# Conformational Analysis. 50. *C*-Methyl-1,2,3,4-tetrahydroisoquinolines†

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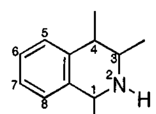
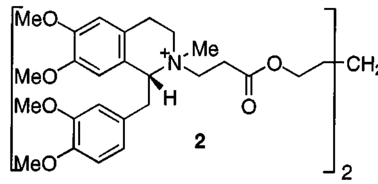
Conformational equilibria in 1-, 3-, and 4-methyl-1,2,3,4-tetrahydroisoquinolines (THIQs) and the diastereomeric pairs of their 1,3- and 1,4-dimethyl homologs have been determined by measurement of $H_3/H_4$(*trans*) coupling constants and have been confirmed by molecular mechanics [MMP2(85)] calculations. The experimental $-\Delta G°$ values (a → e) for the monomethyl compounds (computed values in parentheses) in kcal mol$^{-1}$ are Me-1, 0.56 (0.46); Me-3, 1.63 (1.53); and Me-4, −0.32 (−0.22). Agreement of experimental and calculated values is very good as is the additivity of values for the dimethyl compounds (Table 1). Values for the corresponding hydrochlorides are Me-1, 0.19 (−0.34); Me-3, l.15 (1.46); and Me-4, 0.35 (0.10) kcal mol$^{-1}$. The less than satisfactory agreement of experimental with computed data here is probably due to neglect of solvation. The very small or negative $\Delta G°$ values for Me-1 and Me-4 were ascribed not only to the pseudoaxial (rather than axial) nature of Me(ax) and the absence of a syn-axial hydrogen on the side of the benzene ring but also to a peri interaction with H(8) and H(5), respectively, destabilizing equatorial methyl at positions 1 and 4. This was confirmed by comparing computed conformational energy values with values at corresponding positions in $\Delta^{3,4}$-tetrahydropyridines (THPs). While $\Delta G°$ in the two series is the same for Me-3 (THIQ numbering), that for Me-1 and Me-4 is considerably smaller in the THIQ than in the THP series which latter is devoid of peri hydrogens.

## Introduction

The 1,2,3,4-tetrahydroisoquinoline (THIQ) skeleton (**1**) is found in a variety of alkaloids[1] such as laudanosine [1-[(3′,4′-dimethoxyphenyl)methyl]-2-methyl-6,7-dimethoxy-THIQ], salsoline (1-methyl-6-hydroxy-7-methoxy-THIQ), and anhalonidine (1-methyl-6,7-dimethoxy-8-hydroxy-THIQ). It also occurs in the recently commercially available[2] THIQ-3-carboxylic acid and the 1-substituted bis(1,2,3,4-tetrahydroisoquinolinium) quaternary salts[3] such as atracurium used in general anesthesia (**2**). Despite its wide occurrence, no systematic study has been made of the conformational equilibrium (axial → equatorial) of substituents on the heterocyclic ring of THIQ. In an early X-ray crystallographic study of quaternary salts[4] it was found that this ring has the shape of a half-chair (**3**), a conclusion which was confirmed in later studies of 1-[5] and 3-substituted[6] THIQs.



**1**



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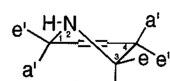

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In the present work we have investigated the conformational equilibria and associated conformational energies ($-\Delta G°$) of the 1-, 3-, and 4-methyl and *cis*- and *trans*-1,3- and 1,4-disubstituted THIQs, both experimentally and computationally. The corresponding energy differences in the saturated system, methyl- and dimethyl-substituted piperidine, have been studied in the past both by low-temperature $^{13}C$ NMR spectroscopy[7] and by molecular mechanics calculation,[8] with good agreement between the two methods. Unfortunately the low-temperature NMR method is not applicable to the THIQs, since the heterocyclic ring, being an analog of cyclohexene,[9] has an inversion barrier so low that we were not able to "freeze out" individual conformers even at −120 °C. We therefore chose the high-resolution $^{1}H$ NMR measurement of the coupling constants of protons located

+ Dedicated to Professor Norman L Allinger on the occasion of his 7oth birthday.

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(3) (a) Stenlake, J. B.; Waigh, R. D.; Dewar, G. H.; Urwin, J.; Dhar, N. C. Patentoffenlegung DE2655883, 1975. (b) Stenlake, J. B.; Waigh, R. D.; Dewar, G. H.; Dhar, N. C.; Hughes, R.; Chapple, D. J.; Lindon, J. C.; Ferige, A. G.; Cobb, P. H. *Eur. J. Med. Chem.* **1984**, *19*, 441−450. (c) Dhar, N. C.; Maehr, R. B.; Masterson, L. A.; Midgley, J. M.; Stenlake, J. B.; Wastila, W. B. *J. Med. Chem.* **1996**, *39*, 556−561 and references there cited.

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(5) Charifson, P. S.; Bowen, J. P.; Wyrick, S. D.; Hoffman, A. J.; Cory, M.; McPhail, A. T.; Mailman, R. B. *J. Med. Chem.* **1989**, *32*, 2050−2058.

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(7) Eliel, E. L.; Kandasamy, D.; Yen, C.-Y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698−3707.

(8) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907−1918.

(9) The barrier in cyclohexene is 5.3 kcal mol$^{-1}$: Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147−3150. Jensen, F. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 5774−5782.

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*trans* to each other at positions 3 and 4 as the experimental method.[10] Molecular mechanics calculations were effected with the MMP2(85)[11] program.

## Synthesis

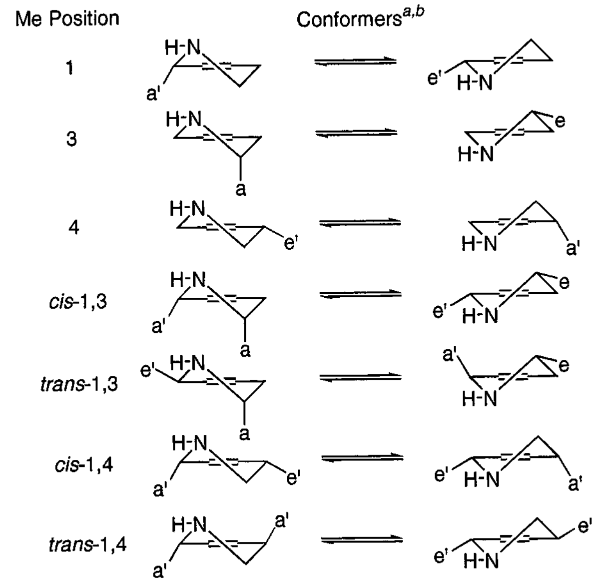
2-Phenylethylamine and its 1- and 2-methyl-substituted homologs were either commercially available or prepared by standard procedures. Formylation of the appropriate amine and Bischler–Naperialski ring closure followed by sodium borohydride reduction provided 1,2,3,4-tetrahydroisoquinoline or its 3- or 4-methyl substituted homologs, respectively. Similarly, acetylation of the amine, ring closure and reduction provided the 1-methyl, 1,3-dimethyl, and 1,4-dimethyl homologs. In the latter two cases the stereoisomers were separated by chromatography: HPLC in the case of the 1,3-, and GC in the case of the 1,4-isomers.

## Methodology

To obtain credible results for the conformational equilibria of methyl- and dimethyl-substituted THIQs, we chose to employ two entirely independent approaches as indicated above, one experimental, the other computational. While the computational approach had proved very successful with methylisochromanes,[12] there was no *a priori* assurance that it would work equally well with the nitrogen analogs, although the piperidine calculations mentioned earlier[8] were a good omen in this regard. On the other hand, while calculations on the position of conformational equilibria from averaged coupling constants have been used frequently and often with good outcome,[10] the problem of the model constants to be used always looms. In view of our inability to freeze out individual conformers, coupling constants had to be inferred indirectly from conformationally averaged spectra. And while it was similarly impossible to see individual conformers in the $^{13}$C NMR spectrum, the positions of $^{13}$C signals in the averaged spectra were used to confirm qualitatively the more precise results obtained from proton coupling constants.

Calculated and experimental results of the free energy differences between the two conformers (a → e) of 1-, 3-, and 4-methyl-1,2,3,4-THIQ and the corresponding *cis* and *trans* isomers of the 1,3- and 1,4-dimethyl compounds (Scheme 1) are shown in Table 1. The model coupling constants were obtained as follows: It was assumed that the *cis*-1,3-dimethyl derivative would exist exclusively in the conformation with both methyl groups equatorial. The large coupling constant in this compound, 11.00 Hz, was thus assumed to be $J_{H3a/H4a}$. Unfortunately there is no $H_{3e}$ in this compound, so $J_{H3e/H4e}$ had to be computed indirectly as follows: The 1-methyl compound displays both $J_{3a^*/4a'^*}$ (8.70 Hz) and $J_{3e^*/4e'^*}$ (5.14 Hz); the starred subscripts indicate that both coupling constants, while predominantly axial/axial or equatorial/equatorial, are in fact averaged by the equilibration of the two conformers of the 1-methyl compound. Now, it can be readily shown[13] that the sum of the *trans* coupling constant is constant; i.e., $J_{3a/4a} + J_{3e/4e} = J_{3a^*/4a'^*} + J_{3e^*/4e'^*}$. Numerically, $11.00 + J_{3e/4e} = 8.70 + 5.14$ when $J_{3e/4e} = 2.84$ Hz.[14] Given thus the values of the two *trans* coupling constants, one can calculate conformational equilibria for all other compounds using the equation[15] $K = (J - J_{ee})/(J_{aa} - J)$ where $J_{ee} = 2.84$ Hz, $J_{aa} = 11.00$ Hz, and $J$ is the observed $H_{3,4-trans}$ shown in Table 2. The equilibrium compositions and free energy differences shown in Table 1 are derived thus. [This treatment assumes that the methyl substituents do not affect the magnitude of $J_{H3/H4}$ (*trans*).]

**Scheme 1**




[a] Lowest-energy conformer is on right. [b] Methyl substituents are at positions a, a′, e, and e′.

**Table 1. Conformational Equilibria and Free Energy Differences for Methyl- and Dimethyl-Substituted 1,2,3,4-Tetrahydroisoquinolines**

| | conformer ratio[a] | | $-\delta G°$, kcal mol$^{-1}$ | |
|---|---|---|---|---|
| substituent(s) | exptl | calcd[b] | exptl | calcd[b] |
| 1-Me | 72/28 | 68/32 | 0.56 | 0.45 |
| 3-Me | 94/6 | 93/7 | 1.63 | 1.53 |
| 4-Me | 37/63 | 41/59 | −0.32 | −0.22 |
| *cis*-1,3-$Me_2$ | (100/0)[c] | 99.8:0.2 | large | 3.68 |
| *trans*-1,3-$Me_2$[d] | 88/12 | 85/15 | 1.18 | 1.03 |
| *cis*-1,4-$Me_2$[e] | 78/22 | 75/25 | 0.75 | 0.65 |
| *trans*-1,4-$Me_2$[e] | 59/41 | 58/42 | 0.22 | 0.19 |

[a] Axial to equatorial conformer. [b] By MMP2(85) assuming $\Delta S = 0$. Separate calculations were performed for structures with equatorial and axial NH; the ratios shown are, in each case, for the sums of the populations of these two structures. [c] In the case of the experimental result, this is an assumed value, based on the calculated one. [d] 3a → 3e. [e] 1a → 1e.

## Results

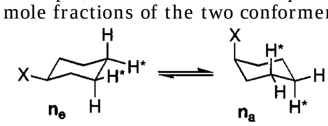
Before discussing the results a few checks on accuracy are in order. The agreement between experimental and calculated results (Table 1) is very satisfactory, considering that they were obtained by totally different methods.

(10) The earliest application of this method we could find is by LaBlanche–Combier, A.; Levisalles, J.; Pete, J.-P.; Rudler, H. *Bull. Soc. Chim. Fr.* **1963**, 1689–1701. See also: Eliel, E. L.; Wilen, S, H. *Stereochemistry of Organic Componds*; Wiley: New York, 1994; pp 641.

(11) Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581–603.

(12) Olefirowicz, E. M.; Eliel, E. L. *J. Comput. Chem.* **1989**, *10*, 407–412.

(13) Take, for example, the conformational equilibrium with $n_e$ and $n_a$ representing mole fractions of the two conformers.




Let us call the coupling constant for diaxially disposed protons $J_{aa}$ and that for diequatorially disposed protons $J_{ee}$. The coupling constant for the unmarked set is $J = n_eJ_{aa} + n_aJ_{ee}$ (i) and that for the starred set is $J^* = n_eJ_{ee} + n_aJ_{aa}$. Adding the two equations, $J + J^* = (n_e + n_a)J_{ee} + (n_e + n_a)J_{aa}$. But $n_e + n_a = 1$; hence, $J + J^* = J_{ee} + J_{aa}$ which is a constant.

(14) Regarding the unusually low $J_{ee}$ coupling constants of protons antiperiplanar to electronegative atoms (in this case N), see: Booth, H. *Tetrahedron Lett.* **1965**, 411–416.

(15) From (i) in ref 13 above and $n_e = 1 - n_a$ it follows that $J = (1 - n_a)J_{aa} + n_aJ_{ee}$ when $J - J_{aa} = n_a(J_{ee} - J_{aa})$ or $n_a = (J - J_{aa})/(J_{ee} - J_{aa})$; hence $1 - n_a = (J_{ee} - J)/(J_{ee} - J_{aa})$ and $K = n_e/n_a = (1 - n_a)/n_a = (J_{ee} - J)/(J - J_{aa}) = (J - J_{ee})/(J_{aa} - J)$.

**Table 2. Proton Parameters for $C_3$, $C_3$-Me (Parentheses), and Vicinal $H_3$–$H_4$ Coupling Constants in the Methyl-Substituted 1,2,3,4-Tetrahydroisoquinolines[a]**

| compound | $\delta_a$ | $\delta_e$ | $J_{3e3a}$ | $J_{3a4a'}$ | $J_{3e4e'}$ | $J_{3a4e'}$ | $J_{3e4a'}$ | $J_{H-Me}$ |
|---|---|---|---|---|---|---|---|---|
| 1-Me | 2.93 | 3.18 | 12.4 | 8.70 | 5.14 | 4.66 | 5.14 | |
| 3-Me | 2.94 | (1.17) | | 10.52 | | 3.88 | | (6.3) |
| 4-Me | 2.75 | 3.13 | 12.3 | | 5.91 | 4.84 | | |
| *cis*-1,3-$Me_2$ | 2.98 | (1.18) | | 11.00 | | 3.56 | | (6.2) |
| *trans*-1,3-$Me_2$ | 3.22 | (1.15) | | 10.03 | | 3.89 | | (6.2) |
| *cis*-1,4-$Me_2$ | 2.88 | 3.05 | 12.6 | | 4.66 | 3.93 | | |
| *trans*-1,4-$Me_2$ | 2.63 | 3.24 | 12.5 | 7.62 | | | 5.25 | |

[a] At room temperature in $CD_2Cl_2$ + 15% CHCl=$CCl_2$.

**Table 3. $^{13}C$ NMR Chemical Shifts of Aliphatic Carbons for *C*-Methyl-1,2,3,4-tetrahydroisoquinolines at Room Temperature[a]**

| compound | $C_1$ | 1-Me | $C_3$ | 3-Me | $C_4$ | 4-Me |
|---|---|---|---|---|---|---|
| 1-Me | $51.9_9$ | $22.9_4$ | $42.1_9$ | | $30.5_2$ | |
| 3-Me | $48.9_8$ | | $49.6_7$ | $22.6_0$ | $37.6_9$ | |
| 4-Me | $49.1_9$ | | $51.5_8$ | | $32.6_3$ | $20.8_4$ |
| *cis*-1,3-$Me_2$ | $53.0_3$ | $22.5_9$ | $49.5_0$ | $22.8_1$ | $38.8_2$ | |
| *trans*-1,3-$Me_2$ | $51.3_3$ | $24.4_6$ | $43.1_6$ | $22.5_8$ | $38.1_1$ | |
| *cis*-1,4-$Me_2$ | $52.3_2$ | $23.0_1$ | $48.9_7$ | | $33.3_9$ | $21.8_8$ |
| *trans*-1,4-$Me_2$ | $52.4_3$ | $23.1_1$ | $49.6_0$ | | $33.3_6$ | $20.0_8$ |

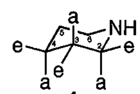
[a] In $CD_2Cl_2$ + 15% CHCl=$CCl_2$.

In most instances the difference is about 0.10 kcal $mol^{-1}$. Another check is additivity of the data. In the conformational analysis of saturated six-membered rings it is generally assumed that conformational energies are additive or subtractive, so that the conformational energy of a disubstituted compound is—depending on whether the substituents are *cis* or *trans*—either the sum or the difference of the conformational energies of the individual substituents. While it cannot be assumed, *a priori*, that this principle also holds for cyclohexenes or heteracyclohexenes (since these compounds are more flexible and lie in a less deep conformational well than their saturated analogs), it does in fact apply quite satisfactorily to the present data set. Thus, based on experimental data, the additively calculated values for the disubstituted compounds in kcal $mol^{-1}$ are as follows (experimental values repeated in parentheses for convenience): *cis*-1,3, 2.19 (large); *trans*-1,3, 1.07 (1.18); *cis*-1,4, 0.88 (0.75); *trans*-1,4, 0.24 (0.22). The agreement strengthens one's confidence in the data set.

Other checks are only qualitative. The $^{13}C$ chemical shifts of the eight compounds studied are given in Table 3. The data are not extensive enough to calculate a reliable parameter set for the ring carbons, and the methyl shifts span too small a range to be quantitatively useful. The *cis*-1,3-$Me_2$ compound is all equatorial (Table 1) and provides values for equatorial Me(1) and Me(3). The corresponding *trans* compound has largely but not entirely equatorial Me(3); its slight upfield shift is undoubtedly caused by the small contribution (12%) of the Me(3a) and a similar upfield shift is seen in the 3-Me compound (6% axial). A different situation arises, however, with Me(4): it is very largely axial in the *cis*-1,4-$Me_2$ compound (78%) which yet has the most *downfield* Me; the 4-Me compound (63% axial) is more upfield and the *trans*-1,4-compound (41% axial) even more so. A similar seemingly anomalous situation is found in the 1-methyl compounds where successive downfield shifts of Me(1) are seen from the *cis*-1,3-$Me_2$ compound (0% axial) to the *cis*-1,4-$Me_2$ (22% axial) and 1-Me (28% axial) to the *trans*-1,4-$Me_2$ (41% axial) to the *trans*-1,3-$Me_2$ (88% axial) compounds. It is evident that in these cases the axial methyl groups resonate downfield of the equatorial ones; a similar situation is seen in 1-methyltetralins.[16] In any case, qualitatively speaking the order of $^{13}C$ chemical shifts is as predicted with only one (very minor) inversion in the case of the 1-Me and *cis*-1,4-$Me_2$ compounds.

## Discussion

We start with a comparison with *C*-methylpiperidines (cf. **4**).[7] The conformational energy ($-\Delta G°_{Me}$) for 4-methyl in piperidine is 1.9 kcal $mol^{-1}$, similar to that in cyclohexane,[17] 1.74 kcal $mol^{-1}$. The value for 3-methyl is smaller, 1.6 kcal $mol^{-1}$, presumably because one of the syn-axial Me/H interactions is replaced by Me/lone pair, the lone pair being less "space consuming" than a hydrogen atom.[18] In contrast, the value for 2-methyl, 2.5 kcal $mol^{-1}$, is substantially larger, presumably because the axial methyl group is considerably closer to the syn-axial hydrogen atom [at C(6)] than in cyclohexane and thus sterically more destabilized. (This results from the shorter C–N distance, 147 pm, as compared to C–C, 153 pm.) However, the conformational energy of the 1-methyl group in 1-MeTHIQ, 0.56 kcal $mol^{-1}$ (Table 1), is much less than that in 2-methylpiperidine. In part, this is presumably due to the absence of the second syn-axial H of the piperidine (the benzene ring in THIQ has no axial hydrogens).



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However, if one assumes that a syn-axial Me/H interaction across a C–C–C juncture amounts to one-half of the conformational energy of (axial) methyl in methylcyclohexane[19] or about 0.87 (1.74/2) kcal $mol^{-1}$, the experimental value is still much smaller than the expected 2.5–0.87 or ca. 1.6 kcal $mol^{-1}$. There is clearly another cause for the low conformational energy of Me(1), and it would seem to be the *peri effect*;[20] i.e., the unfavorable steric interaction of the equatorial Me(1) with the peri hydrogen at C(8) in the benzene ring.

To obtain a quantitative measure of the peri effect, we carried out calculations on the conformational energies of *C*-methyl groups at the 2-, 5-, and 6-positions of $\Delta^{3,4}$-tetrahydropyridine (**5**) (corresponding to the 1-, 4-, and 3-positions in THIQ). The results are shown in Table 4.

Again, the values for the disubstituted compounds in the last column are properly additive, with a slightly

(16) Morin, F. G.; Horton, W. J.; Grant, D. M.; Dalling, D. K.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3992–3998.

(17) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255–259.

(18) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444–3458.

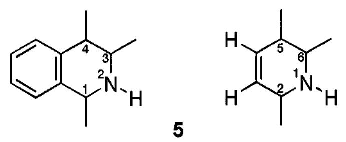
(19) Actually the proper offset may be less, since the interaction energy of axial Me(2) with C(4) is not only with the syn-axial H at C(4) but also with the carbon atom itself. The latter interaction does not go away in axial 1- or 3-methyl-THIQ. By the argument used in the text, the conformational energy of methyl in 3-methyl-THIQ should also be 1.6 kcal $mol^{-1}$. The good agreement of this value with the experimental 1.63 kcal $mol^{-1}$ is not as pleasing as one might think, since the most important steric interaction—that between Me(3) and axial H(1), across the short C–N distances—should be diminished when H(1) is pseudoaxial rather than axial [as is the corresponding H(6) in piperidine (**4**)]. The conclusion from both findings is that the energy advantage of methyl groups at positions 1a′, 3a, and 4a′ due to the absence of a hydrogen substituent in positions 4a and 8a of THIQ amounts to less than 0.87 kcal $mol^{-1}$.

(20) See, for example: Jameson, M. B.; Penfold, B. R. *J. Chem. Soc.* **1965**, 528–536.

**Table 4. Computed Conformational Equilibria and Free Energy Differences for Methyl- and Dimethyl-Substituted Tetrahydropyridines**

| substituents(s)[a] | conformer ratio[b] | $-\Delta G°$, kcal mol$^{-1}$ |
|---|---|---|
| 1-Me | 87/13 | 1.13 |
| 3-Me | 93/7 | 1.53 |
| 4-Me | 77/23 | 0.72 |
| *cis*-1,3-$Me_2$[c] | 100/0 | large |
| *trans*-1,3-$Me_2$[c] | 71/29 | 0.53 |
| *cis*-1,4-$Me_2$[d] | 67/33 | 0.42 |
| *trans*-1,4-$Me_2$[d] | 96/4 | 1.88 |

[a] For easier comparison with Table 1, the THIQ numbering system is used here. Properly the locants should be 2, 6, and 5. [b] e/a as calculated by MMP2(85) assuming $\Delta S = 0$. [c] Me(3) a → e. [d] Me(1) a → e.



**5**

larger than desirable deviation for the *trans*-1,3 compound where a relatively small difference between relatively large numbers is involved. More to the point of the discussion is the fact that, while the value for Me(3) in Table 4 is the same as the calculated value for 3-MeTHIQ in Table 1, the values for Me(1) and Me(4) are much smaller for the THIQ derivatives shown in Table 1—by 0.68 and 0.94 kcal mol$^{-1}$, respectively. These numbers thus express the magnitude of the peri effect in positions 1 and 4, respectively. [That the values differ is presumably due to differences in Me-C−C−$H_{peri}$ torsion angles C(1) and C(4).] It is of particular note that Me(4) in 4-MeTHIQ prefers the axial position; in this case the axial Me has no syn-axial Me/H interaction but the equatorial Me has a peri interaction. In contrast, for the corresponding tetrahydropyridine, which lacks the peri interaction, the equatorial conformer is yet preferred, thus confirming the known fact[21] that the syn-axial Me/H interaction is not the only factor destabilizing axial methyl.

## Experimental Section

**General Procedures.** $^1$H NMR and $^{13}$C NMR spectra were recorded at 250.13 or 399.92 MHz and 62.89 or 100.57 MHz, respectively, using TMS or (in $D_2O$) DSS [3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt] as internal standards. Abbreviations used are s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; and br, broad. All 1,2,3,4-tetrahydroisoquinolines were purified by preparative GC on a 20% Carbowax 20M plus 10% KOH on Chromosorb A, 60/80 mesh. Melting points are uncorrected.

**1-Methyl-1,2,3,4-tetrahydroisoquinoline.** A solution of the crude 3,4-dihydroisoquinoline (1.51 g, 10.4 mmol) and 0.55 g of $NaBH_4$ in 50 mL methanol was refluxed for 1 h and allowed to cool to room temperature.[22] The methanol was removed under reduced pressure, and the product was taken up in $H_2O$ (20 mL) and extracted with $Et_2O$ (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. Kugelrohr distillation yielded the pure product (0.92 g, 60%): bp 76−79 °C (airbath temperature) (0.5 mm), lit.[23] bp 78−80 °C (0.06 mm).

$^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.11−7.02 (m, 4H), 4.03 (quartet, 1H, $J$ = 6.7 Hz), 3.18 (dt, 1H, $J_{gem}$ = 12.4 Hz, $J_{vic}$ = 5.1 Hz), 2.93 (ddd, 1H, $J_{gem}$ = 12.4 Hz, $J_{vic}$ = 8.7, 4.7 Hz), 2.80 (dddd, 1H, $J_{gem}$ = 16.2 Hz, $J_{vic}$ = 8.7, 4.7 Hz, $J_{long\ range}$ = 1.1 Hz), 2.67 (br dt, 1H, $J_{gem}$ = 16.2 Hz, $J_{vic}$ = 4.7 Hz), 1.68 (s, 1H), 1.38 (d, 3H, $J$ = 6.7 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ $141.3_3$, $135.4_9$, $129.4_5$, $126.1_5$, $126.0_6$, $126.0_1$, $51.9_9$, $42.1_9$, $30.5_2$, $22.9_4$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.37−7.26 (m, 4H), 4.67 (quartet, 1H, $J$ = 6.8 Hz), 3.62 (ddd, 1H, $J_{gem}$ = 13.0 Hz, $J_{vic}$ = 6.6, 5.9 Hz), 3.44 (ddd, 1H, $J_{gem}$ = 13.0 Hz, $J_{vic}$ = 7.5, 5.7 Hz), 3.19 (br dt, 1H, $J_{gem}$ = 17.6 Hz, $J_{vic}$ ≈ 6.7 Hz), 3.11 (dt, 1H, $J_{gem}$ = 17.6 Hz, $J_{vic}$ = 6.2 Hz), 1.72 (d, 3H, $J$ = 6.8 Hz). $^{13}$C NMR ($D_2O$ + DCl): $\delta$ $135.5_4$, $133.6_4$, $131.5_5$, $130.5_7$, $129.7_5$, $128.6_9$, $53.7_2$, $41.6_4$, $27.3_3$, $21.2_9$. The $^1$H and $^{13}$C NMR data are in excellent agreement with those reported.[23]

**3-Methyl-1,2,3,4-tetrahydroisoquinoline.** The corresponding crude 3,4-dihydroisoquinoline (25.54 g, 0.176 mol) was reduced with $NaBH_4$ as described above: yield 21.32 g, 82.3%; bp 85−87 °C (0.5 mm), lit.[24] bp 105−107 °C (7 mm). $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.09−7.01 (m, 3H), 6.99−6.96 (m, 1H), 4.02 (d, 1H, $J_{gem}$ = 15.9 Hz), 3.96 (d, 1H, $J_{gem}$ = 15.9 Hz), 2.94 (dd of quartet, 1H, $J_{Me}$ = 6.3 Hz, $J_{vic}$ = 10.3, 3.9 Hz), 2.71 (dd, 1H, $J_{gem}$ = 16.3 Hz, $J_{vic}$ = 3.9 Hz), 2.43 (dd, 1H, $J_{gem}$ = 16.3 Hz, $J_{vic}$ = 10.3 Hz), 1.58 (br s, 1H), 1.17 (d, 3H, $J$ = 6.3 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ $136.1_9$, $135.6_0$, $129.3_5$, $126.2_5$, $126.1_4$, $125.7_8$, $48.9_8$, $49.6_7$, $37.6_9$, $22.6_0$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.39−7.25 (m, 4H), 4.44 (d, 1H, $J_{gem}$ = 16.0 Hz), 4.39 (d, 1H, $J_{gem}$ = 16.0 Hz), 3.59 (dd of quartet, 1H, $J$ = 6.5 Hz, $J_{vic}$ = 10.7, 4.7 Hz), 3.14 (dd, 1H, $J_{gem}$ = 17.5 Hz, $J_{vic}$ = 4.7 Hz), 2.96 (dd, 1H, $J_{gem}$ = 17.5 Hz, $J_{vic}$ = 10.7 Hz), 1.53 (d, 3H, $J$ = 6.5 Hz). $^{13}$C NMR ($D_2O$ + DCl): $\delta$ $133.7_2$, $131.4_0$, $130.4_8$, $129.5_8$, $129.4_5$, $128.9_4$, $52.2_9$, $46.5_7$, $34.8_3$, $20.2_7$. The $^1$H NMR spectrum is in very good agreement with that reported[25] except that the reported spectrum was not resolved in the 2.4−3.5 ppm region.

**4-Methyl-1,2,3,4-tetrahydroisoquinoline.** The corresponding crude 3,4-dihydroisoquinoline (0.41 g, 2.8 mmol) was reduced with $NaBH_4$ as described above: yield 0.32 g, 77%; bp 76−78 °C (airbath temperature) (2 mm), lit.[23] bp 55−60 °C (0.1 mm). $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.17 (d, 1H, $J$ = 7.3 Hz), 7.12 (td, 1H, $J$ = 7.4 Hz, $J$ = 1.6 Hz), 7.07 (td, 1H, $J$ = 7.3, 1.6 Hz), 6.96 (d, 1H, $J$ = 6.6 Hz), 3.94 (d, 1H, $J_{gem}$ = 16.2 Hz), 3.90 (d, 1H, $J_{gem}$ = 16.2 Hz), 3.13 (dd, 1H, $J_{gem}$ = 12.3 Hz, $J_{vic}$ = 4.8 Hz), 2.82 (br sextet, 1H, $J_{vic}$ = 5.9 Hz), 2.74 (dd, 1H, $J_{gem}$ = 12.3 Hz, $J_{vic}$ = 5.9 Hz), 1.92 (s, 1H), 1.24 (d, 3H, $J$ = 6.9 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ $140.8_2$, $136.3_7$, $128.5_0$, $126.3_9$, $126.2_7$, $125.8_6$, $51.5_8$, $49.1_9$, $32.6_3$, $20.8_4$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.46−7.31 (m, 3H), 7.26 (br d, 1H, $J$ = 7.6 Hz), 4.42 (d, 1H, $J_{gem}$ = 15.8 Hz), 4.38 (d, 1H, $J_{gem}$ = 15.8 Hz), 3.64 (dd, 1H, $J_{gem}$ = 12.5 Hz, $J_{vic}$ = 5.6 Hz), 3.34 (sextet, 1H, J≈7.0 Hz), 3.17 (dd, 1H, $J_{gem}$ = 12.5 Hz, $J_{vic}$ = 8.3 Hz), 1.41 (dd, 3H, $J$ = 6.9 Hz, $J_{long\ range}$ = 0.6 Hz). $^{13}$C NMR ($D_2O$ + DCl): $\delta$ $139.2_3$, $130.6_8$, $129.8_8$, $129.5_0$, $129.4_2$, $129.1_2$, $49.9_2$, $47.1_7$, $31.3_9$, $21.0_2$. The $^1$H and $^{13}$C NMR data are in excellent agreement with those reported.[23]

***cis*- and *trans*-1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline.**[26] The corresponding crude 3,4-dihydroisoquinoline (11.04 g, 0.069 mol) was reduced with $NaBH_4$ as described above to yield a diastereomeric mixture (6.86 g, 61.4%, c:t ≈ 3:1 by NMR); bp 119−123 °C (20 mm), lit.[26] bp 125−130 °C (23 mm). The two isomers were separated by HPLC using ethyl acetate/acetone (9/1) as solvent. The *cis* isomer was the first product to be eluted from the column. $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.17−7.05 (m, 3H), 7.03−7.00 (m, 1H), 4.09 (quartet, 1H, $J$ = 6.5 Hz), 2.98 (dd of quartet, 1H, $J$ = 6.2 Hz, $J_{vic}$ = 11.0, 3.6 Hz), 2.68 (dd, 1H, $J_{gem}$ = 15.9 Hz, $J_{vic}$ = 3.6 Hz), 2.49 (dd, 1H, $J_{gem}$ = 15.9 Hz, $J_{vic}$ = 11.0 Hz), 1.49 (br s, 1H), 1.40 (d, 3H, $J$ = 6.5 Hz), 1.18 (d, 3H, $J$ = 6.2 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ $140.8_3$, $135.8_7$, $129.3_1$, $126.2_5$, $126.2_0$, $125.5_7$, $53.0_3$, $49.5_0$, $38.8_2$, $22.8_1$, $22.5_9$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.41−7.24 (m, 4H), 4.64 (quartet, 1H, $J$ = 6.8 Hz), 3.59 (septet, 1H, $J_{vic}$ = 5.8 Hz), 3.12 (dd, 1H, $J_{gem}$ = 17.3 Hz,

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$J_{vic}$ = 4.5 Hz), 2.98 (dd, 1H, $J_{gem}$ = 17.3 Hz, $J_{vic}$ = 12.0 Hz), 1.71 (d, 3H, $J$ = 6.8 Hz), 1.49 (d, 3H, $J$ = 6.4 Hz).[27] $^{13}$C NMR ($D_2O$ + DCl): $\delta$ 135.1$_3$, 134.1$_6$, 131.5$_3$, 130.7$_5$, 130.0$_0$, 128.1$_9$, 55.3$_5$, 52.8$_7$, 35.8$_6$, 20.9$_4$, 20.6$_2$.

The *trans* isomer was the second product to be eluted from the column but, due to the large amount of the *cis* isomer present and the poor separation between the two compounds, could not be obtained completely free of *cis*. The fractions which contained the largest amounts of the *trans* isomer were combined and reseparated by HPLC using the above conditions. This second separation afforded a 7:1 mixture of *trans*:*cis*, suitable for NMR analysis. $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.12−7.01 (m, 4H), 4.17 (quartet, 1H, $J$ = 6.9 Hz), 3.22 (dd of quartet, 1H, $J$ = 6.2 Hz, $J_{vic}$ = 10.0, 3.9 Hz), 2.73 (dd, 1H, $J_{gem}$ = 16.2 Hz, $J_{vic}$ = 3.9 Hz), 2.39 (dd, 1H, $J_{gem}$ = 16.2 Hz, $J_{vic}$ = 10.0 Hz), 1.49 (br s, 1H), 1.39 (d, 3H, $J$ = 6.9 Hz), 1.15 (d, 3H, $J$ = 6.2 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 140.9$_3$, 135.2$_5$, 129.4$_5$, 127.0$_6$, 126.1$_5$, 125.9$_4$, 53.3$_3$, 43.1$_6$, 38.1$_1$, 24.4$_6$, 22.5$_8$.

***cis*- and *trans*-1,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline.**[28] The corresponding crude 3,4-dihydroisoquinoline was reduced with $NaBH_4$ as described above to yield a diastereomeric mixture (13.75 g, 73.3%, c:t ≈ 2:1 by NMR); bp 127−131 °C (21 mm). The two isomers were separated by preparative GC. The *cis* isomer was the first product to come off the column. $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.12−7.07 (m, 4H), 4.00 (quartet, 1H, $J$ = 6.6 Hz), 3.05 (dd, 1H, $J_{gem}$ = 12.6 Hz, $J_{vic}$ = 4.5 Hz), 2.88 (dd, 1H, $J_{gem}$ = 12.6 Hz, $J_{vic}$ = 3.9 Hz), 2.77 (dd of quartet, 1H, $J$ = 7.1 Hz, $J_{vic}$ = 4.5, 3.9 Hz), 1.79 (br s, 1H), 1.40 (d, 3H, $J$ = 6.6 Hz), 1.27 (d, 3H, $J$ = 7.1 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 141.0$_1$, 140.9$_7$, 128.9$_0$, 126.2$_9$, 126.1$_4$, 126.0$_6$, 52.3$_2$, 48.9$_7$, 33.3$_9$, 23.0$_1$, 21.8$_8$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.45−7.31 (m, 4H), 4.70 (quartet, 1H, $J$ = 6.9 Hz), 3.58 (dd, 1H, $J_{gem}$ = 12.0 Hz, $J_{vic}$ = 5.1 Hz), 3.32 (br sextet, 1H, $J_{vic}$ = 7.0 Hz), 3.27 (dd, 1H, $J_{gem}$ = 12.0 Hz, $J_{vic}$ = 8.4 Hz), 1.76 (d, 3H, $J$ = 6.9 Hz), 1.45 (d, 3H, $J$ = 6.7 Hz). $^{13}$C NMR ($D_2O$ + DCl): $\delta$ 138.9$_4$, 135.0$_7$, 130.8$_3$, 129.7$_1$, 129.7$_1$, 128.6$_5$, 53.5$_4$, 46.7$_2$, 31.5$_0$, 21.4$_6$, 20.9$_2$.

The *trans* isomer was the second product to come off the column. $^1$H NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 7.22−7.18 (m, 1H), 7.14−7.08 (m, 3H), 4.05 (quartet, 1H, $J$ = 6.7 Hz), 3.24 (dd, 1H, $J_{gem}$ = 12.5 Hz, $J_{vic}$ = 5.2 Hz), 2.87 (dd of quartet, 1H, $J$ = 7.0 Hz, $J_{vic}$ = 7.6, 5.2 Hz), 2.63 (dd, 1H, $J_{gem}$ = 12.5 Hz, $J_{vic}$ = 7.6 Hz), 1.38 (d, 3H, $J$ = 6.7 Hz), 1.22 (d, 3H, $J$ = 7.0 Hz). $^{13}$C NMR ($CD_2Cl_2$ + CHCl═$CCl_2$): $\delta$ 141.0$_1$, 140.7$_3$, 127.9$_8$, 126.3$_2$, 126.1$_2$, 125.9$_3$, 52.4$_3$, 49.6$_0$, 33.3$_6$, 23.1$_1$, 20.0$_8$. $^1$H NMR ($D_2O$ + DCl): $\delta$ 7.44−7.31 (m, 4H), 4.71 (quartet, 1H, $J$ = 6.8 Hz), 3.70 (dd, 1H, $J_{gem}$ = 12.7 Hz, $J_{vic}$ = 5.7 Hz), 3.39 (br sextet, 1H, $J_{vic}$ = 7.2 Hz), 3.13 (dd, 1H, $J_{gem}$ = 12.7 Hz, $J_{vic}$ = 8.7 Hz), 1.72 (d, 3H, $J$ = 6.7 Hz), 1.39 (d, 3H, $J$ = 7.1 Hz). $^{13}$C NMR ($D_2O$ + DCl): $\delta$ 138.8$_2$, 134.9$_0$, 130.7$_3$, 129.7$_0$, 128.4$_6$, 130.0$_6$, 54.3$_8$, 48.2$_9$, 31.6$_2$, 21.4$_5$, 21.3$_8$.

## Appendix: 1,2,3,4-Tetrahydroisoquinolinium Salts

We add here some data on methyl- and dimethyl-1,2,3,4-tetrahydroisoquinolinium salts. The proton−proton coupling constants [$J_{H3/H4}$(*trans*)] are listed in Table 5. As discussed earlier, the sum of $J_{H3a/H4a}$ and $J_{H3e/H4e}$ is constant and, from the proton spectrum of the 1-methyl compound, is found to be 13.40 Hz. If it is assumed that the *cis*-1,3-Me$_2$ compound exists exclusively in the conformation having both methyl groups equatorial, $J_{H3/H4}$(*trans*) for this compound is $J_{H3a/H4a}$ or 12.05 Hz when $J_{H3e/H4e}$ is 13.40−12.05 or 1.35 Hz. With these value and the averaging calculation described above, one obtains the conformer ratios and conformational energy values shown in Table 6. Also shown in this table are the values calculated by MMP2(85).

**Table 5. Proton Parameters for $C_3$ and $C_3$-Me (Parentheses) Including Vicinal $H_3$−$H_4$ Coupling in the Methyl-Substituted THIQ Hydrochloride Salts at Room Temperature in $D_2O$**

| compound | $\delta_{3a}$ | $\delta_{3e}$ | $J_{3a3e}$ | $J_{3a4a'}$ | $J_{3e4e'}$ | $J_{3a4e'}$ | $J_{3e4a'}$ | $J_{H-Me}$ |
|---|---|---|---|---|---|---|---|---|
| 1-Me | 3.44 | 3.62 | 13.0 | 7.55 | 5.85 | 5.89 | 6.6 | |
| 3-Me | 3.59 | (1.53) | | 10.70 | | 4.65 | | (6.5) |
| 4-Me | 3.17 | 3.64 | 12.5 | 8.25 | | 5.58 | | |
| *cis*-13-Me$_2$ | 3.59 | (1.49) | | 12.05 | | 4.49 | | (6.6) |
| *cis*-14-Me$_2$ | 3.27 | 3.58 | 12.0 | 8.33 | | 5.08 | | |
| *trans*-14-Me$_2$ | 3.13 | 3.70 | 12.7 | 8.73 | | 5.73 | | |

**Table 6. Conformational Equilibria and Free Energy Differences for Methyl- and Dimethyl-Substituted 1,2,3,4-Tetrahydroisoquinolinium Salts[a]**

| | conformer ratio[b] | | −Δ$G$°, kcal mol$^{-1}$ | | |
|---|---|---|---|---|---|
| substituent(s) | exptl | calcd[c] | exptl | calcd[c] | (free amine[d]) |
| 1-Me | 1.37 | 0.56 | 0.19 | −0.34 | 0.56 |
| 3-Me | 6.92 | 11.8 | 1.15 | 1.46 | 1.63 |
| 4-Me | 1.82 | 1.18 | 0.35 | 0.10 | −0.32 |
| *cis*-1,3-Me$_2$ | large | 499 | large | 3.68 | large |
| *trans*-1,3-Me$_2$[e] | *f* | 5.90 | *f* | 1.05 | 1.18 |
| *cis*-1,4-Me$_2$[g] | 1.87 | 1.75 | 0.37 | 0.33 | 0.75 |
| *trans*-1,4-Me$_2$[g] | 2.22 | 1.57 | 0.47 | 0.27 | 0.22 |

[a] Hydrochlorides (or deuteriochlorides) in $D_2O$. [b] e/a. [c] From MMP2(85) using the $N$ = 8 ($NH_2$) parameter. Use of the $N$ = 39 ($NH_2^+$) parameter gives about the same result for 4-Me and a somewhat larger value (1.78 kcal mol$^{-1}$) for the 3-Me, but the result for 1-Me (+0.85 kcal mol$^{-1}$) reverses the e/a ratio; the experimental value lies between the two calculated values. [d] Experimental values for free amine from Table 1 for comparison. [e] 3a → 3e. [f] Not determined, coupling was not resolved. [g] 1a → 1e.

The following observations may be made (1) Additivity for the 1,4-dimethyl-substituted compounds is only moderately good: 0.54 vs 0.47 kcal mol$^{-1}$ observed for the *trans*, 0.16 vs 0.37 for the *cis*. The situation is much worse for the computed values: for $N$ = 8 (see footnote c to Table 6), for example, in the *cis* compound, the 1a,4e conformer should predominate whereas the 1e,4a is the calculated preferred conformation. We believe that lack of specific consideration of solvation of the axial hydrogen of the charged $NH_2^+$ moiety makes the calculated values unreliable. (2) The experimentally determined preference of 1-Me and 3-Me for the equatorial position is considerably less in the salt than in the free amine. A similar observation was made in $N$,2-dimethylpiperidine and its salt[7] and was ascribed to the longer C−N bond in the salts vs the free amines, which increases the distance between an axial methyl group and the axial hydrogen on the other side of the nitrogen. (The alternate solvation argument made[7] for the $N$-methyl compounds probably does not apply to the NH species.) (3) In the case of 4-MeTHIQ, whereas the axial conformer is preferred for the free amine because of the peri effect, the equatorial conformer is preferred for the salt. This is perhaps as expected, since where the free amine has a syn-axial lone pair on nitrogen, the salt, instead, has a hydrogen atom probably further swelled by solvation. Thus the N/4 syn-axial interaction is much enhanced in the salt, to the extent that it outweighs the peri effect.

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