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Basicities of Cycloalkylamines: Baeyer Strain Theory Revisited

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Abstract: A new, accurate NMR titration method was utilized to determine relative basicities in four solvents of the two norbornylamines **2** and a series of cycloalkylamines **3-15**, as well as some *sec*-alkyl amines. Cyclopentylamine (**5**) and cyclohexylamine (**6**) are substantially more basic than the small rings **3-4** and slightly less basic than the medium rings **7-11**, with cyclooctylamine (**8**) the most basic. The large rings **12-15** are significantly less basic than **6**. The basicities reflect CCC angles, hybridization, and also solvation. These results and their relationship to Baeyer strain theory are discussed.

Keywords: Amines; Basicity; Strained Compounds; Solvents and Solvent Effects

INTRODUCTION

Cyclic hydrocarbons have been a fertile area for developing and testing theories of molecular structure. Tying a molecule into a ring often creates strain associated with unusual bond angles, dihedral angles, or transannular repulsions. Acid-base behavior can be a sensitive experimental probe of such structural features. A new NMR titration method now permits the accurate measurement of the relative basicities of a comprehensive series of cycloalkylamines.

In 1885 Baeyer proposed that deviations from the tetrahedral angle of 109°28' make cycloalkanes other than cyclopentane strained.[1] The angle strain can be expressed by eq 1, where 180° - 360°/*n* is the internal angle in a

$$E_{\text{strain}} \propto (\theta - \theta_{\text{tetrahedral}})^2 = [(180^\circ - \frac{360^\circ}{n}) - 109^\circ 28']^2 \quad (1)$$

regular *n*-sided polygon. Baeyer correctly recognized that 3- and 4-membered rings are less stable because of compression of bond angles, and that cyclopentane has angles quite close to tetrahedral, but he erred in assuming that all rings must be planar polygons. Instead, because cyclohexane takes a nonplanar, strain-free chair form,[2] it, rather than cyclopentane, has the minimum strain.

Larger rings are also nonplanar, but these have other sorts of strain besides bond-angle distortions, namely torsional strain and nonbonded repulsions.[3] For very large rings all bond angles revert to tetrahedral and all C-C bonds revert to a staggered conformation, so that the rings again become strain-free. Consequently the total strain energy per CH_2 reaches a local maximum at $n = 9$.[4] What is not clear is the extent to which angle strain contributes to the total strain in medium rings. Do these too have tetrahedral bond angles, or are their angles distorted, and if so, in which direction?

Acid-base behavior can probe angular distortions, separate from torsional strain and nonbonded repulsions. As a CCC angle decreases, the nominally sp^3-hybridized carbon rehybridizes to increase the *p* character of the orbitals directed toward C and correspondingly to increase the *s* character of the other two orbitals.[5] Since *s* electrons are closer to the nucleus, the carbon becomes more electronegative vis-a-vis its hydrogens or other attached groups. It will withdraw electron density from an attached nitrogen and reduce its basicity, which thus can serve as an indicator of hybridization. This comparison is much simpler than other cases of reactivity, such

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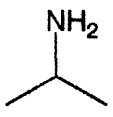
as addition to cycloalkanones or solvolysis of cycloalkyl derivatives, where there is a change of hybridization that can be analyzed in terms of differences in strain energy.[6]

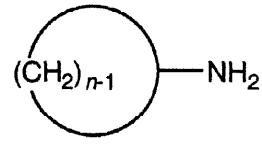
Previous titrations of cyclopropylamine (**3**), cyclobutylamine (**4**) and cyclopentylamine (**5**) in 50% ethanol showed clear evidence for a reduction of basicity due to smaller CCC angles.[7] The behavior of larger rings is less clear. Basicities of cyclohexylamine and larger cycloalkylamines in 80% 2-methoxyethanol had been measured in 1950 with a glass electrode.[8] The medium-sized rings (n = 7-9) are ca. 0.2 pK units more basic than cyclohexylamine and the large-ring amines ($n \geq 12$) are ca. 0.3 pK units less basic than cyclohexylamine. However, these variations are hardly greater than the errors (±0.1?), so no conclusions were drawn. Besides, the basicity of amines can be complicated by solvent effects,[9] which warrant a wider investigation.

A new NMR titration method[10] can be utilized to measure the basicities, relative to the arbitrary but convenient standard, isopropylamine (**1**), of exo- and endo-norbornylamine (**2**), a series of cycloalkylamines **3-15**, and some comparison *sec*-alkyl amines **16-18** across a wide range of solvents. From the variations of the

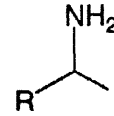


1

2 (exo)
2' (endo)



3-15, n = 3-12,15-16,21



16, R = CH_3, R' = C_2H_5
17, R = C_2H_5 = R'
18, R = C_2H_5, R' = C_3H_7

^{1}H NMR chemical shifts during a titration, the difference in basicities between a pair of amines has now been determined with great accuracy. A linear plot (eq 2) can be created from the chemical shifts of the neutral (δ_A°, δ_B°) and ionic forms (δ_{AH^+}, δ_{BH^+}) and the observed chemical shifts (δ_a, δ_b) of each amine. The slope of the plot gives K, the ratio of acidity constants (eq 3), and thus the $\Delta pK_a = -\log_{10} K$ between the two amines.

$$(\delta_b - \delta_B^\circ)(\delta_{AH^+} - \delta_a) = K(\delta_a - \delta_A^\circ)(\delta_{BH^+} - \delta_b) \quad (2)$$

$$K = \frac{K_a^{AH^+}}{K_a^{BH^+}} = \frac{[A][BH^+]}{[AH^+][B]} \quad (3)$$

EXPERIMENTAL

Materials

Solvents and reagents were obtained from commercial suppliers. Amines not commercially available were prepared by reductive amination of the corresponding cyclic ketone with ammonium acetate and sodium cyanoborohydride.[11] Cyclohexadecanone and cyclouncosanone were prepared by standard procedures.[12] Boiling points and ^{13}C NMR chemical shifts are consistent with expectations.[13]

NMR Spectroscopy

Spectra were recorded on a Varian Unity-500 spectrometer (499.8 MHz ^{1}H) using an indirect probe. Temperatures were calibrated with methanol or ethylene glycol. The C1H signals of the amines are well resolved, downfield from all others.

Titrations

Samples contained 1.00 mL solvent, 5 μL tetramethylsilane or t-BuOH (δ 1.17), 0.05 mmol isopropylamine (or cyclohexylamine in cases of signal overlap), and 0.05 mmol of the cycloalkylamine or *sec*-alkyl amine. An initial spectrum was taken, and 5-μL aliquots of a stock solution of DCl in D_2O or CD_3OD/D_2O

or of trifluoroacetic acid (TFA) in DMSO-d_6 or CD_2Cl_2 were continually added until the chemical shifts no longer changed. The ^1H NMR chemical shifts were recorded after each addition. Titrations in D_2O or CD_3OD/D_2O required an initial spectrum after adding an aliquot of an NaOD stock solution. Titrations at temperatures other than ambient (from -2.1 to +73.6°C) were performed using an apparatus for direct and continual addition of reagents into the sample in the NMR probe.[14]

RESULTS

The relative pK_as of the series of cycloalkylamines **3-15** were determined in D_2O, 3:1 (v/v) CD_3OD/D_2O, DMSO-d_6, and CD_2Cl_2. Each pK_a is referenced to that of isopropylamine (**1**), but some comparisons were confirmed by titration of two amines with each other. A compilation of the results is presented in Table 1, along with values for the *sec*-alkyl amines **16-18** and the two norbornylamines **2**. (Note that these are all *primary* amines, RNH_2, not cyclic amines.) The data can be converted to (less accurate) absolute pK_as by adding to each value 10.63, the pK_a of isopropylamine.[15] Relative basicities of such closely related substances in aqueous media or DMSO are independent of concentration.[10] In CD_2Cl_2 ion pairing is total, and the relative pK_as of **1** and **6** vary slightly with concentration, being 0.027, 0.017, and 0.007 at 0.2, 0.1, and 0.05 M, respectively.

Table 1. ΔpK_as of Cycloalkyl and *sec*-Alkyl Amines at 25°C Relative to Isopropylamine (**1**).

	Amine	*n*	D_2O	3:1 CD_3OD/D_2O	DMSO-d_6	CD_2Cl_2
1	isopropyl		≡ 0.000	≡ 0.000	≡ 0.000	≡ 0.000
2	exo-norbornyl		-0.179±0.002	-0.280±0.003	-0.409±0.004[a]	-0.276±0.008
2'	endo-norbornyl		-0.228±0.002	-0.328±0.006	–	–
3	cyclopropyl	3	-1.57±0.01	-1.48±0.01	-1.73 ± 0.03	-1.64±0.04
4	cyclobutyl	4	-0.607±0.004	-0.666±0.005	-0.836±0.004	-0.716±0.006
5	cyclopentyl	5	-0.011±0.002	-0.073±0.002[b]	-0.163±0.003	-0.129±0.002
6	cyclohexyl	6	-0.002±0.007	-0.083±0.002[c]	-0.103±0.004	-0.017±0.006
7	cycloheptyl	7	0.156±0.003	0.059±0.001	0.043±0.003	0.110±0.004
8	cyclooctyl	8	0.223±0.003	0.103±0.001	0.080±0.003	0.164±0.005
9	cyclononyl	9	0.228±0.005	0.079±0.003	0.051±0.003	0.138±0.005
10	cyclodecyl	10	–[d]	0.028±0.002[e]	0.025±0.005	0.117±0.003
11	cycloundecyl	11	–[d]	-0.049±0.002	-0.078±0.003	0.048±0.002
12	cyclododecyl	12	–[d]	-0.127±0.003	-0.152±0.003	–[f]
13	cyclopentadecyl	15	–[d]	-0.259±0.003	-0.264±0.003	-0.043±0.005
14	cyclohexadecyl	16	–[d]	-0.291±0.004	-0.285±0.003	-0.121±0.007
15	cyclouncosyl	21	–[d]	-0.221±0.003	-0.318±0.004	-0.096±0.004
16	2-butyl		-0.068±0.001	–	-0.173±0.001	–
17	3-pentyl		-0.143±0.001	–	-0.408±0.004	–
18	3-hexyl		-0.112±0.003	–	-0.406±0.007	–

[a]Confirmed as 0.239±0.007 pK units less basic than **5** by titration of mixture of **2** and **5**. [b]Confirmed as 0.006±0.001 pK units more basic than **6** by titration of mixture of **5** and **6**. [c]Confirmed as 0.227±0.009 pK units more basic than **14** by titration of mixture of **6** and **14**. [d]Amine insoluble. [e]From titration against **6**. [f]Salt insoluble.

A plot versus ring size (n) of the pK_as of the cycloalkylamines **3-15**, relative to isopropylamine (**1**), is shown in Figure 1. Error limits are smaller than the symbols.

Relative basicities can be dissected into enthalpy and entropy contributions, since a plot of ln K versus $1/T$ gives a slope of $-\Delta\Delta H^\circ/R$ and an intercept of $\Delta\Delta S^\circ/R$. These parameters for some key comparisons are listed in Table 2.

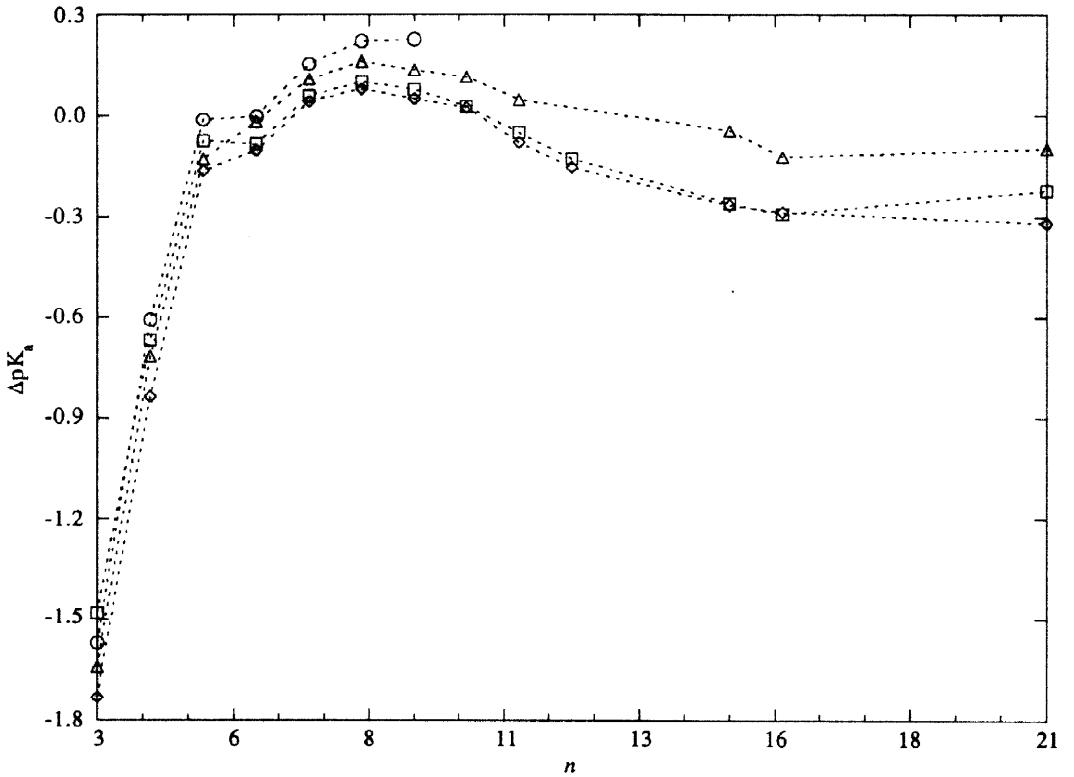


Figure 1. Relative pK_as for cycloalkylamines **3-15** (n = 3-12, 15-16, 21) in D_2O (o), 3:1 CD_3OD/D_2O (□), DMSO-d_6 (◊), and CD_2Cl_2 (Δ) vs. ring size. Dashed lines distinguish solvents and do not imply functional dependence.

Table 2. Thermodynamic Parameters ($\Delta\Delta H^\circ = H^\circ_{AH+} - H^\circ_A - (H^\circ_{BH+} - H^\circ_B)$, likewise S) for Amine Basicities.

amine A	amine B	Solvent	$\Delta\Delta H^\circ$, kcal/mol	$\Delta\Delta S^\circ$, cal/mol-K
cyclopentyl	exo-norbornyl	DMSO-d_6	-0.21±0.02	0.41±0.07
cyclopentyl	exo-norbornyl	CD_3OD/D_2O	0.02±0.03	0.81±0.09
cyclopentyl	exo-norbornyl	D_2O	0.01±0.08	0.73±0.28
cyclohexyl	cyclohexadecyl	DMSO-d_6	-0.12±0.06	0.35±0.21
cyclohexyl	cyclohexadecyl	CD_3OD/D_2O	-0.26±0.06	0.17±0.18

DISCUSSION

Small Rings and CCC Angles

The pK_as of the series of amines range over 1.8 pK units, and twelve of them lie within a range of only 0.4. It is remarkable that their differences can be measured with such accuracy. The high accuracy permits a close consideration of the factors that govern the dependence of amine basicity on ring size.

Key among these is the CCC bond angle. Since cyclohexane has bond angles that are almost exactly tetrahedral, any deviation of pK_a from that of cyclohexylamine (**6**) could be indicative of bent bonds, which have long been an intriguing aspect of the structure of small-ring molecules.[16] A reduced basicity might indicate a compression of the CCC angle, and a decrease might indicate an expansion.

The results for the small rings agree with previous direct titrations in 50% ethanol.[7] In all four solvents studied here both cyclopropylamine (**3**) and cyclobutylamine (**4**) are considerably less basic than cyclohexylamine (**6**), with **3** by far the least basic. This is clearly indicative of the smaller CCC angles of **3** and **4**. The two

stereoisomers of 2-norbornylamine (**2**) were also included in this study. Since the CCC angle of norbornane is ~102.7°,[17] intermediate between the 89° of cyclobutane and the 104.5° of cyclopentane,[18] and closer to the latter, the pK_a should also be intermediate, as observed.

A surprising result apparent from Table 2 is that the lower basicity of norbornylamine (**2**), especially in protic media, is not due to the enthalpy contribution, but to the entropy. Solvation of its cation requires more organization of solvent than around cyclopentylammonium ion. This is unlikely to be due simply to the electron-withdrawing power of the carbon, since the reduced basicity of cyclopropylamine arises from an enthalpy contribution.[19] An entropic contribution is consistent with the lowered basicity of 2,6-di-*t*-butylpyridine, which has been attributed to restricted internal rotations.[20]

A more direct measure of hybridization is the one-bond ^{13}C-^1H NMR spin-spin coupling constant $^1J_{CH}$, which varies linearly with *s* character.[21] The relative pK_as of cycloalkylamines **3-10** and exo-norbornylamine (**2**) in each solvent are plotted against $^1J_{CH}$ in the corresponding cycloalkane (Figure 2). A reasonably linear relation is obtained, even including **2**, which was not used in the fitting, although cyclobutylamine lies well below the line and cyclopentylamine lies slightly above. These deviations might indicate a slight curvature, or else errors in the coupling constants. The relative pK_as are a better indicator of hybridization since they can be measured more accurately. However, it must be recognized that the pK_as reflect the hybridization of C1 alone, rather than an average around a cycloalkane or cycloalkylamine ring. Besides, they may reflect other effects, as discussed below.

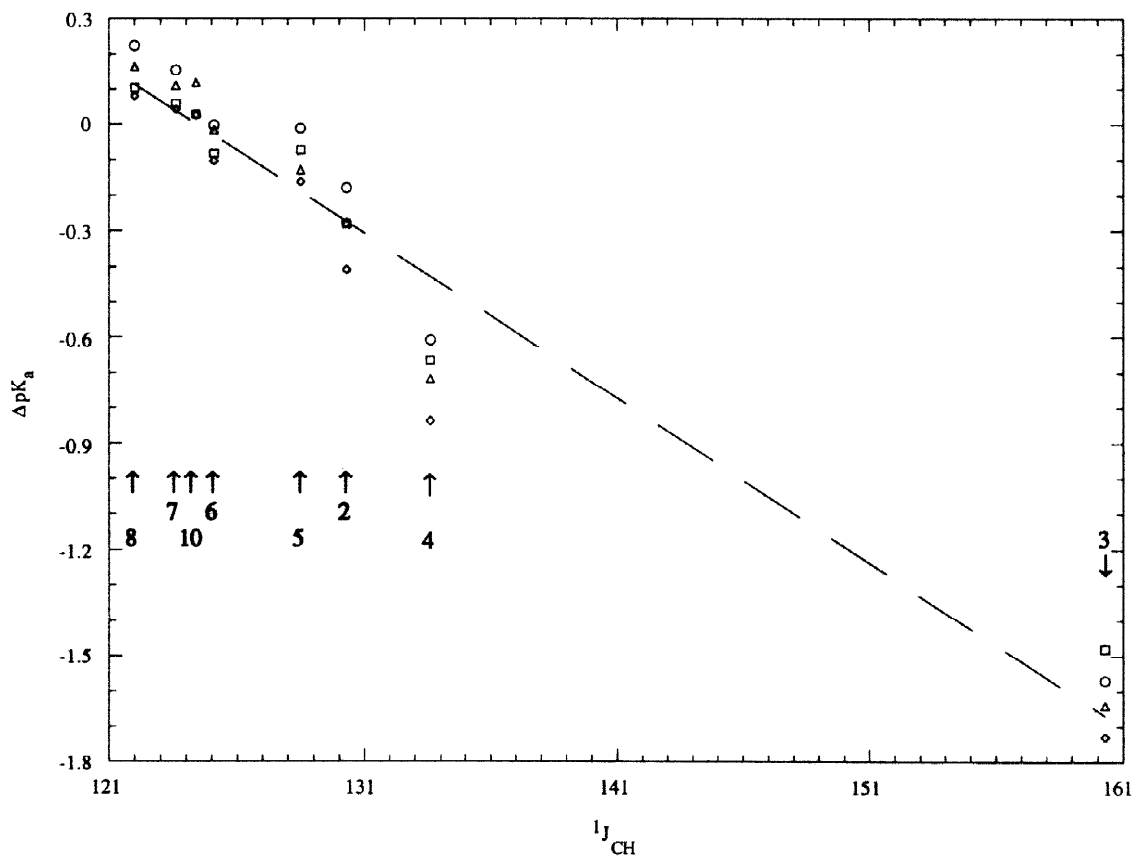


Figure 2. Relative pK_as for cycloalkylamines **3-10** and norbornylamine $\mathbf{2}_{exo}$ in D_2O (o), 3:1 CD_3OD/D_2O (□), DMSO-d_6 (◊), and CD_2Cl_2 (Δ) vs. CH coupling constants in the corresponding cycloalkane (from Ref. 21). The dashed line is a best average linear fit.

Medium Rings and Baeyer Strain

Medium rings are the most sensitive test for bond-angle distortion. In principle these could have tetrahedral bond angles, but there are deviations to relieve torsional strain and transannular repulsion. Angles are rather flexible; a 6° distortion is accessible at room temperature.[22] It is perhaps not obvious that the distortion must be to angles larger than tetrahedral, rather than to smaller. The average CCC angles observed for cycloalkanes of n = 6, 8, 10, and 12 are 111.4±0.2°, 117.4±1°, 116.1±1.1°, and 115.0±0.7°, respectively,[17] and molecular-mechanics calculations reproduce this behavior, although with the largest angle in cyclodecane.[23] In agreement with these distortions, the data in Table 1 show that medium-ring cycloalkylamines **7-11** are all detectably more basic than cyclohexylamine (**6**). This confirms the previous imprecise results.[8] Cyclooctylamine (**8**) is the most basic of all, except in D_2O, where it is equal to **9**. These higher basicities are indicative of CCC angles larger than tetrahedral. This is a clear demonstration of the existence of Baeyer strain in these rings. Even though these larger rings are not planar as Baeyer had thought, they do not have the tetrahedral angles permissible by nonplanarity.

Large Rings

For the large rings the order of basicity is **10** > **11** > **12** > **13** > **14**, appearing (Figure 1) to converge toward a limiting value that is not far from the value for cyclouncosylamine (**15**). The pK_as of *sec*-alkyl amines **16-18** beyond isopropylamine appear to converge toward the same limit. This limit is significantly below the basicity of cyclohexylamine (**6**), by 0.1-0.2. The lower basicity would be consistent with a CCC angle smaller than that of **6**. Of course this is not the case, since these rings are unquestionably strain-free, with bond angles very close to tetrahedral, so they ought to show the same basicity as **6**.

The difference between large-ring amines and cyclohexylamine might be attributed to a lower number of conformations available to a large-ring ammonium ion, compared to amine. This is reasonable, since the necessity of solvent access to the positive charge should constrain the ring. Yet such a conformational origin would be manifested as a lower negative entropy for **6**·H$^+$, or a $\Delta\Delta S^\circ > 0$ in Table 2. In DMSO this is observed, but it is not dominant, since the enthalpy and entropy contributions $\Delta\Delta H^\circ$ and $T\Delta\Delta S^\circ$ are of comparable magnitudes. Moreover, in aqueous methanol, where the conformational restriction might be more important, there is even less evidence that entropy dominates, but these data are somewhat inaccurate. Thus there may be a conformational effect reducing the basicity of the large-ring amines, but a contribution of enthalpic origin is dominant.

If the lower basicity of the large-ring amines is due neither to CCC angle distortions nor to a conformational effect, then we suggest that it is due to their additional carbons. In support, the basicities of the *sec*-alkyl amines also decrease from **1** to **16** to **17** and **18**. Such a base-weakening effect of alkylation at the β carbons has been parametrized, but not ascribed to any cause.[19] The cause is not the electron-releasing ability of the additional carbons, which would increase basicity. Instead we propose that that the additional carbons of **10-18** reduce basicity through their hindrance to solvation of the ammonium cation. In cyclohexylammonium ion (**6**·H$^+$) there is no such hindrance because the ring is rigidly tethered away from the nitrogen, so that its additional carbons, relative to **16-17**, do not reduce the basicity.

Solvent Effects

In support of a solvation contribution there is a small but distinct variation among solvents. The difference between the pK_as of cyclohexylamine (**6**) and cyclohexadecylamine (**14**) or cyclouncosylamine (**15**) is 0.15-0.2 in CD_3OD/D_2O or DMSO and decreases to 0.1 in CD_2Cl_2. As further evidence, the pK_as of the two stereoisomers of 2-norbornylamine (**2**) differ by 0.048-0.049 in D_2O or CD_3OD/D_2O, even though the nitrogens are attached to carbons of the same hybridization. The difference is consistent with a greater steric hindrance to solvation of the endo ammonium ion.[9,13]

The variations of basicity with solvent show some notable trends. For example, the data in Table 1 or the slopes in Figure 1 show that the pK_as of cycloalkylamines **3-9** are more sensitive to ring size in D_2O than in

aqueous methanol. Therefore, although each additional CH_2 increases the basicity, the accompanying hydrophobicity diminishes this tendency toward protonation in the fully aqueous solvent. Also, for the smaller-ring amines **3-7** the sensitivity to ring size is greater in DMSO than in aqueous methanol, but for each of the larger rings the ΔpK_as are nearly equal in these two solvents, except for the largest (**15**). The pK_as in CD_2Cl_2 parallel those in DMSO, but with basicities increased relative to isopropylamine by ca. 0.1. This could be due to a better solvation in DMSO of isopropylammonium ion, relative to a cycloalkylammonium ion, or to a better ion pairing in CD_2Cl_2 of a cycloalkylammonium ion. The parallelism between CD_2Cl_2 and DMSO is lost with the large-ring amines, whose relative basicities are increased even more than 0.1, such that they are not so much less basic than cyclohexylamine. Whether this originates from the solvation of the neutrals or of the cations is unclear.

Although the differences in basicity vary with solvent, the *sequence* of cycloalkylamine basicities is almost independent of solvent. There are two intriguing exceptions, both in aqueous media. One is that in D_2O cyclononylamine (**9**) is the most basic, whereas cyclooctylamine (**8**) is the most basic in the other solvents. The other exception is that in D_2O the pK_as of cyclopentylamine (**5**) and cyclohexylamine (**6**) differ by only 0.01, and in CD_3OD/D_2O they even reverse, although only barely. This reversal was seen previously in 50% ethanol but was viewed as an equalization of basicities for unstrained rings or simply ignored.[7] Yet the CCC angle in cyclopentane must be smaller than in cyclohexane, according to the coupling constants (Figure 2) and to the distortions from planarity that relieve torsional strain in both.[2] Thus according to both the strong dependence of pK_a on ring size in **3-5** (Figure 1) and the difference in coupling constants, **5** ought to be significantly less basic. Indeed, it is less basic in DMSO or CD_2Cl_2.

We propose that both these exceptions are due to special features of aqueous solvation.[9,13] The water must structure itself around both the NH_3^+ and the hydrocarbon, and the effectiveness of solvation depends on how well these two regions merge into each other, which can vary in subtle ways. We cannot be more specific about these interactions, but it is a remarkable feature of the experimental method that it can detect such small variations. Certainly the reversals between **8** and **9** and between **5** and **6** are notable, even if not readily interpretable.

CONCLUSIONS

The relative pK_as of cycloalkylamines (**2-15**) were measured with high accuracy by a new NMR titration method. A clear pattern is observed. The small-ring amines, cyclopropylamine (**3**) and cyclobutylamine (**4**), are significantly less basic, whereas the medium rings **7-11** are slightly more basic than **6**. This corresponds to compression of the CCC angle in the small rings and a slight expansion of that angle in the medium rings. Further, the 2-norbornylamines (**2**) lie between **4** and **5**, indicative of the small angle. All of these correlate with the coupling constants of the corresponding cycloalkanes. However, cyclopentylamine (**5**) is a notable exception in aqueous media.

The basicities of the large-ring cycloalkylamines **12-15** converge toward a limiting value lower than that of cyclohexylamine (**6**). This is not due simply to a greater conformational flexibility of a large-ring amine, compared to its ammonium ion, since it is not manifested exclusively in the entropy. It is proposed that the reduced basicity of the large rings is also due to hindrance by the additional carbons to the solvation of the ammonium cation.

The data are a sensitive probe of the CCC angles in the ring, of the hybridization of the ring carbons, of their effective electronegativities, and of the solvation. These results provide a better understanding of the factors that govern structure and reactivity of cyclic molecules.

Acknowledgments

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