Basic Strength of 9-Methyl-9-azabicyclo[3.3.1]non-1-ene, a Poorly Conjugated Bridgehead Enamine

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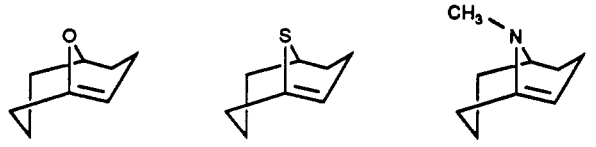
The thermodynamic acidity constant of the N-protonated conjugate acid of the bridgehead enamine, 9-methyl-9-azabicyclo[3.3.1]non-1-ene, was determined in H_2O solution, $pK_a = 8.80$, and in D_2O solution, $pK_a = 9.47$. Comparison of this result with the basic strength of saturated amine analogues indicates that steric constraints in this enamine largely, but not entirely, impede conjugation of its basic electron pair with its carbon–carbon double bond.

In connection with our interest in the protonation of carbon–carbon double bonds bearing conjugatively electron-releasing substituents in systems where steric constraints inhibit electron release, such as 9-oxabicyclo[3.3.1]non-1-ene, **1**, and 9-thiabicyclo[3.3.1]non-1-ene, **2**,[1] we wished to examine the corresponding enamine, 9-methyl-9-azabicyclo[3.3.1]non-1-ene, **3**.[2] This substance



1 **2** **3**

is a basic molecule which will be protonated in the solutions required for such a study, and dissection of observed rate constants into specific rates of the carbon protonation step requires knowledge of the acidity constant of the substrate. Our plan, therefore, was to determine the acidity constant as well as measure rates. Because carbon protonation of enamines is sometimes reversible,[3] we wished also to make measurements in D_2O solution: these would provide a solvent isotope effect, which could prove useful in diagnosing reversibility.

We were unable to achieve this goal because the reaction proved to be very slow, and we could not obtain reliable rate data by the methods at our disposal. We did succeed in making the pK_a measurements, however, and, since this information is of some value by itself, we report the results here.

Experimental Section

Materials. 9-Methyl-9-azabicyclo[3.3.1]non-1-ene was prepared as described in the literature,[2] and samples for quantitative study were purified by gas chromatography. ^1H NMR ($CDCl_3$ solution, 60 MHz): δ 5.85 (t, $J = 6$ Hz, 1 H, =C(H)—), 3.4 (broad, 1 H, >CH), 2.67 (s, 3 H, N-CH_3) 2.6–0.9 (complex, 10 H). The hydrochloride salt of 9-methyl-9-azabicyclo[3.3.1]non-1-ene was formed by bubbling HCl through a $CDCl_3$ solution of the enamine. ^1H NMR ($CDCl_3$ solution, 60 MHz): δ 7.6-5.9 (multiplet, 2 H, =C(H)— and N-H^+), 4.22 (broad, 1 H, >CH), 3.15 (d, J = 5Hz, $^2/_3$ H, N-CH_3^+), 2.95 (d, J = 5Hz, $^1/_3$ H, N-CH_3^+), 2.9–1.2 (complex, 10 H).

All other materials were best available commercial grades. Solutions were prepared from deionized H_2O, purified further by distillation, or from D_2O (Merck, Sharp and Dohme, 99.8 atom % deuterium) as received.

Table I. pK_a Determination of the Conjugate Acid of 9-Methyl-9-azabicyclo[3.3.1]non-1-ene in Aqueous Solution at 25 °C

buffer used	no. of buffer ratios	pH (pD) range		pK_a[a]
H_2O:				
NH_4^+/NH_3	10	8.4–10.1		8.837
NH_4^+/NH_3	8	8.1–9.6		8.822
$TRISH^+/TRIS$	6	8.6–9.1		8.756
H_3BO_3	9	8.0–9.7		8.784
			av	8.800 ± 0.018
D_2O:				
ND_4^+/ND_3	9	9.0–10.2		9.484
ND_4^+/ND_3	9	9.0–9.9		9.473
D_3BO_3	6	8.4–10.2		9.438
			av	9.465 ± 0.014

[a] Thermodynamic acidity constants referred to a hypothetical infinitely dilute standard state of unit molar concentration.

pK_a Determination. The extent of protonation of 9-methyl-9-azabicyclo[3.3.1]non-1-ene was determined spectroscopically by using the strong absorbance of this enamine in the region λ = 230–240 nm, which becomes much diminished as the substance is converted into its conjugate acid. Absorbances of solutions containing a constant stoichiometric concentration of the enamine in appropriate buffers were measured with a Carey Model 118 spectrophotometer whose cell compartment was maintained at 25.0 ● 0.02 °C. Several different buffers and a number of different buffer ratios for each buffer were used; the details are summarized in Table I. Replicate determinations were made, in the case of tris(hydroxymethyl)methylamine buffers, by measuring the absorbance of each solution several times at a single wavelength (λ = 230 nm), and in the case of all other buffers, by measuring the absorbance of each solution once at five different wavelengths (λ = 234, 236, 238, 240, and 242 nm). The ionic strength of these solutions was maintained at 0.10 M by adding NaCl as required.

The data so obtained were transformed into concentration ratios through eq 1, in which A_B is the absorbance of a solution of the enamine completely in its basic form, A_{BH^+} is the absorbance of

$$[BH^+][B] = (A_B - A)/(A - A_{BH^+}) \quad (1)$$

a solution of the enamine completely in its acidic form, and A is the absorbance of a buffer solution containing enamine in both forms. Values of A_B and A_{BH^+} were determined in 0.10 M sodium hydroxide and 0.10 M hydrochloric acid, respectively. Acidity constants were then calculated from these concentration ratios plus the pH values of the buffer solutions according to eq 2, in which γ_{BH^+} (= 0.80)[4] is the activity coefficient of BH^+ used to refer the results to an infinitely dilute standard state and thus

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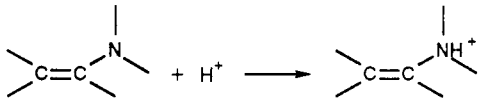
$$pK_a = pH + \log ([BH^+]/[B]) + \log \gamma_{BH^+} \quad (2)$$

provide thermodynamic acidity contants. Measurements of pH were made with a Beckman Model 1019 Research pH meter directly on the buffer solutions used to determine A. The results so obtained are summarized in Table I.

Results and Discussion

Enamines may protonate either on nitrogen, eq 3, or on carbon, eq 4. Nitrogen protonation is clearly indicated by the NMR spectrum of the conjugate acid of 9-methyl-9-



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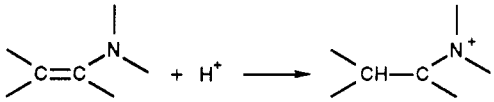
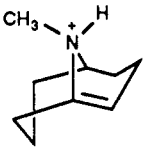


(4)

azabicyclo[3.3.1]non-1-ene formed here in $CDCl_3$ solution, inasmuch as this shows a vinyl proton resonance and two different N-methyl group signals, each split into a doublet by the proton added to nitrogen. Two such signals are, of course, expected from the two positional isomers of the N-protonated conjugate acid, **4** and **5**. It is likely that the



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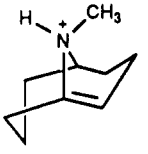

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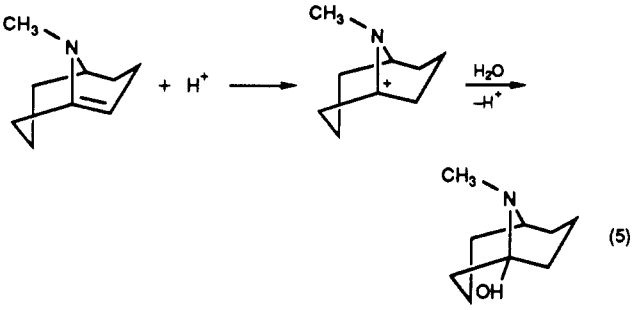
isomer formed in greater amount is that with its methyl group in the less crowded position anti to the carbon–carbon double bond, **4**; this assignment is consistent with the fact that the other methyl group (that in **5**) has the more upfield chemical shift, as expected from diagmagnetic shielding by the π-electrons of the nearby double bond.[6]

It seems likely that nitrogen protonation also occurred in the aqueous solutions used here for pK_a determinations. This is supported by the fact that these changes took place instantaneously and reversibly, as expected for protonation on nitrogen, and were followed by a much slower nonreversible change, which could be attributed to protonation and hydration of the double bond (eq 5). This conclusion is also consistent with the fact that the pK_a determined, 8.80, is lower than that for conjugate acids of corresponding saturated amines, pK_a = 10.3:[7] tertiary enamines are



(5)

generally less basic to protonation on nitrogen and more basic to protonation on carbon than are the corresponding saturated amines.[3,5b,8]

The nitrogen-base-weakening influence of the carbon–carbon double bond in enamines may be attributed to electron-withdrawing inductive and resonance effects of this substituent. The two effects have been evaluated as being approximately equal in magnitude, with each contributing about 1.1 pK units to a total pK_a lowering of ΔpK_a = 2.2.[9] This is somewhat greater than the pK_a lowering, ΔpK_a = 10.3 – 8.8 = 1.5, which may be calculated for 9-methyl-9-azabicyclo[3.3.1]non-1-ene using the estimate pK_a = 10.3 for the saturated analogue.[7] The difference, however, is consistent with the fact that the orbital bearing the basic electron pair on nitrogen and the π-orbitals of the carbon–carbon double bond in this molecule are orthogonal to one another, and conjugated electron withdrawal is consequently impeded. It is interesting as well that ΔpK_a = 1.5 is greater than the expected inductive contribution of 1.1 pK units: this implies that some conjugative interaction nevertheless takes place. That in turn suggests that the molecule is flexible enough to depart from a strictly orthogonal geometry at not too great a cost of energy, which is a conclusion reached previously on the basis of solvolysis studies of related bridgehead chlorides.[2,10]

The measurements in D_2O solution provide the solvent isotope effect $K_a(H_2O)/K_a(D_2O)$ = 4.6. This is consistent with solvent isotope effects for the ionization of other amine conjugate acids, e.g. $K_a(H_2O)/K_a(D_2O)$ = 5.0 for the trimethylammonium ion.[11]

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Registry No. **3**, 51209-44-0; **3**·HCl, 124419-64-3; D_2, 7782-39-0.

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