field shift of C-3 of almost 30 ppm, but shifts C-5 upfield only 3 ppm. This effect has been discussed previously in the case of proton spectra.[11]

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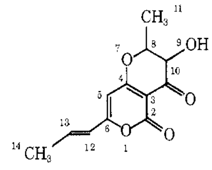

radicinin

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# Possible Bifunctional Catalysis by 2-Dimethylaminoethylamine in the Dealdolization of Diacetone Alcohol[1a]

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Catalysis of the dealdolization of diacetone alcohol by *n*-propylamine, 2-methoxyethylamine, 2-trimethylammonioethylamine, and 2-dimethylaminoethylamine has been studied in water at 35°. Combination of the resultant data with literature observations shows that catalytic efficiency increases with amine basicity when steric factors are kept reasonably constant. In a plot of log $k$ *vs.* p$K_a$ the points for most species of the type $RCH_2NH_2$ lie near a straight line of slope 0.44. The activity of $Me_2NHCH_2CH_2NH_2^+$, however, is about four times as great as would be expected from the data for the other amines. This increased catalytic activity may arise from bifunctional catalysis, in which the primary amino group from the catalyst transforms the carbonyl group of diacetone alcohol to an iminium ion and the tertiary amino group removes a proton from the hydroxy group. An analysis of the propagation of errors in the determination of rate constants for acids and bases from data obtained in buffer solutions is also given.

The dealdolization of hexose derivatives brought about by Class I aldolases is thought to involve iminium-ion formation between a carbonyl group of the substrate (*e.g.*, fructose 1,6-diphosphate) and a lysine residue of the enzyme, followed by base-promoted cleavage.[2,3] The nature of the second basic group may vary from enzyme to enzyme. In the case of at least one transaldolase there is evidence that it is the imidazole ring of a histidine residue.[4] A carboxylate anion group has been postulated to be the second basic group in 2-keto-3-deoxygluconate aldolase.[5]

Observations that simple primary[6-10] and secondary[6-8] amines and amino acids,[10,11] but not tertiary amines,[7] specifically catalyze the dealdolization of diacetone alcohol have contributed to an understanding of enzymatic dealdolizations. The present study was begun with the aim of learning how polar substituents affect the efficiency of primary amine catalysis of dealdolization and of using this knowledge to tell whether a diamine may act as a bifunctional catalyst for dealdolization. After the study was largely completed, an investigation of polar substituent effects on primary amine catalysis of dealdolization was published by Pollack and Cooper.[10]

## Results

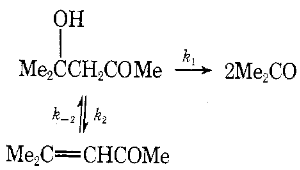
The dealdolization of diacetone alcohol is known to be catalyzed by hydroxide ions.[7,12] To learn the contribution of such catalysis to reactions carried out in the presence of amines we made kinetic studies using sodium hydroxide. The reaction in aqueous solution at 35° and ionic strength 0.10 was followed by spectrophotometric measurements at 264.5 nm, where the transformation of diacetone alcohol ($\lambda_{max}$ 277 nm, $\epsilon_{264.5}$ 23.7 $M^{-1}$ cm$^{-1}$) to acetone ($\lambda_{max}$ 264.5 nm, $\epsilon_{264.5}$ 17.9 $M^{-1}$ cm$^{-1}$) is accompanied by an increase in absorbance, largely because the concentration of carbonyl groups is doubled. The kinetics were complicated by the reversible dehydration of the diacetone alcohol to mesityl oxide ($\lambda_{max}$ 243 nm, $\epsilon_{243}$ 11,400 $M^{-1}$ cm$^{-1}$, $\epsilon_{264.5}$ 2640 $M^{-1}$ cm$^{-1}$). This caused the absorbance at 264.5 nm to increase by an amount about 47% larger than the theoretical amount for the formation of acetone only, and it caused the increase in absorbance to be accompanied by a shift in the absorption maximum to shorter wavelengths. After about 9.5 half-lives the absorbance began to decrease and the absorption maximum to move back toward longer wavelengths. Comparison of the full-length spectrum of the reaction solution after 22 dealdolization half-lives with the spectrum of aqueous acetone solutions showed that the extra absorbance of the reaction solution arose from a material with an absorption maximum at about 243 nm. To allow for this complication the kinetics of the reaction of 0.01466 $M$ diacetone alcohol in the presence of 0.0101 $M$ sodium hydroxide were analyzed in terms of eq 1, in which $y_i$ is the absorbance at time $t_i$.

$$y_i = c_1e^{-k_{\text{obsd}}t_i} + c_2e^{-k'_{\text{obsd}}t_i} + c_3 \qquad (1)$$

$$c_1 = -0.2478\ (0.0002) \qquad k_{\text{obsd}} = 1.986\ (0.004) \times 10^{-4}\ \text{sec}^{-1}$$
$$c_2 = 0.0827\ (0.0066) \qquad k'_{\text{obsd}} = 1.665\ (0.17) \times 10^{-6}\ \text{sec}^{-1}$$
$$c_3 = 0.5139\ (0.0067)$$

The numbers in parentheses are the least-squares estimates of the standard deviations of the respective parameters.

The reaction was assumed to have the mechanism shown in eq 2.



$$\text{Me}_2\overset{\text{OH}}{\overset{|}{\text{C}}}\text{CH}_2\text{COMe} \xrightarrow{k_1} 2\text{Me}_2\text{CO}$$
$$k_{-2} \upharpoonleft\downharpoonright k_2 \qquad (2)$$
$$\text{Me}_2\text{C}{=}\text{CHCOMe}$$

Since only small amounts (<0.3%) of mesityl oxide are ever formed and since the final disappearance of the mesityl oxide that is formed is a relatively slow process, it follows that $k_1 \gg k_2$ and $k_{-2}$. Under these circumstances it may be shown that the kinetics will follow eq 1 with $k_{\text{obsd}} = k_1$, $k'_{\text{obsd}} = k_{-2}$, and $k_2 = k_1(c_2 - \epsilon^{\text{m}}_{264.5}[\text{M}]_0/\epsilon^{\text{m}}_{264.5}[\text{D}]_0)$, where $[\text{M}]_0$ and $[\text{D}]_0$ are the initial concentrations of mesityl oxide and diacetone alcohol. The product $\epsilon^{\text{m}}_{264.5}[\text{M}]_0$ was between zero and 0.016, from which $k_2$ may be calculated to be in the range (3.4–4.2) × $10^{-7}$ sec$^{-1}$.

Most of the runs carried out with sodium hydroxide were not followed for the long time required to get data from which $c_2$ and $k'_{\text{obsd}}$ in eq 1 could be obtained. In these cases we used the single exponential relationship shown in eq 3, in which $a_2$ is a "pseudo-infinity" absorbance approximately equal to $c_2 + c_3$ in eq 2.

$$y_i = a_1e^{-k_1t_i} + a_2 \qquad (3)$$

Each reaction was followed for 2–3 half-lives and $a_1$, $a_2$, and $k_1$ were determined by the method of least squares. The reliability of this method of determining $k_1$ is supported by the estimated standard deviations obtained (~1%) and by the fact that application of eq 3 to the first 3 half-lives of runs that had been carried well into the absorbance-decrease phase of the reaction gave the same $k_1$ values within 1% as were obtained by application of eq 1 to the entire set of data on the reaction. Values of $10^4k_1$ (in sec$^{-1}$) of 1.950, 3.817, 5.735, and 7.662 were obtained at sodium hydroxide concentrations of 0.0102, 0.0202, 0.0301, and 0.0401, respectively. These give a second-order rate constant of (1.91 ± 0.02) × $10^{-2}$ $M^{-1}$ sec$^{-1}$ for the hydroxide ion catalyzed reaction.

Before considering whether dealdolization in the presence of primary amines was complicated by simultaneous formation of mesityl oxide, we should consider another complication that arose in these reactions. The purified diacetone alcohol underwent slow dehydration upon storage at room temperature and the mesityl oxide content had reached about 0.2 mol % after 5 months, when the trouble was diagnosed. The increase in absorbance brought about by the dealdolization of such contaminated reactant was preceded by a much more rapid decrease in absorbance that was ≤10% as large as the later increase. Satisfactory first-order rate constants were obtained from eq 3 when the first 0.3–0.6 half-life (for dealdolization) was neglected and the reaction was then followed for a time 4–15 times as long as the neglected period. To assess the effect of mesityl oxide contamination on the validity of rate constants obtained in this way, we studied the decomposition of mesityl oxide in the presence of one of the primary amine catalysts, 2-dimethylaminoethylamine, at pH 9.9. Pollack and Strohbeen showed that the transformation of mesityl oxide to acetone in the presence of aqueous $n$-propylamine involves the relatively rapid reversible formation of a mesityl oxide–amine adduct, which then decomposes to acetone.[13] In the case of 2-dimethylaminoethylamine, we found the initial rapid formation of mesityl oxide–amine complex to correspond closely in rate to the initial decrease in absorbance observed in the cleavage of mesityl oxide contaminated diacetone alcohol. The rate of the subsequent decomposition of the mesityl oxide–amine complex was about as fast as the dealdolization of diacetone alcohol. For the most highly contaminated diacetone alcohol used the second phase of the mesityl oxide decomposition would change the absorbance by up to 30% as much as the dealdolization would. To estimate the effect of such contributions to the over-all change in absorbance on the calculated rate constants for dealdolization, we analyzed the kinetics in detail. If the only processes occurring are the dealdolization and the cleavage of mesityl oxide by the proposed two-step mechanism,[13] the absorbance should change in accord with eq 4, in which the $c_1$ term arises from the dealdolization and the $c_2$ and $c_3$ terms from the mesityl oxide reaction.

$$y_i = c_1e^{-k_{\text{obsd}}t_i} + c_2e^{-k'_{\text{obsd}}t_i} + c_3e^{-k''_{\text{obsd}}t_i} + c_4 \qquad (4)$$

When the first few points, covering the rapid phase of the mesityl oxide reaction, are discarded, eq 4 reduces to eq 5, in which $k_{\text{obsd}}$ and $k'_{\text{obsd}}$ are of the same order of magnitude. The covariance of the parameters in such equations and the difficulty in obtaining their least-squares estimates unless $k_{\text{obsd}}$ and $k'_{\text{obsd}}$ are well separated is a notorious problem.[14a] For this reason it was not thought worthwhile to try to apply eq 5 to our data.

$$y_i = c_1e^{-k_{\text{obsd}}t_i} + c_2e^{-k'_{\text{obsd}}t_i} + c_4 \qquad (5)$$

Instead we made some calculations to estimate how much error we had introduced by using eq 3. This was done by using eq 4 to generate data, assigning a normal random deviate of 0.00015 (which is considerably better than the experimental data) to each value of $y_i$, and subjecting the resulting synthetic data to least-squares analysis. The relative magnitudes of $k_{\text{obsd}}$, $k'_{\text{obsd}}$, and $k''_{\text{obsd}}$ were taken as 1:0.5:90, similar to those found experimentally in the case of catalysis by 2-dimethylaminoethylamine. Application of eq 3 to the synthetic data obtained between 0.16 and 1.9 half-lives for dealdolization gave values of $k_1$, which may be regarded as biased estimates of $k_{\text{obsd}}$, that deviated from $k_{\text{obsd}}$ by amounts that were approximately linear in the assumed concentration of mesityl oxide in the diacetone alcohol. With the largest mesityl oxide concentration ever present in our diacetone alcohol the value of $k_1$ obtained was 5% larger than the value of $k_{\text{obsd}}$ used to generate the data. Experimentally, when freshly purified diacetone alcohol was used in a repeat of the run carried out with 2-dimethylaminoethylamine the value of $k_1$ was 7.4% smaller than the value obtained with contaminated reactant. Therefore we concluded that the smaller amounts of mesityl oxide present in the previous studies of amine catalysis should have caused less than 10% uncertainty in the rate constants obtained.

In the case of all the runs carried out with $n$-propylamine and 2-methoxyethylamine the calculated infinite absorbance ($a_2$ in eq 3) was much closer to the value calculated assuming no mesityl oxide was being formed as a side reaction than had been the case in the hydroxide-catalyzed reaction. Therefore it was assumed that this side reaction was not occurring to a large enough extent to introduce significant error into the rate constants obtained, which are listed in Table I. There was also no significant

**Table I**
**Kinetics of Dealdolization of Diacetone Alcohol in the Presence of Amine Catalysts at 35°[a]**

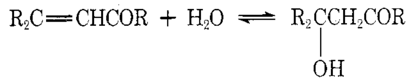
| Amine (registry no.) | $[\text{Amine}]_{\text{total}}$ | $[B]/[BH^+]$[b] | pH | $10^6 k_1$, $sec^{-1}$ Obsd | $10^6 k_1$, $sec^{-1}$ Calcd |
|---|---|---|---|---|---|
| $n$-$PrNH_2$<br>(107-10-8) | 0.0533 | 2.85 | 10.71 | 83.88 | 76.74 |
| | 0.0520 | 1.92 | 10.53 | 65.00 | 61.71 |
| | 0.0524 | 1.65 | 10.48 | 58.62 | 57.98 |
| | 0.0510 | 1.34 | 10.39 | 52.62 | 50.63 |
| | 0.0534 | 1.25 | 10.35 | 48.23 | 50.06 |
| | 0.0539 | 1.09 | 10.29 | 45.10 | 46.83 |
| | 0.0491 | 0.77 | 10.16 | 35.62 | 35.39 |
| | 0.0529 | 0.78 | 10.15 | 35.08 | 37.65 |
| $NH_2$<br>$CH_2$<br>$CH_2$<br>O<br>Me<br>(109-85-3) | 0.0536 | 5.77 | 9.94 | 17.92 | 17.20 |
| | 0.0507 | 4.12 | 9.80 | 14.52 | 14.63 |
| | 0.0544 | 3.58 | 9.74 | 14.87 | 14.71 |
| | 0.0503 | 2.63 | 9.61 | 12.00 | 12.36 |
| | 0.0537 | 2.39 | 9.57 | 12.64 | 12.49 |
| | 0.0512 | 1.87 | 9.47 | 10.35 | 10.86 |
| | 0.0544 | 1.75 | 9.43 | 10.97 | 10.99 |
| | 0.0505 | 1.32 | 9.32 | 8.79 | 9.15 |
| $NH_2$<br>$CH_2$<br>$CH_2$<br>$NMe_2$<br>(108-00-9) | 0.04215 | 19.48 | 10.29 | 28.78 | 26.94 |
| | 0.04254 | 12.78 | 10.15 | 23.86 | 23.65 |
| | 0.04340 | 9.54 | 10.03 | 21.75 | 21.50 |
| | 0.04100 | 8.96 | 10.01 | 20.14 | 20.20 |
| | 0.04163 | 7.99 | 9.94 | 19.39 | 19.33 |
| | 0.04440 | 7.63 | 9.91 | 20.03 | 19.89 |
| | 0.04361 | 6.71 | 9.85 | 17.77 | 18.57 |
| | 0.04227 | 5.85 | 9.80 | 17.27 | 17.19 |
| | 0.04265 | 4.92 | 9.70 | 15.32 | 15.92 |
| | 0.04231 | 4.14 | 9.63 | 13.69 | 14.61 |
| | 0.04322 | 3.67 | 9.53 | 12.64 | 13.78 |
| | 0.04336 | 1.81 | 9.09 | 7.31 | 8.04 |
| | 0.04072 | 1.64 | 8.95 | 6.90 | 6.64 |
| | 0.04138 | 1.51 | 8.86 | 6.32 | 6.06 |
| | 0.04066 | 1.32 | 8.66 | 5.49 | 4.84 |
| | 0.04091 | 1.21 | 8.47 | 4.71 | 4.08 |
| $NH_2$<br>$CH_2$<br>$CH_2$<br>$^+NMe_3$<br>(38170-37-5) | 0.0392[c] | | 9.08 | 2.07 | 2.21 |
| | 0.0291[d] | | 9.07 | 1.85 | 1.79 |
| | 0.0218 | | 9.06 | 1.65 | 1.48 |

[a] At ionic strength 0.10 unless otherwise noted. [b] Stoichiometric buffer ratio calculated from the amounts of amine, amine salt, acid, and/or base used. [c] Ionic strength 0.068. [d] Ionic strength 0.086.

amount of mesityl oxide formed in the runs using 2-dimethylaminoethylamine above pH 8. Runs below pH 8 were discarded because of excessive mesityl oxide formation. The $N$-(2-aminoethyl)trimethylammonium cation is a relatively poor catalyst whose activity is obscured by mesityl oxide formation below pH 8 and by hydroxide ion catalysis above pH 10. As a compromise the rate was studied around pH 9.1, using a borate buffer to maintain the pH since this pH is outside the buffer range of the amine.

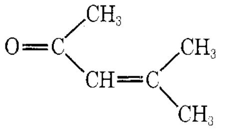
## Discussion

The value 0.0191 $M^{-1}$ $sec^{-1}$ that we have obtained for $k_{OH}$ agrees fairly well with the value 0.0204 $M^{-1}$ $sec^{-1}$ obtained at a hydroxide ion concentration and ionic strength of 0.010[15] and the value 0.0218 $M^{-1}$ $sec^{-1}$ obtained at a hydroxide ion concentration and ionic strength of 0.10,[16] both determined at 35.0° using a dilatometric method. Combination of our values of $k_2$ and $k_{-2}$ (eq 2) gives an equilibrium constant of 4.5 ± 1 for the hydration of mesityl oxide to give diacetone alcohol in aqueous solution at 35°. Values of 13 and 16 may be calculated for the same reaction at 25° from data obtained in aqueous hydrochloric acid[17] and aqueous sodium hydroxide solutions,[18] respectively. The entropy of reaction is expected to be highly negative, since one molecule is being formed from two. The fact that the equilibrium is reasonably favorable shows that the reaction should be significantly exothermic. Hence the rapid decrease in equilibrium constant with increasing temperature is expected. This relatively favorable equilibrium in the hydration of mesityl oxide contrasts sharply with the analogous reaction of 10-methyl-$\Delta^{1,9}$-octalone-2, which can also be regarded as a reaction of the type



$$R_2C{=}CHCOR + H_2O \rightleftharpoons R_2\underset{\displaystyle OH}{\underset{|}{C}}CH_2COR$$

in which the R groups are all saturated hydrocarbon radicals, but in which the *dehydration* reaction is said to proceed essentially quantitatively in aqueous solution at 25°.[19] One probable reason for the difference in equilibrium constants for these two similar equilibria is that the hydration of mesityl oxide gives a species with greatly increased freedom of rotation around bonds whereas hydration of the cyclic unsaturated ketone does not. A second probable reason is that in the most favorable conformation for resonance interaction between the carbonyl group and the carbon-carbon double bond of mesityl oxide (1)



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there will be a destabilizing steric interaction between two methyl groups. No such interaction is present in the analogous conformation of 10-methyl-$\Delta^{1,9}$-octalone-2.

The observed first-order rate constants for dealdolization in the presence of 2-dimethylaminoethylamine buffers at various concentrations and various pH's were correlated in terms of eq 6, in which A represents the unprotonated and $AH^+$ the monoprotonated amine. In treating

$$k_1 = k_{OH}[OH^-] + k_A[A] + k_{AH}[AH^+] \qquad (6)$$

the data on the other amines the $k_{AH}$ term was neglected. In this treatment $k_{OH}$ was given the value obtained using sodium hydroxide as a catalyst. An alternative is to treat $k_{OH}$ as a parameter of the regression analysis. In using either alternative one must choose between different formulae, which are mathematically equivalent but not statistically equivalent, for calculating the concentrations of the various species. Since this problem arises frequently in calculating rate constants from data on buffer solutions and in other cases, we have developed a propagation of errors analysis, which is given in the Appendix.

In Table I are the values of $k_1$ calculated from the catalysis constants obtained, which are listed in Table II. Also listed are values for ethylamine[8] and $n$-propylamine[9,10] interpolated between data at higher and lower temperatures using the Arrhenius equation and values for six other amines[8,10] calculated from data at 25° (53.6° in the case of trifluoroethylamine)[10] assuming that their reactivities differ from that of $n$-propylamine only because of differences in the Arrhenius activation energy. To estimate the polar effect of substituents on the catalytic activity of these amines we have plotted log $k$ against the p$K_a$ of the conjugate acids of the amines,[20,21] as a measure of the polar character of the substituents. Since the p$K_a$ of a singly charged cationic acid is relatively independent of the ionic strength, p$K_a$ values at zero ionic strength have been used for the monoprotonated forms of electrically neutral amines. For the cationic and anionic amines the p$K_a$ values refer to the ionic strengths (0.10 and 0.4, respectively) at which the kinetics were studied.

**Table II**
**Catalysis Constants for the Dealdolizaton of Diacetone Alcohol in Water at 35°[a]**

| Catalyst | p$K_a$[b] | $10^6 k$,[c] $M^{-1}$ sec$^{-1}$ | Registry no. |
|---|---|---|---|
| $EtNH_2$ | 10.31 | 901[d] | 75-04-7 |
| $n$-$PrNH_2$ | 10.21 | 1330 ± 40<br>1070[d] | |
| $i$-$PrNH_2$ | 10.21 | 151[e] | 75-31-0 |
| $^{-}O_2CCH_2NH_2$ | 9.35[f] | 252[e] | 23297-34-9 |
| $Me_2NCH_2CH_2NH_2$ | 9.34[g] | 444 ± 8 | |
| $HOCH_2CH_2NH_2$ | 9.21[h] | 336[e] | |
| $MeOCH_2CH_2NH_2$ | 9.09 | 283 ± 3 | |
| $PhCH_2NH_2$ | 9.00 | 354[e] | 100-46-9 |
| $H_2NCOCH_2NH_2$ | 7.69 | 111[e] | 598-41-4 |
| $Me_3NCH_2CH_2NH_2^+$ | 6.53[i] | 41 ± 8 | |
| $Me_2NCH_2CH_2NH_2 \cdot H^+$ | 6.23[i] | 60 ± 8 | 51380-72-4 |
| $CF_3CH_2NH_2$ | 5.52 | 7.8[j] | 753-90-2 |

[a] From the present study unless otherwise noted. [b] For the monoprotonated form of the amine listed; at zero ionic strength for electrically neutral amines, at the ionic strength at which the kinetics were studied for charged amines. Values from ref 20 unless otherwise noted. [c] The ± figures are estimates of standard deviations. [d] Interpolated from data at higher and lower temperatures.[8-10] [e] Calculated from data at 25°.[8,10] [f] At ionic strength 0.4. [g] Determined in the present study. [h] From ref 21. [i] At ionic strength 0.1. [j] Calculated from data at 53.6°.[10]

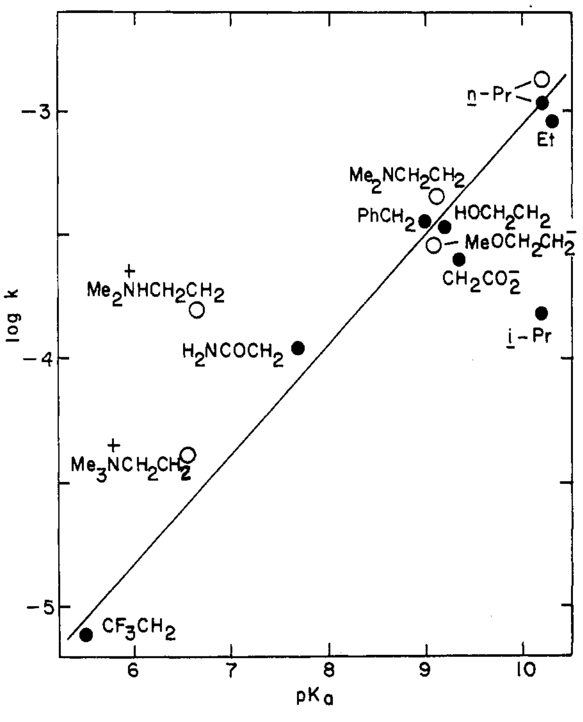
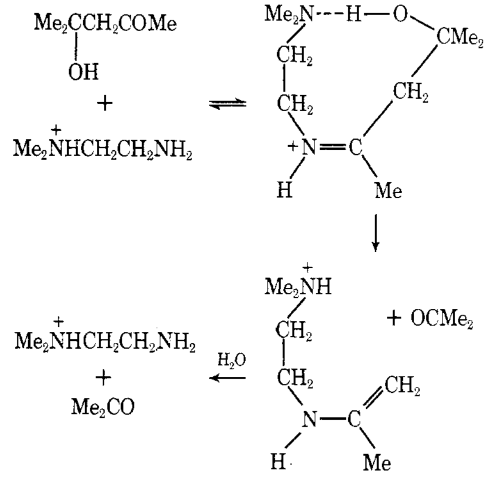


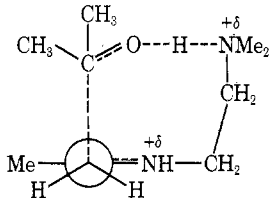
**Figure 1.** Plot of log $k$ vs. p$K_a$ for primary amines. Solid circles from work of other investigators. Point for each $RNH_2$ labeled with the appropriate R.

The value for glycine was extrapolated from the values of King[22] at ionic strengths 0.0, 0.1, and 0.3 using the Guggenheim equation[23] for activity coefficients. The values for the cationic amines were determined by potentiometric titrations in which the ionic strength passed through 0.1, with corrections to that ionic strength being made by use of the Davies equation.[24] All the p$K_a$ values in Table II refer purely to the acidity of primary ammonium ions except those for 2-dimethylaminoethylamine and its conjugate acid. To put these constants on the same basis as the others they must be corrected (to 9.13 and 6.65, respectively) for the fact that monoprotonated 2-dimethylaminoethylamine is protonated at the primary amino group only to the extent of 62%.[25] The corrected values are used in Figure 1. Inasmuch as dealdolization is not catalyzed by tertiary amines, the catalysis by monoprotonated 2-dimethylaminoethylamine must arise from the 38% of this material that is protonated at the tertiary amino group. Hence the catalysis constant listed for $Me_2NCH_2CH_2NH_2 \cdot H^+$ was divided by 0.38 to get the constant plotted for $Me_2NHCH_2CH_2NH_2^+$.

**Scheme I**

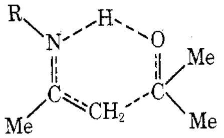


From the plot isopropylamine is seen to be a relatively poor catalyst for its basicity, a fact we attribute to steric hindrance. The line shown in the figure is the least-squares line through all the points for electrically neutral amines of the type $RCH_2NH_2$. The standard deviations of the nine points from this line is 0.09. The points for the $N$-(2-aminoethyl)trimethylammonium cation and the glycinate anion deviate by only 0.07 and 0.25, respectively, but the fact that they are on opposite sides of the line suggests that there may be a small tendency for cationic catalysts to be somewhat more reactive and anionic catalysts somewhat less reactive than similar electrically neutral catalysts.[26,27] The point for $Me_2NHCH_2CH_2NH_2^+$ lies 0.74 log unit above the line. The cationic nature of this catalyst may explain a small part of why this catalyst is 5.5 times as reactive as would be expected from the correlation of the activities of the other catalysts, but it does not plausibly explain it all. We believe that the deviation may well arise from bifunctional catalysis. Imine formation has been shown to be significantly faster than dealdolization for five primary amines ranging in basicity from $n$-propylamine to trifluoroethylamine.[10] Therefore, the rate-controlling step is the carbon–carbon bond cleavage step, and the ability of the protonated dimethylamino group to act as an internal acid catalyst in imine formation by $Me_2NHCH_2CH_2NH_2^+$ [28,29] cannot significantly increase the catalytic activity of this species in dealdolization. Instead, we suggest that the catalyst and diacetone alcohol react as shown in Scheme I to give an intermediate iminium ion in which the alcoholic hydroxy group is hydrogen bonded to the dimethylamino group from the catalyst. The nine-membered ring in the transition state of the rate-controlling step may be unnecessarily large. There is evidence that stereoelectronic constraints make eight members the favored ring size in the bifunctionally catalyzed dedeuteration of acetone-$d_6$ by ω-dimethylamino alkyl amines.[27,30] Because of the demands for coplanarity of six atoms in and attached to the double bond of the iminium ion and of a partly overlapping set of six atoms in the intermediate iminium ion and a preference for linearity in the hydrogen bond, the transition state in the 2-dimethylaminoethylamine-catalyzed reaction should have a structure like that shown in 2, which is a Newman projec-



2

tion down the carbon–carbon bond that is changed from a single to a double bond in the rate-controlling step. Studies with molecular models suggest that transition states with rings as small as seven members can come close to meeting the stereoelectronic requirements. However, the six-membered ring in the cyclic transition state 3 com-



3

monly written for the rate-controlling step in the primary amine catalyzed dealdolization reaction[7,9,10] would suffer great strain in trying to achieve a conformation analogous to that in 2. If this were not true, bifunctional catalysis by a species like 2-dimethylammonioethylamine would probably not be observable.

## Experimental Section

**Reagents.** The diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) used was fractionally distilled at 4-mm pressure. The absorbance of solutions of freshly distilled material in the range 220–270 nm showed that no more than 0.04% mesityl oxide was present. Although material stored at room temperature for 5 months had acquired 0.2% mesityl oxide, material kept in a freezer for 1 year had not deteriorated detectably. The electrically neutral amines used were fractionally distilled at atmospheric pressure, and stored under nitrogen. The (2-aminoethyl)trimethylammonium chloride hydrochloride prepared previously[29] was used.

**Kinetics.** To minimize loss of *n*-propylamine its standard solutions were prepared by additions to volumetric flasks already more than half full of aqueous solutions and standardized by adding excess acid and back titrating. Sodium chloride was present as needed to bring the ionic strength of kinetic solutions to 0.10. A Radiometer pH meter, Model 26, and G202B glass electrode were used to measure pH.

In a typical run 3.00 ml of buffer was pipetted into 1.0-cm uv cells and brought to 35.0 ± 0.2° in the sample chamber of a Cary 16 spectrophotometer. After 5.5 μl of diacetone alcohol had been added to each cell and the cells shaken and returned to the sample holders, the absorbance at 264.5 nm (slit width 0.4 mm) was monitored at preprogrammed time intervals.

**p*K* Determinations.** Standard solutions of 2-dimethylaminoethylamine and (2-aminoethyl)trimethylammonium chloride hydrochloride were titrated potentiometrically at 35° with hydrochloric acid and sodium hydroxide, respectively. After an aliquot of titrant was added the solutions were stirred for 1–2 min and then the pH was read without stirring. During the titration of 2-dimethylaminoethylamine the ionic strength varied from 0.097 to 0.12. Use of the Davies equation gave thermodynamic p$K_a$ values for mono- and diprotonated amine of 9.34 and 6.00, respectively. For the 2-trimethylammonioethylammonium ion a thermodynamic p$K_a$ of 6.30 was obtained from data at ionic strengths 0.14–0.064.

**Analysis of Data.** Absorbance–time data pairs were analyzed by least squares using eq 1 or 3 and a modified Gauss–Newton algorithm,[31] assigning all absorbance values equal weight. The computational algorithm, based in part on that of Deming,[32] for the least-squares treatment of pH–volume data pairs from titrations involved the regression analysis of an implicit function relating pH, volume, and the p*K*'s and will be described in a future publication. The observed pH was taken as $-\log a_{H^+}$. The pH–rate data were subject to standard linear regression analysis to obtain estimates of catalysis constants. The individual rate constants $k_1$, the dependent variables, were assigned unit weight except in the case of *n*-propylamine, where weighting proportional to $1/k_1^2$ was taken as a better measure of the reliability of the data. None of the second-order rate constants listed have been corrected for expansion of the solutions from room temperature to 35°.

**Acknowledgment.** We thank The Ohio State Instruction and Research Computer Center for the use of their facilities.

## Appendix

**Error Propagation Analysis.** The following simple derivation of an expression for the effect of error in primary data on derived quantities leads to a general procedure and formulae. Given a set of functions,

$$\begin{aligned} x_1 &= f_1(\beta_1, \ldots, \beta_p) \\ x_2 &= f_2(\beta_1, \ldots, \beta_p) \\ &\vdots \\ x_n &= f_n(\beta_1, \ldots, \beta_p) \end{aligned} \tag{7}$$

the variances of $x_1, \ldots, x_n$ as a function of the variances of $\beta_1, \ldots, \beta_p$ may be computed from

$$\mathbf{M}_x = \mathbf{J}_\beta^{\mathrm{f}} \mathbf{M}_\beta \mathbf{J}_\beta^{\mathrm{f}'} \tag{8}$$

where the diagonal elements of $\mathbf{M}_x$ are the variances of $x_1, \ldots, x_n$, and $\mathbf{M}_\beta$ is the variance covariance matrix for the parameters $\beta_1, \ldots, \beta_p$, for which a value is assumed. $\mathbf{J}_\beta^{\mathrm{f}}$ is the Jacobian of the vector formed by the $f_i$

$$\mathbf{F} = \begin{bmatrix} f_1 \\ \vdots \\ f_n \end{bmatrix} \tag{9}$$

with respect to $\beta_1, \ldots, \beta_p$. This is the standard propagation of errors formula based on a Taylor series expansion of **F** truncated to the first order and is subject to assumptions discussed elsewhere.[14b]

The functions in eq 7 are explicit in $x_1, \ldots, x_n$, but this need not be the case. If one $x_i$ were the pH, for example, no exact explicit formulation would be available.[33] Thus, more generally, one must deal with a series of functions nonlinear in the $x_i$.

$$\mathbf{G} = \begin{bmatrix} g_1 \\ \vdots \\ g_n \end{bmatrix} \quad \begin{aligned} g_1(x_1, \ldots, x_n, \beta_1, \ldots, \beta_p) &= 0 \\ &\vdots \\ g_n(x_1, \ldots, x_n, \beta_1, \ldots, \beta_p) &= 0 \end{aligned} \tag{10}$$

The vector $\mathbf{X} = x_1, \ldots, x_n$ is then solved for by an iterative procedure, *e.g.*, a Newton sequence.[34]

One may still make use of eq 8 to obtain the variances of **X**, however, by recourse to the implicit function theorem.[35] From this theorem one can construct $\mathbf{J}_\beta^{\mathrm{f}}$ (although not **F**) by using the Jacobian of **G** with respect to **X**, $\mathbf{J}_{\mathrm{x}}^{\mathrm{g}}$, and with respect to $\beta$, $\mathbf{J}_\beta^{\mathrm{g}}$, as shown below.

$$\mathbf{J}_\beta^{\mathrm{f}} = -\mathbf{J}_{\mathrm{x}}^{\mathrm{g}^{-1}} \mathbf{J}_\beta^{\mathrm{g}} \tag{11}$$

Thus

$$\mathbf{M}_{\mathrm{x}} = \mathbf{J}_{\mathrm{x}}^{\mathrm{g}^{-1}} \mathbf{J}_\beta^{\mathrm{g}} \mathbf{M}_\beta \mathbf{J}_\beta^{\mathrm{g}'} \mathbf{J}_{\mathrm{x}}^{\mathrm{g}^{-1'}} \tag{12}$$

All matrix elements are evaluated at the solution, $\mathbf{X} = \mathbf{X}_0$, of the vector function g, *i.e.*

$$g(\mathbf{X}_0, \beta) = 0$$

Note that the elements of $\mathbf{J}_{\mathrm{x}}^{\mathrm{g}^{-1}}$ would be available as a by-product of a Newton sequence used in finding $\mathbf{X}_0$.

Equation 12 has been used to assess the effect of error in primary data on the derived concentrations entering eq 6 for each of several different sets of formulae. In this way it is possible to make a more objective decision concerning which set of formulae and associated primary data gives the least error in computing concentrations.

**Registry No.**—Diacetone alcohol, 123-42-2.

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# *Notes*

## Valence Isomers. Substituent Effects on the Equilibrium between 2*H*-Pyrans and Cis Dienones[1,2]

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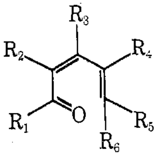
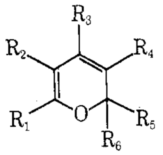
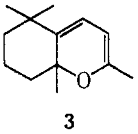
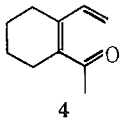
We have recently reported[3] that the system **1a** $\rightleftharpoons$ **2a** exists almost completely as the cis dienone **1a**, and that **2a** has a fleeting, but spectroscopically demonstrable, existence in the synthesis of the system. We have also reported unequivocally that the bicyclic system **3** exists 95% as the 2*H*-pyran at ambient temperatures,[4,5] whereas systems related to **4** exclusively favor the cis dienone owing to the fact that the corresponding valence isomers of **4** would have two relatively unstable exocyclic double bonds.[6,7] Other substituent factors that shift the position of the equilibrium between the valence isomers to the 2*H*-pyran are two alkyl substituents on C-2 of the 2*H*-pyran[8-11] and substituents which extend the conjugation, *e.g.*, phenyl groups.[12]


**1**


**2**

**a**, $R_1 = R_3 = R_5 = \mathrm{Me}$; $R_2 = R_4 = R_6 = \mathrm{H}$
**b**, $R_1 = R_5 = \mathrm{Et}$; $R_3 = \mathrm{Me}$; $R_2 = R_4 = R_6 = \mathrm{H}$
**c**, $R_1 = R_5 = t\text{-Bu}$; $R_3 = \mathrm{Me}$; $R_2 = R_4 = R_6 = \mathrm{H}$
**d**, $R_1 = R_2 = R_4 = R_5 = \mathrm{Me}$; $R_3 = \mathrm{Et}$; $R_6 = \mathrm{H}$


**3**


**4**

The only case, here reported, which has been clearly observed to have a significant fraction of the 2*H*-pyran present in equilibrium with the cis dienone is the sterically hindered system **1d** $\rightleftharpoons$ **2d**. The equilibrium **1d** $\rightleftharpoons$ **2d** is clearly discernible by the lone proton substituent, which discloses that the system exists as 70–75% **2d** (quartet, $J$ = 6.0 Hz, 0.7 H at $\delta$ 4.35) and 25–30% **1d** [quartet of quartets at higher resolutions, $J(\mathrm{H, CH_3})$ = 7.00 and $J(\mathrm{H,allyl\ CH_3}) \cong 1.0$ Hz, 0.3 H at $\delta$ 5.25]. The methyl group $R_5$ at $\delta$ 1.2 also confirms the *ca.* 70% equilibrium concentration of **1d** by its coupling[13] with the lone proton ($J$ = 6.0 Hz) and low integration curve (*ca.* 2 H).

The methyl portion of the ethyl group centered at $\delta$ 0.95 also lends support to the equilibrium mixture in that it appears as two nearly superimposed triplets in the ratio of about 3:1 (total 3 H). All of the other protons are in a very complex pattern between $\delta$ 1.5 and 2.4. No 4*H*-pyran was present in the spectral sample since it would be clearly discernible by its high methyl peak at $\delta$ 0.65 and the broad single hydrogen peak at $\delta$ 2.5.