Kinetics and Mechanism of the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine— an α,β-Unsaturated Schiff Base

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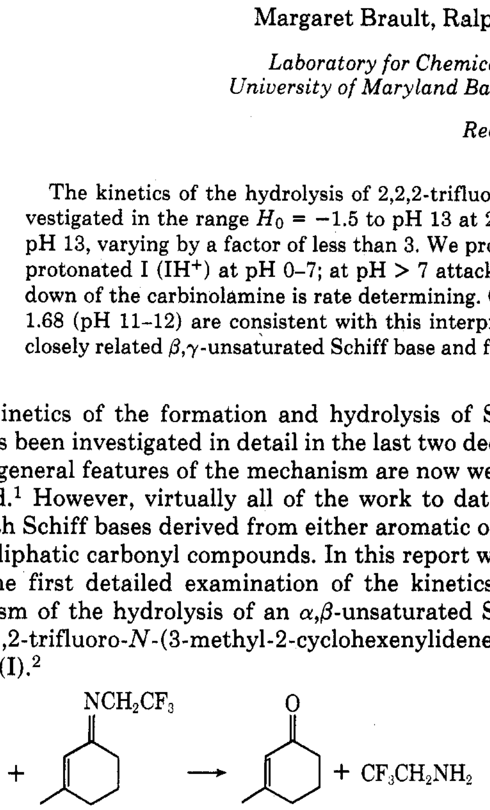
The kinetics of the hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I) has been investigated in the range $H_0 = -1.5$ to pH 13 at 25°. The reaction rate is almost independent of pH from pH 0 to pH 13, varying by a factor of less than 3. We propose a mechanism involving rate-determining attack of water on protonated I (IH^+) at pH 0–7; at pH > 7 attack of hydroxide ion on IH^+ is the slow step; and at $H_0 < 0$ breakdown of the carbinolamine is rate determining. Observed solvent isotope effects (k_{H_2O}/k_{D_2O}) of 2.44 (pH ~2) and 1.68 (pH 11–12) are consistent with this interpretation. Rates of hydrolysis for I are compared with those for a closely related β,γ-unsaturated Schiff base and found to be at least 300-fold slower at pH values near neutrality.

The kinetics of the formation and hydrolysis of Schiff bases has been investigated in detail in the last two decades and the general features of the mechanism are now well established.[1] However, virtually all of the work to date has dealt with Schiff bases derived from either aromatic or saturated aliphatic carbonyl compounds. In this report we describe the first detailed examination of the kinetics and mechanism of the hydrolysis of an α,β-unsaturated Schiff base, 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I).[2]



(1)

I II

The mechanism of the hydrolysis of Schiff bases of α,β-unsaturated carbonyl compounds is of particular interest since α,β-unsaturated Schiff bases derived from enzymatic amine residues have been suggested to be involved in the mechanism of several enzymes, among them dehydroquinase,[4] 5-keto-4-deoxy-D-glucarate dehydratase,[5] and, possibly, maleylacetoacetate isomerase[6] and other isomerases.[7] In addition, compounds of this type are involved in the visual process[8] and perhaps in the NAD-mediated biological reduction of Δ^4-3-keto steroids.[9] Amine catalysis of elimination from β-acetoxy ketones,[10] β-ketol dehydration,[11] and isomerization of β,γ-unsaturated ketones[7,12] have also been shown to proceed through α,β-unsaturated imines.

Results

The hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I) was studied from $H_0 = -1.59$ to pH 13.17 at 25.0° ($\mu = 1.0$). In the pH range 3.3–10.6, acetate, phosphate, or carbonate buffers were used to control the pH as appropriate; outside this range, NaOH, HCl, H_2SO_4, or $HClO_4$ were employed. At pH ≤8 the kinetics were monitored by observing the decrease in absorbance with time at 268 nm due to the loss of the protonated Schiff base; at pH >8 the change in absorbance was followed at 237 nm. Most reactions exhibited good pseudo-first-order kinetic behavior through at least 90% reaction.

The only *substantial* deviations from strict pseudo-first-order behavior occurred in HCl solutions in the pH range 0–3. It appeared that two exponential functions with similar time constants were needed to accurately describe the observed decay. Analysis of several runs using the observed infinity points showed initial rates about 10–20% higher than obtained by the best first-order fit to the entire curve. Conversely, analysis of only the last 30% reaction gave rate constants 10–15% lower than those calculated using all the experimental points. A possible explanation for this behavior is the existence of syn and anti forms of the protonated Schiff base (IH^+) which may hydrolyze at slightly different rates. We have previously shown[7] that the interconversion of these isomers is slow on the NMR time scale and it may also be nonnegligible under the conditions for hydrolysis. A similar explanation has been advanced to account for biphasic kinetics in the hydrolysis of *N*-methylacetimidates.[13] Since we were unable to separate the two decay processes, we used the computer calculated rate constants for the entire reaction (standard deviations less than 2% in all cases).

The product was identified on the basis of the ultraviolet spectra. Uv spectra of several reaction mixtures taken after completion of the reaction showed a peak at 240 nm. An authentic sample of 3-methyl-2-cyclohexenone showed an absorbance maximum at 241 nm (ϵ 1.4 × 10^4). Routine checks of the infinity absorbance at 240 nm at various pH values indicated 85–95% conversion of I to II. The other 5–15% of material may be present as 3-hydroxy-3-methylcyclohexanone since α,β-unsaturated imines are known to be able to add water across the double bond.[11]

The rate of hydrolysis of I varies very little with pH throughout the entire range (Figure 1). The slight downward trend at about pH 6, however, suggests that the protonated Schiff base (IH^+) is the reactive species (pK_a of $IH^+ = 6.76$).[14] The independence of rate on pH above pH 8 could then be accounted for by reaction of hydroxide ion with protonated Schiff base. In the pH range 1 to 13, the observed pseudo-first-order rate constants were analyzed in terms of eq 2, where K_a is the acid dissociation constant

$$k^{\text{obsd}} = k^{H_2O} + k^{OH^-}[OH^-] + k^B[B]\left(\frac{[H^+]}{[H^+] + K_a}\right) \tag{2}$$

of protonated I and k^{H_2O}, k^{OH^-}, and k^B are rate constants for the reaction of IH^+ with water, hydroxide ion, and a general base, respectively. The previously measured value of 1.66×10^{-7} *M* was used for K_a. Both acetate and phosphate buffers strongly catalyze the reaction in their base forms but not as acids; carbonate buffers showed marginal catalytic ability. Analysis of the observed rate constants was performed in the usual manner by plotting $k^{\text{corr}} = k^{\text{obsd}}/[[H^+]/([H^+] + K_a)]$ vs. $[B]_{\text{total}}$ at constant pH. Intercepts of these plots gave the rate constant in the absence of buffer (k_0). Plots of k_0 vs. $[OH^-]$ gave $k^{OH^-} = 1.93 \pm 0.27 \times$

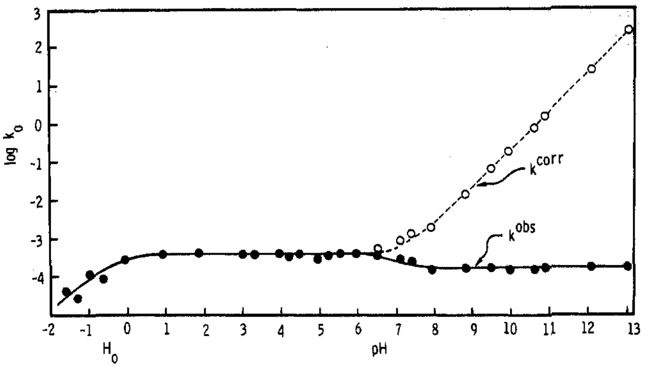


Figure 1. pH–rate profile for the hydrolysis of 2,2,2-trifluoro-N-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0° in the absence of buffers. The actual observed rate constant is given by k^{obsd} and the observed rate constant corrected for the ionization of substrate (see text) is designated by k^{corr}. Below pH 6, k^{corr} and k^{obsd} are identical.

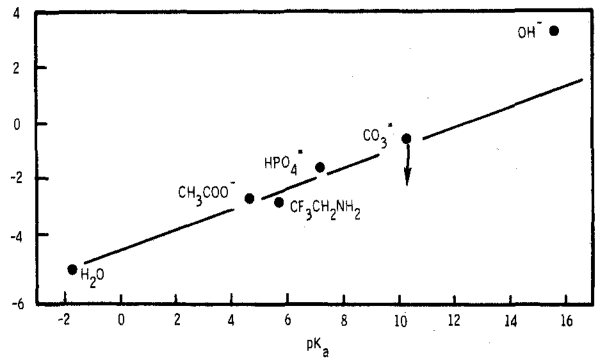


Figure 2. Bronsted plot of the catalytic constants for general-base-catalyzed attack of water on 2,2,2-trifluoro-N-(3-methyl-2-cyclohexenylidene)ethylammonium ion at 25.0°. The point for carbonate represents an upper limit.

$10^3\ M^{-1}$ sec^{-1} and $k^{\mathrm{H_2O}} = 3.55 \pm 0.42 \times 10^{-4}$ sec^{-1}. Values of k^{B} were obtained by plotting the slopes of the buffer plots vs. $[\mathrm{B}]/([\mathrm{B}] + [\mathrm{BH^+}])$. Calculated values of these parameters are given in Table I. A Bronsted plot generated from these catalytic constants gives a reasonably good straight line with $\beta = 0.4$, although the point for hydroxide ion deviates from the line by about 3 log units (Figure 2).

A plot of the corrected rate constants (k^{corr}) at zero buffer concentration is shown in Figure 1. Between pH 1 and 6, k^{corr} is independent of pH. At pH values greater than 6, the rate constant begins to increase with increasing pH, whereas at pH (H_0) < 0, k^{corr} falls off with increasing acid concentration in both sulfuric and perchloric acid solutions. These results suggest a change in mechanism at ca. pH 6 and a change in rate-determining step at ca. pH 0.

In addition to the kinetic measurements in water, rate constants were determined in deuterim oxide solutions of DCl, NaOD, and acetate buffers. The results for the unbuffered solutions are presented in Table II. In both acidic and basic solutions the rate constant is larger in water than in D_2O by a factor of about 2. The measured value of $k_{\mathrm{D_2O}}{}^{\mathrm{B}}$ for the acetate-catalyzed hydrolysis is $1.00 \pm 0.12 \times 10^{-3}$ M^{-1} sec^{-1}, giving an isotope effect for this process of $k_{\mathrm{H_2O}}{}^{\mathrm{B}}/k_{\mathrm{D_2O}}{}^{\mathrm{B}} = 2.2 \pm 0.4$.

Table I
Catalytic Constants of Various Bases for the Hydrolysis of 2,2,2-Trifluoro-N-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0° (μ = 1.0)

Base	pK_a	k^{B}, M^{-1} sec^{-1} [a]
H_2O	−1.7	$6.40 \pm 0.75 \times 10^{-6}$ [b]
$CH_3CO_2^-$	4.7	$2.15 \pm 0.35 \times 10^{-3}$
$CF_3CH_2NH_2$	5.7	$1.40 \pm 0.23 \times 10^{-3}$ [c]
HPO_4^{-2}	7.2	$2.88 \pm 0.38 \times 10^{-2}$
CO_3^{-2}	10.3	$8.0 \pm 5.0 \times 10^{-2}$ [d]
OH^-	15.7	$1.93 \pm 0.27 \times 10^{3}$

[a] Rate constant for general-base-catalyzed attack of water on IH^+. No corrections for statistical factors are included; errors are standard deviations. [b] $k^{\mathrm{H_2O}}$ divided by 55.5 M. [c] Reference 7. [d] Upper limit.

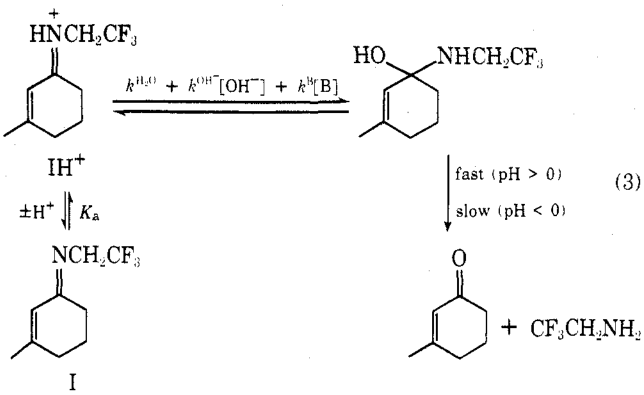
Table II
Solvent Isotope Effects on the Hydrolysis of 2,2,2-Trifluoro-N-(3-methyl-2-cyclohexenylidene)ethylamine

Solution	k^{obsd}, sec^{-1}	$k_{\mathrm{H_2O}}{}^{\mathrm{obsd}}/k_{\mathrm{D_2O}}{}^{\mathrm{obsd}}$
$HCl-H_2O$ [a]	$3.52 \pm 0.06 \times 10^{-4}$	2.44
$DCl-D_2O$ [b]	$1.44 \pm 0.03 \times 10^{-4}$	
$NaOH-H_2O$ [c]	$1.09 \pm 0.03 \times 10^{-4}$	1.68
$NaOD-D_2O$ [d]	$6.50 \pm 0.15 \times 10^{-5}$	

[a] Average of three runs at 10^{-3} to 10^{-1} M HCl. [b] Average of two runs at 1.95×10^{-2} and 3.90×10^{-2} M DCl. [c] Average of two runs at 10^{-2} and 10^{-3} M NaOH. [d] Average of two runs at 10^{-2} and 10^{-3} M NaOD.

Discussion

The general features of the kinetics of the hydrolysis of I in aqueous solution are very similar to those found previously for the hydrolysis of Schiff bases derived from aromatic or saturated aliphatic carbonyl compounds.[1,15-18] The rate of the reaction is proportional to the concentration of protonated Schiff base (IH^+) and shows rate terms in hydroxide ion ($k^{\mathrm{OH^-}}$) and general bases (k^{B}) in addition to a spontaneous reaction rate ($k^{\mathrm{H_2O}}$). The decrease in rate at pH (H_0) less than zero has precedent in the hydrolysis of other types of Schiff bases.



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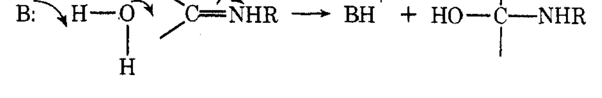
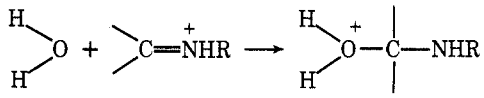
We interpret these kinetic results in terms of the same mechanism postulated earlier for the hydrolysis of Schiff bases of other carbonyl compounds (eq 3).[15-18] In the pH range 1–6, the rate-determining step is attack of water on the protonated Schiff base to give an intermediate carbinolamine which rapidly breaks down to products. This reaction is buffer catalyzed, probably involving true general base catalysis of attack of water on the iminium ion (eq 4). Support for this contention comes from the fact that catalysis by general bases occurs even with the completely protonated Schiff base, ruling out a mechanism involving hydroxide ion attack on I assisted by general acid protonation of the nitrogen.[16] The β of ca. 0.4 for this reaction is compa-



(4)

rable to the Bronsted coefficient of 0.27 observed by Cordes for the analogous general-base-catalyzed attack of water on benzhydrylidenedimethylammonium ion.[17]

The solvent isotope effect, k^{H_2O}/k^{D_2O}, of 2.44 obtained for the pH-independent pathway may be compared with the value of 2.3 calculated from isotopic fractionation factors for the complete conversion of two LO bonds to two LO^+ bonds and one NH^+ bond to an NH bond.[19] The mechanistic implication of the close correspondence between the measured solvent isotope effect and the maximum calculated one, of course, is that the transition state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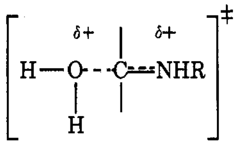
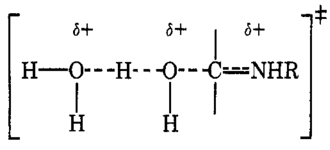
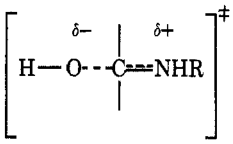
more closely resembles the protonated carbinolamine than the reactants. Cordes has come to a similar conclusion for the attack of water on the conjugate acids of substituted *N*-benzylidene-1,1-dimethylethylamines on the basis of measurements of secondary deuterium isotope effects.[20]

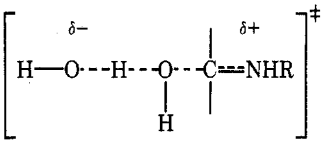
Above pH 6, attack of hydroxide ion on the protonated Schiff base becomes competitive with attack of water. Support for hydroxide ion acting as a nucleophile comes from the large positive deviation (ca. 10^3-fold) of hydroxide ion in the Bronsted plot. Although hydroxide ion often deviates in the Bronsted relationship,[21] a large positive deviation is usually considered to be evidence for nucleophilic attack.[22] A similar deviation of hydroxide ion from the Bronsted plot in Schiff base hydrolysis[17] has also been attributed to nucleophilic attack.[1] Further evidence for hydroxide ion as a nucleophile is seen in the measured solvent isotope effects for this reaction at high pH ($k_{OH^-}{}^{obsd}/k_{OD^-}{}^{obsd} = 1.68$). This number may be converted to a value for the isotope effect for direct attack of OH^- (OD^-) on the protonated Schiff base (k^{OH^-}/k^{OD^-}) by using the relationship $K^{H_2O}/K^{D_2O} = 3.4$ for nitrogen acids[19] and the difference in the autoprotolysis constants of water and deuterium oxide ($K_w{}^{H_2O}/K_w{}^{D_2O} = 7.5$).[23] Applications of these corrections gives $k^{OH^-}/k^{OD^-} = 0.8$, in agreement with the expected inverse isotope effect for nucleophilic attack of hydroxide ion. Calculation of the theoretical isotope effect for hydroxide ion attack on the protonated Schiff base gives a value of 0.5 for a transition state resembling the carbinolamine and 1.0 for one resembling reactants.[19] The observed value of 0.8 indicates that in the transition state the incipient carbon–oxygen bond is formed to a lesser extent for hydroxide ion as the nucleophile than for water attack. This interpretation is in accord with the conclusions of Cordes and Jencks[16] about the nature of the transition states for attack of water and hydroxide ion on substituted benzylidene-1,1-dimethylethylammonium ions. On the basis of substituent effects they concluded that the transition state for water attack on the iminium ion comes later along the reaction coordinate than the one for attack of hydroxide ion. However, more recent work of Cordes[20] using secondary isotope effects in this system indicates that both reactions have transition states with the carbon–oxygen bond almost fully formed.

It should be pointed out here that our conclusions about the structure of the transition states involved rest on the assumption that no other water molecules participate in the actual attack of the nucleophile. In other words we are assuming that the transition states for attack of water and hydroxide ion look like IIIa and IVa, respectively, rather than IIIb and IVb, or some variation of them which may include more than one additional water molecule, although we have no evidence to bear on this question at present.

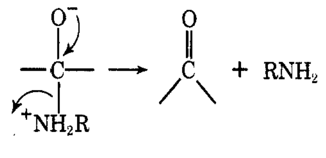

IIIa


IIIb


IVa


IVb

The break in the pH–rate at pH 0 can be accounted for by a change in rate-determining step from formation of the carbinolamine at pH >0 to breakdown of the carbinolamine at pH (H_0) <0. This change in rate-determining step is generally observed in the hydrolysis of Schiff bases, although it usually comes at somewhat higher pH.[1] Base catalysis in more concentrated acid solution can be accounted for by invoking a zwitterionic carbinolamine intermediate which breaks down to products (eq 6), as has been suggested earlier.[1]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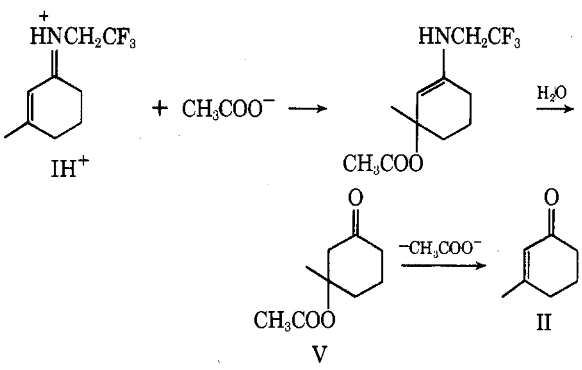
Although the above mechanism involving general-base-catalyzed attack of water on the protonated Schiff base is consistent with the experimental results and has ample precedent in the hydrolytic reactions of saturated Schiff bases, the existence of a conjugated double bond in I compels us to consider the possibility of an alternate mechanistic pathway. Specifically, buffer catalysis might occur by Michael addition to the α,β-unsaturated system, followed by hydrolysis of the enamine and elimination of the nucleophile (shown for acetate as the nucleophile in eq 7). An analogous mechanism has been observed in the deamination of cytosine derivatives catalyzed by bisulfite ion.[24,25]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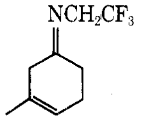
The observation of a substantial solvent isotope effect for the acetate-catalyzed hydrolysis ($k_{H_2O}{}^B/k_{D_2O}{}^B = 2.2$) suggests that nucleophilic catalysis is not operating. An isotope effect of this magnitude is indicative of a proton transfer in the rate-limiting step[19] and is generally interpreted to mean that general base catalysis is occurring.[26] In order to substantiate this conclusion, we synthesized the β-acetoxy ketone V and found that the rate constants for its conversion to the α,β-unsaturated ketone in 0.2 *M* acetate buffers (pH 3.35, 4.43, and 5.00) are at least 10^2-fold slower than the overall rate constants for acetate-catalyzed conversion of I to II in these buffers. Consequently, V cannot be an intermediate in the overall reaction, ruling out nucleophilic catalysis at the carbon–carbon double bond, at least in the case of acetate ion.

Another alternative, direct nucleophilic attack on the carbon–nitrogen double bond of IH^+, may be discarded since it should show a kinetic solvent isotope effect of about 1.0. Furthermore, this mode of catalysis cannot be operating with trifluoroethylamine as a catalyst since the nucleophile in this case would be the same moiety as the leaving group.

The overall conclusion which can be drawn from the above discussion is that the hydrolytic behavior of α,β-unsaturated Schiff bases is very similar to that for Schiff bases derived from either aromatic or saturated aliphatic carbonyl compounds. There is, however, a quantitative difference in the rates of hydrolysis of I and saturated Schiff bases. Investigations of hydrolytic rates of saturated Schiff bases have shown that these reactions are generally very rapid, often in the stopped flow range,[18,27,28] substantially faster than what is observed for I. The structural dissimilarity of I and the previously investigated compounds, however, makes a direct comparison difficult.

In order to make a more valid comparison between the rates of hydrolysis of a saturated and an α,β-unsaturated Schiff base, we can estimate the rate of hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-3-cyclohexenylidene)ethylamine (VII) at several pH values. This compound differs from I



VII

only in the location of the double bond (β,γ rather than α,β). We have previously shown[7] that the trifluoroethylamine-catalyzed isomerization of 3-methyl-3-cyclohexenone to 3-methyl-2-cyclohexenone proceeds via formation of VII in a rapid reversible step followed by isomerization to I and subsequent hydrolysis. We can set a lower limit on the rate of formation of VII from trifluoroethylamine and 3-methyl-3-cyclohexenone by simply noting that this rate must be at least as fast as the overall reaction to the α,β-unsaturated Schiff base (I). At pH's 4.85, 5.77, and 6.90 with 0.5 *M* trifluoroethylamine buffer ($pK_a = 5.77$), the rate constants for formation of I are 4.6×10^{-3}, 1.4×10^{-2}, and 6.5×10^{-3} sec^{-1}, respectively.[7] Using an estimate for the equilibrium constant for Schiff base formation ($K \sim 0.1\ M^{-1}$),[29] we can calculate the following *minimum* rate constants for hydrolysis of VII in the presence of 0.5 *M* trifluoroethylamine buffer: 1.0 (pH 4.85), 5.6×10^{-1} (pH 5.77), and 1.5×10^{-1} sec^{-1} (pH 6.90). The corresponding rate constants for hydrolysis of I under these conditions are 4.2×10^{-4} (pH 4.85), 6.0×10^{-4} (pH 5.77), and 4.6×10^{-4} sec^{-1} (pH 6.90).[7] It can readily be seen that near neutral pH the β,γ-unsaturated Schiff base (VII) hydrolyzes more than 300-fold faster than the corresponding α,β-unsaturated isomer (I).

If one assumes a pK_a of 2.8[31] for $VIIH^+$ (protonated VII), then minimum rate constants for the hydrolysis of $VIIH^+$ in these buffers may be calculated to be 1.0×10^2 (pH 4.85), 5.6×10^2 (pH 5.77), and 1.5×10^3 sec^{-1} (pH 6.90). These results give a rate increase for hydrolysis of $VIIH^+$ over IH^+ of ca. 10^6-fold under these conditions.[34] A large fraction (if not all) of this rate difference can be accounted for simply in terms of the relative pK_a's of the Schiff bases. The observed rate difference of ca. 10^6-fold for a difference in pK_a of the Schiff base of ca. 4 is similar to what was observed by Cordes and co-workers[17] for substituted benzylidene-1,1-dimethylethylamines. They found that the rate constant for attack of water on the cationic Schiff bases varies slightly more than a factor of 10 for each change of 1 pK_a unit in the protonated Schiff base, similar to what we observe for $VIIH^+$ and IH^+.

Experimental Section

Materials. 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine was available from a previous study.[7] A 3.22×10^{-3} *M* stock solution in freshly distilled acetonitrile was prepared and stored under refrigeration. There was no indication of decomposition of the imine as evidenced from the initial absorbances obtained from the spectrophotometric kinetic curves. 3-Acetoxy-3-methylcyclohexanone (V) was synthesized by the following procedure which is analogous to that used by Spencer[10] for the synthesis of 9-acetoxy-10-methyl-*cis*-decalone-2.

3-Methyl-2-cyclohexenone Oxide. A solution of 10.0 g (91 mmol) of 3-methyl-2-cyclohexenone in 70 ml of methanol was cooled to 10° and 75 ml of cold 30% hydrogen peroxide was added. Then 35 ml of 3 *N* sodium hydroxide was added dropwise with stirring over 30 min, keeping the solution at about 10°. When addition was complete, the mixture was allowed to attain room temperature, and stirring was continued for an additional 30 min. The reaction mixture was then diluted with 200 ml of saturated NaCl solution and extracted with methylene chloride (5 × 50 ml). The organic fractions were combined, backwashed with saturated NaCl solution (2 × 100 ml), and dried over Na_2SO_4. The solvent was evaporated to yield 6.44 g (56%) of crude 3-methyl-2-cyclohexenone oxide: NMR ($CDCl_3$) δ 1.40 (s, 3, $-CH_3$), 2.96 (s, 1, -OCHCO–).

3-Methylcyclohexane-1,3-diol. A solution of 6.44 g (51 mmol) of crude 3-methyl-2-cyclohexene oxide in 50 ml of dry tetrahydrofuran was added dropwise over 20 min to a stirred suspension of 5.0 g of lithium aluminum hydride (132 mmol) in 250 ml of ether. When addition was complete the reaction mixture was diluted with 250 ml of anhydrous ether and then stirred at room temperature for 15 min, followed by heating under gentle reflux for 3 hr. At the end of this time, the reaction mixture was cooled to 0° and 125 ml of saturated NaCl solution was slowly added to destroy the excess hydride. A saturated solution of Na_2SO_4 sufficient to form a clear supernatant ether–THF solution (ca. 200 ml) was then added. The organic layer was decanted, dried over $CaSO_4$, and the solvent evaporated to yield 3.23 g of crude product. The aqueous layer was continuously extracted with ether for several hours, the ether fraction dried over $CaSO_4$, and the solvent evaporated to yield 3.09 g (95% total yield) of crude 3-methylcyclohexane-1,3-diol: NMR ($CDCl_3$) δ 1.12 and 1.14 (s, 3 $-CH_3$).

1,3-Diacetoxy-3-methylcyclohexane. A solution of 5.62 g (43 mmol) of crude 3-methylcyclohexane-1,3-diol, 70 ml of isopropenyl acetate, and 15 mg of toluenesulfonic acid was heated under gentle reflux overnight. The reaction mixture was cooled to room temperature and then diluted with 500 ml of ether. The resulting solution was washed with 5% $NaHCO_3$ solution (2 × 250 ml) followed by saturated NaCl (2 × 250 ml). The organic fraction was dried over $CaSO_4$ and the solvent evaporated to yield 6.7 g of crude product. The aqueous washings were combined and back-extracted with ether (2 × 250 ml). These organic extracts were combined and dried over $CaSO_4$, and the solvent was evaporated to yield 0.7 g (80% total yield) of crude 1,3-diacetoxy-3-methylcyclohexane: NMR ($CDCl_3$ δ 1.44 (s, 3, $-CH_3$), 1.92 (s, 6, H_3CCOO-); ir (CCl_4) 1730 cm^{-1} (C=O), no detectable 3600-cm^{-1} (–OH) absorption.

3-Methyl-3-acetoxycyclohexanol. A solution of 1.0 g (25 mmol) of sodium hydroxide in 50 ml of water and 30 ml of methanol was added to a stirred solution of 5.41 g (25 mmol) of crude 1,3-diacetoxy-3-methylcyclohexane in 175 ml of methanol over 2 min at 0°. When addition was complete, the reaction mixture was stirred at 0° for 20 min, and then allowed to attain room temperature over about 40 min with continued stirring. At the end of this time the reaction mixture was diluted with 300 ml of ether. The resulting solution was washed with saturated NaCl (4 × 100 ml). The organic fraction was then dried over $CaSO_4$ and excess solvent was evaporated to yield 2.77 g of crude product. The aqueous washings were combined and back-extracted with ether (4 × 100 ml). These ether extracts were dried over $CaSO_4$ and the solvent was evaporated to yield 0.90 g (77% total yield) of crude 3-methyl-3-acetoxycyclohexanol: NMR (CCl_4) δ 1.42 (s, 3, $-CH_3$), 1.94 (s, 3, H_3CCOO); ir (CCl_4) 3600 (OH), 1725 cm^{-1} (C=O).

3-Methyl-3-acetoxycyclohexanone. Jones reagent[35] (6.0 ml, 24 mmol, [O]) was added to a stirred solution of 2.85 g (15 mmol) of crude 3-methyl-3-acetoxycyclohexanol in 100 ml of reagent-grade acetone at 0°. After 20 min at 0°, 60 ml of methanol was added to quench the excess Jones reagent. The reaction mixture was then poured into 300 ml of saturated NaCl solution and extracted with methylene chloride (3 × 150 ml). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated to yield 2.71 g (96%) of crude 3-methyl-3-acetoxycyclohexanone. Although the product β-acetoxy ketone could be separated from most of the impurities by GLC, it proved to have a retention time identical with that of the reactant, 3-methyl-3-acetoxycyclohexanol, on all columns which were tried. In order to eliminate this impurity, a mixture of 400 mg of crude product from above, 10 ml of isopropenyl acetate, and 3 mg of toluenesulfonic acid was heated at reflux for 3 hr to convert the remaining acetoxycyclohexanol to diacetate. Work-up in the usual manner gave 378 mg of crude material. Purification was effected by GLC (10% DC550 silicon on Chromosorb 60/80, acid washed, 5 ft × 0.25 in., 105°, flow rate 100 ml/min, retention time 14 min). This material showed no absorbance in the uv at 240 nm in water, but had a strong absorbance at 240 mn in 0.1 *N* NaOH (ϵ 13600) due to elimination to give II (ϵ 14000). On this basis, the product is ca. 97% pure: NMR (CCl_4) δ 1.48 (s, 3, $-CH_3$), 1.86 (s, 3, CH_3COO-), 2.27 [s, 2, $AcOC(CH_3)CH_2CO-$]; ir (CCl_4) 1740 and 1725 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.26; H, 8.34.

Kinetic Procedures. Distilled water was used for all kinetic runs. Deuterium oxide solutions were prepared using 99.87% D_2O. The deuterium chloride used was a 38% solution of DCl in D_2O containing 99% D, obtained from Stohler Isotope Chemicals. The sodium hydroxide-*d* used was a 40% solution in D_2O from Bio-Rad Laboratories. The ionic strength of all solutions was maintained at 1.00 with either 1.00 *M* NaCl or 1.00 *M* KCl solutions for aqueous solutions and 1.00 *M* NaCl in D_2O for deuterium oxide solutions. Buffers were reagent grade and used without purification. All kinetic measurements were carried out spectrophotometrically at 25.0 ± 0.1°C in a thermostated cell compartment of Gilford instruments, Model 2400 or 2400-2. pH measurements were made on a Radiometer Model 26 pH meter and spectra were obtained on a Cary Model 16K spectrophotometer. Kinetic runs were initiated by the addition of 5–20 μl of a stock solution of the imine in acetonitrile (ca. 10^{-2} *M*) to 3.0 ml of the solution in the cell compartment of the spectrophotometer. The reaction was monitored by following the disappearance of the protonated imine vs. time at 268 nm at low pH. At pH 8.75–13.0, the disappearance of the unprotonated imine was followed at 237 nm. Most reactions exhibited first-order behavior through at least 4 or 5 half-lives. All first-order rate constants were obtained by a nonlinear least-square regression analysis and linear plots were analyzed by a weighted least-squares program which assumed an equal percent error for all ordinate points. Standard deviations were, in most cases, less than 1% of the observed first-order rate constants except for the reactions in HCl solutions (pH 0–3) which showed kinetic behavior which was not *strictly* first order. Although these deviations were not large, it was apparent that the observed process was somewhat more complex (see Results).

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Registry No.—I, 57256-10-7; II, 1193-18-6; V, 57256-11-8; 3-methyl-2-cyclohexenone oxide, 21889-89-4; 3-methylcyclohexane-1,3-diol, 57256-12-9; 1,3-diacetoxy-3-methylcyclohexane, 57256-13-0; isopropenyl acetate, 108-22-5; 3-methyl-3-acetoxycyclohexanol, 57256-14-1.

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