rate and product ratios. It is clear from these results that high exo/endo rate and product ratios can be present in 2-norbornyl derivatives without the involvement of σ bridging. Steric hindrance to ionization provides an alternative explanation for such high exo/endo ratios in the tertiary derivatives. We are left with the question as to whether the high exo/endo rate and product ratios in the parent 2-norbornyl system can be explained in terms of similar factors and as to the precise nature of the factor or factors responsible for the low exo/endo rate ratios in systems 1–4. We are currently examining this question.

Experimental Section

2-Aryl-3-methylene-*endo*-norbornanols. Addition of 5-coumaranyllithium, phenyllithium, *p*-(trifluoromethyl)phenyllithium, and 3,5-bis(trifluoromethyl)magnesium bromide to 3-methylene-2-norbornanone (Aldrich) provided the corresponding endo alcohols. These alcohols were purified by distillation.

2-Aryl-3-methylene-*endo*-norbornyl *p*-Nitrobenzoates. These *p*-nitrobenzoates were made by the addition of *p*-nitrobenzoyl chloride to the lithium alkoxide of the endo alcohols in THF.[22] The physical properties and analytical data are summarized in Table II.

2-Aryl-3-methylene-*exo*-norbornanols. 2-Aryl-3-methylene-*endo*-norbornyl *p*-nitrobenzoates were solvolyzed in 80% aqueous acetone in the presence of a 10% molar excess of sodium acetate for 10 half-lives. After the usual workup, the exo alcohols obtained were used for the next reaction without any further purification.

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2-Aryl-3-methylene-*exo*-norbornyl *p*-Nitrobenzoates. These *p*-nitrobenzoates were made by the addition of *p*-nitrobenzoyl chloride to the lithium alkoxide of the exo alcohol in THF.[22] The 2-(5′-coumaranyl)-3-methylene-*exo*-norbornyl *p*-nitrobenzoate could not be isolated because of its extreme reactivity; instead, the corresponding benzoate ester was made and used as such for the kinetic work. The physical and analytical data are summarized in Table II.

Kinetic Measurements. The method used for determining the rate constants of the *p*-nitrobenzoates and benzoates is essentially the same as that described earlier.[22] The rates and thermodynamic parameters are listed in Table I.

Solvolysis Products. The *p*-nitrobenzoates were solvolyzed in 80% aqueous acetone containing a 10% molar excess of sodium acetate for 10 half-lives. Then the reaction mixtures were worked up and analyzed by ^{1}H NMR. In all of the cases, the solvolysis products were almost exclusively the tertiary exo alcohols.

Registry No. **12** (Z = *p*-OCH_2CH_2-*m*), 71185-52-9; **12** (Z = *p*-H), 71185-53-0; **12** (Z = *p*-CF_3), 71243-01-1; **12** (Z = 3,5-$(CF_3)_2$), 71185-54-1; **13** (Z = *p*-OCH_2CH_2-*m*), 71185-55-2; **13** (Z = *p*-H), 71185-56-3; **13** (Z = *p*-CF_3), 71185-57-4; **13** (Z = 3,5-$(CF_3)_2$), 71185-58-5; **14** (Z = *p*-OCH_2CH_2-*m*), 68150-99-2; **14** (Z = *p*-H), 21845-81-8; **14** (Z = *p*-CF_3), 20530-03-4; **14** (Z = 3,5-$(CF_3)_2$), 56068-59-8; **14** (Z = 2-Me), 71185-59-6; **15** (Z = *p*-OCH_2CH_2-*m*), 68150-98-1; **15** (Z = *p*-H), 20550-35-0; **15** (Z = *p*-CF_3), 20530-02-3; **15** (Z = 3,5-$(CF_3)_2$), 56068-58-7; **15** (Z = 2-Me), 71185-60-9; 2-(5′-coumaranyl)-3-methylene-*endo*-norbornanol, 71185-61-0; 2-(5′-coumaranyl)-3-methylene-*exo*-norbornanol, 71185-62-1; 2-phenyl-3-methylene-*endo*-norbornanol, 30781-91-0; 2-phenyl-3-methylene-*exo*-norbornanol, 30781-92-1; 2-[4-(trifluoromethyl)phenyl]-3-methylene-*endo*-norbornanol, 71185-63-2; 2-[4-(trifluoromethyl)phenyl]-3-methylene-*exo*-norbornanol, 71185-64-3; 2-[3,5-bis(trifluoromethyl)phenyl]-3-methylene-*endo*-norbornanol, 71185-65-4; 2-[3,5-bis(trifluoromethyl)phenyl]-3-methylene-*exo*-norbornanol, 71185-66-5; *p*-nitrobenzoyl chloride, 122-04-3.

Internal Acid Catalysis in the Reactions of Monoprotonated Diamines with Cyclopentanone and 3-Pentanone to Give Imines[1a]

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Equilibrium constants for oxime formation in water at 35 °C have been determined for 3-pentanone (7.9×10^4 M^{-1}) and cyclopentanone (40×10^4 M^{-1}), as have the pK_a values for the protonated oximes. The kinetics of oximation and secondary deuterium kinetic isotope effects were determined in the pH range 6–11, where dehydration of the intermediate carbinolamine is rate controlling. With hydroxylamine to capture the relatively unstable imines, the kinetics of imine formation from seven primary amines were studied in this pH range. For amines of the type $XCH_2CH_2NH_2$, where X is neutral in charge and in acid–base behavior, plots of log k for imine formation vs. pK_a for the corresponding primary ammonium ions give straight lines. The monoprotonated forms of 2-(dimethylamino)ethylamine, 3-(dimethylamino)propylamine, and *N*,*N*,2,2-tetramethyl-1,3-propanediamine are too reactive to fit these lines, the tertiary-protonated form of 2-(dimethylamino)ethylamine being more than 2000 times too reactive. This is attributed to internal acid catalysis of dehydration of the intermediate carbinolamine $R_2C(OH)NH\sim\sim NHMe_2^+$ by the dimethylammonio group. The effect of structure on reactivity is discussed.

The formation of iminium ions in the reactions of primary and secondary amines with aldehydes and ketones involves intermediate formation of a carbinolamine, which then loses a hydroxide ion.[2,3] This last step is ordinarily rate controlling in neutral or basic aqueous solutions. The loss of hydroxide ions is uncatalyzed in sufficiently basic solutions, but in less basic solutions it is catalyzed by hydrogen ions. The loss of hydroxide ion is brought about by an internal acidic hydrogen atom (eq 1) in the reactions of certain monoprotonated diamines with acetone[4,5] and isobutyraldehyde.[6] This increases the efficiency with which some monoprotonated diamines bifunctionally catalyze α-hydrogen exchange reactions that proceed via

(1) (a) Dedicated to Professor Melvin S. Newman on his 70th birthday. This research was supported in part by NIH Grant GM 18593. Abstracted in part from the Ph.D. Dissertation of James P. Zeigler, The Ohio State University, 1978. (b) NSF Undergraduate Research Participant, summer 1977.

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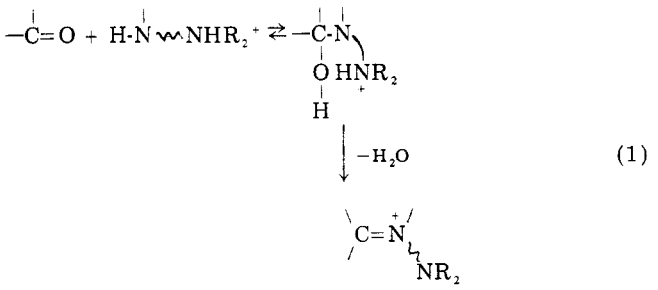

(1)

iminium ion intermediates.[7] To study the effect of structure on internal acid catalysis in iminium ion formation, we have investigated iminium ion formation from 3-pentanone and cyclopentanone. We have followed the reactions, as previously,[4,5] by capturing the iminium ions with hydroxylamine. (The equilibrium constants for formation of the imines and iminium ions are so small that direct measurement of the reaction rate would be difficult.)

Results

The reactions of the ketones with hydroxylamine were first studied in the absence of added primary amines. The apparent equilibrium constants for oxime formation were determined at several acidic pH's, where hydroxylamine is essentially 100% protonated but the oximes are protonated to varying extents. From the results, as described previously for acetone,[8] equilibrium constants for oxime formation and acidity constants for protonated oximes (K_{OxH}) were determined, with the results shown in Table I. In the definition of K_{Ox} (eq 2), K is the ketone, Ox the

$$K_{Ox} = [Ox]/([K][Hx]) \quad (2)$$

oxime, and Hx hydroxylamine. From these values it follows that in the kinetic studies to be described the reactions of the ketones are always more than 99.95% complete at equilibrium. Second-order rate constants for oxime formation were determined spectrophotometrically at various pH's. The values obtained for 3-pentanone are plotted logarithmically against pH in Figure 1. Cyclopentanone gives a similar plot. The reaction is seen to be subject to both acid and base catalysis. Least-squares treatment of the data in terms of eq 3 gives the pH-in-

$$k_{Ox} = k_H[H^+] + k_h[OH^-] + k_w \quad (3)$$

dependent rate constants shown in Table II for the two ketones and their completely α-deuterated derivatives. General acid and base catalyses were not sought extensively, having been found to be negligible in this pH range with acetone.[4,8,9] Changes in the concentrations of the components of the tertiary amine buffers used gave no evidence for such catalysis. Measurements of the type that gave an equilibrium constant of 0.59 M^{-1} for addition of hydroxylamine to acetone to give the carbinolamine[8] did not clearly detect any carbinolamine formation with 3-pentanone or cyclopentanone. The amounts of these ketones tied up as carbinolamines were therefore assumed to be negligible.

Scheme I

$$K + Hx \xrightarrow{k_{Ox}} Ox$$

$$K + Am \underset{k_d}{\overset{k_{Im}}{\rightleftharpoons}} Im$$

$$Im + Hx \xrightarrow{k_{Hx}} Ox + Am$$

Table I. Equilibrium in Oxime Formation[a]

ketone	10^{-4} K_{Ox}, M^{-1}	10^{-4} σ[b] M^{-1}	pK_{OxH}	σ[b]	no. of points
acetone[c]	46.5	3.0	1.54	0.05	9
3-pentanone	7.7	0.4	1.2	0.8	26
cyclopentanone	40.1	0.7	1.20	0.02	11

[a] In water at 35 °C. [b] Estimated standard deviation. [c] Results from ref 8.

Table II. Kinetics of Oximation[a]

ketone	10^{-5} k_H, M^{-2} s^{-1}	10^{-5} σ,[b] M^{-2} s^{-1}	k_h, M^{-2} s^{-1}	σ,[b] M^{-2} s^{-1}	10^4 k_w, M^{-1} s^{-1}	10^4 σ,[b] M^{-1} s^{-1}
3-pentanone	2.59	0.06	1.37	0.04	4.54	0.55
3-pentanone-2,2,4,4-d_4	2.97	0.10	[c]	[c]	11.3	1.4
cyclopentanone	2.51	0.30	2.80	0.30	8.8	3.8
cyclopentanone-2,2,5,5-d_4	3.14	0.20	1.75	0.18	16.9	2.8

[a] In water at 35 °C and ionic strength 0.3. [b] Estimated standard deviation. [c] The measurements on 3-pentanone-2,2,4,4-d_4 were carried out only over the pH range 6.26-8.53 so that the solutions were never basic enough for the k_h term in eq 3 to become important.

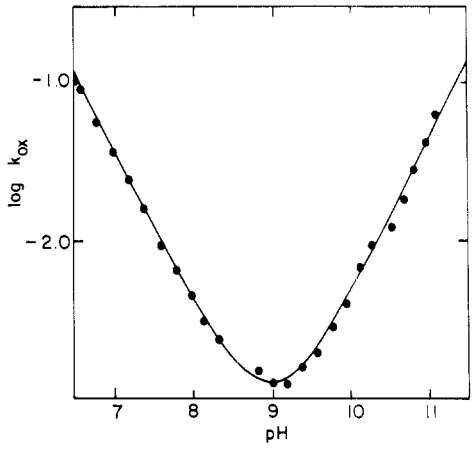

Figure 1. Apparent second-order rate constants for oximation of 3-pentanone in water at 35 °C and ionic strength 0.3 vs. pH.

Primary amine catalysis of the oximation of ketones is interpreted in terms of Scheme I, in which Am is the amine and Im the imine. If the produce $k_{Hx}[Hx]$ is much larger than k_d, capture of the imine by hydroxylamine is essentially quantitative. Under these conditions eq 4, in

$$-d[K]/dt = k_{Ox}[Hx][K] + k_{Im}[Am]_t[K] \quad (4)$$

which $[Am]_t$ is the concentration of all states of protonation of the amine, is applicable. Since k_{Ox} is known from the separate experiments carried out with no added amine, k_{Im} is readily obtained from measurements of the rate of reaction of the ketone. If there is not enough hydroxylamine present to capture essentially all the intermediate imine, the value of k_{Im} obtained by using eq 4 will increase with increasing hydroxylamine concentration. By this test 0.03 M hydroxylamine was found to be enough to capture all the intermediate imine formed from every amine studied except 2-(dimethylamino)ethylamine, for which 0.10 M hydroxylamine was needed. The values of k_{Im} obtained vary with the pH as the degree of protonation of the amine varies. They may be expressed in terms of eq 5, in which f_0 is the fraction of amine that is un-

$$k_{Im} = k_{Am}f_0 + k_{AmH}f_1 \quad (5)$$

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Table III. Rate Constants for Imine Formation from Cyclopentanone and 3-Pentanone and Various Primary Amines[a]

amine	pK_a[b]	$10^2 k_{cp}$,[c] M^{-1} s^{-1}	$10^2\sigma$,[d] M^{-1} s^{-1}	$10^3 k_{3p}$,[e] M^{-1} s^{-1}	$10^3\sigma$,[d] M^{-1} s^{-1}
n-$BuNH_2$	10.33	5.34	0.90	13.8	3.0
endo-2-norbornylamine	10.03	2.62	0.40	5.34	0.90
$Me_2NCH_2CMe_2CH_2NH_2$	10.03	2.17	0.64	2.69	1.25
$Me_2N(CH_2)_3NH_2$	9.91	2.25	0.30	7.31	1.57
$MeO(CH_2)_3NH_2$	9.80	2.71	0.41	6.93	1.42
$Me_2NCH_2CH_2NH_2$	9.34	1.10[f]		2.46[f]	
$MeOCH_2CH_2NH_2$	9.17	1.09	0.24	2.37	0.80
$Me_2NH^+(CH_2)_3NH_2$	8.50[g]	6.23	0.40	20.8	2.1
$Me_2NH^+CH_2CMe_2CH_2NH_2$	8.00[g]	12.1	1.5	24.1	2.3
$Me_2N(CH_2)_3NH_2 \cdot H^+$	7.97[h]	1.87	0.12	6.23	0.62
$Me_2NCH_2CMe_2CH_2NH_2 \cdot H^+$	7.04[h]	1.33	0.16	2.65	0.25
$Me_2NH^+CH_2CH_2NH_2$	6.72[g]	77.3	7.4	209	15
$Me_2NCH_2CH_2NH_2 \cdot H^+$	6.31[h]	29.4	2.8	79.6	5.7

[a] In water at 35 °C and ionic strength 0.30. [b] K_a is the concentration acidity constant of the monoprotonated form of the amine in water at 35 °C and ionic strength 0.3. To the extent to which activity coefficients are correctly calculated by the limiting form of the Debye-Huckel equation, the Davies equation, etc., this is equal to the thermodynamic acidity constant in the case of electrically neutral amines, but for monoprotonated diamines the thermodynamic acidity constant must be multiplied by γ^2, where γ is the activity coefficient of a unicharged ion. [c] Rate constant for cyclopentanone. [d] Estimated standard derivation of the k_{cp} or k_{3p} value. [e] Rate constant for 3-pentanone. [f] Calculated from the assumption that the rate constant fits the Brønsted plot for electrically neutral amines of the type $XCH_2CH_2NH_2$ (see text). [g] This acidity constant is for loss of a proton from only the primary ammonio group of the diprotonated amine (to give the specific monoprotonated diamine shown). [h] This acidity constant is for loss of a proton from the diprotonated amine to give the mixture of monoprotonated diamines indicated.

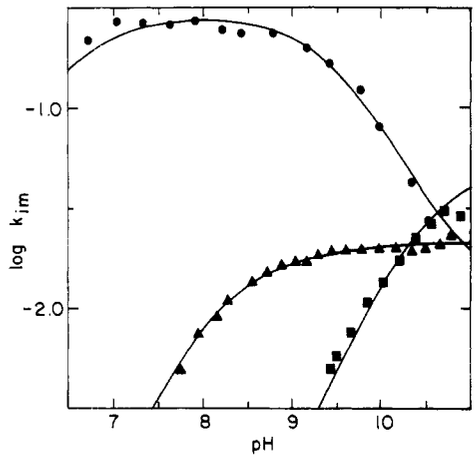


Figure 2. Apparent second-order rate constants for imine formation from cyclopentanone in water at 35 °C and ionic strength 0.3 vs. pH: ■, n-butylamine; ●, 2-dimethylaminoethylamine; ▲, 3-(dimethylamino)propylamine.

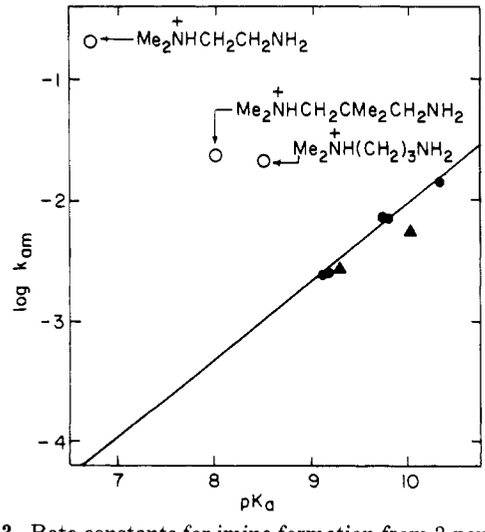


Figure 3. Rate constants for imine formation from 3-pentanone and primary amines in water at 35 °C and ionic strength 0.3 vs. the pK_a values of the primary ammonium ions: ●, amines of the type $XCH_2CH_2NH_2$, where X is neutral; ○, amines of the type $Me_2N^+H\sim\!\sim NH_2$; ▲, other primary amines.

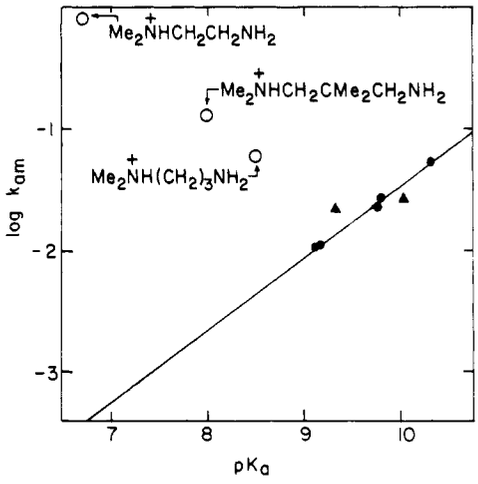


Figure 4. Rate constants for imine formation from cyclopentanone and primary amines in water at 35 °C and ionic strength 0.3 vs. the pK_a values of the primary ammonium ions: ●, amines of the type $XCH_2CH_2NH_2$, where X is neutral; ○, amines of the type $Me_2N^+H\sim\!\sim NH_2$; ▲, other primary amines.

protonated and f_1 is the fraction monoprotonated. In Figure 2 is a plot of log k_{Im} vs. pH for the reactions of n-butylamine, 2-(dimethylamino)ethylamine, and 3-(dimethylamino)propylamine with cyclopentanone. For n-butylamine the rate drops as the pH drops below 10 because k_{AmH} in eq 5 is negligible in this pH range. For 2-(dimethylamino)ethylamine the rate passes over a plateau in the pH range where the amine is largely monoprotonated; k_{AmH} is much larger than k_{Am}. The curve for 3-(dimethylamino)propylamine shows that k_{Am} is slightly larger than k_{AmH}. Values of k_{Am} and k_{AmH} calculated from eq 5 by a least-squares method are listed in Table III.

The reactions of 2-(dimethylamino)ethylamine with both cyclopentanone and 3-pentanone are so dominated by the k_{AmH} terms that the values of k_{Am} obtained by the least-squares treatment were smaller than the estimated standard deviations. It was therefore felt that the more reliable k_{Am} values could be obtained by assuming that the values fall on log–log plots of k values vs. the acidity constants of the corresponding ammonium ions (see Figures 3 and 4). These k_{Am} values are listed in Table III

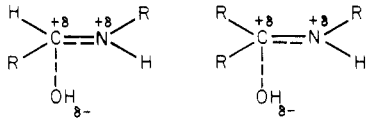
for 2-(dimethylamino)ethylamine and were used to obtain k_{AmH} values in a least-squares application of eq 5 to the k_{Im} values. The resulting k_{AmH} values, which are in Table III, are within 2% of the values obtained when both k_{Am} and k_{AmH} were treated as unknowns. Values of k_{AmH} for monoamines were within the estimated standard deviation of zero and were therefore taken to be zero. The values listed for the monoprotonated diamines ($Am{\cdot}H^+$) are the k_{AmH} values obtained for those diamines. Inasmuch as the monoamine data are based on a reactant of the type RNH_2 we have also calculated values for the monoprotonated diamines on the same basis. This was done by dividing the appropriate k_{AmH} values by f_t, the fraction of the monoprotonated diamine in which the tertiary amino group has been protonated, which has the values 0.38, 0.30, and 0.11 for 2-(dimethylamino)ethylamine,[11] 3-(dimethylamino)propylamine,[11] and *N*,*N*,2,2-tetramethyl-1,3-propanediamine,[12] respectively. The resulting rate constants refer to that form of the monoprotonated diamine in which the tertiary amino group is protonated. The lines in Figures 2 were drawn from the k_{Am} and k_{AmH} values in Table III.

Discussion

The smaller value of K_{Ox} for 3-pentanone than for acetone or cyclopentanone suggests that the oxime of 3-pentanone is sterically destabilized by repulsion between the hydroxy group and the ethyl group that is cis to it.

The secondary deuterium kinetic isotope effects (k^D/k^H) for 3-pentanone and cyclopentanone, respectively, are 1.15 and 1.25 for the k_H constant in eq 3 and 2.5 and 1.9 for the k_w constant. Like the corresponding values for acetone[5] these values are larger than 1.0, but the values for k_w are probably not very reliable because the k_w term was never large enough to constitute the main part of the reaction. We are not sure why the secondary isotope effect is only 0.62 for k_h for cyclopentanone. Although the estimated standard deviations shown were calculated in a standard manner,[10] we feel that they overestimate the precision of our results, especially in certain cases (e.g., the k_w values).

In order to correlate the rate of imine formation of the various RNH_2's with the polar character of R we have made a logarithmic plot of the rate constants vs. the pK_a values of the corresponding RNH_3^+'s, as shown in Figure 3 for 3-pentanone and Figure 4 for cyclopentanone. The pK_{al} values of the diamines are not pK_a values for species of the type RNH_3^+, however, since the monoprotonated diamines are partly tertiary protonated and partly primary protonated. When K_{al} is divided by f_p, the fraction of the monoprotonated diamine that is primary protonated, we obtain K_{TPH}, which is the acidity constant of a primary ammonium ion. The values of f_p and pK_{TPH} are 0.62[11] and 9.13, 0.70[11] and 9.75, and 0.18[12] and 9.29 for 2-(dimethylamino)ethylamine, 3-(dimethylamino)propylamine, and *N*,*N*,2,2-tetramethyl-1,3-propanediamine, respectively. These values for the unprotonated diamines and the pK_a values listed in Table III for the conjugate acids of the tertiary protonated diamines (which are pK_{HTPH} values) are used in plotting the diamine data in Figures 3 and 4. In each plot the four points (the point for 2-(dimethylamino)ethylamine not being included) for amines of the form $XCH_2CH_2NH_2$, in which X is neutral (electrically and in the acid–base sense), approximate a straight line. The slopes of 0.60 for cyclopentanone and 0.66 for 3-pentanone may be within the experimental uncertainties of the value 0.59 obtained in a similar plot for acetone[4] but are significantly smaller than the value 0.80 obtained with isobutyraldehyde.[13] The second-order rate constants for isobutyraldehyde are about 400 times as large as those for acetone, which is slightly more reactive than cyclopentanone. Thus, isobutyraldehyde is the most reactive and the most selective of the four carbonyl compounds studied. In interpreting this fact, one should remember that the second-order rate constants are products of equilibrium constants for carbinolamine formation and first-order rate constants for loss of hydroxide ion by the carbinolamine. Equilibrium constants for addition of simple primary amines to acetone are too small to measure, but equilibrium constants for addition of hydroxylamine,[8,14] water,[15,16] and bisulfite ions[16,17] are larger for isobutyraldehyde than for acetone by factors of 180, 310, and 320, respectively. Therefore, the rate constants for dehydration of carbinolamines may be about the same for isobutyraldehyde as for acetone. We suggest an explanation for the greater selectivity of isobutyraldehyde in terms of transition states 1 and 2 for the aldehyde and



1 2

ketone, respectively. Departure of the hydroxide ion leaves an iminium ion with positive charge on the nitrogen atom and the carbon atom from which the hydroxide ion departed. This positive charge is delocalized onto the attached alkyl groups, and more of it is delocalized in the ketiminium ion than in the aldiminium ion because the former has one more alkyl group attached. Thus there is less charge on the nitrogen atom in the ketiminium ion and in the transition state leading to this ion and hence less sensitivity of the rate to the polar character of the alkyl group attached to this nitrogen atom. It may also be that, because of repulsions between the *N*-alkyl group and the *C*-alkyl group that becomes cis to it in the ketiminium ion, the three groups attached to the nitrogen atom do not as easily become coplanar and have not proceeded as far toward coplanarity in **2** as in **1**. Such repulsions are suggested by the fact that the equilibrium constant for *N*-methylimine formation is 350 times as large for isobutyraldehyde[18] as for acetone.[14]

The triangular points in Figures 3 and 4 are for *N*,*N*,2,2-tetramethyl-1,3-propanediamine and *endo*-2-norbornylamine. In the latter compound the amino group is attached to a secondary carbon; steric effects presumably cause the points for this compound to lie below the lines in Figures 3 and 4. We do not understand why the point for *N*,*N*,2,2-tetramethyl-1,3-propanediamine lies above the line in Figure 4.

The points for the monoprotonated diamines all lie well above the lines, with 2-(dimethylamino)ethylamine being, in each case, more than 1000 times as reactive as it would be if it fell on the line. It seems highly unlikely that any major fraction of these deviations arises from the electrical charge on the monoprotonated diamines. Electrical charge does not cause a substantial deviation in the analogous plot

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Table IV. Structural Effects on Internal Acid Catalysis of Iminium Ion Formation[a]

	k_{obsd}/k_{calcd}			
$Me_2NH^+—R—NH_2$	*i*-Pr-CHO[b]	Me_2-CO[c]	C_4H_8-CO[d]	Et_2-CO
$Me_2NH^+CH_2CH_2NH_2$	4200	1700	2100	3300
$Me_2NH^+(CH_2)_3NH_2$	540	17	15	22
$Me_2NH^+CH_2CMe_2CH_2NH_2$		32	56	55

[a] In water at 35 °C. [b] Calculated from data in ref 6 and 13. [c] Calculated from data in ref 4 and 5. [d] Cyclopentanone.

of rate constants for imination of acetone; the point for 2-(trimethylammonio)ethylamine lies near the line described by electrically neutral primary amines.[4] We conclude that the deviations arise from internal acid catalysis of the dehydration of the intermediate carbinolamines, as shown in eq 1. Evidence for such internal catalysis has been described earlier for imine formations (via iminium ion formation) by acetone[4,5] and isobutyraldehyde.[6] It has also been seen in the reverse reaction, the hydrolysis of iminium ions. Fife and Hutchins showed that the hydrolyses of *N*-[2-(methylamino)ethyl]-methylbenzylideneammonium ions are probably internally base catalyzed by the methylamino groups.[19] Kayser and Pollack explained the rates of hydrolysis of imines derived from cyclohexene-1-carboxaldehyde and amino acids in terms of internal basic catalysis, by the carboxylate anion groups, of attack by water on the iminium ions.[20] These mechanisms for iminium ion hydrolysis are the microscopic reverse of our mechanism for iminium ion formation.

Structural effects on internal acid catalysis of iminium ion formation are summarized in Table III and in Table IV, which contains values of k_{obsd}/k_{calcd} where k_{calcd} is the rate constant that would be observed if the data fit the best straight line through the points for amines of the type $XCH_2CH_2NH_2$, in which X is neutral. With each carbonyl compound, 2-(dimethylammonio)ethylamine is the most reactive amine, whether we measure by k_{obsd}/k_{calcd} values or by k_{cp} and k_{3p} values. We are dealing with acid catalysis, and the dimethylammonio group in this catalyst is more acidic than those in the 1,3-propanediamine derivatives. However, the k_{cp} and k_{3p} values for 2-(dimethylammonio)ethylamine must be lowered, relative to those for the 1,3-propanediamine derivatives, owing to the fact that an iminium ion derived from a more weakly basic amine is being formed. (This difference in basicities has been allowed for, albeit imperfectly, in the k_{obsd}/k_{calcd} ratios.) From the magnitudes of the differences in acidities and basicities and the fact that two effects are operating in opposite directions, it can be seen that the differences in reactivities cannot be explained in such terms. We believe that the relative reactivities are controlled more by ring-strain effects in the cyclic transition states. The 2,2-dimethylation of 3-(dimethylammonio)propylamine to give the tertiary protonated form of *N*,*N*,2,2-tetramethyl-1,3-propanediamine increases the k_{obsd}/k_{calcd} ratios. This is an example of the "*gem*-dimethyl effect", which often encourages processes involving cyclization.[21]

The rate constant ratios shown are larger with isobutyraldehyde than with any of the ketones. This may be related to the increased susceptibility of iminium ion formation to acid catalysis caused by electron-withdrawing substituents.[2,13,22] (A hydrogen atom attached to a carbonyl group is certainly electron withdrawing relative to an alkyl group.) It is not clear, however, why the 3-(dimethylammonio)propylamine is markedly more reactive toward isobutyraldehyde but 2-(dimethylammonio)-ethylamine is only slightly more reactive.

Experimental Section and Data Treatment

Reagents. The α-deuterated ketones were prepared by repeated base-catalyzed exchange with deuterium oxide in a manner similar to published procedures.[23-25] Sodium carbonate was used as the catalyst with cyclopentanone, and with the less reactive and less water-soluble 3-pentanone, sodium deuterioxide was used. Exchange was continued until the product was at least 98% α-deuterated. The method described previously[26] was used to prepare *N*,*N*,2,2-tetramethyl-1,3-propanediamine, which was treated with hydrogen chloride in ether to give the dihydrochloride, mp 221–223 °C (methanol). The other amines and the ketones were distilled before use and their purity was checked by VPC.

Equilibrium in Oximation. Spectrophotometric measurements were used to determine apparent equilibrium constants for oximation[8] as defined in eq 6. Cyclopentanone was studied

$$K_{app} = \frac{[OxH^+] + [Ox]}{[K]([HxH^+] + [Hx])} \quad (6)$$

at 290 nm, where the molar absorbance of the ketone (and the standard deviation) is 15.6 (0.1) M^{-1} cm^{-1} and that of its oxime is 0.596 (0.043) M^{-1} cm^{-1}. 3-Pentanone was studied at 285 nm, where the molar absorbance of the ketone is 15.4 (0.3) M^{-1} cm^{-1} and that of its oxime 0.135 (0.060) M^{-1} cm^{-1}. Values of K_{app} obtained over the pH range from about 1 to about 7 were treated by least-squares methods[8,10] to give the values of K_{Ox} and pK_{OxH} listed in Table I. The K_{app} values for 3-pentanone in the most acidic solutions are too small to be determined very reliably. This greatly decreases the reliability of the pK_{OxH} value and slightly decreases the reliability of the K_{Ox} value obtained.

Acidity Constants. Amines were titrated with hydrochloric acid potentiometrically by using a Radiometer PHM-26 pH meter with a GK-2301-C combination electrode under nitrogen at 35 °C. Activity coefficients were calculated from the Davies equation,[27] and observed pH values were taken as $-\log a_{H^+}$. Thermodynamic pK_a values were calculated by the implicit multifunctional nonlinear least-squares method of Sachs.[28] Titrations in which the ionic strength was below 0.06 gave pK_a values of 7.61, 9.81, 9.17, and 9.80 for *N*-ethylmorpholinium, (2-hydroxyethyl)diisopropylammonium, (2-methoxyethyl)ammonium, and (3-methoxypropyl)ammonium ions, respectively. At ionic strength 0.3 (NaCl), with ca. 0.08 M amines, (2-methoxyethyl)ammonium and (3-methoxypropyl)ammonium ions gave pK_a values of 9.15 and 9.75; the changes with changing ionic strength probably arise in part from imperfections in the Davies equation. The other pK_a values in Table III were determined earlier in this laboratory.[4,12,29]

Kinetics. The reactions were followed by spectrophotometric measurements on the reacting ketone by using methods similar to those used previously.[4,5,8] At zero time 5 μL of cyclopentanone or 6 μL of 3-pentanone was added to 3.00 mL of reaction solution in a 1-cm cell. The cyclopentanone runs were followed at 290 nm and the 3-pentanone runs at 285 nm. Ordinarily 40 points were taken, equally spaced in time.

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When oximation of the protio ketones was carried out in the absence of primary amines, *N*-methylmorpholine buffers were used over the pH range 6.2–8.6, trimethylamine buffers over the range 8.8–10.2, and triethylamine buffers over the range 10.5–11.2. *N*-Ethylmorpholine buffers were used in all the 3-pentanone-d_4 runs and in the cyclopentanone-d_4 runs from pH 6.2 to 8.7. From pH 8.9 to 10.8 (2-hydroxyethyl)diisopropylamine buffers were used for cyclopentanone-d_4. Total buffer concentrations were 0.10 M except for the three runs where 0.05 M buffer was used to test for general catalysis. Fourteen runs were made on 3-pentanone-d_4, and more than 20 were made on each of the other three ketones.

In the absence of primary amines, second-order rate constants (k_2) for oximation were obtained from eq 7, in which c is defined

$$A_t = \frac{c(A_0 - A_\infty)}{[\mathrm{Hx}]_{t_0} \exp(ck_2t) - [\mathrm{K}]_0} + A_\infty \quad (7)$$

in eq 8. All values of the absorbance at time t (A_t) were weighted

$$c = [\mathrm{Hx}]_{t_0} - [\mathrm{K}]_0 \quad (8)$$

equally in the nonlinear least-squares treatment,[10] which gave initial and infinite absorbance values (A_0 and A_∞) as well as the rate constant. The molar absorbances of the ketone and oxime (ϵ_K and ϵ_{Ox}) and the initial total concentration of hydroxylamine in both states of protonation ($[\mathrm{Hx}]_{t_0}$) were taken as knowns. Equations 9 and 10 were assumed for the absorbances, with Δ

$$A_0 = \epsilon_K[\mathrm{K}]_0 + \Delta \quad (9)$$

$$A_\infty = \epsilon_{Ox}[\mathrm{K}]_0 + \Delta \quad (10)$$

being a factor to allow for imperfectly matched cells, machine drift, etc. In the first iteration of the nonlinear least-squares treatment Δ was set equal to zero and $[\mathrm{K}]_0$ treated as a known. In subsequent iterations a value of Δ was calculated from the A_∞ value obtained with eq 10, and then a $[\mathrm{K}]_0$ value was calculated from eq 9. A value of c was then obtained from eq 8. The observed rate constant k_2 was transformed to k_{Ox}, the second-order rate constant for the reaction of the ketone with free hydroxylamine, by use of eq 11. To obtain values of k_H, k_h, and k_w, we transformed eq

$$k_{Ox} = k_2[\mathrm{Hx}]_t/[\mathrm{Hx}] \quad (11)$$

3 to the logarithmic form (eq 12) and each log k_{Ox} value was weighted equally in the least-squares treatment.[10]

$$\log k_{Ox} = \log (k_H[\mathrm{H}^+] + k_h[\mathrm{OH}^-] + k_w) \quad (12)$$

For primary-amine-catalyzed oximation, eq 13 was used, with

$$A_t = \frac{(k_1 + k_2c)(A_0 - A_\infty)}{(k_1 + k_2[\mathrm{Hx}]_{t_0}) \exp[(k_1 + k_2c)t] - k_2[\mathrm{K}]_0} + \epsilon_{Ox}[\mathrm{K}]_0 + \Delta \quad (13)$$

k_1 as defined in eq 14. From the values of k_H, k_h, and k_w obtained

$$k_1 = k_{lm}[\mathrm{Am}]_t \quad (14)$$

in the absence of primary amines, k_{Ox} and then k_2 were calculated. The nonlinear least-squares treatment[10] gave values for Δ, $[\mathrm{K}]_0$, and k_1. From these values, improved values of $A_0 - A_\infty$ were calculated iteratively. The average value of Δ obtained was about 0.015, and no value was larger than 0.08. The standard deviations of the calculated from the experimental absorbance values averaged about 0.001 and never exceeded 0.005.

Registry No. 3-Pentanone, 96-22-0; cyclopentanone, 120-92-3; butylamine, 109-73-9; *endo*-2-norbonylamine, 31002-73-0; *N,N*,2,2-tetramethyl-1,3-propanediamine, 53369-71-4; *N,N*-dimethyl-1,3-propanediamine, 109-55-7; 3-methoxy-1-propanamine, 5332-73-0; *N,N*-dimethylethanediamine, 108-00-9; 2-methoxyethanamine, 109-85-3; protonated *N,N*-dimethyl-1,3-propanediamine, 61507-91-3; protonated *N,N*,2,2-tetramethyl-1,3-propanediamine, 71171-48-7; protonated *N,N*-dimethyl-1,2-ethanediamine, 51380-72-4; hydroxylamine, 7803-49-8; *N*-ethylmorpholinium, 57133-80-9; *N*-(2-hydroxyethyl)-*N,N*-diisopropylammonium ion, 71171-49-8; (2-methoxyethyl)ammonium ion, 54005-66-2; (3-methoxypropyl)ammonium ion, 54005-67-3.

Carbon-13 Study of Oxygen Function Rearrangement in the Acid-Catalyzed Rearrangement of 2,2,4-Trimethyl-3-pentanone-3-^{13}C to 3,3,4-Trimethyl-2-pentanone-3-^{13}C[1a]

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The acid-catalyzed rearrangement of 2,2,4-trimethyl-3-pentanone-3-^{13}C, **1b**, affords, as predicted, rearranged 3,3,4-trimethyl-2-pentanone-2-^{13}C, **2b**, and, in lesser amounts, its isotopic isomer 3,3,4-trimethyl-2-pentanone-3-^{13}C, **2c**. In addition, an isotopic isomer of **1b**, 2,2,4-trimethyl-3-pentanone-2-^{13}C, **1c**, is formed in small amounts. Measurements of the amount of this oxygen function rearrangement were carried out by using ^{1}H NMR ^{13}C satellite and direct ^{13}C NMR techniques, and the utility of these techniques compared to carbon-14 methods is discussed. The mechanisms of these rearrangements are discussed in terms of competing alkyl shifts and oxygen function rearrangements in the ketone conjugate acids and carbocations derived from them.

Acid-catalyzed ketone rearrangements[2] sometimes involve oxygen function rearrangements[3] (OFR) such as would be required in the formation of **2c**, 3,3,4-trimethyl-2-pentanone-3-^{13}C, and **1c**, 2,2,4-trimethyl-3-pentanone-2-^{13}C, from **1b**, 2,2,4-trimethyl-3-pentanone-3-^{13}C (the natural-abundance molecules are designated **1a**, **2a**, etc., and labeled isotopic isomers are designated **1b**, **1c**, etc.; *C = ^{13}C):

(1) (a) Taken from the Ph.D. dissertation of M.O., University of Arkansas, 1973; presented in part at the 2nd Rocky Mountain Regional Meeting of the American Chemical Society, Albuquerque, N.M., July 8–9, 1974. A brief summary of this work appears in ref 5. (b) Address correspondence to this author at California State Polytechnic University, Pomona, Calif. 91768.

(2) For a review, see A. Fry, *Mech. Mol. Migr.*, 4, 113 (1971).

(3) A. Fry, W. Carrick, and C. Adams, *J. Am. Chem. Soc.*, 80, 4743 (1958), and other research cited in ref 2.

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