Rate-Determining Role of Strain for Nitrogen Inversion in Polycyclic Tertiary Amines[1]

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Abstract: The nitrogen inversion barriers for *N*-isopropyl-, *N*-butyl-, *N*-isobutyl-, and *N*-*tert*-butyl-7-azabicyclo-[2.2.1]heptanes were measured using dynamic NMR line shape analysis. These barriers as well as those for different bicyclic and tricyclic tertiary amines were analyzed *via* the molecular mechanics method (MM3 force field). A new MM3 steric energy-based parameter, including the energy of substitution-induced disturbances (E_{sid}), is proposed for the estimation of relative strain among related compounds with one variable substituent. A linear relationship was found between N-inversion barriers and this parameter for 7-azabicyclo[2.2.1]heptanes with a β-unbranched N-substituent, which allows an accurate prediction of the barrier values for these amines. For all polycyclic systems studied, the change of strain in the transition state relative to the ground state of the amine, simulated by MM3, makes up 76−106% of the experimental value of the corresponding N-inversion barrier. Among these amines some azabicycles ("bicyclic effect" systems) display the largest deviation (∼25%) from the experimental barrier value. From the point of view of the classical model, this deviation may be attributed to a bicyclic effect which would have an orbital origin.

Introduction

Usual values of nitrogen inversion barriers for alkylamines lie in the 5−9 kcal/mol range.[2−4] However, significantly larger barriers were found for the derivatives of 7-azabicyclo[2.2.1]-alkanes.[2,3,5−9] For instance, the reported $\Delta G^{\ddagger}$ values of the N-inversion barriers at 25 °C for *N*-Me and *N*-Et compounds **1a** and **1b** are 13.77 and 13.17 kcal/mol, respectively,[5] while the enthalpy of nitrogen inversion ($\Delta H^{\ddagger}$) for *N*-methylpyrrolidine is 8.7 kcal/mol.[10] A simple explanation of this phenomenon based on the influence of angle strain on the pyramidal inversion[2,3] was considered insufficient.[2,5] According to this view a distortion of the endocyclic CNC angle in the transition state of the bridged backbone cannot cause such a considerable increase of the N-inversion barrier in azanorbornanes and related systems.

A complementary "bicyclic effect" was therefore postulated[2] to compensate for the difference between experimental barrier values and those estimates based on the angle strain concept. The most extensive analysis of the N-inversion barriers in bicyclic effect systems was performed[5] using a comparison of the AM1-calculated inversion barriers between monocyclic and bicyclic amines, on the basis of the value of the average CNC angle α(av)[5,11] for the amino fragment. The deviation of the AM1-calculated barrier for the azabicycloalkane from the barrier for the corresponding monocyclic compound of the same α-(av) value was proposed as the magnitude of a bicyclic effect.[5] However, (1) this semiempirical approach suffers from low accuracy (see below) and (2) the conclusions reached about the increase of N-inversion barriers were based on studies of *N*-Me compounds,[5] while an observed[5] small but clear decrease of the measured barriers for *N*-Et bicycles in relation to *N*-Me analogs was not discussed.

The latter effect as well as a similar decrease of the N-inversion barriers for azanorbornenes going from the *N*-Me to the *N*-CH_2Ph compound was attributed by other authors[6] to an expression of the role of steric factors in the rate of inversion in these amines. It was suggested also[6] that destabilization of the ground state due to steric interactions involving the *N*-Me substituent plays a major role in the lowering of N-inversion barriers upon sequential saturation of one and two C=C bonds in *N*-methylazanorbornadiene. Another study mentioned[12] that the steric strain of the bicyclic backbone may be responsible for the unusually high inversion barriers for *N*-chloroazanor-bornanes with respect to other *N*-chloroamines. Recently the strain-based approach led to a qualitative conclusion about the relationship between torsional strain and the barrier height for bicyclic amines (including azanobornanes).[13]

In order to check the influence of the bulk of the N-substituent and thus the hypothesis of the importance of steric interactions on the rate of nitrogen inversion for 7-alkyl-7-azabicyclo[2.2.1]-heptanes, we have studied differently-N-substituted azanorbor-nanes **1a**−**f** (see Figure 1) using dynamic NMR (DNMR) and molecular mechanics calculations (MM3 force field). The latter method was also applied to the related bicyclic amines **2a,b,f**, **3a**, **4a**, **5a**, **6a**, and **7a**, hydrazine **8a**, diisopropylamines **9a**−**c**, and methylisopropylamines **11b,c,f**.

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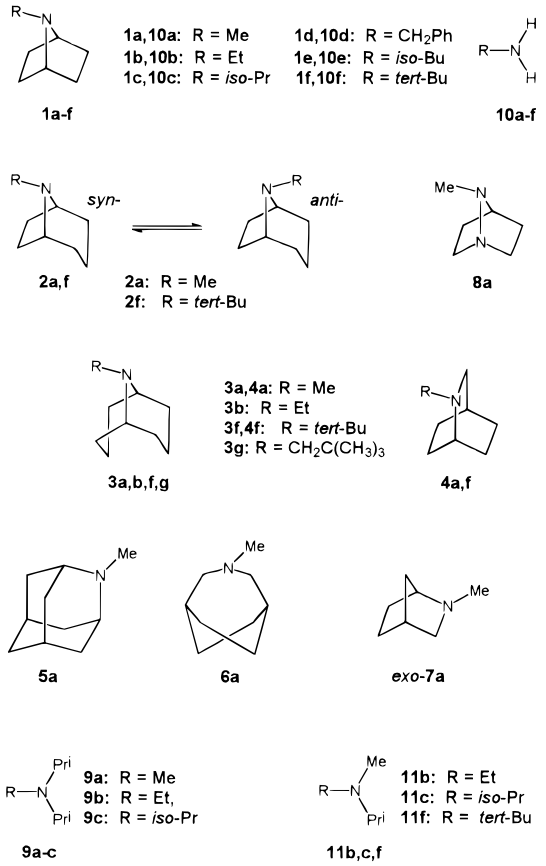

Figure 1. Bicyclic amines **1a**−**f**, **2a**,**f**, **3a**,**b**,**f**,**g**, **4a**,**f**, **5a**, **6a**, and **7a**, hydrazine **8a**, and open chain amines **9a**−**c**, **10a**−**c**, and **11b**,**c**,**f**.

Table 1. ^{13}C NMR Data for Azanorbornanes **1c**−**f** in $CDCl_3$ at 25 °C (ppm)

entry	C-2,3; C-5,6[a]	C-1; C-4	N−C	others
1c	28.37[a]	57.01	45.01	22.18 (Me)
1d	28.50[a]	59.14	52.00	147.37 (*i*), 128.52 (*m*), 128.13 (*o*), 126.60 (*p*)
1e	28.18[a]	59.40	55.43	32.44 (CH_2), 20.35 (Me)
1f	31.22	55.33	64.47	30.00 (Me)

[a] Broadened.

Results

Data for the room temperature ^{13}C NMR spectra of compounds **1c**−**f** are given in Table 1. The activation parameters for the intramolecular motion in piperidines **1c**−**f** were obtained by iterative fitting of the signals of the methylene carbons of the pyrrolidine rings to their simulated line shapes at different temperatures (see Table 2).

No dichotomy for the signal of the *t*-Bu group of the most crowded compound **1f** was observed in the monitored temperature range, and only a small broadening of this signal was detected at 157 K. Thus, consideration of the parallel C−N rotation process[3,4,14,15] may be excluded, and the measured values of the free energy of activation for amines **1c**−**f** should be assigned to $\Delta G^{\ddagger}$ for the nitrogen inversion process only.

MM3 calculations were performed for azanorbornanes **1a**−**f**, alkyldiisopropylamines **8a**−**c**, open chain alkylamines **9a**−**c**, **10a**−**f**, and **11b,c,f**, and bicyclic amines **2a,b,f**, **3a**, **4a**, **5a**, **6a**, **7a**, and **8a** (see Figure 1). Energy parameters related to the minimized steric energy (E_{min}) and the α(av) values for the optimized structures are given in Table 3. The MM3 force field parameters were devised for hindered as well unhindered amines,[16] and we also tested highly crowded triisopropylamine (**9c**), an open chain analog of bicyclic triisopropylamine **1c**. The calculated geometry for **9c** is quite similar to the flattened geometry obtained[17] by electron diffraction (e.g., the calculated and experimental CNC angles are 119.4° and 119.2°, respectively). We believe, therefore, that the calculated values are applicable to all considered amines.

Discussion

N-Inversion Barriers: Angle-Based Approach. A strong dependence of the rate of nitrogen inversion on the steric bulk of the N-substituent was found for azabicycloheptanes **1a**−**f**: an increase of the size of this substituent causes a decrease of the N-inversion barrier (see Table 3). This change is drastic, when one compares *N*-Et and *N*-*t*-Bu bicycles **1b** and **1f** (∼6.1 kcal/mol), and it is significant even for *N*-Me and *N*-Et compounds **1a** and **1b** (0.6 kcal/mol). In contrast, only a weak dependence of this kind is seen in the other crowded amines: the change of $\Delta G^{\ddagger}$ for nitrogen inversion for methylethylisopropylamine (a *N*-Et compound) and methylisopropyl-*tert*-butylamine (a *N*-*tert*-Bu compound) is 1.25 kcal/mol.[15] The $\Delta G^{\ddagger}$ difference between diisopropylamines **9a** and **9b** is only 0.15 kcal/mol,[15] 4 times less than the one between their bicyclic analogs **1a** and **1b**. For *N*,*N*′,*N*″-trimethyl-1,3,6-triazacyclohexane and the *N*,*N*′,*N*″-tri-*t*-Bu analog this $\Delta G^{\ddagger}$ change is 1.1 kcal/mol.[18]

Table 3 shows that the $\Delta G^{\ddagger}$ values for amines **1c**−**e** are much higher than the usual N-inversion barriers for aliphatic amines[2−4] including *N*-alkyl-*N*,*N*-diisopropylamines[15] and *N*-methylpyrrolidine,[5,10] but are only moderately lower than the ones for azanorbornanes **1a** and **1b** with an unbranched N-substituent. In contrast, the barrier for *N*-*tert*-butyl compound **1f** lies in the region of the usual nitrogen inversion barriers. In terms of the accepted approach,[2,5,6] bicyclic amines **1a**−**e** demonstrate the bicyclic effect while bicyclic amine **1f** does not. Thus, two features are found for the nitrogen inversion process in azabicyclonorbornanes: a strong dependence of the N-inversion barrier on the volume of the N-substituent and a near normal value of the N-inversion barrier for the *N*-*t*-Bu compound **1f**.

We suggest that sole consideration of the geometry of the amino fragment[2,5,19] is not sufficient even for a qualitative prediction of the N-inversion barrier for bicyclic amines. For example, the fact that a four-membered cycle, *N*-chloroazetidine, possesses a lower inversion barrier than *N*-chloroazanorbornanes is given[5] as an argument for the postulation[2] of the bicyclic effect. But no estimate of the strain of the endocyclic CNC angle in azanorbornanes in the transition state has been made. A change of this angle obviously causes deformation of the bicyclic backbone. Indeed, it is difficult to assess *a priori* which is most strained: a CNC angle included in one azetidine ring, or in two pyrrolidine rings (as in **1**).

A semiempirical approach using AM1 calculations[5] seems too crude to estimate the nitrogen inversion barriers as a function of the angle geometry of the amine group and thus to support or to disprove the bicyclic effect concept. A quantative correlation of a calculated energy with any structural parameter is only as good as the accuracy of the calculation results, yet

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Table 2. Kinetic Parameters for Nitrogen Inversion in Amines **1c**−**f** (k, s^{-1}; $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$, kcal/mol; $\Delta S^{\ddagger}$, cal/(mol·K))

	1c ($\Delta H^{\ddagger} = 14 \pm 1$, $\Delta S^{\ddagger} = 10 \pm 3$)		**1d** ($\Delta H^{\ddagger} = 13 \pm 1$, $\Delta S^{\ddagger} = 3 \pm 5$)		**1e** ($\Delta H^{\ddagger} = 13 \pm 1$, $\Delta S^{\ddagger} = 8 \pm 4$)		**1f** ($\Delta H^{\ddagger} = 10 \pm 1$, $\Delta S^{\ddagger} = 13 \pm 5$)	
T, K	k	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$
156.9							48±9	7.8±0.2
166.4							350±40	7.6±0.1
176.5							(1.8±0.2)x10^3	7.5±0.1
216.9	4.5 ± 0.9	11.9 ± 0.2	4.0 ± 0.7	12.0 ± 0.2	10 ± 2	11.6 ± 0.2	$(4.0 \pm 1.7) \times 10^5$	7.0 ± 0.3
237.1	42 ± 4	12.0 ± 0.1	40 ± 5	12.0 ± 0.1	130 ± 20	11.5 ± 0.1		
257.4	500 ± 50	11.8 ± 0.1			1400 ± 160	11.3 ± 0.1		
277.6	$(4.6 \pm 0.6) \times 10^3$	11.6 ± 0.1	$(2.5 \pm 0.3) \times 10^3$	11.9 ± 0.2	$(1.2 \pm 0.2) \times 10^4$	11.0 ± 0.2		
299.9	$(5.0 \pm 0.9) \times 10^4$	11.1 ± 0.2	$(1.8 \pm 0.5) \times 10^4$	11.7 ± 0.3	$(6.0 \pm 1.9) \times 10^4$	11.7 ± 0.3		

Table 3. Barrier Values Obtained by DNMR (at ∼300 K) and MM3 Calculation Results for Amines **1a**−**f**, **2a**, **3a,b**, **4a**, **5a**, **6a**, **7a**, and **8a**

compd	α(av), deg	$\Delta G^{\ddagger}$, kcal/mol (ref)[a]	E_{sid}, kcal/mol	ΔE_{min}, kcal/mol	$\Delta E_{min}/\Delta G^{\ddagger} \times 100\%$	ΔE_{rot}, kcal/mol
1a	110.1	13.77 (5)	44.7	10.6	77	
1b	110.2	13.17 (5)	45.5	10.1	77	6.2
1c	110.7	11.1 (this work)	46.9	9.3	84	11.0
1d	110.8	11.7 (this work)	47.0	9.6	82	4.9
1e	110.7	11.6 (this work)	44.9	11.2	97	10.6
1f	115.4	6.1 (this work)	53.0	4.9	80	4.5
2a		7.8 (36)	33.6	8.3	106	
3a		7.1 (30)	28.5	6.6	93	
3b		6.6 (31)	30.1	5.3	80	
4a		5.65 (38)		4.3	73	
5a		7.8 (30)		6.6	84	
6a		8.8 (3)[b]		8.0	91	
7a		5.4(13)		5.3	98	
8a		14.35 (5)[c]		10.9	76	

[a] A reliable $\Delta G^{\ddagger}$ value is known only at low temperatures. Extrapolation of the $\Delta G^{\ddagger}$ value to 300 K was performed using the obtained $\Delta S^{\ddagger}$ values for amines **1c**−**f**. For other amines the extrapolation was undertaken using the $\Delta S^{\ddagger}$ values from the literature. [b] At 202 K for the NCD_3 compound. [c] Temperature was not given.

among the nine considered barriers the difference between experimental and AM1-calculated values is more than 40% of the experimental value for two amines and 27−35% for four amines.[5] Therefore, the correlation of the AM1-*calculated* $\Delta H^{\ddagger}$ for the N-inversion in monocyclic amines and the 120 − α(av) parameter (change of averaged CNC angle during inversion) is more indicative of the relationship between the error of the AM1 method and the amine structure than of the real dependence of the N-inversion barrier on the amino group geometry. In fact, no quantitative correlation between *experimental* $\Delta H^{\ddagger}$ values and this angle parameter, which would reveal a real structure−property relationship, exists. Moreover, a recent investigation of the applicability of some semiempirical methods for amines, including cyclic ones, has recommended not to use the AM1 method due to drastic errors which lead in many cases to inadequate results.[20]

The angle-based approach turned out to be unsuccessful also for explaining the difference between $\Delta G^{\ddagger}$ changes in azanorbornanes and those in open chain amines in terms of α(av) or the related 120 − α(av) parameter (which may be considered as describing the flattening of the amino group in the ground state). The difference of α(av) values (MM3 data; see Table 3) is ∼0.1° for the bicyclic *N*-methyl- and *N*-ethylamines **1a** and **1b** and ∼2.6° for the open chain *N*-Me and *N*-Et analogs **9a** and **9b**. These findings do not agree with the general view on an acceleration of the pyramidal inversion process by flattening of the amino group: the essentially unchanged averaged CNC angle for bicyclic amines **1a** and **1b** causes a 4 times larger $\Delta G^{\ddagger}$ change than the greater flattening of the amino fragment for the open chain analogs **9a** and **9b**. Another study[21] of secondary bicyclic amines containing a pyrrolidine ring concluded that the N-inversion barrier is not determined simply by the CNC angle (for similar problems of the angle-based approach see ref 13). Thus, an approach based exclusively on the geometry of the amino fragment is significantly limited.

N-Inversion Barriers: Strain-Based Approach. Steric strain is known as a rate-influencing factor for nitrogen inversion.[2,3] However, the strain-based approach applied to bicyclic amines[13] suffers from serious inaccuracies: (a) The methodology itself (deleting the lone nitrogen electron pair) obviously is very crude for a quantitative modeling of the transition state for nitrogen inversion. (b) The quantitative MMX-based results are not reliable (a "generalized" parametrization for the MMX is essentially less accurate than the careful parametrization for original MM2). Furthermore, the conclusion about the significant role of torsional strain for the height of the nitrogen inversion barriers in bicyclic amines[13] is also nonreliable. It was shown that consideration of individual steric interactions may lead to an incorrect explanation of the observed conformational features.[22,23]

In the following, we develop a qualitative view of the *strain*−nitrogen inversion barrier relationship[3,6,12,13] into a quantitative approach for the description of nitrogen inversion barriers in 7-alkyl-7-azabicyclo[2.2.1]heptanes and other nitrogen-bridged bicycles. Within the limits of this approach the features of the N-inversion process for azanorbornanes mentioned in the previous section turn out to be consequences of the general concept.

It should be noted that the term "steric strain", when used regarding nitrogen inversion,[2,3] relates to the qualitative estimation of an "excess" of intramolecular energy caused by the deviation of structural parameters (e.g., bond lengths or distances

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between nonbonded atoms) from certain optimal "strainless" values. This definition differs from the one accepted in the quantitative thermochemical strain concept[24,25] which uses heats of formation and thermal increments, but is similar to the concept of steric energy in molecular mechanics,[26,27] which has been used as a description of strain.[27−29] The difference between E_{min} for two stereoisomers or conformers may serve as a quantitative measurement of the relative strain for these species.

A new MM3 steric energy-based parameter, namely, the steric energy that includes the energy of substitution-induced disturbances (E_{sid}), is proposed to estimate the steric strain among compounds with the same central atom which differ only in one of the substituents (e.g., among amines **1a**−**f**). The E_{sid} is defined as the difference between the MM3-calculated steric energy of the whole structure and that of the structure consisting of this variable substituent connected to the central atom, to which are attached hydrogens to complete its valence (e.g., E_{sid} of amines **1a**−**f** = E_{min} of amines **1a**−**f** − E_{min} of amines **9a**−**f**). Thus, E_{sid} for each compound includes the MM3 steric energy of the unchanged portion of the structure among the compared species (the bicyclic backbone in the case of compounds **1a**−**f**) and an additional energy related to a distortion involving the variable substituent (e.g., for amines **1a**−**f** the variable substituent is R in Figure 1).

While the E_{sid} parameter itself has no physical sense, the difference between E_{sid} for two compounds (ΔE_{sid}) indicates the strain of one compound in relation to another. This E_{sid}-based approach to compare steric strain is at the very least no less accurate than a comparison based on the thermochemical strain concept. In the first case, structures are compared *via* reliable force field parametrization while in the second case the estimation is performed *via* sometimes problematic, hypothetically strainless structures.

A perfect linear dependence of nitrogen inversion barriers on E_{sid} was found for compounds **1a**−**d,f** (see Figure 2). This dependence may be represented by a linear function,

$$\Delta G^{\ddagger} = -a\Delta E_{sid} + b \qquad (1)$$

where $a = 0.84$ and $b = 51.4$. Therefore,

$$\Delta(\Delta G^{\ddagger}) = -a\Delta E_{sid} \qquad (2a)$$

or, in differential form,

$$\mathrm{d}\Delta G^{\ddagger} = -a\,\mathrm{d}E_{sid} \qquad (2b)$$

In other words, *a decrease of the nitrogen inversion barrier for 7-alkyl-7-azabicyclo[2.2.1]heptanes with β-unbranched N-substituents is proportional to the relative strain in the ground state*. This also means that the transition state energies for these azanorbornanes depend linearly on the relative strain of these amines in the transition state.

Equation 1 permits accurate prediction (∼0.1−0.2 kcal/mol) of barriers for other azanorbornanes with β-unbranched N-substituents using readily calculated E_{sid} values only. Moreover, eq 1 also holds for other tertiary amines. For instance, the E_{sid} *vs* $\Delta G^{\ddagger}$ plot is linear (see Figure 2; $a = 0.19$ and $b = 10.5$) for methyl isopropylamines **11b,c,f** (these compounds were chosen

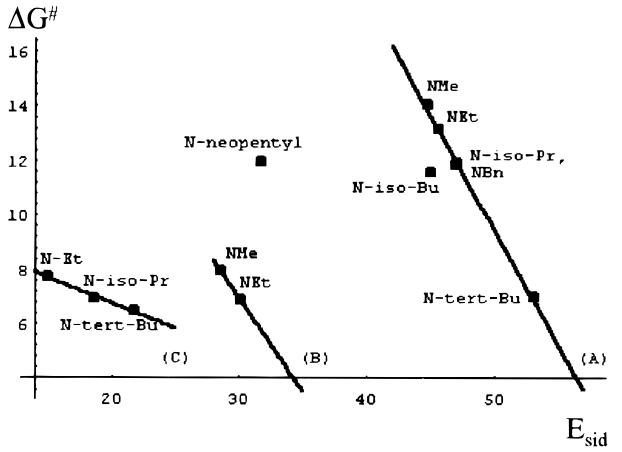

Figure 2. A linear dependence of the height of the N-inversion barriers (at 220 K) on the relative strain for 7-alkyl-7-azabicyclo[2.2.1]heptanes **1a**−**d**,**f** (A: $\Delta G^{\ddagger} = -0.84E_{sid} + 51.4$), 9-alkyl-9-azabicyclo[3.3.1]-nonanes **3a**,**b** (B: $\Delta G^{\ddagger} = -0.69E_{sid} + 27.6$), and alkylmethylisopropylamines **11b**,**c**,**f** (C: $\Delta G^{\ddagger} = -0.19E_{sid} + 10.5$). Points for *N*-isobutylamine **1e** and *N*-neopentylamine **3g** lie outside of lines A and B, respectively.

in order to confine the data to one source[15]). Furthermore, we used the barriers, measured by Nelsen[30,31] for *N*-methyl- and *N*-ethylamines **3a,b**, to attain $\Delta G^{\ddagger}/E_{sid}$ dependence for 9-alkyl-9-azabicyclo[3.3.1]nonanes and found that this plot (B in Figure 2; $a = 0.69$ and $b = 27.6$) is nearly parallel to the plot for azanorbornanes.

In fact, for alkylamines the nitrogen inversion process is a concerted nitrogen inversion−C−N rotation process (NIR).[4,13,32,33] Examples of isolated nitrogen inversion (leading to total eclipsing; see Figure 3) for monocyclic, bicyclic, and open chain amines have so far not been described. When an amine geometry is changed during NIR on going from the ground state to the transition state, the high-energy point of the *rotational* process (*i.e.*, eclipsing of substituents) and the high-energy point of the *inversional* process (*i.e.*, planar nitrogen) may lie on the transformation coordinate of the *concerted* process in several possible ways: (i) the high-energy point for inversion is at the peak of the NIR barrier, and the high-energy point for rotation is below the peak (the transition state of the overall process has a planar amino fragment geometry), (ri) both high-energy points for inversion and rotation are at the peak of the barrier (the transition state possesses a planar nitrogen geometry with eclipsing of one pair of vicinal substituents), and (r) the high-energy point for rotation is at the peak of the common barrier, and the high-energy point for inversion is below (in the transition state one pair of vicinal substituents is eclipsed and the nitrogen pyramid is flattened; Figure 3).

Since the relative strain of transition states of different geometries depends not only on the bulkiness of the N-substituent but also on the transition state geometry, the linearity implied in eq 2a for alkylamines remains valid when the transition states of NIR for these amines have the same geometry. Therefore, the dependence represented by eq 1 is relevant for homologous amines which undergo one type of NIR process, (i), (ri), or (r). The point for the β-branched compound *N*-isobutylamine **1e** deviates from plot A (see Figure 2). Also the point for the other β-branched amine, *N*-neopentyl-9-

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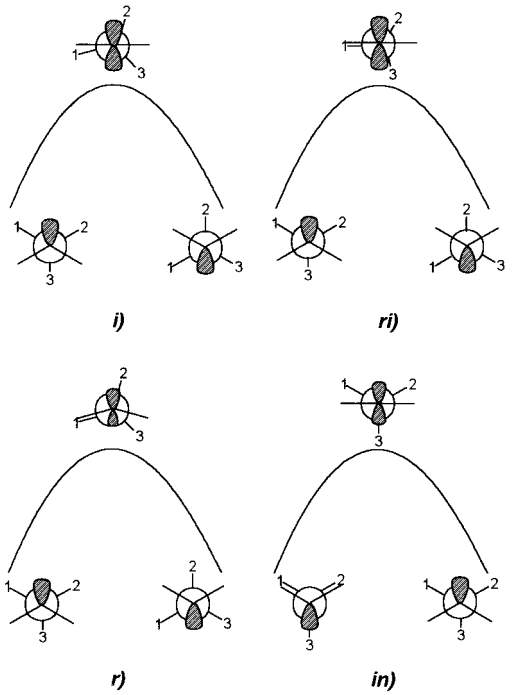

Figure 3. Concomitant nitrogen inversion−rotation and isolated nitrogen inversion. The peaks correspond to (i) the nitrogen inversion transition state (planar amino group), (ri) nitrogen inversion and rotation transition states (planar amino group and two eclipsed vicinal substituents), (r) the rotation transition state (two eclipsed vicinal substituents), or (in) the isolated nitrogen inversion transition state.

azabicyclo[3.3.1]nonane (**3g**) (E_{sid} = 31.6 kcal/mol; the experimental barrier[33] is 12.05 kcal/mol at 263 K), deviates significantly from the corresponding plot B (see Figure 2). The unusually high inversion barrier for amine **3g** was explained[33] by assuming that its transition state belongs to (ri), while NIR for *N*-Me and *N*-Et analogs **3a,b** belongs to (i). Thus, the origin of the deviation of the point for azabicycle **3g** from the azabicyclononane plot becomes clear. However, the deviation for amine **1e** has an opposite direction than the deviation for amine **3g**, and therefore C−N rotation is not expected to be a factor in the deviation.[34]

Nevertheless, in order to compare the geometry of the transition state of the *N*-*i*-Bu compound **1e** and of the other amines **1b**−**d,f**, the barriers of C−N rotation were calculated for *N*-alkylazanorbornanes **1b**−**f** in the inversion ground state (pyramidal nitrogen; see ΔE_{rot} in Table 3), and also the dependence of the high-energy point of rotation on the NIR coordinate was obtained for amines **1c,f** on going from a pyramidal to a planar amino group (see Figure 4). Since for amines **1b,d**−**f** the NIR barrier (for calculations of the NIR barriers using MM3, see below) is higher than the C−N rotation barrier in the ground state, the NIR process for these compounds corresponds to (i). Azabicycloheptane **1f** due to a destabilization of the ground state possesses a unique conformational feature: the barrier of rotation of the *N*-*t*-Bu substituent is the *lowest* barrier among the rotation barriers for the less crowded azanorbornanes **1b,d**−**f**.

For compound **1f** this difference in the height of the rotation and the NIR barriers is 0.4 kcal/mol only (see Table 3) which is not a reliable value (smaller than the calculation accuracy). Nevertheless, the NMR results show that isolated rotation for **1f** (see the Results) is a faster process than NIR, and thus the assignment of the NIR process to (i) for amine **1f** is confirmed. In addition, the dependence of the high-energy point of rotation

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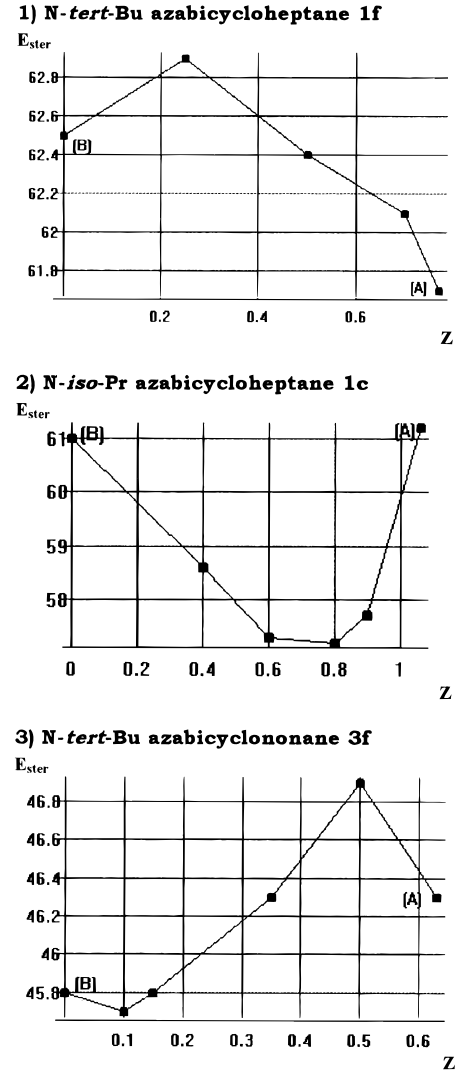

Figure 4. Change of the high-energy point (kcal/mol) of the C−N rotation for amines **1c**,**f** and **3f** during the transformation ground state−transition state (A, ground state; B, transition state; *Z*, coordinate of transformation; E_{ster}, steric energy).

of the *N*-*t*-Bu substituent in **1f** *vs* the inversion coordinate (see Figure 4) demonstrates an increase of the high-energy point values for rotation on the pathway going from pyramidal nitrogen to planar nitrogen. These data support the conclusion that rotation during the NIR process (6-fold rotation in terms of Bushweller[14]) for **1f** occurs in the ground state of N-inversion.

For *N*-*i*-Pr compound **1c** the high-energy points of rotation on the inversional pathway (Figure 4) have their lowest value for an intermediate structure (*e.g.*, rotation for **1c** occurs in this intermediate structure before achieving a planar nitrogen). Thus, the NIR process for compound **1c** also relates to (i).

These results confirm the similarity of the geometry of the transition state for the considered azanorbornanes. Therefore, we explain the deviation of the point for the *N*-*i*-Bu compound **1e** from plot A by the poor MM3-based representation of E_{sid} for this amine relative to the E_{sid} representation for amines **1a**−**d,f**. In molecular mechanics a difference between two values of steric energy (ΔE) should represent a ΔH value. However, many torsional parameters for the MM3 force field (as well as for MM2) were derived on the basis of ΔG data. Since torsional energy is usually the biggest component of the molecular mechanics steric energy, it is possible to consider ΔE values as approximating ΔG. The absolute entropy of the *N*-*i*-Bu azacycle **1e** is obviously larger than for the other analogs **1a**−**d,f**.

Therefore, the deviation of the point for azanorbornane **1e** is caused by the significant error in the $\Delta G^{\ddagger}$ calculation (and thus the E_{sid} calculation) for this amine.

According to the high-energy point dependence (see Figure 4), NIR for the barrier of the *N*-*t*-Bu compound **3f** ($E_{sid} = 37.1$ kcal/mol) relates to (i) and the predicted barrier value for this amine should be 2.0 kcal/mol (the MM3-calculated value of the barrier for this compound is 1.5 kcal/mol; for these calculations see below). For azabicyclononane **3f** this prediction is confirmed qualitatively: the barrier of nitrogen inversion for 9-*tert*-butyl-9-azabicyclo[3.3.1]nonan-3-one is too low to be measured by DNMR.[35] Thus, the values of low N-inversion barriers (not measurable by NMR) are also attainable by the proposed approach.

We prefer not to discuss separate steric interactions, or in other words a certain structural fragment of the molecule, as a strain-determining portion. However, for a crude estimation of the *a* value in eq 1 (*i.e.*, the slope of the plot in Figure 2) for other bicyclic amines, for instance, for 9-alkyl-9-azabicyclo-[3.3.1]nonanes, the steric interactions between the N-substituent and the atoms of the bicyclic backbone should be considered; this is because an increase of the bulk of this substituent correlates with the N-inversion barrier (as shown above). The energy of these through-space interactions for the *N*-Me substituent was calculated as a sum of the MM3 energies of the pairwise interactions between all atoms of the Me substituent and all atoms of the bicyclic backbone for compounds **1a**, **2a**, **3a**, and **4a**. These energies are near 3 kcal/mol for the nitrogen-bridged bicycles **1a**, **2a**, and **3a** and near 2 kcal/mol for the nitrogen−carbon-bridged bicycle **4a**. Therefore, a larger decrease of the N-inversion barrier may be expected for *N*-*t*-Bu azabicycles **1f**, **2f**, and **3f** in relation to *N*-Me analogs **1a**, **2a**, and **3a**, respectively (actually, the $\Delta G^{\ddagger}/E_{sid}$-based plots for compounds **1** and **3** are nearly parallel; see Figure 2), while for *N*-*t*-Bu compound **4f** this barrier change in relation to the *N*-Me compound **4a** should not be as significant.

According to this crude estimation of the *a* value, the coefficient for *N*-alkylnortropanes **2** should be near the *a* values for azanorbornanes **1** and norpseudopelletierines **3**. For 8-alkyl-8-azabicyclo[3.2.1]octanes **2** the *syn* conformation predominates: the MM3-calculated value of ΔH for the *anti*−*syn* transformation, e.g., for *N*-methyl- and *N*-*tert*-butylnortropanes **2a,f**, is 1.2 and 2.1 kcal/mol, respectively (this work); the experimental value for **2a**[36] is 0.9 kcal/mol at 200 K. Therefore, the steric interactions of the N-substituent with the bicyclic skeleton in the ground state of 8-alkyl-8-azabicyclo[3.2.1]-octanes **2** should be approximately the same as the ones for 7-alkyl-7-azabicyclo[2.2.1]heptanes **1** (by necessity *syn*); NIR can be described as a (i) type process, and the substitution of an *N*-alkyl group for another should cause the same changes of steric strain in both cases. In other words, the coefficient *a* (eq 1) should be closer for bicycles **1** and **2** than for bicycles **2** and **3**. Unfortunately, the barrier value in the *N*-alkylnortropane series is known for *N*-Me compound **2a** only (9.17 kcal/mol at 233 K).[36] We believe we can at least roughly estimate $\Delta G^{\ddagger}$ values of N-inversion in *N*-alkylnortropanes by using the *a* value of the azanorbornane series (0.84) for these E_{sid}-based calculations. For *N*-*tert*-butyl-8-azabicyclo[3.2.1]octane (**2f**) (E_{sid} is 42.0 kcal/mol) the predicted barrier of 2.2 kcal/mol is outside the NMR time scale (similarly to the barrier for the *N*-*tert*-butylamine **3f**).

Since steric strain is important for the relative height of the nitrogen inversion barriers among bicycles **1a**−**d,f**, we assume that this energy-derived factor determines the rates of N-inversion for various polycyclic amines. This assumption was checked by MM3 modeling of the transition state geometry for *N*-Me azabicycles **1a-f**, **2a**, **3a**, **4a**, **5a**, **6a**, and **7a** and hydrazine **8a**. The MM3 force field (differing from the MM2 force field) does not include the lone electron pair as a separate structural element, and these electrons are taken into account by parametrization.[15] Therefore, it is possible to use the MM3 force field to create an amino group with three N-substituents located in one plane (for details see the Experimental Section), and if the region of the energy maximum is flattened, it is possible to minimize steric energy at this maximum point. We found in the literature only a single previous example of a similar MM3 study,[37] on azacycloheptane. Obviously, very accurate results cannot be expected since no force field parameters are derived for an sp^2-hybridized nitrogen atom of *amines*.

The minimized steric energies for these azacyclic compounds in the ground state and in the geometry with a planar amino fragment were calculated (the latter is assumed to model the geometry of the transition state for these amines during N-inversion; the restriction-free option was used for minimization of the steric energy for the transition state). The ΔE_{min} values for these amines (for each, $\Delta E_{min} = E_{min}$ of the transition state $- E_{min}$ of the ground state) represent approximately the strain of the transition state relative to the ground state. For **1a**−**8a** the ΔE_{min} values correlate well with the experimental $\Delta G^{\ddagger}$ values[3,5,13,30,31,36,38] for these amines and are in all cases 76−101% of these experimental barriers (see Table 3). Thus, *the relative strain between the transition and ground states of polycyclic tertiary amines is the main factor in determining the rate of nitrogen inversion for these compounds.* A crude but simple prediction of N-inversion barriers for other azacycles of different structure is possible using this general approach: the easily available ΔE_{min} value should be ∼75−100% of the height of the unknown barrier at ambient temperature. For the β-branched compound *N*-isobutylamine **1e**, the calculated barrier practically does not deviate from the experimental value, probably due to a similar error in the entropy increment for both ground and transition states. Interestingly, this approach reproduces well even the inversion barrier of NH_3: 5.5 kcal/mol, to be compared with the experimental value[19] of 5.8 kcal/mol.

For amine **7a** the MM3-based calculations show a 0.7 kcal/mol preference of the *exo*-conformer which differs from the assignment[13] of the NMR-monitored major conformer to the *endo*-compound. Our MM2 results for **7a** led to the same MM2-based estimate (0.1 kcal/mol[13]), but this slight preference refers now to the *exo*-conformer (in ref 13 it was assigned to *endo*-**7a**).

Thus, N-inversion barriers for various tertiary polycyclic amines may be represented *quantitatively* (within 25% accuracy) within the limits of classical (nonorbital) chemical theory. In terms of this simple approach the steric strain obtained from MM3 calculations (ΔE_{min}) is the origin of nitrogen inversion barriers. It may be used also as a universal quantitative criterion for comparison and estimation of these barriers.

The most inaccurate calculated values for N-inversion barriers relate to the azanorbornane system. The absolute deviation of these values from the experimental ones is 3.2 and 3.3 kcal/mol for compounds **1a** and **8a**, and 1.8 and 2.1 kcal/mol for compounds **1c** and **1d**, respectively (for other amines this

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deviation is less than 1.3 kcal/mol; Table 3). While the E_{sid}-based approach explains well N-inversion correlations among azanorbornanes, the approximate ΔE_{min}-based approach, though more accurate than the AM1 semiempirical approach,[5] still displays only moderately enchanced N-inversion barriers for bicycles **1a**−**d** and **8a** compared to the barriers in monocyclic amines.

According to an accepted view,[39,40] a phenomenon may be assigned to a conformational effect if it cannot be explained by molecular mechanics calculations. Effects related to the N-inversion rate are considered as conformational effects too.[39] Thus, our data support (differing from the less accurate concept[13]) the quantum chemical approach[5] to the bicyclic effect, which is estimated now to represent a ∼25% contribution to the experimental barrier.

Except for less accurate semiempirical[5,19] or laborious *ab initio*[2] (see discussion in refs 5 and 19 and references therein) quantum chemical approaches, no methods for estimation of nitrogen inversion barriers were known earlier. Also no successful N-inversion barrier−structure relationship was previously found for different cyclic amines (see discussion above and ref 5). We conclude that strain (in terms of the molecular mechanics steric energy) is a good parameter for description of this relationship.

Conclusions

Estimation or comparison of the nitrogen inversion barriers for tertiary amines using CNC angle geometry is not always reliable. A linear dependence of the values of N-inversion barriers on the relative strain (in terms of the MM3 steric energy) of 7-alkyl-7-azabicyclo[2.2.1]heptanes in the ground state shows that this strain value is a good parameter for the accurate prediction of N-inversion barriers for bicyclic amines. The fact that the strain (as determined by MM3) is more than 75% of the experimental value of the inversion barrier for the corresponding polycyclic amine demonstrates the possibility of classical (nonorbital) representation of the values of nitrogen inversion barriers at least for tertiary azapolycycles of various structures.

Experimental Section

Amines **1c**−**f** were obtained according to a reported procedure.[41] All ^{1}H and ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer. ^{13}C NMR measurements were performed for compounds **1c**−**f** at 4−5 different temperatures. TMS was used as the internal standard. Samples of 20−50 mg in 0.5 mL of CD_2Cl_2 were equilibrated for ∼10 min at each temperature before each NMR experiment. Temperatures were measured with a calibrated Eurotherm 840/T digital thermometer and are believed to be accurate to 0.5 K. For the complete line shape analysis a modified version of a program written by R. E. D. McClung, University of Alberta, Edmonton, Canada T6J2G2, was used with visual fitting. Resonance frequencies, corrected line widths, rate constants, and amplitudes were adjusted to achieve the best fit of simulated to experimental spectra. The activation parameters were calculated using the Eyring equation. The 1994 version of the MM3 program[15] was used for molecular mechanics calculations (using the option of full matrix minimization for the transition state). Modeling of amine structures with a planar amino group was achieved by the following algorithm: orientation of the molecule to place the N-atom and two cyclic C_α-atoms in the *xy*-plane; change of the *z*-coordinate of the third C_α-atom to zero and block diagonal minimization of this structure with restricted motion along the *z*-coordinate for the N-atom and three C_α-atoms; full matrix minimization. Intermediate structures were designed in a similar way with a fixed value of the *z*-coordinate for the C_α-atoms of the N-substituent, and the geometry optimization was performed by the block diagonal minimization option. For the calculation of the rotation barrier in the ground state the Driver option was used (1° rotation step; NDRIVE = −1). For the calculation of rotation barriers for intermediate structures and the transition state the following algorithm was used: crude search of the range of the barrier maximum for intermediate structures by the Driver option (1° rotation step; NDRIVE = −2); minimization for all structures in this range using block diagonal minimization with restriction of motion of the N-atom and the C_α- and C_β-atoms of the N-substituent (motion is restricted in selected directions to fix the ordered geometry of the amino fragment).

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