Relevance of Torsional Effects to the Conformational Equilibria of 1,5-Diaza-*cis*-decalins: A Theoretical and Experimental Study

Bishwajit Ganguly, Dana A. Freed, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

marisa@chem.upenn.edu

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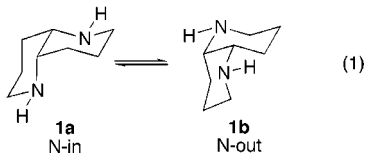
1,5-Diaza-*cis*-decalin populates two conformations in which the nitrogen atoms are either gauche (N-in) or anti (N-out) to one another. The equilibrium mixture of the two conformers depends on the substituents at the nitrogen atom, as well as the reaction conditions. Ab initio (HF/6-31G*, B3LYP/6-31+G*) and molecular mechanics (Amber*) calculations have been performed to examine the possible role of stereoelectronics and steric effects in controlling the equilibrium of substituted 1,5-diaza-*cis*-decalins. In the present study, *N*,*N*′-diethyl- and *N*,*N*′-bistrifluoroethyl-1,5-diaza-*cis*-decalins have been synthesized, and the equilibrium mixtures have been measured using ^{1}H and ^{13}C NMR experiments. Steric effects appear to control the equilibria between the two conformational isomers of 1,5-diaza-*cis*-decalin while torsional effects appear to dominate the equilibria for the *N*,*N*′-dialkyl derivatives.

Introduction

An ongoing research interest in our group is the design and development of new chiral auxiliaries and catalysts for asymmetric synthesis. The development of effective chiral auxiliaries (stoichiometric) and catalysts (substoichiometric) for asymmetric reactions depends largely on the identification of the appropriate chiral ligands. As an aid toward this end, a series of computer-aided design protocols for the identification of new chiral ligands for reactions which proceed through well-defined transition states has been developed.[1] This process identifies ligand families via computational screening of data incorporated within large structural databases such as the Cambridge Structural Database. The critical motifs from the resultant lead compounds are identified and are used as the basis for potential ligands. The benefit of this method lies in the large number of potential scaffolds which can be rapidly and efficiently screened by the end user. Using this method, novel ligands containing a *cis*-decalin ring system, including 1,5-diaza-*cis*-decalin (**1**), have been identified as potential chiral auxiliaries for the boron allylation and aldol addition reactions.



(1)

The 1,5-diaza-*cis*-decalins, which have also found utility in asymmetric lithiation/substitution[2] and oxidative biaryl coupling chemistry,[3] exist predominantly in two conformations (eq 1). The position of the conformational equilibrium depends on the nitrogen substituents, as well as on solvent and additives.[4] These experimental results have generally been rationalized on the basis of stabilizing C−H to C−N delocalization, hydrogen bonding, and solvent effects.[4] Since the N-in form of these compounds is presumably the effective form, a thorough understanding of the factors controlling the equilibrium of the neutral species in eq 1 was required so that derivatives which would favor the N-in form could be selected for synthesis and experimental evaluation.

We report herein a detailed computational study of the conformational isomers of 1,5-diaza-*cis*-decalin (**1**) and its substituted derivatives using molecular mechanics and ab initio analyses. In addition, ^{1}H and ^{13}C NMR experiments have been used to measure the conformational isomer ratio for the *N*,*N*′-diethyl- and *N*,*N*′-bistrifluoroethyl-1,5-diaza-*cis*-decalin derivatives. These studies have allowed the specific interactions controlling the conformational equilibria of substituted 1,5-diaza-*cis*-decalins to be delineated.

Results and Discussion

A prior combined study by Santos et al.[4] examined the conformational equilibria of the 1,5-diaza-*cis*-decalins in $CDCl_3$ (Scheme 1, entries 1−3). The NH compound **1** has a clear tendency to populate conformer **a**, in which heteroatoms are gauche (N-in). The conformer equilibrium shifts in the direction of the **b**-type anti isomer (N-out) upon alkylation of the nitrogens. The conformational preference is completely shifted in the case of the *N*,*N*′-di-*n*-butyl derivative (Scheme 1). ^{1}H and ^{13}C NMR studies have shown that the N-in and N-out isomers in each case are symmetric in nature.

To gain additional insight to this problem, *N*,*N*′-diethyl and *N*,*N*′-bistrifluoroethyl derivatives **4** and **5** have been synthesized in our laboratory as outlined in eq 2 and have

(1) Kozlowski, M. C.; Evans, C. A. Submitted.
(2) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875−8.
(3) Li, X.; Yang, J.; Kozlowski, M. C. Submitted.
(4) Santos, A. G.; Klute, W.; Torode, J.; Böhm, V. P. W.; Cabrita, E.; Runsink, J.; Hoffmann, R. W. *New J. Chem.* **1998**, *993*−*997*, 1411.

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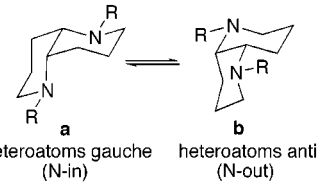
Table 1. Relative Energies (kcal/mol) Calculated with Amber* as well as ab Initio HF/6-31G* and B3LYP/6-31+G* for the Lowest Energy Forms of Conformers a and b of 1,5-Diaza-*cis*-decalin 1 and *N,N′*-Dialkylated Derivatives 2, 4, and 5

method	1a	1b	2a	2b	4a	4b	5a	5b
Amber*	0.0	3.4	0.0	0.4	0.7	0.0	0.0	0.8
HF/6-31G*[a]	0.0 (0.0)	2.0 (1.7)	1.7 (4.5)	0.0 (0.0)	3.9 (2.9)	0.0 (0.0)	3.6 (3.7)	0.0 (0.0)
B3LYP/6-31+G*	0.0	1.4	1.1	0.0	3.8	0.0	2.9	0.0

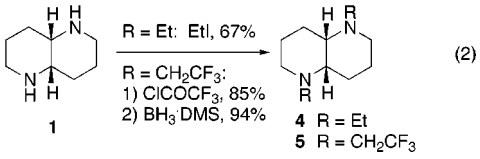
[a] Relative solvation energies calculated using the IPCM method for $CHCl_3$ are given in parentheses.

Scheme 1



	R	a (N-in)	b (N-out)
1	H	>90	>10
2	Me	60	40
3	*n*-Bu	<10	>90
4	Et	<10	>90
5	CH_2CF_3	<10	>90

been characterized by ^1H and ^{13}C NMR spectroscopy (Scheme 1). Our motivation for examining these derivatives was to determine what effects groups with different steric sizes and different electronic characteristics would have on the conformational equilibria of these systems. The experimental data from these additional analogues would allow dissection of the stereoelectronic, electrostatic, and steric components in the conformational equilibria of the diaza-*cis*-decalin systems. Analysis of the NMR structural results revealed that the *N,N′*-diethyl and *N,N′*-bistrifluoroethyl derivatives populate N-out conformer **b** almost exclusively (Scheme 1).

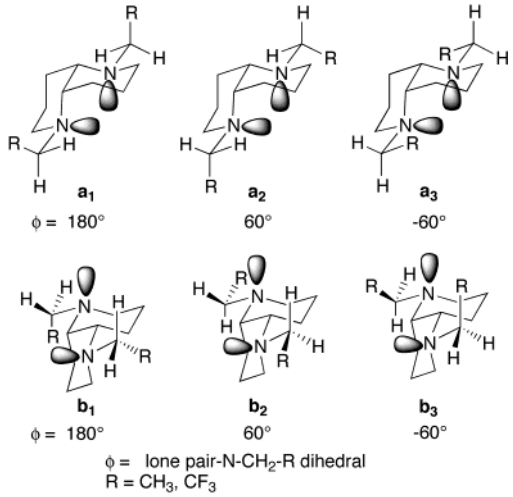


(2)

The relative stability of the conformers of 1,5-diaza-*cis*-decalin and their substituted derivatives has been calculated using molecular mechanics[5] and ab initio[6] approaches. The reliability of these methods to examine the relative stability of conformers of similar N−C−C−N systems has previously been acknowledged.[7] In this study, the possible role of stereoelectronic interactions (such as C−H to C−N* delocalization, negative hyperconjugation), steric, electrostatic, torsional, and solvent effects in controlling the conformational equilibria of 1,5-diaza-*cis*-decalins has been examined and compared with experimental results. The possibility of conformational variation in the ethyl and trifluoroethyl groups was considered by using different initial geometries.

Minimization of 1,5-diaza-*cis*-decalin **1** and its substituted derivatives using the Amber* force field as implemented in MacroModel provided the energies illustrated in Table 1 (the *N,N′*-di-*n*-butyl derivative **3** was not examined due to its relatively large size). In a second set of calculations, further optimization at the ab initio HF/6-31G* and B3LYP/6-31+G* levels of theory was undertaken (Table 1). In addition, solvent calculations have been incorporated into the HF/6-31G* calculations using the IPCM model.

Scheme 2



Due to the conformational flexibility of the ethyl and trifluoroethyl groups, three conformers were examined for each N-in and N-out isomer in these cases (Scheme 2). The illustrated conformations represent the most stable form of the *cis*-decalin system, a chair−chair conformation, and include all of the possible symmetrical staggered conformations arising from rotation of the substituent ethyl or trifluoroethyl groups (the nonsymmetrical possibilities were also considered, but constitute intermediary energy points and are not presented in order to simplify the analysis). The ϕ-angles (180°, 60°, −60°) shown in Scheme 2 illustrate the orientation of ethyl and trifluoroethyl groups with respect to the nitrogen lone-pair.

Table 2 summarizes the relative stability of *N,N′*-diethyl **4** and *N,N′*-bistrifluoroethyl 1,5-diaza-*cis*-decalin **5** conformational isomers outlined in Scheme 2. The anti conformation $\mathbf{a_1}$ (Scheme 2) is preferred over the gauche conformations $\mathbf{a_2}$ and $\mathbf{a_3}$ for the N-in isomer, while the gauche conformations $\mathbf{b_2}$ and $\mathbf{b_3}$ are preferred over anti $\mathbf{b_1}$ for N-out isomers (Scheme 2). Solvent calculations performed using the IPCM model are qualitatively in agreement with the calculated gas-phase results for **4a** and **5**. For **4b**, the solvent calculations show that $\mathbf{4b_2}$ and $\mathbf{4b_3}$ are very close in energy similar to the gas phase and solvent results obtained for **5b**. Regardless, the relative stability of **4a** vs **4b** and **5a** vs **5b** is unaffected upon consideration of solvation as illustrated in Table 1, which contains the lowest energy geometries of the N-in and N-out conformers from Table 2.

(5) (a) Macromodel v4.0, v5.0, v6.0; Still, W. C.; Columbia University. (b) Mohamdi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, *11*, 440−467.

(6) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1988.

(7) Chang, Y.-P.; Su, Li, T.-W.; Chao, I. *J. Phys. Chem. A* **1997**, *101*, 6107−6117. (b) Reany, O.; Goldberg, I.; Abramson, S.; Golender, L.; Ganguly, B.; Fuchs, B. *J. Org. Chem*. **1998**, *63*, 8850−8869. (c) Star, A.; Goldberg, I.; Lemcoff, N. G.; Fuchs, B. *Eur. J. Org. Chem*. **1999**, *2033*, 3−2043.

Table 2. Relative Energies[a](kcal/mol) Calculated with Amber* as well as ab Initio HF/6-31G* and B3LYP/6-31+G* Levels for the N-in and N-out Conformers of *N,N′*-Diethyl 4 and *N,N′*-Bistrifluoroethyl 5

method	$\mathbf{4a_1}$	$\mathbf{4a_2}$	$\mathbf{4a_3}$	$\mathbf{4b_1}$	$\mathbf{4b_2}$	$\mathbf{4b_3}$
Amber*	0.0	1.1	2.6	3.9	0.0	0.5
HF/6-31G*[b]	0.0 (0.0)	1.2 (1.0)	1.2 (1.0)[c]	4.5 (4.1)	0.0 (0.3)	1.0 (0.0)
B3LYP/6-31+G*	0.0	0.0	0.0[c]	4.5	0.0	0.7
	$\mathbf{5a_1}$	$\mathbf{5a_2}$	$\mathbf{5a_3}$	$\mathbf{5b_1}$	$\mathbf{5b_2}$	$\mathbf{5b_3}$
Amber*	0.0	2.2	3.0	5.3	0.0	0.4
HF/6-31G*[b]	0.0 (0.0)	1.5 (3.0)	1.5 (3.0)[d]	3.9 (6.2)	0.0 (0.0)	0.0 (0.0)[e]
B3LYP/6-31+G*	0.0	1.7	1.7[d]	3.1	0.0	0.0[e]

[a] Relative energies are reported with respect to the lowest energy isomer within each of the series $\mathbf{4a_{1-3}}$, $\mathbf{4b_{1-3}}$, $\mathbf{5a_{1-3}}$, and $\mathbf{5b_{1-3}}$. [b] Relative solvation energies calculated using the IPCM method for $CHCl_3$ are given in parentheses. [c] Converged to the same conformation as $\mathbf{4a_2}$. [d] Converged to the same conformation as $\mathbf{5a_2}$. [e] Converged to the same conformation as $\mathbf{5b_2}$.

Generally, the calculated results for the N-in and N-out isomers (Table 1) are in agreement with experimental observations (Scheme 1). Molecular mechanics results indicate that N-in **1a** should be the more stable conformer for 1,5-diaza-*cis*-decalin in agreement with experimental data. With the *N,N′*-dimethyl derivative **2** and *N,N′*-diethyl derivative **4**, the energy differences calculated using molecular mechanics also corroborate the experimentally determined stabilities. In one case (**5**, *N,N′*-bistrifluoroethyl), the molecular mechanics results indicate that the N-in isomer is more stable contrary to experimental observations. This result has been investigated further and is discussed later in this study.

Further refinement was undertaken with ab initio calculations (Table 1). Solvent calculations using the IPCM model for the conformers of **1**, **2**, **4**, and **5** qualitatively agree with the gas phase ab initio results.[8] As such, it appears that solvation is not playing a key role in influencing the *relative* stabilities of the conformers in this series. The HF/6-31G* calculation for the parent system **1** agrees with the molecular mechanics result that N-in conformer **1a** is more stable. On the other hand, the HF/6-31G* calculation for *N,N′*-dimethyl derivative overestimates the stability of N-out conformer **2b**. Calculations performed at B3LYP6-31+G* level[9] reduce the energy differences, but do not change the preferences (Table 1). HF/6-31G* and B3LYP/6-31+G* calculations correctly reproduce the stability of the N-out form over the N-in for *N,N′*-diethyl **4** and *N,N′*-bistrifluoroethyl **5**, in agreement with experimental observations (Scheme 1). It is interesting to note that the energy difference between the N-in and N-out isomers for *N,N′*-bistrifluoroethyl derivative **5** changes at the B3LYP/6-31+G* level of theory by 0.7 kcal/mol but only by 0.1 kcal/mol for the *N,N′*-diethyl derivative **4** (Table 1). The greater energy difference for **5** can be accounted for by negative hyperconjugation. The low-lying C−C σ^*-orbital of the CH_2CF_3 group is appropriately oriented to interact with the nitrogen lone-pair in conformer $\mathbf{5a_1}$, which stabilizes the N-in isomer. Apparently, such negative hyperconjugation is not as significant for *N,N′*-diethyl derivative **4**.

The failure of molecular mechanics calculations (Amber*) to predict **5b** (N-out) as the more stable conformer for the *N,N′*-bistrifluoroethyl case might be due to the poor charge description of CH_2CF_3 group in **5** by molecular mechanics. Since standard force fields typically do not perform well with polar functional groups,[5] the electrostatic charges for *N,N′*-bistrifluoroethyl derivative **5** were calculated separately using a semiempirical (AM1) method.[10] These electrostatic charges were then incorporated into the molecular mechanics (Amber*) calculations. As mentioned above, three different conformers were examined for the N-in and N-out isomers of **4** and **5** (Scheme 2). As before, the anti conformation $\mathbf{a_1}$ is preferred for the N-in arrangement and the gauche conformation $\mathbf{b_2}$ is preferred for the N-out arrangement in **4** and **5** (Scheme 2). 1,5-Diaza-*cis*-decalins **1**, **2**, and **4** were also reanalyzed using this method, and the results are summarized in Table 3. The calculated results with the AM1 charges do not significantly change for **1**, **2**, and **4** compared to the results using the Amber* charges. With *N,N′*-bistrifluoroethyl derivative **5** there is a dramatic change upon application of AM1 charges (Table 2 vs Table 3). Using this technique, the calculated results are qualitatively in agreement with the experimental results (Scheme 1 vs Table 3). While the poor treatment of the CH_2CF_3 using the standard Amber* force field might arise from other parameters (such as van der Waals and torsional terms), agreement between experiment and theory across the series indicates that application of corrected charges is useful for a qualitative assessment in this particular case.

Table 3. Relative Energies (kcal/mol) Calculated with Amber* Using AM1 Charges for the Conformers of 1, 2, 4, and 5

	1a	**1b**	**2a**	**2b**	**4a**	**4b**	**5a**	**5b**
Amber*	0.0	4.5	0.0	0.4	0.7	0.0	2.9	0.0

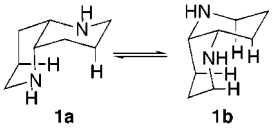
The interactions that control the relative stability of conformers of 1,5-diaza-*cis*-decalin and their substituted derivatives could arise from a number of sources (steric, electrostatic, stereoelectronic, and torsional). In the following paragraphs each of these interactions is analyzed with the aim of identifying the critical interactions. The stability of N-in isomer **1a** over N-out isomer **1b** can be explained on the basis of 1,4-nonbonded axial hydrogen interactions. In the case of the N-in isomer, 1,4-nonbonded hydrogen interactions are absent, whereas the N-out isomer **1b** has three 1,4-nonbonded hydrogen interactions (within 2.4 Å), which presumably destabilize the latter isomer (Scheme 3).[11] However, these interac-

(8) For one case, **2a**, a substantial energy change between gas phase (1.7 kcal/mol) and IPCM $CHCl_3$ (4.5 kcal/mol) calculations is observed. While the increase may reflect stabilization of **2b** by $CHCl_3$, the experimental ratio in chloroform (60:40 **2a**:**2b**) indicates that the calculations overestimate the magnitude.

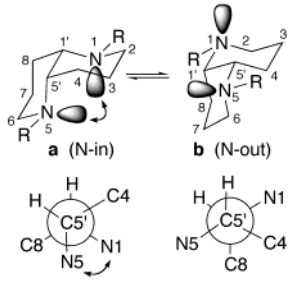
(9) For this system (**1**, **2**, **4**, **5**), less costly single point B3LYP/6-31+G*//HF/6-31G* calculations gave essentially the same energies (within 0.1 kcal/mol) as the more extensive B3LYP/6-31+G* calculations.

(10) (a) SPARTAN version 5.1.2. Wavefunction, Inc.; 18401 Von Karman Ave., Suite 370; Irvine, CA 92612 U.S.A. (b) Chirlian, L. E.; Francl, M. M. *J. Comput. Chem.* **1987**, *8*, 894−905. (c) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361−373.

Scheme 3



Scheme 4



tions are also present in the *N,N′*-dialkylated derivatives. As such, an additional interaction(s) must be responsible for the shift in the equilibria toward the N-out form upon *N*-alkylation.

For parent **1**, an N-in conformer with an axially disposed hydrogen which can undergo a weak intramolecular hydrogen bond is also possible.[12] Fleischhauer et al. have examined the stability of this hydrogen bonded conformer and found that the hydrogen bonded N-in isomer is more stable than the non-hydrogen bonded N-in isomer (**1a**).[13] Therefore, the hydrogen bonded conformational isomer would also contribute toward the stability of the N-in conformer. While such an effect might serve to explain the greater stability of the N-in conformer for parent **1** relative to **2**, **4**, and **5**, it does not account for the observed effects within the *N,N′*-dialkylated series. In addition, a similar preference for the N-in isomer has been observed for 1-aza-*cis*-decalin which cannot undergo such a hydrogen bond indicating that other factors are critical (see above).[14] Even though hydrogen bonded **1a** was not used explicitly in this study (due to the different geometry as compared to the *N,N′*-dialkyl derivatives), inclusion of hydrogen bonded **1a** does not alter any of the trends or conclusions drawn.

Another factor that can influence the relative stability of the N-in isomers of 1,5-diaza-*cis*-decalins arises from repulsion between the nitrogens due to lone pair interactions or nitrogen electrostatic interactions. From Scheme 4 it is anticipated that both of these effects would destabilize the N-in form relative to the N-out form across the series. The addition of electron donating *N*-alkyl groups such as methyl (**2**) and ethyl (**4**) should enhance this repulsive interaction between the nitrogen lone pairs, destabilizing the N-in isomers relative to the parent **1** (R = H). On the other hand, the electron-withdrawing *N*-trifluoroethyl group (**5**) should reduce the repulsions between the nitrogen atoms and stabilize the N-in isomer. Experimentally, the N-out conformers were found to be increasingly preferred over the N-in conformers in the series R = H, Me, Et, CH_2CF_3 (Scheme 1). As such, the differences in nitrogen lone pair and nitrogen electrostatic repulsions between these compounds do not appear to be the predominant factors governing the conformational equilibria of the 1,5-diaza-*cis*-decalins.

Stereoelectronic interactions were also evaluated as a potential source of the different stabilities of the N-in and N-out forms of the 1,5-diaza-*cis*-decalins.[15,16] The relevant interactions include (i) negative hyperconjugation between the nitrogen lone-pair and a properly oriented σ^*-acceptor (C−H and C−C bonds) and (ii) donation from the best σ-donor (C−H bond) to the best σ^*-acceptor (C−N bond). Comparing negative hyperconjugation interactions, the N-in isomer has four σ^* acceptor C−H bonds available to interact with the nitrogen lone-pair while the N-out isomer has two σ^* acceptor C−H and two σ^* acceptor C−C bonds. Upon examination of the relative C−H and C−C bond lengths of **1** calculated at HF/6-31G* level, it appears that the C−H and C−C bonds anti to nitrogen lone-pairs are relatively longer than the other C−H and C−C bonds. Similar trends were observed for the *N,N′*-dialkyl derivatives **2**, **4**, and **5**. While this observation supports the presence of negative hyperconjugation interactions,[16] Wiberg et al. have proposed that such behavior may also be explained by repulsive interactions between the nitrogen lone-pair and the backside of the C−H σ-bond orbital.[17]

Examination of the parent system **1** reveals that four C−H σ-bonds are aligned to interact with σ^* acceptor C−N bonds in the N-in isomer while two C−H and two C−C σ-bonds can interact in the N-out isomer. Assuming that C−H bonds are stronger donors than C−C bonds,[18] the stability of N-in isomer **1a** over N-out isomer **1b** can be explained, but the stability of N-out isomers **2b**, **4b**, and **5b** cannot be accounted for using this analysis (Scheme 1 and Table 1). Since the *number* of stereoelectronic interactions is equivalent in the N-out and N-in isomers of **1**, the real issue centers on the *magnitude* of these interactions; there is no definitive evidence to indicate that these interactions differ enough to cause the degree of preferential stabilization that is observed.[19,20,21] Moreover, the stabilities of the N-in isomers

(11) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York; p 138. (b) Booth, H.; Bostock, A. H. *J. Chem. Soc., Chem. Commun.* **1967**, 177−178.

(12) The N−H−N bond angle in this "hydrogen bond" is almost 90°. As such, the term hydrogen bond is used only in a descriptive sense since almost no orbital overlap is possible. This interaction is more accurately considered as an electrostatic interaction between the axial hydrogen and the nitrogen across the ring.

(13) Fleischhauer, J.; Raabe, G.; Santos, A. G.; Schiffer, J.; Wollmer, A. *Z. Naturforsch* **1998**, *53a*, 896−902.

(14) (a) Booth, H.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 2* **1975**, 111−118. (b) Booth, H.; Griffiths, D. V. *J. Chem. Soc., Chem. Commun.* **1973**, 666−667.

(15) (a) Epiotis, N. D.; Yates, J. R.; Larson, C. R.; Kirmaier, C. R.; Bernardi, F. *J. Am. Chem. Soc.* **1977**, *99*, 8379−8391. (b) Brunck, T. K.; Weinhold, F. *J. Am. Chem. Soc.* **1979**, *101*, 1700−1703. (c) Dionne, P.; St-Jacques, M. *J. Am. Chem. Soc.* **1987**, *109*, 2616−2623. (d) Senderowitz, H.; Golender, L.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9707−9728. (e) Allinger, N. L.; Yuh, Y. H.; Lii, J−H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8566.

(16) (a) Brockway, L. O. *J. Phys. Chem.* **1937**, *41*, 185. (b) Patrick, C. R. *Adv. Fluorine Chem.* **1961**, *2*, 1. (c) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley: New York, 1985; p 171.

(17) (a) Wiberg, K. B.; Breneman, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 8765−8775. (b) Wiberg, K. B. *J. Org. Chem.* **1991**, *56*, 544−561.

(18) Rablen, P. R.; Hoffman, R. W.; Hrovat, D. A.; Borden, W. T. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1719−1726.

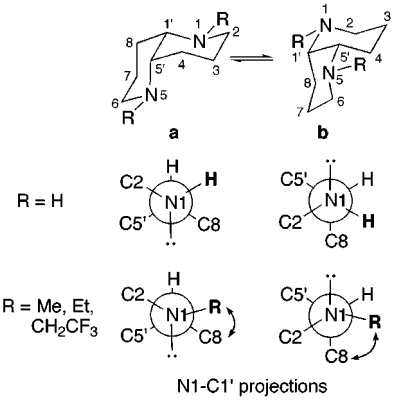
(19) Whether the σ-orbital of a C−H bond is a better donor than that of a C−C bond has been a subject of debate for many decades (see ref 17). The hyperconjugative effect as first suggested by Baker-Nathan ranks the C−H bond as a stronger donor than the C−C bond; however, there is no compelling evidence to support such a statement. Even though negative hyperconjugation is manifested in the conformational behavior of many experimentally studied systems, its origin and magnitude are a subject of continual debate (see ref 21).

(20) (a) March, J. *Organic Reactions and Mechanism*, VCH: New York. (b) Cooney, B. T.; Happer, D. A. R. *Aust. J. Chem.* **1987**, *40*, 7−1555.

Table 4. The Degree of Pyramidalization (360° − Σ RNR Angles) of the Two Nitrogen Atoms and the Torsional Angle (R−N1−C1′−C8) for 1, 2, 4, and 5 as Observed in the B3LYP/6-31+G* and (Amber*) Calculated Geometries

	compound	N-in (**a**)	N-out (**b**)
pyramidalization (deg)	**1**	27.0 (28.6)	23.7 (25.2)
	2	24.8 (27.0)	18.7 (20.6)
	4	18.8 (20.2)	19.0 (21.0)
	5	13.4 (5.0)	15.5 (0.3)
R−N1−C1′−C8 (deg)	**1**	54.9 (55.9)	57.5 (52.7)
	2	55.7 (56.7)	62.8 (59.4)
	4	48.0 (50.1)	63.1 (59.6)
	5	41.1 32.4)	67.5 (109.3)

Scheme 5



relative to the N-out isomer for **1**, **2**, **4**, and **5** are borne out in the molecular mechanics calculations even though the geometries do not show lengthening of C−H and C−C bonds anti to nitrogen lone pairs expected from such stereoelectronic interactions. Since the standard force fields used do not appear to reproduce these stereoelectronic effects, our initial hypothesis was that the stability of isomers N-in vs N-out is primarily governed by nonbonded steric effects.[22]

Analyzing B3LYP/6-31+G* and molecular mechanics calculated N-in and N-out geometries of **1** and the *N*,*N*′-dialkyl derivatives **2**, **4**, and **5** reveals a possible source for such a steric effect. The degree of pyramidalization of nitrogen atoms decreases with the increasing size of the alkyl groups (Table 4).[23] As a consequence, the R−N1−C1′−C8 torsional interaction becomes more eclipsed in the case of N-in isomers **a**, which presumably destabilizes the N-in form as the alkyl groups increase in size (Scheme 5 and Table 4).[24] On the other hand, the R−N1−C1′−C8 angle increases with substitution in the N-out isomers **b** relieving torsional strain between C1′−C8 and N1−R.

In general, the ab initio and molecular mechanics geometries predict similar degrees of pyramidalization at the nitrogen atoms for the 1,5-diaza-*cis*-decalin conformers and the *N*,*N*′-dialkyl derivatives. *N*,*N*′-Bistrifluoroethyl **5** proves to be the exception as molecular mechanics (Amber*) calculations appear to underestimate the degree of pyramidalization of nitrogen atoms (Table 4). This result is most likely a consequence of the electrostatic charges introduced from AM1 calculations; however, the direction of the perturbations are consistent with all the other calculated results. Overall, the results from the molecular mechanics and ab initio calculations suggest that *N*-alkylation flattens the nitrogen atom, inducing unfavorable eclipsing torsional interactions in the N-in isomers **a** and slightly relieving unfavorable gauche interactions in the N-out isomers **b**.

Conclusion

The conformational equilibria of 1,5-diaza-*cis*-decalin and its substituted derivatives have been calculated using molecular mechanics (Amber*) and ab initio calculations. *N*,*N*′-Diethyl- and *N*,*N*′-bistrifluoroethyl-1,5-diaza-*cis*-decalins have been synthesized and the equilibrium mixtures have been measured by means of ^{1}H and ^{13}C NMR experiments. The calculated results correlate with the experimentally determined stabilities of conformational isomers in almost all the cases. The apparent failure of molecular mechanics calculations to predict **5b** as the more stable isomer for the *N*,*N*′-bistrifluoroethyl derivative has been accounted for by introducing electrostatic charges from AM1 calculations. Molecular mechanics and ab initio calculations have allowed an understanding of the relative importance of stereoelectronic, steric, and torsional effects in controlling the stability of 1,5-diaza-*cis*-decalin conformers. Overall, the calculated results suggest that stereoelectronic interactions are largely equivalent in both forms, and the relative stability of conformers is governed by steric and torsional effects.

Experimental Section

Computational Methodology. Molecular mechanics (Amber*) calculations have been performed using Macromodel.[5] The AM1 electrostatic charges have been calculated using Spartan.[10] Ab initio calculations have been performed using Gaussian94 program.[25] Geometries were fully optimized using both the RHF method with a 6-31G* basis set and the B3LYP HF-DFT method with a 6-31+G* basis set.[26] The calculated geometries have been characterized as true minima via harmonic vibrational frequency analyses. The C_2-symmetry has been maintained in all the calculations. Nitrogen inversion equilibrium has not been considered in this study; only equatorial conformations have been calculated at all levels of theory. The solvation energies have been calculated using isodensity polarized continuum model (IPCM), which is a dielectric continuum type method, where the shape and size of the cavity occupied by the solute molecules is defined by an isodensity surface of the solute.[27] The IPCM calculations have

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(22) The molecular mechanics calculations used in this study do contain explicit parameters for the anomeric effect, but parameters for other stereoelectronic effects such as the lp-N−C−X (X = H, C) interactions under discussion are absent. The inability of molecular mechanics to reproduce the expected geometrical parameters indicates that the force fields did not incorporate such effects from the standardization set into other parameters.

(23) There is precedent for decreasing pyramidalization with increasing substitution on nitrogen. For example, in the following series the degree of pyramidalization (360 − Σ RNR angles) decreases with increasing substitution: NH_3: 39.9°, CH_3NH_2: 36.2°, $(CH_3)_2NH$: 28.0°, and $(CH_3)_3N$: 27.3°. These pyramidalization angles were calculated from the experimental bond angles: Pozzoli, S. A.; Rastelli, A.; Tedeschi, M. *J. Chem. Soc., Faraday Trans. 2* **1973**, *69*, 256−261.

(24) For a related proposal in the *cis*-decahydroisoquinolines, see ref 14.

(25) Gaussian 94: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defreees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1995.

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been performed using HF/6-31G* basis set at the appropriate (gas phase) optimized geometries in chloroform.

General Information. Unless otherwise noted, all nonaqueous reactions and distillations were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. THF and CH_2Cl_2 were dried and deoxygenated using a solvent column purification system.[28] A 450 mL reactor (No. N4767 from Parr) was used for the high-pressure reactions with stirring by an external magnetic stir plate. For the chromatographic and instrumentation methods used as well as the spectral formats, see the Supporting Information.

1,5-Diaza-*cis*-decalin (1).[2] To a solution of naphthyridine (20.0 g, 0.154 mol) in HOAc (120 mL) was added 10% Rh/Al_2O_3 (2.0 g). The mixture was stirred for 36 h at room temperature under H_2 (1100 psi). The mixture was filtered through Celite to give a 90:10 mixture of the *cis*-**1** and *trans*-**1**. While cooling to 0 °C, saturated NaOH was added until pH > 14. After saturation with NaCl, the mixture was extracted extensively with Et_2O. The combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to leave a 94:6 mixture of the *cis*-**1** and *trans*-**1** isomers (13.7 g, 63%). Crystallization from Et_2O (~20 mL) furnished *cis*-**1** containing <5% of *trans*-**1**. Distillation (88−90 °C, 2 mmHg) afforded the pure product as a waxy white solid.

***N,N′*-Dimethyl-1,5-diaza-*cis*-decalin (2).**[4] Compound *cis*-**1** (0.730 g, 5.21 mmol) was added to a mixture of formic acid (2 mL) and 37% formaldehyde solution (4 mL). After warming for 1 d to 70 °C, water was added followed by 50% aqueous NaOH to obtain pH > 14. The mixture was extracted with CH_2Cl_2. The combined extracts were dried with K_2CO_3, and the solvent was evaporated. Purification by distillation (100 °C, 1 mmHg) afforded the product as a colorless liquid in 87% yield (0.760 g, 4.53 mmol). The ^{1}H NMR data obtained from this material was identical to that previously reported.

***N,N′*-Diethyl-1,5-diaza-*cis*-decalin (4).** Aqueous NaOH (50%, 2 mL) was added to a solution of *cis*-**1** (0.280 g, 2.00 mmol) in THF (3 mL) followed by EtI (0.400 mL, 5.00 mmol). After stirring for 1 d, water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried with K_2CO_3, and the solvent was evaporated. Purification by distillation (110 °C, 2 mmHg) afforded the product as a colorless liquid in 67% yield (0.262 g, 1.34 mmol): ^{1}H NMR (500 MHz, $CDCl_3$, 260 K) δ 1.10 (t, J = 7.2 Hz, 6H), 1.51−1.60 (m, 6H), 1.73 (d, J = 8.3 Hz, 2H), 2.34 (t, J = 10.5 Hz, 2H), 2.51−2.59 (m, 6H), 3.10 (d, J = 7.8 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$, 260 K) δ 12.70, 14.34, 24.17, 46.46, 47.71, 56.84; MS (ES) m/z calcd for $C_{12}H_{24}N_2^+$ requires 197.2020, found 197.2017. Comparison of the NMR data from the N-out and N-in conformers of **2** indicated that only the N-out isomer was populated at room temperature.

***N,N′*-Bis-trifluoroacyl-1,5-diaza-*cis*-decalin.** Trifluoroacetic anhydride (2.16 mL, 15.3 mmol) was added to a solution of *cis*-**1** (0.535 g. 3.82 mmol), Et_3N (3.20 mL, 23.0 mmol), and DMAP (~2 mg) in CH_2Cl_2 (10 mL) at 0 °C. After stirring 1d, water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried with $MgSO_4$, and the solvent evaporated. The residue was purified by chromatography (CH_2Cl_2) to provide the product as a light yellow solid in 85% yield (1.08 g, 3.25 mmol): ^{1}H NMR (200 MHz, $CDCl_3$, 298 K) δ 1.63−2.08 (m, 6H), 2.13−2.37 (m, 2H), 2.83 (t, J = 13.1 Hz, 2H), 3.15 (m, 2H), 3.50−3.66 (m, 2H), 3.84 (bd, J = 13.9 Hz, 2H) 3.97−4.10 (m, 2H) 4.46 (d, J = 15.1 Hz, 2H), 4.60−4.73 (m, 2H).

***N,N′*-Bis-trifluoroethyl-1,5-diaza-*cis*-decalin (5).** Selective reduction was accomplished without deacylation.[29] After BH_3·DMS (1.32 mL, 13.9 mmol) was added dropwise to a stirred solution of *N,N′*-bis-trifluoroacyl-1,5-diaza-*cis*-decalin (1.03 g, 3.09 mmol) in THF (20 mL) at 0 °C, the mixture was heated at reflux for 2 d. While cooling in an ice bath, MeOH was added until evolution of gas stopped, and then a large amount of water was added. The resulting mixture was extracted with Et_2O, and the extracts were dried over Na_2SO_4. Concentration afforded the product as a yellow solid in 94% yield (0.88 g, 2.89 mmol): ^{1}H NMR (500 MHz, $CDCl_3$, 260 K) δ 1.42−1.69 (m, 8H), 2.61−2.63 (m, 4H), 2.93−3.07 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$, 260 K) δ 16.93, 24.55, 47.20, 56.00 (q, J = 123 Hz)) 60.37, 126.2 (q, J = 1105 Hz); MS (ES) m/z calc′d for $C_{12}H_{19}F_6N_2^+$ requires 305.1439, found 305.1452. Comparison of the NMR data from the N-out and N-in conformers of **2** indicated that only the N-out isomer was populated at room temperature.

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Supporting Information Available: Spectral assignments for compounds **4** and **5** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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