Chem. Soc., 97, 675 (1975).
(22) J. D. Hobson and W. D. Riddell, *Chem. Commun.*, 1178 (1968).
(23) L. F. Hines and J. K. Stille, *J. Am. Chem. Soc.*, **94**, 485 (1972).
(24) (a) J. X. McDermott and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 947 (1974); (b) J. X. McDermott, J. F. White, and G. M. Whitesides, *ibid.*, **95**, 4451 (1973).
(25) H. Dirkzwager, T. J. Nieuwstad, A. M. Van Wijk, and H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **92**, 35 (1973).

Trifluoroethylamine-Catalyzed Isomerization of β,γ-Unsaturated Ketones. Nucleophilic Catalysis via Schiff Base Formation

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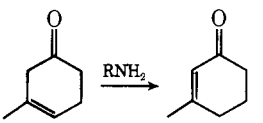
Abstract: The isomerizations of 3-methyl-3-cyclohexenone (**1**) to 3-methyl-2-cyclohexenone (**2**), and 1-acetyl-2-cyclohexene (**5**) to 1-acetyl-1-cyclohexene (**6**) are efficiently catalyzed by trifluorethylamine (TFEA). In the case of **1** → **2**, the reaction proceeds via the intermediate formation of trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (**3**), the Schiff base of TFEA and **2**. Formation of **3** is rapid under the conditions employed (pH 4.85–6.90, TFEA buffers) with hydrolysis of **3** to **2** occurring as a subsequent slow reaction. The formation of **3** was investigated in detail. The rate of this reaction is predominantly dependent on a second-order term in TFEA ($k^{AB}[RNH_2][RNH_3^+]$) with small first-order terms in free amine ($k^B[RNH_2]$) and protonated amine ($k^A[RNH_3^+]$). A mechanism is proposed which involves preequilibrium formation of the β,γ-unsaturated Schiff base from **1** (**8**) followed by isomerization through a dienamine (**9**) to the α,β-unsaturated Schiff base (**3**). Examination of solvent isotope effects on this reaction shows that protonation of **9** occurs with approximately equal facility to give **3** and to regenerate **8**. In contrast to **1**, the TFEA-catalyzed isomerization of **5** proceeds directly to **6** with no detectable accumulation of intermediate. These reactions are discussed as possible models for enzymatic interconversions of α,β-unsaturated ketones and their β,γ isomers.

The interconversion of β,γ-unsaturated ketones and their α,β-unsaturated isomers has been shown to be catalyzed by both acids[1-5] and bases.[3,6-8] The acid-catalyzed reaction involves the formation of a dienol intermediate, followed by protonation at the α or γ carbon to give β,γ or α,β product, respectively,[1,2] and an analogous pathway through an enolate ion intermediate has been proposed[3] for the base-catalyzed process. In addition, several enzymes are known which carry out this type of isomerization.[9-11] The only enzyme of this type which has been studied in detail is the Δ^5-3-keto steroid isomerase from *P. testosteroni*,[9] although the mechanism for this reaction has yet to be fully elucidated.

In a preliminary communication[12] we reported that primary amines are capable of catalyzing the isomerization of β,γ-unsaturated ketones to their α,β-unsaturated isomers through the formation of a dienamine intermediate, analogous to the dienol in the corresponding acid-catalyzed rearrangement. Furthermore, the amine-catalyzed reaction is much more efficient than either the acid- or base-catalyzed reactions at neutral pH, and may represent a model for some of the corresponding enzymatic isomerizations. Benisek and Jacobson[13] have also reported that this type of isomerization is subject to amine catalysis and have advanced essentially the same mechanism to account for their results. In this report, we present a full account of our investigation into the kinetics and mechanism of the trifluoroethylamine catalysis of the isomerization of 3-methyl-3-cyclohexenone and 1-acetyl-2-cyclohexene.

Results

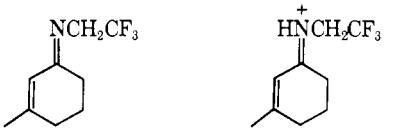
3-Methyl-3-cyclohexenone. The isomerization of 3-methyl-3-cyclohexenone (**1**) to the conjugated isomer, 3-methyl-2-cyclohexenone (**2**), was found to be efficiently catalyzed by primary amines. Our investigation of this reaction



1 **2**

with 2,2,2-trifluoroethylamine (TFEA) buffers showed that, although **2** was the sole final product ($\lambda_{max}^{H_2O}$ 240), another uv-absorbing species was produced during the reaction. During the initial phases of the reaction, an intermediate was formed with an absorption maximum at approximately 268 nm. Addition of **1** to TFEA produced a rapid rise in absorbance at 268 nm followed by a slower decay, suggesting that this species is involved in the overall catalytic process. When the appearance of **2** was monitored at 240 nm, an induction period was observed, providing further evidence for the existence of an intermediate on the reaction pathway.

In order to isolate and identify this intermediate, **1** was allowed to react with TFEA in carbon tetrachloride, using molecular sieves to remove the water produced to prevent hydrolysis of the intermediate to **2**. Purification of the product



3 **4**

by GLC yielded a colorless oil which was shown to be the α,β-unsaturated Schiff base **3**, based on elemental analysis and spectral data.

The NMR spectrum of **3** showed a singlet at δ 5.75 assigned to the olefinic proton, a quartet at δ 3.58 with J = 10 Hz (incorrectly given as δ 5.58, J = 16 Hz in our preliminary com-

munication[12]) due to the methylene group adjacent to the trifluoromethyl group, a multiplet at δ 1.6–2.4 assigned to the aliphatic ring protons, and a singlet for the methyl group at δ 1.80. The uv (λ_{max} 228, ϵ 2.2 × 10^4 in cyclohexane) also is consistent with the proposed structure.[14] Other structures for **3** were eliminated as follows: (1) the Schiff base of the β,γ-unsaturated ketone would not give a singlet vinyl hydrogen in the NMR and should have a much lower extinction coefficient in the uv; (2) the corresponding endo dienamine should show two vinyl hydrogens (one singlet and one multiplet); (3) the exo dienamine should show no methyl peak and would have a λ_{max} about 280 nm.[15]

Although the absorption spectrum of **3** in cyclohexane (λ_{max} 228 nm) or unbuffered water (λ_{max} 238 nm) was not characteristic of the intermediate observed during the TFEA-catalyzed isomerization of **1** to **2** (268 nm), addition of the free Schiff base (**3**) to slightly acidic buffer solutions caused an instantaneous shift of the λ_{max} to 268 nm, characteristic of the protonated α,β-unsaturated Schiff base structure (**4**).[14-16] The apparent acid-base equilibrium of the ketimine was confirmed by NMR. Addition of the free base to D_2O containing 0.2 N DCl resulted in a splitting of the olefinic proton into two peaks of approximately equal area with a downfield shift from δ 5.75 to 6.25 and 6.50.[17] A corresponding splitting of the methyl peak was observed with a downfield shift from δ 1.80 to 2.10 and 2.16. The appearance of doublets of equal intensity in the NMR of the protonated ketimine suggests that it exists in syn and anti forms and that these isomers interconvert slowly on the NMR time scale at room temperature. The free ketimine, on the other hand, shows an NMR spectrum with only one olefinic signal, perhaps due to rapid equilibration of the syn and anti isomers.[18,19]

The identification of the intermediate observed in the TFEA-catalyzed isomerization as **4** was confirmed by monitoring the isomerization of **1** to **2** in 70% Me_2SO-D_2O ($[TFEA]_t$ = 1.0, 1:1 buffer). The NMR spectrum of the intermediate in the isomerization was identical with the spectrum of the protonated ketimine (**4**). The pK_a of **4** was determined at ionic strength 1.0 to be 6.76 ± 0.04, higher than the pK_a of TFEA (5.77).

Formation of the Schiff Base. Rate constants for the isomerization of **1** to **2** were determined at 25.0 ± 0.2° (μ = 1.0) in TFEA buffers from pH 4.85 to 6.90, with a concentration of TFEA ranging from 0.05 to 0.6 M. The formation and decay of **4** were monitored spectrally at 268 nm and the absorbance data were analyzed in terms of eq 1, in which both the formation and hydrolysis of **4** are assumed to be irreversible. The pseudo-first-order rate constants, k_i and k_h, were obtained by

$$\mathbf{1} \xrightarrow{k_i} \mathbf{4} \xrightarrow{k_h} \mathbf{2} \qquad (1)$$

a modification of the method of Fersht and Jencks,[20] as described in the Experimental Section. Alternatively, k_i was determined by monitoring the isomerization at the isosbestic wavelength for the conversion of **4** to **2** (ca. 251 nm). This procedure made the hydrolysis effectively "invisible" and thus the formation of **4** could be followed directly as a pseudo-first-order reaction. The rate constants for the hydrolysis reaction (k_h) were also obtained by direct measurement since we had samples of the pure Schiff base (**3**). In addition, rate constants for the overall reaction were measured at 240 nm (appearance of **2**) at pH 5.25 and 5.77. These rate constants were identical with the k_h values determined at 268 nm, except for the occurrrence of the expected induction period at 240 nm.

The rate constants for formation of protonated ketimine (**4**) were analyzed in terms of the equation

$$k_i = k^A[TFEAH^+] + k^B[TFEA] + \sum k^{AB}[TFEAH^+][B] \qquad (2)$$

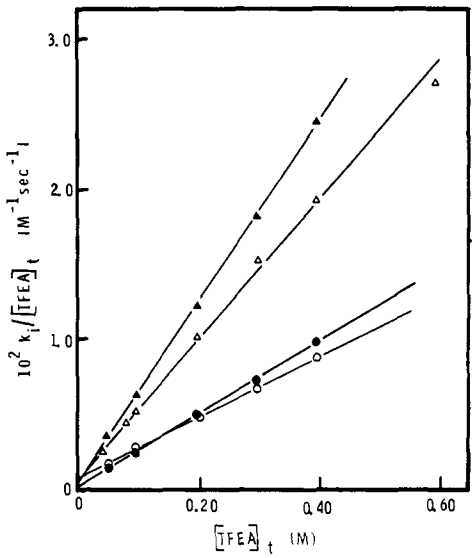


Figure 1. Plot of $k_i/[TFEA]_t$ vs. $[TFEA]_t$ for the formation of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium ion (**4**) from 3-methyl-3-cyclohexenone (**1**) and trifluoroethylamine at 25.0° (μ = 1.0). The data were obtained by monitoring the reactions at the isosbestic point for conversion of **4** → **2**: (○) pH 4.85; (●) pH 6.90; (△) pH 5.25; (▲) pH 5.77.

Table I. Slopes and Intercepts for Plots of $k_i/[TFEA]_t$ vs. $[TFEA]_t$ for Formation of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium Ion (**4**) from 3-Methyl-3-cyclohexenone (**1**) and Trifluoroethylamine at 25.0° (μ = 1.0)[a]

pH	10^2 slope, $M^{-2}\ s^{-1}$	10^4 intercept, $M^{-1}\ s^{-1}$	[TFEA]/[TFEAH$^+$]
4.85	2.03 ± 0.05[b]	7.02 ± 0.58[b]	0.10
5.25	4.67 ± 0.24[b]	6.32 ± 2.40[b]	0.30
	3.88 ± 0.49[c]	9.48 ± 11.6[c]	
5.77	5.81 ± 0.16[b]	5.64 ± 1.47[b]	1.00
6.05	4.84 ± 0.36[c]	5.46 ± 4.90[c]	2.04
6.90	2.35 ± 0.08[b]	2.37 ± 0.66[b]	6.67

[a] Errors are standard deviations. [b] Measured at isosbestic point for **4** → **2**. [c] Measured at 268 nm.

where B represents any general base in the solution, including TFEA. In the absence of external general bases, the TFEA-catalyzed formation of **4** was almost entirely second order in amine in the pH range examined (4.85–6.90). Thus, the observed rate constants were divided by total amine concentration ($[TFEA]_t$) and plotted vs. $[TFEA]_t$ at constant pH. As shown in Figure 1, these plots are linear with intercepts near zero. Table I summarizes the values of the slopes and intercepts obtained from a weighted least-squares analysis.

The slopes given in Table I increase as the pH approaches the pK_a of TFEA (5.77), suggesting that the rate term which is second order in amine is proportional to [TFEA][TFEAH$^+$] and not to $[TFEA]_t^2$. A plot of the slopes in Table I vs. the quantity [TFEA][TFEAH$^+$] calculated at $[TFEA]_t$ = 1 M gives the linear relationship shown in Figure 2, confirming this prediction. The slope of this line gives the actual third-order rate constant, k^{AB} = 0.225 ± 0.014 $M^{-2}\ s^{-1}$.

The intercepts given in Table I which were calculated by measurements at 268 nm have larger errors than those determined at the isosbestic point; this is not surprising due to the uncertainty inherent in calculating both the appearance and decay rates by the rather involved procedure (see Experimental Section). Therefore, the first-order terms for catalysis by

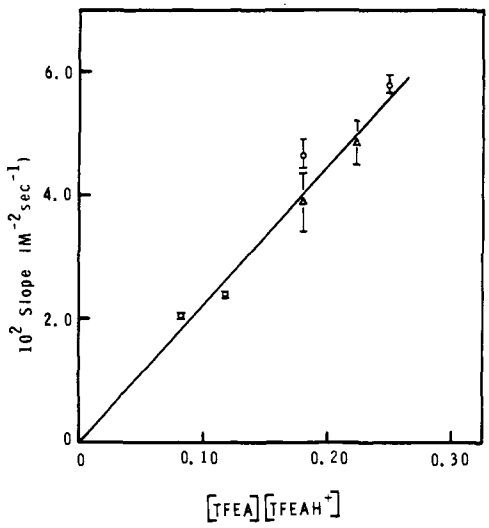
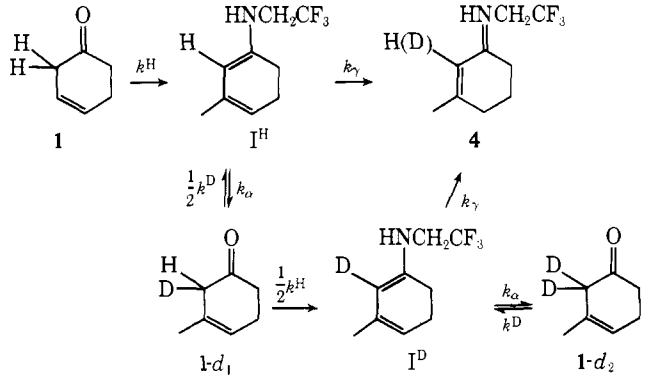


Figure 2. Plot of slopes in Table I vs. [TFEA][TFEAH$^+$] at [TFEA]$_t$ = 1.0 M. Error bars represent standard deviations. (○) measured at the isosbestic point for **4** → **2**; (△) measured at 268 nm.

TFEA and TFEAH$^+$ were evaluated by plotting only those intercepts obtained at the isosbestic point vs. the fraction of free amine, [TFEA]/[TFEA]$_t$. This plot was linear, giving the first-order term in both free amine (k^B = (1.92 ± 0.27) × 10^{-4} M^{-1} s^{-1}) and protonated amine (k^A = (7.91 ± 0.53) × 10^{-4} M^{-1} s^{-1}) by extrapolation to [TFEA]/[TFEA]$_t$ = 1.0 and 0, respectively.[21]

Solvent isotope effects for the formation of protonated ketimine **4** were measured at the isosbestic wavelength for **4** → **2** in D_2O containing TFEA buffers. Although the absorbance showed a monotonic increase, the kinetics could not be analyzed in terms of a simple first-order process. The absorbance increased very rapidly at first, followed by a much slower increase at later times. These curves were analyzed on the basis of a mechanism which involves concurrent exchange of H for D at the α positions of the β,γ-unsaturated ketone (**1**). We also include in our scheme two possible forms of an intermediate I (I^H and I^D) which can either return to reactants or proceed to products. The most reasonable structure for this intermediate is the dienamine. All forms of the unconjugated ketone (**1**) were assumed to proceed to the product ketimine by way of deuterated dienamine, I^D, or undeuterated dienamine, I^H (Scheme I). All secondary isotope effects were assumed to be

Scheme I



negligible, and thus the rate of reaction of **1**-d_1 is $\frac{1}{2}k^H$ if a proton is lost and $\frac{1}{2}k^D$ if a deuteron is abstracted. The rate constants k_α and k_γ refer to protonation at the α carbon to give **1** (d_0, d_1, or d_2) and **4**, respectively. The integrated rate expression is then given by the equation

Table II. Rate Constants and Isotope Effects for Formation of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium Ion (**4**) from 3-Methyl-3-cyclohexenone (**1**) and Trifluoroethylamine in D_2O at 25.0° (μ = 1.0)[a]

pD	$k_H^{AB}(D_2O)$, M^{-2} s^{-1}	k^H/k^D	R	$k_H^{AB}(H_2O)/k_H^{AB}(D_2O)$
5.33	0.189 ± 0.008 0.177[b]	6.18 ± 0.09	0.417 ± 0.003	1.19 ± 0.09
6.25	0.181 ± 0.005	6.41 ± 0.56	0.426 ± 0.010	1.24 ± 0.08
Av	0.185 ± 0.004	6.30 ± 0.28	0.422 ± 0.005	1.22 ± 0.06

[a] Rate constants were determined by the integrated rate expression unless otherwise noted; errors are standard deviations. [b] From initial rates.

$$P = A_0 - \left[\frac{k^H(R-1)}{Rk^D - k^H}\right]^2 A_0 e^{-k^D R t} - \left[\frac{R(k^D - k^H)}{(Rk^D - k^H)}\right]^2 A_0 e^{-k^H t} - \left[\frac{2R(k^H - k^D)k^H(1-R)}{(Rk^D - k^H)^2}\right] A_0 e^{-(1/2)(k^H + k^D R)t} \quad (3)$$

$$= A_0 - a_1 A_0 e^{-k^D R t} - a_2 A_0 e^{-k^H t} - a_3 A_0 e^{-(1/2)(k^H + k^D R)t} \quad (3a)$$

where A_0 is the initial concentration of **1**, $R = k_\gamma/(k_\alpha + k_\gamma)$, a_1, a_2, and a_3 are the preexponential terms, and P is the concentration of ketimine at time t. The detailed method by which the parameters of this equation were evaluated is given in the Experimental Section. Although the procedure used to calculate k^D, k^H, and R is rather involved, most rate constants had standard deviations less than 1%. In addition, values of $k^H R$ were determined from initial rates at pD 5.33 and are in good agreement with those determined from the integrated rate expression. Finally, the experimental curves are well described by the calculated parameters.[22]

Since the rate constant for the overall process is $k^H R$ for **1** and $k^D R$ for **1**-d_2, these quantities were analyzed by plotting $k^L R$ (L = H or D) divided by [TFEA]$_t$ vs. [TFEA]$_t$ at constant pD. The slopes of these plots were then divided by [TFEA][TFEAH$^+$] at [TFEA]$_t$ = 1.0 M to obtain k_H^{AB} and k_D^{AB} in D_2O. The ratio of these two quantities gives the kinetic isotope effect for the formation of dienamine (I) from **1** and **1**-d_2 (k^H/k^D). The value for k_H^{AB} in D_2O can also be compared to the corresponding value in H_2O to give the solvent isotope effect on the overall process (**1** → **4**). These results are shown in Table II. For both pD's, the plots of $k^L R/$[TFEA]$_t$ vs. [TFEA]$_t$ gave intercepts indistinguishable from zero; thus, isotope effects for the first-order terms k^A and k^B could not be determined.

The rates of formation of **4** were also examined in TFEA buffer solutions containing an external general base. Addition of acetate or imidazole to 0.1 M TFEA buffer solutions caused a rate increase over that observed in the presence of 0.1 M TFEA alone at the same pH. Using the same procedure as described above, values of k_i were obtained at the isosbestic point for **4** → **2** in acetate buffers with 0.1 M TFEA at pH 4.45, 5.28, and 5.82. Analysis of plots of k_i vs. total concentration of acetate showed the presence of a term in [RNH_3^+]·[OAc^-] ($k_{OAc^-}^{AB}$ = 0.103 ± 0.003 M^{-2} s^{-1}). Use of imidazole as the general base rather than acetate was complicated by the absence of a well-defined isosbestic point for the hydrolysis of **4** in imidazole buffers. However, a value for k_{Im}^{AB} in the presence of 0.1 M TFEA was estimated by

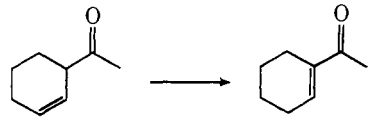
following Schiff base formation at a wavelength which appeared to be an isosbestic point for the hydrolysis during the initial phases of the reaction. Thus, the rate of Schiff base formation was only followed to 50–75% reaction in imidazole buffers containing 0.1 M TFEA at pH 5.80 and 6.35. Plots of k_i vs. [Im] gave $k_{Im}^{AB} = 0.81 \pm 0.05\ M^{-2}\ s^{-1}$.

Hydrolysis of the Schiff Base. As described above, the rate of hydrolysis of the α,β-unsaturated Schiff base (**3**) to the corresponding α,β-unsaturated ketone (**2**) can be obtained from the overall absorbance curve for the isomerization of **1** to **2** at 268 nm. However, because the Schiff base can be easily synthesized and isolated, most values of the hydrolysis rate constants were obtained by directly monitoring the decay at 268 nm upon addition of **3** to the buffer solutions. Where both methods were employed the agreement is excellent. The rate constants for hydrolysis (k_h) in the presence of TFEA buffers were treated according to our previously observed rate expression for the hydrolysis of **3** (eq 4)[23]

$$k_h = (k_h^{H_2O} + k_h^{OH^-}[OH^-] + k_h^{B}[RNH_2]) \times \left(\frac{[H^+]}{[H^+] + K_a}\right) \quad (4)$$

which assumes that the protonated Schiff base (**4**) is the reactive species. Analysis of plots of $k_h/[[H^+]/([H^+] + K_a)]$ vs. $[RNH_2]$ gave a value for $k_h^B = (1.40 \pm 0.23) \times 10^{-3}\ M^{-1}\ s^{-1}$ from the slopes. The intercepts of these plots ($k_h^{H_2O} + k_h^{OH^-}[OH^-]$) were consistent with values expected from the known parameters $k_h^{H_2O}$ and $k_h^{OH^-}$ [23,24] No term in protonated amine could be detected.

Isomerization of 1-Acetyl-2-cyclohexene. The isomerization of 1-acetyl-2-cyclohexene (**5**) to the conjugated isomer (**6**) was



5 **6**

also found to be catalyzed by TFEA; however, the reaction was much slower than the corresponding isomerization of **1**. In addition, no buildup of an intermediate could be detected. All reactions were followed in TFEA buffers (0.2–0.8 M) at 240 nm at 25.0° with ionic strength maintained at 1.0 with NaCl. A significant induction period was observed in all runs so that the first 5–10% of the reaction had to be ignored in calculating pseudo-first-order rate constants. Plots of $k^{obsd}/[TFEA]_t$ vs. $[TFEA]_t$ gave straight lines. The slopes and intercepts of these plots are shown in Table III. Analysis of these results by the same method used for 3-methyl-3-cyclohexenone gave $k^{AB} = (2.86 \pm 0.11) \times 10^{-4}\ M^{-2}\ s^{-1}$. The k^A term was estimated as $(1.5 \pm 0.5) \times 10^{-5}\ M^{-1}\ s^{-1}$ and k^B was indistinguishable from zero.

Table III. Slopes and Intercepts for Plots of $k^{obsd}/[TFEA]_t$ vs. $[TFEA]_t$ for the TFEA-Catalyzed Isomerization of 1-Acetyl-2-cyclohexene (**5**) to 1-Acetyl-1-cyclohexene (**6**) at 25.0° ($\mu = 1.0$)[a]

pH	10^5 slope, $M^{-2}\ s^{-1}$	10^6 intercept, $M^{-1}\ s^{-1}$	[TFEA]/[TFEAH$^+$]
5.25	5.46 ± 0.32	11.9 ± 1.3	0.30
5.77	6.68 ± 0.24	7.92 ± 1.01	1.00

[a] Errors are standard deviations.

Discussion

3-Methyl-3-cyclohexenone Isomerization. Identification of the Intermediate. The existence of an intermediate on the reaction pathway for the TFEA catalyzed isomerization of **1** to **2** is strongly indicated by the observation of a peak in the ultraviolet spectrum at 268 nm which is not due to either reactant or product. That this intermediate is involved in the overall catalytic scheme is shown by the occurrence of an induction period for formation of **2**. If the intermediate were being formed from **1** in a parasitic side reaction, one would expect that the initial rate of formation of **2** would be increased rather than decreased. Furthermore, we have previously shown[23] that **4** hydrolyzes exclusively to **2** with no formation of **1**, ruling out reversible formation of **4**, followed by direct reaction of **1** to **2** in the isomerization.

The product from the reaction of TFEA with **1** in CCl_4 was identified as the α,β-unsaturated Schiff base **3**. The NMR and uv spectra of **3** in acidic solution were found to be identical with the corresponding spectra of the intermediate observed in the isomerization of **1** to **2**. Protonation of conjugated azomethines on the nitrogen is known to result in a bathochromic shift of the absorption maxima.[14] The spectrum of the *n*-butylimine of crotonaldehyde, for example, undergoes a red shift from 220 to 247 nm in acetonitrile upon protonation with perchloric acid.[16] In addition, α,β-unsaturated iminium salts derived from secondary amines and α,β-unsaturated ketones are reported to give absorption maxima in the range 270–280 nm.[15,17] Therefore, the change in λ_{max} observed upon acidification of **3** is consistent with protonation on the nitrogen to give **4**.

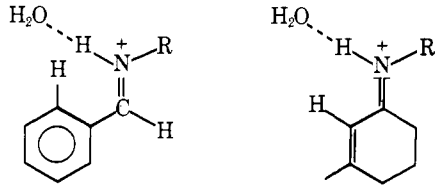
The downfield shifts noted in the NMR spectrum of **3** upon protonation are also compatible with structure **4**. The largest downfield shift is seen for the methylene hydrogens adjacent to the nitrogen (δ 3.58 to 4.39). The shift for the methyl singlet (δ 1.80 to 2.10 and 2.16) is smaller because the methyl group is further removed from the site of protonation (i.e., the nitrogen). The splitting of the olefinic and methyl singlets in the NMR spectrum of **4** is attributed to possible syn-anti isomerization about the carbon–nitrogen double bond.[18,19] The larger splitting of the olefinic signal ($\Delta\delta = 0.25$) compared to the methyl signal ($\Delta\delta = 0.06$) is reasonable due to the proximity of the vinyl hydrogen to the carbon–nitrogen double bond.

It is possible to rule out dienamine structures for intermediate **4** on the basis of the NMR. For example, an exocyclic dienamine (presumably protonated on the nitrogen in acid) would yield olefinic signals of unequal intensity and no methyl signal, while the endocyclic dienamine would have to show singlet and triplet olefinic signals. In addition, the splitting of the methyl singlet ($\Delta\delta = 0.06$) is difficult to explain by any structure other than **4**. In any case, dienamines usually undergo rapid tautomerization in acid to yield iminium ions.[15,17]

The pK_a of **4** was found to be 6.76 ± 0.04, about 1 pK_a unit higher than TFEA itself (5.77). In general, it appears that aliphatic Schiff bases are about 10^3-fold weaker bases than the amines from which they are derived.[25–27] However, the conjugated system in **4** apparently stabilizes the positive charge to such an extent that this Schiff base is more basic than the corresponding amine. This result is initially somewhat surprising in view of the fact that imines of aromatic aldehydes and ketones do not show an enhanced basicity relative to the free amines, in spite of the ability of phenyl groups to stabilize a positive charge on an adjacent carbon.[28] However, a comparison of the pK_a values for the corresponding ketones reveals that this type of olefinic conjugation is far more effective in stabilizing protonated carbonyl groups than phenyl conjugation. Using reported pK_a values for **2** (−3.5),[29] acetophenone (−6.4),[30] benzaldehyde (−7.5),[30] and cyclohexonone (−7.1),[30] it can be seen that **2** is ca. 10^3- to 10^4-fold more basic than the other carbonyl compounds. If a comparable stabilization by the olefinic group occurs in the protonated Schiff base **4**, the

greater basicity of **3** compared to Schiff bases of benzaldehyde and saturated ketones appears reasonable.

Another factor which might lower the basicity of Schiff bases of aromatic aldehydes is that solvation of the proton on the nitrogen may be inhibited by the ortho hydrogens of the phenyl group (**7**). This steric interaction can be relieved by rotation around the bond to the ring, but only at the expense of a loss in resonance stabilization. The smaller steric requirements in **4**, on the other hand, allow solvation to occur

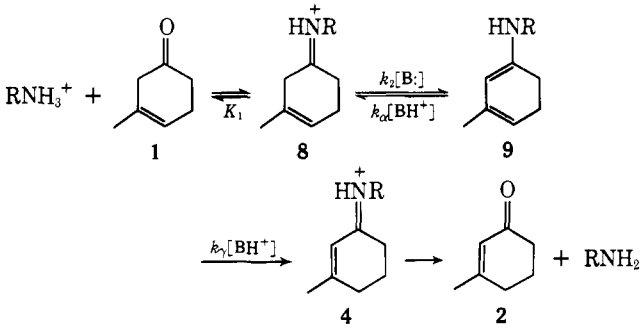


7 **4**

with a minimum of steric hindrance. A similar explanation has been advanced for the difference in pK_a's of ca. 1.5 pK units for the E and Z isomers of phenyl N-methylacetimidates.[32]

Formation of the α,β-Unsaturated Schiff Base. The kinetic results for the formation of **4** show that the rate of formation is almost entirely dependent on a second-order term ($k^{AB}[RNH_2][RNH_3^+]$), with small first-order terms in free amine ($k^B[RNH_2]$) and protonated amine ($k^A[RNH_3^+]$). A mechanism consistent with these results is shown in Scheme II.

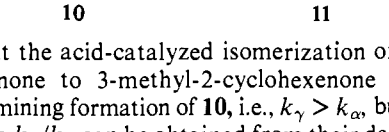
Scheme II



The three-term rate law is explicable by assuming a fast prior equilibrium between **1** and **8**, followed by deprotonation of **8** by OH^- (k^B), H_2O (k^A), or TFEA (k_{AB}). Slow formation of **8** followed by rapid isomerization to **4** is ruled out by the primary hydrogen isotope effect observed in D_2O for k^{AB} ($k_H^{AB}/k_D^{AB} = 6.30 \pm 0.28$). However, the fact that a primary isotope effect was observed at all when starting with **1** in D_2O reveals that exchange in the α position took place through formation of the dienamine **8**.[33] The partitioning of the dienamine between protonation in the α position (k_α) and protonation at the γ carbon (k_γ) was calculated to be slightly in favor of formation of **8**, i.e., $k_\gamma/k_\alpha = 0.73 \pm 0.02$. This ratio was independent of both amine concentration and pH.

In terms of Scheme II, $k^{AB} = K_1k_2[k_\gamma/(k_\gamma + k_\alpha)]$, where K_1 is the equilibrium constant for formation of the β,γ-unsaturated iminium ion ($K_1[RNH_3^+] = [\mathbf{8}]/[\mathbf{1}]$). The origin of the small solvent isotope effect on k^{AB} (1.22 ± 0.06) probably reflects the effect of D_2O) on the prior equilibrium of **1** and **8**, since deuteration of the amine (RND_2 and RND_3^+) should have a negligible effect on both k_2 and the partitioning ratio of the dienamine.[35] A small solvent isotope effect on K_1 is consistent with the effect on the equilibrium constant for ketimine formation from propylamine and diacetone alcohol ($K^{H_2O}/K^{D_2O} = 1.34 \pm 0.13$).[36]

The partitioning ratio for protonation of the dienamine **9** ($k_\gamma/k_\alpha = 0.73$) may be compared to the same ratio for the analogous dienol **10** and enol ether **11**. Noyce and Evett[2] have



10 **11**

shown that the acid-catalyzed isomerization of 3-methyl-3-cyclohexenone to 3-methyl-2-cyclohexenone proceeds via rate-determining formation of **10**, i.e., $k_\gamma > k_\alpha$, but no estimate of the ratio k_γ/k_α can be obtained from their data. Similarly, the enol ether **11** has been also found to protonate preferentially at the γ carbon ($k_\gamma/k_\alpha = 9$).[37]

As would be predicted according to this mechanism, the formation of **4** was found to be efficiently catalyzed by the addition of external bases due to a term in the rate expression involving $k^{AB}[RNH_3^+][B]$. The k^{AB} terms for different bases are summarized in Table IV where the value for H_2O was calculated by dividing k^A by 55 M, on the assumption that the k^A term arises from water acting as a base in the conversion of **8** to **9**. Analogously, the k^{AB} term for hydroxide is obtained by assuming the k^B term comes from abstraction of a proton from **8** by hydroxide ion, and using the identity $k^B = k^{AB}K_w/K_a$. A Bronsted plot of log k^{AB} vs. pK_a (Figure 3) reveals a reasonable correlation with a slope of $\beta = 0.55$. This value is consistent with the β of 0.4 obtained by Bender and Williams[26] for the deprotonation of the iminium ion from glycine and

Table IV. Third-Order Rate Constants for Various Bases in the Formation of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene) ethylammonium Ion (**4**) from 3-Methyl-3-cyclohexenone (**1**) and Trifluoroethylamine at 25.0° (μ = 1.0)

Base	pK_a	k^{AB}, M^{-2} s^{-1} [a]
H_2O	−1.74	$(1.44 \pm 0.10) \times 10^{-5}$ [b]
Acetate	4.50[c]	0.103 ± 0.003
TFEA	5.77[c]	0.225 ± 0.014
Imidazole	7.10[c]	0.81 ± 0.05
OH^-	15.7	$(3.3 \pm 0.3) \times 10^4$ [b]

[a] Errors are standard deviations. [b] Calculated as described in the text. [c] pH of a 1:1 buffer solution at μ = 1.0.

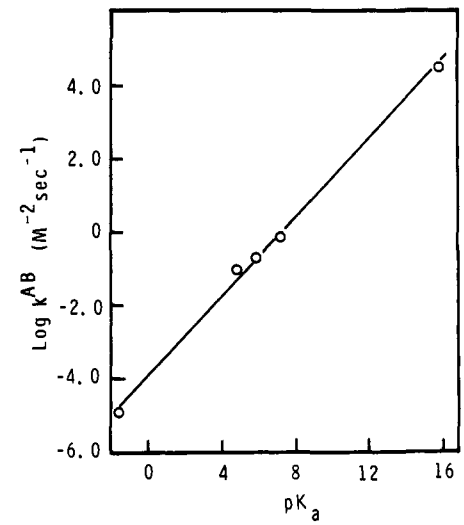
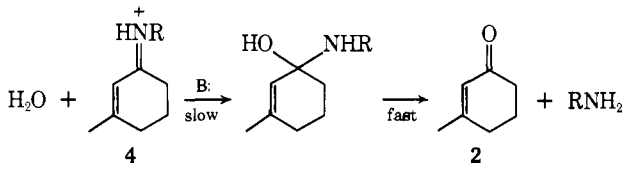


Figure 3. Bronsted plot of log k^{AB} vs. pK_a for different bases in the formation of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium ion (**4**) from 3-methyl-3-cyclohexenone (**1**) and trifluoroethylamine at 25.0° (μ = 1.0).

acetone, and is similar to the value of 0.5 found by Spencer for the α-proton abstraction from iminium ions of decalones and primary amines.[38]

Hydrolysis of the α,β-Unsaturated Schiff Base. We have previously reported on the kinetics and mechanism of the hydrolysis of **3** in some detail.[23] Briefly, we found that in the pH region of the current investigation hydrolysis occurs by rate-determining attack of water or hydroxide ion on the protonated Schiff base, with attack of water subject to general base catalysis. The initially formed carbinolamine then rapidly decomposes to ketone (Scheme III). In the range of TFEA con-

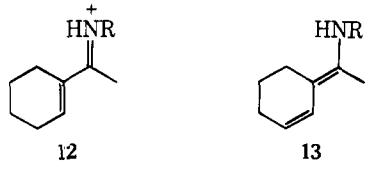
Scheme III



4 2

centrations used ($\leq$0.3 M), the reverse reaction is negligible and can be ignored, so that the measured pseudo-first-order rate constants refer simply to the rate of formation of **2.** At high concentrations of amine, however, the observed kinetics start to deviate appreciably from first-order behavior, possibly due to attack of amine on the double bond of **4.** Consequently, the kinetics were only analyzed at $[TFEA]_t \leq 0.3$ M. Since the rate constant for general base catalysis of the hydrolysis reaction by TFEA does not deviate from the Bronsted plot for other bases, there is reason to believe that the mechanism of hydrolysis in the presence of TFEA is identical with that previously described.[23]

Isomerization of 1-Acetyl-2-cyclohexene (5). Although the isomerization of **5** to its conjugated isomer (**6**) is catalyzed by TFEA, no intermediate protonated α,β-unsaturated Schiff base (**12**) could be detected. Furthermore, the overall reaction is substantially slower than the analogous isomerization of **1.**



12 13

The lack of buildup of an unsaturated Schiff base, coupled with the similarity in the observed kinetics for the isomerization of **5** to **6** and the formation of **4** from **1**, suggests that the same mechanism is operating, except that the hydrolysis of the intermediate protonated α,β-unsaturated Schiff base (**12**) is much faster than its formation.

The slow formation of **12** relative to the corresponding formation of **4** (ca. 760-fold) is probably due to a change in the partitioning ratio of dienamine **13** relative to **9.** If the partitioning of the intermediate dienamine (**13**) favors formation of the β,γ-unsaturated Schiff base at the expense of the α,β-unsaturated species (i.e., $k_\gamma \ll k_\alpha$), then the rate-determining step will be protonation of the dienamine (k_γ) and the observed rate of formation of **12** would be expected to be relatively slow. A parallel to this situation may be found in the work of Noyce and Evett.[2] They observed that the dienol from **5** protonates preferentially in the α position in contrast to the dienol from **1,** which protonates primarily in the γ position. The reasons for this difference are discussed in their reports[2] and an analogous explanation probably exists for the dienamines.

General Comments. Nucleophilic catalysis by primary amines of reactions of aldehydes and ketones is a well known process, including such reactions as enolization,[25,26,34] β-ketol dehydration,[38] elimination from β-acetoxy ketones,[39] retroaldol condensations,[36,40-42] and the decarboxylation of β-keto acids.[43,44] In addition, another case of primary amine-catalyzed isomerization of β,γ-unsaturated ketones has recently been reported.[13] In all of these cases the formation of a protonated Schiff base gives the molecule an electron sink into which an electron pair may be put during a cleavage reaction.

An estimate for the catalytic ability of trifluoroethylamine relative to hydronium ion for 3-methyl-3-cyclohexene (**1**) and 1-acetyl-2-cyclohexene (**5**) may be obtained from the published[2] rates of the acid-catalyzed isomerization of these compounds. For **1,** the overall catalytic efficiency is limited by the rate of hydrolysis of the protonated Schiff base (**4**) to the α,β-unsaturated ketone (**2**). At 1 M amine (pH 6) the rate constant for hydrolysis of **4** is 1.12×10^{-3} s^{-1}. A comparison of this rate constant with the rate constants for the corresponding acid-catalyzed reaction[2] and spontaneous isomerization[45] at this pH shows a rate-enhancement of $>10^6$-fold and 10^4-fold, respectively. Since the actual rate of bond migration (formation of **4**) under these conditions is about 100 times greater than imine hydrolysis, it is apparent that trifluoroethylamine is a superb catalyst for this isomerization. An analogous comparison of the rate of isomerization of **5** at 1 M TFEA (pH 6) with the corresponding acid-catalyzed reaction[2] shows a rate enhancement of ca. 10^6-fold.

Since enzymatic catalysis of various other carbonyl reactions is known to proceed via the formation of an intermediate Schiff base,[46] it is of interest to speculate on the possibility of enzymatic catalysis of double bond migration via this mechanism. The only enzyme of which we are aware which is thought to catalyze this reaction via Schiff base formation is 2-keto-3-deoxy-L-arabonate dehydratase. One of the steps in the proposed mechanism[11] involves the migration of a double bond α,β to a Schiff base to the β,γ position, with the Schiff base derived from an enzymatic amine residue. Several other enzymes are known which catalyze double bond migrations in ketones, among them the Δ^5-3-keto steroid isomerases[9] and prostaglandin A isomerase;[51] however only the Δ^5-3-keto steroid isomerase from *Pseudomonas testosteroni* has been investigated in detail. The function of amine residues in this enzyme has been investigated by Benisek and Jacobson,[13] who found that, although modification of the amine groups of this isomerase by either sodium trinitrobenzene sulfonate or maleic anhydride produces an inactive enzyme, modification of the amino groups by methyl acetimidate has no effect on the enzymatic activity. They concluded that imine intermediates are not involved in the enzyme mechanism. The corresponding mammalian enzymes, however, as well as prostaglandin A isomerase, may act via Schiff base formation. To our knowledge, no work has been done to date on the question of whether amine groups on these enzymes are necessary for catalytic activity.

Experimental Section

Materials. 3-Methyl-3-cyclohexenone (1) and **1-acetyl-2-cyclohexene (5)** were prepared by the procedures of Noyce and Evett.[2] Kinetic samples of both compounds were collected by preparative gas chromatography (Carbowax 20M on Chromopak 60/80). Spectral data were consistent with published results.[2]

2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (3) was prepared by mixing 0.5 g of 3-methyl-3-cyclohexenone and 0.6 g of 2,2,2-trifluoroethylamine in 5 ml of carbon tetrachloride over molecular sieves. The flask was tightly stoppered to prevent escape of the volatile amine. After 1 h at room temperature, analysis by NMR revealed that no starting material remained. The solution was decanted, the sieves washed with carbon tetrachloride, and the solvent removed under vacuum to yield a yellow oil. Analytic and kinetic samples were obtained by preparative gas chromatography (Carbowax 20M on Chromopak 60/80): ir (CCl_4) 1640 cm^{-1} (C=N), 1615 (C=C); NMR (CCl_4) δ 5.75 (s, 1), 3.58 (q, J = 10 Hz, 2), 1.6-2.4

(m, 6), 1.80 (s, 3); NMR (D_2O-DCl)[52] δ 6.50 and 6.25 (s, 1), 4.39 (q, 2), 1.7–2.9 (m, 6), 2.10 and 2.16 (s, 3); $\lambda_{max}^{cyclohexane}$ 228 nm (ϵ 22 000), $\lambda_{max}^{H_2O}$ (pH 12) 238 nm (ϵ 20 000), $\lambda_{max}^{H_2O}$ (pH 2) 268 nm (ϵ 18 500). Anal. Calcd for $C_9H_{12}NF_3$: C, 56.54; H, 6.28; N, 7.33. Found: C, 56.43; H, 6.10; N, 7.11.

Other Materials. 2,2,2-Trifluoroethylamine hydrochloride was a commercial product (Aldrich) and was purified by recrystallization from absolute ethanol before use. Free trifluoroethylamine was prepared by neutralizing a sample of the hydrochloride salt with aqueous saturated sodium bicarbonate and distilling the volatile amine (bp 36–38 °C). Imidazole was purified by recrystallization from chloroform. Acetate buffers were prepared from reagent grade sodium acetate and standardized hydrochloric acid. Distilled water was used for all kinetic runs. D_2O solutions were made up using 99.8% D_2O, along with NaOD in D_2O (99% D) and trifluoroethylamine hydrochloride. At the concentrations of TFEA in D_2O which were used ($\leq$0.3 M), the exchangeable hydrogens of the TFEA made only a minor contribution to the total deuterium content of the water (<2%).

Kinetic and Equilibrium Measurements. All kinetic measurements were carried out at 25.0 ± 0.2° with an ionic strength of 1.0 maintained with either NaCl or KCl. Spectra were obtained on a Cary 16K spectrophotometer and rates were followed on either a Gilford 2000 or 2400 spectrophotometer. All first-order rate constants were calculated by a nonlinear least-squares regression analysis. Buffer plots were analyzed by a weighted least-squares analysis which assumes a constant percent error in each rate constant. pH values were measured on a Radiometer Model 26 pH meter. pH values for each series of buffer runs were constant to ±0.02 pH units. pD values were obtained by adding 0.4 to the pH meter reading.[53]

Calculation of K_a of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium Ion (4). A constant volume of a stock solution of the free α,β-unsaturated Schiff base (**3**) in acetonitrile was added to 3.00 ml of phosphate buffer solutions of varying pH at ionic strength 1.0. The absorbances at 268 nm, extrapolated to the time of mixing to correct for hydrolysis, were used to calculate K_a from the equation

$$[H^+] = K_a\,[(A - A_3)/(A_4 - A)] \tag{5}$$

where A is the measured absorbance, A_3 is the absorbance of the free ketimine (**3**), A_4 is the absorbance of the protonated ketimine (**4**). A least-squares plot of $[H^+]$ vs. $(A - A_3)/(A_4 - A)$ was forced through an intercept of zero to give a value of $K_a = (1.73 \pm 0.15) \times 10^{-7}$ ($pK_a = 6.76 \pm 0.04$).

Rate of Ketimine Formation. The reaction was initiated by adding 10 μl of a stock solution of the ketone (**1**) in acetonitrile ($\sim 10^{-2}$ M) to 3 ml of the buffer solution in the spectrophotometer. The formation of ketimine was followed in one of two ways. At 268 nm (λ_{max} of **4**), the absorbance showed a rapid increase followed by a relatively slow decrease. The data were treated by the equation

$$A = \frac{\epsilon C_O k_i}{k_i - k_h}(e^{-k_h t} - e^{-k_i t}) \tag{6}$$

where A is the measured absorbance at 268 nm, C_O is the initial concentration of **1**, and k_i and k_h are the first-order rate constants for formation and hydrolysis of the ketimine. Both the β,γ-unsaturated ketone (**1**) and the α,β-unsaturated ketone (**2**) have negligible absorbances at 268 nm. Under the conditions used, the decay of **4** was at least 5–10 times slower than its formation so that the decay at 268 nm could be analyzed as a simple exponential function by waiting until after 8–10 half-lives for the formation reaction. The value of k_h determined from a nonlinear least-squares analysis, along with the preexponential term calculated from extrapolation to the time of mixing, were then used to determine k_i from a semilogarithmic plot using eq 7, a rearranged form of eq 6.

$$-k_i t = \ln\left(e^{-k_h t} - \frac{A(k_i - k_h)}{\epsilon C_O k_i}\right) \tag{7}$$

An alternate method of calculating k_i was to follow the reaction at the isosbestic point for the hydrolysis of **4**. This procedure gave good first-order kinetics for 6–8 half-lives in most cases and yielded stable infinity points. Because agreement between k_i values determined by both methods was good (within 10%), the simpler procedure of monitoring the reaction at the isosbestic point was generally used.

Rate constants for formation of **4** were also determined in TFEA solutions containing an additional general base. Buffer solutions were used which contained a constant total concentration of TFEA (0.10 M) and varying amounts of the other buffer component at constant pH and ionic strength (1.0). Values for k_i were determined by monitoring the reaction at the isosbestic point as described above. Catalysis of the overall isomerization reaction (**1** → **2**) by the general bases used (acetate and imidazole) was negligible in the absence of TFEA.

Ketimine Hydrolysis. The rate constant for the hydrolysis of the Schiff base (**3**) was obtained by direct measurement of the absorbance at 268 nm due to the protonated Schiff base (**4**); 10–20 μl of a stock solution of **3** in acetonitrile was added to the cuvette to initiate the reaction. The decay was first order and yielded k_h directly. The rate constants determined in this way were in agreement with those obtained from the integrated rate expression for the overall reaction.

Isomerization of 1-Acetyl-2-cyclohexene (5). The rate of this reaction was determined by monitoring the reaction at 240 nm. After a short induction period (5–10% reaction), the absorbance curves were analyzed by nonlinear least-squares regression to give the observed rate constants.

Solvent Isotope Effects. Rate constants for the formation of **4** were calculated from absorbance data in TFEA buffers in D_2O at the isosbestic point for hydrolysis of **4**. Although the absorbance increase was monotonic, the curves could not be fit by a simple first-order expression. The curves could, however, be analyzed in terms of eq 3. This equation is derived in detail in the Appendix. On the assumption that the slowest process is the reaction of the dideuterated material (**1**-d_2), the last 15–20% of the absorbance curve was treated as first order, giving values for k^DR and, by extrapolation to $t = 0$, a_1. Waiting until later times did not significantly alter the parameters obtained. From the a_1 term the other two preexponential terms could be calculated using the relationships below.

$$a_2 = (1 - \sqrt{a_1})^2 \tag{8}$$

$$a_3 = 2(\sqrt{a_1} - a_1) \tag{9}$$

A value for k_H was then estimated and varied until a good fit was obtained with the experimental curve. To judge goodness of fit, eq 3 was arranged to give eq 10.

$$\left[\frac{(A_0 - P)}{A_0} - a_1 e^{-k^D R t} - a_2 e^{-k^H t}\right] = a_3 e^{-1/2(k^H + k^D R)t} \tag{10}$$

A nonlinear least-squares analysis of this expression gave values for the exponential term ($\frac{1}{2}(k^H + k^DR)$) and the preexponential term (a_3). k^H was then calculated using the value for k^DR. When the calculated value of k^H agreed with the estimated k^H *and* when the a_3 obtained agreed with the previously calculated a_3, the curve was judged to be fit. In most cases the standard deviations of k^H and k^DR were less than 1%. Values for R could then be calculated from the preexponential terms. Agreement of the calculated curves with the experimental points was excellent. This procedure was followed for several runs at various amine concentrations and two different buffer ratios. Values for k^HR were also determined from initial rates at the isosbestic point in some cases and agreement with the values determined from the complete reaction was excellent.

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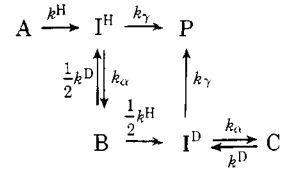
Appendix

In a rigorous analysis of the formation of ketimine in D_2O one must consider the scheme shown in eq 11; in this scheme



(11)

A is **1**, B is **1**-d_1, and C is **1**-d_2. All forms of the unconjugated ketone are assumed to proceed to the ketimine, P, by way of dienamine I^H, which is not deuterated, or I^D, which is the dienamine $-d_1$. All secondary isotope effects are assumed to be negligible and, thus, the rate of proton abstraction from B

is assumed to be $\frac{1}{2}k^H$ and the rate for deuterium abstraction from B is given by $\frac{1}{2}k^D$. Therefore, the rate of ketimine formation is

$$\frac{d[P]}{dt} = k_\gamma([I^H] + [I^D])$$

and, assuming a steady state for both I^H and I^D, this becomes

$$\frac{d[P]}{dt} = \frac{k_\gamma}{k_\alpha + k_\gamma}(k^H[A] + k^D[C] + \frac{1}{2}(k^D + k^H)[B])$$

In the absence of appreciable H_2O, the disappearance of A is strictly first order; thus $A = A_0e^{-k^Ht}$. Also, using the identity $[C] = A_0 - [P] - [A] - [B]$, the formation of P becomes

$$\frac{d[P]}{dt} = \frac{k_\gamma}{k_\alpha + k_\gamma}((k^H - k^D)A_0e^{-k^Ht} + k^DA_0 - k^D[P] + \frac{1}{2}(k^H - k^D)[B])$$

In a similar fashion, the rate of formation of B is given by

$$\frac{d[B]}{dt} + [B]\left[\frac{1}{2}(k^H + k^D) - \frac{1}{2}\left(\frac{k_\alpha k^D}{k_\gamma + k_\alpha}\right)\right] = \frac{k_\alpha k^H}{k_\gamma + k_\alpha}(A_0e^{-k^Ht})$$

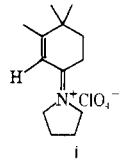
Integrating, the following expression is obtained for B

$$[B] = A_0\left[\frac{2(1 - R)k^H}{k_DR - k_H}\right][e^{-k^Ht} - e^{-(1/2)(k^H + k^DR)}]$$

where $R = k_\gamma/(k_\alpha + k_\gamma)$. Substitution of the integrated expression for B into the rate equation for P followed by a similar integration yields eq 3 of the main text.

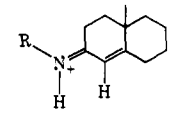
References and Notes

(1) S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965).
(2) (a) D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 394 (1972); (b) *ibid.*, **37**, 397 (1972).
(3) J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **47**, 4459 (1969).
(4) F. S. Kawakara, S-F. Wang, and P. Talalay, *J. Biol. Chem.*, **237**, 1500 (1962).
(5) W. R. Nes, E. Loesser, R. Kirdant, and J. Marsh, *Tetrahedron Lett.*, 299 (1963).
(6) H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 699 (1962).
(7) S. K. Malhotra and H. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).
(8) G. Subrahmanyam, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **88**, 1332 (1966).
(9) P. Talalay and A. M. Benson, *Enzymes, 3rd Ed.*, **6**, 591 (1972).
(10) R. L. Jones, *Biochem. J.*, **139**, 381 (1974).
(11) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, **242**, 2751 (1967).
(12) R. H. Kayser and R. M. Pollack, *J. Am. Chem. Soc.*, **97**, 952 (1975).
(13) W. F. Benisek and A. Jacobson, *Biorg. Chem.*, **4**, 41 (1975).
(14) R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds", 2nd ed, Wiley, New York, N.Y., 1967, p 162.
(15) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. B. Stafford, and F. W. Heyl, *J. Am. Chem. Soc.*, **78**, 430 (1956).
(16) E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, **28**, 692 (1963).
(17) N. F. Firrell and P. W. Hickmott, *J. Chem. Soc. B*, 293 (1969). These authors report that the olefinic hydrogen in the iminium salt derived from isophorone and pyrrolidine (i) gives one signal at δ 6.49. This is consistent with the δ



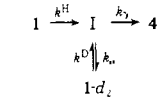
i

values found for the vinyl hydrogen in **4**. Of course, unlike **4**, there is only one geometrical isomer of i; therefore only one olefinic signal is observed.
(18) For a review of syn–anti isomerizations of Schiff bases, see C. G. McCarty in "The Chemistry of the Carbon–Nitrogen Double Bond", S. Patai, Ed., Wiley, New York, N.Y., 1970, p 363.
(19) (a) The barrier to inversion for iminium ions is predicted to exceed that for the parent imine on the basis of theoretical calculations: P. A. Kollman, W. F. Trager, S. Rothenberg, and J. E. Williams, *J. Am. Chem. Soc.*, **95**, 458 (1973). (b) H. E. Ferran, Jr., D. A. Drake, and T. A. Spencer, *J. Org. Chem.*, **40**, 2017 (1975), have reported what appears to be syn and anti isomers of an eniminium ion (EH^+) formed as an intermediate in the



EH^+

amine-catalyzed dehydration of the parent β-ketol. The eniminium ion derived from ethoxyethylamine (R = $CH_2CH_2OCH_2CH_3$) was synthesized and showed two peaks in the NMR spectrum (δ 6.30 and 6.55) due to the vinyl hydrogen. Interestingly, the corresponding neutral enimine (E) also appears to exist in syn and anti forms (vinyl protons at δ 5.85 and 6.18). Therefore, the appearance of only one vinyl signal in the NMR spectrum of **3** may be due to a preponderance of only one isomer rather than to a fast interconversion.
(20) A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432 (1970).
(21) The k_A and k_B terms were not detected in our initial investigation.[12]
(22) Interestingly, an alternate analysis of the rates in D_2O based on a simpler scheme with only one intermediate (see below) gives values of k^HR and



k^DR indistinguishable from those obtained by using the complete scheme (Scheme I), although k^H, R, and k^D differ. The value of R based on the scheme below is 0.67, whereas R = 0.42 for Scheme I. Remarkably, the fit of the integrated rate expression for the scheme below to the observed experimental points is almost identical with the fit of eq 3. Our choice of the more complex scheme was based on mechanistic considerations.
(23) M. Brault and R. M. Pollack, *J. Org. Chem.*, **41**, 346 (1976).
(24) Our preliminary communication[12] reported values for $k_h^{H_2O} = 3.41 \times 10^{-3}$ s^{-1} and $k_h^{OH^-} = 4.08 - 10^3$ M^{-1} s^{-1}. Further studies over a much wider pH range[23] have shown $k_h^{H_2O} = 3.55 \times 10^{-3}$ s^{-1} and $k_h^{OH^-} = 1.9 \times 10^3$ M^{-1} s^{-1}.
(25) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).
(26) M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966).
(27) J. Hine, J. C. Craig, Jr., J. G. Underwood II, and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970).
(28) (a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962); (b) *ibid.*, **85**, 2843 (1963).
(29) R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **47**, 2263 (1969), report a pK of -2.83 ± 0.03 using the H_A scale. The authors also found that pK values determined using H_A can be related to the H_0 function as follows: $pK^{H_A} + 0.68 = pK^{H_0}$. Thus the value of -3.5 for **2**.
(30) E. M. Arnett, *Prog. Phys, Org. Chem.*, **1**, 223 (1963). All pK values used in this discussion were corrected to the H_0 scale as recently evaluated.[31]
(31) M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).
(32) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7045 (1974).
(33) Primary amines have been shown to catalyze exchange of protons α to carbonyl groups through the intermediate formation of enamines.[25,26,34]
(34) J. Hine, M. S. Cholod, and R. A. King, *J. Am. Chem. Soc.*, **96**, 835 (1974), and earlier papers in this series.
(35) R. L. Schowen, *Prog. Phys. Org. Chem.*, **9**, 275 (1972).
(36) R. M. Pollack and S. Ritterstein, *J. Am. Chem. Soc.*, **94**, 5064 (1972).
(37) N. A. J. Roger and A. Sattar, *Tetrahedron Lett.*, 1471 (1965).
(38) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Am. Chem. Soc.*, **95**, 2271 (1973).
(39) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Am. Chem. Soc.*, **94**, 1254 (1972).
(40) F. H. Westheimer and H. Cohen, *J. Am. Chem. Soc.*, **60**, 90 (1938).
(41) R. W. Tay and K. R. Tate, *Aust. J. Chem.*, **19**, 1651 (1966).
(42) R. M. Pollack and J. D. Cooper, *J. Org. Chem.*, **38**, 2689 (1973).
(43) J. P. Guthrie and F. H. Westheimer, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **26**, 562 (1967).
(44) K. J. Pedersen, *Acta Chem. Scand.*, **8**, 710 (1954).
(45) R. M. Pollack and D. L. Whalen, unpublished results.
(46) Examples include D-amino acid oxidase,[47] aldolase,[48] acetoacetate decarboxylase,[49] and dehydroquinase.[50]
(47) L. Hellerman and D. S. Coffey, *J. Biol. Chem.*, **242**, 582 (1967).
(48) D. E. Morse and B. L. Horecker, *Adv. Enzymol. Relat. Subj. Biochem.*, **9**, 520 (1966).
(49) S. Warren, B. Zerner, and F. H. Westheimer, *Biochemistry*, **5**, 817 (1966).
(50) J. R. Butler, W. L. Alworth, and M. H. Nugent, *J. Am. Chem. Soc.*, **96**, 1617 (1974).
(51) R. L. Jones, *Biochem. J.*, **139**, 381 (1974).
(52) The NMR spectrum of 4 was recorded immediately upon addition of **3** (0.15 M) to 0.2 N DCl in D_2O. Formation of **2** did not complicate the initial spectrum due to the relatively slow hydrolysis of 4 ($t_{1/2} > 20$ min) under these conditions.
(53) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).