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# Heterocyclic Analogues of Cyclohexene: Theoretical Studies of the Molecular Structures and Ring-Inversion Processes

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The equilibrium geometry, ring-inversion barrier, and pathway for heterocyclic analogues of cyclohexene have been studied using the MP2/6-311G(d,p) level of theory. It is concluded that the replacement of one methylene group in cyclohexene by heteroatom results in significant changes in the character of the potential-energy surface in comparison with cyclohexene. The equilibrium conformation of ring strongly depends on the position of the heteroatom due to the existence of the n−$\pi$ conjugation. However, the character of the ring-inversion process is determined by the nature of the heteroatom. In the case of sulfur- and selenium-containing rings, the boat or twist−boat conformation corresponds to an additional minimum on the potential-energy surface. Moreover, the barriers of the conformational transition from this conformer to two different half-chair forms are significantly different. Nitrogen-containing heterocycles possess two pairs of minima corresponding to the different configurations of the nitrogen atom. However, the transition between the two minima with the same configuration of the heteroatom proceeds only in two steps that include ring inversion and nitrogen inversion.

## Introduction

The tetrahydroaromatic rings represent the fundamental structures of organic compounds.[1,2] These rings are very popular building blocks of many natural organic and bioorganic molecules.[3] Therefore, knowledge of the conformational characteristics of tetrahydroaromatic rings is very useful for understanding the properties, from a practical point of view, of a number of important compounds.

Cyclohexene is considered to be a parent molecule for all tetrahydroaromatic rings. Therefore the molecular structure and conformational characteristics of cyclohexene were extensively investigated using various experimental[1,4,5] and theoretical methods.[1,5,6] It was established that the equilibrium conformation of cyclohexene represents a half-chair structure possessing $C_2$ symmetry and can be described by a twist angle (the C(sp$^3$)−C(sp$^3$)−C(sp$^3$)−C(sp$^3$) torsion angle) being about 60°. Ring inversion processes from one half-chair conformation to another symmetrical conformation proceed via the boat conformer, and the barrier of this conformational transition is 4.2−10.3 kcal/mol as determined by the different experimental and theoretical methods.[4−6] The most difficult problem for investigating ring inversion in cyclohexene is the question concerning the character of the boat conformation. In accordance with many molecular mechanics calculations, this conformation is a shallow minimum.[1,5,6] Similar results were obtained using ab initio quantum-chemical methods within the Hartree−Fock approximation.[5] The consideration of electron correlation effects results in a description of the boat conformation as a saddle point but with a very low imaginary frequency.[6] Moreover, it should be noted that the values of the barrier of the ring inversion, the character of the boat conformation, and the energy profile for the ring inversion strongly depend on the method of calculation.[1,5,6] Investigations of the two-dimensional vibrational potential-energy surface of cyclohexene in terms of ring-bending and ring-twisting coordinates using experimental data[4] did not resolve this problem because of the large systematic errors of the potential function in the vicinity of the boat conformation.

The extended calculations of the equilibrium geometry, ring-inversion barrier, and pathway for cyclohexene using the MP2 and density functional theory (DFT) methods with different basis sets[7] reveal that cyclohexene possesses an unusual energy profile of ring inversion. This process is characterized by an extremely top-flattened potential-energy surface in the area of the boat conformation. The transition from one twist−boat conformation to another via boat virtually does not cause changes in energy.[7] The size of this plateau on the potential energy surface in terms of the value of the C(sp$^3$)−C(sp$^3$)−C(sp$^3$)−C(sp$^3$) torsion angle is about ±30° (DFT) and ±40° (MP2). Such a feature of the energy profile for the cyclohexene ring inversion results in the formation of a multitude of saddle points for this process. From a physical viewpoint, almost all points within the plateau may be considered as saddle points. The boat conformation is just a central point of the plateau. Therefore, the cyclohexene ring inversion should be described as a three-step process. The first step includes the transition from a half-chair to a twist−boat conformation accompanied by a significant increase in energy. The second step may be described as an almost-free transformation of one twist−boat to another analogous to pseudorotation. The third step involves the transition from a twist−boat to a half-chair conformation leading to a significant decrease in energy.[7]

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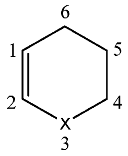
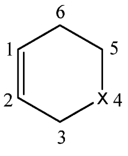
The heterocyclic analogues of cyclohexene containing one heteroatom instead of a methylene group in different positions have been studied less often. The oxygen-containing tetrahydroheterocycles were extensively investigated by experimental[8−13] and theoretical[14−16] methods. It was established that the equilibrium conformation of 3,4-dihydro-2H-pyran and 3,6-dihydro-2H-pyran is a half-chair with a twist angle of approximately 35°. The barrier of the ring inversion process is 6.6−10.0 kcal/mol for 3,4-dihydro2H-pyran and 5.9−10.1 kcal/mol for 3,6-dihydro-2H-pyran. The structure of 1,2,3,4-tetrahydropyridine and 1,2,3,6-tetrahydropyridine were only optimized at the HF/6-31G(d) and MP2/6-31G(d) levels of theory.[17] It was demonstrated that the equilibrium conformation of these compounds is half-chair. It was discussed that these rings can, in principle, exist in two half-chair conformers, having the hydrogen atom attached to the nitrogen in the axial or equatorial positions. Two minima on the potential-energy surface corresponding to the axial and equatorial isomers were located for 1,2,3,6-tetrahydropyridine. However, only the equatorial conformer was found for 1,2,3,4-tetrahydropyridine. A comparison of the energy of these isomers demonstrates that 1,2,3,4-tetrahydropyridine is the lowest energy isomer with the axial conformer of 1,2,3,6-tetrahydropyridine lying 5.5 kcal/mol higher in energy. The barriers of ring inversion for these molecules were not determined. According to experimental and theoretical data the equilibrium geometry of the sulfur-containing tetrahydroheterocycles is half-chair,[15,18−20] and the barrier of ring inversion via the boat form is 3.9−11.8 kcal/mol. As far as we know the conformational characteristics and the ring inversion for the selenium-containing rings have not been discussed in the literature.

Thus, only the equilibrium conformation and the value of the barrier of ring inversion were investigated for heterocyclic analogues of cyclohexene. The conformation of the transition state and the lowest energy pathway of ring inversion for tetrahydroheterocycles have not been considered. However, the replacement of one methylene group in cyclohexene by a heteroatom leads to the formation of an asymmetric molecule. Therefore, it could be assumed that the asymmetry of the heterocycle may significantly change the unusual energy profile of the ring inversion found in cyclohexene.

In this paper we present the first systematic consideration of the molecular structure and conformational characteristics of tetrahydroheterocycles. Our data demonstrate that the asymmetry of heterocyclic analogues of cyclohexene results in some asymmetry in the equilibrium half-chair conformation and drastic changes in the ring-inversion pathway. Moreover the ring inversion process in sulfur- and selenium-containing heterocycles is multistage due to the appearance of an additional minimum on the potential energy surface corresponding to a twist−boat or a boat conformation. Therefore, the inversion of these rings cannot be characterized by one value of barrier.



**1** **X=O**
**2** **X=NH**
**3** **X=S**
**4** **X=Se**



**5** **X=O**
**6** **X=NH**
**7** **X=S**
**8** **X=Se**

## Methods of Calculations

The molecular structures of molecules **1**−**8** were optimized using the second-order Møller-Plesset perturbation theory.[21] The standard 6-311G(d,p) basis set[22] was applied. Vibrational frequencies were calculated within the harmonic approximation, using analytical second derivatives at the same level of theory.

The barrier of ring inversion in all molecules was calculated as the difference between the energy of the equilibrium and the saddle point conformations. The investigation of the ring inversion pathway has been carried out using the intrinsic reaction path (IRC) procedure.[23,24] All calculations were performed using the PC GAMESS program.[25]

The n-$\pi$ interactions between the C═C double bond and the lone pair of the heteroatom in molecules **1**−**4** and the hyperconjugation interactions of the lone pairs of heteroatom and the C−H bonds of the neighboring methylene groups were investigated within the natural bonding orbitals theory[26] using NBO 5.0 program.[27] The n−$\pi$ and hyperconjugation interactions are referred to as “delocalization” corrections to the zeroth-order natural Lewis structure. For each donor NBO ($i$) and acceptor NBO ($j$), the stabilization energy $E(2)$ associated with delocalization (“2e-stabilization”) $i \rightarrow j$ is estimated as

$$E(2) = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\epsilon_j - \epsilon_i}$$

where $q_i$ is the donor orbital occupancy, $\epsilon_j$ and $\epsilon_i$ are the diagonal elements (orbital energies), and $F(i,j)$ is the off-diagonal NBO Fock matrix element.

The potential-energy surfaces for molecule **2** in terms of the N−C(sp$^3$)−C(sp$^3$)−C(sp$^3$) and C(sp$^2$)−C(sp$^2$)−N−H torsion angles and molecule **6** in terms of the C(sp$^3$)−N−C(sp$^3$)−C(sp$^3$) and C(sp$^2$)−C(sp$^3$)−N−H torsion angles were constructed using systematic scans at fixed values of these torsion angles in the ranges of ±80° for the N−C−C−C and C−N−C−C angles and 60−300° for the C−C−N−H angles with 10° steps. These calculations were performed by the MP2/6-31G(d) method using the Gaussian03 program.[28] Conformation of the ring has been described by Zefirov−Palyulin−Dashevskaya puckering parameters[29] where $S$ is the degree of puckering and $\theta$ and $\Psi$ are polar angles determining the type of conformation. The value of these angles for ideal conformations are $\Theta = 45°$ and $\Psi = 30°$ for the half-chair conformation, $\Theta = 90°$ and $\Psi = 0°$ for the boat conformation, and $\Theta = 90°$ and $\Psi = 30°$ for the twist−boat conformation.

## Results and Discussion

**Equilibrium Conformation.** The equilibrium geometry of cyclohexene is governed by two groups of factors.[1] The first group is characterized by a trend toward a staggered conformation along the C(sp$^3$)−C(sp$^3$) bonds and a bending strain due to the deformation of the endocyclic bond angles at the saturated carbon atoms which stabilize a nonplanar conformation of the ring. The second group includes the 1,2-allylic strain. These interactions favor the flattened geometry of cyclohexene.

The replacement of one methylene group by a heteroatom results in a considerable change in the intramolecular interactions influencing the conformation of the tetrahydroheterocycle. Therefore, it is possible to divide all tetrahydroheterocycles into two groups according to the position of the heteroatom relative to the double bond. The first group includes the tetrahydrocycles in which the lone pairs of the heteroatom are conjugated with $\pi$-electrons of the double bond (molecules **1**−**4**). It is assumed that n−$\pi$ interactions can influence the conformation of the ring. The second group of tetrahydroheterocycles contains rings with the heteroatom and double bond being separated by the methylene group (molecules **5**−**8**). In these molecules conjugation is absent, but hyperconjugation interactions of the lone pairs

**TABLE 1: Selected Geometrical and Ring Puckering Parameters of Equilibrium Conformations of Molecules 1−8 and Cyclohexene (CH)**

| | | bond length, Å | | | torsion angles, deg | | | | puckering parameters | | | ΔE, |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| molecule | conformation | 2−3 | 3−4 | 4−5 | 1−2−3−4 | 2−3−4−5 | 3−4−5−6 | 2−1−6−5 | S | $\theta$ | $\Psi$ | kcal/mol[a] |
| CH | half-chair | 1.505 | 1.529 | 1.527 | 14.52 | −46.06 | 63.40 | 14.54 | 0.78 | 36.3 | 30.0 | |
| **1** | half-chair | 1.362 | 1.430 | 1.523 | 13.52 | −47.67 | 64.40 | 12.26 | 0.78 | 38.8 | 27.5 | |
| **2a**[b] | half-chair | 1.400 | 1.460 | 1.527 | 20.42 | −51.33 | 64.06 | 12.70 | 0.81 | 34.7 | 22.0 | 0 |
| **2b**[c] | half-chair | 1.378 | 1.449 | 1.531 | 2.49 | −33.89 | 57.58 | 20.19 | 0.73 | 40.7 | 12.4 | 0.94 |
| **3** | half-chair | 1.753 | 1.812 | 1.527 | 10.70 | −44.35 | 69.13 | 15.34 | 0.83 | 38.6 | 24.5 | 0 |
| | twist−boat | 1.760 | 1.826 | 1.534 | 43.88 | −59.91 | 25.39 | -55.75 | 0.86 | 82.8 | 17.2 | 3.63 |
| **4** | half-chair | 1.900 | 1.960 | 1.527 | 6.88 | −39.66 | 68.57 | 19.62 | 0.83 | 38.9 | 16.2 | 0 |
| | twist−boat | 1.906 | 1.975 | 1.531 | 42.36 | −60.06 | 27.61 | −59.04 | 0.88 | 83.7 | 18.7 | 2.82 |
| **5** | half-chair | 1.506 | 1.416 | 1.420 | 11.66 | −47.23 | 69.25 | 16.42 | 0.84 | 37.8 | 25.8 | |
| **6a**[d] | half-chair | 1.511 | 1.465 | 1.466 | 12.50 | −43.75 | 62.70 | 14.51 | 0.77 | 37.1 | 27.4 | 0 |
| **6e**[e] | half-chair | 1.505 | 1.462 | 1.463 | 14.54 | −50.91 | 71.17 | 16.01 | 0.86 | 37.0 | 29.4 | 0.30 |
| **7** | half-chair | 1.505 | 1.811 | 1.810 | 17.48 | −44.76 | 64.41 | 17.73 | 0.83 | 34.8 | 25.2 | 0 |
| | boat | 1.498 | 1.835 | 1.823 | −53.72 | 39.40 | 13.02 | 56.20 | 0.89 | 83.3 | 8.2 | 2.82 |
| **8** | half-chair | 1.504 | 1.958 | 1.957 | 18.61 | −43.51 | 62.40 | 18.24 | 0.82 | 34.0 | 24.6 | 0 |
| | boat | 1.495 | 1.988 | 1.969 | −54.86 | 38.97 | 13.91 | 60.24 | 0.92 | 82.4 | 8.4 | 0.87 |

[a] Values of absolute energy for the most stable conformers of **2a** (−249.96889 au), **3** (−592.41942 au), **4** (−2594.66674 au), **6a** (−249.95927 au), **7** (−592.41547 au), and **8** (−2594.66434 au). [b] **2a**−conformer with pyramidal configuration of nitrogen atom. [c] **2b**−conformer with planar configuration of nitrogen atom. [d] **6a**−conformer with axial orientation of hydrogen atom. [e] **6e**−conformer with equatorial orientation of hydrogen atom.

of the heteroatom with the neighboring methylene groups may provide an additional factor influencing the conformation of **5−8**. Therefore, taking into account the difference in the intramolecular interactions between the two groups of tetrahydroheterocycles, we will consider the conformational characteristics of these groups separately.

The results of the calculations demonstrate (Table 1) that the equilibrium conformation of molecules **1−4** is half-chair. However, this conformation in **1−4** is asymmetric. It should be noted that the equilibrium conformation of molecule **1** is very close to that of cyclohexene. But a change of the heteroatom leads to significant deformation of equilibrium geometry. The degree of asymmetry of the half-chair conformation systematically increases, and the $\mathrm{C{=}C{-}X{-}C(sp^3)}$ fragment becomes more flattened in the series O···S···Se for **1−4** (Table 1).

The total interaction energy of the endocyclic double bond with two lone pairs of the heteroatom can be estimated using the $E(2)$ values within the NBO theory. The results of the calculations demonstrate a systematic decrease of $E(2)$ for **1**, **3**, and **4** (Table 3). This allows for the assumption that the equilibrium conformation of these molecules strongly depends on the conjugation between the double bond and the heteroatom lone pairs.

The nitrogen atom of tetrahydropyridine **2** has only one lone pair. The energy of the interaction of this lone pair with the double bond is 25.5 kcal/mol and does not follow the general trend for molecules **1−4**. However, the conformational characteristics of the ring are intermediate between those predicted for **1** and **3** (Table 1). This allows one to assume that steric repulsion between hydrogen atoms of the NH fragment and the neighboring methylene group also influence the conformation of ring.

In general tetrahydropyridine **2** may exist in two half-chair conformations with the axial and equatorial orientations of the hydrogen atom of the NH group. Earlier it was concluded[17] that only one minimum exists on the potential energy surface of **2** corresponding to the equatorial orientation of the hydrogen atom. However, these data were obtained based only on the results of optimization using the MP2/6-31G(d) method. An analysis of the potential-energy surface (Figure 1) constructed as a function of the $\mathrm{N{-}C(sp^3){-}C(sp^3){-}C(sp^3)}$ and $\mathrm{C(sp^2){-}C(sp^2){-}N{-}H}$ torsion angles reveals that the situation is much more complex. These two torsion angles describe the conformation of the ring and the orientation of the hydrogen atom of the NH group, which is closely related to the configuration of the nitrogen atom. Therefore, such a cross-section of the potential-energy surface describes the ring conformation, the configuration of the NH fragment, and the relationship between them.

The results of the calculations reveal the existence of two pairs of minima on the potential-energy surface (Figure 1). The hydrogen atom of the NH group has two stable orientations for every conformation of the ring (Figure 2). These orientations differ only by the value of the C−C−N−H torsion angle, but both can be classified as equatorial. The most significant difference between the two conformers of the NH group is caused by a change in the configuration of the nitrogen atom. A conformer with a pyramidal configuration of the nitrogen atom (the sum of bond angles centered on N is 339.2°) is more stable (by 0.9 kcal/mol) in comparison to a conformer with a planar configuration of the nitrogen atom (the sum of bond angles is 359.6°). The barrier of transition between the pyramidal and planar configurations is 2.0 kcal/mol. A comparison of the interaction energies of the endocyclic double bond with the lone pair of the heteroatom for these conformers demonstrates that the planar configuration of the NH group provides the most favorable conditions for the n-$\pi$ interactions (the value of $E(2)$ is 41.2 kcal/mol for the conformer with the planar configuration of the nitrogen atom and 25.5 kcal/mol for the conformer with the pyramidal configuration of N). However, a conformer with a planar configuration of the nitrogen atom adopts an intermediate conformation between half-chair and sofa (Table 1), which results in an increase in steric repulsion between the hydrogen atom of the NH fragment and the equatorial hydrogen atom of the neighboring methylene group. Probably, both of these effects are important for tetrahydropyridine leading to existence two minima on the potential-energy surface.

The equilibrium half-chair conformation of the heterocycle in molecules **5−8** is also slightly asymmetric (Table 1). However, the values of the polar angles are very close in all compounds. Thus, contrary to **1−4**, the change of heteroatom in **5**, **7**, and **8** does not influence the conformational characteristics of the ring.

Tetrahydropyridine **6**, like molecule **2**, represents a special case due to the two possible orientations of the hydrogen atom of the NH fragment. The results of the calculations reveal the

**TABLE 2: Total Energy of the Interaction of the Lone Pairs of the Heteroatom with Double Bond and Methylene Groups (In the Case of Methylene Groups the Values of *E*(2) Energy Represent Sum of All Interactions between Orbitals of Lone Pairs and Methylene Fragments)**

| molecule | extreme point | donor NBO | acceptor NBO | *E*(2), kcal/mol |
|---|---|---|---|---|
| **1** | HCI | LP(O) | BD* (C═C) | 37.27 |
| | | LP(O) | BD* $C(4)H_2$ | 9.85 |
| | TS1 | LP(O) | BD* (C═C) | 23.51 |
| | | LP(O) | BD* $C(4)H_2$ | 11.85 |
| | HCII | LP(O) | BD* (C═C) | 37.32 |
| | | LP(O) | BD* $C(4)H_2$ | 9.85 |
| **2** | HCI | LP(N) | BD* (C═C) | 25.54 |
| | | LP(N) | BD* $C(4)H_2$ | 7.48 |
| | TS1 | LP(N) | BD* (C═C) | 20.74 |
| | | LP(N) | BD* $C(4)H_2$ | 6.29 |
| | HCII | LP(N) | BD* (C═C) | 21.21 |
| | | LP(N) | BD* $C(4)H_2$ | 10.79 |
| **3** | HCI | LP(S) | BD* (C═C) | 27.83 |
| | | LP(S) | BD* $C(4)H_2$ | 5.39 |
| | TS1 | LP(S) | BD* (C═C) | 18.01 |
| | | LP(S) | BD* $C(4)H_2$ | 7.40 |
| | TB | LP(S) | BD* (C═C) | 18.75 |
| | | LP(S) | BD* $C(4)H_2$ | 7.40 |
| | TS2 | LP(S) | BD* (C═C) | 18.90 |
| | | LP(S) | BD* $C(4)H_2$ | 4.98 |
| | HCII | LP(S) | BD* (C═C) | 27.74 |
| | | LP(S) | BD* $C(4)H_2$ | 5.37 |
| **4** | HCI | LP(Se) | BD* (C═C) | 22.01 |
| | | LP(Se) | BD* $C(4)H_2$ | 4.19 |
| | TS1 | LP(Se) | BD* (C═C) | 14.83 |
| | | LP(Se) | BD* $C(4)H_2$ | 5.64 |
| | TB | LP(Se) | BD* (C═C) | 12.30 |
| | | LP(Se) | BD* $C(4)H_2$ | 5.60 |
| | TS2 | LP(Se) | BD* (C═C) | 12.47 |
| | | LP(Se) | BD* $C(4)H_2$ | 5.18 |
| | HCII | LP(Se) | BD* (C═C) | 22.09 |
| | | LP(Se) | BD* $C(4)H_2$ | 4.20 |
| **5** | HCI | LP(O) | BD* $C(5)H_2$ | 11.49 |
| | | LP(O) | BD* $C(3)H_2$ | 12.17 |
| | TS | LP(O) | BD* $C(5)H_2$ | 11.77 |
| | | LP(O) | BD* $C(3)H_2$ | 11.29 |
| | HCII | LP(O) | BD* $C(5)H_2$ | 11.44 |
| | | LP(O) | BD* $C(3)H_2$ | 12.16 |
| **6** | HCI | LP(N) | BD* $C(5)H_2$ | 7.27 |
| | | LP(N) | BD* $C(3)H_2$ | 7.15 |
| | TS | LP(N) | BD* $C(5)H_2$ | 9.34 |
| | | LP(N) | BD* $C(3)H_2$ | 7.98 |
| | HCII | LP(N) | BD* $C(5)H_2$ | 7.62 |
| | | LP(N) | BD* $C(3)H_2$ | 7.51 |
| **7** | HCI | LP(S) | BD* $C(5)H_2$ | 8.33 |
| | | LP(S) | BD* $C(3)H_2$ | 8.53 |
| | TS1 | LP(S) | BD* $C(5)H_2$ | 6.23 |
| | | LP(S) | BD* $C(3)H_2$ | 4.50 |
| | B | LP(S) | BD* $C(5)H_2$ | 8.04 |
| | | LP(S) | BD* $C(3)H_2$ | 7.38 |
| | TS2 | LP(S) | BD* $C(5)H_2$ | 8.62 |
| | | LP(S) | BD* $C(3)H_2$ | 7.68 |
| | HCII | LP(S) | BD* $C(5)H_2$ | 8.35 |
| | | LP(S) | BD* $C(3)H_2$ | 8.53 |
| **8** | HCI | LP(Se) | BD* $C(5)H_2$ | 6.38 |
| | | LP(Se) | BD* $C(3)H_2$ | 6.41 |
| | TS1 | LP(Se) | BD* $C(5)H_2$ | 4.59 |
| | | LP(Se) | BD* $C(3)H_2$ | 2.61 |
| | B | LP(Se) | BD* $C(5)H_2$ | 3.98 |
| | | LP(Se) | BD* $C(3)H_2$ | 3.62 |
| | TS2 | LP(Se) | BD* $C(5)H_2$ | 6.61 |
| | | LP(Se) | BD* $C(3)H_2$ | 5.61 |
| | HCII | LP(Se) | BD* $C(5)H_2$ | 6.38 |
| | | LP(Se) | BD* $C(3)H_2$ | 6.42 |

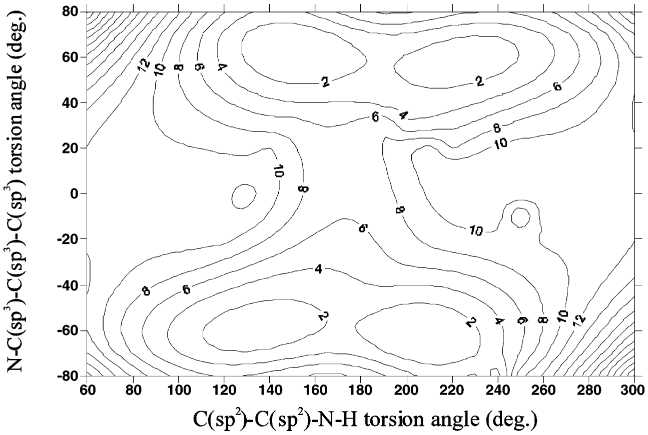


**Figure 1.** The potential-energy surface for molecule **2** constructed by scanning two torsion angles.

existence of two minima on the potential-energy surface (Figure 3) corresponding to axial and equatorial orientations of the hydrogen atom for every half-chair conformation of the ring (Figure 4). The configuration of the nitrogen atom in both conformers is pyramidal (the sum of bond angles centered at N is 325.1° for the axial conformer and 328.3° for the equatorial conformer). The equatorial conformer of **6** lies 0.3 kcal/mol above the axial conformer. The heterocycle in the equatorial conformer of **6** is slightly more flattened in comparison with the axial conformer. An analysis of the potential energy surface (Figure 3) reveals that the transition from the axial to the equatorial conformer without ring inversion proceeds via the transition state with a planar configuration of the nitrogen atom (the sum of the bond angles centered at the N atom is 359.9°). However, the barrier of this conformational transition (6.7 kcal/mol) is significantly higher compared to tetrahydropyridine **2**.

**Ring Inversion.** The results of the calculations demonstrate that only one transition state is located on the potential energy surface for oxygen-containing rings **1** and **5**. Accordingly, the inversion process for these molecules has two-stage characteristics. Above it was discussed that the equilibrium geometry of **1** is very close to cyclohexene (Table 1). However, an analysis of the inversion pathway using the IRC procedure demonstrates the complete loss of the flattened character of the potential-energy surface around the saddle point in molecule **1** compared to cyclohexene (Figure 5). On the contrary, the potential-energy profile for the ring inversion of **5** is similar to cyclohexene despite the slight asymmetry of the equilibrium conformation. Despite the unambiguously determined one saddle point, the character of the potential-energy surface is noticeably flattened around the transition state (Figure 5). This allows for the assumption that the top-flattened character of the potential-energy surface around the saddle point in the cyclohexene is the result of the balance of the subtle intramolecular interactions and their symmetry. The replacement of the methylene group by a heteroatom destroys this balance and leads to a significant change in the character of the ring inversion pathway, in comparison to cyclohexene. The presence of some degree of a flattened potential-energy surface around the saddle point in **5** and its absence in **1** allows one to assume the significant role of symmetry of the intramolecular interactions in the formation of an unusual energy profile of the ring inversion in cyclohexene. Conjugation between the lone pairs of the oxygen atom and the double bond in **1** results in significant asymmetry of the intramolecular interactions leading to a complete loss of the top-flattened character of the energy profile. In the case of **5** the replacement of the methylene group of cyclohexene by a heteroatom also causes some asymmetry of the intramolecular interactions due to the appearance of hyperconjugative interactions with participation of the lone pairs and a decrease of the H···H repulsion. However, these interactions are significantly

**TABLE 3: Selected Geometrical Parameters, Puckering Parameters, and Barrier of the Ring-Inversion Process for Molecules 1−8 in the Transition State Calculated by the MP2/6-311G(d,p) Method**

| | | | bond length, Å | | | torsion angles, deg | | | | puckering parameters | | | $\Delta E_{inv}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| molecule | TS | conformation | 2−3 | 3−4 | 4−5 | 1−2−3−4 | 2−3−4−5 | 3−4−5−6 | 2−1−6−5 | S | $\theta$ | $\Psi$ | kcal/mol |
| CH | | boat[a] | 1.505 | 1.545 | 1.550 | 49.25 | −46.68 | 0.03 | −49.24 | 0.81 | 90.0 | 0.0 | 5.55 |
| **1** | | boat | 1.371 | 1.440 | 1.544 | −47.21 | 52.06 | −9.31 | 46.09 | 0.78 | 84.5 | 7.3 | 7.53 |
| **2** | | boat | 1.406 | 1.478 | 1.545 | 48.36 | −51.75 | 6.79 | −48.54 | 0.81 | 86.6 | 5.8 | 6.12 |
| **3** | TS1 | twist−boat | 1.759 | 1.817 | 1.524 | 37.60 | −63.83 | 44.89 | −39.74 | 0.81 | 68.1 | 27.4 | 4.14 |
| | TS2 | boat | 1.757 | 1.834 | 1.544 | 44.02 | −39.39 | −4.88 | −57.20 | 0.84 | 82.0 | 2.1 | 4.03 |
| **4** | TS1 | twist−boat | 1.904 | 1.962 | 1.522 | 34.61 | −63.08 | 50.47 | −36.98 | 0.80 | 65.1 | 22.2 | 3.85 |
| | TS2 | boat | 1.901 | 1.983 | 1.543 | 42.39 | −41.37 | −0.41 | −60.45 | 0.85 | 82.3 | 1.3 | 3.30 |
| **5** | | twist−boat | 1.505 | 1.424 | 1.419 | −44.30 | 63.89 | −32.63 | 36.21 | 0.79 | 69.3 | 22.8 | 6.40 |
| **6** | | twist−boat | 1.504 | 1.470 | 1.471 | −45.24 | 64.68 | −32.08 | 39.00 | 0.81 | 70.8 | 21.8 | 7.87 |
| **7** | TS1 | twist−boat | 1.502 | 1.838 | 1.813 | −35.95 | 12.63 | 34.38 | 47.65 | 0.81 | 67.1 | 23.6 | 3.29 |
| | TS2 | twist−boat | 1.500 | 1.819 | 1.815 | −48.87 | 61.29 | −34.65 | 34.16 | 0.78 | 64.1 | 24.0 | 5.97 |
| **8** | TS1 | twist−boat | 1.500 | 1.983 | 1.957 | −29.45 | 5.29 | 38.22 | 46.81 | 0.79 | 61.8 | 27.2 | 1.89 |
| | TS2 | twist−boat | 1.497 | 1.969 | 1.963 | −49.73 | 60.30 | −35.25 | 33.84 | 0.77 | 62.7 | 24.7 | 5.38 |

[a] Boat conformation for cyclohexene is the central point on the plateau.

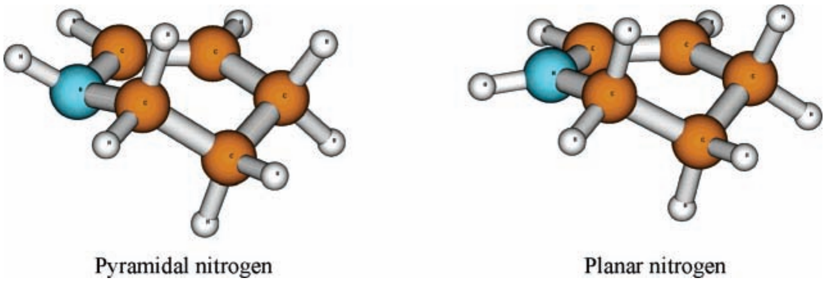


**Figure 2.** Structure of two half-chair conformers of tetrahydropyridine **2** with a different orientation in the hydrogen atom of the NH fragment.

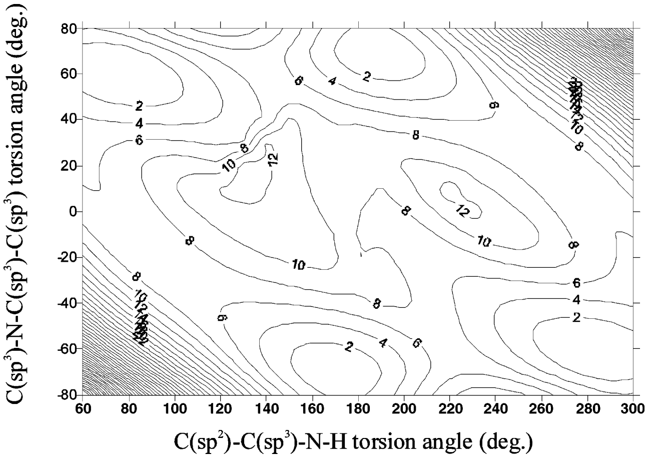


**Figure 3.** The potential-energy surface for molecule **6** constructed by scanning two torsion angles.

weaker compared to the n−$\pi$ conjugation. Therefore, the degree of asymmetry is considerably smaller leading to a retention of some degree of flattening of the potential energy surface around the saddle point.

An analysis of the conformational characteristics of the ring in the saddle point for molecules **1** and **5** also demonstrates some difference. Molecule **1** has a boat conformation in the transition state (Table 3). The geometry of **1** at this point is very close to the geometry of cyclohexene in the central point of the plateau. Unlike **1** the ring conformation in the transition state for **5** is twist−boat. The value of the barrier of ring inversion is higher for **1** (Table 3). This may be explained by the influence of the conjugation effects as was demonstrated for the equilibrium geometry of molecules **1**−**4**. The values of the barrier of ring inversion for the oxygen-containing heterocycles are slightly above those for cyclohexene (Table 3).

The ring inversion process in **2** is very similar to **1** (Figure 5). The conformation of **2** in the transition state is boat. The barrier of ring inversion for **2** is slightly lower than for **1** but is higher than for cyclohexene. The presence of the NH group provides some features related to the configuration of the nitrogen atom. However, an analysis of the conformational characteristics in both equilibrium states and at the saddle point demonstrates that the ring inversion of **2** is not accompanied by an inversion of the nitrogen atom (Figure 1). The nitrogen atom at these points of conformation retains the pyramidal configuration (the sum of bond angles is 339.2° in half-chair **I**, 342.5° in half-chair **II**, and 334.9° in the transition state). However the orientation of the hydrogen atom with respect to the double bond is different in the equilibrium geometry and in the transition state. The C($sp^2$)−C($sp^2$)−N−H torsion angle is 150.4° in half-chair **I**, 135.0° in half-chair **II**, and 173.2° in the transition state. It should be noted that only one saddle point is observed on the potential-energy surface of tetrahydropyridine **2** despite the presence of two pairs of minima (Figure 1). A close inspection of the ring inversion pathway obtained by the IRC procedure reveals that the lowest energy profile corresponds to a transition from the pyramidal conformer of HC **I** to the pyramidal conformer of HC **II**. The transformation from a planar conformer of HC **I** to a planar conformer of HC **II** is possible only as a three-stage process. The first stage involves the transition from the planar conformer of HC **I** to the pyramidal conformer HC **I** without ring inversion. The second stage is only the ring inversion process. The third stage may be described as the transition from a pyramidal conformer of HC **II** to a planar conformer of HC **II**.

On the contrary, the ring-inversion process in **6** is always accompanied by nitrogen inversion. The potential-energy surface of **6** (Figure 3) contains two saddle points corresponding to the ring-inversion process and two saddle points corresponding to the nitrogen-inversion process without the ring inversion. The

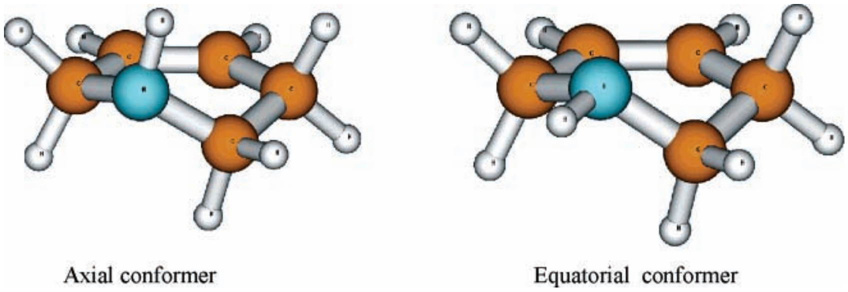


**Figure 4.** Structure of two half-chair conformers of tetrahydropyridine **6** with axial and equatorial orientations of the hydrogen atom in the NH fragment.

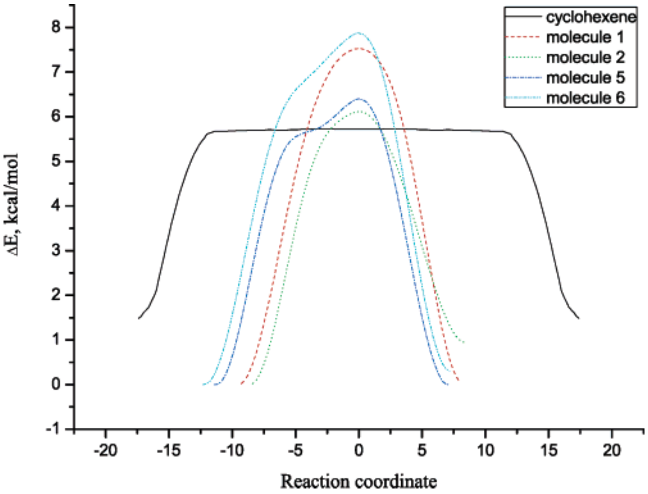


**Figure 5.** Energy profiles for ring inversion of molecules **1**, **2**, **5**, **6**, and cyclohexene.

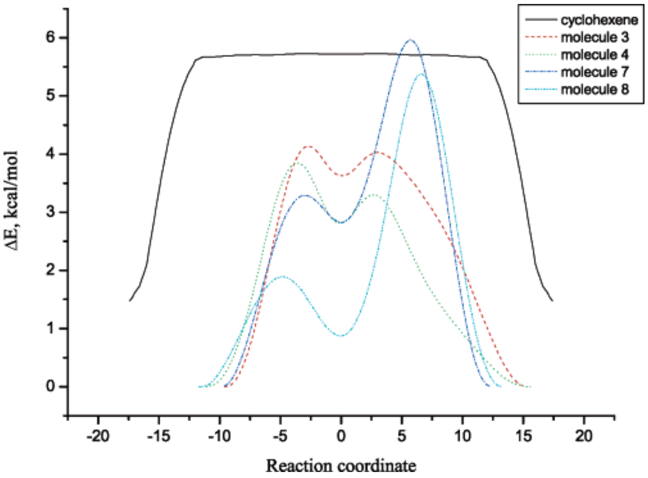


**Figure 6.** Energy profiles for ring inversion of molecules **3**, **4**, **7**, **8**, and cyclohexene.

transition state of the-ring inversion process accompanied by nitrogen inversion possesses a twist−boat conformation as a saddle point similar to **5**. The nitrogen atom has a pyramidal configuration in the transition state (the sum of the bond angles is 330.9°). The potential-energy profile is asymmetric with some flattening around the saddle point (Figure 5). The value of the barrier for the ring inversion is slightly higher than for **2** and cyclohexene (Table 3). Therefore, a transition between two half-chair conformers with equatorial orientation of the hydrogen atom of the NH group is possible in **6** as well as **2**. However, in the case of tetrahydropyridine **6,** such a conformational transformation occurs in two steps and requires significantly more energy because this transition includes ring inversion occurring simultaneously with the nitrogen inversion and additional inversion of the configuration of the nitrogen atom (Figure 3).

The investigation of the potential energy surface of the sulfur- and selenium-containing rings **3**, **4** and **7**, **8** result in the localization of an additional minimum (Figure 6). A comparison of the potential-energy profile of ring inversion for cyclohexene and these molecules allows one to assume that the flattened form of the potential-energy surface of cyclohexene is transformed to additional minimum due to significant stabilization of one of the central points of the plateau because of the presence of a heteroatom.

The ring conformation in the additional minima is different for **3**, **4** and **7**, **8** (Table 1). Molecules **3** and **4** have a twist−boat conformation at this point. The conformation of **7** and **8** at the additional minimum corresponds to boat. The energy of the additional minimum relative to the energy of the equilibrium geometry for **3** and **4** is slightly higher than for **7** and **8** (Table 1). This may be explained by the influence of the conjugation effects in **3** and **4** that stabilize the equilibrium conformation of the ring.

The existence of the additional minimum on the potential-energy surface results in the appearance of two saddle points. The first saddle point (TS1) corresponds to the transition state for ring transformation from one half-chair to boat or twist−boat. Accordingly, the second saddle point (TS2) corresponds to the transition state between boat or twist−boat and the other half-chair conformation.

Two transition states on the potential-energy surface of **3** and **4** have different conformations (Table 3). The heterocycle in TS1 and TS2 has a twist−boat and a boat conformation, respectively. The difference in conformation presumably causes a difference in energy between the two saddle points which is 0.1 kcal/mol for **3** and 0.6 kcal/mol for **4**. It is noticeable that a comparison of the bond length in **3** and **4** for different extreme points on the potential energy surface demonstrates some elongation of the C(sp$^3$)−X bond in the equilibrium twist−boat conformation and TS2.

Both transition states (TS1 and TS2) in **7** and **8** correspond to a twist−boat conformation with very similar geometries and slightly different degrees of puckering (Table 3). However, the energy of these transition states is very different (the difference in energy between TS1 and TS2 is 2.7 kcal/mol for **7** and 3.5 kcal/mol for **8**).

To ensure accuracy for these results, we have performed additional calculations of the energy of the transition states of **7**, **8** at the MP2 levels of theory with the standard extended basis sets (Table 4). The results of the calculations confirm the difference in energy between the two transition states for **7** and **8**.

**TABLE 4: Energy of the Transition States in Molecules 7 and 8 Calculated with Respect to Equilibrium Conformation at the MP2 Level of Theory with Different Basis Sets**

| basis set | TS1 | TS2 |
|---|---|---|
| Molecule **7** | | |
| 6-31G(d) | 3.29 | 5.90 |
| 6-311G(d,p) | 5.83 | 5.97 |
| 6-311G(2df,2p) | 5.76 | 5.94 |
| 6-311G(d,f,p) | 5.74 | 5.90 |
| Molecule **8** | | |
| 6-31G(d) | 2.23 | 5.64 |
| 6-311G(d,p) | 1.89 | 5.38 |
| cc-pVTZ | 2.12 | 5.23 |
| aug-cc-pVTZ | 2.12 | 5.14 |
| aug-cc-pVQZ | 2.14 | 5.10 |

An analysis of the geometry of molecules **7** and **8** at all extreme points demonstrates some difference in the C(sp$^3$)−X bond lengths (where X is a heteroatom). It is expected that the values of the C(3)−X and X−C(5) bond lengths should be equal or very close. This is observed for the half-chair conformation and TS2. However, these bonds become longer in TS1 and in the additional minimum (Tables 1 and 3). Moreover, the elongation of these two bonds is different because the values of the C(3)−X and C(5)−X bond lengths differ from each other in TS1 and a boat conformation. A comparison of the energy of the hyperconjugation interaction of the lone pair of the heteroatom with the neighboring methylene groups in all extreme points shows weakening in the hyperconjugation effects in TS1 and additional minima for **7** and **8** (Table 2). Moreover the energy of the hyperconjugation interaction with one neighboring methylene group is greater than with the other methylene group. This allows for the assumption that the elongation of C(3)−X and C(5)−X and their nonequivalence may be caused by the hyperconjugation interactions.

The existence of the additional minimum and two transition states on the potential-energy surface allows one to describe ring inversion as a four-step process for sulfur- and selenium-containing rings. The first step involves the transition from a half-chair conformation to a twist−boat conformation (TS1) with a significant increase in energy. The second step is the transformation from TS1 to the twist−boat or the boat conformation of the additional minimum with a smaller decrease in energy. The third step may be described as the transition from an additional minimum to the boat or the twist-boat conformation (TS2). The increase in energy is very small for this process for **3** and **4** and is significant for **7** and **8**. The final step includes the transition from TS2 to a half-chair conformation accompanied by a significant decrease in energy. Accordingly, two values of the barrier of ring inversion (HC **I**→TB and B or TB→HC **II**) should be considered for each of these molecules (Table 3). The values of these barriers are smaller compared to cyclohexene with one exception (TB→HC **II** for **7**).

A comparison of the barrier for the ring inversion in **1**−**4** demonstrates the systematic decrease of its value in the series O···N···S···Se. This correlates well with the decrease of the total interaction energy of the endocyclic double bond with the lone pairs of heteroatom (Table 2) reflecting a weakening of n−$\pi$ conjugation.

Almost the same trend of change for the ring inversion-barrier is observed for molecules **5**−**8** despite the absence of n−$\pi$ conjugation (Table 3). This should be a result of the change of the other components of the intramolecular interactions in the studied compounds. There are two possible reasons for the systematic decrease of the ring-inversion barrier: hyperconjugative interactions between lone pairs of the heteroatom and neighboring methylene groups and a decrease in the barrier of rotation around the C(sp$^3$)−X bond.

The NBO analysis for **5**−**8** demonstrates that the total energy of the interactions of the lone pairs of the heteroatom with two neighboring methylene groups is 23.7 for **5**, 14.4 for **6**, 16.9 for **7**, and 12.8 kcal/mol for **8**. Thus, the value of the total energy of the interactions of the lone pairs of the heteroatom with the methylene groups decreases also in the series O···S···Se. However, this value for **6** is smaller than for **5**, contrary to the value of the ring-inversion barrier. Thus the change of the barrier for ring inversion does not agree completely with change of the hyperconjugation interactions. However, some contribution of these interactions toward the change of ring inversion barrier is expected.

A transition of the heterocycle from an equilibrium conformation to a saddle point of the ring inversion process includes rotation around the C(5)−X bond for about 60°. The energy of such a rotation should depend on the nature of the heteroatom and may significantly influence the ring inversion barrier. In order to estimate this effect we calculate energy for a 60° rotation around the central C(sp$^3$)−X bond in **9**−**12**

$$CH_3-CH_2-X-CH_3$$

**9**, X = O; **10**, X = NH; **11**, X = S; **12**, X = Se

The results of the calculations demonstrate that the energy of the rotation is 2.6 kcal/mol in **9,** 3.6 kcal/mol in **10**, 1.5 kcal/mol in **11**, and 1.1 kcal/mol in **12**. It should be noted that the tendency of the change of the barrier of ring inversion in **5**−**8** agrees well with the change of the energy of the rotation around the C(sp$^3$)−X bond in **9**−**12**. A correlation coefficient between the values of the barriers and energy of rotation in **9**−**12** is 0.97. This allows for the assumption that the main contribution to variation of the ring inversion barriers in **5**−**8** is provided by the dependence of the rotation energy around the C(sp$^3$)−X bond on the nature of the heteroatom.

## Conclusions

The results of the calculations demonstrate that the replacement of one methylene group in cyclohexene by a heteroatom leads to asymmetry in the equilibrium conformation and a significant change in the ring inversion profile compared to cyclohexene.

On the basis of the predicted equilibrium geometry, all investigated analogues of cylohexene should be classified as conjugated or nonconjugated heterocyles, according to the position of the heteroatom (relative to the double bond). The heteroatom influences the conformational characteristics of the ring in the equilibrium half-chair conformation of the conjugated heterocycles. The degree of asymmetry of the half-chair conformation correlates with the conjugation between the lone pairs of the heteroatom and the double bond. On the contrary, changing the heteroatom in nonconjugated heterocycles does not influence the conformational characteristics of the ring.

An investigation of ring inversion processes allows all heterocycles to be divided into two groups, depending on the nature of the heteroatom. The first group includes nitrogen- and oxygen-containing heterocycles possessing a classical ring-inversion pathway. The second group consists of sulfur- and selenium-containing analogues of cyclohexene with multistep conformational transition between two half-chair conformations and stable additional minima localized on the potential energy surface. It should be noted that the character of the ring-inversion pathway does not depend on the presence or absence of conjugation between the lone pairs of a heteroatom and the $\pi$-system of a C=C double bond.

A change in the ring inversion barriers in conjugated heterocycles correlates well with change of the total interaction energy between the lone pairs of the heteroatom and double bond. The main contribution to the variation of the ring-inversion barriers in nonconjugated molecules is provided by the energy of rotation around the C(sp$^3$)−X bond.

Two pairs of minima for every half-chair conformation are observed on the potential-energy surface for the nitrogen-containing heterocycles. These minima correspond to a pyramidal or planar configuration in the nitrogen atom in 1,2,3,4-tetrahydropyridine and to the axial or equatorial orientation of the hydrogen atom of the NH fragment in 1,2,3,6-tetrahydropyridine. The ring inversion process in 1,2,3,4-tetrahydropyridine is not accompanied by a change in the configuration of the nitrogen atom. On the contrary, the ring inversion in 1,2,3,6-tetrahydropyridine is always accompanied by nitrogen inversion.

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**Supporting Information Available:** Table of endocyclic bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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