are coplanar except some of the hydrogens of the methyl groups.*
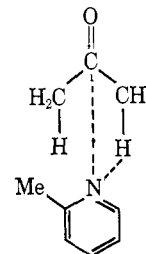
The dashed line from nitrogen to carbon reflects a postulate of "some kind of conjugative interaction" whose "theoretical explanation...is not clear." Inasmuch as we view this suggestion as implausible, we felt it desirable to give somewhat more detailed consideration to the question of whether the observed data could be explained in terms of a transition state of the type commonly accepted. The desirability of such consideration is increased by Lewis and Allen's remark that "with models, even 2-t-butyl-6-methylpyridine with 2-nitropropane shows no conspicuous hindrance either with reagent-like or product-like structures. Perhaps the hindrance is connected with transition-state solvation."[20]

For the transition state in the formation of carbanions by the attack of pyridine derivatives on the α-hydrogen atoms of aldehydes and ketones, we have used a model of which two views are shown in Figure 3. This figure is a superposition of the figures that would be necessary to represent one conformer of the transition state for the reaction of pyridine or 2,6-lutidine with isobutyraldehyde, acetone, or pinacolone. The carbonyl carbon atom is denoted C_c, the hydrogen atom attached to it (if there is one) is H_c, and the hydrogen being transferred is H. Except for these and the nitrogen and oxygen atoms, which are unique, a subscript "p" is added to atoms in the pyridine base and a subscript Greek letter to atoms in the carbonyl compound. Atoms on one side of the molecule are indicated by a prime sign; in the carbonyl compound the primed atoms are on the opposite side of the carbonyl group from the hydrogen being transferred. Thus, in pinacolone C_α' and the C_β''s are the carbon atoms of the t-butyl group, the H_α's are the α-hydrogen atoms that are not transferred, and the C_β's do not exist; whereas in isobutyraldehyde the C_β''s are the methyl carbon atoms and C_α', the C_β''s, and the H_α's do not exist. To simplify the treatment, all methyl groups are treated as being spherically symmetrical, with van der Waals radii of 2.00 Å.,[23] so

hindered pyridines.[18] They also presented evidence that steric hindrance is an important factor in determining the reactivity of aliphatic amines toward nitroethane. Gutsche and co-workers showed that steric hindrance probably decreases the reactivity of 2,6-lutidine as a catalyst in the aldolization of glyceraldehyde[19] and Lewis and Allen showed that the importance of steric hindrance increases significantly on going from nitroethane to 2-nitropropane.[20] Gold has reviewed the subject of steric effects in acid–base reactions, covering the literature through about 1961,[21] and more recently, with Feather, has described a particularly detailed study, in which the iodination of five different ketones in the presence of eleven different pyridine derivatives was investigated kinetically.[22] For each of the ketones studied, these workers found that the data on pyridines lacking 2-substituents yielded a satisfactory Brønsted plot, the pyridines with one 2-methyl substituent were less reactive (forming a separate Brønsted line when enough data were available), and 2,6-lutidine and 2,4,6-collidine were even less reactive. The extent to which the reactions were slowed by steric hindrance is meas-

(18) R. G. Pearson and F. V. Williams, *J. Am. Chem. Soc.*, **75**, 3073 (1953); **76**, 258 (1954).

(19) C. D. Gutsche, R. S. Buriks, K. Nowatny, and H. Grassner, *ibid.*, **84**, 3775 (1962).

(20) E. S. Lewis and J. D. Allen, *ibid.*, **86**, 2022 (1964).

(21) V. Gold, *Progr. Stereochem.*, **3**, 169 (1962).

(22) J. A. Feather and V. Gold, *Proc. Chem. Soc.*, 306 (1963); *J. Chem. Soc.*, 1752 (1965).

(23) L. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1960, p. 260, 261.

that with acetone and isobutyraldehyde the only conformers that need be considered are those produced by rotation around the NHC_α bond.

The bond lengths shown were chosen by reference to data on related compounds.[24] All bond angles to sp^2 carbon and nitrogen atoms were set at 120° and those to sp^3 carbon at 109° 28'. Our value of 0.49 for the Brønsted β and the values of Feather and Gold, ranging from 0.27 to 0.77 suggest an average value near 0.50 and therefore suggest that the proton is about half-transferred in the average transition state. For this reason we have chosen the value 99° 44' for the angles $C_cC_\alpha H$, $C_{\beta_1}C_\alpha H$, etc., midway between their initial values of 109° 28' and their final values of 90°. The lengths of the bonds joining C_α to C_c, C_{β_1}, C_{β_2}, H_{α_1}, and H_{α_2} have been taken as midway between their estimated initial and final values. We have assumed that the NHC_α hydrogen bond present in the transition state is linear and have used the bifluoride anion, a symmetrical hydrogen bond with an over-all length of 2.26 Å.,[25] as a starting point in estimating the distance between N and C_α. If the single bond radius for C_α is midway between 0.74 Å., the value for sp^2 carbon, and 0.77 Å., the value for sp^3 carbon, it is 0.115 Å. greater than the single bond radius of fluorine.[2b] If the single bond radius of nitrogen, like that of carbon, is 0.03 Å. smaller for the sp^2 than for the sp^3 hybridized atom, then the value for sp^2 nitrogen is 0.03 Å. larger than that for fluorine.[2b] It is therefore estimated that the NHC_α bond length is 2.40 Å., about 0.115 Å. plus 0.03 Å. larger than the F–F distance in the bifluoride ion. The conformer of pinacolone shown is the one in which the plane described by C_c, C_α', and C_{β_1}' is perpendicular to the plane described by C_α, C_c, and O.

For the six cases in which the base is pyridine or 2,6-lutidine and the carbonyl compound is isobutyraldehyde, acetone, or pinacolone, the distance between the 2-substituents on the pyridine ring and the various atoms of the carbonyl compound were calculated. This was done not only for the conformer shown in Figure 3, but also for the conformers obtainable from it by rotation of the pyridine ring around the axis described by the NHC_α bond through 180° at intervals of 15°, and, in the case of pinacolone, for several of the conformers obtainable by rotation of the t-butyl group. When the distances were less than the summed van der Waals radii (1.20 Å. for hydrogen, 1.40 Å. for oxygen, and 1.85 Å. for C_c[26]), the extent of interpenetration was noted. Interactions involving C_α and the hydrogen being transferred were ignored, partly because it is not clear what van der Waals radii should be used and partly because these interactions will be the same for all carbonyl compounds and will not change as the pyridine ring is rotated. Such interactions should contribute to the extent of steric hindrance estimated for all the carbonyl compounds and thus explain the steric hindrance observed in the reaction of acetone with 2,6-dimethylpyridines.[22] However since the contribution will be the same for all the compounds, they need not be considered in the present discussion of how steric

effects change with changes in the nature of the carbonyl compound.

For a rigorous treatment of steric hindrance,[27] in which the transition state is permitted to become distorted in order to minimize the strain, it is necessary to know the force constants for various unusual bonds present in the transition state, to be able to calculate the van der Waals repulsive forces reliably, to treat interactions involving C_α, H, and N, etc. Such a rigorous treatment is beyond our capabilities, but useful conclusions may be drawn from a rough estimate of the maximum steric strain, in which no distortion of the transition state is permitted. Since these conclusions are largely independent of the exact manner in which the estimate is made, we shall describe our method of calculating strain energies from extents of interpenetration, without critical discussion of its basis and merit.

According to Amdur's equation,[27] the energy of repulsion of argon atoms held at 70% of their summed van der Waals radii, $i.e.$, at 2.45 Å., is 11.20 kcal./mole. With the assumptions that the Lennard-Jones equation[27] is applicable and that the same amount of energy of repulsion will result when the distance between a 2-substituent on the pyridine ring and an atom or methyl group in the carbonyl compound is reduced to 70% of the summed van der Waals radii, the following equation may be derived. The estimated maximum

$$E_r = 0.3493\left(\frac{d_0}{d}\right)^{11} - 0.5489\left(\frac{d_0}{d}\right)^7 + 0.20 \quad (2)$$

energy of repulsion, E_r, is given in kcal./mole, d_0 is the sum of the van der Waals radii, and d is the internuclear distance.

For pinacolone, E_r values were calculated for the conformers in which the t-butyl group is oriented as shown in Figure 3 (type A conformers), conformers in which the t-butyl group is rotated 60° around the C_c–C_α' bond from its position shown in Figure 3 (type B conformers), and for other conformers on which detailed data will not be given. According to eq. 2, type B conformers contain 1.85 kcal./mole more internal strain (from differences in interactions involving H_{α_1}) than do type A conformers, if interactions with the pyridine base are neglected. Therefore it is necessary to add 1.85 kcal./mole to the energies of repulsion between pyridine bases and type B conformers to put these E_r values on the same basis as those for type A conformers.

In Figure 4a, E_r is plotted against the angle of rotation around the NHC_α bond for the reaction of pyridine with isobutyraldehyde and both type A and type B conformers of pinacolone. The values of E_r for the reaction of pyridine with acetone (zero from 30 to 120° and never as much as 0.09 kcal./mole) are too small to show up on the graph (and to have any significant effect on the reaction rate). Figure 4b is a similar plot for the reactions of 2,6-lutidine with acetone, isobutyraldehyde, and both type of conformers of pinacolone. For isobutyraldehyde the values of E_r are seen to increase from the range 0.02–0.18 kcal./mole in reaction with pyridine to 9.4–14.7 kcal./mole

(24) Cf. G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, Appendix.
(25) S. W. Peterson and H. A. Levy, J. Chem. Phys., 20, 704 (1952).
(26) This is equal to the half-thickness of an aromatic ring.[2b]

(27) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 531, 532.
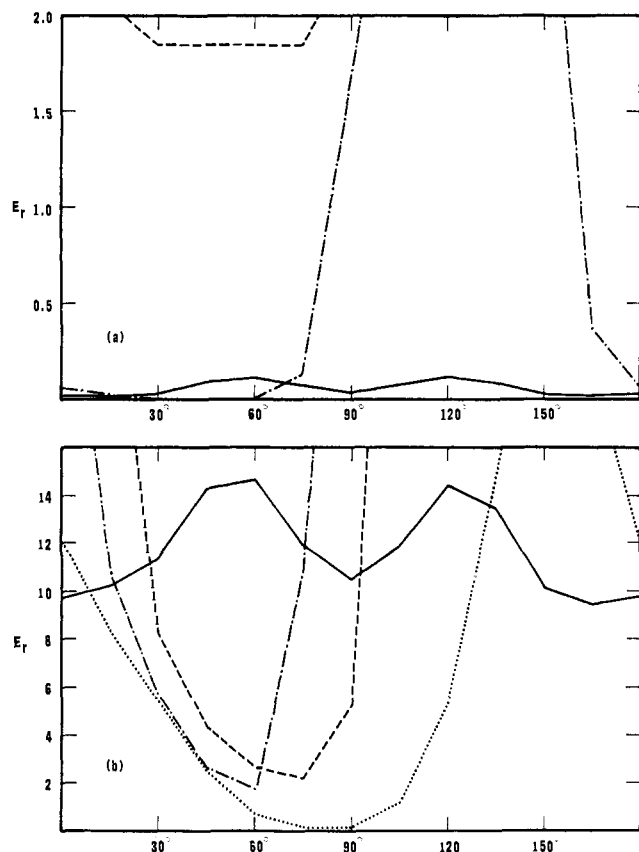
Figure 4. Plots of estimated maximum repulsion energy (E_r) in reactions of carbonyl compounds with pyridine bases vs. extent of rotation of the pyridine from the conformation shown in Figure 3: solid line, isobutyraldehyde; dotted line, acetone; dot-dashed line, type A conformers of pinacolone; dashed line, type B conformers of pinacolone.

in reaction with 2,6-lutidine, a clear increase in steric hindrance. The reaction of pinacolone with pyridine via the more stable type A conformers is almost unhindered for nearly half of the possible orientations of the pyridine base, whereas in reaction with 2,6-lutidine E_r has a minimum value of 1.8 kcal./mole and the range of orientations of the pyridine base that will bring about reaction at a significant rate has been narrowed. Thus pinacolone should be hindered although not so much as isobutyraldehyde. For acetone the values of E_r increase from about zero in the reaction with pyridine to 0.17 kcal./mole for 2,6-lutidine orientations between 75 and 90° and less than 2.0 kcal./mole for orientations between about 50 and 110°. Thus acetone should be the least hindered of the three carbonyl compounds. Less complete calculations on methyl isopropyl ketone show that it should be hindered to an extent intermediate between that of acetone and pinacolone. Although the values of E_r, the estimated maximum energy of repulsion, are much larger than are needed to explain the observed $\Delta \log k$ values, if the transition states are distorted so as to reduce the extent of interpenetration of atoms and groups by 30%, then the minimum values of E_r for reaction of acetone, pinacolone, and isobutyraldehyde with pyridine would be 0, 0, and 0.01 kcal./mole, and for reaction with 2,6-lutidine would be 0.06, 0.59, and 2.19 kcal./mole, respectively. Without consideration of any complications due to variations in the fractions of the conformers that are reactive, the E_r

values, as activation energy increments, would lead to $\Delta \log k$ values for pinacolone and isobutyraldehyde that are 0.39 and 1.50 larger than the value for acetone. Observed values of $\Delta \log k$ are 0.52 and 1.32 larger for pinacolone and isobutyraldehyde, respectively, than for acetone. This moderately good agreement is probably not of great fundamental significance but, with the other results described, leads us to the conclusion that the commonly accepted transition state, in which the carbon–hydrogen bond being broken is nearly perpendicular to the plane described by the carbonyl group and the atoms attached directly to it, permits a plausible rationalization of the observed fact that the reactivity of 2,6-lutidine is slowed by steric hindrance to an increasing extent in the series acetone, methyl isopropyl ketone, pinacolone, and isobutyraldehyde. The commonly accepted transition state also has the advantage of letting the geometrical configuration of the transition state approach that of the products so that some of the resonance stabilization of the carbanion being formed may be reflected in the transition state leading to it, and therefore seems much more plausible to us than a transition state in which the carbon–hydrogen bond being broken is in the same plane as the carbonyl group and the atoms attached directly to it.

A more complete treatment of steric hindrance in carbanion formation reactions would allow for changes due to the varying acidity of the species from which carbanions are formed. Other factors remaining equal, an increase in acidity would be expected to cause the transition state to occur earlier in the reaction.[2c] Since the shortest hydrogen bonds are symmetrical ones,[28] it is probable that the NHC_α bond will be shortest at about half-reaction and longer either before or after this point. Transition-state bond angles of the type of $C_cC_\alpha H$ will tend to decrease steadily from 109° 28' at the beginning to 90° at the end of the proton transfer. These two factors will work together to cause steric hindrance to increase in magnitude during the first half of the reaction but during the latter half they will oppose each other with a result that cannot be predicted without a more quantitative treatment.

Treatment of the reactions of a number of compounds in terms of a single model, as we have done, should be more successful when the compounds treated are carbonyl compounds than it would be if a compound of a different type, such as a nitro compound, were included. Nevertheless, we had not expected that the value of $\Delta \log k$ (0.67) calculable from the data of Lewis and Allen on the reaction of 2,6-lutidine with 2-nitropropane[20] would be smaller than the value (2.16) we have obtained for the reaction with isobutyraldehyde. Isobutyraldehyde may be regarded as 2-nitropropane in which the nitro group has been replaced by the smaller formyl group, and therefore might be expected to display smaller steric effects. The much more strongly electron-withdrawing nitro group causes 2-nitropropane to be far more acidic than isobutyraldehyde, so that the transition state should come earlier in the reaction, resulting in decreased steric repulsion between the pyridine base and the weak acid with which it is reacting. Nevertheless the decrease in steric

(28) Cf. G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Section 9.3.1.

effects seems surprisingly large in view of the fact that the β that may be calculated from the reported data on 2-nitropropane is 0.45, not much smaller than the value (0.49) for isobutyraldehyde. Perhaps there are other factors that decrease steric effects in the case of 2-nitropropane. The NHC_α bond, which can be regarded, in one canonical structure, as an ammonium ion that is hydrogen bonded to the partially negative carbon atom of a carbanion, may be longer in the case of the nitro compound where the more strongly electron-withdrawing nitro group takes more of the negative charge upon itself and leaves less on the α-carbon atom. Or perhaps steric hindrance to transition-state solvation is important, as Lewis and Allen have suggested, and with the nitro compound the incipient negative charge is more efficiently dispersed so that it needs solvation less and it is removed more efficiently from the α-carbon atom to the outside of the transition state where there is less hindrance to solvation.

Although Feather and Gold found that in each of the four cases for which the requisite data were obtained the Brønsted line described by the points for 2,6-lutidine and 2,4,6-collidine gave a β smaller than that obtained for the unhindered pyridines, our data on the reaction of 2,6-lutidine and 2,4,6-collidine with isobutyraldehyde yield a β of about the same magnitude as that obtained for unhindered pyridines. However, the rate constants we obtained for the 2,6-dimethylated pyridines are the most likely of all our rate constants to be in error because of impurities in the catalysts, and they were obtained from total first-order rate constants that had to be corrected by about 50% for catalysis by the water, isobutyrate ions, and hydroxide ions also present in the reaction mixtures. We therefore feel that the β calculated from the rate constants we obtained for these two compounds is not reliable enough to support any significant conclusions.

Evidence for steric hindrance may also be seen in the catalytic constants for the saturated amines. The most reactive amines for their basicity are the relatively unhindered trimethylamine and 1,4-diazabicyclo[2.2.2]-octane. If the points for these two compounds are assumed to comprise a Brønsted plot for unhindered saturated tertiary amines, then the extents to which the points for the other saturated tertiary amines deviate from this line may be taken as a measure of the steric hindrance to proton removal from isobutyraldehyde by these bases. The amount of such hindrance is seen to increase with the extent of branching of the groups attached to nitrogen, reaching a maximum with tris-2-hydroxypropylamine whose reactivity is diminished by about 3000-fold. It is possible that with the hydroxyamines hydrogen bonding between the amino and hydroxygroups is of importance in decreasing the reactivity. In reaction with nitroethane, steric hindrance was much less marked; quinuclidine reacted less than twice as rapidly as triethylamine, whose basicity is essentially identical.[18]

The phenoxide ions may be thought of (sterically) as pyridines in which the basic atom has been made more accessible by moving it one atom out from the ring. Any steric hindrance due to 2-methyl substituents should therefore be smaller with phenoxide ions than with pyridines. Hence, it is not surprising that the points for the o-cresolate anion (and the o-

chlorophenoxide anion) fit satisfactorily on the Brønsted plot for phenoxide ions.

The relatively low reactivity of N-methylimidazole is interesting. Because of the smaller ring present, the basic nitrogen atom in this compound should be somewhat less shielded than the nitrogen atom in pyridine, 4-picoline, or 3,4-lutidine. The reactivity of the imidazole, however, is less than one-third of that which would be expected from the Brønsted plot for unhindered pyridines. We suggest that this decreased reactivity is an example of the generalization that reactions involving significant changes in the internal geometry of the reactants will be slower than closely related reactions involving smaller changes in internal geometry.[29] The carbon atom attached to two nitrogen atoms in an imidazole must be closer to the one attached by a double bond than it is to the one attached by a single bond, but in the corresponding imidazolium ion this carbon atom is equidistant from the two nitrogen atoms. Thus the protonation of an imidazole must be accompanied by changes in internal geometry that are far greater than any required in the protonation of a pyridine. Stated alternatively, the basicity of the unsaturated nitrogen is due in considerable measure to the ability of the saturated nitrogen to share its unshared electron pair with the intermediate carbon atom; this ability is less in the transition state for protonation, where the carbon–nitrogen bond distance is still almost as long as in the reactant, than it is in the imidazolium ion, where the carbon–nitrogen bond distance is significantly shorter. This effect should also tend to decrease the reactivity of acetate ions and perhaps also that of phenoxide ions.

Like various earlier workers, we have found that there may be large deviations from the Brønsted catalysis equation when major changes are made in the structure of the catalysts.[30] When the minimally hindered examples are compared it is noted that saturated tertiary amines are more effective catalysts for their basicity than are pyridines, aryloxide ions, carboxylate ions, or amine oxides. We have found no satisfying rationalization for this observation.

It is interesting to compare the rate constant for the removal of α-hydrogen atoms from isobutyraldehyde by the action of hydroxide ions with the analogous rate constants for acetaldehyde, acetone, and diisopropyl ketone. When Bell and McTigue's rate constant for the reaction of acetaldehyde with hydroxide ions in aqueous solution at 25°[31] is multiplied by 2.2 to allow for the hydration of the aldehyde, divided by three to obtain the rate per α-hydrogen, and divided by an estimated[31] k_H/k_D value of 10 to obtain the value for the deuterium compound, the value 6.6×10^{-3} M^{-1} sec.$^{-1}$ is obtained. At 35° the value is probably two or three times as large, or around 1.5×10^{-2} M^{-1} sec.$^{-1}$. The rate constant for hexadeuterioacetone at 35° (interpolated from values at higher and lower temperatures)[32] divided by a statistical factor of six is 6×10^{-3} M^{-1} sec.$^{-1}$. The rate constant for diisopropyl ketone in water at 35° is 3.67×10^{-3} M^{-1} sec.$^{-1}$,[33]

(29) Cf. F. O. Rice and E. Teller, J. Chem. Phys., 6, 489 (1938); 7, 199 (1939).
(30) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter X.
(31) R. P. Bell and P. T. McTigue, J. Chem. Soc., 2983 (1960).
(32) J. R. Jones, Trans. Faraday Soc., 61, 95 (1965).
(33) J. R. Hulett, J. Chem. Soc., 430 (1965).

which is changed by a statistical factor of 2 and an assumed kinetic isotope effect of 10 to 1.8×10^{-4} M^{-1} sec.$^{-1}$. Our value for isobutyraldehyde when corrected for hydration is 4.4×10^{-2} M^{-1} sec.$^{-1}$. It is not surprising that the α-hydrogen atoms of isobutyraldehyde are more reactive than those of diisopropyl ketone and even slightly more reactive than those of acetone. It is surprising, however, that acetaldehyde is less reactive than isobutyraldehyde and only slightly more reactive than acetone.

Experimental Section[34]

Isobutyraldehyde-2-d. In the first procedure used, isobutyraldehyde was shaken with about six times its volume of a 2 M trimethylamine–0.7 M trimethylammonium perchlorate buffer in deuterium oxide and extracted with *m*-xylene. Distillation of the acid-washed and dried xylene solutions gave isobutyraldehyde-2-*d* in about 33% yield. The trimethylamine content of the buffer had been depleted considerably.

For the preferred procedure, isobutenyl acetate was prepared by the method of Bedoukian[4] except that anhydrous sodium acetate was used instead of crystalline potassium acetate. The n.m.r. spectrum of isobutenyl acetate (neat) consists of a septet centered at τ 3.18 ($J = 1.6$ c.p.s.), a singlet at 7.98, and an apparent triplet centered at 8.37 ($J = 1.7$ c.p.s.) with integrated intensity ratios of 1:3:6. The apparent triplet must be two overlapping doublets due to the two methyl groups. In a typical preparation 35 g. (0.307 mole) of isobutenyl acetate was refluxed under nitrogen for 15 hr. with 10 ml. (0.56 mole) of deuterium oxide and 1 drop of deuterium sulfate. The mixture, which had become homogeneous during this time, was distilled, yielding 18 g. (80% yield) of material in the range 55–60°. Redistillation under nitrogen gave material boiling at 63–63.5°, n^{19}D 1.3750. The n.m.r. spectrum of this material contained a triplet ($J = 1.05$ c.p.s.) at τ 8.94 and a broad peak at 0.57. In deuterium oxide solution this triplet was centered at τ 8.90 and the broad peak at 0.43; in addition, two broad peaks at 5.23 and 9.09 had appeared. The n.m.r. spectrum in protium oxide was essentially the same except that the τ-5.23 peak was hidden by the water absorption.

Analysis of Isobutyraldehyde–Isobutyraldehyde-2-d Mixtures. In aqueous solutions of mixtures of isobutyraldehyde and isobutyraldehyde-2-*d* the τ 8.90 doublet of the protium compound is seen to surround the corresponding, more closely spaced, triplet of the deuterium compound. Taking the isobutyraldehyde-2-*d* as isotopically pure material,[35] mixtures of aqueous solutions of known amounts of isobutyraldehyde and isobutyraldehyde-2-*d* were made up and their n.m.r. spectra measured. Denoting the height of the larger of the two components of the protium doublet (the downfield component) as *h* and the larger of the three components of the deuterium triplet (the middle

one) as *d*, a plot of $d/(d + h)$ *vs.* the known fraction of isobutyraldehyde-2-*d* present in the aldehyde mixture was made. The points on this plot fall within the experimental uncertainty of a straight line. From this line the deuterium content of isobutyraldehyde may be determined in the absence of compounds with n.m.r. absorption at the frequencies where measurements are made. Similar treatment of data on standard solutions in chloroform gave a slightly curved line.

Kinetics of Deuterium Exchange of Isobutyraldehyde-2-d. Most of the kinetic runs were carried out by the following method. An n.m.r. sample tube was flushed with nitrogen and 0.50 ml. of 0.2 M aqueous isobutyraldehyde-2-*d* was added by syringe. At "zero" time, 0.25 ml. of an aqueous solution of the catalyst was added to this n.m.r. tube, which had been allowed to reach thermal equilibrium in a bath at 35 $\pm$ 0.1°. The deuterium content of the isobutyraldehyde in the reacting solution was then determined at recorded times by placing the n.m.r. tube in the n.m.r. probe (at 35 $\pm$ 1°) and making measurements as described in the preceding section.

In the case of certain rapid reactions the tube was kept in the n.m.r. probe throughout the entire period over which the reaction was followed.

In studies of catalysis by 2,6-lutidine, 2,4,6-collidine, and 3,4-lutidine limited solubility made it difficult or impossible to obtain the concentration of catalyst desired when the technique just described was used. In these cases 0.05 ml. of isobutyraldehyde-2-*d* was added to 1.00 ml. of an aqueous solution of the catalyst under nitrogen in an n.m.r. tube at zero time. Catalysis by N-methylimidazole, triethanolamine, pyridine, trimethylamine oxide, and, in some runs, sodium acetate and 4-picoline was also studied by use of this technique.

Triethylamine and sodium hydroxide, at the concentrations used, gave aqueous solutions in which the hydration–dehydration equilibrium of isobutyraldehyde proceeded at such a rate that the spectra were very poorly resolved. For this reason a technique of the following type was used in studying catalysis by sodium hydroxide. At zero time 0.20 ml. of 0.973 M sodium hydroxide solution was added by syringe to 10 ml. of a 2% (by volume) solution of isobutyraldehyde-2-*d* in water. At recorded times 0.50-ml. samples were removed and added to an n.m.r. sample tube containing at least 10% more than enough acetic acid to neutralize the base. The deuterium content of the aldehyde was then determined.

A further complication in the study of catalysis by triethylamine was the fact that the n.m.r. peak due to the methyl groups of the triethylammonium ion overlaps the downfield part of the doublet due to the methyl groups of the protium form of isobutyraldehyde. For this reason *t*-butyl alcohol was added to the reaction solution to serve as a standard. The contribution of the triethylammonium ion to the apparent value of *h* could be determined as a function of the height of the *t*-butyl alcohol peak in the absence of aldehyde. It will be the same in the presence of aldehyde, so that measurements on the *t*-butyl alcohol peak show what correction should be made on *h*. Otherwise, the technique used was of the same general type as that used in studying sodium hydroxide.

(34) All n.m.r. spectra were determined using a Varian A-60 instrument. Chemical shifts are referred to tetramethylsilane for those spectra run in organic solvents and to sodium 3-(trimethylsilyl)-1-propanesulfonate for those spectra run in water.

(35) As has been pointed out previously, this procedure, which is used for convenience, has no effect on the values of the first-order rate constants obtained, since these depend only on the deuterium concentration at a given time *relative* to that present initially.[36]

(36) J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Am. Chem. Soc.*, 79, 1406 (1957).

The n.m.r. spectra of tris-2-hydroxypropylamine, N,N-diisopropylethanolamine, and N-ethylbis-2-hydroxypropylamine also overlap that part of the spectrum of isobutyraldehyde used for isotopic analysis, but with these amines the problem was solved in a different manner. A sample was withdrawn from the reaction mixture, treated with acetic acid to stop the reaction, and extracted with a considerably smaller volume of chloroform. The isotopic content of the aldehyde in the chloroform solution was then determined by n.m.r. measurements as described in the preceding section. Inasmuch as the extraction step yields a chloroform solution in which the aldehyde concentration is much higher than it was in the aqueous solution, this technique permits the study of more dilute aqueous solutions of aldehyde. For this reason the chloroform extraction technique was also used in determining the catalytic constant for hydroxide ions in those cases where aldehyde concentrations below 0.1 M were employed.

The n.m.r. tubes used in kinetic runs at 35° were kept tightly stoppered; those used in runs at 60 and 100° were sealed. When the tubes used in the runs at 60 and 100° were removed from their constant temperature baths they were immediately cooled to about 35°, where the reaction has a half-life of about 1 year, so that a negligible amount of reaction occurred during the time required for n.m.r. analysis. Only the time during which the tubes were in their constant temperature baths was counted as reaction time.

The acid content of the isobutyraldehyde-2-d and its aqueous solutions that were used was determined by titration with standard alkali. In most cases titrations were made on a blank (without catalyst) throughout the time of the kinetic runs and no further oxidation was found to occur. The n.m.r. peaks for isobutyric acid are very near those for isobutyraldehyde so that the n.m.r. spectra used in determining the extent of reaction also show whether the aldehyde is being oxidized to a significant extent. Near the end of some of the longer kinetic runs oxidation was found to have occurred, and therefore the later points in these runs were not used in determining the rate constant. The acid concentration contributed to the reaction solutions by the aldehyde used, ranged from 10^{-4} to 0.02 M.

A typical first-order plot, for exchange in the presence of 4-picoline, is shown in Figure 5.

For about half the catalysts studied several kinetic runs were made, using different concentrations of catalysts, with satisfactory agreement (less than 6% average deviation from the mean) between the second-
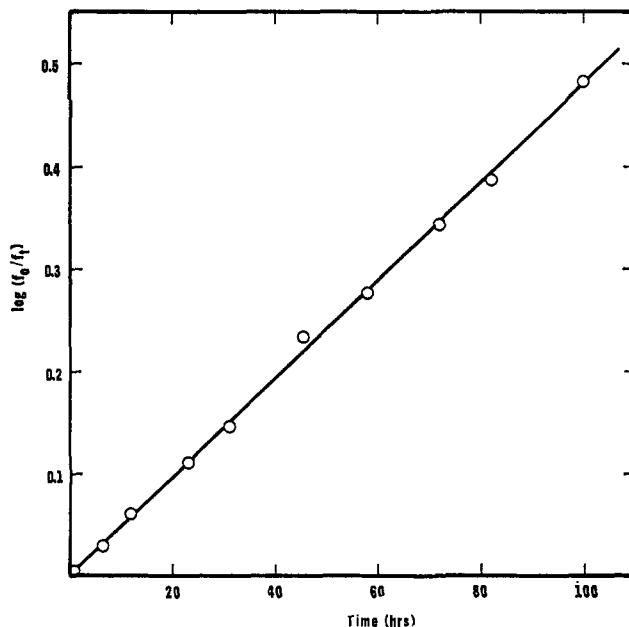

Figure 5. Kinetic plot for the deuterium exchange of isobutyraldehyde-2-d in the presence of aqueous 0.1788 M 4-picoline-0.341 M 4-picolinium ion at 35°.

order rate constants obtained. For each of the other catalysts only one kinetic run was made.

Determination of pK_B Values. Weighed samples of the amines studied were dissolved in 25 ml. of water and titrated at 26 ± 1° using a Beckman Research pH meter, Model 101900. The pK_a of the conjugate acid of the amine was taken as the pH of the half-neutralized solution (in which the hydrogen ion concentration was in all cases negligible compared to the concentration of base and its conjugate acid). For each amine one determination was made at an ionic strength (at the half-neutralization point) of about 0.005 and one at an ionic strength of about 0.012. The pK_a at zero ionic strength was then determined for each amine from a plot of pK_a *vs.* ionic strength. The pK_B values listed in Table I are equal to $14 - pK_a$.