Basicity of Some Mono- and Bicyclic Enamines and Tricyclenamines

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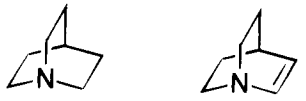
A comparison of the basicity of cyclic enamines with that of the corresponding cyclic saturated amines shows that the six-membered ring enamines are only slightly stronger bases than the saturated amines, whereas five- and seven-membered ring enamines are much stronger bases than the saturated amines. This is attributed to a large steric strain present in six-membered enamines. The predominance of this steric factor is illustrated further with NMR rotational barrier studies of cyclic enaminoketones and acyclic β-nitroenamines. The basicity of bicyclic enamines and tricyclenamines is also reported. The syntheses of two new tricyclenamines are reported.

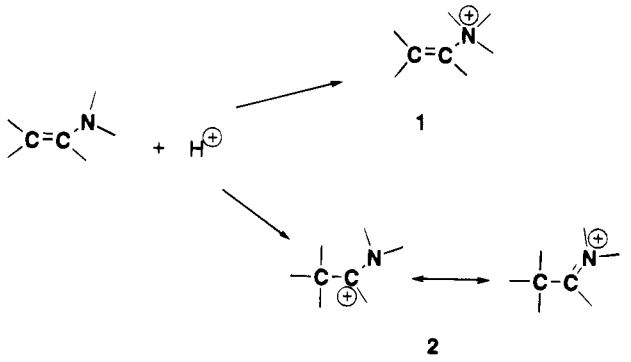
Enamines can be protonated at two different sites, namely the nitrogen atom and the β-carbon atom[1] (Scheme 1). The kinetically favored site for protonation of the enamine in solution is the nitrogen atom (**1**). The thermodynamically favored protonation site is the β-carbon atom to form iminium salt **2**. Protonation of enamines in solution at room temperature or in the gas phase favors C-protonation. The intrinsic C-protonation basicity of enamines is greater than the N-protonation basicity of the corresponding saturated amines. On the other hand, the intrinsic N-protonation basicity of enamines is less than the N-protonation basicity of the corresponding saturated amines. The greater C-protonation basicity of enamines as compared to that of the saturated amines is due to the stabilization afforded iminium ion **2** by the delocalization of the positive charge between the carbon atom and the adjacent nitrogen atom. The saturated amine has no such delocalization possibility. The N-protonated enamine **1** also does not have this possibility of charge delocalization. In addition, it is actually less stable than the saturated amine because of the inductive/field effect of the carbon–carbon double bond in the enamine. This is demonstrated by comparing pK_a values of quinuclidine (**3**) and dehydroquinuclidine (**4**). Resonance interaction between the lone-pair nitrogen electrons and the alkene π-system is impossible in **4** because the potential interaction orbitals are orthogonal. Therefore, only N-protonation takes place with **4**. The pK_a values for these amines are 11.29 for **3** and 9.82 for **4**.[2]



3 **4**

We are reporting the relative basicities of several cyclic enamines and comparing these values with those of the corresponding saturated amines (see Table 1). These enamines and saturated amines were made according to standard methods[1,3] (see Scheme 2). One can compare pK_a values of the tertiary saturated amines with each other, and those of the tertiary enamines with each other. When this comparison is made using the same cycloalkane or cycloalkene but various cyclic amine moieties, the pK_a ordering is the same as those reported elsewhere for the corresponding secondary amines.[4] However, when one compares the difference in pK_a values of tertiary saturated amines with their corresponding tertiary enamines, a significant trend appears. The pK_a difference with the cyclohexane/cyclohexene pairs for all of these saturated amine/enamine pairs is much smaller (from 0.25 to 0.54) than that of cyclopentane/cyclopentene pairs (from 1.83 to 2.90) or cycloheptane/cycloheptene pairs (from 1.42 to 3.06).

Scheme 1



1 **2**

There are two primary factors that determine the magnitude of the pK_a differences with these tertiary saturated amine/enamine pairs, namely, the varying n–π interaction across the C_{sp2}–N bond in the enamine and the steric factor arising from changing the ring size of the cycloalkene moiety. The former factor varies with each enamine, but the steric factor remains constant and is the dominant factor in these systems. Of the cycloalkane/cycloalkene systems studied, the six-membered cyclohexyl ring system has the greatest steric interaction when the cycloalkene ring and the amine rings are coplanar. This conclusion has been confirmed by the authors' using semiempirical AM1 and molecular mechanics calculations. For example, AM1 calculations show the planar cyclopentenyl- and cycloheptenylpyrrolidine iminium ions to be over twice as stable as the planar cyclohexenylpyrrolidine iminium ion. Coplanarity with the concomitant orthogonality to the double-bond

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1995.

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(3) Stork, G.; Birzzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.*, **1963**, *85*, 207.

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Table 1. pK_a Values of Some Enamines and Saturated Amines[a]

component reactants						
amine	m	ketone	n	enamine	pK_a satd amine	ΔpK_a enamine−satd amine
pyrrolidine	4	cyclopentanone	3	11.32 ± 0.02	8.75 ± 0.06	2.57
pyrrolidine	4	cyclohexanone	4	9.47 ± 0.02	8.93 ± 0.03	0.54
pyrrolidine	4	cycloheptanone	5	12.25 ± 0.06	9.19 ± 0.06	3.06
piperidine	5	cyclopentanone	3	11.54 ± 0.03	8.64 ± 0.02	2.90
piperidine	5	cyclohexanone	4	8.98 ± 0.05	8.73 ± 0.05	0.25
piperidine	5	cycloheptanone	5	10.44 ± 0.04	8.88 ± 0.03	1.56
morpholine	*b*	cyclopentanone	3	8.47 ± 0.03	6.26 ± 0.03	2.21
morpholine	*b*	cyclohexanone	4	6.72 ± 0.09	6.43 ± 0.09	0.29
morpholine	*b*	cycloheptanone	5	7.96 ± 0.09	6.54 ± 0.04	1.42
hexamethylenimine	6	cyclopentanone	3	10.78 ± 0.09	8.95 ± 0.02	1.83
hexamethylenimine	6	cyclohexanone	4	9.30 ± 0.02	9.05 ± 0.02	0.25
hexamethylenimine	6	cycloheptanone	5	11.55 ± 0.05	8.77 ± 0.02	2.78

[a] Potentiometric titration by perchloric acid with acetonitrile solvent. [b] m is $-(CH_2)_2O(CH_2)_2-$.

Table 2. Barriers to Rotation about the C_{sp2}–N Bond in Some β-Nitroenamines[a,b]

$-NR_2$	T_C (K)	$\Delta G^{\ddagger}$ (kcal/mol)
pyrrolidino	330	19.38
N,*N*-dimethylamino	319	18.88
piperidino	312	18.69
N-methylpiperazino	294	17.53
3,5-dimethylmorpholino	302	17.05

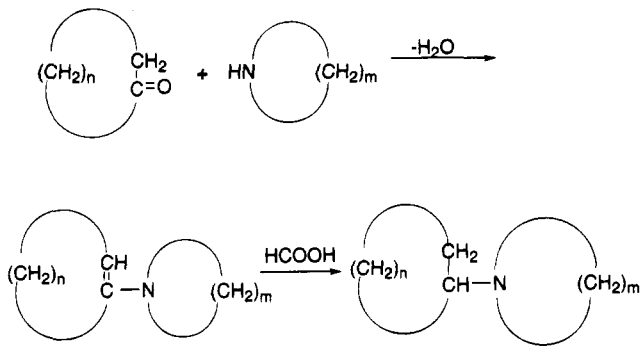
[a] NMR specta determined in $DCCl_3$ solvent. [b] Proton magnetic resonance used.

Table 3. Barriers to Rotation about the C_{sp2}–N Bond in Some Enaminoketones[a,b]

$-NR_2$	n	T_C (K)	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta\Delta G^{\ddagger}$ (2−3)
pyrrolidino	2	368	20.80	
pyrrolidino	3	287	17.43	3.37
piperidino	2	309	17.46	
piperidino	3	245	13.83	3.64
morpholino	2	290	16.37	
morpholino	3	228	12.91	3.46

[a] NMR spectra determined in $DCCl_3$ solvent. [b] ^{13}C magnetic resonance used.

Scheme 2



plane of the nitrogen lone pair is a necessity for conjugative interaction (and hence stabilization) of the iminium ion. Hence, the minimal conjugative interaction in the cyclohexyl iminium ion results in only a very small pK_a increase for the enamine relative to that of the saturated amine.

NMR studies of the rotation about the enamine C_{sp2}–N bond with a series of pyrrolidine cycloalkene enamines indicate the same conclusion.[5] The six-membered ring enamine has a 2 kcal/mol lower rotational barrier than the five-membered ring enamine and a 1 kcal/mol lower barrier than the seven-membered ring enamine. This demonstrates the large steric interaction of the pyrrolidine ring with the cyclohexene ring as compared to the cyclopentene or cycloheptene rings.

The results of a NMR rotational study of a series of acyclic β-nitroenamines (**5**) is shown in Table 2. These

$O_2NHC{=}CHNR_2$

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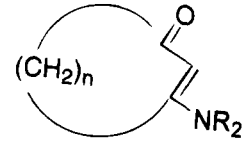
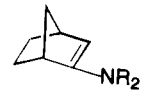
β-nitroenamines have been shown to have minimal steric inhibition of resonance and maximum conjugative interaction.[6] So the rotational barriers are due almost entirely to π-barriers. The order of these barriers by amine moieties as seen in Table 2 is pyrrolidine > dimethylamine > piperidine > *N*-methylpiperazine > morpholine.

A study of cyclic enaminoketones **6** shows this same order of π-rotational barrier by amine moieties as β-nitroenamines (see Table 3). However, these enaminoketones have a significant steric factor in the six-membered ring just as was reported for simple enamines. In this series the barriers are about 3.5 kcal/mol lower for cyclohexenone as compared to the corresponding cyclopentenone. This is larger than that observed with the cycloalkenes in simple enamines, and it is similar to observations reported for other enaminoketones.[7]

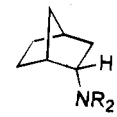


6

The pK_a difference between saturated amines and enamines in the bicyclo[2.2.1]heptane (**7b**) and -heptene



7a



7b

(**7a**) series ranges from 0.31 to 1.27 (see Table 4). This places the pK_a values of this system somewhere between those of the cyclohexyl and those of the other cycloalkyl systems in the monocyclic enamines.

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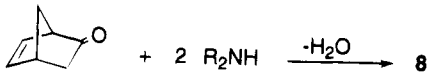
Table 4. pK_a Values of Some Bicyclic and Tricyclic Enamines/Saturated Amines[a]

system	$-NR_2$	pK_a enamine (**7a**)	pK_a saturated amine (**7b**)	ΔpK_a
7	pyrrolidino	9.56 ± 0.12	8.49 ± 0.04	1.07
7	piperidino	9.39 ± 0.10	8.26 ± 0.09	1.13
7	hexamethylenimine	8.78 ± 0.02	8.47 ± 0.07	0.31
7	morpholino	7.31 ± 0.04	6.04 ± 0.04	1.27

system	$-NR_2$	pK_a 2-position	pK_a 5-position	ΔpK_a
8	piperidino	4.13 ± 0.03	7.88 ± 0.05	3.45
8	*N*-methylpiperazino	1.17 ± 0.18	6.48 ± 0.07	3.75
8	morpholino	1.65 ± 0.03	5.10 ± 0.06	5.67

[a] Potentiometric titration by perchloric acid with acetonitrile solvent.

Scheme 3



The only tricyclenamine (**8**) whose synthesis has been reported previously is that with a morpholine amine group.[8] We now report the synthesis of two additional

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tricyclenamines with piperidine and *N*-methylpiperazine amine groups (see Scheme 3). The pK_a values of two of these tricyclenamines are shown in Table 4. The amine group not directly attached to the cyclopropyl group is a somewhat weaker base than the corresponding amine group in a bicyclic system. The amine group attached directly to the cyclopropyl group is a much weaker base than one not attached to a cyclopropyl group. This is due to the electron withdrawing inductive/field effect of the cyclopropyl group[9] which destabilizes the N-protonated amine. In this case there is not a counteracting conjugative effect such as is present in enamines.

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Experimental Section

Both proton- and carbon-NMR spectra were recorded on a 200 MH FT-NMR.[10] NMR spectra were obtained in $CDCl_3$ solvent. The barriers to rotation were obtained by the coalescence point method.[11] The pK_a values were determined by titrating a 0.01 M solution of the amine in acetonitrile with a 0.1 M solution of 70% perchloric acid in acetonitrile delivered by an automatic pump and measured potentiometrically with glass and calomel electrodes. The millivolt potential was analyzed using Grans plot to obtain the pK_a values.

The simple monocyclic enamines were prepared using the method of Stork.[1,3] The saturated monocyclic amines were synthesized by formic acid reduction of the corresponding enamines.[1,12] The preparation and properties of the β-nitroenamines used were reported earlier.[6] The enaminoketones were synthesized using the method of Stork,[1,3] and their properties correspond to those reported earlier.[7,13] The bicyclic enamines and corresponding saturated amines were prepared in a manner similar to that for the monocyclic system, and their properties correspond to those reported earlier.[8,14]

The tricyclenamines were prepared using the Stork method,[1,3] but it was found that the titanium tetrachloride method[15] also can be used to produce tricyclenamines. The ^{13}C NMR chemical shifts for the tricyclic skeletal carbon atoms only are reported, and they are reported in ascending numerical order of carbon atom label number.

The analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

2,5-Bis(*N*-morpholino)tricyclo[2.2.1.0^{2,6}]heptane: mp 76–78 °C (lit.[8] mp 79–80); ^{13}C NMR δ 20.57, 51.60, 27.56, 18.44, 70.86, 32.89, 29.73.

2,5-Bis(*N*-piperidino)tricyclo[2.2.1.0^{2,6}]heptane: mp 68–70 °C; ^{13}C NMR δ 21.62, 52.09, 27.60, 18.95, 71.66, 33.36, 30.01. Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84. Found: C, 78.46; H, 10.81.

2,5-Bis[*N*-(*N*-methylpiperazino)]tricyclo[2.2.1.0^{2,6}]heptane: mp 108–110 °C; ^{13}C NMR δ 21.32, ..., 27.76, 18.86, 70.90, 33.38, 29.97. Anal. Calcd for $C_{17}H_{30}N_4$: C, 70.29; H, 10.41. Found: C, 70.50; H, 10.24.

Acknowledgment. We are grateful for Dow Summer Fellowships for M.L.A. and V.K.B. and for a Council on Undergraduate Research Summer Fellowship for V.K.B.

JO9500702

(10) Bruker Model AC-200 FT-NMR spectrometer equipped with a Eurotherm temperature controller.
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