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Conformational Dynamics in Nitrogen-Fused Azabicycles

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Using molecular mechanics (MM3 force field)-based methodology, conformational dynamics have been studied for 1-azabicyclo[2.2.0]hexane, 1-azabicylo[3.3.0]octane, and 1-azabicylo[4.4.0]decane. Obtained conformational schemes describe the flexibity of these parent azabicyles as well as permit us to estimate conformational mobility in related N-fused systems. Quantum mechanics ab initio calculations have been used in order to check the reliability of molecular mechanics-provided estimates of relative energy of conformers. The previous dynamic NMR (DNMR) data have been reinterpreted for some polycyclic alkaloids.

Introduction

Concerning conformational dynamics of organic molecules, 4- to 6-membered monocycles are the most thoroughly studied systems excluding substituted ethanes. Indeed, rates of conformational transformations have been measured for quite different cyclic compounds varying systematically the number and position of ring substituents.[1a−f] Theoretical studies, in the first instance for six-membered cycles, provided detailed information for itineraries of conformational transformations, geometry and energy of the corresponding transition states.[2a−d] A full conformational scheme for, e.g., cyclohexane is included in stereochemistry books.[1a,3a,b] Conformational dynamics in piperidines is significantly more complex due to the presence of additional dynamic processes. Nevertheless, full conformational schemes for different alkylpiperidines[4a−c] as well as *N*-Me azetidine and *N*-Me pyrrolidine,[4a] which are in good agreement with experimental DNMR data, have been reported.

The intramolecular dynamics-related knowledge is significantly poorer for bi- or polycyclic aza-analogues of similar ring size in which two or more rings are fused. Only a few experimental barriers of conformational transformations were measured for these compounds by DNMR.[5a−i] Sometimes nonrigid systems, e.g., α-isosparteine (**1a**) or marcfortine A (**1c**; see Figure 1), are erroneously considered as rigid ones[5a,6a] because of experimental detection of one conformer in these quinolizidine derivatives. Remarkably, sparteine (**1b**), a stereoisomer of **1a**, has been correctly related[6a] to flexible compounds.[7]

Intramolecular motions were analyzed theoretically for condensed bicyclic systems that undergo only ring inver-

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(7) Our ab initio calculations at the MP2/6-31G* level provide Δ*E* differences of 5.8 and 3.4 kcal/mol (gas phase) for the pairs of the two lowest energy conformers for **1a** and **1b**, respectively (this work; a 3.6 kcal/mol value has been obtained[9] for the pair of these conformers for isomer **1b** using the B3P86/6−311 + G* level). The above Δ*E* data explain experimental detection[6] of the strong predominance of one conformer for tetracycles **1a** and **1b** in aprotic solvents. In addition, these Δ*E* values as well as the presence of several other conformers of higher energy for **1a** and **1b** (located by MM2*-assisted conformational search; this work; see also ref 9 for the case of **1b**) show that there is no principal difference in conformational flexibility of these stereoisomers. Compound **1a** may be considered as less flexible than compound **1b** but cannot be characterized as a rigid one (for quantitative approaches to molecular flexibility see Koča, J.; Carlsen, P. H. J. *THEOCHEM* **1992**, *257*, 105−130 and Arteca, G. A. *J. Comput. Chem.* **1993**, *14*, 718−727).

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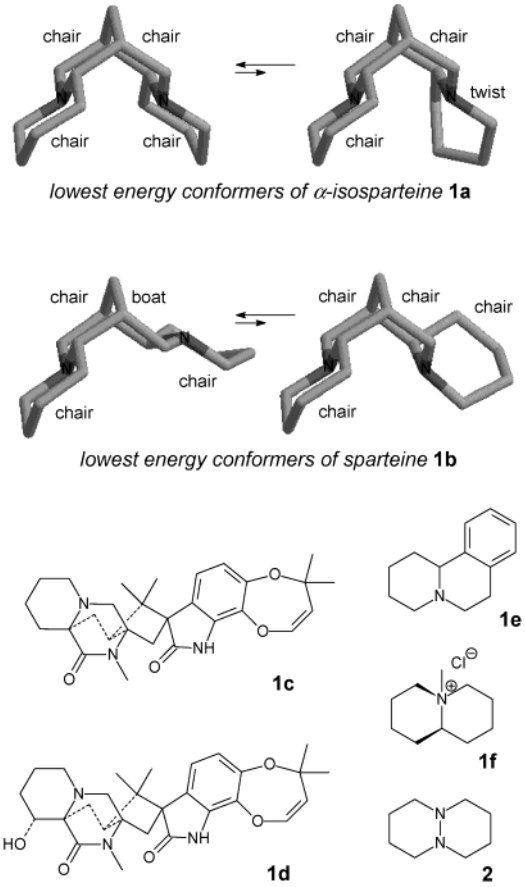

FIGURE 1. N-Fused polycycles **1a**−**f** and **2** and the lowest energy conformers for compounds **1a**,**b** (MP2/6-31G*-optimized geometries are shown for these conformers; hydrogen atoms are omitted for clarity). Conformations of piperidine rings (structural components of tetracycles **1a**,**b**) are indicated.

sion (RI).[8a−c] However, there is no close analogy between intramolecular dynamic processes in related carbo- and azabicycles since the latter compounds contain an inverting nitrogen pyramid additionally to two or more inverting rings. On the other hand, conformational dynamics in azamonocycles[4a−c] and in bi- or polycyclic analogues is not the same owing to additional restrictions of conformational mobility in fused systems.

A single example of the modeling of conformational dynamics in polycyclic amines, a quantum mechanical ab initio study of cis−trans interconversion in bis-quinolizidine **1b**[9] actually does not reflect the dynamics of the same conformational transformation in parent quinolizidine **5**. One piperidine cycle [that undergoes a concerted ring inversion−nitrogen inversion (RINI) during this interconversion] of the lowest energy conformer of tetracycle **1b** adopts a boat conformation,[6a,b] while a chair form is the conformation of the both piperidine rings in each of the two minimal energy conformers of bicycle **5** (see Figure 2).[10a−c] Therefore, the geometry of the inverting two-ring fragment in the transition states and

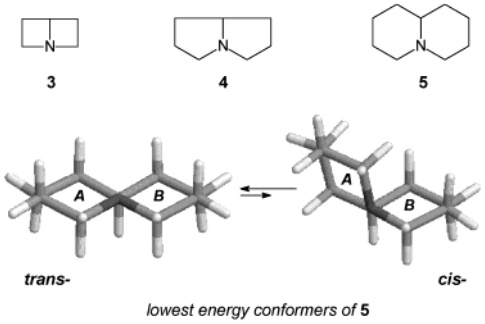

FIGURE 2. N-Fused bicycles **3**−**5** and the lowest energy conformers for quinolizidine **5** (MP2/6-31G*-optimized geometries are shown for these conformers). During cis ⇌ trans interconversion in **5** ring ***A*** is inverted (a chair−chair ring inversion) and the configuration of the nitrogen atom is also reversed. Isolated nitrogen inversion does not take place in bicycle **5** because of geometry restrictions.

thus the rate for the cis−trans interconversion should be different in bis-quinolizidine **1b** and mono-quinolizidine **5**.

Furthermore, because of the absence of the data for relative energies for these transition states it is difficult to assign NMR-measured barriers to a certain type of intramolecular motion for the systems that possess two or more of the motions in a system [e.g., RI, RINI or a concerted nitrogen inversion−rotation (NIR) for azamonocycles; for the discussion of assignment problems see refs 4a,b]. For instance, several assumptions are necessary to assign the experimental barrier of the NMR-detected conformational change in bicyclic hydrazine **2** (Figure 1) to RINI.[5b] The assignment of the NMR-measured barrier in other systems, hydroxylated marcfortine A **1d**[5a] or benzoquinolizidine **1e**[5e] to nitrogen inversion (NI) is incorrect since isolated NI in quinolizidines does not lead to stable conformations (bis-chair, chair/twist or bis-twist) and therefore does not take place in these N-fused systems. The cis−trans interconversion in quinolizidine azacycles (see Figure 2) obviously requires two formal intermolecular motions, NI and RI. Thus, the assignment problem for the barrier in, e.g., quinolizidine **1d** or **1e**, should be considered as the question whether RINI or RI is the rate-determining step in the lowest energy conformational pathway between the lowest energy conformers (cis and trans conformers of **1d**[5a]). In addition, the barrier value for **1e**[5e] is problematic in the light of the criticism[4c,g] of the validity of the kinetic protonation method used.

The present study is intended to describe conformational dynamics in the simplest N-fused azabicycles **3**−**5** (Figure 2). These tertiary amines represent an unusual case of azabicycles: NI is necessarily coupled with RI, i.e., no isolated NI takes place (see, e.g., the quinolizidine case above). Conformational schemes for monocyclic azacycles[4a−c] turned out to be convenient for a simple description of conformational dynamics for compounds possessing different intramolecular motions as well as usable as an effective tool for the assignment of NMR-

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measured barriers of conformational transformations. Therefore, we employ this approach for amines **3**−**5** possessing identical monocyclic fragments of bicyclic backbone as well as amine **6** possessing different fragments.

Results and Discussion

A successful MM3 force field[11a−c] methodology (proposed by Aped[4a−d]), which leads to conformational schemes of relatively simple organic compounds without preliminary assumptions for the number, geometry, and relative energy of their stable conformers and conformational transition states as well as types of intramolecular dynamic processes, was employed in the present study of azabicycles **3**−**5**. Full conformational schemes (Figures 3−5) were built by the MM3-assisted stochastic conformational search (for details see the Experimental Section), which finds stationary points. Some of them correspond to energy minima (stable conformers) and others correspond to energy maxima (transition states; they are distinguished from the stable conformers by means of the normal mode vibrational analysis, an MM3 package utility). The geometry and relative energy of these conformations are provided by the full matrix procedure of energy minimization. Formal relationships between the transition states and corresponding stable conformers were established by geometry optimization for intermediate structures which lie between the transition state and the corresponding stable conformers. These structures are obtained by the Vibplot program (a MM3 package component) using the eigenvectors for the transition states. Since quantitative conformational analysis by molecular mechanics is problematic for bicycle **3** (see below), quantum mechanical ab initio calculations were also performed for this compound.

1-Azabicyclo[2.2.0]hexane (3). Azetidines are not a suitable subject for a reliable molecular mechanics-based study owing to the absence of an explicit parametrization for these four-membered cycles in various force fields, which should be also compatible with the parametrization for other structural units.[11d] This includes a version of the MM3 force field with parameters developed for amines,[11b] which is usually capable of an accurate conformational analysis of monoamines (in particular, cyclic amines[4f]) with no neighboring functional groups. Nevertheless, a MM3-supported description of conformational dynamics of N-Me azetidine satisfactorily corresponds to experimental data.[4a] On the basis of these results, we have used MM3 in theoretical study of "bis-azetidine" **3** in order to identify stable conformations and the corresponding conformational transition states. On the other hand, due to a serious doubt in the ability of MM3 force field to estimate reasonably the steric energy of azetidine structures, the relative stability of MM3-derived conformations of amine **3** was determined by ab initio calculations, minimizing their energy at the MP2/6-31G* level. We demonstrated recently that this calculation level, while not particularly economical in computer time, is quite successful for a good quantitative estimation of conformational equilibria in cyclic compounds as well as an estimation of NIR barriers in azacycles.[4f,g]

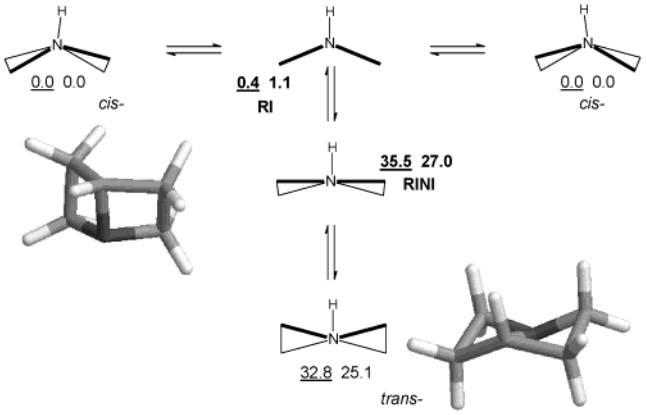

FIGURE 3. Conformational scheme for azabicycle **3**. Energies (kcal/mol; underlined: ΔE values; not underlined: ΔE_S values) are relative to the lowest energy conformer. The names and relative energies for the transition states are in bold. Optimized geometries (by MM3) are shown for the cis and trans conformers.

As our molecular mechanics calculations show, only two conformations, one with a cis junction of the envelope-shaped azetidine rings and the other with a trans junction, are stable for this compound (see Figure 3). MM3 predicts a drastic predominance of the cis form over the trans form: the difference in steric energy (ΔE_S; relatively the lowest energy conformer) is 25.1 kcal/mol. Ab initio calculations strongly support this qualitative estimate: the difference of electron energy (ΔE) between the cis and trans structures is 32.8 kcal/mol. Since these forms are separated by an extremely high RINI barrier (35.5 kcal/mol according to the ab initio calculations), they may be treated as stereoisomers. In contrast, RI, which occurs simultaneously for both cis-fused azetidine cycles, is characterized by a very low barrier which lies in the energy range of vibrational transitions. Therefore the *cis*-form should be considered actually as a system with a large amplitude internal motion,[12] i.e., as a double minimum oscillator.

1-Azabicyclo[3.3.0]octane (4). Three stable cis conformers ***A***−***C*** (see Figure 4) as well as trans conformer ***D*** are near in energy (within a 0.4 kcal/mol limit for ΔE_S in the case of the cis conformers[13] and the ΔE_S value of 2.6 kcal/mol in the case of the trans conformer). A predominance of the cis conformers in **4** over the trans one is in agreement with the experimental conformational analysis of various unhindered pyrrolizidines.[14a−c]

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(13) A *small* difference in ΔE_S for these cis conformers does not reflect their real relative stability. Therefore we do not indicate conformer ***A*** with calculated ΔE_S of 0.0 kcal/mol as the lowest energy conformer of **4**.

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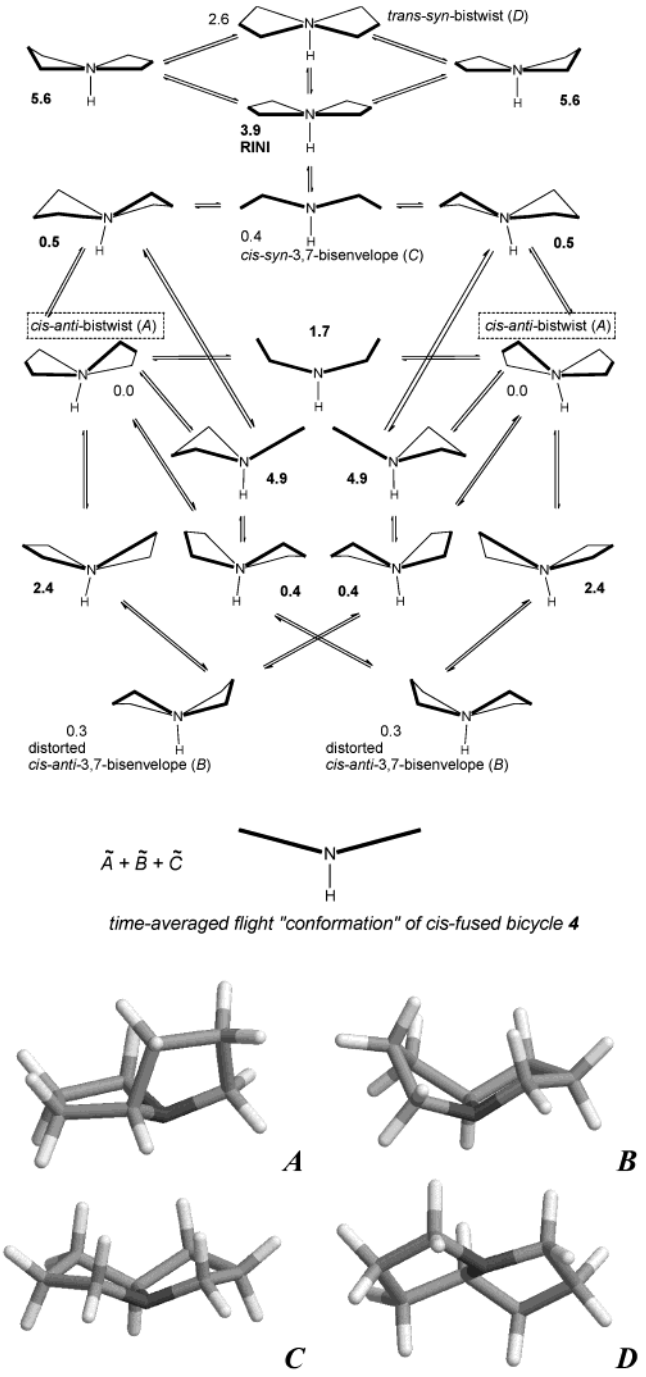

FIGURE 4. Conformational scheme for pyrrolizidine **4**. Energies (kcal/mol; in bold for transition states) are relative to the lowest energy conformers (in dotted rectangles). Transition states belong to RI and only one transition state belongs to RINI (depicted by symbol **RINI**). Optimized geometries (by MM3) are shown for stable conformers ***A***−***D***.

The barriers in the lowest energy conformational itineraries, which connect all the cis conformers in the conformational scheme, do not exceed 2.4 kcal/mol. Thus, the cis-fused cycle of **4** may be treated as a three-minimum oscillator. The lowest RINI barrier for the cis−trans interconversion is higher than the low energy transitions among the population of cis conformers ***A***−***C***. Hence, it is possible to characterize the conformational dynamics in **4** as a two-position conformational exchange between a time-averaged "flight"-shaped virtual cis form (Figure 4) of lower energy and a more rigid trans form of higher energy.

We have used the same MM3 methodology for analysis of conformational dynamics of *N*-Me pyrrolidine.[4a] The calculated lowest barrier of the ring substituent topomerization in this compound is 5.3 kcal/mol.[4a] The highest value for the barriers in the lowest energy conformational pathways, which connect all the conformations of **4**, is 3.9 kcal/mol (for the RINI transition state). Thus, bicyclic system **4** turns out to be more flexible than the monocyclic analogue.

1-Azabicyclo[4.4.0]decane (5). The lowest energy trans-bis-chair conformer (see Figures 2 and 5) totally predominates over the other conformers. In terms of steric energy, the second in energy cis-bis-chair conformer is less stable by 3.4 kcal/mol. Ab initio-based calculations at the MP2/6-31G* level provide a ΔE of 4.1 kcal/mol for these conformers. These concordant data obtained here by independent calculation methods support the NMR-established preference[10a−c] for the trans conformer of **5** and presume the impossibility of the detection of the cis conformer by DNMR. Other conformers, cis- or trans-bicycles of a chair-twist or bis-twist geometry, possess significantly higher energy.

Since the trans-bis-chair form of **5** possesses a symmetry plane, conformational dynamics of this bicyclic amine may be represented as a half-scheme (Figure 5). It shows a formal relationship between conformations $A_1...A_n$ which result from spatial reorganization of ring ***A*** alone of the symmetrical trans-bis-chair as well as from further transformations of ring ***B*** in resulted conformations. Similar ring ***B***-related transformations of the trans-bis-chair lead to an equal set of enantiomeric conformations $B_1...B_n$ (the corresponding half-scheme of the same structure is not shown). These half-schemes, when connected by three conformations possessing a symmetry plane (trans-bis-chair, 4-sofa/7-sofa and 2,5-boat/7,10-boat in Figure 5), form an entire conformational scheme for quinolizidine **5**.

Remarkably (see also the Introduction), the conformational dynamics for bicycle **5** differ from those for monocyclic piperidines[4a−c] and *cis*-decalin[8a] (**5a**) as well. For instance, while the interconversion cis-bis-chair ⇌ cis-bis-chair in carbocyclic analogue **5a** proceeds with participation of high energy bis-twist conformers,[8a] a similar interconversion of cis-bis-chairs A_1 and B_1 in azacycle **5** occurs involving lower energy conformers with only one ring in a twist conformation (see Figure 5 for different chair-twist conformers in conformational itinerary j). In comparison with monocycles, we note that continuous ring pseudorotation, an attribute of conformational dynamics in cyclohexane[1a,3a−c] or piperidines,[4a−c] is not relevant for bicycle **5**. For six-membered rings, an entire pseudorotation cycle is a conformational pathway that provides interconversion of all twist conformers via transitions states of boat geometry and does not include chair, half-chair, or sofa forms. In **5**, only one step in the pseudorotation cycle takes place: a stable conformation containing at least one six-membered ring in a twist form is converted through the corresponding boat transition state into another twist conformer and then pseudorotation is interrupted by RI via transition states with a sofa or half-chair geometry of one of the rings.

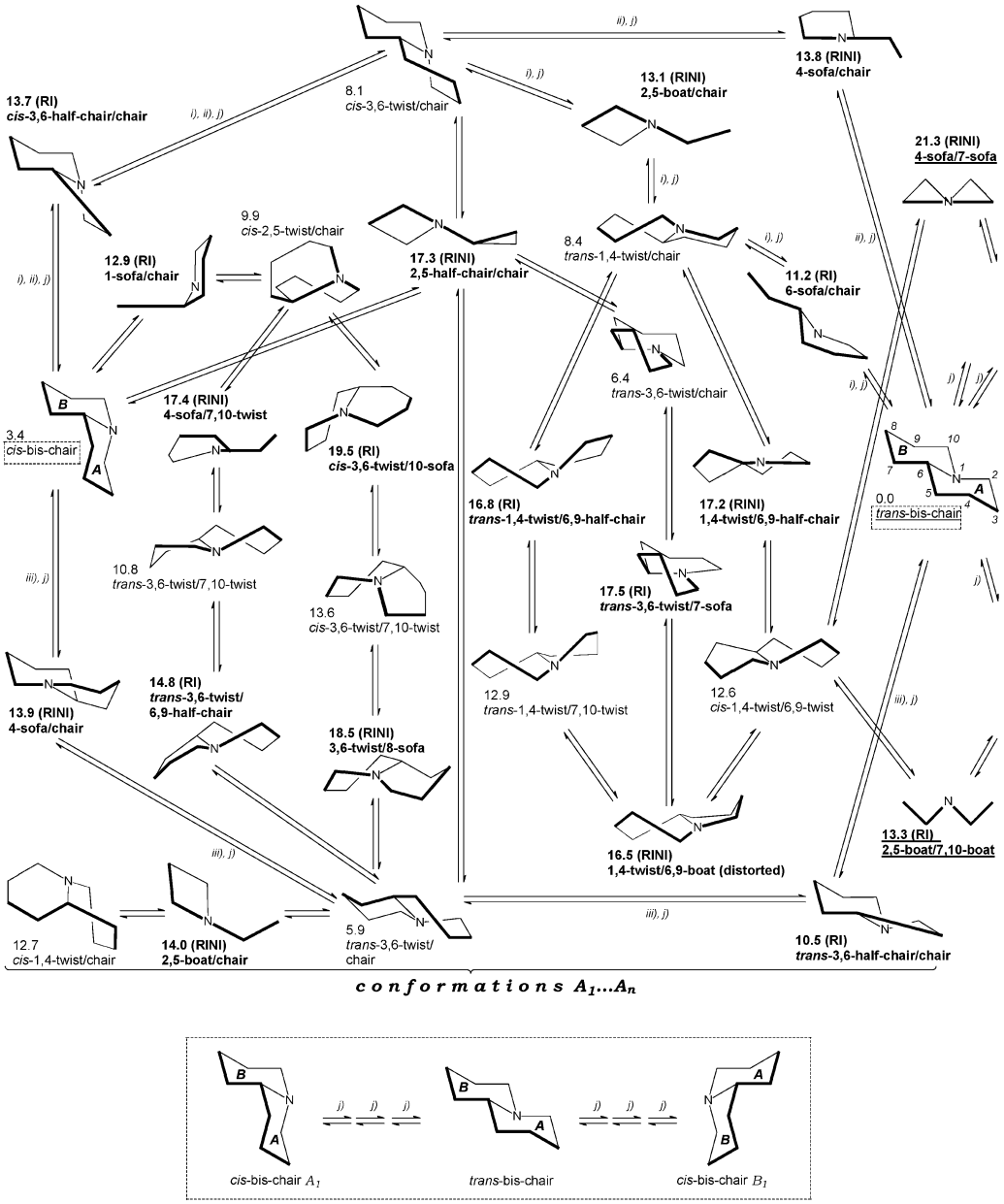

FIGURE 5. Conformational scheme for azabicycle **5** (as a half-scheme; equivalent piperidine rings are marked by formal labels ***A*** and ***B***). Energies (kcal/mol) are relative to the lowest energy conformer. The names and relative energies for the transition states are in bold. Stable conformers with relative energy higher than 15 kcal/mol as well as transition states with relative energy higher than 22 kcal/mol are not shown for clarity. We present only conformations $A_1...A_n$ with no symmetry elements, which are derived by transformations of ring ***A*** of the lowest energy conformer for **5** (trans-bis-chair) as well as derived from these conformers by transformations of ring ***B***. Enantiomeric conformations $B_1...B_n$, which formally relate to the equal transformations of ring ***B*** of the lowest energy conformer of **5**, form structurally the same conformational scheme (not shown). Symmetry plane-possessing conformations (their names are underlined), through which conformational transitions between $A_1...A_n$ and $B_1...B_n$ occur, are grouped in a column on the right side of the scheme. A pair of enantiomeric conformers A_i and B_i is shown for the example of cis-bis-chairs A_1 and B_1 (in the dotted rectangle). The lowest energy conformational itineraries between the two lowest energy conformers, i.e., between trans and cis-bis-chairs (their names are depicted in the scheme by dotted rectangles), as well as between cis-bis-chairs A_1 and B_1 are marked by symbols i−iii and j, respectively.

Furthermore, for quinolizidine **5** the lowest ΔE_S value for conformational barriers is 10.5 kcal/mol (trans-3,6-half-chair/chair) while other barriers are higher than 12.9 kcal/mol. This bicyclic amine may be considered therefore as less flexible than piperidines. Indeed, our MM3 results demonstrate[4a] that the all barriers for *N*-Me piperidine are lower than 12.6 kcal/mol.

Three transitions states correspond to the high energy points in three conformational itineraries of lowest energy connecting the trans-bis-chair and the cis-bis-chair of **5**: 4-sofa/chair, cis-3,6-half-chair/chair, and the other 4-sofa/chair of **5** with the ΔE_S values of 13.8, 13.7, and 13.9 kcal/mol, respectively (see Figure 5 for itineraries i−iii). Despite the finding that MM3 provides a good and sometimes excellent correspondence between calculated and experimental barriers for conformational transformations,[4a−c] the accuracy of our calculations is insufficient to choose the lowest barrier among the above-

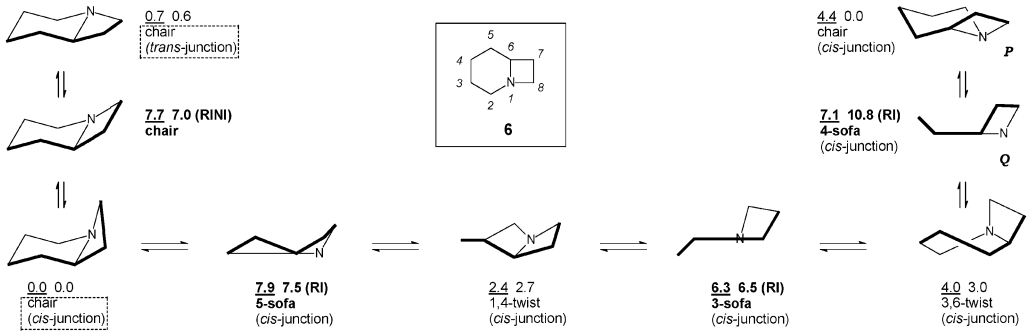

FIGURE 6. Lowest energy conformational pathway for interconversion of the lowest energy conformers of azabicycle **6**. Energies (kcal/mol; underlined: ΔE values; not underlined: ΔE_S values) are relative to the lowest energy conformer. Conformations of the six-membered ring only are indicated. The names of the two lowest energy conformers are depicted by dotted rectangles, the names and relative energies for the transition states are in bold. Symbols ***P*** and ***Q*** depict conformations with appreciably different relative stability by MM3 vs ab initio calculations.

mentioned three highest ones in conformational pathways i−iii. Nevertheless, this accuracy is quite sufficient to conclude that the corresponding transition states are obviously very close in energy. It means that, from a kinetics viewpoint, these itineraries are approximately equivalent. Thus, both RI (see conformational pathways i and ii) and RINI (see conformational pathways i, ii, and iii) are intramolecular processes which determine the rate for the cis−trans interconversion in quinolizidine **5**. As expected, the calculated value of the barrier for **5**, 13.7−13.9 kcal/mol, differs significantly from the ab initio-derived value for the cis−trans interconversion in bisquinolizidine **1b** (6.8 kcal/mol;[9] see the Introduction for the explanation). Obviously, the same value (13.7−13.9 kcal/mol) determines the rate of cis-bis-chair−cis-bis-chair interconversion in azabicycle **5** since pathway j for this conformational transformation is actually a doubled pathway i or ii or iii (see Figure 5). Unfortunately, the measured barrier of 13.7 kcal/mol (by DNMR)[5d] for cis-bis-chair−cis-bis-chair interconversion in quaternary salt **1f** of a cis configuration cannot serve an estimate of the accuracy of our calculations. The similarity of the barrier values (the calculated herein for **5** and the experimental[5d] for **1f**) of an equivalent cis-bis-chair−cis-bis-chair flip in bicycles **5** and **1f** should be considered as coincidental. While the cis-bis-chair−cis-bis-chair interconversion in **5** necessarily includes RINI (see the Introduction as well as Figure 5), the conformational pathway for this transformation in **1f**, a compound possessing a not-inverting nitrogen center,[15] should be similar to that in *cis*-decalin.[16]

Our theoretical analysis of conformational behavior of saturated azamonocycles[4a−c,f,g] led to a revision of some earlier conclusions for these systems which are based mostly on interpretation of NMR data. In addition, comparison of full conformational schemes for several methyl piperidines showed that conformational dynamics in crowded piperidines differs from that in the parent *N*-Me piperidine in details (different lowest energy conformational pathways, additional conformational itineraries of higher energy), but the general structure of these schemes is similar (ring inversion with participation of certain transition states and twist conformers interconversion of which forms a separate pseudorotation cycle). Consequently, the full conformational schemes for unsubstituted azabicycles **3**−**5** give a general representation of conformational dynamics in N-fused systems constructed from 4- to 6-membered rings. [2.2.0]-Systems are very flexible cis bicycles with a locked cis−trans "switch", [3.3.0]-systems are flexible bicycles with a rapid "switch" between the cis and trans junction, and [4.4.0]-systems are significantly less flexible bicycles with a relatively slow cis−trans "switch". We are aware of the limitations of these general statements: conformational dynamics may quite differ for, e.g., crowded or functionalized azabicycles. Nevertheless, the present description of conformational mobility for the N-fused systems we considered is of value in analyzing intramolecular motions in close analogues. For instance, it is sufficient to indicate a need to reexamine a few azapolycycles (see below).

(A) A brief consideration of the NMR spectra of azabicycle **6** led to the conclusion[17] that the piperidine ring of **6** (Figure 6) adopts a chair conformation with cis-positioned ring substituents, namely an axial N-substituent and an equatorial C-substituent. This single conformation, as the authors claimed,[17] is rigid and neither RI nor N inversion occur in this bicyclic amine.

Such a rigidity of azabicycle **6** is scarcely possible. As our calculations show, more strained analogue **3** is

(15) The variable-temperature ^{13}C NMR spectra of quinolizidinium chloride **1f** in CD_3OD show that there are six resonance signals at high temperatures (fast conformational dynamics) and eight sharp signals at 253 K (slow conformational dynamics).[5d] The number of the signals at high temperatures corresponds to structure **1f** as a time-averaged structure with chemically equivalent piperidine rings. However, when RI of bicycle **1f** is frozen these rings become nonequivalent. Then, 10 resonance signals of 10 spatially nonequivalent ^{13}C nuclei should be in principle observable in the spectra. However, in accordance with experimental results,[5d] ab initio calculations of ^{13}C chemical shifts at the MP2/6-31-G* level for the geometry of cation of **1f** optimized at the same level of theory show that there are two different pairs of two chemically nonequivalent carbon atoms (C-3/C-9 and C-5/C-7) with a close resonance frequency for C-3 and C-9 (29.7 and 30.1 ppm; calculated for gas phase) as well as for C-7 and C-9 (33.8 and 34.4 ppm; calculated for gas phase) in the noninverting backbone of **1f**.

(16) Steric interactions with the bridgehead-attached Me substituent of compound **1f** scarcely influence on the barrier of cis-bis-chair−cis-bis-chair interconversion in this bicycle. For instance, experimental values for this conformational transformation in *cis*-decalin and 9-methyl-*cis*-decalin are equal (12.6 kcal/mol; by DNMR): Dalling, D. K.; Grant, D. M.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 3678−3682. For a theoretical description of conformational dynamics in *cis*-decalin, see ref 8a.

(17) Mühlbach, K.; Schulz, R. C. *Macromol. Chem.* **1988**, *189*, 1267−1277.

capable to undergo fast RI. To confirm this speculation on the flexibility of the backbone of **6**, we employed the MM3-based methodology (see above) for analysis of its conformational dynamics. Also, ab initio calculations at the MP2/6-31G* level were used as a test of the MM3 applicability to this azetidine derivative. Indeed, we found that (a) there are two conformers of near energy and (b) these conformers interconvert rapidly in the NMR time scale. Besides, as in the case of fused azetidine **3**, MM3 turned out to be unreliable for quantitative conformational analysis of azetidine-containing homologue **6**. For instance, the relative stability of some stationary point conformations of **6** (conformations ***P*** and ***Q***) is significantly different by molecular mechanics and ab initio calculations (see Figure 6).

(a) A *cis*-junction of the rings is present in the lowest energy conformer. The second in energy conformer is a chair with a trans configuration of the ring substituents (Figure 6). The ΔE difference for these conformers is only 0.7 kcal/mol (0.6 kcal/mol as the ΔE_S value). (b) According to ab initio calculations, the barrier of RINI is only 7.7 kcal/mol (7.0 kcal/mol by MM3). Thus, room-temperature NMR spectra of **6** represent only time-averaged "virtual" geometry of this bicycle resulted from a fast RINI. In addition, the barriers of RI are relatively low in the lowest energy itinerary which provides interconversion of other low energy conformers. The highest barrier belongs to the RI transition state with the piperidine cycle in a 5-sofa conformation and is 7.9 kcal mol.

Therefore, the interpretation of NMR data as well as the conformational analysis/dynamics-related conclusions[17] (see above) are incorrect. Bicycle **6** is flexible. Actually two lowest energy conformers (one with a cis-substituted piperidine chair and one with a trans-substituted piperidine chair) determine the conformational equilibrium for this azabicycle. Furthermore, since a low barrier RINI takes place for this amine, the maintenance of the presence of two chiral centers in **6** (N-1 and C-6) and related reasoning[17] have no basis. This compound obviously possesses only one asymmetry center (C-6) as every 1,2-disubstituted piperidine bearing achiral substituents.

(B) The conformational dynamics of two quinolizidine derivatives, the *Corynanthe* alkaloids dihydrocorynantheine (**7a**) and corynantheine (**7b**; Figure 7), has been recently studied by DNMR and computational methods.[18] For each, ^{1}H NMR signal dichotomy was detected, experimental barriers of the corresponding intramolecular dynamic process (14.6 kcal/mol for **7a** and 12.6 kcal/mol for **7b**; calculated here for 300 K using the obtained values[18] of activation enthalpy and entropy) were assigned to rotation of the 15-substituent since (1) rotamers which correspond to the energy minima for the rotation of the 15-substituent are the lowest energy conformers of **7a** and (2) calculated rotation barriers for **7a** and **7b** are higher than calculated barriers for cis−trans interconversion in these quinolizidine derivatives and are near the measured values. It is important to note that these conclusions resulted mostly from calculations using the Amber* force field (a slightly modified version of Amber).

(18) Staerk, D.; Norrby, P.-O.; Jaroszewski, J. W. *J. Org. Chem.* **2001**, *66*, 2217−2221.

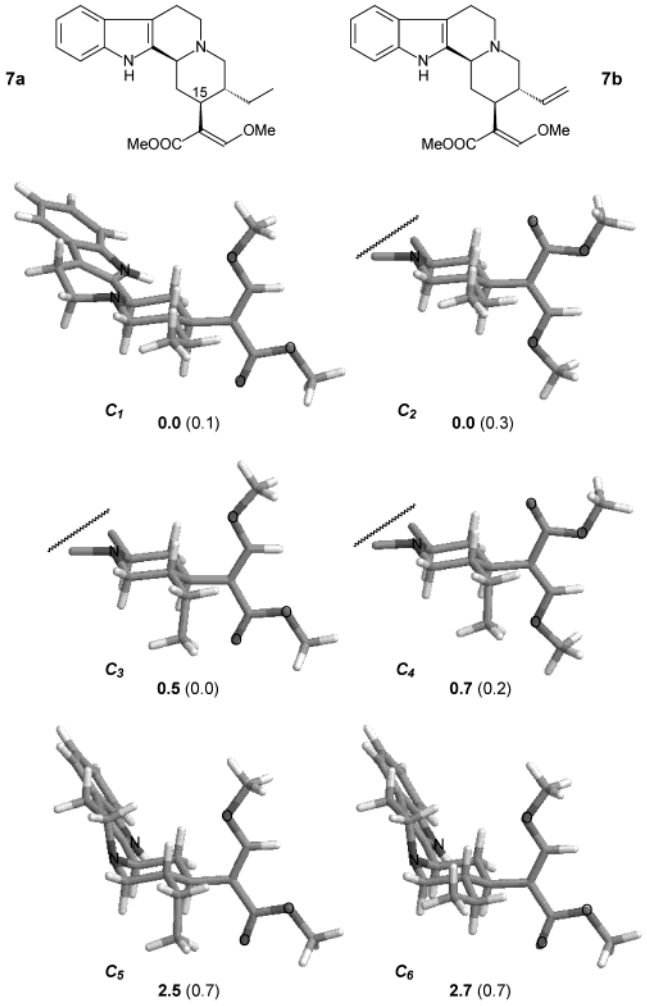

FIGURE 7. Alkaloids **7a** and **7b** and the lowest energy conformers among the trans and cis families of conformers of quinolizidine **7a** (C_1−C_4 and C_5−C_6, respectively). Only substituted piperidine fragment is shown for trans conformers C_2−C_4. Energies (below the structures; kcal/mol; in bold for ΔE by B3LYP/6-31G*-assisted calculations and in parentheses for ΔE_S by Amber*-assisted calculations) are relative to the lowest energy conformer.

However, Amber* force field-based conclusions are quite unreliable for functionalized azacycles **7a**,**b**. (a) According to our examination, the Amber* parametrization is not an accurate tool for conformational analysis of these alkaloids. For instance, the same Amber* version (see the Experimental Section) that was employed in ref 18, uses 6, 13, and 54 medium quality and 2, 4, and 0 low quality stretch, bend, and torsion parameters, respectively, using the same options of energy minimization of stable conformers of **7a**. Obviously, the quality of such a parametrization is insufficient for the modeling of a flattened RINI transition state for the cis−trans interconversion in cyclic amines **7a** and **7b** as well as for comparison of the relative stability of the cis and trans conformers of each alkaloid. Furthermore, the Amber force field has no special parametrization for amines.[11d] (b) The experimental estimate of relative stability of the lowest energy conformers for **7a** in $CDCl_3$ (by NMR) is 0.3 kcal/mol.[18] The difference of the Amber*-derived ΔE_S values[18] for the lowest energy conformer of the *cis*-

conformer family and the corresponding trans conformer of, e.g., azacycle **7a** (identified[18] as structures C_3 and C_6, respectively; see Figure 7), does not exceed 0.5 kcal/mol. The similar difference for the lowest energy rotamers of the trans configuration of **7a** (identified[18] as structures C_3 and C_4; see Figure 7) is 0.4 kcal/mol. In other words, the choice of a pair of the lowest energy conformers of **7a** (i.e., C_3/C_4 and not C_3/C_6) is actually based on a 0.1 kcal/mol prevalence (in terms of ΔE_S) of conformer C_4 over C_6. Practically no calculation method cannot represent *reliably* a 0.1−0.3 kcal/mol energy difference for not small molecules even in an unsolvated state. Therefore it is problematic to put in order of relative stability conformers (e.g., of polycycles **7a** as well as **7b**), which differs only in 0.1−0.3 kcal/mol of *calculated* energy.

Interestingly, when we performed a conformational search for polycycle **7a** with Amber*-assisted energy minimization calculating also the distance-dependent energy of electrostatic interactions (a utility of geometry optimization in MacroModel), the ΔE_S value for trans and cis conformers C_3 and C_6 of **7a** increases up to 0.7 kcal/mol (see Figure 7 for relative energy for six lowest energy conformers C_1, C_2, C_3, C_4, C_5, and C_6; the most stable conformers C_1 and C_2 were not identified by the previous study[18] of alkaloids **7a**,**b**). Nevertheless, we cannot take into account these values because of the above-mentioned insufficiency of the Amber* parametrization.

Thus, it is questionable whether the both conditions (1) and (2) are fulfilled. If not, an alternative hypothesis is possible: the lowest energy conformers for **7a** or **7b** are a pair of cis/trans conformers and the measured barrier relates to their rate of interconversion. This alternative was considered and then rejected on the basis of the Amber*-provided calculations.[18] However, in the light of the above-mentioned Amber* problems, reconsideration of this hypothesis is clearly in order. Besides, cis−trans interconversion in quinolizidine **5** occurs with barriers near 14 kcal/mol (see above as well as Figure 5). Therefore, one may speculate that barriers of the same order of magnitude, which were measured for didehydroquinolizidine analogues **7a** and **7b**,[18] belong to RINI or, at least, to RINI and the 15-substituent rotation as well.

Our ab initio calculations do not confirm this hypothesis. The lowest energy conformers of **7a** arise from rotation of the substituted vinyl as well as ethyl substituents and not from the cis−trans interconversion of the didehydroquinolizidine fragment. The ΔE values for conformers C_1, C_2, C_3, C_4, C_5 and C_6 (see Figure 7), which geometry has been optimized at the B3LYP/6-31G* level, are 0.0, 0.0, 0.5, 0.7, 2.5 and 2.7 kcal/mol, respectively.[19] Hence, the contribution of cis conformers of **7a** (C_5 and C_6) in conformational equilibrium is negligibly small and is not detectable by usual NMR techniques (including effects of conformational dynamics of the cis conformers on temperature variable NMR spectra). Condition (1) is thus satisfied.

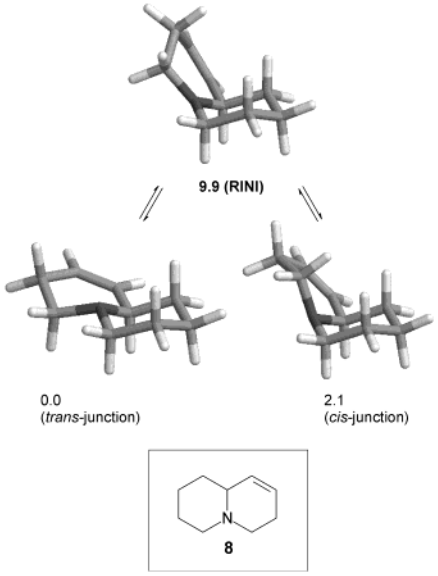

FIGURE 8. RINI for azabicycle **8**. Energies (ΔE_S; kcal/mol; in bold for the transition state) are relative to the lowest energy conformer. Optimized geometries (by MM3) are shown.

Remarkably, the ΔE value for minimal energy trans conformer C_1 and the corresponding cis conformer C_5 is 2.5 kcal/mol (see also Figure 8 for the relative stability of trans and cis conformers of analogue **8**) while the ΔE_S value is only 0.7 kcal/mol (by Amber*; this work).[20] Such appreciable deviation of the Amber* estimate from the estimate that was obtained by ab initio calculations supports our scepticism concerning the consideration of the Amber* force field as a suitable tool for conformational analysis of didehydroquinolizidine alkaloids **7a**,**b**.

Hence, NMR spectra of compound **7a** should be interpreted as a time-averaged superposition of spectra of four near energy rotamers C_1, C_2, C_3, and C_4 and not of two rotamers C_3 and C_4. Transitions between these four conformers are fast at increased temperatures (fast rotation of the Et group as well as the substituted vinyl group). Low-temperature spectra of **7a** reflect four-position conformational equilibrium as (a) a fast interconversion of conformers of each pair C_1/C_3 and C_2/C_4 (a fast Et rotation) and a slow interconversion between conformers C_1 and C_2 or C_3 and C_4 of the different pairs (freezing of the rotation of the bulky 15-substituent) or (b) a slow interconversion between conformers C_1 and C_3 or C_2 and C_4 (freezing of a concerted rotation of the both substituents) and a free isolated rotation of the Et group.

An MM3-based conformational study of **7a** is not feasible owing to the absence in this "pedantic" force field

(19) This work. The ΔE value of 0.1 kcal/mol was obtained for rotamers C_3 and C_4 in ref 18 using the same basis set and the same theory level. Our calculations led to the 0.2 kcal/mol value for these rotamers. The difference of 0.1 kcal/mol between the previous[18] and our results arises probably from a slightly different accuracy of calculation algorithms in Gaussian and Jaguar packages.

(20) This MM3-derived barrier value for model compound **8** is ~2.0 kcal/mol higher than the corresponding Amber*-supplied values[18] for **7a**,**b**. Estimates of relative stability for trans and cis conformers of **8** (this work) are similar by MM3 (2.1 kcal/mol) and ab initio calculations at the MP2/6-31G* level (2.9 kcal/mol). Similarly, trans conformer C_3 of **7a** is more stable than cis conformer C_5 (B3LYP/6-31G*; this work) by 2.0 kcal/mol. In contrast, the Amber*-derived estimate of relative stability for these conformers of **7a** (0.5 kcal/mol[18]) is appreciably different. The *distance-dependent electrostatics* option of MacroModel6.5 increases the ΔE_S value between these trans and cis conformers of **7a** only up to 0.7 kcal/mol (this work). The above differences between estimates provided by MM3 or high level of theory ab initio calculations for bicyclic amines **7a** as well as **8** and the Amber* estimates for **7a** actually reflect the magnitude of the mentioned inaccuracy of Amber* when applied to conformational investigations of alkaloids **7a**,**b**.

of several parameters for the treatment of the alkaloid structure. Therefore we employed the above-described MM3-based methodology for calculations of RINI barrier for one-step cis−trans interconversion in amine **8** (see Figure 8). RINI in this simple compound obviously may be considered as a good model of RINI in polycycles **7a,b** due to the same didehydroquinolizidine backbone for **7a,b** and **8**. On the other hand, no explicit parametrization problems are present for the MM3-mediated optimization of geometry of amine **8**.

Similar to the case of trans conformer C_1 and cis conformer C_5 of **7a** (see above for the ab initio-based estimate), the trans-fused conformer of **8** is more stable than the corresponding cis conformer by 2.1 kcal/mol of ΔE_S. The calculated RINI barrier (9.9 kcal/mol)[20] is essentially lower than the experimental barriers for analogues **7a**,**b**. Excluding low barrier rotations of the fragments of the 15-substituent, polycyclic systems **7a**,**b** possess only two types of conformational mobility, a bulky substituent rotation and interconversion of the bicyclic fragment of the backbone. Consequently, the rotation barrier in **7a**,**b** is higher than the interconversion barrier, i.e., also condition (2) is fulfilled.

Thus, despite inadequate computational analysis of conformational dynamics of N-fused polycycles **7a,b**[18] the assignment of DNMR-measured barriers to rotation and not to RINI is surprisingly correct. However, the further assignment of these barriers to rotation of the 15-substituent[18] remains problematic. Inaccuracy of the Amber*-based calculation methodology (see above as well as ref 20) does not permit distinguish between the slowing of isolated rotation of the substituted vinyl group and the slowing of a concerted rotation of this bulky substituent and the neighboring Et group.

Experimental Section

Conformational schemes were built by means of molecular mechanics calculations using the 1996 version of the MM3 package.[11a,b] A stochastic search followed by full-matrix minimization (option 9) was used for the generation of an entire set of transition states and stable conformations. This search (200 pushes) was performed four times starting from different ring conformations (until no new conformations were generated in the last search). Coordinates derived from the eigenvectors (produced by option 5 and singled out by Vibplot program) of vibrational modes with imaginary frequency were employed as starting coordinates for full matrix minimization in the establishment of the formal relationship between conformers and transition states.

Amber* and MM2* force fields (Macromodel 6.5 package[21a−c]) were used for the conformational analysis of alkaloid **7a** and tetracycles **1a**,**b**, respectively. The no solvent as well as distance-dependent dielectric electrostatics options were employed for the energy minimization. The Monte Carlo option was used for conformational search in the case of **7a** (generation of 5×10^5 structures with the energy upper limit 5 kcal mol^{-1} from the lowest energy conformer found).

Geometry of MM2*- and MM3-optimized structures was used as the starting geometry for ab initio calculations (Gaussian98 package[22]) of amines **1a**,**b**,**f**, **3**, **6**, **7a**, and **8**, respectively, for the gas phase. The difference ΔE between full electron energies is not corrected to the zero point energy. Initial *ab initio* geometry optimization was performed at the restricted Hartree−Fock level using the 3-21G basis set. The resulting geometry was reoptimized at the 6-31G* level and then at the MP2/6-31G* (for conformers of **1a,b,f**, **3**, **6** and **8**) or B3LYP/6-31G* level (for conformers of **7a**). If the initial optimization of the geometry of a MM3-derived conformer at the RHF/3-21G level led to another conformer, the energy minimum which corresponds to the desired conformer was located by calculations at the MP2/6-31G* level omitting the lower theory levels. **Transition States.** The Berny optimization algorithm and the Newton−Raphson optimization procedure implemented into Gaussian98 package[22] were used in ab initio calculations for conformational transition states of bicycles **3** and **6**. MM3-optimized Cartesian coordinates of the transition states were used as the starting structure for optimization at the MP2/6-31G* level. For the location of the first-order transition states NoEigenTest option was employed at the initial optimization followed by the calculations of the force constants at every point (the CalcAll option) in the next optimization at the same level of theory. If the initial optimization resulted in location of another conformation, the CalcAll option was recruited straight away starting the calculations at the MP2/6-31G* level.

^{13}C NMR chemical shifts for the cation of **1f** as well as tetramethylsilane were calculated at the MP2/6-31G* level for the MP2/6-31G*-optimized geometry by means of the GIAO utility of the Gaussian98 package.[22]

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Supporting Information Available: Absolute electron energies (au) or steric energies (kcal/mol) as well as optimized geometry (Cartesian coordinates or *Z*-matrixes) for conformations of studied compounds; frequencies for transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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