Conformational Preferences for 3-Piperideines: An Ab Initio and Molecular Mechanics Study

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Abstract: Conformational preferences in alkyl- as well as Ph-substituted 3-piperideines (1,2,3,6-tetrahydropyridines) have been characterized by ab initio and molecular mechanics calculations. A set of rules and subrules for estimation of the conformational equilibrium (in terms of preferred substituent orientation) in these systems, with differently positioned ring substituent (-s), is presented. Examples of the revision of some previous stereochemical assignments demonstrate the reliability of these rules.

Keywords: ab initio calculations · conformation analysis · nitrogen heterocycles · NMR spectroscopy

Introduction

From the point of view of conformational analysis, six-membered saturated carbo- and heterocycles are probably the most studied organic systems. Surprisingly, the conformation-related knowledge for six-membered rings with one endocyclic double bond is poor: only cyclohexene compounds have been studied systematically. The unsaturated carbocyclic backbone adopts a half-chair conformation[1a–c] (see Figure 1) in the absence of additional sp^2-hybridized ring atoms or covalent fixation of another conformation by a rigid structural fragment. A slight predominance of equatorial (*e*) over axial (*a*) substituent orientation has been determined for nonbulky 4-substituents (halogen, OH, CN),[1a, 2a–c] while pseudoaxial (ψa) orientation versus pseudoequatorial (ψe) orientation is slightly preferred for these substituents in the 3-position of the ring.[1a] In contrast, determination of the conformational energy for a Me group in the cyclohexene half-chair gave the same preference (1 kcal mol^{-1}) for both ψe and *e* orientations (i.e., for 3-Me and 4-Me groups, respectively).[1a, 2b]

The piperideine (tetrahydropyridine) cycle, a cyclohexene azaanalogue, is a basic structural fragment of many alkaloids[3a–c] (e.g., arecoline, lobenine, anatabine, salsolidine). Conformation analysis of these biologically active amines is necessary for the understanding of the molecular mechanisms of their action.[3d, e] In addition, establishment of conformational preferences in these partly unsaturated systems is desirable for development of the strategies of stereospecific synthesis of azacycles.

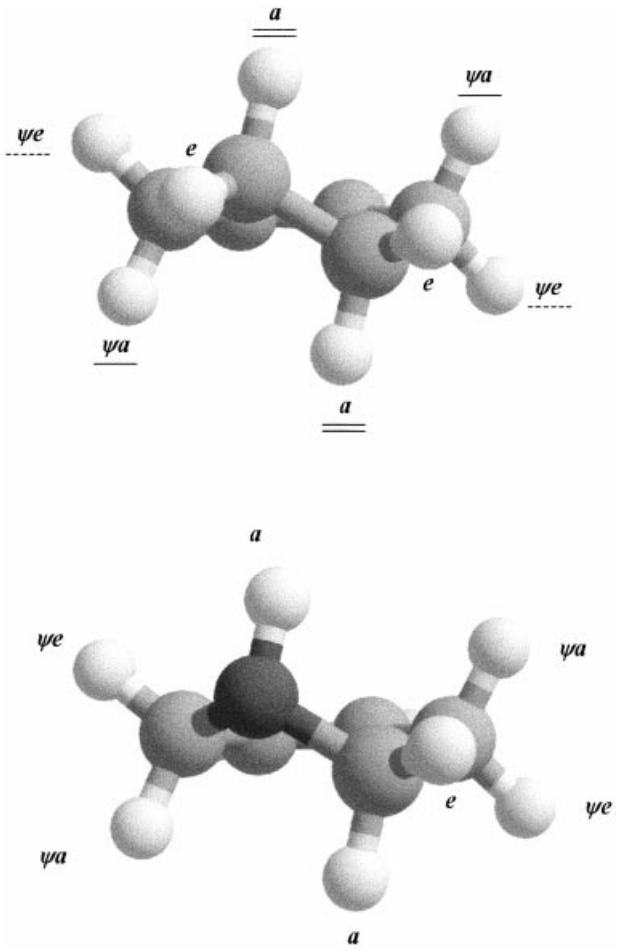

Figure 1. Substituent orientations in the half-chair conformation (optimized by MM3; a = axial, e = equatorial, ψa = pseudoaxial, ψe = pseudoequatorial; spatially equivalent orientations are underlined) of cyclohexene (the upper structure) and 3-piperideine (the lower structure). For 3-piperideine, the conformer with the axially oriented *N*-H substituent is shown.

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  0947-6539/01/0721-4715 $ 17.50+.50/0

Similarly to cyclohexenes, a half-chair is the predominant conformation for the piperideine ring.[4] It is questionable whether other conclusions regarding conformational equilibrium in cyclohexenes may be transferred to substituted piperideines. For instance, while ψe or *e* orientations for Me groups would also be expected for piperideine compounds, both *a* and *e* orientations have been reported to predominate for 6-alkyl substituents in different *N*-benzyl-2,6-disubstituted 3-piperideines.[5a, b] A ψa orientation of the Me group has been deduced from CD (circular dichroism) data for 1-methyl tetrahydroisoquinolines (structural components of several important alkaloids).[6]

Herein we report *quantitative* conformation analysis of differently substituted 3-piperideines that is performed by ab initio quantum mechanical as well as molecular mechanics calculations. We have examined mainly Me substitution of six-membered cycles in order to establish conformational preferences for the basic piperideine systems, which possess no special electronic effects of substituents (e.g., anomeric effect) on conformation. In order to prove the accuracy of our calculations for these piperideines **1a**–**n**, selected compounds with an experimentally determined conformational equilibrium, such as cyclohexenes **2a**,**b**, piperidines **3a**,**b**, and piperideine **4**, are included in the calculations (see Figures 2–9). Examples of piperideines **5a**–**j** and **6a**–**e** (see Figure 7 and 8) provide information on the preferential orientation of a Me substituent in these piperideine rings in the presence of neighboring Ph or *t*Bu groups.

Results and Discussion

A substituent on a sp^3-hybridized carbon atom of a cyclohexene cycle can occupy four nonequivalent spatial orientations: ψe, ψa, *e*, and *a* (see Figure 1). Regarding 3-piperideines, there are eight such substituent orientations (four pairs of nonequivalent ψe, ψa, *e*, and *a* orientations). Thus, monosubstituted compounds **1a**–**d** and **5a**,**e**,**h** (see Figure 5 and 7) represent 3-piperideines whose conformational equilibrium is determined by a methyl or a phenyl group, respectively, in different positions of the cycle.

No additivity of conformational energies is present evidently for vicinally dialkylated systems due to steric interactions between these substituents in synclinal conformation (for an analysis of the conformational energy in vicinally methylated cycles see, e.g., refs. [1a] and [7]). Also 1,3-disubstituted six-membered cycles possess a repulsive steric interaction in the 1,3-*a*,*a* (or *a*,ψa) conformation. Thus, 3-piperideines **1e**–**n**, **5b**–**d**,**f**,**g**,**i**,**j**, and **6a**–**d** (see Figure 6, 7, and 8) represent systems of nonadditive conformational energies.

Molecular mechanics as well as ab initio calculations were used for conformation analysis of these compounds (for details see Experimental Section).

a) Molecular mechanics calculations were performed using the MM3 force field[8a] implemented into the Macromodel 6.5 package.[8b, c] A Monte-Carlo-based conformational search (also a Macromodel utility) was applied to Ph-containing "multiconformer" systems. MM3 has already been used for the conformational analysis of some piperideines[9] although there was no evidence for satisfactory accuracy for these compounds. Nevertheless, the high accuracy of MM3-derived results for piperidines[10, 11a] permitted us to assume that this force field may be applicable to conformational analysis of their partially unsaturated analogues.
b) In contrast to alkylamines,[12] allylamines have not been explicitly parameterized in the force field frames. Therefore, quantum mechanical ab initio calculations have been employed in order to provide an independent estimation of conformational equilibrium in piperideines. The molecular geometry of piperideine conformers has been optimized on the HF/6-31G* level as well as on the MP2/6-31G* level of theory (i.e., taking into account the electron correlation energy).

We should mention that MM3-provided steric energy (E_s) partly takes into account the entropy contribution in the Gibbs energy at ambient temperature (see, e.g., ref. [11b]). Therefore, in order to compare the MM3- and ab initio derived data, our ab initio calculations provide results for the difference in full electron energy (ΔE) of conformers as well as for the difference in free energy ΔG^0_{calcd} (in harmonic approximation) of conformers at 298.15 K (at the MP2/6-31G* level).

The calculation accuracy was estimated by comparison of the obtained values of the conformational energy with the experimental data for cyclohexenes **2a**,**b**,[1a, 2b] piperidines **3a**[13] and **3b**, as well as piperideine **4**[14] (see Figure 2 for our data for **3b** and Figures 3 and 4 for the reported experimental values). The conformational equilibrium for tropane **3b** (in CD_2Cl_2) was measured by NMR spectroscopy at 185.1, 205.6, 216.1, and 226.6 K by the integration of the ^{13}C signal intensities for the major (*exo*-*N*-Me) and the minor (*endo*-*N*-Me) conformers (see Figure 2). The measured population of the minor conformer was 5, 7, 7, and 8.5% proceeding from the lowest temperature to the highest one. Thus, the ΔG^0 value is 1.1 kcal mol^{-1} in this temperature interval for the *exo*-*N*-Me–*endo*-*N*-Me conformational transformation of **3b**.[15] Taking into account a weak $\Delta G^0 - (T)$ dependence for this compound, we can conclude that our experimental data are in good agreement with the ab initio (for 298 K) as well as molecular mechanics calculation results for the conformational equilibrium in **3b**.

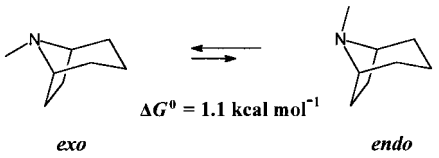

Figure 2. NMR-detected conformational *exo*–*endo* transformation for tropane **3b** (the ΔG^0 value determined in this work is shown).

Furthermore, NMR data for piperideine **1d** support qualitatively the calculation-based estimation of the conformational equilibrium for this compound. In spite of the observed dichotomy of the signals of the geminal ring protons of **1d** at low temperature (down to 165 K in CD_2Cl_2), that is, under

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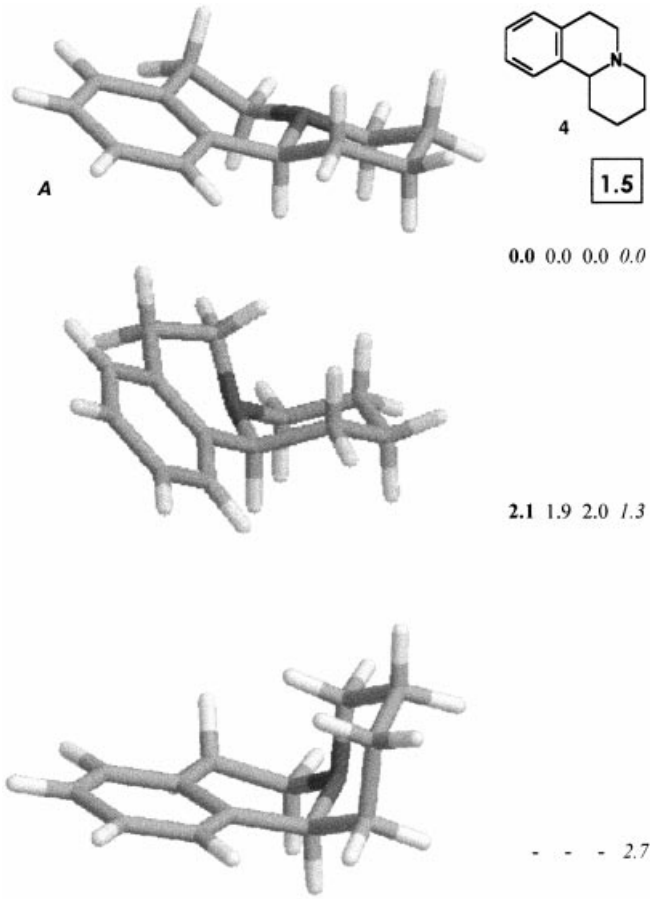

Figure 3. Optimized geometry (by MM3) and energy differences (kcal mol^{-1}; relative to the lowest-energy conformer by different calculation methods for the geometries optimized by these methods) of conformers of benzoquinolizidine **4**. The values in bold show the ΔG^0_{calcd} values calculated at the MP2/6-31G* level for 298.15 K and 1 atm. The second and the third value in each line are related to ΔE values calculated at the MP2/6-31G* and RHF/6-31G* level, respectively. The values in italics represent the MM3-derived ΔE_s values. Experimental ΔG^0 value (kcal mol^{-1}) at ambient temperature (in square) is taken from ref. [14].

conditions of slow conformational exchange, no signals for a minor conformer (with an α-*N*-Me group) were detected in ^{13}C as well as ^1H spectra. In other words, the minor conformer is present in less than 4–5%. The results from the ab initio as well as MM3 estimations also lie below this content limit (see Figure 5).

Values of ΔE (*in vacuum* approximation) for optimized structures for compounds **1a–m** and **4** are presented for the HF/6-31G* level as well as MP2/6-31G* level (Figures 3, 4, 5, and 6). Values of ΔG^0_{calcd} at 298.15 K for these compounds are presented for the MP2/6-31G* level. Also molecular mechanics-derived values of ΔE_s (steric energy difference; Figures 3–10) belong to *in vacuum* approximation. We can conclude that:

a) The MP2/6-31G* level is sufficient to estimate quantitatively the conformational equilibrium for six-membered flexible cycles: ab initio estimates of ΔG^0_{calcd} at 298 K for conformers of cyclohexenes **2a**,**b**, piperidines **3a**,**b**, and piperideine **4** deviate only by 0.1, 0.3, 0.1, 0.3, and 0.6 kcal mol^{-1} (0.4 kcal mol^{-1} for ΔE), respectively, from the experimental data (obtained for solutions of these compounds in nonpolar aprotic solvents). It also means that the influence of solvation effects on the conformational equilibrium is negligible for these compounds. Even taking into account only full electron energy gives a small correction in energy (the difference between ΔG^0_{calcd} vs. ΔE is 0.0–0.4 kcal mol^{-1}) for every *i*-conformer of most of the compounds. Only for one conformer for each of the compounds **1g**,**k** and **3a**, the difference is 0.8, 0.9, and 1.2 kcal mol^{-1}, respectively. At the same time, the 6-31G* level is less reliable: the difference between experimental and the 6-31G*-derived values of ΔE is 0.7 kcal mol^{-1} for compound **2a** and 0.6 kcal mol^{-1} for compound **3a**.

b) MM3-derived ΔE_s values are usually near the corresponding ab initio ΔG^0_{calcd} values (for 298 K) for the studied conformers of piperideines **1a–m**,**4** as well as of cyclohexenes **2a**,**b** and piperidines **3a**,**b**: linear regression analysis for ΔE_s and ΔG^0_{calcd} values (for 56 structures) gives the 0.3 kcal mol^{-1} value of the standard regression error. Such a good correlation between the differences in conformer energies, which have been provided by two quite different calculation methodologies, demonstrates a significant degree of reliability of the results. It shows also the applicability of MM3 for *quantitative* estimation of the conformational equilibrium for piperideines with a relatively large number of atoms (e.g., alkaloids).

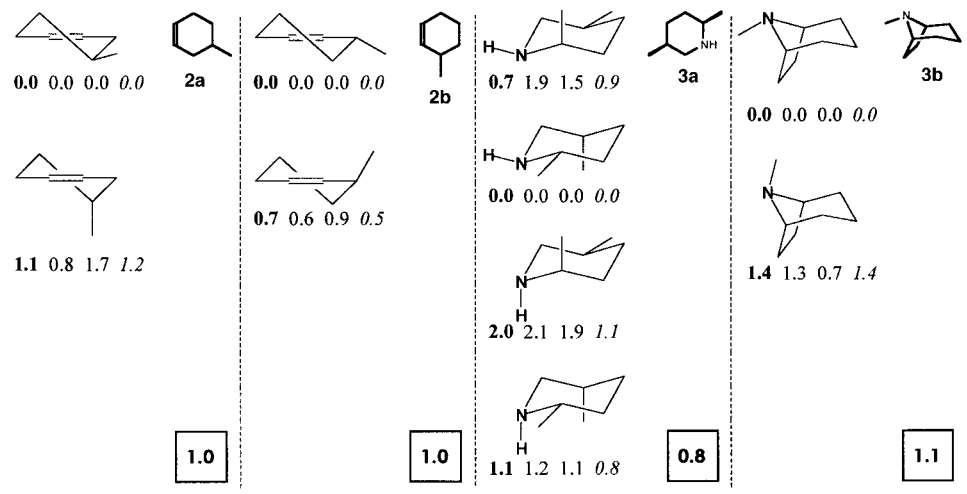

Figure 4. Calculated (values below the structures) and experimental (values in squares) relative energies (kcal mol^{-1}) for conformers of compounds **2a**,**b** and **3a**,**b**. The values in bold show ΔG^0_{calcd} values calculated at the MP2/6-31G* level for 298.15 K and 1 atm. The second and the third value in each line are related to ΔE values calculated at the MP2/6-31G* and RHF/6-31G* level, respectively. The values in italics represent the MM3-derived ΔE_s values. The experimental values for **2a**,**b** and **3a** are taken from refs. [1a, 2b, 13], respectively, and that for **3b** has been determined in this work.

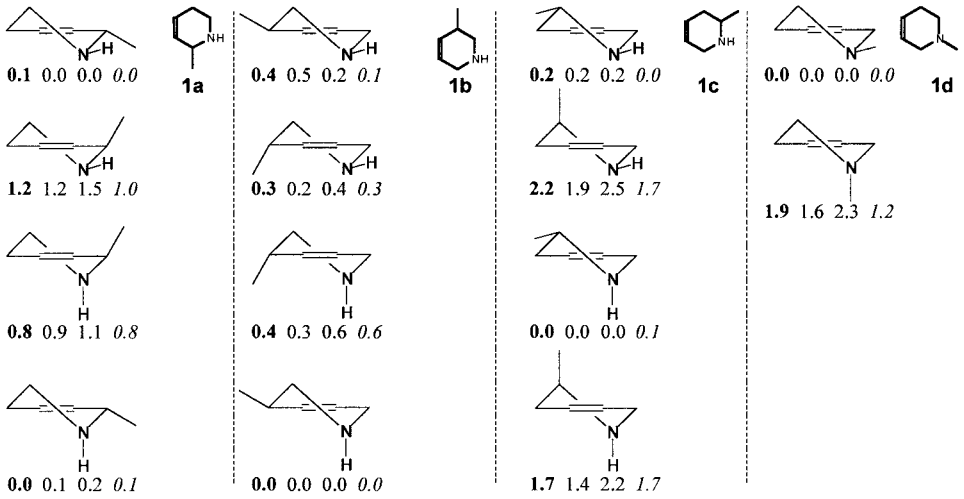

Figure 5. Relative energies (kcal mol^{-1}; the values are shown below the structures) for conformers of monomethyl piperideines **1a**–**d**. Calculated values are shown in the same manner as for Figure 4.

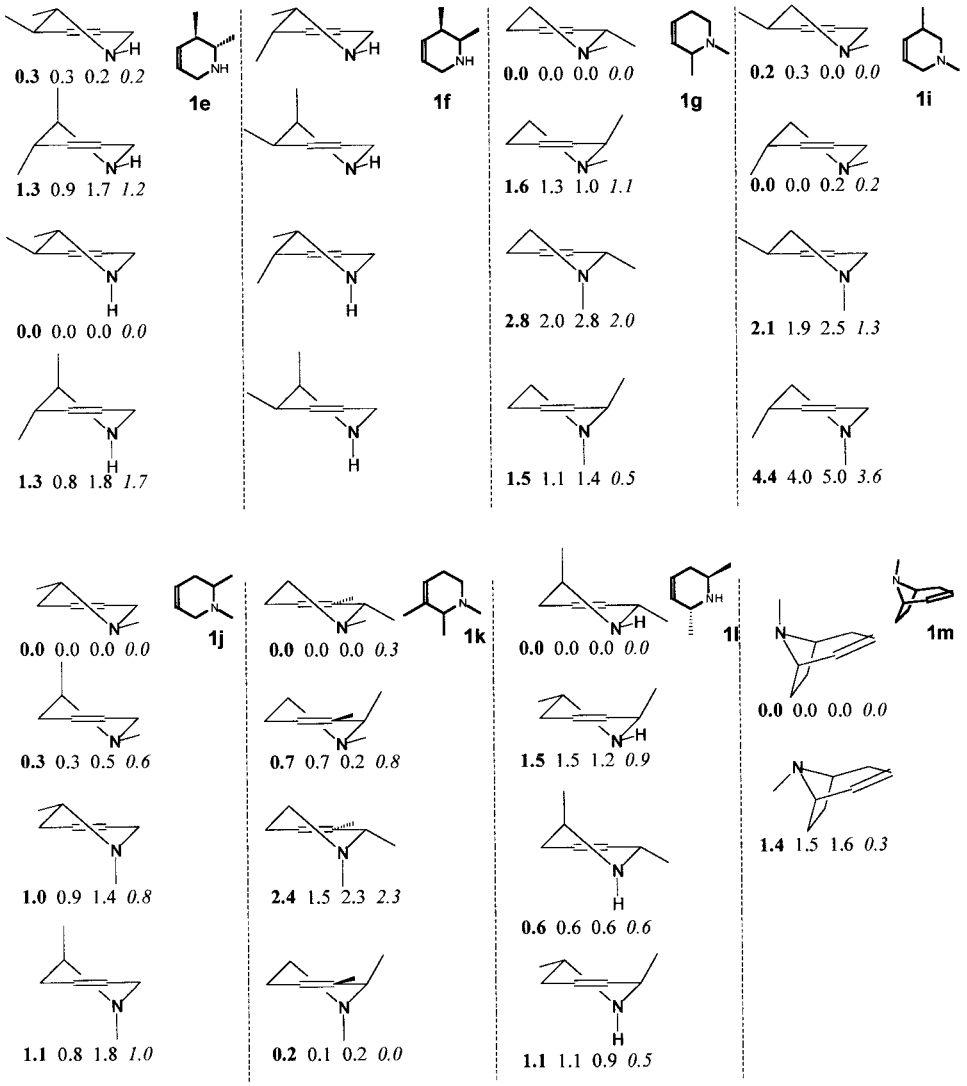

Figure 6. Energy differences (kcal mol^{-1}) for conformers of polysubstituted piperideines **1e**–**m** (relatively the lowest energy conformer for each compound; the values are depicted as in Figure 4). The piperideine cycle in **1m** adopts a sofa conformation.

Conformational preferences for the substituent orientation in 3-piperideines turn out to be more complicated than for cyclohexenes. Nevertheless, the obtained results may be classified as semiquantitative conformational rules and subrules, which describe substituent orientation (at 298 K) according to its position in the cycle. We consider here the ab initio derived results for the Me-substituted compounds and the molecular mechanics-derived ones for the Ph- as well as *t*Bu-substituted compounds. In rare cases, when the ΔG^0_{calcd} and ΔE_s values obtained by ab initio and molecular mechanics are essentially different for some conformers, the averaged value $[(\Delta G^0_{calcd} + \Delta E_s)/2]$ is taken into account (i.e., for compounds **1d** and **1m**). The scope of the rules is limited to piperideines without strong interactions between vicinal or 1,3-positioned substituents, while the subrules describe the systems with such steric interactions.

Position 1 rule: *No explicit preference for an e vs. a orientation of a N-H substituent and significant predominance* (*more than 1.0 kcal mol*$^{-1}$) *of an e orientation for a N-Me substituent*. The absolute value of the difference of ΔG^0_{calcd} for the lowest energy conformers, which differ only in spatial orientation of the nitrogen proton, does not exceed 0.3 kcal mol^{-1} for most of the studied *N*-H piperideines. Therefore, *N*-H piperideines do not appear to have an explicit tendency for an *e* or *a* orientation of the proton. Only for 6-Ph piperideines (compounds **5a**,**c**,**d**), a *ψe* orientation of the nitrogen proton predominates appreciably (more than 1.0 kcal mol^{-1} by MM3). In contrast, the *N*-Me group of unhindered 3-piperideines shows a definite trend to be *e*-oriented. Conformational energies for *N*-Me compounds **1g**–**j** and **5b**,**f**,**i** are more than 1.0 kcal mol^{-1}.

0947-6539/01/0721-4718 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 21

Subrule: A bulky vicinal α-substituent forces the *N*-Me group away from an *e* spatial position: the conformational preference for an *a* *N*-Me is 0.8 and 1.9 kcal mol^{-1} in 2- and 6-*t*Bu compounds **6c** and **6d**, respectively. Also for **1k**, the 3-Me group, which stabilizes a ψa orientation of the vicinal 2-Me group, almost equalizes the stability of conformers with *a* and *e* orientations of the *N*-Me substituent due to the absence of vicinal steric interactions for antiperiplanar 2-Me- and *N*-Me groups.

In the saturated tropane system **3b**, the *N*-Me group occupies mainly the *exo* position with respect to the six-membered ring,[15] which adopts a chair conformation (see Figure 2). Our calculations demonstrate that in 2-tropene **1m**, the six-membered ring possesses a sofa conformation with the N atom outside the ring plane (see Figure 6). In addition, the *endo* orientation of the *N*-Me group is significantly preferred.

Position 2 rule: *A moderate (0.5–1.0 kcal mol^{-1}) preference for a ψe orientation for a Me as well as a Ph group.* Indeed, conformational energies for *N*-H compounds **1a**, **1l**, **5e**, and **5g** (Figure 7) as well as *N*-Me piperideine **1g** lie in this value range.

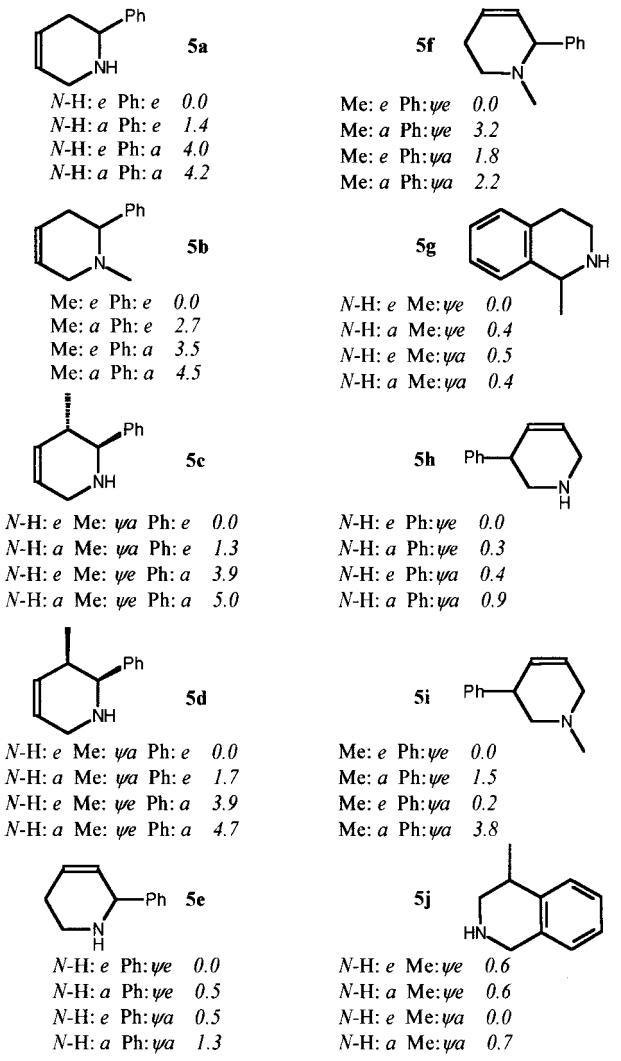

Figure 7. Relative steric energies (kcal mol^{-1}, by MM3; in italics) of conformers of piperideines **5a**–**j**. The values for the lowest energy rotamer among the Ph rotamer families are given for each substituent orientation.

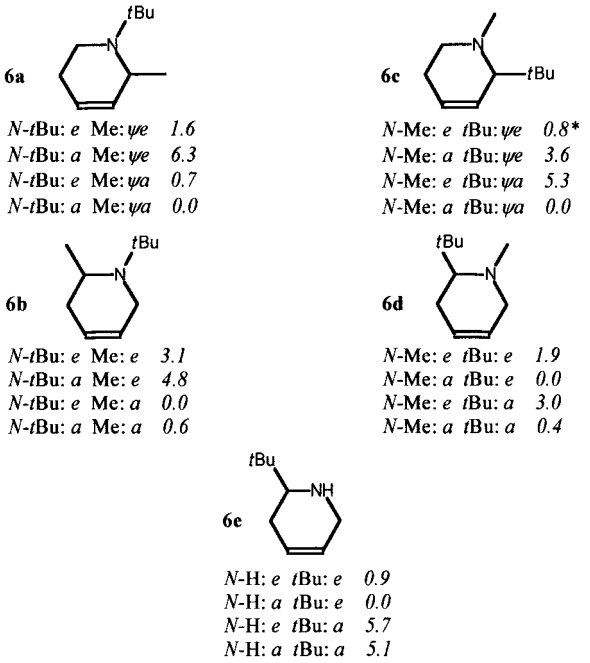

Figure 8. Relative steric energies (kcal mol^{-1}, by MM3; in italics) for conformers of piperideines **6a**–**e**. The asterisk indicates a sofa conformation with the C-6 atom out the plane.

Subrule: The presence of a *N*-Me substituent may increase the population of the 2-ψe conformer (e.g., for *N*-Me piperideine **5f** the conformational energy is 1.8 kcal mol^{-1}). However, a bulky *N*-*t*Bu substituent leads to a significant predominance of the ψa orientation for the 2-Me group (the difference between the lowest energy 2-ψe- and 2-ψa-oriented conformers for **6a** (Figure 8) is 1.6 kcal mol^{-1}).

Position 5: *No appreciable preference for a ψe or ψa orientation*. Our calculations show a slight predominance of the ψe orientation in compounds **1b**, **5h**, and **5i** (by 0.4, 0.4, and 0.2 kcal mol^{-1}, respectively), while a ψa orientation is slightly preferred in piperideines **1i** and **5j** (for 0.2 and 0.6 kcal mol^{-1}, respectively).

For **1l**, a *trans* compound with sterically noninteracting methyl groups, the conformation with a 2-ψe-oriented Me group should be favored over the conformation with a 5-ψe-oriented Me group in the 2-ψe-Me,5-ψa-Me $\leftrightarrow$ 2-ψa-Me, 5-ψe-Me conformational equilibrium due to the additivity of conformational energies. Indeed, MP2/6-31G*-based and MM3 calculations give 1.1 and 0.5 kcal mol^{-1} values of conformational energy, respectively, in favor of the conformer with a 2-ψe-oriented Me group (these values include also a contribution of the *N*-H substituent).

Subrule: A vicinal 6-substituent stabilizes a ψe orientation of the 5-Me group in *trans*-disubstituted cycles (1.3 and 3.9 kcal mol^{-1} for conformational energy for 6-Me and 6-Ph compounds **1e** and **5c**, respectively) and stabilizes a ψa orientation in *cis*-disubstituted cycles (-1.6 and -3.9 kcal mol^{-1} for the conformational energy for 6-Me and 6-Ph compounds **1f** and **5d**, respectively).

Position 6: *A significant predominance* (*more than 1.0 kcal mol*$^{-1}$) *of the* e *orientation for the 6-substituent in N-H compounds.* *N*-H piperideines **1c**, **1e**, **1f**, **5a**,**c**,**d**, and **6e** as well as *N*-Me piperideine **5b** adopt a conformation with an *e*-oriented 6-substituent. The energy difference between the lowest energy conformer and the corresponding conformer with an *a* orientation of the 6-Me group is higher than 1.3 kcal mol^{-1}.

Subrule: *N*-Substitution decreases this *e*/*a* ratio due to vicinal *gauche*-interactions between 1- and 6-positioned substituents. The energy difference between 6-*e*- and 6-*a*-conformers is 0.3 and -3.1 kcal mol^{-1} for *N*-Me compound **1j** and *N*-*t*Bu compound **6b**, respectively (i.e., increase of the bulkiness of the *N*-alkyl substituent leads to predominance of an *a*-6-Me orientation). Nevertheless, for 2,6-*cis*-disubstituted compounds, the content of the 1,3-*a*,ψa conformer is decreased due to the 1,3-*a*,ψa steric interactions between 2,6-substituents (see Figure 9); this is similar to the negligible content of 1,3-diaxial conformers in piperidine cycles even though these interactions are weaker than those in saturated six-membered rings (see example of *cis*-piperideine **1n** in Figure 9).

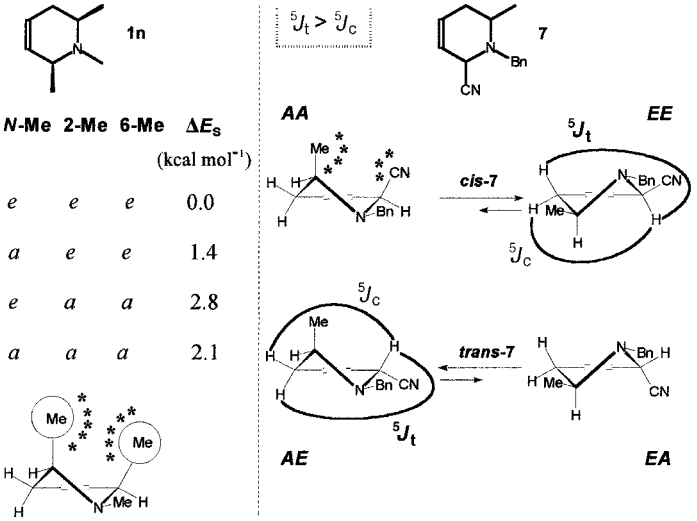

Figure 9. Assignment of isomers of piperideine **7** to the *cis* and *trans* series based on the literature NMR[5a] as well as MM3 data for *cis* compound **1n**. Larger pseudoallylic coupling constants (^5J_t) are marked in bold. Asterisks depict 1,3-*a*,ψa steric interactions.

Below we present a few examples of how the above rules can assist in studies of the stereochemistry of 3-piperideines.

a) It was concluded from CD spectra of 1-methyl tetrahydroisoquinolines (including **5g**; as free amines in MeOH) that the Me group adopts a ψa orientation.[6] According to the Position 2 rule (see, e.g., the results for **5g**), the *opposite* orientation should be favored.

We maintain that the evidence for the CD-based estimation of the conformational equilibrium is weak. The above CD study[6] is based on the application of the Craig semiempirical quadrant model.[16] The Craig model considers tetrahydroisoquinolines with a protonated nitrogen atom,[16] while no appreciable *N*-protonation is present under the employed conditions of the CD measurement[6] (amines are only H-bonded in alcohol solutions[17a–c] but they are too weak as bases to cause formation of alkoxide anions). Simply stated, the Craig quadrant model is not applicable to free amines. Indeed, quite recently unambiguous ^{1}H NMR data for some methyl tetrahydroisoquinolines[18] actually confirm our remark regarding the scope of the Craig model (unfortunately, the observed discrepancy between the NMR and CD spectra based estimations of the conformational equilibrium was explained[18] by a limitation of the Craig model and not by its incorrect use). In contrast, the above rules provide a reliable conformational analysis of tetrahydroisoquinolines. For instance, our calculations, in good agreement with the experimental quantitative results for a *free* amine,[14] demonstrate a strong predominance of conformation ***A*** of tricyclic analogue **4** with a ψe orientation for the alkyl substituent neighboring the nitrogen atom (see Figure 3). Another example is 6,7-dimethoxy-1-phenyltetrahydroisoquinoline: as could be expected from the Position 2 rule, x-ray analysis found the phenyl group to be ψe-oriented.[19]

b) On the basis of ^{1}H NMR spectra,[5a] isomers of 2,6-disubstituted piperideine **7** were assigned to the *cis* and *trans* series, and it was claimed that a half-chair with ψa-2-CN and *a*-6-Me groups is the favored conformation for the *cis* isomer of **7** (conformation ***AA*** in Figure 9). However, the Position 6 subrule establishes a preference for the conformation without 1,3-*a*,ψa interactions, that is, a half-chair with ψe-2-CN and *e*-6-Me substituents. These conflicting conclusions led us to review the NMR-based analysis[5a] for isomers of **7**.

Indeed, it was correctly established (see ref. [5a] for arguments) that the 6-Me group is *a*-oriented for one isomer (assigned *cis*) and *e*-oriented for the other (assigned *trans*). This means that only conformers ***AA*** and ***EA*** should be considered as predominant according to this assignment. On the other hand, higher values of homoallylic coupling constants (^5J) for protons 2-H and 5-H$_{\psi ax}$ versus the constants for the 2-H and 5-H$_{\psi eq}$ protons have been detected for both isomers. Since homoallylic constants are consistently larger for cyclic *trans* protons versus *cis* protons,[20a, b] only conformers ***EE*** and ***AE*** satisfy the magnitudes of the measured ^5J constants. Hence, the conformational analysis results in an unexpected conclusion: the former *cis*–*trans* assignment[5a] for isomers of **7** should be reversed. The isomer, which was assigned to the *cis* geometry, is the *trans* isomer and vice versa. Now the NMR data[5a] for **7** fit well with the predominance of conformers ***EE*** and ***AE*** for the *cis* and *trans* isomers, respectively. Thus, the Position 6 rule predicts the conformational equilibrium for *cis*-**7** correctly.

c) Preliminary studies of the stereochemistry of disubstituted piperideines **8** (synthetic precursors of some alkaloids) concluded that the isolated isomer possesses a *trans* configuration and adopts a conformation with ψa-5-PhSO$_2$ and *a*-6-Ar groups[21a, b] (conformation ***AC***$_s$ in Figure 10 for the 6-(*p*-MeC$_6$H$_4$)-substituted compound **8a**). The conclusion was based on taking into account a relatively small coupling constant between 5-H and 6-H protons (2.7 – 3.5 Hz) as well as NOE interactions between aromatic and ring protons.[21a, b] However, these preliminary conformation-related conclusions contradict the Position 5 and 6 rules (see, e.g., a total predominance for the conformation with synclinal orientation

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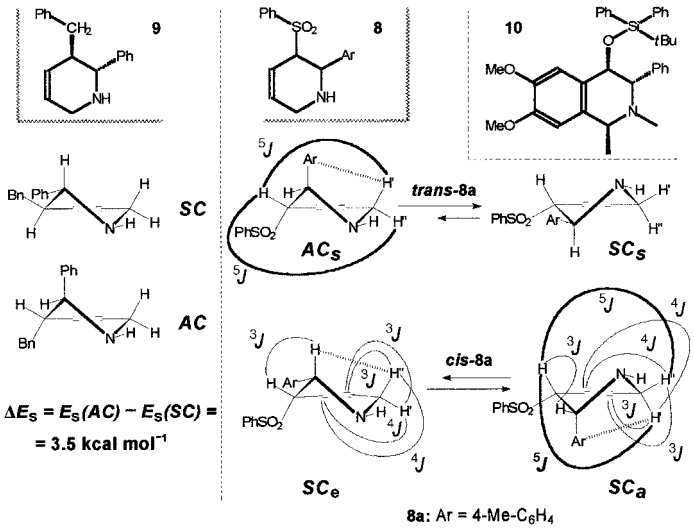

Figure 10. Conformational equilibrium for 5-$PhSO_2$-6-Ar-disubstituted piperideines. Conformations with anticlinal and synclinal orientation of Ph and $PhSO_2$ groups are depicted ***AC*** and ***SC***, respectively. Arcs show selected H,H-spin–spin couplings (a larger homoallylic coupling constant ^5J is marked in bold). Dotted lines depict selected NOE interactions.

of 5- and 6-substituents in *trans* compound **5c**; Figure 7). MM3-based calculations for a sterically close analogue **9** of *trans* geometry demonstrate an ultimate preference for synclinal conformation ***SC***: the minimal energy conformers, which have been found by a Monte-Carlo-based conformation search among the conformers of the ***AC*** and ***SC*** families, differ by 3.5 kcal mol^{-1} (Figure 10).[22]

Therefore we again turned to ^{1}H NMR data[21a–c] for these piperideines. The above-mentioned small vicinal constant ^3J, for example, for **8a** (2.9 Hz) excluded fully the presence of conformer $\boldsymbol{SC}_s$ in an appreciable amount. However, also a prevalence of conformation $\boldsymbol{AC}_s$ does not correspond to the NMR data. The detected NOE enhancement of a moderate magnitude for one *ortho* proton (at $\delta = 7.14$) of the 6-aromatic substituent and the upfield 2-H′ proton (at $\delta = 3.08$; see Figure 10) of the piperideine ring indeed confirms the presence of the half-chair with *a* and *ψa* orientation of these ring substituents, respectively (as in $\boldsymbol{AC}_s$). A lower vicinal coupling constant ^3J for the proton pair 2-H′–3-H (2.7 Hz) than for the pair 2-H″(at $\delta = 3.37$)–3-H (3.6 Hz) also indicates some predomination of the *ψa* orientation of proton 2-H′ (dihedral angle between the protons of each pair is obviously larger in the case of the first pair; see Figure 1). Nevertheless, a homoallylic spin–spin interaction of the 2-H′ proton with the 5-H proton is stronger ($^5J = 3.1$ Hz) than a similar interaction of the 2-H″ proton ($^5J = 1.5$ Hz). As mentioned above, a larger coupling homoallylic constant belongs to the spin–spin interaction of the *trans* protons. Thus, the protons 5-H and 2-H′ are in a *trans* relationship. These data indicate that the reported[21a, b] isomers of piperideines **8** possess a *cis* configuration of 5- and 6-substituents (and not a *trans* configuration).

The close values of vicinal spin–spin coupling constants for 2-H′–3-H and 2-H″–3-H (see above) as well as the equal values of allylic coupling constants ^4J for the 2-H′–4-H and 2-H″–4-H interactions (2.1 Hz) for **8a** show that the NMR spectra of these compounds correspond to a time-averaged mixture of conformers $\boldsymbol{SC}_a$ and $\boldsymbol{SC}_e$ with some predominance of $\boldsymbol{SC}_a$. Also the sets of observed NOE interactions[21a–c] for **8** (e.g., the moderate interactions between 2-H′ and the *ortho* proton as well as 2-H″ and 6-H in **8a**; Figure 10) satisfy this time-averaged "virtual" conformation, while separate structures $\boldsymbol{SC}_a$ and $\boldsymbol{SC}_e$ do not fit.

Thus, the above conformation rules can be a useful tool for stereochemical studies of piperideines, even including those bearing some functionalized substituents. Nevertheless, we are aware of the limitations of these general rules since they cannot obviously comprise all possible substitution types. For instance, a conformation of type ***AC***, which is quite unfavorable for 5,6-*trans* compounds **5c** and **9**, is the most stable conformation for the more crowded *trans* analogue **10** in the solid state.[23] While it contradicts the Position 5 subrule, the established conformational preference for **10** may be predicted a priori by taking into account steric interactions between the α-positioned Ph group and the extremely bulky β-substituent of the piperideine ring.

Experimental Section

The commercially available hydrochloride of **1b** and tropane **3b** (Aldrich) were used for NMR studies (**1b** · HCl was transformed into the free amine before the NMR experiments). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DMX-600 spectrometer, with TMS as internal standard. Samples (≈30 mg in 0.5 mL CD_2Cl_2) were equilibrated for ≈10 min at each temperature before measuring. Temperatures were measured with a calibrated Eurotherm 840/T digital thermometer and were believed to be accurate to 0.5 K.

Molecular mechanics calculations were performed using MM3 as well as Amber force fields (Macromodel 6.5 package[8b, c]). The *no solvent* as well as *distance-dependent dielectric electrostatics* options were employed for the energy minimization. The *Monte-Carlo* option was used for the conformational search in the case of Ph-containing compounds (generation of 5×10^4 structures for each compound with the energy upper limit 5 kcal mol^{-1} from the lowest-energy conformer found).

Geometry of MM3-minimized structures was used as the starting geometry for ab initio calculations (Gaussian 98 package[24]) for the gas phase. Initial ab initio geometry optimization was performed at the restricted Hartree–Fock level using the 3-21G basis set. The resulting geometry was optimized at the 6-31G* level and then at the MP2/6-31G* level. Free energies were calculated at the MP2/6-31G* level within the limits of harmonic approximation of vibrational frequencies implemented into a standard Gaussian 98 procedure.

Acknowledgements

Financial support of this research by the governmental KAMEA program and by the Marcus Center for Medicinal Chemistry is gratefully acknowledged. The Bar-Ilan University research grant to A.M.B. is also acknowledged. We thank Drs. R. Kumareswaran and T. Balasubramanian for supplying NMR data of phenylsulfonyl piperideines synthesized by them.

[1] a) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 700–732; b) S. McN. Sieburth, *J. Chem. Soc. Chem. Commun.* **1994**, 1663–1666; c) F. A. L. Anet in *Conformational Analysis of Cyclohexenes, Cyclohexadienes and Related Hydroaromatic Compounds* (Ed.: P. W. Rabideau), VCH, New York, **1989**, pp. 3–45.

[2] a) J. B. Lambert, D. E. Marko, *J. Am. Chem. Soc.* **1985**, *107*, 7978 – 7982; b) R. V. Concepcion, J. J. Breeyear, J. G. Jewett, C. H. Bushweller, *J. Phys. Org. Chem.* **1998**, *11*, 84 – 90; c) L. Došen-Mićović, B. Šolaja, *J. Phys. Org. Chem.* **1995**, *8*, 89 – 93.
[3] a) K. Wiesner, *Alkaloids*, Butterworths, London, University Park Press, Baltimore, **1973**, pp. 2 – 143; b) J. Mukherjec, M. Menge, *Adv. Biochem. Eng./Biotechnol.* **2000**, *68*, 1 – 20; c) S. Urban, S. J. H. Hickford, J. W. Blunt, M. H. G. Munro, *Curr. Org. Chem.* **2000**, *4*, 765 – 807; d) Although amines are protonated under physiological conditions, some receptors are activated by the nonprotonated form of alkaloids: A. Goldblum, G. H. Loew, *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1991**, *206*, 119 – 131; e) B. J. Oleksyn, A. Suszkopurzcka, G. Dive, J. Lamottebrasseur, *J. Pharm. Sci.* **1992**, *81*, 122 – 127.
[4] S. M. Bachrach, M. Liu, *Tetrahedron Lett.* **1992**, *33*, 6771 – 6774.
[5] a) M. Bonin, J. R. Romero, D. S. Grierson, H.-P. Husson, *J. Org. Chem.* **1984**, *49*, 2392 – 2400; b) Diastereomeric structures resulting from N-inversion as well as ring inversion are undoubtedly conformers, see, for example, N. S. Zefirov, *Tetrahedron* **1977**, *33*, 3193 – 3202.
[6] T. Shimonara, A. Takeda, J. Toda, T. Sano, *Chem. Pharm. Bull.* **1998**, *46*, 430 – 433.
[7] A. M. Belostotskii, A. B. Shapiro, T. V. Timofeeva, Yu. T. Struchkov, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1991**, *40*, 77 – 82.
[8] a) N. L. Allinger, Y. Yuh, J.-H. Lii, *J. Am. Chem. Soc.* **1989**, *111*, 8551 – 8582; b) M. Saunders, K. N. Houk, Y. D. Wu, W. C. Still, M. Lipton, G. Chang, W. C. Guida, *J. Am. Chem. Soc.* **1990**, *112*, 1419 – 1427; c) F. Mohamadi, N. G. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440 – 467.
[9] A. F. Ibanez, G. Y. Moltrasio, J. M. Delfino, *J. Heterocycl. Chem.* **1996**, *33*, 265 – 270.
[10] A. M. Belostotskii, P. Aped, A. Hassner, *J. Mol. Struct.* **1998**, *429*, 265 – 273.
[11] a) A. M. Belostotskii, H. E. Gottlieb, P. Aped, A. Hassner, *Chem. Eur. J.* **1999**, *5*, 449 – 455; b) A. M. Belostotskii, H. E. Gottlieb, A. Hassner, *J. Am. Chem. Soc.* **1996**, *118*, 7783 – 7789.
[12] L. R. Schmitz, N. L. Allinger, *J. Am. Chem. Soc.* **1990**, *112*, 8307 – 8315.
[13] E. L. Eliel, D. Kandasamy, C. Yen, K. D. Hargrave, *J. Am. Chem. Soc.* **1980**, *102*, 3698 – 3707.
[14] M. Sugiura, N. Takao, K. Iwasa, Y. Sasaki, *Chem. Pharm. Bull.* **1978**, *26*, 1901 – 1907.
[15] A slightly lower value of ΔG^0 for **3b** (0.91 kcal mol^{-1}) has been measured by NMR in $CFCl_3$: H.-J. Schneider, L. Sturm, *Angew. Chem.* **1976**, *88*, 574 – 575; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 545 – 546.
[16] J. C. Craig, S.-Y. C. Lee, R. P. K. Chan, I. Y.-F. Wang, *J. Am. Chem. Soc.* **1977**, *99*, 7996 – 8002.
[17] a) U. Berg, W. P. Jencks, *J. Am. Chem. Soc.* **1991**, *113*, 6997 – 7002; b) E. Grunwald, E. K. Ralph, *Acc. Chem. Res.* **1971**, 107 – 113; c) S. Tripathy, G. S. Roy, B. B. Swain, *Indian J. Pure Appl. Phys.* **1993**, *31*, 828 – 833.
[18] J. Toda, S. Matsumoto, T. Saiton, T. Sano, *Chem. Pharm. Bull.* **2000**, *48*, 91 – 98.
[19] T. A. Olszak, A. Stepien, M. J. Grabowski, E. Brzezinska, *Acta Crystallogr. Sect. C* **1996**, *52*, 1038 – 1040.
[20] a) C. Mahaim, P.-A. Carrupt, P. Vogel, *Helv. Chim. Acta* **1985**, *68*, 2182 – 2194; b) M. Barfield, S. Sternhell, *J. Am. Chem. Soc.* **1972**, *94*, 1905 – 1913.
[21] a) T. Balasubramanian, A. Hassner, *Tetrahedron: Asymmetry* **1998**, *9*, 2201 – 2205; b) R. Kumareswaran, T. Balasubramanian, A. Hassner, *Tetrahedron Lett.* **2000**, *41*, 8157 – 8162; c) R. Kumareswaran, T. Balasubramanian, A. Hassner, unpublished results (personal communication).
[22] This difference is 4.5 and 4.3 kcal mol^{-1} for sulfone **8a** by MM3 and Amber force fields, respectively. However, we consider these results only a crude qualitative estimation since the reliability of parameters of these force fields is dubious in the case of functionalized piperideine **8a**.
[23] J. L. Pizarro, M. I. Arriortua, I. Telliti, D. Badia, E. Domingues, L. Ochando, J. M. Amigo, T. Debaerdemaeker, *Acta Crystallogr. Sect. C* **1997**, *53*, 355 – 358.
[24] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**..

Received: April 23, 2001 [F3216]

  0947-6539/01/0721-4722 $ 17.50+.50/0