

## Bifunctional Catalysis of $\alpha$ -Hydrogen Exchange of Aldehydes and Ketones<sup>1</sup>

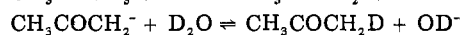
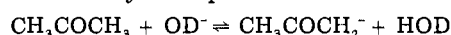
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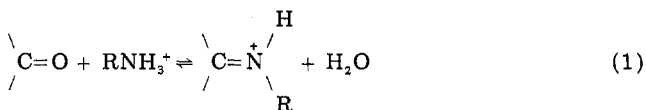
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Polyfunctional catalysis contributes greatly to the remarkable catalytic activity and selectivity of enzymes. Studies of enzymes and reactions they bring about have taught us much about such catalysis.<sup>2,3</sup> However, the high molecular weights of enzymes and the large number of functional groups in each molecule cause difficulties and ambiguities. We therefore wished to study relatively simple reactions proceeding by enzyme-like mechanisms. We started with reactions in which: (1) the catalyst uses one functional group to form a complex with, and perhaps activate, the substrate; (2) a second functional group brings about the desired reaction on the complexed substrate; (3) the complexed product is released.

The specific type of reaction we studied, the removal of  $\alpha$  hydrogen from an aldehyde or ketone, could be the first step of an aldol condensation, an epimerization reaction, or an elimination reaction, but for simplicity we studied isotopic exchange of  $\alpha$  hydrogen. Simple monofunctional bases bring about  $\alpha$  hydrogen exchange of carbonyl compounds. The electron-withdrawing

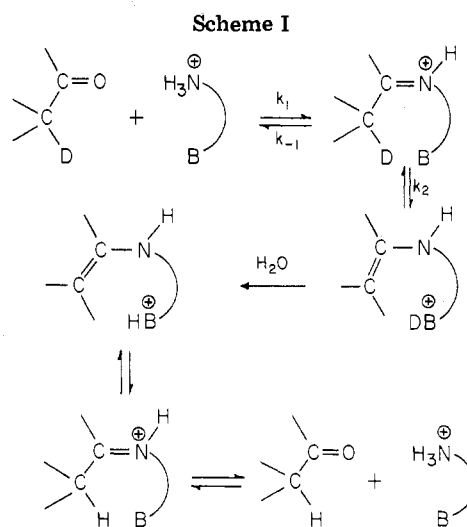


power of the doubly bonded oxygen atom makes possible resonance stabilization of the intermediate anion. The rapid reaction of primary amine salts with aldehydes and ketones gives a way of complexing a catalyst with a carbonyl substrate (eq 1). In the re-



sulting iminium ion, the neutral oxygen atom has been replaced by a positively charged nitrogen atom. This more strongly electron-withdrawing center makes the hydrogen atoms in the iminium ion more acidic than those in the original carbonyl compound. Evidence for

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this type of catalysis can be found in primary amine catalysis of "enolizations",<sup>4</sup> decarboxylation of  $\beta$ -keto acids,<sup>5</sup> and aldol condensations.<sup>6</sup> Analogously, enzymes are known to use the primary amino groups of lysine residues to coordinate with substrate carbonyl groups in decarboxylations of  $\beta$ -keto acids<sup>7</sup> and in aldol condensations.<sup>8</sup>

On the preceding basis we sought bifunctional catalysis of the  $\alpha$ -deuterium exchange of aldehydes and ketones by a mechanism that is given in an abbreviated form in Scheme I. The bifunctional catalyst B-NH<sub>3</sub><sup>+</sup> is a salt of a primary amine that contains a second functional group (B), which removes an  $\alpha$  deuterium

(1) Supported in part by Grants AM 06829, AM 10378, and GM 18593 from the National Institutes of Health.

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(3) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley, New York, N.Y., 1971.

(4) N. V. Volkova, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, 31, 56 (1965), and references cited therein.

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internally in the intermediate iminium ion. This gives an enamine with a  $-BD^+$  group that exchanges with the solvent to become  $-BH^+$ . The exchanged enamine then gives exchanged iminium ion, which hydrolyzes to exchanged carbonyl compound by mechanisms that are the reverse of those by which the enamine was formed.

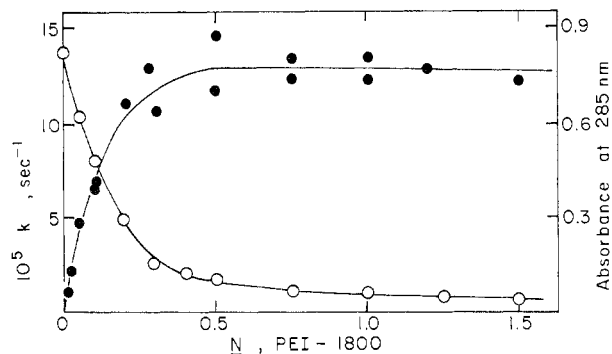
### Studies with Monofunctional Species

We were not interested merely in finding polyfunctional catalysis. We wanted to understand what we found. Hence we first studied analogous reactions of monofunctional species in detail. The first carbonyl compound studied was isobutyraldehyde. Its rate and equilibrium constants for aldolization<sup>9</sup> and hydration<sup>9-11</sup> were determined because these are possible complicating processes. A study of the dedeuteriation of  $Me_2CDCHO$  in the presence of a variety of different bases showed that, for their basicity, unhindered tertiary amines are the most effective catalysts.<sup>12</sup> Equilibrium constants for imine formation with primary amines were determined and were found to be lowered by steric hindrance<sup>13</sup> and electron-withdrawing substituents.<sup>14</sup>

Before studying bifunctional catalysts we studied cases in which  $Me_2CDCHO$  should undergo exchange by a mechanism like that shown in Scheme I, except that the B group and the  $NH_2$  group are not in the same molecule. The first such study used  $MeNH_2$ - $MeNH_3^+$  buffers, in which the aldehyde often existed largely in the form of the imine.<sup>15</sup> The major term in the rate equation can be expressed in any of the kinetically equivalent ways shown in eq 2. This is in agreement

$$\begin{aligned} k [Me_2CDCH=NMe][MeNH_3^+] = \\ k' [Me_2CDCHO][MeNH_3^+][MeNH_2] = \\ k'' [Me_2CDCH=NHMe^+][MeNH_2] \end{aligned} \quad (2)$$

with a mechanism in which the rate-controlling step is transformation of the iminium ion to  $Me_2C=CHNHMe$  by  $MeNH_2$ . Rough experiments showed that iminium ion formation from isobutyraldehyde is much too fast to be rate controlling in dedeuteriation. When  $Me_2CDCHO$  was dedeuteriated in the presence of  $MeNH_3^+$  and a number of buffers,<sup>16</sup> a major term in the rate equation was of the form  $k[Me_2CDCHO] \cdot [MeNH_3^+][base]$ . The values of  $k$  obtained for the various buffer bases give the relative rate constants for removal of  $\alpha$  deuterons from  $Me_2CDCH=NHMe^+$  by the bases. A Brønsted plot of these  $k$  values showed a rather poor correlation. However, a log-log plot of the constants vs. the corresponding rate constants for removal of  $\alpha$  deuterons from  $Me_2CDCHO$  by the same base closely approached a straight line. Apparently, the steric and other factors that cause the data to fit the



**Figure 1.** Isobutyraldehyde (0.053 M) in water at 35 °C and pH  $8.48 \pm 0.06$  in the presence of various concentrations of PEI-1800: (●) first-order rate constants for the dedeuteriation of  $Me_2CDCHO$ ; (○) absorbance at 285 nm.

Brønsted equation rather poorly are about the same for attack on the iminium ion as for attack on the aldehyde. The slope of the line (0.84) reflects the lesser selectivity of the iminium ion, which is considerably more reactive than the aldehyde. With this limitation, the aldehyde is seen to be a good model for the iminium ion as far as relative rates of deuterium removal are concerned. Hence, what was learned from the study of the rates of attack of various bases on  $Me_2CDCHO$  can be extrapolated to the iminium ion.

Next, the base was kept constant, and the primary amine salts were varied. The dedeuteriation of  $Me_2CDCHO$  was carried out in pyridine buffers using the hydrochlorides of 11 different primary amines.<sup>17</sup> The values of  $k$  in kinetic terms of the form  $k \cdot [Me_2CDCHO][RNH_3^+][C_5H_5N]$  were determined. A plot of  $\log k$  vs.  $pK_a$  for  $RNH_3^+$  for the eight cations of the type  $XCH_2NH_3^+$  agreed fairly well with a straight line of slope 0.4. That is, electron-withdrawing substituents increased the reactivity under conditions where the primary amine is largely protonated. This effect is as expected because the nitrogen atom must be more strongly positive in  $RNH_3^+$  than in the transition state for transformation of iminium ion to enamine.

### Bifunctional Catalysis of the Dedeuteriation of $Me_2CDCHO$

**Catalysis by Poly(ethylenimines).** Meanwhile, we had started seeking bifunctional catalysis. The first compounds shown to be bifunctional catalysts were poly(ethylenimines) (PEIs),<sup>18,19</sup> which were branched to such an extent that the ratio of primary to secondary to tertiary amino groups was about 1:2:1. This represents a "shotgun" approach to the problem in that once an iminium ion is formed from  $Me_2CDCHO$ , as in 1, the entire surrounding landscape will be dotted with amino groups. The evidence for bifunctional catalysis includes saturation effects, as illustrated in Figure 1. The plot, in solid circles, of the first-order rate constant for dedeuteriation of 0.053 M  $Me_2CDCHO$  vs. the concentration of PEI (average molecular weight 1800) at pH 8.5 shows no further significant increase after the PEI concentration passes about 0.5 N. Also plotted, as

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

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

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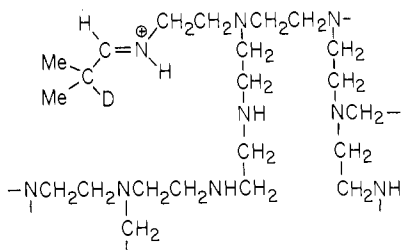
(15) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).

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

(17) J. Hine, B. C. Menon, J. Mulders, and J. P. Idoux, *J. Org. Chem.*, **32**, 3850 (1967).

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

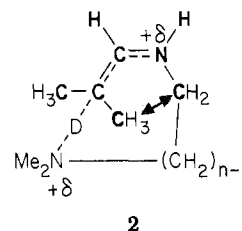
(19) J. Hine, E. F. Glod, R. E. Notari, F. E. Rogers, and F. C. Schmalstieg, *J. Am. Chem. Soc.*, **95**, 2537 (1973).



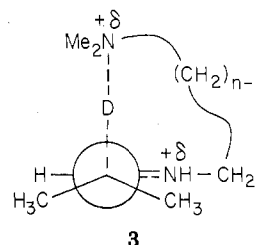
open circles, is the absorbance at the isobutyraldehyde absorption maximum. This plot shows that most of the aldehyde has been complexed by the time the PEI concentration has reached 0.5 N. The complexed aldehyde must be present as a mixture of imines, iminium ions, imidazolidines, etc. The iminium ions are dedeuterated by amino groups in the same molecule. (If they were dedeuterated by amino groups in other PEI molecules, the rate would continue to rise with increasing PEI concentration.) Just as the aldehyde could be saturated with PEI, the PEI could be saturated with aldehyde. That is, the rate asymptotically approaches a limit as the aldehyde concentration is increased in the presence of constant PEI concentration and constant pH. These two types of saturation are not subject to Michaelis-Menten, Lineweaver-Burk, etc., treatments, because there are many different types of binding sites on any PEI molecule. The proposal of bifunctional catalysis is also consistent with a maximum at about pH 8 in the plot of the rate constant for exchange vs. pH. At higher pHs not enough complexed imines are protonated to give iminium ions. At lower pHs too many amino groups have been protonated or have had their basicities decreased by protonation of nearby amino groups.

**Catalysis of Me<sub>2</sub>CDCHO Exchange by Bifunctional Species.** Studies of the effect of the average molecular weight of a PEI sample on its catalytic activity show that cyclic transition states have a variety of ring sizes.<sup>20</sup> However, the large number of amino groups present in every catalyst molecule makes it hard to be sure of what any one of them is doing. Less ambiguous results have been obtained by use of bifunctional catalysts.  $\omega$ -Aminoalkanoic acids<sup>21</sup> and monoprotonated  $\omega$ -dimethylaminoalkylamines,<sup>22,23</sup> both of which have been studied, are of the form B-(CH<sub>2</sub>)<sub>n</sub>NH<sub>3</sub><sup>+</sup>, where B is a basic group. The optimum value for  $n$  is a function of the optimum ring size for the cyclic transition state. One might suppose that a five- or six-membered ring would be best because these are the commonly favored ring sizes in organic chemistry. However, there are stereoelectronic complications that tend to make the optimum ring size larger. As seen in Scheme I, internal deuteron transfer transforms an iminium ion to an enamine. The double bond in the iminium ion enforces near-coplanarity on the doubly bonded carbon and nitrogen atoms and on the four atoms attached directly to them. The double bond in the enamine requires another set of six atoms to be nearly coplanar. From the principle of least motion,<sup>24</sup>

each of these sets of six atoms is expected to be roughly coplanar in the transition state. Since there are four atoms that are common to the two sets, all eight atoms involved are required to lie near a common plane. These atoms are shown in boldface in 2, which rep-



resents the transition state for an  $\omega$ -dimethylaminoalkylamine catalyst. The carbon-deuterium bond being broken should be in a plane nearly perpendicular to that approximated by the eight boldfaced atoms. The carbon sp<sup>3</sup> orbital used for bonding to deuterium is transformed in the enamine to a p orbital that is parallel to a p orbital on the adjacent carbon atom. Hence, the carbon-deuterium bond in the transition state should be almost parallel to the p orbital on the adjacent carbon atom. This situation can be seen more clearly in 3, which is a Newman projection looking from the



$\alpha$ -carbon atom to the nitrogen-bound carbon atom of the isobutyraldehyde part of the transition state. It is also seen that there is a N-D-C hydrogen bond in the transition state. Inasmuch as hydrogen bonds are preferably linear, the nitrogen atom should attack the deuterium atom on the extension of the carbon-deuterium bond. The preceding considerations fix the approximate relative positions of six ring atoms (N-D-C-C-N-C) in the cyclic transition state. Yet it is obvious from 3 that a considerable gap in the ring remains. By use of molecular models, we estimated that three more atoms ( $n = 4$ ) would be required to fill the gap satisfactorily.

We were sure that the  $\omega$ -aminoalkanoic acids and the  $\omega$ -dimethylaminoalkylamines, like any bases, would be catalysts for the dedeuteration of Me<sub>2</sub>CDCHO. Bifunctional catalytic activity should give greater activity than would be reasonable for monofunctional catalysis alone. One way of estimating what is reasonable for monofunctional catalysis is from the Brønsted equation. The second-order rate constants for dedeuteration of Me<sub>2</sub>CDCHO by monoprotonated diamines of the form Me<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub> (where  $n = 2, 3, 4,$  and  $5$ ) are plotted as open circles in Figure 2 against the pKs of the diprotonated diamines (which measure the basicities of the monoprotonated diamines).<sup>22,23</sup> The catalytic activities increase monotonically with increasing basicity of the catalysts, and the basicity increases monotonically with the increasing numbers of carbon atoms between the two amino groups. (The two positive

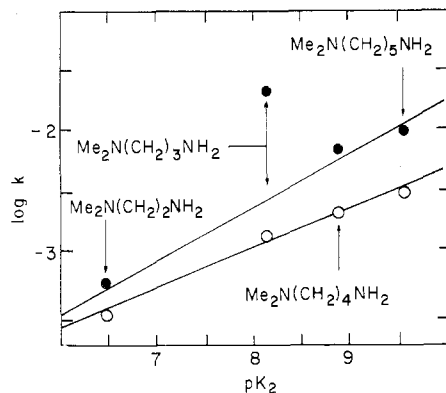
(20) J. Hine and R. L. Flachskam, Jr., *J. Org. Chem.*, **39**, 863 (1974).

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

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**Figure 2.** Brønsted plot for the dedeuteriation of  $\text{Me}_2\text{CDCHO}$  (open symbols) and acetone- $d_6$  (solid symbols).  $K_2$  is the acidity constant for the diprotonated diamine and  $k$  is the apparent second-order rate constant (in  $\text{M}^{-1} \text{s}^{-1}$ ) for catalysis by the monoprotinated diamine in water at  $35^\circ \text{C}$ .

charges in the diprotonated amine destabilize each other to an extent that decreases with increasing distance between the amino groups.) Thus, there is little evidence for bifunctional catalysis by any of the four diamines. Similar results were obtained for the  $\omega$ -aminoalkanoic acids containing 2, 3, 4, 5, and 6 carbon atoms.<sup>21</sup> We hypothesized that this lack of bifunctional catalysis arose in part from steric hindrance of the type indicated by the double-headed arrow in 2. In order for the dimethylamino group to reach the  $\alpha$ -deuterium atom with chains of the length we were dealing with, there must be a cis orientation around the double bond of the reacting iminium ion. In the transition state, where the boldfaced atoms have become nearly coplanar, this orientation results in repulsion between the carbon-bound methyl group and the nitrogen-bound methylene group indicated. Poly(ethylenimines) contain such long chains that internal attack on deuterium can occur from iminium ions that are trans, like 1. Bifunctional catalysis was also observed with monoprotinated  $\text{Me}_2\text{NCH}_2\text{C}\equiv\text{C}(\text{CH}_2)_5\text{NH}_2$ , where the chain between the two amino groups is long enough to permit the  $\alpha$ -deuterium atom to be reached internally from the trans form of the intermediate iminium ion.<sup>23</sup>

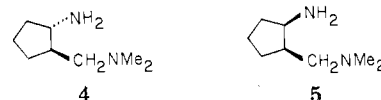
### Bifunctional Catalysis of the Dedehuteriation of Acetone- $d_6$

**Catalysis by  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2\text{H}^+$ .** There are many aldehydes and ketones for which the type of steric hindrance to bifunctional catalysis indicated by the double-headed arrow in 2 is not possible. Some such compounds should be susceptible to bifunctionally catalyzed  $\alpha$ -hydrogen exchange if our explanation of the behavior of  $\text{Me}_2\text{CDCHO}$  is correct. Therefore the dedeuteriation of acetone- $d_6$  was studied. First, appropriate monofunctional catalysts were studied, and the occurrence of catalysis via iminium ion formation<sup>4,25</sup> was confirmed.<sup>26</sup> Then, the diamines of the type  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2$  were studied.<sup>22</sup> The solid circles in Figure 2 show that, with acetone- $d_6$ , the point for one of the four diamines lies markedly above the line described by the points for the other three. The catalytic activity of  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}_2\text{H}^+$  is about seven times that which would be required for it to fall on the

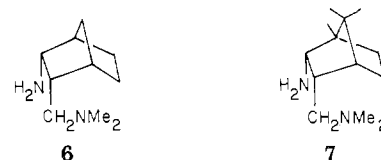
Brønsted line for  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2\text{H}^+$ , where  $n = 2, 4$ , and 5. Apparently,  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}_2\text{H}^+$  is a bifunctional catalyst for the dedeuteriation of acetone- $d_6$ . We had guessed that the best bifunctional catalyst of the  $\omega$ -dimethylaminoalkylamines would be the one with four carbon atoms between the two amino groups. This guess had been based on examination of molecular models, which suggested that the C--D--N hydrogen bond in the transition state would be bent by about  $30^\circ$  if there were only three carbon atoms between the two nitrogen atoms of the catalyst. Subsequent molecular mechanics calculations, however, gave an estimate of only about  $5^\circ$  bending by the hydrogen bond in the transition state.<sup>27</sup>

**More Rigid Catalysts.** Examination of models of the transition state for bifunctional catalysis by  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}_2\text{H}^+$  suggested that there were two possible conformers of comparable energy. These two conformers differ in respect to the conformation around the bond between C-1 and C-2. In both conformers this bond is in an approximately eclipsed conformation. In what appears to be the more stable conformer, the bond from C-1 to N is eclipsed by one of the bonds from C-2 to H. There should certainly not be eclipsing around the C-1--C-2 bond in  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}_2\text{H}^+$ . Therefore, the energy required to bring about such eclipsing must be part of the activation energy for the reaction. Hence, a similar species in which the eclipsing was already present should be a better catalyst. The first compounds studied to test this hypothesis were the 2-(dimethylaminomethyl)cyclopentylamines.<sup>22,28</sup> Because of the flexibility of cyclopentane rings, the desired eclipsing would be only approximated in these compounds. However, they appeared to be easier to synthesize than more appropriately rigid compounds.

It was easy to separate the pure trans isomer (4) from



the mixture of isomers, but the purest sample of cis isomer (5) obtained still contained 19% trans isomer as impurity. Both isomers were more than 10 times as effective as  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}_2$  in catalyzing the dedeuteriation of acetone- $d_6$ . The cis isomer was about twice as effective as the trans. With this encouragement we synthesized 3-endo-dimethylaminomethyl-2-endo-norbornanamine (6), a compound in which the desired



eclipsing is more rigidly enforced.<sup>29</sup> To study the effect of varying the dihedral angle and the relative conformational populations in various ways, we also prepared several other 1,3-primary-tertiary diamines.<sup>29,30</sup> The most effective catalysts were 6 and its trimethyl derivative 7, the only two with the C--NH<sub>2</sub> and C-

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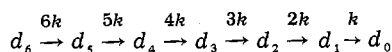
(29) J. Hine and W.-S. Li, *J. Org. Chem.*, **40**, 289 (1975).

(30) J. Hine and W.-S. Li, *J. Am. Chem. Soc.*, **97**, 3550 (1975).

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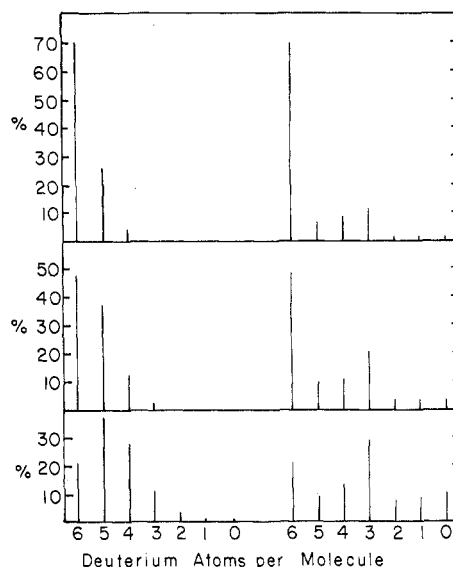
(26) J. Hine, J. C. Kaufmann, and M. S. Cholod, *J. Am. Chem. Soc.*, **94**, 4590 (1972).

Scheme II



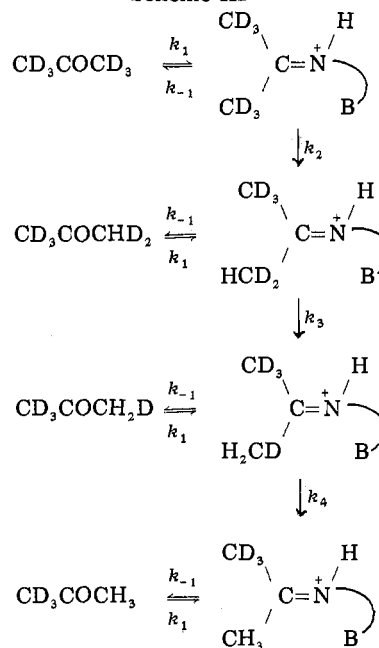
$\text{CH}_2\text{NMe}_2$  bonds rigidly eclipsed.<sup>31</sup>

**Rate Control by Iminium Ion Formation.** When acetone- $d_6$  was dedeuterated in the presence of methylamine buffers, iminium ion formation was more than 200 times as fast as dedeuteration.<sup>32</sup> That is, the step in which deuterium is removed from carbon was clearly rate controlling. With a bifunctional catalyst, however, deuterium removal is more efficient. Hence, dedeuteration should be faster, relative to iminium ion formation. If deuterium removal becomes efficient enough, rate control may shift to the iminium ion formation step. This tendency is detectable with all the bifunctional catalysts studied. It has characteristic effects on the pattern of changes in the isotopic content of the acetone- $d_6$  as it loses deuterium. When acetone- $d_6$  is dedeuterated by a simple basic catalyst or via an iminium ion intermediate (with the iminium equilibrium being rapid relative to dedeuteration), the reaction follows Scheme II (neglecting secondary deuterium kinetic isotope effects). Under these conditions the isotopic analyses of the acetone always pass through the same sequence when material of a given isotopic content is used as the starting material. Thus, if the starting material is 100%  $d_6$ , when the  $d_6$  content has dropped to 70% there will be 26%  $d_5$ , 4%  $d_4$ , and less than 1% of the less deuterated species present, as shown in the upper left bar graph of Figure 3. With an effective catalyst this sequence will occur in a short time; with a poor catalyst it will take a long time, but, except for the time scale, the pattern is the same. The three bar graphs on the left of Figure 3 show the pattern. As the lower left graph shows, when the  $d_6$  content has dropped to 21%,  $d_5$  has become the most abundant species. Later,  $d_4$  becomes the most abundant. The right side of Figure 3 shows three analyses obtained in a run using 6 as a catalyst.<sup>31,33</sup> Obviously, acetone- $d_3$  and - $d_4$  are being formed from the beginning of the reaction. They are being formed from acetone- $d_6$  without passing through acetone- $d_5$  as an intermediate, as required by Scheme II. There is no point in the reaction at which either  $d_5$  or  $d_4$  is the most abundant species. When  $d_6$  loses that distinction it is taken over by  $d_3$ . These facts are explained by Scheme I, which has been rewritten as Scheme III for this purpose. Under the conditions used in the kinetic run covered by the right side of Figure 3, the iminium- $d_6$  cation loses deuterium faster than it hydrolyzes back to acetone- $d_6$ . The rate constant  $k_2$  is more than three times as large as  $k_{-1}$ . Having only two cis deuterium atoms to operate on,  $k_3$  is two-thirds as large as  $k_2$  and therefore more than twice as large as  $k_{-1}$ . Hence, the iminium- $d_5$  cation hydrolyzes to acetone- $d_5$  less than one-third of the time. More than two-thirds of the time it is transformed to the iminium- $d_4$  cation, which usually loses another deuterium atom to give an iminium- $d_3$  cation. Having no deuterium atoms cis to the internal dimethylamino



**Figure 3.** Bar graphs of percent acetone- $d_6$ , - $d_5$ , etc., starting with acetone- $d_6$ . The three on the left are points in a reaction that follows Scheme II and the three on the right are experimental points for a run using 6 as a catalyst.

Scheme III



group (B), the iminium- $d_3$  cation essentially always hydrolyzes to acetone- $d_3$ . Thus, in dedeuteration under these conditions the rate is controlled more by the rate constant for iminium ion formation than by the rate constant for internal transfer of deuterium.

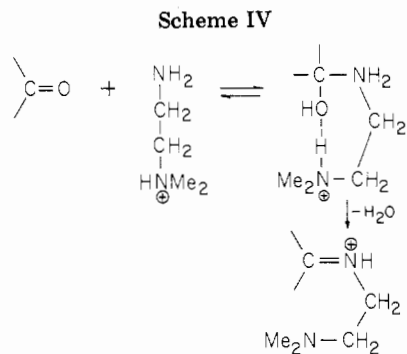
**Internal Acid Catalysis of Iminium Ion Formation.** The evidence that iminium ion formation can be largely rate controlling increased our interest in the mechanism of iminium ion formation. Starting in the late 1950s, the work of Jencks and others had enormously increased our understanding of compounds with carbon-nitrogen double bonds and their formation from and transformation to carbonyl compounds.<sup>34</sup> For various reasons, however, little work had been done on imines and iminium ions with only hydrogen atoms and saturated carbon atoms attached to the carbon-nitrogen

(31) J. Hine and W.-S. Li, *J. Am. Chem. Soc.*, **98**, 3287 (1976).

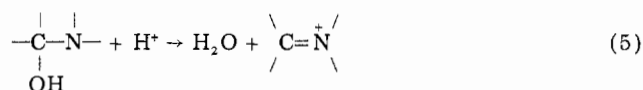
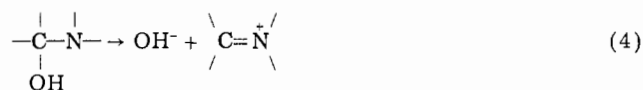
(32) This is a conservative estimate, based on the assumption that the rate constant for imine formation from acetone- $d_6$  and methylamine at 35 °C is twice as large as the value for acetone and methylamine at 25 °C.<sup>25</sup>

(33) W.-S. Li, 1975, unpublished observations.

(34) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964); ref 2, Chapter 10.



double bonds. We studied the kinetics of the formation<sup>35</sup> and hydrolysis<sup>36</sup> of *N*-isobutyridene-methylamine. The results supported the accepted mechanism, which in neutral and basic aqueous solutions involves the relatively rapid addition of amine to the carbonyl compound to give a carbinolamine that is transformed to iminium ion in the rate-controlling step (eq 3-5). In strongly basic solutions the carbinolamine



simply ionizes to give iminium and hydroxide ions. In more nearly neutral or acidic solutions, however, a hydrogen ion catalyzed reaction becomes important. We reasoned that if iminium ion formation can be catalyzed by an external acid, why not by an internal acid? Might not monoprotonated  $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ , for example, give internal acid catalysis of its own iminium ion formation, as shown in Scheme IV? If catalysis of this type can be achieved, perhaps it can be used to increase the efficiency of polyfunctional catalysis of  $\alpha$ -hydrogen exchange. If iminium ion formation by the mechanism in Scheme IV is very important,  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHMe}_2^+$  will form iminium ions at a rate that is unreasonably fast for the mechanisms shown in eq 3-5.

To tell how fast iminium ion formation ought to be in the absence of internal catalysis, the kinetics of the reactions of isobutyraldehyde<sup>37</sup> and acetone<sup>38</sup> with a series of primary amines were studied. The amines were of the type  $\text{RCH}_2\text{NH}_2$ , with R chosen so as to vary the polar substituent effect markedly without changing steric effects excessively. In Figure 4 is a plot of  $\log k$  for uncatalyzed iminium ion formation from acetone vs.  $\text{p}K_a$ .<sup>38</sup> (The  $\text{p}K_a$  of the conjugate acid of the amine is a simple measure of the electron-withdrawing power of R.) The solid circles refer to electrically neutral amines and fall close to a straight line. The point for the cationic amine  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NMe}_3^+$  lies near this line.

(35) J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *J. Am. Chem. Soc.*, **92**, 5186 (1970).

(36) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970).

(37) J. Hine and F. A. Via, *J. Am. Chem. Soc.*, **94**, 190 (1972).

(38) J. Hine, M. S. Cholod, and W. K. Chess, Jr., *J. Am. Chem. Soc.*, **95**, 4270 (1973).

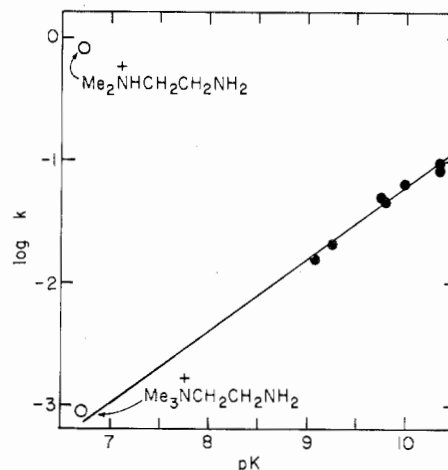


Figure 4. Plot of logarithms of second-order rate constants for the formation of imines from acetone and various species of the type  $\text{RCH}_2\text{NH}_2$  in water at 35 °C and ionic strength 0.3 vs.  $\text{p}K_a$  for the corresponding  $\text{RCH}_2\text{NH}_3^+$  species under the same conditions: (●) amines of the type  $\text{XCH}_2\text{CH}_2\text{NH}_2$  without acidic substituents.

Table I  
Dedeuteration of Acetone- $d_6$  in the Presence of  $8^a$

$[\text{Am}]_t$ , M	pH	$10^5 k$ , $\text{s}^{-1}$
0.0123	6.29	0.66
0.0452	6.21	2.54
0.0124	9.75	35
0.0249	9.78	72
0.0497	9.80	136

<sup>a</sup> In water at 35 °C.<sup>31</sup>

However,  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHMe}_2^+$  reacts far too rapidly to fall on the line.<sup>39</sup> Uncatalyzed iminium ion formation by monoprotonated diamine is, of course, kinetically indistinguishable from hydrogen ion catalyzed iminium ion formation by unprotonated diamine. However, from the observed relative insensitivity of the reactions of the other amines to hydrogen ion catalysis, this explanation for the reaction of  $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NH}_2$  is quite implausible. Similar evidence for internal acid catalysis in iminium ion formation was also obtained in the reaction of  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHMe}_2^+$  with isobutyraldehyde.<sup>41</sup> Also studied were the kinetics of iminium ion formation from the reaction of acetone with  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2$  ( $n = 3-5$ ) and with most of the other diamines that had been studied as bifunctional catalysts for the dedeuteration of acetone- $d_6$ .<sup>38,42</sup> The monoprotonated forms of most of them appeared to give iminium ions largely by an internal acid-catalyzed mechanism.<sup>43</sup> (For none, however, did the reactivity exceed that expected in the absence of such catalysis by as large a factor as for  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHMe}_2^+$ .) Thus, it turned out that, purely by luck, the desired internal acid catalysis of iminium ion formation was already taking place with most of the catalysts that had been

(39) A rate constant based on total monoprotonated diamine (denoted  $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NH}_2\text{H}^+$ ) is about 400 times too large to fall on the line. This rate constant was divided by 0.38, the fraction of the total monoprotonated diamine that is protonated at the tertiary nitrogen atom,<sup>40</sup> to obtain a rate constant based on  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHMe}_2^+$ . This rate constant, the one plotted in Figure 4, is more than 1000 times too large to fall on the line.

(40) J. Hine, F. A. Via, and J. H. Jensen, *J. Org. Chem.*, **36**, 2926 (1971).

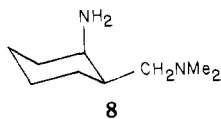
(41) J. Hine and F. A. Via, *J. Org. Chem.*, **42**, 1972 (1977).

(42) J. Hine and W.-S. Li, *J. Org. Chem.*, **40**, 2622 (1975).

(43) The rate constants for iminium ion formation thus obtained directly were all within 30% of values that were calculated less directly from the kinetics of the dedeuteration of acetone- $d_6$  under slightly different conditions. This confirms Scheme III for dedeuteration.

selected before we knew that iminium ion formation would be largely rate controlling.

**Dedeuteration of the  $-NMe_2^+$  Group.** There is evidence not only that the first two steps of Scheme I may contribute to rate control of the overall reaction, but that the third step may contribute also. With our catalysts this step is a transformation of a  $-NMe_2^+$  group to a  $-NHMe_2^+$  group. It would be initiated by removal of the deuterium from the  $-NMe_2^+$  group by some base. There is strong evidence that proton transfers between oxygen and nitrogen atoms in aqueous solution ordinarily proceed at essentially the diffusion-controlled rate if the equilibrium constant is significantly larger than 1.0. Since the reaction solutions all contain such bases as amines and hydroxide ions, we had assumed that exchange of the  $-NMe_2^+$  group would always be too fast to be rate controlling. However, for the more effective bifunctional catalysts, data like those shown in Table I for *cis*-2-(dimethylaminomethyl)cyclohexylamine<sup>31</sup> (**8**) are obtained. The

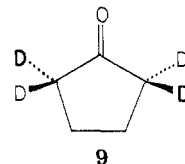


dedeuteration at  $\text{pH } 9.78 \pm 0.03$  is first order in **8**, whereas at  $\text{pH } 6.25 \pm 0.04$  it is almost second order in **8**. The explanation for this difference in behavior is that at the lower pH the removal of a deuterium from the  $-NMe_2^+$  group of the enamine is largely rate controlling, but at the higher pH it is not. Only one molecule of **8** is required to transform acetone- $d_6$  to the iminium ion and on to the enamine. Around pH 9.78 there are enough hydroxide ions and amine molecules to remove deuterons from the enamine essentially every time it is formed. Around pH 6.25, however, there are only 0.03% as many hydroxide ions and very few unprotonated amine molecules. Hence, the  $-NMe_2^+$  substituted enamine usually reverts to iminium- $d_6$  cations and only occasionally loses deuterons to any external base. Therefore, deuterium removal, which is apparently done largely by unprotonated or mono-protonated **8**, is rate controlling. Thus, most of the reaction at low pH involves a second molecule of **8** acting as a basic catalyst.

### Stereoselective Bifunctional Catalysis

Enzymes are not only very effective catalysts but are also stereoselective ones. Stereoselectivity is not easily demonstrated with acetone or isobutyraldehyde. Therefore we studied cyclopentanone, whose  $\alpha$ -carbon atoms are prochiral centers. In cyclopentanone-2,2,5,5- $d_4$  (**9**) two of the deuterium atoms (shown in boldface), if replaced by protium, would give an *R* configuration at the attached carbon atom. The other

two would give *S*. Toward an achiral catalyst the deuterium atoms in **9** are all equally reactive. Neg-



lecting secondary deuterium kinetic isotope effects, the  $d_4$ ,  $d_3$ ,  $d_2$ , and  $d_1$  species simply lose deuterium at a rate proportional to the number of deuterium atoms present. That is, the deuterium atoms can be treated as a single pool with a given rate constant for disappearance under a given set of conditions. Toward a chiral catalyst, however, there are two different types of deuterium atoms in **9**. With (1*R*,2*S*,3*R*,4*R*)-3-dimethylamino-methyl-1,7,7-trimethyl-2-norbornanamine (**7**) the reactivity of these two types of deuterium atoms differs by as much as 70-fold, depending on the reaction conditions.<sup>30,33</sup> If the reaction is stopped when about half the total amount of deuterium in the cyclopentanone has been removed, the remaining ketone is largely optically active cyclopentanone-2,5- $d_2$ . Molecular models of the two possible diastereomeric transition states show that this ketone must be the *S,S* isomer. This result is the opposite of that obtained from the observed positive Cotton effect and the octant rule<sup>44</sup> in its simplest form. However, the need for modifications of the octant rule has been pointed out frequently in recent years.<sup>45-47</sup>

### Future Utility of Polyfunctional Catalysis

Polyfunctional catalysis does not have to be limited to physiologically significant types of reactions. It could be used for many reactions of chemical and commercial interest. It is doubtful that a chemist interested in preparing a new compound would ever routinely start out by synthesizing a new polyfunctional catalyst for the purpose. It could be worthwhile, however, to prepare such a catalyst for some step in the synthesis of an important compound that is to be made regularly on a commercial scale. Polyfunctional catalysts that act on most members of a given class of substrates could also become sufficiently well known and available to be widely used.

*I thank a large number of graduate students and postdoctoral research associates, many of whose names are given in the references, for carrying out the work described here.*

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(45) N. L. Allinger and C. K. Riew, *J. Org. Chem.*, **40**, 1316 (1975).

(46) T. D. Bouman and D. A. Lightner, *J. Am. Chem. Soc.*, **98**, 3145 (1976).

(47) M. R. Giddings, E. E. Ernstbrunner, and J. Hudec, *J. Chem. Soc., Chem. Commun.*, 954, 956 (1976).