ment as hydrophobic as, for example, the pocket in chymotrypsin into which aromatic or hydrophobic side chains bind. Accordingly, one will anticipate some molecular reorganization as the hydrophobic pocket opens with concomitant entry of a group from the small molecule which is binding. For hydrophilic regions of the active sites of enzyme, these comments may not apply, for, in these situations, water may occupy sites in the absence of substrates and binding may occur by displacement of water; thus hydrophilic regions of an active site may have geometries that differ little as a function of the presence or absence of substrate.

Even after being bound to the enzyme, certain portions of the small molecule may still retain considerable steric mobility, as, for example, does the trifluoromethyl group of N-trifluoroacetyl-D-tryptophan with a $\tau_c \leqslant 10^{-10}$ sec representing possibly only rotational freedom about the C_3 axis.

Experimental Section

Chemicals. N-Trifluoroacetyl-D-tryptophan was prepared as reported elsewhere.[5]

α-Chymotrypsin was obtained from Sigma Chemical Co. and contained 80% active protein as determined by titration.[7] Solutions were prepared in 0.1 M citrate buffer as previously described.[7]

Spectrometric Modification. All spectra were obtained on a modified Varian 100-15 spectrometer using a 12-mm probe. Modification consisted of adapting the control amplifier and phase detector in the Internal Reference Stabilization unit so that a field-frequency lock could be obtained while monitoring the dispersion mode of a resonance with the analytical channel. The sweep frequency oscillator was replaced by a stable voltage controlled oscillator of our own design that could either be swept linearly by a suitable ramp, the voltage of which is proportional to the memory address of a time averaging computer, or be swept rapidly by application of a sudden voltage jump.

The input voltage for the rapid sweep was obtained by monitoring the voltage drop across a capacitor while the capacitor was being charged or discharged. The circuitry was arranged in such a way that the time constant for charging or discharging the capacitor could be varied from 0.005 to 0.01 sec. The magnitude of the voltage jump was also variable so that the amount of frequency swept could be varied from 0 to 400 Hz. In practice, we commonly swept 200 Hz into the center of the resonance using a time constant for the capacitor of 0.01 sec. As the nuclei of interest become excited only in the last several cycles, $t\pi/2$ in eq 8 is much less than 0.01 sec (probably less than 0.001 sec) and accordingly negligible compared to T_1 or T_2.

The spectrometer was locked on a capillary of hexafluoroacetone and the lock frequency adjusted to center the resonance for a given state of capacitor charge. The frequency can then be moved off resonance by changing the state of charge on the capacitor and then, after an appropriate length of time, swept back to the position of resonance. More simply, the apparatus is so arranged that one is either on resonance with the capacitor charged and off resonance when the capacitor is discharged or *vice versa*. One, then, sweeps onto resonance by discharging a charged capacitor, or charging a discharged capacitor. Either procedure gives an equivalent result.

A Fabri-tek 1062 time averaging computer was used as the recorder because it provided a fast, accurate time base and an adequate frequency response. The spectra were transferred to paper for subsequent analysis.

Catalysis of α-Hydrogen Exchange. XI. Monofunctional Catalysis of the Dedeuteration of Acetone-d_6[1,2]

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Abstract: The kinetics of the transformation of acetone-d_6 to acetone-d_5 and then acetone-d_4 in aqueous solution have been studied by a mass spectral method. As catalysts, hydrogen ion, hydroxide ion, trimethylamine, 1,4-diazabicyclo[2.2.2]octane, and methylamine buffers were studied. In the presence of methylamine buffers part of the reaction involves the rate-controlling removal of deuterium from the reversibly formed N-isopropylidenemethylammonium ion (the iminium ion). The rate constants reported for the attack of hydroxide ion on acetone-d_6 and of water and methylamine on the iminium ion differ significantly from earlier literature values.

E arlier papers in this series have described attempts to find bifunctional catalysis of the removal of the α-hydrogen atom of isobutyraldehyde in the presence of bifunctional species of the type B–R–NH₂, where B is a basic group and R is a divalent radical chosen to give an appropriate stereochemical relationship between B and the amino group. In the case of an ω-amino-alkanoic acid it was hoped that internal removal of the deuteron by the carboxylate anion group in the iminium ion **1** would yield bifunctional catalysis of the type de-
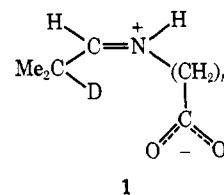
1

sired. The fact that no such catalysis was observed with the amino acids for which n is 1–5 was attributed to the tendency of aldiminium ions to exist almost en-

tirely in a trans form instead of a cis form like **1**.[3] For this reason it was obviously of interest to study a ketone having α-hydrogen atoms on both sides of the carbonyl group so that the basic functional group in an intermediate iminium ion would always be cis to activated hydrogen.[4] The rate of "enolization" of ketones has been studied by many workers who followed the reaction by measuring the rate of uptake of halogen. However, halogens and the halo ketones they produce tend to react with some of the types of compounds we wish to use as catalysts. Therefore, we have studied the kinetics of the dedeuteration of acetone-d_6. We describe here monofunctional catalysis of this reaction, followed by mass spectral measurements rather than proton magnetic resonance measurements, which are useful only for measuring the total amounts of protium and deuterium present and will give constant rate constants for the overall loss of deterium only if secondary deuterium kinetic isotope effects are negligible.

Results

The deuterium content of the acetone that was undergoing exchange was followed by mass spectral measurements on dried chloroform extracts of the reaction solutions. Corrected heights of the parent peaks for the d_6, d_5, d_4, d_3, d_2, d_1, and d_0 forms of acetone (that is, the heights that would have been obtained if ^{12}C and ^{16}O were the only isotopes of carbon and oxygen present) were calculated by assuming normal abundances of ^{13}C and ^{18}O. The fraction of the acetone present in its various deuterated forms was then calculated by neglecting isotope effects on the fragmentation. Thus, for example, the fraction that was hexadeuterated (f_6) was calculated as shown in eq 1, where h_i is the cor-

$$f_6 = h_{64}\left/\left(\sum_{i=58}^{64} h_i\right)\right. \tag{1}$$

rected height of the peak whose mass–charge ratio is i. Values of f_5, f_4, etc., were calculated analogously. Mass spectral analysis at 15 eV gave 99.6% deuterium for a sample of acetone-d_6 found by proton magnetic resonance (pmr) measurements to contain 99.6 ± 0.2% deuterium.[6] The peaks obtained at 15 eV were too weak for the study of fairly dilute aqueous solutions of acetone to be convenient, however. Hence, measurements were made at 70 eV, where the same sample of acetone was found to contain 99.0% deuterium. Analysis of synthetic mixtures of acetone-d_6 and ordinary acetone gave experimental values of f_6 that were 95.1 ± 3.4% of the values calculated on the basis of the pmr analysis. The low values of f_6 in the 70-eV analysis appeared to be due to the presence of M − 2 peaks. However, as long as the experimental value of f_6 is a linear function of the true value, the calculated first-

order rate constants will be unaffected. Hence, the 70-eV mass spectral analysis was used in our kinetic equations without correction.

The dedeuteration of acetone-d_6 was assumed to involve the consecutive transformation of acetone-d_6 to acetone-d_5, acetone-d_4, etc., as shown in eq 2. The

$$d_6 \xrightarrow{k_6} d_5 \xrightarrow{k_5} d_4 \xrightarrow{k_4} \text{etc.} \tag{2}$$
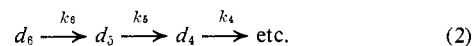
value of k_6, the first-order rate constant for dedeuteration of acetone-d_6, may be obtained from a plot of ln f_6 vs. time. The value of f_5 may be expressed as shown in eq 3, where $(f_6)_0$ and $(f_5)_0$ are the values of these frac-

$$f_5 = (f_5)_0 e^{-k_5 t} + \frac{k_6(f_6)_0}{k_6 - k_5} \left(e^{-k_5 t} - e^{-k_6 t}\right) \tag{3}$$

tions at initial time.[8] After k_6 had been determined in a given run, k_5 was calculated from a computer program that obtained the value for which the sum of the squares of the deviations of the f_5 values calculated from eq 3 from the experimental values was a minimum. The values of k_5 obtained were found to be considerably more uncertain than the values of k_6. In some runs values of k_4, k_3, etc., were calculated by a method analogous to that used for k_5; these values were found to contain still more uncertainty and are not reported here.

A value of about $8 \times 10^{-12} M^{-1} sec^{-1}$ has been reported for the water-catalyzed enolization of acetone at 25° in aqueous solution.[9] The value for acetone-d_6 at 35° should be smaller than this because the primary deuterium kinetic isotope effect should be larger than the 10° temperature effect. It follows that water catalysis would not contribute as much as 0.03% to any of the runs we made at 35°, and for this reason we have neglected water catalysis.

Catalysis constants for hydroxide ions and hydrogen ions were calculated by dividing the observed first-order rate constants by the catalyst concentrations, with the results shown in Table I. The reaction was also studied in the presence of buffer solutions composed of trimethylamine and trimethylamine hydrochloride and of 1,4-diazabicyclo[2.2.2]octane and its monohydrochloride. If the catalysis constants for these amines and their conjugate acids fit Bronsted plots of the catalysis constants[9-12] for carboxylate anions and carboxylic acids, respectively, the free amine will be a better catalyst than its conjugate acid by a factor of about 10^6 in the case of 1,4-diazabicyclo[2.2.2]octane and a factor of about 10^8 in the case of trimethylamine. For this reason we neglected general acid catalysis by these two ammonium ions; we also neglected general base catalysis by the monoprotonated form of 1,4-diazabicyclo[2.2.2]octane which, being only about one-millionth as basic as the unprotonated form, should be less than one-thousandth as good a basic catalyst. The concentrations of hydroxide ions present in the trimethylamine buffer solutions were calculated from literature pK

(3) J. Hine, B. C. Menon, J. Mulders, and R. L. Flachskam, Jr., *J. Org. Chem.*, **34**, 4083 (1969).

(4) Another obvious possibility is to accept the predominantly trans character of aldiminium ions and use a bifunctional catalyst in which B is attached to the amino group by a long enough chain to permit it to reach the activated hydrogen from the trans side of the iminium ion. Such an approach has led to the observation of bifunctional catalysis of the dedeuteration of isobutyraldehyde-2-d by polyethylenimines.[5]

(5) J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

(6) The uncertainty given here and elsewhere is the standard deviation[7] unless otherwise noted.

(7) W. J. Youden, "Statistical Methods for Chemists," Wiley, New York, N. Y., 1951, Chapters 2 and 5.

(8) *Cf.* N. M. Rodiguin and E. N. Rodiguina, "Consecutive Chemical Reactions, Mathematical Analysis and Development," Van Nostrand, Princeton, N. J., 1964, p 13.

(9) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940).

(10) H. M. Dawson and F. Powis, *J. Chem. Soc.*, **103**, 2135 (1913).

(11) H. M. Dawson and W. Lowson, *ibid.*, 1217 (1929).

(12) O. Reitz and J. Kopp, *Z. Phys. Chem., Abt. A*, **184**, 429 (1939).

Table I. Catalysis Constants for the Dedeuteration of Acetone-d_6 in Aqueous Solution[a]

Catalyst	Ionic strength	Temp, °C	No. of runs	$10^5 k_6$,[b] M^{-1} sec^{-1}	$10^5 k_5$,[b] M^{-1} sec^{-1}	k_6/k_5
NaOH	0.027 ± 0.018	0.5	3	305 ± 13	273 ± 26	1.12 ± 0.12
NaOH	0.011	25.0	2	3100 ± 80	2630 ± 120	1.18 ± 0.06
NaOH	0.027 ± 0.018	35.0	8	7220 ± 410	6030 ± 480	1.20 ± 0.12
NaOH[c]	0.011 ± 0.003	35.0	2	6370 ± 370	5440 ± 450	1.17 ± 0.12
NaOH	0.19	35.0	2	5950 ± 490	4990 ± 650	1.19 ± 0.18
HClO$_4$	0.19	25.0	2	0.437 ± 0.015	0.353 ± 0.021	1.24 ± 0.09
HClO$_4$	0.19	34.9	2	1.37 ± 0.03	1.13 ± 0.06	1.21 ± 0.07
Me$_3$N	0.19	35.0	2	1700 ± 70	1390 ± 80	1.22 ± 0.09
Dabco[d]	0.19	35.0	2	444 ± 10	371 ± 36	1.20 ± 0.12

[a] Using 0.52 M acetone-d_6 unless otherwise noted. [b] The uncertainties listed are equal to $\sqrt{\delta^2 + \Delta^2}$ where δ^2 is the average of the variances[7] obtained in the various individual runs and Δ is the standard deviation of the rate constants obtained in individual runs from the average rate constant listed. [c] 0.17 M acetone-d_6. [d] 1,4-Diazabicyclo[2.2.2]octane.

values[13] and those in the 1,4-diazabicyclo[2.2.2]octane buffers from pK values determined in the present study. The catalysis constants for the two amines were obtained by correcting the observed first-order rate constants (never by as much as 10%) for hydroxide ion catalyzed exchange and then dividing by the amine concentration. Values obtained at different amine concentrations were in satisfactory agreement, as shown in Table I.

Enthalpies and entropies of activation calculated from eq 4 for the k_6 values for hydrogen ion catalyzed

$$\ln k = \ln (kT/h) + \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/(RT) \quad (4)$$

exchange and for hydroxide-ion catalyzed exchange at low ionic strength are listed in Table II.

Table II. Enthalpies and Entropies of Activation for the Dedeuteration of Acetone-d_6 in Aqueous Solution[a]

Catalyst	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Hydrogen ions	20.5 ± 0.8	−14 ± 3
Hydroxide ions[b]	14.8 ± 0.2	−16 ± 1

[a] Using 0.52 M acetone-d_6. [b] At ionic strengths below 0.045 N.

To learn more about catalysis *via* the formation of intermediate iminium ions, the reaction was studied in the presence of methylamine buffers and gave the values of k_6 shown in Table III. These reactions were not all followed as far as needed for the determination of re-

Table III. Kinetics of the Dedeuteration of Acetone-d_6 in the Presence of Methylamine Buffers at 35°[a]

Total amine, M	pH	$10^5 k_6$, sec^{-1}	$10^5 k_{corr}$, sec^{-1}
0.1925	10.42	50.2	47.0
0.0722	10.40	14.4	10.5
0.0962	10.39	22.3	18.5
0.2888	10.37	105.1	104.4
0.0962	10.34	23.5	20.2
0.0722	10.21	11.6	9.01
0.1925	9.47	14.3	13.8
0.0962	9.46	5.32	4.87
0.0966	8.35	0.454	0.418
0.0962	7.88	0.156	0.144

[a] Using 0.52 M acetone-d_6 and ionic strengths in the range 0.197 ± 0.008 M.

(13) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc., Ser. A*, 177, 499 (1941).

liable values of k_5. The seven runs in which $f_5 + f_6$ was followed below the value 0.85 gave k_6/k_5 values in the range 1.08–1.21. The three runs that were not followed this far gave k_6/k_5 values as large as 1.48. In no case is it believed that there was an experimentally significant deviation from the value 1.2.

Discussion

If the reaction proceeds according to eq 2 and if there are no secondary deuterium kinetic isotope effects, the ratio k_6/k_5 will be 1.2. All the values of k_6/k_5 listed in Table I are within their standard deviations of 1.2. Any interpretation of these observations is complicated by the fact that about 40% of k_5 is determined by a reaction for which there is an α-deuterium isotope effect and 60% by a reaction in which there is a γ-deuterium isotope effect (both effects relative to the reaction governed by k_6).

The only rate constant we have found reported for the hydrogen ion catalyzed dedeuteration of acetone-d_6 in protium oxide solution was determined at 25° using concentrations of acetone and strong acid similar to those we have used.[14] Rates of bromination were determined for samples of acetone containing 0, 87, and 95.5% deuterium, the amount of deuterium in the acetone being calculated in a somewhat complicated way from the bromination rates. The rate constant for enolization (3.7 × 10^{-6} M^{-1} sec^{-1}) obtained by extrapolation to 100% deuterium is 15% smaller than the value we have obtained. Uncertainties in the deuterium content of the acetone studied by Reitz may contribute to the difference between the two rate constants.

Combination of our rate constant for the acid-catalyzed enolization of acetone-d_6 at 25° with the average of 18 rate constants for the acid-catalyzed halogenation of ordinary acetone in reasonably dilute aqueous solution at 25°[9,10,12,14–24] [(2.84 ± 0.07) × 10^{-5} M^{-1} sec^{-1}] yields a value of 6.5 ± 0.3 for k_H/k_D. Although this is no doubt largely a primary isotope effect it also con-

(14) O. Reitz, *Z. Phys. Chem., Abt. A*, 179, 119 (1937).
(15) H. M. Dawson and C. K. Reiman, *J. Chem. Soc.*, 107, 1426 (1915).
(16) H. M. Dawson and T. W. Crann, *ibid.*, 109, 1262 (1916).
(17) F. O. Rice and M. Kilpatrick, *J. Amer. Chem. Soc.*, 45, 1404 (1923).
(18) F. O. Rice and C. F. Fryling, *ibid.*, 47, 379 (1925).
(19) H. M. Dawson and A. Key, *J. Chem. Soc.*, 1239 (1928).
(20) H. M. Dawson and G. V. Hall, *Proc. Leeds Phil. Lit. Sci. Sect.*, 2, 289 (1932).
(21) G. F. Smith, *J. Chem. Soc.*, 1744 (1934).
(22) D. P. N. Satchell, *ibid.*, 2878 (1957).
(23) R. P. Bell and K. Yates, *ibid.*, 1927 (1962).
(24) B. T. Baliga and E. Whalley, *Can. J. Chem.*, 42, 1835 (1964).

tains a double α deuterium secondary isotope effect and a triple γ deuterium secondary isotope effect.

The rate constants we have obtained for the hydroxide ion catalyzed reaction tend to decrease with increasing salt concentration and decreasing acetone concentration. Both results are qualitatively those that would be expected for a reaction involving charge dispersal in the transition state. We have found reports of rate constants for the removal of deuterium from acetone-d_6 by hydroxide ions by two other groups of workers. A value at 25° that is 23% smaller than ours was reported in a brief communication,[25] for which full publication does not seem to have appeared. No experimental details were given beyond the fact that the kinetics of reaction with hypobromite were studied. If the study was carried out at low acetone concentration and low ionic strength this rate constant may be in reasonable agreement with our results. A determination of rate constants for the reaction of about 0.0007 M acetone-d_6 with hypobromite in the presence of a few hundredths molar hydroxide ions at 1.1, 25.2, 34.7, and 42.9°[26,27] yielded rate constants 40–55% smaller than ours at very similar temperatures and ionic strengths. The difference between these values and ours seems too large to explain in terms of the difference in concentrations of acetone used. The rate constants of Jones yield values of 14.0 kcal/mol and −20 eu for $\Delta H^{\pm}$ and $\Delta S^{\mp}$, respectively, according to which our larger rate constant arises from a considerably more favorable entropy of activation that is only partly cancelled by a higher enthalpy of activation. It is noteworthy that the work of Jones gives what appears to be the largest known deviation from the equation of Swain and coworkers that relates k_H/k_T and k_H/k_D values.[28] The rate constants of Jones for the deprotonation of acetone by hydroxide ions in water at 25° average about 10% smaller than the other four most recently reported values, all of which were determined using <0.003 M acetone and not more than a few hundredths molar sodium hydroxide.[25,29,30] The average of all seven rate constants is 0.166 ± 0.011 M^{-1} sec^{-1}. The rate constant for detritiation of 0.26 M acetone under the same conditions, including the appropriate statistical factor of 6, was 0.014 M^{-1} sec^{-1}.[26,27] This rate constant may have been increased by the presence of the 0.26 M acetone in the solvent but certainly by no more than 20%. These results give a range of 11.1–15.2 for k_H/k_T. From the equation of Swain and coworkers a k_H/k_D value in the range 5.3–6.6 would be expected. When this is combined with a double α and triple γ secondary deuterium kinetic isotope effect that Jones has found to amount to about 6.7% ($k_H > k_D$)[26] the range 0.024–0.029 M^{-1} sec^{-1} is calculated for the dedeuteration of dilute acetone-d_6 by hydroxide ions in water at 25°. Considering the effect of acetone concentration on the reaction rate, the rate constant we have obtained is in satisfactory agreement with this result, which is more than 50% larger than the rate constant determined by Jones. It therefore seems doubtful that the rate constants for removal of protium, deu-

terium, and tritium from acetone by hydroxide ions deviate significantly from the equation of Swain and coworkers.[31]

The catalysis constant we have obtained for trimethylamine is somewhat smaller than that (0.026 M^{-1} sec^{-1}) found by Bender and Williams in the exchange of light acetone with deuterium oxide at 25°.[32] The primary deuterium kinetic isotope effect is apparently only partly counterbalanced by the difference in reaction temperatures and perhaps by a solvent isotope effect.

If the mechanism of the dedeuteration of acetone-d_6 in the presence of methylamine buffers is analogous to that of isobutyraldehyde-2-d,[33–35] it proceeds via rate-controlling attack of bases on the carbonyl compound and on the N-methyliminium ion derived from it. Williams and Bender have shown that at 25° over the pH range 8.4–12.5 the first-order rate constant for the formation of the N-methylimine of acetone (via the N-methyliminium ion) is equal to 0.11 [MeNH$_2$] sec^{-1}.[36] If the rate of imine formation is faster at 35°, then in each of the kinetic runs listed in Table III it will be more than 12 times as fast as the dedeuteration reaction. Hence we shall be justified in treating the equilibrium formation of iminium ions as rapid compared with the subsequent removal of deuterium from the iminium ions. The only three bases in the solution that might plausibly participate to a significant extent in deuteron removal are water, hydroxide ions, and methylamine. We have already pointed out that attack of water on acetone may be neglected. Thus we arrive at eq 5, in

$$d[(CD_3)_2CO]/dt = \{k_h[OH^-] + k_m[MeNH_2] +$$
$$K_1(k_w' + k_h'[OH^-] +$$
$$k_m'[MeNH_2])[MeNH_3^+]\}[(CD_3)_2CO] \quad (5)$$

which K_1 is the equilibrium constant for the formation of the N-methyliminium ion from acetone and methylammonium ions, k_w', k_h', and k_m' are rate constants for dedeuteration of the N-methyliminium ion by water, hydroxide ions, and methylamine, respectively, and k_h and k_m are rate constants for attack of hydroxide ions and methylamine on acetone-d_6. The values of k_6 listed in Table III were based on eq 6, in which $[(CD_3)_2$

$$d[(CD_3)_2CO]/dt = k_6[(CD_3)_2CO]_t \quad (6)$$

CO]$_t$, the total concentration of acetone-d_6, differs from the actual concentration of acetone-d_6 by as much as 3.9%[37] because of the equilibrium transformation of some of the ketone to imine. The fact that k_h has been determined makes it convenient to define a corrected rate constant (k_{corr}) as $k_6[(CD_3)_2CO]_t/[(CD_3)_2CO]$ −

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(26) J. R. Jones, *Trans. Faraday Soc.*, **61**, 95 (1965); *J. Chem. Educ.*, **44**, 31 (1967).

(27) J. R. Jones, *Trans. Faraday Soc.*, **65**, 2138 (1969).

(28) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **80**, 5885 (1958).

(29) R. P. Bell and H. C. Longuet-Higgins, *J. Chem. Soc.*, 636 (1946).

(30) C. F. Cullis and M. H. Hashmi, *ibid.*, 2512 (1956); 3080 (1957).

(31) *Cf.* E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.*, **90**, 4337 (1968).

(32) M. L. Bender and A. Williams, *ibid.*, **88**, 2502 (1966).

(33) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *ibid.*, **88**, 3367 (1966).

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

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

(36) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2580 (1966).

(37) Based on the assumption that the equilibrium constant for the formation of the N-methylimine from methylamine is the same for acetone-d_6 as it is for light acetone, for which a value of 0.26 M^{-1} has been determined in water at 35°.[38]

(38) M. S. Cholod, unpublished observations.

$k_h[OH^-]$.[39] By combining eq 5 and 6, k_{corr} may be expressed as shown in eq 7, in which K_m is the ionization

$$k_{corr} = (k_m + K_I K_m k_h')[MeNH_2] +$$
$$K_I k_w'[MeNH_3^+] + K_I k_m'[MeNH_2][MeNH_3^+] \quad (7)$$

constant of methylamine. The equilibrium concentrations of methylamine and methylammonium ions in any given run may be calculated from the observed pH, the total concentrations of acetone-d_6 and methylamine used, the equilibrium constant for imine formation,[37] and the acidity constant for methylammonium ions, for which the value $4.2 \times 10^{-11} M^{-1}$ at 35° and ionic strength 0.19 M was interpolated from the data of Everett and Wynne-Jones.[13] According to eq 7 there are three constants, $k_m + K_I K_m k_h'$, $K_I k_w'$, and $K_I k_m'$, whose values might be determinable by varying the concentration of the components of the methylamine buffers. A least-squares treatment of the values of k_{corr} listed in Table III (minimizing the sum of the squares of the *per cent* deviations) gave the following values, $k_m + K_I K_m k_h' = 2.36 \times 10^{-3} M^{-1} sec^{-1}$, $K_I k_w' = 8.4 \times 10^{-7} M^{-1} sec^{-1}$, and $K_I k_m' = 4.02 \times 10^{-2} M^{-2} sec^{-1}$, from which the ten k_{corr} values may be calculated with a standard deviation of 9.0%. The $K_I k_w'$ term in eq 7 is the smallest term under all the conditions covered by Table III; it never contributes more than 2% to the overall rate in any run except the one at pH 7.88, where it contributes 6%. If this term is dropped from the equation the k_{corr} values may still be fit with a standard deviation of 9.1%. Hence it is possible that $K_I k_w'$ is considerably smaller than the optimum value we have calculated, and it may be negligible.

In a study of the enolization of light acetone at 25°, followed by iodination, the $K_I k_m'$ term for methylamine was reported to be negligible although corresponding terms for glycine and certain other amines were significant.[32] To evaluate the significance of this term in the present case, it was dropped from eq 7 and the best values of the constants for the other two terms were determined by a least-squares procedure. The standard deviation of the resulting calculated values of k_{corr} from the experimental values jumped to 28%. It therefore seems clear that the term is real. It is not clear what concentrations of buffers were used by Bender and Williams; if they were significantly smaller than ours the fraction of reaction *via* the $K_I k_m'$ term would have been smaller and less noticeable. For the constant we denote $k_m + K_I K_m k_h'$, Bender and Williams report the value $19.1 \times 10^{-3} M^{-1} sec^{-1}$. This is eight times as large as our value for the hexadeutero compound at a temperature 10° higher. Perhaps a large deuterium kinetic isotope effect has overwhelmed the 10° temperature effect. The term corresponding to our $K_I k_w'$ reported by Bender and Williams is about $\frac{1}{60}$th the size of their $k_m + K_I K_m k_h'$ term. In contrast, our $K_I k_w'$ is only about $\frac{1}{2800}$th as large as our $k_m + K_I K_m k_h'$ term, if not considerably smaller. The $K_I k_w'$ value of Bender and Williams was determined from the rather small intercept in a plot that requires the $K_I k_m'$ term to be negligible. The plot contains a theoretical line based on a change in the rate-controlling step from imine formation to enamine formation, but some of the

rate constants in the more acidic solutions appear to be less than half as large as they should be to fall on this line. Several workers[40,41] have noted that the value of $K_I k_w'$ reported[32] requires the N-methyliminium ion of acetone to be more rapidly deprotonated by water than would be expected from the reactivities of acetone and of isobutyraldehyde-2-d and its N-methyliminium ion toward water. Thus, Bender and Williams estimate that the N-methyliminium ion of acetone is about 10^9 times as reactive as acetone. By combining the pK of the N-methyliminium ion of isobutyraldehyde[42] with previous data,[35] the iminium ion may be calculated to donate carbon-bound α deuterons to water about 10^3 times as rapidly as the aldehyde does. Our results indicate that the rate constant for attack of water on the N-methyliminium ion derived from acetone reported earlier[32] is too high by more than tenfold. Nevertheless, there is still evidence that the change in structure on going from carbonyl compound to N-methyliminium ion increases the reactivity of acetone by a larger factor than it does that of isobutyraldehyde. Combination of the estimated pK (7.6) for the N-methyliminium ion of acetone,[32] the pK of methylammonium ions,[13] the equilibrium constant for imine formation,[37] and our value of $K_I k_m'$ gives a value of about 90 $M^{-1} sec^{-1}$ for k_m', the rate constant for dedeuteration of the N-methyliminium ion of acetone-d_6 by methylamine. If the term k_m is the dominant part of the constant $k_m + K_I K_m k_h'$ for acetone-d_6, as it appears to be in the case of the analogous constant for isobutyraldehyde-2-d,[35] then methylamine is about $10^{4.6}$ times as reactive toward the N-methyliminium ion as it is toward acetone; if the k_m term is not dominant this factor will be larger. In contrast, a similar calculation shows that methylamine is only about $10^{3.0}$ times as reactive toward the N-methyliminium ion of isobutyraldehyde-2-d as toward the aldehyde itself.[43]

Experimental Section

Kinetics of Dedeuteration of Acetone-d_6. A typical kinetic run was begun by injecting 0.20 ml of acetone-d_6 (Stohler, 99.5% D) through the serum stopper into each of nine thermostated ampoules containing 5 ml of catalyst solution under nitrogen. At a recorded time a slight excess of hydrochloric acid (usually 0.25 ml) was added to stop the reaction. Then 0.50 ml of chloroform was injected, the ampoule shaken, and the chloroform extract transferred by syringe to a 5-ml flask containing a small amount of Drierite. (The acid-catalyzed reactions were so slow that the catalyst was not neutralized to stop the reaction, which was considered stopped upon the addition of the chloroform.) The chloroform extracts were stored in a freezer until they were transferred by vacuum-line techniques to the gas bulbs used to introduce the samples into the mass spectrometer (AEI, Model MS-902). The peak heights on the recorded mass spectra were measured with a magnifying glass and ruler.

When sodium hydroxide was used as a catalyst its concentrations were in the range 0.006–0.044 M, with sodium chloride added to adjust the ionic strength in some cases. In spite of all our precautions to keep the solutions carbonate-free, there were often found, by potentiometric titration, to contain several per cent carbonate. In view of the observations that hydroxide ions transform glyceraldehyde and dihydroxyacetone to carbanions about 1000 times as

(40) W. Tagaki and F. H. Westheimer, *Biochemistry*, 7, 901 (1968).

(41) G. E. Lienhard and T.-C. Wang, *J. Amer. Chem. Soc.*, 90, 3781 (1968).

(42) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, 92, 5194 (1970).

(43) In this connection it should be noted that the next to the last sentence in the discussion section of ref 35 is in error and should end "... a k_m value of 1.55 or 2.52 × 10⁻³ $M^{-1} sec^{-1}$, depending on which C₂ value is used."

(39) The correction for hydroxide ion catalysis never amounted to as much as 28% of the total rate.

fast as carbonate ions do,[44] we neglected catalysis by carbonate ions.

The methylamine buffer solutions were prepared from standard solutions of methylamine, methylammonium chloride, hydrochloric acid, and sodium hydroxide with sodium chloride added as needed to bring the ionic strength into the range 0.197 ± 0.008 M. In all cases the pH was measured before the addition of acetone-d_6. After the first runs were made it was noted that addition of the acetone decreased the pH (by 0.10 ± 0.02) and, later, that the pH of the solutions usually increased by a few hundredths of a pH unit during the course of the run. The pH used in our calculations was that taken during (or after) the run if a value was taken or 0.10 less than the pH of the buffer without acetone (preferably determined during or after the run).

The second-order rate constants reported have been corrected for thermal expansion or contraction of the reaction solution as well as for the volume change that accompanied the addition of acetone.

(44) C. D. Gutsche, D. Redmore, R. S. Buriks, K. Nowatny, H. Grassner, and C. W. Armbruster, *J. Amer. Chem. Soc.*, **89**, 1235 (1967).

pK Determinations. The pK values of 1,4-diazabicyclo[2.2.2]-octane were determined by titration of 16 ml of a 0.07 M solution with 1.0047 M hydrochloric acid using apparatus[45] and methods of calculation[46] described previously. The thermodynamic pK values for the monoprotonated and diprotonated species were determined from data in the ionic strength ranges 0.015–0.045 and 0.107–0.155, respectively. These values, 8.77 ± 0.02 and 2.78 ± 0.01, respectively, showed no clear trend with changing ionic strength. These are comewhat higher than the values 8.65 and 2.67 that may be obtained from earlier data at 25° and ionic strength 0.1 M[47] by use of the Davies equation[46] and the calorimetrically determined enthalpies of reaction.[47]

(45) J. Hine and F. C. Kokesh, *ibid.*, **92**, 4383 (1970).
(46) J. Hine, F. A. Via, and J. H. Jensen, *J. Org. Chem.*, **36**, 2926 (1971).
(47) P. Paoletti, J. H. Stern, and A. Vacca, *J. Phys. Chem.*, **69**, 3759 (1965).

Bonding Studies in Group IV Substituted Anilines. I. A Comparison of Charge-Transfer and Electrochemical Methods for Determining Ground-State Energies

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Abstract: The energies of the long-wavelength transitions for charge-transfer complexes and the electrolytic half-peak oxidation potentials ($E_{P/2}$) are reported for a series of substituted anilines including p-tert-butyl-, p-trimethylsilyl-, p-trimethylgermyl-, and m-trimethylsilyl-N,N-dimethylaniline. The charge-transfer spectra do not provide reliable measurements of the relative energies of the ground-state molecular orbitals for this series of compounds. Correlations between $E_{P/2}$ values and ionization potentials determined by photoelectron spectroscopy are used to calculate ionization energies for the anilines. The results indicate a small stabilization of the highest filled molecular orbital (HFMO) when silicon or germanium is substituted for carbon in the para position of N,N-dimethylaniline.

In 1934 Koopmans proposed that the energy of the highest occupied molecular orbital of a molecule is equal to the negative of the observed molecular ionization energy.[1] Because the energy of a molecular orbital reflects the overall perturbation of that orbital by substituents, the ionization energies of a series of closely related molecules provide a basis for comparing substituent effects on their ground-state orbitals. While direct measurements of the ionization energies of larger molecules are rather difficult and expensive to obtain, electrolytic oxidation potentials and intermolecular charge transfer band maxima, both of which may be related to the ionization energy of a molecule, are readily determined.

The energy of the long-wavelength transitions for weak complexes between donors (D) and acceptors (A) has been related to the ionization potential of the donor (I^D) and the electron affinity of the acceptor (E^A) by Mulliken using perturbation theory, eq 1,[2] where $G_1 -$

$$hv_{CT} = I^D - (E^A + G_1 - G_0) + \frac{\beta_0{}^2 + \beta_1{}^2}{I^D - (E^A + G_1 - G_0)} \quad (1)$$

(1) T. Koopmans, *Physica*, **1**, 104 (1934).
(2) R. S. Mulliken, *J. Amer. Chem. Soc.*, **72**, 600 (1950); **74**, 811 (1952).

G_0 represents the difference in energy between the coulombic attraction in the excited state (G_1) and the van der Waals interaction in the ground state (G_0) of the complex, and $\beta_0{}^2$ and $\beta_1{}^2$ are intermolecular resonance terms in the ground and excited states, respectively. With the assumption that the terms $G_1 - G_0$ and $\beta_0{}^2 + \beta_1{}^2$ are constant for a series of complexes of different donors with the same acceptor, eq 1 may be somewhat simplified, but remains a parabolic relationship between hv_{CT} and I^D.[3] McConnell and coworkers have demonstrated that an empirical linear relationship between hv_{CT} and I^D, eq 2, is applicable to a wide variety of complexes.[4] Although it has been pointed out that

$$hv_{CT} = a_{CT}I^D + b_{CT} \quad (2)$$

there is no theoretical justification for such a linear relation,[5] it has been applied to the estimation of ionization potentials for a large variety of donors and acceptors with considerable success.[6–8]

(3) G. Briegleb and J. Czekalla, *Z. Elektrochem.*, **63**, 6 (1959).
(4) H. McConnell, J. S. Ham, and J. F. Platt, *J. Chem. Phys.*, **21**, 66 (1953).
(5) R. S. Mulliken and W. B. Person, *Annu. Rev. Phys. Chem.*, **13**, 107 (1962).
(6) See, for example, R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York, N. Y., 1969, and references therein.
(7) H. Bock and H. Alt, *J. Amer. Chem. Soc.*, **92**, 1569 (1970).
(8) H. Bock and H. Alt, *J. Organometal. Chem.*, **13**, 103 (1968).