

Nature of the Rate Acceleration Due to Added Dioxane on the Hydrolysis of an α,β -Unsaturated Schiff Base

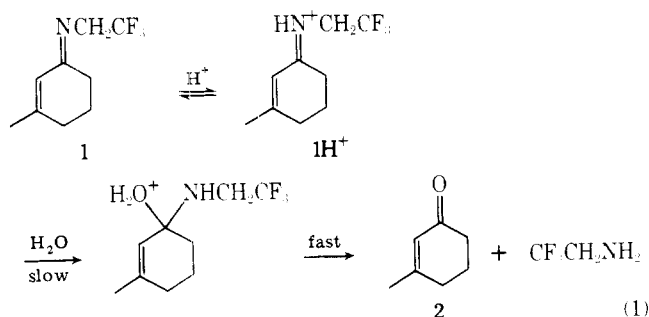
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Received December 2, 1977

Equilibrium ionization constants for the dissociation of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium ion (1H^+) and 2,2,2-trifluoroethylammonium ion (TFEAH $^+$) and overall equilibrium constants for the hydrolysis of 1H^+ have been measured as a function of solvent composition in dioxane-water mixtures. The parallel between the rates of hydrolysis of 1H^+ and the equilibrium ionization constants of 1H^+ suggests that the rate variation with solvent composition may be simply explained by preferential solvation of oxygen acids relative to nitrogen acids by increasing amounts of dioxane.

We recently reported¹ a remarkable solvent effect on the hydrolysis of the α,β -unsaturated Schiff base 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (1) in acidic solution (eq 1). A lowered solvent polarity (by addition



of dioxane to aqueous solutions) produces a marked increase in the rate of water attack on 1H^+ , even though the concentration of water is diminished. For example, the observed rate constant for attack of water in 90% dioxane is 18-fold larger than in pure water.

Although we initially suggested that this rate increase might be due to greater charge delocalization in the transition state than in the protonated Schiff base, it has been previously concluded²⁻⁴ that the transition state for attack of water on a protonated Schiff base quite closely resembles the protonated carbinolamine (i.e., there is little charge delocalization). In an effort to discern the true nature of the solvent effect on this reaction, we have measured the $\text{p}K_a$ of 1H^+ in the various dioxane-water mixtures and correlated this change with the variation in the rate of water attack on 1H^+ . In addition we have measured the effect of medium composition on the equilibrium constant for the overall hydrolysis.

Results

Ionization constants for 1H^+ and trifluoroethylammonium ion (TFEAH $^+$), as well as equilibrium constants for the overall reaction, were determined in several solvent mixtures as described in the Experimental Section. These are summarized in Table I.

The equilibrium constant for Schiff base formation from trifluoroethylamine (TFEA) and 3-methyl-2-cyclohexenone (2) is given by $K^{\text{C}=\text{N}}$ in the equation

$$K^{\text{C}=\text{N}} = [1]/([2][\text{TFEA}]) \quad (2)$$

As would be expected, the Schiff base becomes more favored relative to the ketone plus amine as the solution becomes less aqueous. In contrast, however, the equilibrium constant for the reaction of the protonated amine plus ketone to yield the protonated Schiff base ($K^{\text{C}=\text{NH}^+}$) varies only slightly with solvent.

$$K^{\text{C}=\text{NH}^+} = [1\text{H}^+]/([2][\text{TFEAH}^+]) \quad (3)$$

As is required by the different responses of $K^{\text{C}=\text{N}}$ and $K^{\text{C}=\text{NH}^+}$ to solvent variation, the $\text{p}K_a$ of 1H^+ shows a more pronounced decrease with decreasing solvent polarity than the $\text{p}K_a$ of TFEAH $^+$ (Table I). The complete reaction cycle for these processes is given in Scheme I.

In order to ascertain whether the previously observed¹ rate variation was a specific effect of dioxane, we measured rate constants for the hydrolysis of 1 in acetonitrile-water mixtures, and these are given in Table II. In addition, a rate constant of $4.75 \times 10^{-3} \text{ s}^{-1}$ was determined for the hydrolysis of 1H^+ in 82% dioxane-water.

Discussion

Before undertaking a detailed analysis of the relationship between the various rate and equilibrium constants for the hydrolysis reaction in dioxane-water, it is necessary to establish that the rate variations are not artifacts. Since peroxides have previously been reported⁵ to catalyze Schiff base formation, it is particularly important to show that peroxide impurities are not the cause of these rate variations. We do not believe that peroxides are important in these reactions for the following reasons. First, the measured rate constants do not depend on whether the solutions were made up from freshly purified dioxane or dioxane which had been purified several months earlier. Second, acetonitrile-water solutions show the same trend as dioxane-water solutions and acetonitrile is unlikely to be contaminated with peroxides. Furthermore, we have found that addition of benzoyl peroxide does not alter the rates of hydrolysis of the Schiff bases derived from cyclohexane-1-carboxaldehyde in aqueous dioxane and these Schiff bases, too, show rate increases in dioxane-water mixtures relative to water.⁶

It is of interest to try to determine whether this rate variation can be explained by a corresponding gain in stability of

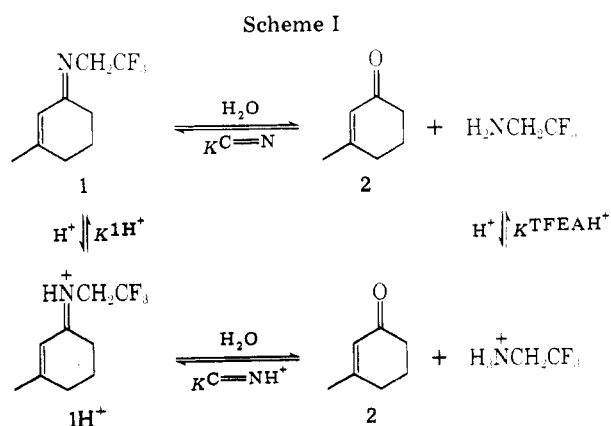


Table I. Variation of Ionization Constants,^a Equilibrium Constants, and Rate Constants for Schiff Base Formation with Solvent Composition

% dioxane	$K^{C=N^b}$	$K^{C=NH^+c}$	pK^{1H^+d}	pK^{TFEAH^+d}	$\log k$	$\log [H_2O]$
0	0.022 ^e	0.22 ^e	6.60 (6.76) ^e	5.77 ^e	-3.46 ^e	1.74
20	0.067	0.22	6.21	5.65	-3.15 ^e	1.64
50	0.11	0.16	5.47	5.32	-2.67 ^e	1.44
70	0.23	0.14	5.00	5.21	-2.43 ^e	1.22
82	0.27	0.12	4.73	5.08	-2.32	1.00

^a All ionization constants are given in terms of hydrogen ion concentration, $K = [H^+][A]/[HA]$. ^b $K^{C=N} = [1]/([2][TFEA])$. $\mu = 0.2-0.4$. ^c $K^{C=NH^+} = [1H^+]/([2][TFEAH^+])$. $\mu = 0.2-0.4$. ^d μ 0.1. ^e Reference 1.

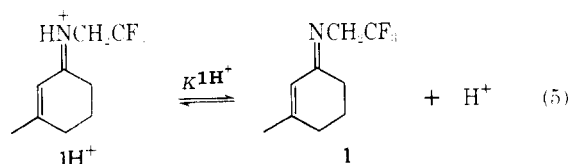
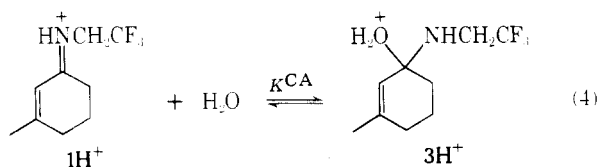
Table II. Rate Constants for the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0 ± 0.1 °C in Acetonitrile-Water Mixtures

% acetonitrile ^a	$k_{obsd} s^{-1}$	
	0.10 M HCl	0.01 M HCl
0	3.47×10^{-4}	3.61×10^{-4}
20	6.10×10^{-4}	
50	1.18×10^{-3}	1.19×10^{-3}
70	1.38×10^{-3}	1.38×10^{-3}

^a No other ions were added to control the ionic strength.

the intermediate relative to the reactants as the solvent polarity is decreased. The rate-determining step in the pH range 0-6 is the attack of water on $1H^+$ in aqueous solution,² and the near invariance of rate with acidity from 0.1 to 0.01 M HCl in aqueous dioxane¹ argues that this is also true in dioxane-water mixtures. Since the transition state for the attack of water on a protonated Schiff base quite closely resembles the protonated carbinolamine,²⁻⁴ any increase in the stability of the protonated carbinolamine relative to the reactants should manifest itself in a rate increase for the hydrolysis of $1H^+$. In the following discussion we will use the protonated carbinolamine as a model for the transition state.

Although it is not possible to directly determine the equilibrium constants for protonated carbinolamine formation in these solutions, we may approximate the effect of solvent variation on this equilibrium (eq 4) by the effect of solvent variation on the dissociation of $1H^+$ (eq 5). Here H^+ represents a proton solvated by the medium; the only bases in the solution which are present in appreciable quantities are water and dioxane, so this proton will of necessity be bound to an oxygen. In each of these equilibria (eq 4 and 5) a proton is



being transferred from a nitrogen to an oxygen; the major difference between the two reactions, of course, is the formation of a carbon-oxygen bond in eq 4 which does not occur in eq 5. Since solvation effects will most likely be of greatest importance at the protonated atoms (N and O), these two equilibria might be expected to behave similarly in response to any change in solvent. If one accepts this basic postulate then it becomes possible to explain the observed rates in dioxane-water solutions as a function of the relative stabilities

of the protonated carbinolamine and the reactants in various solvents.

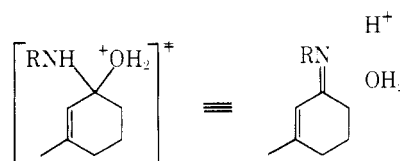
The equilibrium constant for formation of the protonated carbinolamine may be given by the equation

$$K^{CA} = K^0 \gamma_{H_2O} \gamma_{1H^+} / \gamma_{3H^+} \quad (6)$$

where K^0 is the thermodynamic equilibrium constant in water and all activity coefficients (γ_i) refer to the standard state in water and assume a value of unity at infinite dilution in water. Similarly the measured equilibrium constant for the dissociation of $1H^+$ is given by the equation

$$K^{1H^+} = K_a^0 \gamma_{1H^+} / \gamma_{1} \gamma_{H^+} \quad (7)$$

where K_a^0 is the thermodynamic dissociation constant of $1H^+$ in water. Our assumption that K^{CA} and K^{1H^+} behave identically in response to solvent variation then requires that the activity coefficient ratios of eq 6 and 7 be equal in all solvent systems; that is, $\gamma_{3H^+} = \gamma_{1} \gamma_{H^+} / \gamma_{H_2O}$. The statement $\gamma_{\pm} = \gamma_{1} \gamma_{H^+} / \gamma_{H_2O}$ corresponds to the qualitative assertion that (1) there is no effect of solvent variation on the formation of covalent bonds, and (2) the equilibrium constant for protonation of an alcohol is invariant with solvent composition. Thus, the transition state can be represented by



as far as its variation with solvent is concerned. Although this assumption *need* not be true, it is a reasonable one and the following discussion supports it.

The above approximation may be used to analyze the nature of the rate accelerations in the following way. The observed first-order rate constant for attack of water on $1H^+$ is given by the equation

$$k^{obsd} = k [H_2O] \gamma_{H_2O} \gamma_{1H^+} / \gamma_{\pm} \quad (8)$$

where $k [H_2O]$ is the observed rate constant in pure water.⁷ Dividing eq 8 by eq 7, taking logarithms, and rearranging gives the equation

$$\log \left(\frac{k^{obsd}}{[H_2O]} \right) = -pK^{1H^+} + \log \left(\frac{k}{K_a^0} \right) - \log \left(\frac{\gamma_{\pm}}{\gamma_{1} \gamma_{H^+} \gamma_{H_2O}} \right) \quad (9)$$

If the transition state resembles the protonated carbinolamine, then $\gamma_{\pm} = \gamma_{3H^+} = \gamma_{1} \gamma_{H^+} / \gamma_{H_2O}$ and a plot of $\log k^{obsd} / [H_2O]$ vs. pK^{1H^+} will be linear with a slope of -1.0. An examination of this plot (Figure 1) shows that it is, in fact, linear with a slope of -0.98 ± 0.03 , in good agreement with prediction.⁹ The fact that it is possible to fully account for the rate variations in terms of the relative stabilities of the reactants and a protonated carbinolamine intermediate shows that it is unnecessary to invoke any special stabilization of the transition state

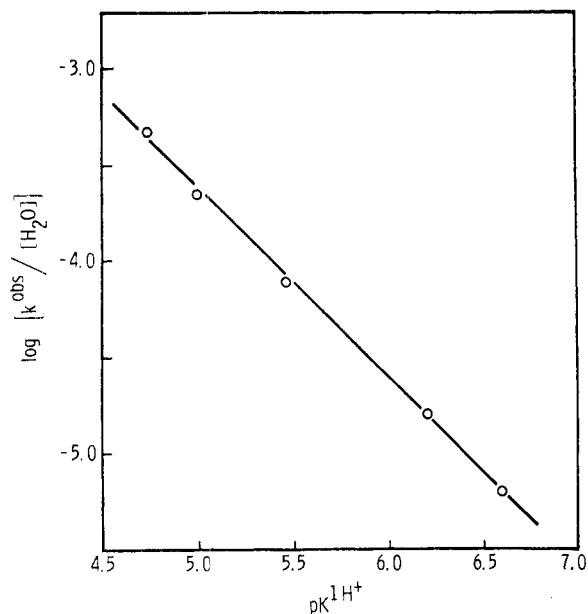


Figure 1. Plot of $\log k^{obs}/[H_2O]$ vs pK^{1H^+} as the dioxane composition of the medium is varied between 0 and 82% dioxane. The slope of the line is 0.98 ± 0.03 .

by solvent which is not possible for the protonated carbinolamine intermediate. Consequently, it appears that there is little or no charge delocalization in the transition state and the observed rate variation with solvent can be accounted for by a preferential stabilization of an oxygen acid (the transition state) relative to a nitrogen acid (the reactant) by increasing amounts of dioxane in the solution.

Since the equilibrium constant for the overall reaction in acid solution ($K^{C=NH^+}$) is known, the solvent effect on the rate of formation of $1H^+$ from **2** and TFEAH⁺ can also be readily calculated. The rate constant for formation of $1H^+$ in water and 50 and 82% dioxane can be obtained simply by multiplying $K^{C=NH^+}$ by the rate constant for hydrolysis of $1H^+$. Values of 7.6×10^{-5} , 3.4×10^{-4} , and $5.7 \times 10^{-4} s^{-1}$ are obtained, respectively, giving rate accelerations for formation of **1** in 50 and 82% dioxane of 4.5-fold and 7.5-fold over the rate constant in water. Consequently, addition of dioxane to aqueous HCl solutions increases both the rate of hydrolysis of $1H^+$ and its rate of formation from **2** and TFEAH⁺. It does this by preferentially stabilizing the transition state relative to both reactants and products. Surprisingly, the equilibrium constant for this reaction ($K^{C=NH^+}$) is actually slightly lower in 50 and 82% dioxane than it is in pure water, leading to the conclusion that more aqueous solutions actually favor formation of the protonated Schiff base.

In contrast to the effect of the solvent variation on $K^{C=NH^+}$, a decrease in solvent polarity changes $K^{C=N}$ markedly, with the Schiff base being favored over the hydrolysis products by decreasing the aqueous content of the medium. This result is, of course, expected, since water is involved as a reactant in the hydrolysis. The difference between the behavior of $K^{C=N}$ and $K^{C=NH^+}$ with solvent may be attributed to the difference in the solvent variation of the pK_a s for $1H^+$ and TFEAH⁺. The ionization constant of $1H^+$ changes much more markedly with solvent than the one for TFEAH⁺. For example pK^{1H^+} changes nearly two units between water and 82% dioxane, whereas the corresponding variation in pK^{TFEAH^+} is less than one unit. Although there is no readily apparent explanation for this difference, it is interesting to note that a similar effect has been observed for the variation of pK_a with solvent for tertiary amines vs. primary amines; the basicity of tertiary amines depends more on solvent composition than the basicity of primary amines.¹⁰

Conclusions

The effect of solvent variation on the rate constants for interconversion of $1H^+$ with **2** and TFEAH⁺ is due primarily to a preferential solvation of the transition state with a positive charge on oxygen relative to both reactants and products which have positive charges on a nitrogen. Although the reason for the greater relative acidity of nitrogen acids vs. oxygen acids in the more nonaqueous solutions is unclear, it is apparent that substantial rate variations with solvent changes may be realized because of it.

It is interesting to speculate on the possibility that enzymes which function via Schiff base intermediates use an apolar active site to accelerate Schiff base formation and hydrolysis, since the active site of many, if not most, enzymes is probably less polar than water. It is clear from the present results that a decrease in medium polarity is an efficient method for catalyzing both Schiff base formation and hydrolysis. In order for this mechanism to be effective, however, the Schiff base and parent amine must both be significantly protonated at the active site. There is a limit to the rate acceleration which might be achieved by this method. If the active site is too nonpolar then the Schiff base would exist primarily in the free form and the rate of hydrolysis would be decreased by further reductions in the polarity of the active site.

Experimental Section

Materials. Dioxane was purified by distillation from sodium. Acetonitrile was spectral grade and used without purification. Other materials have been described.¹

Kinetics. The rate of hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine was monitored by observing the decrease in absorbance at 268 nm due to the protonated Schiff base as described earlier.¹

Dissociation Constants. Hydrogen ion concentration was measured using a Corning Model 112 pH meter equipped with a combination glass electrode calibrated at pH 7 and 4 with aqueous standards. pH meter readings (B) in dioxane-water were converted to $-\log [H^+]$ using the equation,¹¹ $-\log [H^+] = B + \log U_H$. Values of $\log U_H$ were calculated as described by Van Uitert and Fernelius.¹² Stoichiometric dissociation constants for TFEAH⁺ in dioxane-water mixtures were calculated from pH meter readings of 0.1 M buffer solutions at half-neutralization with $\mu = 0.10$ (NaCl). Dissociation constants for $1H^+$ in the mixed solvents were determined spectrophotometrically at 268 nm using acetate or chloroacetate buffers at $\mu = 0.1$ (NaCl) to vary hydrogen ion concentration.

Equilibrium Constants. A known amount of **2** was added to 3 mL of 0.01 N HCl containing 0.2–0.4 M TFEAH⁺Cl⁻ and the formation of $1H^+$ was monitored spectrophotometrically at 268 nm. Using the extinction coefficient for $1H^+$ at 268 nm measured in water ($\epsilon = 1.8 \times 10^4$)¹³ the final concentration of $1H^+$ was calculated from the absorbance change at 268 nm. Knowing the initial concentration of ketone, the equilibrium constant for formation of $1H^+$ from TFEAH⁺ ($K^{C=NH^+}$) was calculated using eq 3. The equilibrium constant $K^{C=N}$ was then calculated from the known dissociation constants for TFEAH⁺ and $1H^+$ using the relationship $K^{C=N} = K^{C=NH^+} K^{1H^+}/K^{TFEAH^+}$.

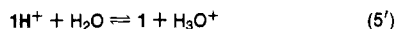
Acknowledgment. This work was supported by Grant No. GM20188 from the National Institutes of Health.

Registry No.—**1**, 57256-10-7; $1H^+$, 60415-90-9; **2**, 1193-18-6; TFEAH⁺Cl⁻, 373-88-6; dioxane, 123-91-1.

References and Notes

- R. M. Pollack and M. Brault, *J. Am. Chem. Soc.*, **98**, 247 (1976).
- M. Brault, R. M. Pollack, and C. L. Bevins, *J. Org. Chem.*, **41**, 346 (1976).
- J. Archila, H. Bull, C. Langenauer, and E. H. Cordes, *J. Org. Chem.*, **36**, 1345 (1971).
- E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).
- T. I. Crowell, C. E. Bell, Jr., and D. H. O'Brien, *J. Am. Chem. Soc.*, **86**, 4973 (1964).
- R. H. Kayser and R. M. Pollack, *J. Am. Chem. Soc.*, **99**, 8232 (1977).
- This equation and the arguments following from it are analogous to the ones used by Zucker and Hammett⁸ in the pioneering work on rate-acidity correlations in strongly acidic solutions.
- L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

(9) It has been suggested by a referee that eq 5 should be rewritten as



to explicitly take into account a water molecule acting as the base in the solution. Analysis using eq 5' gives $\gamma_{\text{3H}^+} = \gamma_1\gamma_{\text{H}_2\text{O}}$ rather than $\gamma_1\gamma_{\text{H}^+}\gamma_{\text{H}_2\text{O}}$ and predicts that a plot of $k^{1\text{H}^+}$ (as defined by eq 5) vs. $\log k^{\text{obsd}}$ should be linear. This plot is decidedly curved. We chose to use eq 5 rather than eq 5' since the exact state of solvation of the proton in these solutions is un-

known and, furthermore, probably changes with solvent composition. Although we have no proof that eq 5 represents the true situation better than eq 5', the agreement of our results with prediction is gratifying.

- (10) H. P. Marshall and E. Grunwald, *J. Am. Chem. Soc.*, **76**, 2000 (1954).
 (11) L. G. Van Uiter and C. G. Haas, *J. Am. Chem. Soc.*, **75**, 451 (1953).
 (12) L. G. Van Uiter and W. C. Fernelius, *J. Am. Chem. Soc.*, **76**, 5887 (1954).
 (13) R. M. Pollack and R. H. Kayser, *J. Am. Chem. Soc.*, **98**, 4174 (1976).

Synthesis and Reducibility of Homo-2-methoxyazocines and Their Benzo-Fused Derivatives. An Examination of Heteroatomic Influences on the Possible Generation of 9C-10 π Homoaromatic Dianions¹

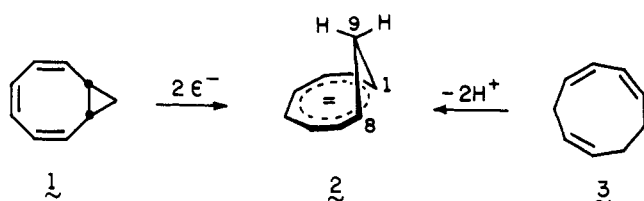
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Received August 25, 1978

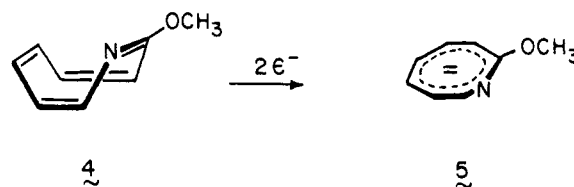
The behavior of a series of homo-2-methoxyazocines, benzohomo-2-methoxyazocines, and a dibenzo derivative upon polarographic and alkali metal reduction has been studied. Several of the systems have been prepared by reaction of azocinyl dianions with dichloromethane. However, these methylenations proved to be site specific, and the remaining substrates were therefore synthesized by appropriate ring expansion of the structurally related homotropone. The result of replacing a double bond by a cyclopropane ring is to cause a marked decrease in the facility of electrochemical reduction. All proved to be more difficult to reduce than the azocines from which they were derived, although the $\Delta E_{1/2}$ values varied as a function of the manner in which the imidate group was fixed in the medium ring. Chemical reduction of 3,8-dimethyl-3,4-homo-2-methoxyazocine (10) ultimately gave the fused pyridines 36a and 36b after protonation or methylation of the monocyclic anion 33. Cleavage of the internal cyclopropane σ bond was also encountered with 16, 28, and 31; only in the latter example was subsequent disrotatory cyclization again apparent. Reduction of benzohomoazocines 18 and 23 proceeded without cleavage of their three-membered rings. These apparently disparate observations have been reconciled by due consideration of the important controlling influence of the nitrogen atom in negative charge stabilization and maintenance of imidate character. The various mechanistic ramifications are described in detail.

The monohomocyclooctatetraene dianion (2) occupies a unique position among homoaromatic ions² in that it is the sole doubly charged homoconjugate species known at the present time.³ Available either from the two-electron reduction of *cis*-bicyclo[6.1.0]nonatriene (1)⁴⁻⁶ or from the dime-



tallation of *cis*-3,1,3,6-cyclononatriene with *n*-butyllithium in TMEDA,⁷ 2 exhibits ¹H NMR features revealing its adoption of the conformation shown, where each original double bond is somewhat twisted to accommodate the homoconjugate C₉ carbon while maintaining cyclic delocalization. Dianion 2 is more basic than the cyclooctatetraene dianion, being subject to ready protonation by ammonia at C₁ or C₈ with formation of the fully conjugated cyclononatrienyl anion.⁶ Methyl-substituted derivatives of 2 are less reactive toward NH₃, enabling their ¹H NMR spectra to be recorded in ND₃ prior to deuteration by solvent.⁶

Previous reports from this laboratory have revealed that substitution of a ring nitrogen atom for trigonal carbon in cyclooctatetraene, leading to π -equivalent azocines such as 4,⁸ modifies chemical reactivity in an interesting way. Alkali metal reduction of 4⁹ and its homologues¹⁰ affords stable planar 10 π -electron dianions such as 5 in a fashion comparable to the hydrocarbon system. However, electrochemical mea-



surements indicate that direct two-electron transfer operates, the multielectron addition phenomenon not being shared by the related cyclooctatetraene.^{11,12} The azocinyl dianions are entirely stable in the absence of air and do not undergo skeletal rearrangement upon prolonged standing at room temperature. They capture electrophiles regioselectively,^{9,13} the apparent consequence of unique inductive and resonance contributions, although steric effects can gain importance. The particularly favorable balance between electron repulsion, bond strain, and delocalization energy which prevails in 5 can be modified by benzo fusion, the capability of the individual benzologues to accept electrons varying with the extent and position of aromatic annulation.^{10,14}

In this paper, we address the question of whether the properties conveyed by the imidate functionality to 5 might also persist in homoaromatic dianion systems such as 6-8. Additionally, we have sought to determine if perturbation of

