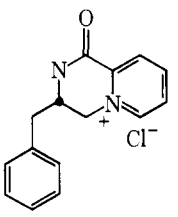

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using PtO_2 and 40 psi of hydrogen yielded verruculotoxin (**1**) and its C(10) epimer in 98% yield. Thin layer chromatography (silica gel-PF_{254}, $CHCl_3$–acetone 1:1) and visualization with ninhydrin showed two light yellow spots of which the major (~80%, R_f = 0.64) was identical with natural verruculotoxin (**1**). Recrystallization of the crude reaction mixture from benzene gave pure **1** which possessed physical and biological properties identical with natural **1**. In contrast the C(10) epimer had no observable biological effect at 25 mg/kg (oral, 1-day-old cockerel) dose levels.

The absolute configuration was established by observing that both natural and synthetic verruculotoxin (**1**) had a positive Cotton effect for the 220-nm band (θ = +3300). Since L-phenylalanine was used as a starting material and since epimerization was considered unlikely in the synthesis, the absolute configuration of verruculotoxin is as shown in Figure 1. This is reasonable as verruculotoxin is most probably derived biogenetically from the two L-amino acids, phenylalanine and pipecolinic acid.

Supplementary Material Available: fractional coordinates (Table I), important bond distances (Table II), important bond angles (Table III), temperature factors (Table IV), observed and calculated structure factors (Table V) (9 pages). Ordering information is given on any current masthead page.

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Synergism of the Effect of Solvent and of General Base Catalysis in the Hydrolysis of a Schiff Base

Sir:

The kinetics and mechanism of the formation and hydrolysis of Schiff bases have been the subject of intensive study for quite some time.[1] A major impetus for these investigations has been the intermediacy of these compounds in the catalytic mechanism of several enzymes, including acetoacetate decarboxylase,[2] dehydroquinase,[3] 2-keto-3-deoxy-L-arabonate dehydratase,[4] δ-aminolevulinic acid dehydratase,[5] D-4-deoxy-5-oxoglucarate hydrolyase,[6] and various aldolases.[7-9] Although the rates of formation and hydrolysis of many Schiff bases are very rapid,[10-12] their interconversion with the corresponding aldehydes or ketones is often several orders of magnitude too slow to account for observed enzymatic rates.[13]

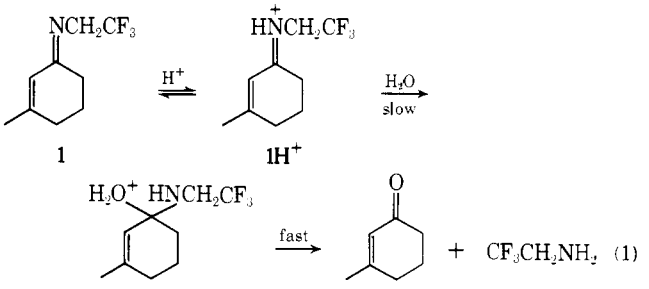
Table I. Solvent Effects on the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine in Dioxane–Water Solutions at 25.0 ± 0.1°[a]

	k^{obsd} (sec^{-1})	
% dioxane[b]	(0.1 *M* HCl)	(0.01 *M* HCl)
0	3.47×10^{-4}	3.61×10^{-4}
20	7.08×10^{-4}	
50	2.13×10^{-3}	2.27×10^{-3}
60	2.83×10^{-3}	
70	3.70×10^{-3}	4.05×10^{-3}
80	4.37×10^{-3}	
90	3.92×10^{-3}	6.43×10^{-3}[c]

[a] The reactions were monitored spectrally as previously described (ref 18). [b] Solutions are volume/volume. No other ions were added to the solutions to control the ionic strength. [c] 6.80×10^{-3} sec^{-1} at 0.001 *M* HCl.

Previous investigations have shown that these reactions are subject to general acid-base catalysis,[16,17] but it does not appear that general catalysis alone can account for this discrepancy. We now wish to report that lowering the solvent polarity also accelerates Schiff base hydrolysis. Furthermore, a combination of general base catalysis and a reduced solvent polarity is much more effective than would be predicted from the magnitude of these effects acting individually, i.e., a synergism exists between the two effects. Since both of these methods of facilitating Schiff base hydrolysis are potentially available to enzymes, our results may provide a basis for understanding the corresponding enzymatic reactions.

In the pH range 0–6, 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (**1**) hydrolyzes by general base assisted rate-determining attack of water on the conjugate acid ($\mathbf{1H^+}$) to produce a carbinolamine which decomposes to products (eq 1).[18] Addition of increasing amounts of dioxane to aqueous HCl solutions produces a marked increase in the rate of hydrolysis (Table I). For example, the rate constant for the hydrolysis of **1** in 90% dioxane (0.01 *N* HCl) is 18-fold larger than in pure water (0.01 *N* HCl) even though the concentration of water is ten times lower in 90% dioxane. Since the pK_a of $\mathbf{1H^+}$ is 6.77[19] virtually all of **1** is present as $\mathbf{1H^+}$ in this pH range so the observed rate constant refers to water attack on $\mathbf{1H^+}$. Consequently, it appears that the actual rate constant for attack of water on the protonated Schiff base ($\mathbf{1H^+}$) is 180-fold greater in 90% dioxane than in water.



The effect of changing the polarity of the solvent on the rate of hydrolysis is even more dramatic for the general base catalyzed reaction in chloroacetate buffers (Table

Table II. Catalytic Constants for the Chloroacetate Catalyzed Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0 ± 0.1°

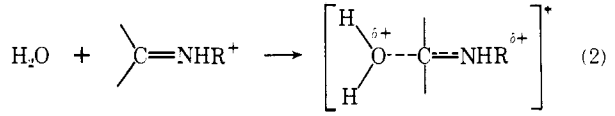
Solvent	k^B (M^{-1} sec^{-1})[a]	Buffer ratio[b]
H_2O[c]	$4.17 \pm 0.42 \times 10^{-4}$	2:1
	$5.78 \pm 1.16 \times 10^{-4}$	1:1
	$5.90 \pm 0.25 \times 10^{-4}$	1:4
50% dioxane[d]	$2.19 \pm 0.96 \times 10^{-2}$	2:1
	$2.20 \pm 0.15 \times 10^{-2}$	1:1
	$2.11 \pm 0.05 \times 10^{-2}$	1:4
70% dioxane[e]	$1.34 \pm 0.02 \times 10^{-1}$	2:1
	$1.26 \pm 0.13 \times 10^{-1}$[f]	1:1
	$1.26 \pm 0.13 \times 10^{-1}$[f]	1:4

[a] Rate constant for general base catalyzed attack of water on $1H^+$. [b] Acid/base. [c] μ = 1.0 (NaCl). [d] μ = 0.5 (NaCl). [e] μ = 0.3 (NaCl). [f] Calculated by dividing the observed rate constant for chloroacetate catalyzed hydrolysis by the percent of protonated **1**. $[1H^+]/([1] + [1H^+]) = 0.88$ (1:1 buffer) and 0.51 (1:4 buffer).

II).[20] Although chloroacetate is only feebly catalytic in water ($k_b = 5.28 \times 10^{-4}\ M^{-1}$ sec^{-1}), it is a powerful catalyst in 70% dioxane ($k_b = 1.29 \times 10^{-1}\ M^{-1}$ sec^{-1}). The effect of changing the solvent from pure water to 70% dioxane is to increase the rate constant for the chloroacetate catalyzed attack of water on $1H^+$ by almost 250-fold whereas the corresponding rate increase produced by this solvent change for direct water attack is only 11-fold.

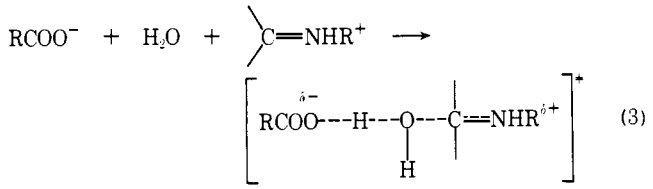
Although both chloroacetate and added dioxane accelerate the hydrolysis reaction individually, a combination of a lowered solvent polarity and addition of the general base has an effect much greater than expected on the basis of the accelerations observed for each effect separately. A comparison of the first-order rate constant extrapolated to 1 *M* chloroacetate in 70% dioxane (1.29×10^{-1} sec^{-1}) with the rate constant in pure water-HCl (3.55×10^{-4} sec^{-1}) reveals a rate enhancement of 350-fold. If both the solvent effect (11-fold) and the effect of general base catalysis (2.5-fold) were acting independently, one would predict a rate increase of 28-fold. Clearly, the total observed rate enhancement is substantially greater than the sum of the two individual effects.

A look at the probable transition states for these two processes suggests an explanation for this synergism. Attack by water on the protonated Schiff base causes a delocalization of the positive charge in the transition state, resulting in the observed rate increase as the solvent polarity is lowered (eq 2).[22] General base catalysis by the negatively charged car-



(2)

boxyl group, on the other hand, involves charge destruction rather than simply charge dispersal (eq 3). This process is



(3)

expected to show a much greater solvent dependence than that of eq 2.[22] It is tempting to speculate that many enzymes which function via Schiff base intermediates use a combination of general base catalysis and an apolar active site to facilitate the formation and hydrolysis of these imines. It is also possible that some of the large rate enhancements of enzymatic reactions may be due in part to synergistic effects.

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New Synthetic Methods. A Stereocontrolled Approach to Cyclopentane Annelation

Sir:

The occurrence of five-membered rings in an increasing number of natural products of biological importance has stimulated the development of a variety of new methods for the synthesis of cyclopentane rings.[1,2] We recently developed a method for preparing masked cyclopentanone systems utilizing the base opening of oxaspiropentanes to form siloxyvinylcyclopropanes followed by thermolysis.[1a] The limitations of this method appeared to be the inability to use α,β-unsaturated ketones as precursors and the poor yields of siloxyvinylcyclopropanes obtained from conformationally rigid six-membered rings. We wish to report (1) a method using the recently developed reagent 1-lithiocyclopropyl phenyl sulfide[3] for cyclopentanone formation which overcomes the limitations of the earlier method, (2) the stereochemistry of the migration of the vinylcyclopropane rearrangement, and (3) an interesting dichotomy in the reaction in the gas phase vs. the condensed phase.