Nitrogen Inversion Barrier of 2-Methyl-2-azabicyclo[2.2.1]heptane. The Role of Torsional Strain in Pyramidal Inversion

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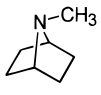
Low-temperature ^{13}C NMR measurements indicate that the endo isomer of 2-methyl-2-azabicyclo-[2.2.1]heptane is about 0.3 kcal mol^{-1} more stable than the exo isomer. Rate constants for inversion from the endo to exo isomer were determined by NMR line shape analysis. The inversion barrier, $\Delta G^{\ddagger}$, of 7.2 kcal mol^{-1} is lower than that in model acyclic amines, despite an internal CNC bond angle that is less than the tetrahedral angle of 109.47°. Comparison with 7-methyl-7-azabicyclo-[2.2.1]heptane that has a small internal CNC angle and an unusually high barrier, as well as other cyclic and bicyclic amines, leads to the conclusion that torsional (eclipsing) strain plays a significant role along with angle strain in determining inversion barriers. Molecular mechanics calculations of the change in energy between pyramidal ground state and planar transition state account reasonably well for the observed barriers. New measurements of inversion barriers and their dependence on solvent are also reported for 2-methyl-2-azabicyclo[2.2.2]octane and 1-methyl-4-piperidone.

The factors that influence inversion at pyramidal nitrogen in amines have been discussed for many years.[1−5] Inversion is often complicated by the occurrence of other conformational changes, either simultaneously or as part of a sequence.[6−10] Some *N*-methyl bicyclic amines that are otherwise essentially rigid afford nearly unambiguous views of nitrogen inversion and have played a central role in the discussions, although even in these cases a methyl rotation must occur to avoid eclipsing that would occur after a pure inversion process.[11] Several recent studies have focused on the unusually high inversion barriers ($\Delta G^{\ddagger}$ 14−15 kcal mol^{-1}) in 7-methyl-7-azabicyclo[2.2.1]-heptane (**1**),[12] and closely related systems.[13,14] Clearly, one important factor is the constriction of the internal CNC bond angle that introduces more strain into the transition structure with its planar nitrogen than into the pyramidal ground state structure. There has been less agreement regarding other factors that may be involved since Lehn's initial suggestion of some special feature ("bicyclic effect") operating to raise the barrier beyond that expected from the bond angle constriction in the 7-azabicyclo[2.2.1]heptyl system.[1,12−14]

In this paper, we report the dynamic NMR (DNMR) analysis of ^{13}C spectra of an isomeric bicyclic amine, 2-methyl-2-azabicyclo[2.2.1]heptane (**2**). A relatively *low* barrier for nitrogen inversion is found for **2**, despite an internal CNC bond angle that is less than the tetrahedral angle of 109.47°. This result clearly demonstrates the involvement of another significant factor controlling the relative rates of inversion in simple bicyclic amines. Additional DNMR measurements were also conducted for 2-methyl-2-azabicyclo[2.2.2]octane (**3**) for which two earlier studies of inversion reported barriers differing by about 2 kcal mol^{-1}.[15,16] Inversion in these and other systems providing examples of nearly pure inversion processes is examined in a molecular mechanics study utilizing a modified nitrogen for the planar transition state.



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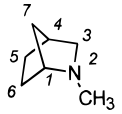

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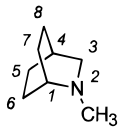

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Results

In contrast to the situation in **1** and **3**, nitrogen inversion in **2** is not a degenerate process, i.e., two different isomers are involved, namely, *exo*-2-methyl-2-azabicyclo[2.2.1]heptane, (**2-exo**) and *endo*-2-methyl-2-azabicyclo[2.2.1]heptane, (**2-endo**). Initially, we had expected a low population of **2-endo**, based upon the many arguments regarding steric hindrance in the *endo* direction in norbornane structures by an opponent of the concept of nonclassical bonding in 2-norbornyl cations.[17] However, it is actually the **2-endo** isomer that is slightly energetically favored over the **2-exo** isomer, as described below.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

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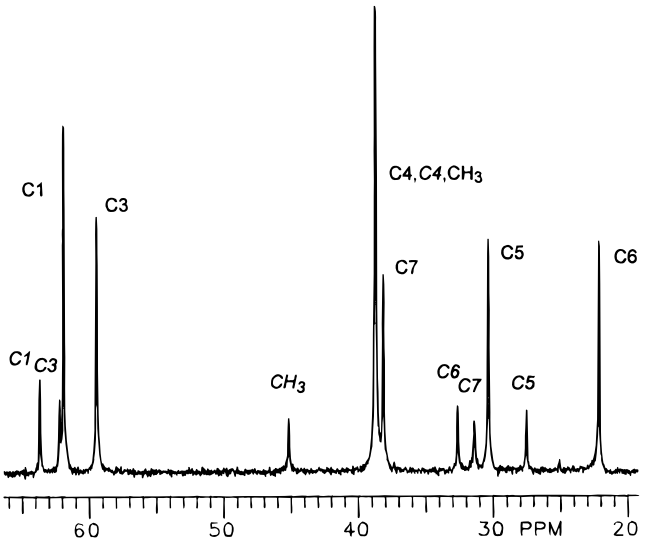
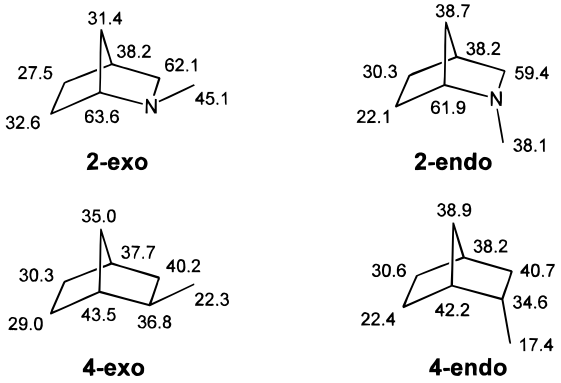


Figure 1. The 126 K, 75.43 MHz $^{13}C\{^1H\}$ NMR spectrum of **2**. The major isomer is **2-endo**; signal assignments for **2-exo** are indicated by italics.

Scheme 1



The ^{13}C NMR spectrum of **2** at room temperature in $CDCl_3$ or at 195 K in CF_2Cl_2 displays one sharp peak for each of the seven nonequivalent carbons. The peaks were assigned by a ^1H-coupled ^{13}C experiment and by comparison with shifts reported for a similar compound, 2-ethyl-2-azabicyclo[2.2.1]heptane.[18] As the temperature is lowered further, the peaks become broad and eventually all except the C4 peak are split into two peaks for a total of 12 visible peaks (two overlap), as shown in the 126 K spectrum in Figure 1. The observed peaks at the lower temperatures can easily be divided into two sets, one for the major and one for the minor isomer. The assignment of peaks to particular carbons is based partly on the exchange between carbons at matching positions in the two isomers, i.e., peaks assigned to a particular carbon must undergo mutual exchange and appear at a weighted average position in the fast exchange spectra. Comparison is also made to ^{13}C signal positions in *exo*-2-methylbicyclo[2.2.1]heptane (**4-exo**) and *endo*-2-methylbicyclo[2.2.1]heptane (**4-endo**), as shown in Scheme 1.[19] The most obvious chemical shift differences between *exo* and *endo* structures are related to the well-known γ-substituent effect in which a syn or gauche alignment of a γ-substituent shields an α-carbon relative to the chemical shift in an anti alignment.[20] Due to the γ-substituent effect, the C6 carbon in **4-endo** is shielded by about 7 ppm and the C7 carbon is deshielded by about 4 ppm compared to **4-exo**.[19] Assigning the isomer of **2** by the γ-substituent effect, **2-endo** is the major isomer and has C6 shielded by about 10 ppm and C7 deshielded by about 7 ppm compared to **2-exo**. Part of the larger substituent effects in **2** may be due to an additional hyperconjugative influence of the lone pair when it is in near anti alignment with C6 or C7.

The **2-exo**/**2-endo** ratio was obtained from the line shape analysis (see below) of ^{13}C spectra for five temperatures from 126 to 175 K for four carbons: C1, C3, C5, and C6. The average **2-exo**/**2-endo** is 0.34 at 126 K, corresponding to an equilibrium free energy difference, $\Delta G°$, of 0.28 kcal mol^{-1}. From the van't Hoff plot of ln K vs $1/T$ (where K = **2-exo**/**2-endo** and T is temperature on Kelvin scale), $\Delta H°$ is 0.30 ± 0.06 kcal mol^{-1} and $\Delta S°$ is 0.4 ± 0.9 eu. An earlier study of 2-alkyl-2-azabicyclo-[2.2.1]heptanes by Menger *et al.* came to the conclusion that moderately sized groups seem to experience no serious steric problems within the endo cavity.[18] Their study was based on protonation in aqueous HCl and the resulting percentages of *exo*-2-alkyl or *endo*-2-alkyl aminium ions. However, in the 2-methyl and 2-ethyl cases, their assignments of *exo* and *endo* aminium isomers was uncertain.

The rate constants for inversion in CF_2Cl_2 from **2-endo** to **2-exo** at five temperatures from 146 to 185 K were obtained by complete line shape analysis (modified DNMR5)[21] of two regions of the ^{13}C spectra: 18−37 ppm containing C5 and C6 signals and 58−65 ppm containing C1 and C3 signals as shown in Figure 2. Chemical shifts used for analysis of the higher temperature spectra were estimated by linear extrapolation of the shifts at 146 and 126 K. The $\Delta G^‡$ is 7.2 ± 0.2 kcal mol^{-1} at 165 K (approximately the coalescence temperature, T_c, for C6 signals), $\Delta H^‡$ is 9.3 kcal mol^{-1}, and $\Delta S^‡$ is 13 cal deg^{-1} mol^{-1} (eu). We can find no previous literature giving an inversion barrier for **2**.

For comparison to **2**, the inversion barrier of **3** is of interest. In 1970, Lehn and Wagner reported a $\Delta G^‡$ of 8.4 ± 0.3 kcal mol^{-1} at 155 K for deuteriomethyl **3** in $CHFCl_2$ based on the coalescence temperature for the C3 methylene ^1H signals in 60 MHz spectra.[15] In 1976, Nelsen and Weisman reported a $\Delta G^‡$ of 6.51 ± 0.15 kcal mol^{-1} at 146 K for **3** in 35% acetone-d_6/65% CF_2Cl_2 solution based on total line shape analysis of C6,7 ^{13}C signals at 25.16 MHz.[16] Since the $\Delta G^‡$ in these reports differ by about 2 kcal mol^{-1} and since the studies were conducted in different solvents, we reinvestigated the inversion barrier for **3**.

DNMR studies of **3** in four solvents were based on 75.4 MHz ^{13}C spectra in the 16−34 ppm region that contains the C6,7, C5,8, and C4 signals. The C4 signal remains sharp while the C6,7 and C5,8 signals broaden and decoalesce into two pairs of signals as the temperature is lowered. Results of the DNMR analysis are given in Table 1. The inversion is faster in $CFCl_3$ and CF_2Cl_2

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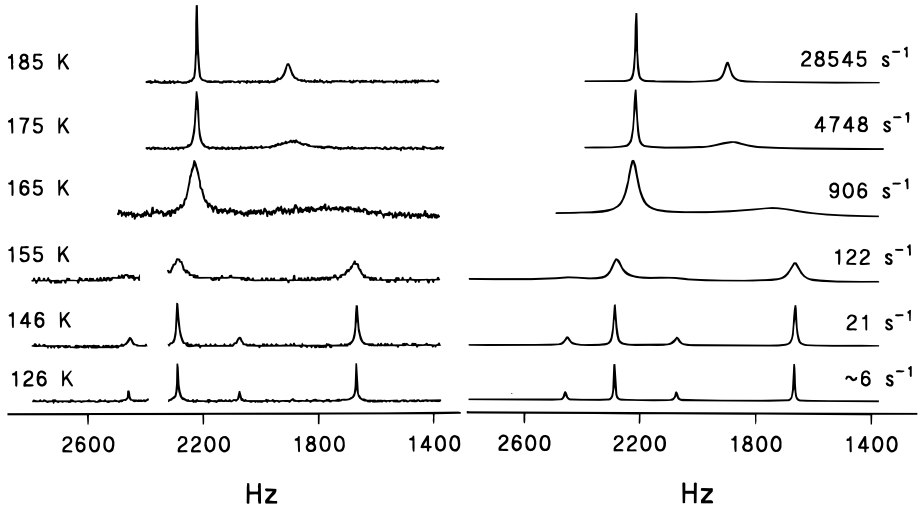

Figure 2. Experimental 75.43 MHz $^{13}C\{^1H\}$ NMR spectra of the C5,C6 region of **2** in the left column and DNMR5 theoretical simulations in the right column. The experimental spectra were digitized in the DNMR5 program, and the C7 signal of **2-exo** has been removed for clarity from the three lowest temperature spectra.

Table 1. Activation Parameters for Exchange in Amines 2, 3, and 5 from DNMR Analysis

compd	solvent	no. of points/temp range	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal mol^{-1}	temp, K
2	CF_2Cl_2	9/39°	9.3	13	7.2	165
3	$CDFCl_2$	5/30°	10.3	17	7.4	170
	CD_3OD	8/46°	8.1	4.4	7.3	170
	$CFCl_3$[a]	6/30°	7.6	5.9	6.7	153
	CF_2Cl_2	6/26°	8.3	11	6.6	153
5	$CDFCl_2$	7/41°	9.8	7.1	8.5	185
	CF_2Cl_2	5/35°	7.8	−1.1	8.0	180

[a]Chemical shift separations used in DNMR analysis were obtained from frozen-out spectrum in CF_2Cl_2.

solutions than in CD_3OD and $CDFCl_2$. The higher barrier in CD_3OD than $CFCl_3$ or CF_2Cl_2 was expected because the barrier-raising influence of a hydrogen-bonding solvent is well known.[1,7,22] Hydrogen bonding to the amine lone pair is thought to stabilize the pyramidal ground state. By our measurement, although we find a lower barrier than did Lehn and Wagner, $CDFCl_2$ influences the barrier to the same extent as CD_3OD, perhaps also due to hydrogen bonding.[23] Lehn previously noted examples indicating that inversion barriers may be increased by about 0.5 kcal mol^{-1} in $CDCl_3$ compared to hydrocarbon solvents and in $CHFCl_2$ compared to $CFCl_3$.[1] The barriers to inversion for **3** in $CFCl_3$ of 6.7 ± 0.2 kcal mol^{-1} in $CFCl_3$ and 6.6 ± 0.2 kcal mol^{-1} in CF_2Cl_2 are in excellent agreement with the previous value of 6.5 kcal mol^{-1} found by Nelsen and Weisman in acetone-d_6/CF_2Cl_2 solution.[16] Clearly, the lower inversion barrier determined in CF_2Cl_2 is more appropriate for comparison with predicted (gas phase) values than those obtained in hydrogen-bonding solvents.

We also repeated a DNMR study of 1-methyl-4-piperidone-*3,3,5,5-d*$_4$, (**5**). Lehn and Wagner had reported a barrier of 8.6 ± 0.3 kcal mol^{-1} in $CHFCl_2$, based on the coalescence temperature of the C2,6-methylene ^1H signals at 60 MHz. Our line shape analysis of ^1H measurements at 300 MHz in $CDFCl_2$ gave a $\Delta G^{\ddagger}$ of 8.5 ± 0.2 kcal mol^{-1} at 185 K for the chair-chair exchange process, in excellent agreement with the earlier study. In CF_2Cl_2, the $\Delta G^{\ddagger}$ is 8.0 ± 0.2 kcal mol^{-1}, so **5** exhibits a similar sensitivity to solvent effects as seen for **3**.

Discussion

The barriers to exchange, $\Delta G^{\ddagger}$, in CF_2Cl_2 for **2** and **3** of 7.2 and 6.6 kcal mol^{-1}, respectively, are both lower than expected for inversion in a strain-free tertiary amine. The least sterically crowded, tertiary amine for which an inversion barrier has been determined by direct DNMR methods is *N,N*-dimethylpentanamine-*d*$_1$, (**6**), with a $\Delta G^{\ddagger}$ of 8.2 kcal mol^{-1}.[24] Trimethylamine, **7**, was deduced to have an inversion barrier of 8.3 kcal mol^{-1} from photophysical measurements.[25] These should be considered as inversion-dominated barriers because rotation is thought to accompany the inversion process. Some structural feature in **2** and **3** apparently causes a lower barrier than in sterically uncrowded, acyclic tertiary amines. Barriers for inversion-dominated exchange processes for several additional monocyclic and bicyclic amines, **8**−**14**, are listed in Table 2 for use in the further comparisons below.

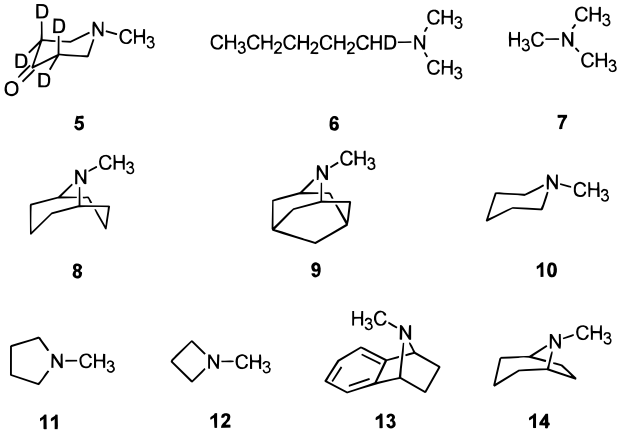

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Table 2. Comparison of Nitrogen Inversion Barriers with MMX Calculations

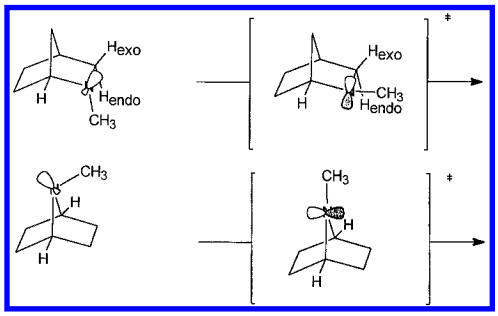
compd	ref	$\Delta G^{\ddagger}$, kcal mol^{-1}	ΔE, MMX kcal mol^{-1}	MMX CNC,[a] deg	MMX $\Delta\alpha$(av),[b] deg
1	12	14.1	14.1	95.6	10.8
2[c]	this paper	7.2	5.1	104.9	8.3
3	this paper	6.6	4.3	110.4	8.0
5	this paper	8.0	9.1	111.3	8.9
6	24	8.2	7.3	111.2[d]	8.8
7	25	8.3	7.1	111.0[d]	9.0
8	28	8.1	8.1	109.7	8.1
9	28	8.2	8.1	110.8	7.9
10[e]	29	8.7	9.0	111.4	8.9
11	f	8.3	7.5	104.3	9.4
12	f	10.0	9.3	93.2	11.7
13	14	14.4[g]	13.5	93.4	11.7
14[e]	22b	9.2	10.0	103.0	8.3

[a] Internal CNC angle. [b] Change in the average CNC angle from pyramidal structure to planar.[1] [c] For **2-endo** to planar. For **2-exo**, ΔE is 5.0 kcal mol^{-1}. [d] Average external angle. [e] For inversion from equatorial to axial. [f] Lambert, J. B.; Oliver, W. L., Jr.; Packard, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 933. [g] Average barrier for five halogenated derivatives.

Bond angle spreading due to a ring constraint could lower the inversion barrier, but that is obviously not responsible for a lower barrier in **2** and **3**. Molecular mechanics calculations, using the MMX forcefield[26] that employs Allinger's MM2 parameters for amines,[27] predict an internal CNC angle of 104.2° for **2-exo**, 104.9° for **2-endo**, and 110.4° for **3**, compared to 111.0° for the predicted CNC angle in trimethylamine. Indeed, with the restriction imposed by the rings on expansion of the internal CNC angle in progressing to the planar transition structure, it would be expected that the barriers in both **2** and **3** should be higher than in an acyclic amine. It is also difficult to argue that there is significant steric crowding of the NCH_3 group by the C6 methylene in **2-endo** or by the C6,7 methylene in **3** when we have found that **2-endo** and **2-exo** have nearly the same stability. There is slight flattening around the N predicted for **3** by MMX, which could reflect a slight steric crowding: the sum of the predicted CNC bond angles in **3** is 336°, compared to 333° predicted for trimethylamine. The CNC bond angle sum is predicted to be 330° in **2-exo** and 335° in **2-endo**, so any role of steric crowding in **2** is not obvious.

Other useful comparisons are to inversion barriers in other cases with N in a six-membered ring, such as **5** and **8**−**10**. Predicted bond angles are very similar for **3**, **8**, and **9**: internal CNC angles are 110.4°, 109.7°, and 110.8° for **3**, **8**, and **9**, respectively, and the sum of CNC angles is 336° for each. Thus, there is no obvious ground state structural feature regarding CNC bond angles or steric crowding to distinguish these cases, but the inversion barrier is almost 2 kcal mol^{-1} higher for **8** and **9** in CF_2Cl_2/acetone-d_6 with $\Delta G^{\ddagger}$ of 8.1 and 8.2 kcal mol^{-1}, respectively.[28] Nelsen *et al.* suggested that the extent of α-branching was an important factor raising the barrier in bicyclic systems, perhaps due to increased ground state stabilization caused by lone pair, alkyl group σ^* orbital mixing.[12] The barriers for **8** and **9** vs **2** and **3** are consistent with Nelsen's proposal, since **8** and **9** are bis-α-branched while **2** and **3** are mono-α-branched. However, if monocyclic systems are included in the comparison, the α-branching hypothesis does not seem appropriate. Thus, the monocyclic amines **5** and **10** are not α-branched but have similar or slightly higher barriers of 8.0 and 8.7 kcal mol^{-1}, respectively.[15,29] Both **5** and **10** have CNC angles nearly the same as in trimethylamine, with predicted endocyclic angles of 111.3° and external angles of 111.0°, for sums of 333°.

Scheme 2



The one qualitative feature that does seem consistent with barrier differences not related to CNC bond angles is the occurrence of eclipsing interactions (torsional strain). In **2-exo**, the N−CH_3 bond is approximately eclipsing the C3−H_{exo} bond (C−N−C3−H dihedral angle is 10° by MMX) and similar near eclipsing occurs with C3-H_{endo} in **2-endo** (C−N−C3−H dihedral of 14°). The lone pair is also involved in eclipsing with the C3 methylene hydrogens. These eclipsing interactions are relieved in the planar transition state (C−N−C3−H dihedrals of 57° and 66°; see below for MMX calculations of planar structure). The eclipsing interaction of the N−CH_3 with the C1-H would be expected to increase as the C−N−C1−H dihedral of 68° in **2-endo** or 37° in **2-exo** change to a C-N-C1−H alignment of 23° in the planar structure, but with the greater CNC angles for a planar N and with the lone pair in a p orbital, overall torsional strain in the transition structure should be reduced. Similar considerations apply in the case of **3**, i.e., torsional strain surrounding the N-CH_3 should decrease in proceeding to the transition structure. In contrast, torsional strain should increase at the transition state for **1**, **5**, and **8**−**10**, although torsional strain should be of less significance energetically in transition structures than in pyramidal ground state structures for equivalent C−N−C−H dihedral angles because of the larger CNC bond angles for planar nitrogen.

Scheme 2 illustrates the geometry changes from ground state to transition state for **1** and **2**. The influence of torsional strain on the inversion barriers of **1** and **2** should be opposite, lowering the barrier for **2** and raising it for **1**. The barrier to methyl rotation in trimethylamine is 4.35 kcal mol^{-1}, which is noticeably higher than the 3.0 kcal mol^{-1} barrier for ethane because of the shorter C-N bond.[27] Thus, it seems likely that a substantial portion of the ∼7 kcal mol^{-1} difference in inversion barriers between **1** and **2** should be ascribed to the difference in the influence of torsional strain. Angle strain should be the other significant factor, as **1** has a

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smaller internal CNC angle of 95.6° (MMX) compared to the 104.9° calculated for **2**. The original suggestion of a special "bicyclic effect" for 1-azabicyclo[2.2.1]heptyl systems was proposed because of the higher barrier than in 1-methylazetidine (**12**), despite the smaller CNC angle in **12** (93.2° by MMX). Here again, torsional strain could account for the discrepancy, as it increases for **1** and decreases for **12** in reaching the transition structure.

If the major factors influencing inversion barriers in tertiary amines are angle strain, torsional strain, and steric crowding rather than a specific orbital interaction requiring appropriate alignment of certain bonds with the lone pair, then a molecular mechanics model might account for the observed trends. Nelsen[12] and others[10,30] have noted the success of Allinger's MM2 parameterization in describing ground state structures and rotational barriers of amines. Indeed, MM2 predicts that **2-endo** should be 0.1 kcal mol^{-1} more stable than **2-exo**, in close agreement with our experimental finding. However, MM2 parameters have not been defined for the planar nitrogen of the transition structure.[12] In the MM2 method, the lone pair of an amine nitrogen is treated as a pseudoatom.[27] If the amine framework is forced to be planar, then very distorted geometries occur due to odd placements of the lone pair. We have taken the approach of simply deleting the lone pair pseudoatom after setting up the molecular geometry to constrain the nitrogen and three attached carbons to the same plane. This step is easily accomplished through use of the PCMODEL software implementation of the MMX forcefield.[26]

The MMX-predicted energy differences, ΔE, between the ground state and planar structures are given in Table 2 for methyldialkylamines **1-3** and **5**−**14**, representing a variety of structural frameworks. The $\Delta G^{\ddagger}$ at the midpoint of the experimental temperature range or at the coalescence temperature in each case is chosen for comparison in Table 2 rather than $\Delta H^{\ddagger}$ because $\Delta G^{\ddagger}$ values are much more accurately determined than $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

For the purpose of comparing with predicted ΔE values, we are assuming $\Delta S^{\ddagger}$ is zero so that $\Delta G^{\ddagger}$ is equivalent to $\Delta H^{\ddagger}$. Anet has suggested that $\Delta S^{\ddagger}$ values for conformational exchanges from DNMR data are so likely to be inaccurate that they are not worth discussing.[31] Inaccurate temperature measurement is a well-known source of systematic error that has a relatively small effect on $\Delta G^{\ddagger}$ and large effect on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.[33] The large variation in entropies of activation for inversions listed in Table 1 may be due to inaccurate temperature measurement and narrow temperature intervals;[33] note, however, that good agreement with previous reports of $\Delta G^{\ddagger}$ for **3** and **5** was found. Nelsen[12] chose to use an arbitrary $\Delta S^{\ddagger}$ value of 5 cal mol^{-1} K^{-1} (first suggested by Lehn[1]) in order to convert $\Delta G^{\ddagger}$ values from the various coalescence temperatures to $\Delta H^{\ddagger}$ values. The primary effect of using a constant $\Delta S^{\ddagger}$ value for such conversions is to introduce corrections that are smaller for the lower barrier cases (measured at lower temperatures) and larger for the higher barrier cases. Since we are looking for significant trends in the data, the use of uncorrected

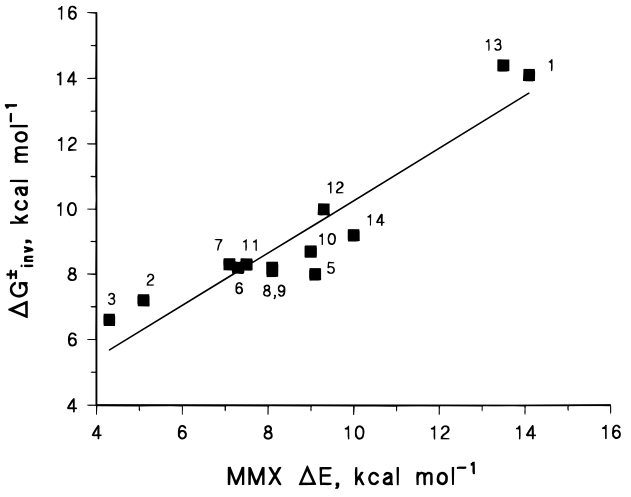

Figure 3. Plot of inversion-dominated amine exchange barriers, $\Delta G^{\ddagger}$, vs MMX calculation of energy change, ΔE, between pyramidal and planar forms.

$\Delta G^{\ddagger}$ values should serve as well as arbitrarily corrected data, and probably better than either experimentally determined $\Delta H^{\ddagger}$ values or temperature extrapolated $\Delta G^{\ddagger}$ values. For example, at the coalescence temperatures of 183 K for **8** and **9**, the $\Delta G^{\ddagger}$ are in close agreement at 8.1 and 8.2 kcal mol^{-1}, respectively, but the $\Delta G^{\ddagger}$ values diverge to 7.1 and 7.8 kcal mol^{-1} when extrapolated to 298 K through use of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.[28] The MMX-predicted ΔE values for **8** and **9** are identical at 8.1 kcal mol^{-1} as shown in Table 2.

Another source of error in activation parameters is temperature dependence of chemical shifts. Temperature-dependent shifts can be recognized and taken into account in DNMR analysis for spectra near the slow-exchange limit, but the best that can be done in medium to fast exchange spectra is to linearly extrapolate shifts from lower temperatures.[33] As clearly demonstrated by Lambert, the temperature dependence of chemical shifts is usually but not necessarily linear.[34] Use of data from more than one set of exchanging nuclei where possible should ameliorate the problem, as was done in our analyses of ^{13}C NMR data from **2** and **3**.

The $\Delta G^{\ddagger}$ for inversion are plotted *vs* the MMX-predicted ΔE for the inversion process in Figure 3. The success of the overall correlation is only fair (slope = 0.803; intercept = 2.23; corr coeff = 0.935). However, the calculations account for the general trend and correctly predict that **2** and **3** have the lowest inversion barriers while the 7-azabicyclo[2.2.1]heptyl systems **1** and **13** have the highest among the systems compared.[35] Since the lower barriers for **2** and **3** and the higher barrier for **1** compared to the acyclic systems **6** and **7** are accounted for reasonably well in the molecular mechanics model, there appears to be no need to invoke any special orbital interactions to explain a unique bicyclic effect. If any special orbital interactions are involved, such as lone pair−σ^{*} interaction, they must be hidden by the empirical parameterization of the molecular mechanics method.

Further dissection of the correlation in Figure 3 may not be justified because of the simplicity of the compu-

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(32) Binsch, G., ref 31, Chapter 3.

(33) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; Chapter 7.

(34) Lambert, J. B.; Vagenas, A. R.; Somani, S. *J. Am. Chem. Soc.* **1981**, *103*, 6398.

(35) The 3-membered ring case, 1-methylaziridine, was not included because MM2 parameters for the special case of the aziridine ring were not derived: see ref 27.

tational model, but it is interesting that those systems containing N in a chair structure of a six-membered ring, namely **5**, **8**−**10**, and **14**, all fall below the correlation line in Figure 3. Unfortunately, the range of $\Delta G^{\ddagger}$ values for these systems is too narrow to be certain that a separate correlation line is appropriate. The correlation with MMX ΔE values is much better than a correlation with either the internal CNC angle (slope = −0.268; intercept = 37.5; corr coeff = −0.795) or the change in the average CNC angle,[12] $\Delta\alpha$(av) (slope = 1.45; intercept = −4.22; corr coeff = 0.811).

Our qualitative conclusion is that in addition to angle constraints torsional strain is a significant factor in determining inversion barriers in cyclic and bicyclic amines and likely accounts for a substantial part of the nearly 7 kcal mol^{-1} difference in inversion barriers for 7-methyl-7-azabicyclo[2.2.1]heptane, (**1**), and 2-methyl-7-azabicyclo[2.2.1]heptane, (**2**). The bond angle strain is greater for **1** than for **2**, and the influence of torsional strain works to raise the barrier in **1** and lower it in **2**. The barrier is lowered sufficiently in **2** that it is even lower than expected for an amine without bond angle constraint.

Experimental Section

Materials. All compounds used in this study are known compounds. 2-Methyl-2-azabicyclo[2.2.1]heptane, (**2**), was prepared by the method of Grieco.[36] 2-Methyl-2-azabicyclo-[2.2.2]octane, (**3**), was prepared by lithium aluminum hydride reduction of 2-methyl-2-azabicyclo[2.2.2]octan-3-one.[37] 1-Methyl-4-piperidone-*3,3,5,5-d*$_4$ (**5**), was obtained following two exchanges in deuterium oxide.[15] Dichlorofluoromethane-d_1 was synthesized by the method of Siegel and Anet.[38]

NMR spectra were run on a Varian XL-300 FT NMR spectrometer operating at a frequency of 300 MHz for ^{1}H and 75.43 MHz for ^{13}C. A Waltz-16 decoupler was used for ^{13}C spectra, which were typically obtained with a spectral window of 16501 Hz, 30016 data points, a 1.0 s acquisition time, and 5 s delay. The variable temperature device was calibrated with a standard methanol sample. The device was not calibrated below the freezing point of methanol, so the temperatures are uncorrected readings from the probe sensor. The temperature varied no more than ±0.5 K during acquisition, and temperatures are estimated to be accurate to ±3.0 K (used in error estimation for $\Delta G^{\ddagger}$). The DNMR spectra were run unlocked when the solvent contained no deuterium.

MMX calculations were carried out with the PCMODEL program.[26] The model structures for the inversion transition states were constrained to have the nitrogen and the three attached atoms in the same plane, and the lone pair pseudo-atom was deleted for the minimization. No other geometrical constraints were applied except in the case of the transition state for **11**, where the entire ring was confined to the same plane because the ring changes from an envelope shape in the ground state to a twist shape in the transition state if only the nitrogen is kept planar.

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