Conformational Schemes: An Available Tool for the Assignment of NMR-Measured Barriers, Demonstrated with the Example of Crowded Piperidines

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Abstract: MM3-derived full conformational schemes are proposed as a powerful and convenient tool for the currently problematic assignment of NMR-measured barriers for flexible systems that possess more than one type of independent intramolecular motion. Hindered piperidines were chosen as a molecular model with seven possible intramolecular dynamic processes. The free energies of activation for methyl group topomerization in 1,2,2,5,5-pentamethyl-, 1-ethyl-2,2,6,6-tetramethyl-, and 1-butyl-2,2,6,6-tetramethylpiperidines were determined at different temperatures by means of line-shape analysis of ^{13}C NMR spectra. Schemes of conformational transformations for the *N*-Me and *N*-Et compounds were created with MM3-based methodology. These schemes permit the assignment of the measured barriers to ring inversion for the *N*-Me compound and to ring inversion – nitrogen inversion, ring inversion, and C–N rotation for the *N*-Alk^{primary} piperidines (for the *N*-Et and *N*-Pr derivatives the experimental barriers had previously been attributed to isolated C–N rotation only). A unique dynamic process for tertiary amines, isolated nitrogen inversion, is described for the *N*-alkylpiperidines with an *N*-substituent bulkier than Me.

Keywords: conformation analysis · molecular dynamics · nitrogen heterocycles · NMR spectroscopy

Introduction

Three different types of intramolecular motion (rotation around single bonds of the ring substituents, pyramidal nitrogen inversion, and ring inversion) form the whole set of conformational dynamic processes for the six-membered saturated azacycles.[1–5a] Thus, seven intramolecular processes are in principle possible for *N*-alkylpiperidines: three isolated processes, namely isolated C–N rotation (ISR), isolated nitrogen inversion (INI), and ring inversion (RI), and four concerted processes, namely nitrogen inversion – C–N rotation (NIR), ring inversion – nitrogen inversion (RINI), ring inversion – *N*-substituent rotation (RIR), and ring inversion – nitrogen inversion – *N*-substituent rotation (RINIR). RI[6a–c] and ISR[5a,b] are trivial cases for substituted six-membered rings, NIR necessarily takes place for most tertiary amines,[7–12] and the possibility of RINI or RINIR in piperidine compounds has also been considered.[2, 4, 5b, 13a–c] In contrast, INI was mentioned as not relevant for alkylamines.[7, 12] Each of these dynamic processes may cause a splitting of peaks in the NMR spectra at low temperatures, and it is usually not possible to determine a priori which process is responsible for this peak dichotomy.[1, 2, 13a] For instance, solid arguments (including calculation results) were given in Bushweller's pioneering experimental work[7] concerning the distinction between ISR and NIR by observing the temperature-induced changes in NMR spectra of open-chain tertiary amines.

However, not all speculations in the literature are as reliable (for criticism see refs. [1, 12, and 13d]) in the analysis of conformational dynamics in amines. In particular, assignment of temperature-induced changes in the NMR spectra of piperidine compounds has been performed considering a) only three processes (ISR, NIR, and RI in the present terms as reviewed in refs. [2, 3]) or b) also ring-inversion-related concerted processes (RINI or RINIR).[13a–c] In case a) the considerations are obviously not complete. In case b) the arguments are insufficient. For instance, concerted processes were assumed arbitrarily to be higher in energy and therefore were not taken into account in the assignment of the experimental barriers for sterically crowded piperidines.[13b] Moreover, the authors mentioned a *two-barrier* sequence of intramolecular motions as a combined process which may occur *in addition* to isolated processes in other piperidines[13c] (concerted dynamic processes have obviously one barrier in a one-step conformational transformation; see, for example, ref. [12]). Only NIR (but not the RI-related processes) was included[12] in the consideration of the NMR-measured barrier[13b] for hindered piperidines with β-branched *N*-substituents.

These assignment problems would clearly be overcome if a full conformational scheme, which includes relative energies

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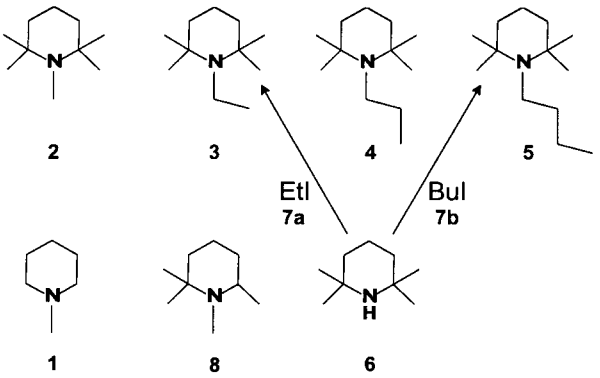
of stable conformers as well as transition states, were available for the compound under consideration. For instance, a comparison of the barriers for isolated and concerted processes permits the identification of the lowest energy conformational pathways by which the geminal substituents of the piperidine ring become isochronous (a process which is monitored by NMR[13a–d, 14]). Surprisingly, no practical approach to the design of quantitative full conformational schemes has been introduced for organic compounds with complex conformational dynamics. Only recently was the MM3 force field found to be effective in establishing the formal relationship between stable conformers and the corresponding transition states for cyclic compounds and in modeling isolated as well as concerted intramolecular processes.[13d] Thus, a simple assignment of the experimental barriers becomes possible using conformational schemes derived by our MM3-based methodology.[12, 13d] In particular, for *N*-Me-piperidine **1**, RINIR and RI turn out to be the processes whose rate is measured by dynamic NMR (DNMR) techniques.[13d]

Unfortunately, the conformational scheme for piperidine **1** cannot be extended a priori to the more hindered analogues. Experimental barriers (by NMR) for the unhindered piperidine **1** and its crowded analogue **2** are 12.0[14] and 8.2[13b] kcal mol^{-1}, respectively. In other words, the lowest energy conformational pathways, which lead to isochronism of the geminal substituents for these piperidines, differ by approximately 4 kcal mol^{-1}. Thus, it is reasonable to assume that the conformational schemes for unhindered and hindered piperidines are fundamentally different.

In order to obtain more reliable information about intramolecular motion in *N*-*n*-alkyltetramethylpiperidines **2**–**5**



and to assign the NMR-measured barriers for these compounds, we have approached this problem by building full conformational schemes for these azacycles by means of MM3-based calculations.

Results and Discussion

NMR study: Compounds **3**[15] and **5** were obtained by alkylation of the secondary piperidine **6** with an excess of ethyl- or *n*-butyl iodide (**7a**,**b**, respectively). The room temperature ^{1}H and ^{13}C NMR data, as well as the high-resolution mass spectra of compounds **3** and **5**, are reported in Tables 1 and 2.

Table 1. Data of the ^{1}H NMR[a] (δ_H/J [Hz]) and high-resolution mass spectra (m/z) for piperidines **3** and **5**.

	α-Me	cycl. CH_2	*N*-CH_2	Others	MH^+ (calcd MH^+)
3	1.02 s	1.3–1.6	2.47 q/6.9	0.98 t/6.9 (Me)	170.190 (170.191)
5	1.12 s	1.3–1.6	2.35 m	0.90 t/5.7 (Me) 1.21 qm/5.7 (β-CH_2) 1.4 m (γ-CH_2)	198.219 (198.222)

[a] In $CDCl_3$ at 25 °C; s = singlet, t = triplet, q = quartet, m = multiplet.

Table 2. ^{13}C NMR data (δ) for piperidines **2**, **3**, and **5** in $CDCl_3$ at 25 °C.

	C-2, C-6	C-3, C-5	C-4	α-Me	C-1′	C-2′	C-3′	Me
2	53.76	41.31	17.96	26.34	28.51	–	–	–
3	53.38	41.30	17.81	26.24 b[a]	38.11	20.85	–	–
5	54.48	41.25	17.83	27.51 b[a]	44.85	38.23	20.61	14.11

[a] b = broadened.

Barriers for the rate-determining dynamic process in piperidines **2** and **3** were previously measured[13b] by the coalescence method, which is less accurate than full line-shape analysis.[16] We have therefore used the latter method to redetermine these barriers as well as the yet unknown barrier of the *N*-Bu analogue **5** (see Experimental Section). The activation parameters for the intramolecular motion in these piperidines were obtained by fitting of the ^{13}C signals of the α-methyl groups of the piperidine ring to their simulated lineshapes. The results shown in Table 3 demonstrate only weak dependence of the free energy of activation ($\Delta G^{\neq}$) on the temperature (thus, $\Delta S^{\neq}$ may be estimated as nearly zero). We can, therefore, reliably compare $\Delta G^{\neq}$ values and MM3-calculated barriers (for problems with such comparisons see refs. [11, 12]).

Lowest energy conformers and nitrogen inversion for piperidines 2–5: The widely used MM3 force field, explicitly parameterized for amines,[17a–c] was employed for geometry optimization of stable conformations and transition states involved in rotational and inversional processes for piperidines **2** and **3**. These conformations were found by stochastic search options (for details see the Experimental Section and also refs. [12, 13d]). High-energy conformations found with

Table 3. Kinetic parameters for intramolecular motion in amines **2**, **3**, and **5** (k [sec^{-1}]; $\Delta G^{\neq}$ [kcal mol^{-1}]).

T [K]	**2**		**3**		**5**	
	k	$\Delta G^{\neq}$	k	$\Delta G^{\neq}$	k	$\Delta G^{\neq}$
175.5	250 ± 25	8.2 ± 0.1				
195.6	3500 ± 360	8.1 ± 0.1				
215.6	$(3.7 \pm 0.4) \times 10^4$	8.0 ± 0.1	88 ± 10	10.6 ± 0.2	45 ± 6	10.9 ± 0.2
235.6	$(3.2 \pm 0.7) \times 10^5$	7.8 ± 0.2	550 ± 60	10.7 ± 0.1	400 ± 40	10.9 ± 0.1
256.2			6000 ± 600	10.5 ± 0.1	3500 ± 400	10.8 ± 0.1
276.9			$(3.1 \pm 0.4) \times 10^4$	10.5 ± 0.2		
301.7			$(1.7 \pm 0.7) \times 10^5$	10.5 ± 0.3	$(1.0 \pm 0.1) \times 10^5$	10.8 ± 0.1

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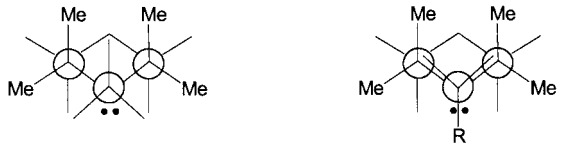
ΔE (relative to the lowest energy conformer) above 14.5 kcal mol^{-1} (e.g., 1-sofa for **3**, $\Delta E = 14.7$ kcal mol^{-1}) were not considered. C–Me rotation transition states were also excluded as not important for the assignment problem. We assume that all relevant conformations were found because:

1) The number of such conformations for six-membered rings is essentially restricted, and
2) expected conformations (e.g., some 2,5-half-chair forms), which were not generated by the stochastic search, are not relevant for the compounds studied. These conformations were designed by fixation of ring atoms in the proper geometry followed by block-diagonal energy minimization with geometry optimization. Restriction of motion along the z axis (perpendicular to the ring mid-plane) of four or five selected ring atoms was used successfully in this optimization procedure in order to keep the desired conformations. However, all the structures built in this way reverted to conformations already found by the stochastic search when the restrictions were removed in the next energy minimization step (e.g., by the full-matrix minimization option). Thus, the conformational schemes for piperidines **2** and **3** (formal relationships between stable conformations and transitions states were established using the MM3-derived methodology;[12, 13d] see below and Experimental Section) may be considered as representative.

The calculation results obtained for the lowest energy conformers of **2, 3**, and **5** lead to a simple conclusion. A staggered conformation (the common case for vicinal single bonds; see Figure 1) of the β-bonds of the *N*-substituent and



2 **3-5**

Figure 1. Lowest energy stable conformations of piperidines **2**–**5**.

the endocyclic C–N bonds is present only in the case of the *N*-Me compound **2**. The conformational search performed for **3**–**5** confirms the previous findings[18] that these bonds are eclipsed in the lowest energy conformation of 2,2,6,6-tetramethylpiperidines with an *N*-substituent bulkier than Me. This conformation is an exception among alkylamines, for which a staggered conformation is invariably present[5a, 8, 19, 20] (for instance, as for **1** and **2**). Mechanistic considerations of nitrogen inversion show[7, 12] that this is always a concerted NIR process (and not INI[12, 21]) in alkylamines. In this case, C–N bonds are staggered with other bonds in stable conformations. INI is possible provided there is vicinal eclipsing of these bonds in one of the stable conformations.[12] Thus, piperidines **3**–**5** and more hindered analogues[18] are unique amines for which nitrogen inversion may occur also as an INI process (see Figure 2). Hence, conformational schemes for amines **2** and **3** should be different.

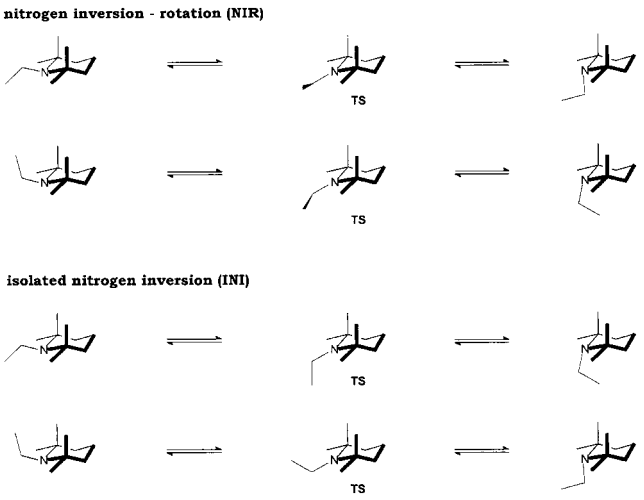


Figure 2. NIR and INI (TS = transition state). NIR is not seen for piperidine **3** (see Figure 4), while both INI and NIR occur for piperidines **9** and **10**.

Conformational schemes for piperidines 2 and 3: The full conformational scheme for piperidines with equal geminal substituents may be considered to consist of two identically constructed fragments (*d* and *l* in Figure 4). These fragments represent the same conformational transformations, *within* each of two groups, of structures which are formal ring enantiomers (see, e.g., chair **A** and chair **B** in Figures 3–5). Interconversion *between* the two groups (formal enantiotopomerization of the piperidine ring) actually leads to the NMR-detected isochronism of geminal ring substituents (see Table 1), since this finally provides interchange between the lowest energy conformers, chairs **A** and **B** (see Figure 5). In order to simplify the comparison of the given schemes with that for piperidine **1**,[13d] one of the schemes, namely that for piperidine **2**, is given as a representative half-scheme (the *d*-fragment of the full scheme with elements of the *l*-fragment, as was done for **1**[13d]). A full conformational scheme is given for *N*-Et-piperidine **3** (see Figure 4).

1,2,2,6,6-Pentamethylpiperidine (**2**): The conformational scheme for piperidine **2** (see Figure 3) includes the usual elements of conformational schemes for saturated six-membered rings (pseudorotation cycle, 1- and 4-sofa and half-chair)[6a–c, 13d, 22] as well as elements which are absent in the scheme for unhindered piperidine **1**[13d] (2-sofa forms and 1,4-half-chair including the NIR transition state for the 1,4-half-chair conformation). These additional elements enable new conformational pathways which lead to the NMR-observed topomerization of geminal ring substituents (see Figure 3 and Tables 1 and 2). These pathways are: *i*) chair **A** →1,4-half-chair →1,4-twist →1,4-twist (planar N) →1,4-twist →1,4-half-chair →chair **B,** and *ii*) chair **A** →chair (planar N) →chair (axial *N*-Me) →2-sofa →1,4-twist →1,4-half-chair →chair **B**. Another low-energy pathway is *iii*) chair **A** →4-sofa →1,4-boat →2,5-twist →2,5-boat →1,4-twist →1,4-half-chair →chair **B**.

The 8.1, 8.1, and 8.5 kcal mol^{-1} highest energy points along these pathways *(i–iii)* correspond to the 1,4-half-chair, 1,4-

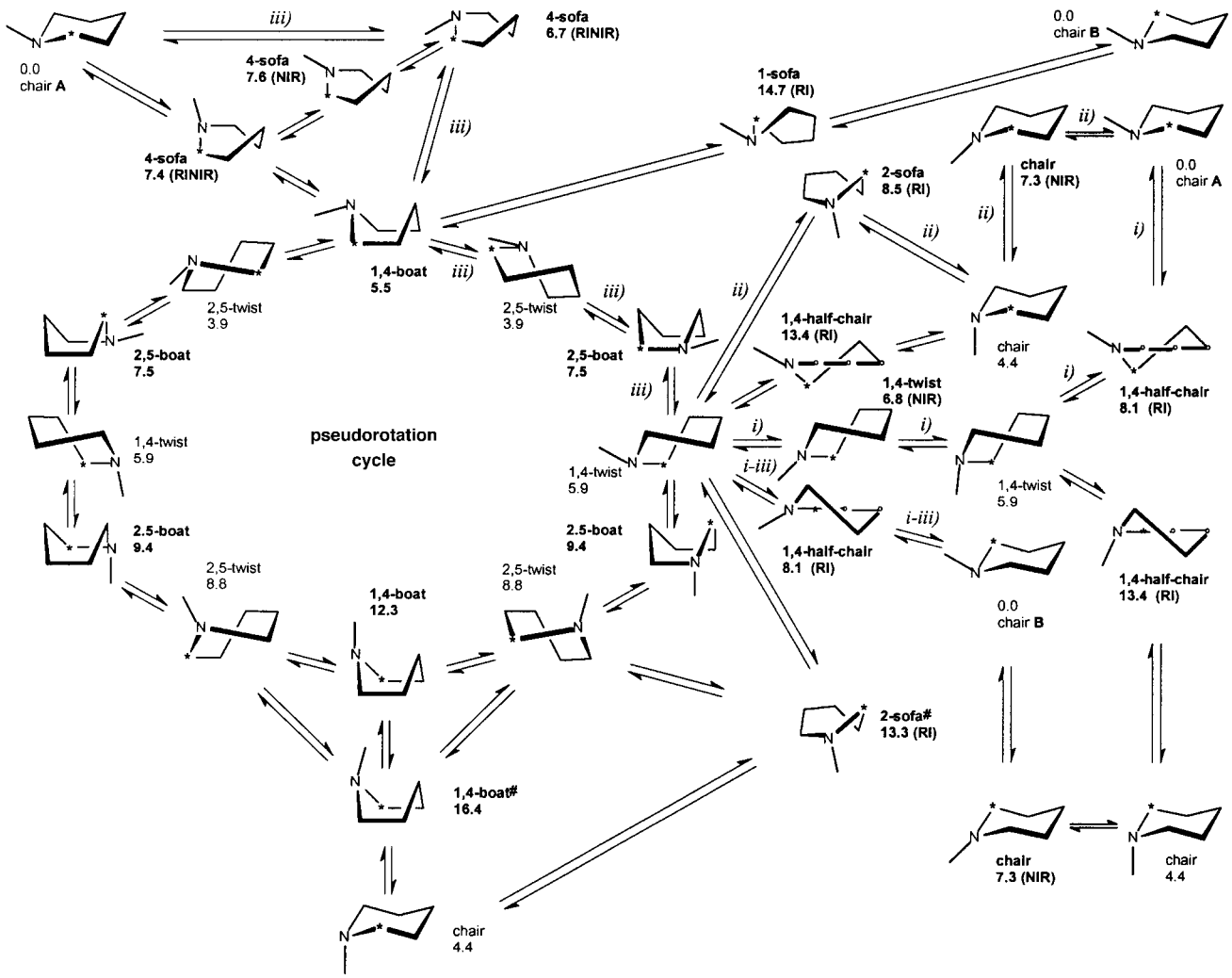


Figure 3. Scheme of conformational transformations for piperidine **2** (α-methyl groups are not shown). Energies (kcal mol^{-1}) are relative to the lowest energy conformer, the names (in parentheses) and the relative energies for the transition states are in bold. * is a formal label, $^{+}$ depicts second-order transition states. Low-energy conformational pathways *(i – iii)* are marked by the corresponding characters.

half-chair and 2-sofa transition states, respectively. Pathways of significantly higher energy are of the C_S (involving both 1- and 4-sofa transition states) and C_2 (involving 1,4-half-chair forms with both pseudoequatorial and pseudoaxial *N*-Me orientations) modes, which are inherent also to the cyclohexane case[17] (only the C_S mode is present for piperidine **1**[13d]). Thus, the NMR-determined barrier for piperidine **2** indeed belongs to RI in agreement with the previous[13b] report. Since the difference between the calculated values for the barriers in these pathways is small (0.4 kcal mol^{-1}), both conformational pathways contribute to the temperature-dependent changes in the NMR spectra of **2**.

There is very good agreement (0.1 or 0.5 kcal mol^{-1}) between the experimental and the calculated barriers for both pathways (as was also the case for piperidine **1** and azetidine compounds[13d]). It is important to emphasize that these values are extracted from the low energy pathways obtained from the designed conformational schemes. Thus, the fit confirms the validity of these schemes.

1-Ethyl-, 1-propyl-, and 1-butyl-2,2,6,6-tetramethylpiperidine (3 – 5): The scheme of conformational transformations for the *N*-Et compound **3** (Figure 4) differs from that for the *N*-Me compound **2** in several aspects. 1) The *N*-Et substituent provides several structures (which are located in vertical columns in the scheme) for almost all of the ring forms. These structures differ mainly in the orientation of the methyl group of the *N*-Et substituent. 2) The pseudorotation cycle is not closed for **3** [no direct transformation of the form 1,4-boat (flagstaff-oriented *N*-Et substituent) →2,5-twist (pseudoaxial *N*-Et substituent) takes place]. 3) The expected INI transition states are present only for the chair forms of **3**. 4) For piperidines **2** and **3** "entry" into the pseudorotation cycle occurs via different sets of ring conformations. In the case of **2** they are 1,4-half-chairs and 1-, 2-, and 4-sofa, while for **3** they are 1,4-half-chairs, 2,5-half-chair and 1-, 3- and 4-sofa. 5) Three of the *d*- (*l*-) →*l*- (*d*-) interconversions are the same for **2** and **3** (via 1-sofa and 1,4-half-chair conformations and the NIR transition state in the 1,4-twist conformation). Additional interconversions via the 1,4-half-chair of lower energy and the 2,5-boat with a pseudoaxial *N*-substituent are present for compound **3**.

The pathways (L_1 and L_2) of low energy for conformational transformation chair **A** →chair **B** in *N*-Et-piperidine **3** are

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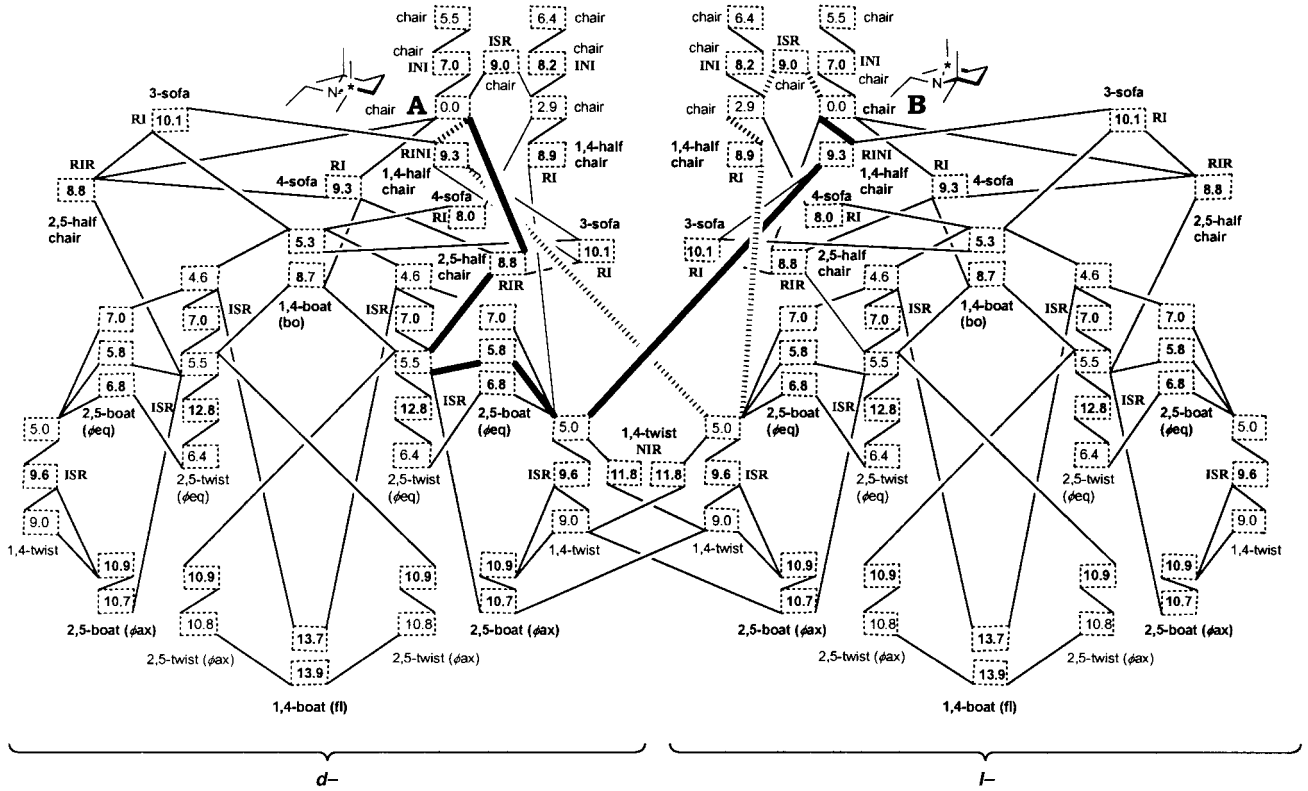

Figure 4. Scheme of conformational transformations for *N*-Et compound **3** (* is a formal label). Energies (in rectangles; kcal mol^{-1}) are relative to the lowest energy conformer. The names and the relative energies for the transition states are in bold. The orientation of the *N*-Et substituent is shown in parentheses (ϕ_{eq} = pseudoequatorial, ϕ_{ax} = pseudoaxial, bo = bowsprit, fl = flagstaff). Conformations with the same ring form are grouped in columns. Chair **A** – chair **B** pathway L_1 of low energy is marked by bold lines. Another low-energy pathway L_2 is shown by dotted lines.

Figure 5. Diastereotopomerization of geminal ring substituents and homotopomerization of 1,3-geminal fragments (enantiotopomerization chair **A** – chair **B**) for piperidines **2** – **5** lead to isochronism of α-methyl groups (numbers depict Me groups, * is a formal label).

detailed in Figure 4. The highest energy point in the former energy pathway is the RINI transition state in the 1,4-half-chair form ($\Delta E = 9.3$ kcal mol^{-1}). Two other pathways (via the NIR transition state in the 1,4-twist conformation ($\Delta E =$ 11.8 kcal mol^{-1}) and via the 2,5-boat with a pseudoaxial *N*-substituent ($\Delta E = 10.7$ kcal mol^{-1}) are less favorable. Thus, only pathways L_1 and L_2 are equally involved in the NMR-observed topomerization of the Me groups.

There are two transition states in the L_2 pathway (1,4-half-chair, 8.9 kcal mol^{-1}, RI; chair, 9.0 kcal mol^{-1}, ISR) which are near in energy to the 9.3 kcal mol^{-1} point for L_1 and L_2. The small energy difference between these calculated barriers permits assignment of the experimental barrier for **3** to RINI, ISR, and RI (similarly to the assignment of the barrier for the *N*-Me analogue to two RI transition states). In kinetics terms, these dynamic processes are the first amongst all others to become slow relative to the NMR time scale as the temperature is lowered. On the other hand, the accuracy of MM3-based calculations is insufficient to estimate separate contributions of these close energy processes to the temperature-induced changes of NMR spectra of **3**.

The difference between the experimental barriers (measured in CD_2Cl_2) for the *N*-Et compound **3** (10.3 kcal mol^{-1}) and the *N*-Pr compound **4** (10.6 kcal mol^{-1}) is 0.3 kcal mol^{-1}.[13b] Our experiments, also in CD_2Cl_2, demonstrate the same difference (Table 4) between the barriers for

Table 4. The barrier values obtained by DNMR and MM3 calculations for compounds **2** – **5** (kcal mol^{-1})

	DNMR ($\Delta G^{\neq}$)	MM3 (ΔE) for ISR (chair)	MM3 (ΔE) for RI (lower energy 1,4-half-chair)	MM3 (ΔE) for RINI (higher energy 1,4-half-chair)	Previous assignment	New assignment (this work)
2 *N*-Me	8.0 (this work) 8.2[a]	7.3	–	8.1	RI[a]	RI
3 *N*-Et	10.6 (this work) 10.3[a]	9.0	8.9	9.3	ISR[a]	RINI + ISR + RI
4 *N*-Pr	10.6[a]	9.5	9.1	9.5	ISR[a]	RINI + ISR + RI
5 *N*-Bu	10.9 (this work)	9.5	9.0	9.4	–	RINI + ISR + RI

[a] Data from ref. [13b].

N-Et and *N*-Bu compounds **3** and **5**. Since the difference in measured barrier values from one source is usually reliable, we conclude that the experimental barrier for *N*-Et piperidine **3** is 0.3 kcal mol^{-1} lower than those for higher *N*-*n*-alkyl homologues. This small energy difference suggests that conformational transformations for the *N*-Pr and the *N*-Bu compounds **4** and **5** are described by the same scheme as for *N*-Et compound **3** (excluding additional rotations around the C–C bonds of the *N*-substituents for **4** and **5**).

The calculated barrier values for ISR in the ring chair conformation show an increase of 0.5 kcal mol^{-1} for *N*-Pr and *N*-Bu piperidines **4** and **5** relative to **3** and a smaller increase for the RINI and RI transition states in 1,4-half-chair conformations (see Table 4). The difference between the two highest barriers of the low-energy pathways L_1 and L_2 (i.e., between high-energy points corresponding to RINI and ISR) changes only by -0.3 and 0.1 kcal mol^{-1} on going from *N*-Et piperidine **3** to *N*-Pr and *N*-Bu piperidines **4** and **5**, respectively. Therefore, we can conclude that the measured barriers for compounds **4** and **5** also belong to RINI, ISR, and RI. This finding corrects the previous speculative barrier assignment[13b] for piperidines **3** and **4** to ISR only. However, the calculations performed here for *N*-alkylpiperidines **3**–**5** show a bigger deviation from the experimental barrier values (1.1–1.5 kcal mol^{-1}) than the ones obtained for the *N*-Me compounds (see Table 4).

Thus, this MM3-based conformational scheme methodology (this work and ref. [13d]; see also ref. [23, 24] for a related but more complicated procedure of scheme design) *allows a reliable barrier assignment independent of the number and type of the expected isolated or concerted processes* (within the limits of compound classes included in MM3 parameterization[17a,b, 27]). We are not aware of any other approach which can achieve this (see Introduction and also refs. [25, 26]). Moreover, these schemes demonstrate that considerable differences in experimental barriers for related compounds (e.g., between **1** and **2** as well as between **2** and **3**–**5**) arise from different isochronism-determining conformational pathways. This suggests that structure-based analogies as well as common (actually symbolic) or arbitrarily simplified conformational schemes (e.g., the four-position scheme, which is often used for saturated azacycles,[1, 2, 13a, 28a,b, 29] the related eight-position conformational cube,[13b,c] and protonation/inversion schemes[2, 30] for piperidines) are essentially problematic methods for the assignment of such barriers. In addition, unexpected dynamic processes may be responsible for temperature-induced changes in NMR spectra, as was discovered[13d] from the conformational schemes for azetidines and pyrrolidines.

We can even maintain that previous assignments, which were based on the limited methodology of common conformational schemes as well as on assumptions of the similarity of the barrier values for related compounds, require additional support, at least in the case of the systems with complex conformational dynamics. For instance, assignment of the experimental barrier (11.0 kcal mol^{-1}) for 1,2,2,6-tetramethylpiperidine (**8**) to nitrogen inversion (this assignment is based on the common four-position scheme for piperidines)[28a] ignores the possibility of concerted processes (such as for **1** and **2**). Furthermore, our MM3-based calculations (which in general only underestimate NIR barriers by less than 1.3 kcal mol^{-1}[12]) give only 8.8 kcal mol^{-1} as an NIR barrier for **8**. This is a normal value for NIR, while enhanced 11.0 kcal mol^{-1} and higher NIR barriers occur only in the exceptional cases of some bicyclic alkylamines[13d, 31] and some neopentylamines (see ref. [10] and below; small azacycles possessing high NIR barriers are obviously not included in the discussion). Therefore the measured barrier for piperidine **8**[28a] belongs rather to an RI-associated intramolecular dynamic process.

An example of the intensive use of structural analogies is the recent assignment of experimental barriers for the *N*-alkylpiperidine series.[13c] According to this assignment the measured barriers, for example, for *N*-neopentylpiperidine (**9**) and *N*-neopentyl-3,3-dimethylpiperidine (**10**) (10.6 kcal mol^{-1} and 11.8 kcal mol^{-1}) undoubtedly represent ring inversion[13c] since these values are near to experimental values for the ring inversion of *N*-Me compound **1** (11.8 kcal mol^{-1}[32] and 12.0 kcal mol^{-1}[14]). As shown above, this methodology is extremely unreliable. The 1.2 kcal mol^{-1} difference between experimental values shows rather the discrepancy in conformational dynamics for these *N*-neopentylamines. In addition, the calculated ISR barriers for **9** and **10** (this work; see also ref. [13c]) are 10.3 and 10.6 kcal mol^{-1}, respectively. Our calculations also give 12.0 and 12.1 kcal mol^{-1} for the corresponding NIR barriers (the conformational cube diagram[13c] includes INI but ignores NIR as well as other concerted processes). Based on the speculative level of comparison of selected barriers,[13c] ISR for **9** and NIR for **10** could be considered as experimental barrier-forming components. However, a question about low-energy conformational pathways remains open for these amines. Therefore, similarity in the values of measured and previously assigned barriers does not indicate their identity independently of the source of selected barriers (e.g., assumed to be similar to the experimental RI barrier for related amine **1**[13c] as well as the NIR and ISR barriers calculated here). To accurately assign experimental barriers for **9**, **10**, and other piperidines,[13c] full conformational schemes (similar to those for **1**–**3**) must be built.

Conclusions

Conformational schemes may be designed successfully with the MM3 package without arbitrary assumptions about the structure of these schemes. Since they overcome the problems mentioned above, MM3-derived conformational schemes are in our opinion an essential (and convenient) tool for barrier assignment in systems with more than one type of intramolecular motions.

The conformational energy surface, at least for piperidines, may be susceptible to relatively small structural changes. The discrepancy in conformational pathways among 1-methyl-, 1,2,2,6,6-pentamethyl-, and 1-ethyl-2,2,6,6- tetramethylpiperidine is accompanied by a significant difference in experimental barriers. Therefore we view a considerable value for such a difference as an indication of a significant change of the

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potential energy surface for related compounds with complex conformational dynamics. We conclude also that several intramolecular dynamic processes may simultaneously contribute to experimental barriers for such systems.

Experimental Section

Amines **2** and **6** are commercially available compounds.

Piperidines 3 and **5**: A mixture of piperidine **6** (10 mmol) and iodide **7a** or **7b** (150 mmol) was heated in a sealed tube for 8–10 h at 100 or 135 °C, respectively. After addition of hexane and filtration, the solution was treated with 1M HCl to pH ≈ 1 and extracted with CH_2Cl_2. The aqueous phase was basified with NaOH to pH ≈ 12 and extracted with CH_2Cl_2. The organic phase was concentrated at 25 °C and loaded on to a 4-cm layer of silica gel. Subsequent elution with CH_2Cl_2 and CH_2Cl_2/ether (5:1) afforded compounds **3** and **5** in 70–80% yield.

All ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer. TMS was used as internal standard. Samples of **2, 3**, and **5** (20–25 mg in 0.5 mL of CD_2Cl_2) were equilibrated for approx. 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 within 0.5 K. For the complete lineshape analysis a modified version of a program written by R. E. D. McClung, University of Alberta, Edmonton T6J 2G2 (Canada) was used with visual fitting. The activation parameters were calculated using the Eyring equation. The 1994 version of the MM3 program[17a–c] was used for molecular mechanics calculations. Stochastic search followed by full-matrix Newton–Raphson minimization (option 9) was used for locating the transition states and stable conformations. Stochastic search (200 pushes) was performed 3 and 4 times for **2** and **3**, respectively, starting from different ring conformations. Coordinates derived from the eigenvectors (produced by option 5) of vibrational modes with negative imaginary frequencies were employed as starting coordinates for minimization in the establishment of the formal relationship between conformers and transition states.

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