Conjugation and Hyperconjugation in Conformational Analysis of Cyclohexene Derivatives Containing an Exocyclic Double Bond

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The equilibrium geometry, ring-inversion pathway barriers for analogues of cyclohexene with an exocyclic double bond have been studied using the MP2/6-311 G(d,p) level of theory. The equilibrium conformation of the ring depends on conjugation between the endocyclic and exocyclic double bonds. Interactions between conjugated double bonds include the $\pi-\pi$ conjugation and interactions between the lone pair of the heteroatom of the exocyclic double bond and the σ-antibonding orbital of the endocyclic single bond. In the case of the tetrahydrocycles with double bonds separated by a methylene group the balance between the $\pi \rightarrow \sigma^*$ hyperconjugation interactions between the exocyclic double bond and the neighboring methylene group and the $n \rightarrow \sigma^*$ interaction between the lone pair of the heteroatom and the σ-antibonding orbitals of the $C(sp^2)-C(sp^3)$ bond determine the geometrical parameters of the ring. The character of the potential-energy surface around the saddle point depends on the position of the exocyclic double bond and the orientation of the hydrogen atom attached to the heteroatom of the V group of the periodic table in the tetrahydrocycles with double bonds separated by a methylene group.

Introduction

The tetrahydrocycles represent the fundamental molecules in the stereochemistry of organic compounds.[1,2] Tetrahydroaromatic rings are part of the building blocks of many natural and biological substances.[3] Therefore, knowledge of the conformational characteristics and intramolecular interactions in tetrahydroaromatic rings is very important for understanding the properties of a number of different compounds.

The parent molecule for all tetrahydroaromatic rings is cyclohexene. Therefore, its molecular structure and conformational characteristics have been extensively investigated using various experimental[1,4,5] and theoretical methods.[1,5,6] It was established that the equilibrium conformation of cyclohexene is a half-chair with C_2 symmetry, and it can be described by a twist angle (the $C(sp^3)-C(sp^3)-C(sp^3)-C(sp^3)$ torsion angle) of about 60°. According to the classic conception of conformational analysis the ring-inversion process from one half-chair conformation to another symmetrical conformation proceeds via the boat conformation with C_s symmetry. The barrier of this conformational transition for cyclohexene is 4.2−10.3 kcal/mol, as determined by different experimental and theoretical methods.[4–6] However, investigation of the pathway of the ring-inversion process in cyclohexene leads to a question concerning the character of the boat conformation. In accordance with many molecular mechanics and ab initio (within the Hartree−Fock approximation) calculations, this conformation is a shallow minimum on the potential-energy surface.[1,3,5,6] Application of correlated quantum chemical methods results in a description of the boat conformation as a saddle point but with a very low imaginary frequency.[6] Thus, it should be noted that the character of the boat conformation and the energy profile for the ring inversion strongly depend on the method of calculation. 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 ring-inversion pathway for cyclohexene using the MP2 and density functional theory (DFT) methods with different basis sets[7] suggested a possible solution for this problem. It was demonstrated that the potential-energy surface in the area of the boat conformation is extremely top-flattened. The transition from one twist-boat conformation to another via boat 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 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 like pseudorotation. The third step involves the transition from a twist-boat to a half-chair conformation leading to a significant energy decrease.[7]

One can assume that conformational characteristics of the cyclohexene ring and especially the top-flattened character of the potential-energy surface around the saddle point are determined by a subtle balance of intramolecular interactions.

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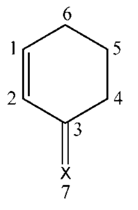
Recently it was demonstrated[8] that replacement of one methylene group in cyclohexene by a heteroatom leads to asymmetry of the equilibrium conformation and a significant change in the ring-inversion profile compared to cyclohexene. It was established that conformational characteristics of tetrahydroheterocycles significantly depend on the character of $n-\pi$ conjugation between the lone pair of the heteroatom and the π system of the endocyclic double bond as well as hyperconjugation interactions between the lone pair and neighboring methylene groups. Asymmetry of these interactions leads to asymmetry of the equilibrium conformation and ring-inversion profile. Moreover, the ring-inversion process in the sulfur- and selenium-containing heterocycles can be described as a four-step process owing to the appearance on the potential-energy surface of the additional minimum and two saddle points.

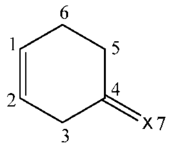
Another way for distortion of symmetry of intramolecular interactions in cyclohexene is replacement of one methylene group by an exocyclic double bond. In this case it is possible to expect strengthening of the $\pi-\pi$ conjugation (for example, in cyclohex-2-enone) and hyperconjugation (for example, in cyclohex-3-enone) with participation of the exocyclic double bond due to extension of the total π system of the molecule. This may lead to considerable deformation of the equilibrium conformation and especially affect the ring-inversion profile.

The analogues of cyclohexene containing the exocyclic double bond in different positions relative to the endocyclic double bond are significantly less studied as compared to cyclohexene and tetrahydroheterocycles. Only 2-cyclohexene-1-one has been investigated by different experimental[9–12] and theoretical[13,14] methods. However, even for this molecule the equilibrium conformation was described in a controversial way. In some cases[10,11] it was defined as a sofa, and other investigations led to the conclusion of a half-chair conformation.[14] The ring-inversion process has not been investigated at all.

In this paper we present the first systematic study of the molecular structure and conformational characteristics of derivatives of cyclohexene containing an exocyclic double bond. Our data demonstrate that the asymmetry of conjugation/hyperconjugation interactions in these molecules results in asymmetry of the equilibrium half-chair conformation and drastic changes in the ring-inversion pathway. Moreover, the ring-inversion process in molecules with nonconjugated double bonds remains similar to cyclohexene despite the presence of considerable hyperconjugation interactions between the exocyclic double bond and neighboring methylene groups.



1 X=O
2 X=S
3 X=Se
4 X=NH
5 X=PH
6 X=AsH
7 X=CH$_2$



8 X=O
9 X=S
10 X=Se
11 X=NH
12 X=PH
13 X=AsH
14 X=CH$_2$

Method of Calculations

The structures of molecules **1**−**14** were optimized using second-order Møller−Plesset perturbation theory.[15] The standard 6-311G(d,p) basis set[16] was applied. The character of stationary points on the potential-energy surface was verified by calculations of vibrational frequencies within the harmonic approximation using analytical second derivatives at the same level of theory. All stationary points possess zero (minima) or one (saddle points) imaginary frequencies.

The geometry of saddle points for the ring-inversion process was located using standard optimization technique.[17,18] The barrier of ring inversion in all molecules was calculated as the difference between the energy of the equilibrium and the saddle-point conformations. Investigation of the ring-inversion pathway has been carried out using the intrinsic reaction coordinate (IRC) procedure.[19,20] The IRC is defined as the minimum energy path connecting the reactants to products via the transition state. It is going from the saddle point, down the steepest descent path in mass-weighted Cartesian coordinates. This is accomplished by numerical integration of the IRC equations. The reaction coordinate is the special vector of movement of the system on the potential-energy surface. Usually this vector corresponds to the normal mode with negative frequency. Therefore, the reaction coordinate in the IRC procedure in general does not correspond to a single geometrical parameter. All calculations were performed using the PC GAMESS program.[21]

The conjugation within the heterobutadiene fragment and hyperconjugation interactions between the C=X double bond and neighboring methylene groups was investigated within the natural bonding orbitals theory[22] using NBO 5.0 program.[23] The conjugation 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

$$E(2) = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\epsilon_j - \epsilon_i} \qquad (1)$$

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

The conformation of the ring has been described by Zefirov−Palyulin−Dashevskaya puckering parameters,[24] where S is the degree of puckering and θ and Ψ 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.

Analysis of the electron density distribution in molecules **1**−**7** was carried out within Bader's "atoms in molecules" (AIM) approach[25] using the MP2/6-311G(d,p) wave function. The characteristics of the (3,-1) critical points for the Csp^2−Csp^2 bonds were calculated using the AIM2000 program[26] with all default options.

Results and Discussion

Conjugation and Hyperconjugation in Equilibrium Conformation. According to classic conformational analysis[1] the equilibrium geometry of cyclohexene is determined, first, by a trend toward a staggered conformation along the C(sp^3)−C(sp^3) bonds and a bending strain due to deformation of the endocyclic bond angles at the saturated carbon atoms which stabilize a nonplanar conformation of the ring. Some flattening of the ring fragment neighboring the exocyclic double bond is caused by the presence of 1,2-allylic strain.

Replacement of one methylene group by an exocyclic double bond results in the appearance of an additional factor influencing the conformation of the tetrahydrocycle caused by electronic interactions with participation of the π system of this bond. Therefore, all derivatives of cyclohexene containing the exocyclic double bond may be divided into two groups according to the position of the exocyclic C=X bond relatively to the

TABLE 1: Selected Values of Bond Lengths (Å), Electron Density (ρ, e/Å^3), and Ellipticity (ϵ) in the Bond Critical Point of the C2−C3 Bond and E(2) Energy for $\pi-\pi$ ($\pi \rightarrow \pi^*$) Conjugation and $n \rightarrow \sigma^*$ Hyperconjugation Onteractions with Participation of Exocyclic Double Bond in Equilibrium Conformation of Molecules 1−7

		bond lengths, Å		characteristics of the C2−C3 BCP		E(2), kcal/mol		
molecule	X	C1−C2	C2−C3	ρ, e/Å^3	ϵ	$\pi \rightarrow \pi^*$	$n \rightarrow \sigma^*$(C2−C3)	$n \rightarrow \sigma^*$(C3−C4)
1	O	1.349	1.484	0.269	0.098	25.88	20.79	21.91
2	S	1.354	1.464	0.275	0.092	33.88	13.10	14.02
3	Se	1.356	1.458	0.278	0.097	38.01	10.83	11.76
4t	NH	1.349	1.472	0.273	0.098	27.43	1.22	12.85
4c	NH	1.349	1.475	0.270	0.091	27.46	12.36	1.19
5t	PH	1.354	1.462	0.273	0.085	34.39		7.76
5c	PH	1.354	1.460	0.273	0.085	33.84	7.46	
6t	AsH	1.356	1.456	0.276	0.092	38.15		6.90
6c	AsH	1.356	1.455	0.276	0.092	37.50	6.51	
7	CH_2	1.351	1.466	0.273	0.096	29.63		

endocyclic C═C bond. The first group includes the tetrahydrocycles containing conjugated double bonds (molecules **1**−**7**). One can assume that the degree of the $\pi-\pi$ interactions should noticeably influence the conformational characteristics of the ring. Molecules with two double bonds separated by the methylene group belong to the second group (molecules **8**−**14**). In these molecules there are no direct $\pi-\pi$ interactions. However, investigation of heterocyclic tetrahydroaromatic analogous of cyclohexene revealed[8] that hyperconjugation interactions between lone pair of the heteroatom and neighboring methylene groups may significantly influence the conformational characteristics of the ring. Therefore, it is possible to expect that such interactions represent an additional factor influencing the conformational characteristics of **8**−**14**. Thus, taking into account the difference in the intramolecular interactions between the two groups of molecules under consideration, it is reasonable to consider the conformational characteristics of these groups separately.

The presence of conjugated system in molecules **1**−**8** allows assuming that strengthening of the $\pi-\pi$ interactions between double bonds should lead to flattening of the ring and an increase of the ring-inversion barrier. It is well recognized[27] that conjugation in the heterobutadiene system depends on the electronegativity of the terminal heteroatom. The increase of electronegativity must result in polarization of the C═X bond and formation of partial positive charge on the carbon atom of this bond. This also must lead to a shift of the π-electron density from the C═C bond toward the carbon atom of the C═X bond. This redistribution of the π-electron density causes an increase of the bond order of the central single C−C bond. Usually the increase of its bond order is accompanied by shortening of this bond. Therefore, it is possible to assume that the length of the C2−C3 bond may be used as an indicator of the conjugation degree in molecules **1**−**7**. According to the values of relative electronegativity[28] one can expect a decrease of conjugation between π systems of the double bond in the row O > S > C ≈ Se (relative electronegativities are 3.5, 2.6, 2.5, and 2.5, respectively) and N > C > P > As (relative electronegativities are 3.1, 2.5, 2.2, and 2.1, respectively).

Thus, the C2−C3 bond should be shortest in molecules **1** (X = O) and **4** (X = NH) and longest in **3**, **6**, and **7**. However, analysis of the bond lengths revealed that the Csp^2-Csp^2 bond is longest in the oxygen- and nitrogen-containing molecules (Table 1). In agreement with this finding the $Csp^2{=}Csp^2$ bond is the shortest in **1** and **4**. According to classic considerations mentioned above this should correspond to the weakest conjugation between π systems of double bonds. On the contrary, the shortest length of the C2−C3 bond is observed for **3** and **6** (X = Se, As).

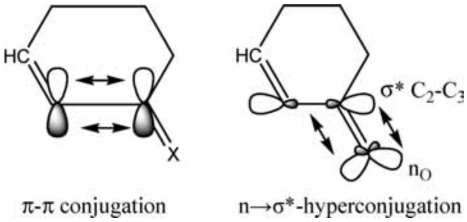
The same conclusion may be made based on the analysis of the electron density distribution within AIM theory.[25] It is well known that the value of the electron density in (3,-1) bond critical point (BCP) correlates well with the energy of the bond. Therefore, it is possible to use these values for comparison of the energy of bonds in different compounds. Results of calculations demonstrate (Table 1) that the value of ρ in BCP correlates well with the length of the C2−C3 bond. The highest electron density is observed for molecules **3** and **6** (X = Se and As) and smallest for **1** and **4** (X = O and NH). This should correspond to the weakest C2−C3 bond in the oxygen- and nitrogen-containing molecules.

An efficiency of conjugation may be also estimated using NBO theory.[22] According to this theory the $\pi-\pi$ interactions manifest themselves in charge transfer from the bonding π orbital of one double bond to the antibonding π orbital of the conjugated double bond. The energy of conjugation may be estimated as the sum of the E(2) values for interactions between bonding and antibonding π orbitals of two double bonds. The results of the calculations demonstrate (Table 1) that the total energy of the $\pi-\pi$ interactions is smallest in the oxygen- and nitrogen-containing molecules as compared with **7**. The highest E(2) values are observed in **3** and **6** (X = Se and As). Thus, the results of the estimation of the conjugation within NBO theory confirm the weakest conjugation in the oxygen- and nitrogen-containing molecules.

It is well known[25] that ellipticity values in BCP are sensitive to the contribution of the π component of covalent bonds. This especially concerns the carbon−carbon bonds. Comparison of the ellipticity of the C2−C3 bond in molecules **1**−**7** indicates that the contribution of the π component is highest in the case of oxygen- and nitrogen-containing molecules **1** and **4**, in agreement with earlier suggestions concerning the influence of the electronegativity of the terminal heteroatom on conjugation in the heterobutadiene system. However, the lowest ellipticity is observed for **2** (X = S) and **5** (X = P) possessing slightly higher electronegativity as compared to the C, As, and Se atoms. This allows assuming the existence of additional interactions influencing the length of the C2−C3 bond.

Analysis of all possible interactions in the heterobutadiene fragment of molecules **1**−**7** using NBO theory reveals the presence of an interaction of the lone pair of the heteroatom with σ-antibonding orbitals of neighboring C−C bonds, namely, C2−C3 and C3−C4 (Table 1). The energy of such interactions falls in the row O > S > Se and N > P > As. Therefore, one can suggest that the length of the C2−C3 bond is determined by an interplay of two factors: (i) the $\pi-\pi$ conjugation leading to shortening of the C2−C3 bond and (ii) the $n \rightarrow \sigma^*$ hyperconjugation causing weakening and elongation of the

SCHEME 1: $\pi-\pi$ Conjugation and $n \rightarrow \sigma^*$ Hyperconjugation in 3-Oxocyclohexene 1



C2−C3 bond due to population of the σ-antibonding orbital (Scheme 1). In the case of oxygen- and nitrogen-containing molecules **1** and **4** the energy of the hyperconjugation interaction is considerably higher as compared to the $\pi-\pi$ conjugation (Table 1). This results in elongation of the C2−C3 bond. A decrease of the heteroatom electronegativity leads to a significant decrease of hyperconjugation accompanied by shortening of the C2−C3 bond.

In general, this $n \rightarrow \sigma^*$ hyperconjugation is similar to the well-known anomeric effect which is responsible for many features of the structure and reactivity of heteroatomic compounds.[29] However, in our case the electron-donating heteroatom is bonded to the central carbon atom by a double bond. This makes it difficult to find shortening of the central C−Het bond observed in systems with anomeric interactions because of the dependence of the length of this bond also on the $\pi-\pi$ conjugation degree.

Analysis of geometrical parameters of molecules **1**−**7** demonstrates that the tetrahydroaromatic ring has an equilibrium conformation which is intermediate between a sofa and half-chair (Table 2). The conformation of the oxygen-containing molecule is slightly more flattened and closer to a sofa, as compared to the other molecules. The sulfur- and selenium-containing molecules adopt the conformation that is closer to a half-chair in comparison with **1**. It should be noted that **7** has the closest to a half-chair conformation, which is caused, probably, by the absence of the additional influence of the conjugation owing to polarization of the $Csp^2{=}X$ bond. This allows one to assume that the conformation of the tetrahydroaromatic ring is much more sensitive to the $\pi-\pi$ conjugation within the heterobutadiene system as compared to the $n \rightarrow \sigma^*$ hyperconjugation. The same trend is observed for molecules **4**−**6** (Table 2). The conformation of the tetrahydroaromatic ring is shifted to a half-chair in the row N−P−As. It is interesting to point out that the trans isomers of **4**−**6** adopt closer to a sofa conformation as compared to their cis isomers.

In the molecules **8**−**14** endocyclic and exocyclic double bonds are separated by the methylene group. Therefore, conjugation between them does not exist. However, recently it was demonstrated[8] that hyperconjugation interactions may also influence conformational characteristics of tetrahydroaromatic rings. Therefore, we performed an analysis of such interactions in **8**−**14** using NBO theory.

Molecule **14** differs from the other considered molecules by the absence of the lone pairs, which results in the presence of only the interaction involving the π orbital of the double bond with neighboring methylene groups. The distances between hydrogen atoms of the methene and methylene groups are greater that the van der Waals radii sum[30] (2.34 Å). Therefore, the effects of steric repulsion can be ignored. Detailed analysis of the bond lengths in this molecule demonstrates that the lengths of the C(3)−C(4) and C(4)−C(5) bonds are very close. Some elongation of the C(3)−C(4) bond can be explained, evidently, by the higher energy of the hyperconjugation interaction of the π orbital of the double bond with the $C(3)H_2$ methylene group than the interaction energy with the $C(5)H_2$ methylene group (Table 2).

The hyperconjugation interactions in molecules **8**−**13** include the interactions of the π orbital of the double bond with neighboring methylene groups ($\pi \rightarrow \sigma^*$ interactions) and the interactions of the lone pairs of the heteroatom with the antibonding orbital of the Csp^2-Csp^3 bond ($n \rightarrow \sigma^*$ interactions). The $\pi \rightarrow \sigma^*$ interactions are very similar in **8**−**14**. On the contrary, analysis of the $n \rightarrow \sigma^*$ interactions allows dividing these molecules into two subgroups. One subgroup includes molecules containing a heteroatom of the VI group of the periodic table. The heteroatom in these molecules possesses two lone pairs, and the $n \rightarrow \sigma^*$ hyperconjugation interactions should be symmetric, similar to intramolecular interactions in **14**. The second subgroup contains molecules with a heteroatom from the V group which has only one lone pair. In these molecules this hyperconjugation interaction should be asymmetric.

Detailed analysis of the bond lengths in molecules **8**−**10** demonstrate that the C(3)−C(4) and C(4)−C(5) bonds are slightly different. According to the data of NBO analysis (Table 3) the energy of the interaction of the exocyclic double bond with the $C(3)H_2$ methylene group in all molecules is greater than the interaction energy with the $C(5)H_2$ methylene group. This allows one to assume that the hyperconjugation interactions of the exocyclic double bond with methylene groups influence the difference in the C(3)−C(4) and C(4)−C(5) bond lengths in **8** and **11**. However, it does not explain the significant elongation of the C(3)−C(4) and C(4)−C(5) bonds in the oxygen-containing molecule **8** as compared to **9**, **10**, and **14** (Table 3). NBO analysis for **8**−**10** (Table 5) reveals the existence of $n \rightarrow \sigma^*$ interactions of the lone pairs of the heteroatom with the antibonding orbitals of the C(3)−C(4) and C(4)−C(5) bonds. The energy of this hyperconjugation interaction is significantly greater for **8**. Therefore, it allows one to assume that elongation of the Csp^3-Csp^2 bonds in **8** may be caused by the $n \rightarrow \sigma^*$ interactions.

In molecules **11**−**13** one of the lone pairs is replaced by the hydrogen atom. This results in the asymmetry of the hyperconjugation interactions with participation of the lone pair of the heteroatom. Moreover, the repulsion between the hydrogen atom attached to the heteroatom and neighboring methylene groups appears in **11**, where the C=XH bond is shortest among molecules **11**−**14**. Analysis of the bond lengths in **11**−**13** demonstrates some differences between the C(3)−C(4) and C(4)−C(5) bonds only in one isomer for each molecule (Table 3). The difference in these bond lengths is observed only in the cis isomer of the nitrogen-containing molecule **11c** and trans isomers of the phosphorus- and arsenic-containing molecules (**12t** and **13t**). It is possible to assume that this results from the superposition of subtle intramolecular interactions. A strong interaction of the π orbital of the double bond with the methylene group leads to very small elongation of the corresponding Csp^2-Csp^3 bond. The interaction of the lone pair with the antibonding orbital of the single bond must result in lengthening of the Csp^2-Csp^3 bond. One can assume that the case when these two types of intramolecular interactions influence one Csp^2-Csp^3 bond results in a noticeable difference in bond lengths. In the opposite case these interactions must balance each other and bond lengths must be very close. The repulsion between the hydrogen atoms must effect the Csp^2-Csp^3 bond which interacts with the lone pair of the heteroatom. Thus, the steric effects and $\pi \rightarrow \sigma^*$ interactions effect that one bond and increase each other.

TABLE 2: Selected Torsion Angles, Puckering Parameters, and Relative Energy of Conformers for Molecules 1−14

			torsion angles, deg		puckering parameters			
molecule	X	conformation	C1−C2−C3−C4	C3−C4−C5−C6	S	Θ, deg	Ψ, deg	ΔE, kcal/mol
1	O	half-chair	5.3	58.7	0.74	38.2	13.8	
2	S	half-chair	7.9	60.1	0.75	37.6	18.7	
3	Se	half-chair	7.2	59.9	0.75	37.9	17.2	
4t	NH	half-chair	6.2	59.2	0.75	37.9	15.4	0.03
4c	NH	half-chair	7.7	59.7	0.75	37.3	17.6	0
5t	PH	half-chair	8.2	60.8	0.76	37.8	19.8	0
5c	PH	half-chair	10.3	61.6	0.77	37.4	23.2	0
6t	AsH	half-chair	6.8	60.2	0.75	38.3	17.6	0
6c	AsH	half-chair	9.3	61.2	0.76	37.8	21.9	0
7	CH_2	half-chair	8.4	60.4	0.76	37.4	19.3	-
8	O	half-chair	2.9	59.3	0.74	38.7	10.3	-
9	S	half-chair	9.4	65.0	0.80	37.3	21.8	0
		boat	−44.8	8.1	0.76	85.0	5.6	3.51
10	Se	half-chair	9.5	64.7	0.79	37.4	22.4	-
11t	NH	half-chair	7.8	61.9	0.77	37.0	18.4	0
		boat	−41.0	13.6	0.73	80.6	9.2	3.01
11c	NH	half-chair	6.8	61.2	0.76	37.3	16.8	0
12t	PH	half-chair	11.5	64.6	0.79	36.7	25.1	0
		boat	48.6	0.4	0.80	89.4	0.2	4.40
12c	PH	half-chair	11.0	64.3	0.79	37.0	24.6	0
13t	AsH	half-chair	11.7	64.8	0.80	36.9	26.0	0
		boat	48.6	0.6	0.80	89.3	0.0	4.45
13c	AsH	half-chair	10.7	63.8	0.85	36.8	27.5	-
14	CH_2	half-chair	10.1	62.9	0.78	36.6	22.7	0

Analysis of the hyperconjugation interactions in **11** demonstrates that the interaction between the π orbital of the exocyclic double bond and neighboring C(3)H_2 methylene group and the interaction of the lone pair of the nitrogen atom with the antibonding orbital of the C(3)−C(4) bond endorse each other in the cis isomer. It leads to a significant lengthening of the C(3)−C(4) bond as compared with the C(4)−C(5) bond. Accordingly, these interactions balance each other in the trans isomer of **11**. This results in the close values of the C(3)−C(4) and C(4)−C(5) bond lengths. However, in **12** and **13** the interaction of the lone pair with the antibonding orbital of the Csp^2-Csp^3 bond is weaker as compared with the nitrogen-containing molecule owing to lengthening of the C═X bond. Here the energy of the hyperconjugation interactions of the double bond with methylene groups remains practically without change. It is also noted that the decreasing of the $n \rightarrow \sigma^*$ interactions of the lone pair results in systematic shortening of the Csp^2-Csp^3 bonds in **8**−**13**.

The equilibrium conformation of the tetrahydrocycle in **8**−**14** is intermediate between a sofa and a half-chair (Table 2) and very close to the conformation of molecules **1**−**8**, despite the absence of conjugated system. Molecules **8** and **11** are more flattened, and their conformation is closer to a sofa. Such conformational features of the oxygen- and nitrogen-containing molecules are in agreement also with the hyperconjugation energy of the interactions of the lone pairs of the heteroatom with the C(3)−C(4) and C(4)−C(5) bonds. This allows suggesting that the hyperconjugation in **8**−**14** plays the same role as conjugation in **1**−**7** with respect to the equilibrium conformation of tetrahydroaromatic rings. The decrease of hyperconjugation interactions in **14** due to the absence of the heteroatom results in the maximal shift of the equilibrium conformation of the ring toward an ideal half-chair. It should be also noted that the orientation of the hydrogen atom attached to the heteroatom in molecules **11**−**13** does not effect the conformational characteristics of the tetrahydrocycle, in contrast to **4**−**6** with the conjugated endocyclic and exocyclic double bonds.

Ring Inversion. Analysis of the ring-inversion profile (the main conformations of the ring are given in Figure 1) reveals a remarkable difference between molecules with conjugated and nonconjugated double bonds. The results of the calculations demonstrate that only one transition state is located on the potential-energy surface for the molecules with conjugated endo- and exocyclic double bonds. Accordingly, the inversion process for molecules has two-stage character, in contrast to cyclohexene (Figure 2). Analysis of the ring-inversion pathway performed using the IRC procedure reveals complete loss of the top-flattened character of the potential-energy surface around the saddle point in molecules **1**−**7** as compared to cyclohexene. This allows for the assumption that replacement of one methylene group by the C═X group in the conjugated position relative to the endocyclic double bond leads to a significant destruction of the balance of the intramolecular interactions within the tetrahydrocycle. This results in a fundamental change in the character of the ring-inversion pathway.

Tetrahydrocycle adopts a slightly twisted boat conformation in the transition state of ring inversion for **1**−**7** (Table 4). Some asymmetry of the conformation in the saddle point probably causes a very small asymmetry of the ring-inversion pathway. Calculation of the puckering parameters for these molecules in the transition state shows that the puckering degree is smallest for the oxygen- and nitrogen-containing molecules in agreement with the higher electronegativity of the heteroatom.

It is noted that the values of the ring-inversion barrier for **1**−**7** are significantly higher than for the cyclohexene (the value of the ring-inversion barrier in cyclohexene calculated by the MP2/6-311G(d,p) method is 5.55 kcal/mol). The oxygen- and nitrogen-containing molecules have the highest value of the ring-inversion barrier in the rows O−S−Se and N−P−As. It allows assuming that the presence of the conjugated system in **1**−**7** determines the increase of the ring-inversion barrier as compared with cyclohexene. However, the change of the value of the ring-inversion barrier is determined by the strength of the $\pi-\pi$ interactions between double bonds in agreement with the electronegativity of the heteroatom.

The separation of the endocyclic and exocyclic double bonds by the methylene group results in significant changes

TABLE 3: Selected Bond Lengths and Values of $\pi \rightarrow \sigma^*$ and $n \rightarrow \sigma^*$ Hyperconjugation Interactions in Molecules 8−14[a]

			bond lengths, Å		*E*(2), kcal/mol			
molecule	X	conformation	C3−C4	C4−C5	$\pi\rightarrow\sigma^*$(C3−H)	$\pi\rightarrow\sigma^*$(C5−H)	$n\rightarrow\sigma^*$(C3−C4)	$n\rightarrow\sigma^*$(C4−C5)
8	**O**	**half-chair**	**1.522**	**1.514**	**10.30**	**7.06**	**22.58**	**22.09**
		twist-boat	1.531	1.519	11.73	10.66	22.51	21.79
		boat	1.526	1.527	8.18	11.98	22.88	22.46
		twist-boat (TS)	1.518	1.521	7.03	10.75	21.28	20.88
9	**S**	**half-chair**	**1.509**	**1.504**	**9.99**	**6.83**	**13.50**	**14.84**
		twist-boat (TS1)	1.509	1.511	6.39	10.89	15.17	14.93
		boat	**1.518**	**1.518**	**10.66**	**12.71**	**14.77**	**14.44**
		twist-boat (TS2)	1.509	1.511	6.39	10.91	15.16	14.92
10	**Se**	**half-chair**	**1.507**	**1.502**	**10.66**	**7.51**	**12.88**	**12.61**
		twist-boat	1.523	1.509	13.22	10.83	12.21	11.85
		boat	1.515	1.518	9.08	13.05	12.55	12.39
		twist-boat (TS)	1.507	1.509	6.55	11.37	12.91	12.71
11t	**NH**	**half-chair**	**1.510**	**1.509**	**9.79**	**6.71**	**1.31**	**13.47**
		twist-boat (TS1)	1.508	1.516	7.38	10.74	1.33	13.41
		boat	**1.519**	**1.521**	**10.22**	**11.96**	**1.35**	**13.02**
		twist-boat (TS2)	1.508	1.516	7.39	10.76	1.33	13.40
11c	**NH**	**half-chair**	**1.515**	**1.505**	**10.11**	**7.05**	**13.52**	**1.24**
		twist-boat (TS)	1.514	1.512	6.82	10.50	13.62	1.30
		boat	1.521	1.520	8.40	11.68	13.58	1.38
		twist-boat	1.528	1.512	11.71	10.45	13.04	1.29
12t	**PH**	**half-chair**	**1.511**	**1.504**	**9.68**	**6.92**		**8.68**
		twist-boat (TS1)	1.513	1.510	6.58	10.30		8.73
		boat	**1.520**	**1.520**	**8.42**	**11.88**		**8.24**
		twist-boat (TS2)	1.530	1.513	11.21	10.37		7.85
12c	**PH**	**half-chair**	**1.507**	**1.508**	**9.71**	**7.09**	**8.75**	
		twist-boat (TS)	1.510	1.514	6.12	10.22	8.64	
		boat	1.518	1.526	8.13	11.29	8.22	
		twist-boat	1.526	1.515	11.63	10.28	7.89	
13t	**AsH**	**half-chair**	**1.510**	**1.503**	**10.17**	**7.36**	**0.55**	**7.84**
		twist-boat (TS1)	1.512	1.509	6.70	10.67	0.52	7.91
		boat	**1.519**	**1.519**	**8.56**	**12.31**	**0.51**	**7.44**
		twist-boat (TS2)	1.530	1.512	11.71	10.69		7.01
13c	**AsH**	**half-chair**	**1.507**	**1.507**	**10.23**	**7.58**	**7.85**	**0.56**
		twist-boat (TS)	1.510	1.513	6.31	10.66	7.78	0.58
		boat	1.518	1.525	8.40	11.79	7.27	0.55
		twist-boat	1.526	1.515	12.05	10.74	7.06	0.50
14	**CH_2**	**half-chair**	**1.507**	**1.504**	**9.33**	**6.85**		
		twist-boat	1.509	1.511	11.12	10.64		
		boat	1.517	1.520	8.59	11.49		
		twist-boat (TS)	1.525	1.512	6.96	10.23		

[a] Characteristics of conformers corresponding to minima on the potential-energy surface are listed in bold.

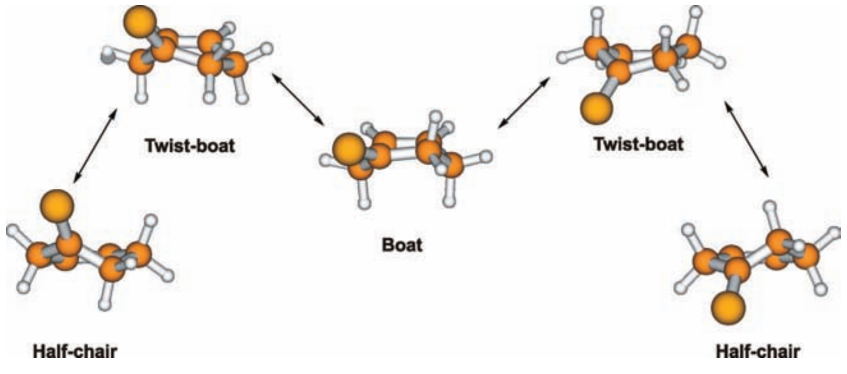


Figure 1. Change of ring conformation during the ring-inversion process for the 4-thione derivative of cyclohexene **9**.

in the character of the ring-inversion process. Only one transition state is located on the potential-energy surface for **8**, **10**, and **14** (Figure 3). Accordingly, the inversion process in these molecules has two-stage character as observed in **1**−**7**. The tetrahydrocycle in **8**, **10**, and **14** adopts a twist-boat conformation in the saddle point (Table 4). However, analysis of the ring-inversion pathway using the IRC procedure reveals considerable differences between their energy profiles. The potential-energy surface around the saddle point in molecules **8**, **10**, and **14** does not possess top-flattened character like **1**−**7**. Nevertheless, the energy profile is highly asymmetric and has a flattened enough area corresponding to the transition from the saddle point to the equilibrium conformation HCI. This flattened part of the potential-energy profile is very similar to the top-flattened character of the potential-energy surface around the saddle point in cyclohexene. The size of this plateau in terms of the C(sp^3)−C(sp^2)−C(sp^3)−C(sp^3) torsion angle is ap-

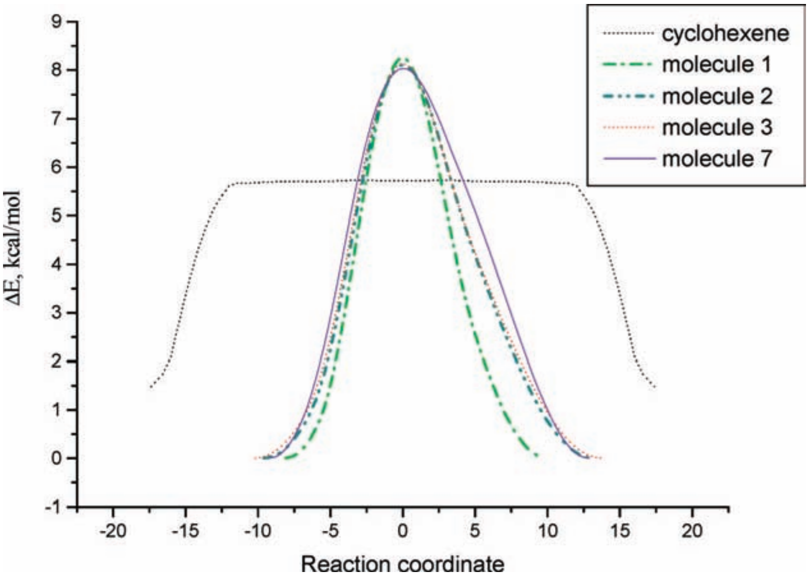


Figure 2. Energy profile for ring inversion of molecules **1**, **2**, **3**, and **7** and cyclohexene.

TABLE 4: Values of Selected Torsion Angles, Puckering Parameters, and Ring-Inversion Barriers for Transition States of Ring Inversion in Molecules 1−14

			torsion angles, deg		puckering parameters			
molecule	X	conformation	C1−C2−C3−C4	C3−C4−C5−C6	*S*	Θ, deg	Ψ, deg	Δ*E*, kcal/mol
1	O	boat	28.4	11.0	0.49	80.6	13.4	8.25
2	S	boat	34.8	13.0	0.61	81.5	13.4	8.11
3	Se	boat	34.2	11.6	0.61	83.2	12.8	8.13
4t	NH	boat	32.3	12.5	0.58	82.2	14.1	8.38
4c	NH	boat	35.9	13.4	0.62	81.2	13.2	8.04
5t	PH	boat	38.6	13.8	0.69	83.6	13.4	8.02
5c	PH	boat	40.0	12.4	0.71	84.3	11.8	7.67
6t	AsH	boat	37.0	12.2	0.67	85.1	13.0	8.20
6c	AsH	boat	38.4	11.7	0.69	85.2	12.1	7.88
7	CH_2	boat	37.6	14.3	0.68	83.0	14.2	8.03
8	O	twist-boat	−38.3	−32.3	0.66	61.0	24.9	3.96
9	S	twist-boat	43.0	34.5	0.73	62.6	23.6	4.88
		twist-boat	−43.0	−34.3	0.73	62.8	23.5	4.88
10	Se	twist-boat	−43.5	−34.4	0.74	63.5	23.3	4.90
11t	NH	twist-boat	39.5	32.3	0.69	63.2	24.1	4.62
		twist-boat	−39.5	−32.1	0.69	63.3	24.0	4.62
11c	NH	twist-boat	41.2	30.9	0.71	65.5	22.1	4.86
12t	PH	twist-boat	43.5	32.6	0.74	65.7	22.2	5.36
		twist-boat	34.4	−28.0	0.72	70.0	20.7	4.86
12c	PH	twist-boat	45.5	31.1	0.77	68.1	20.3	5.60
13t	AsH	twist-boat	43.4	32.7	0.75	65.9	22.4	5.33
		twist-boat	34.6	−28.1	0.72	70.1	20.7	4.87
13c	AsH	twist-boat	45.5	30.8	0.77	68.6	20.1	5.56
14	CH_2	twist-boat	−41.9	−30.6	0.72	67.1	21.6	5.36

proximately 30°, 32°, and 28° for **8**, **10**, and **14**, respectively. This corresponds to a change of the energy within this plateau of about 0.8 kcal/mol for **8** and about 0.4 kcal/mol for **10** and **14**.

Detailed analysis of the conformational characteristics of the ring during the inversion process demonstrates that the tetrahydrocycle adopts twist-boat and boat conformations in the points corresponding to the borders of the plateau. Therefore, the ring-inversion process in **8**, **10**, and **14** can be described as a four-stage process. The first stage involves the transition from an equilibrium half-chair conformation (HCI) to the twist-boat conformation (TBI) with a significant increase in energy. The second stage may be described as easy enough transformation from the twist-boat to the boat (B) conformation with very small changes in energy. The third stage includes the transition from a boat conformation to another twist-boat conformation (TBII) corresponding to the saddle point, and it is accompanied again by some increase in energy. The fourth stage is the transformation from TBII to an equilibrium half-chair conformation (HCII) with a significant decrease in energy.

The NBO analysis for **8**, **10**, and **14** demonstrates (Table 3) that the total energy of the interactions of the exocyclic double bond with two neighboring methylene groups is different for each stage of the inversion pathway. In the equilibrium conformation (HCI) the hyperconjugation interactions of the exocyclic double bond with the $C(3)H_2$ methylene group is greater as compared to the $C(5)H_2$ group. The difference between the total energy of interactions with two methylene groups is about 3 kcal/mol (Table 3). The first stage of the ring-inversion process is characterized by the decrease of this difference. Transformation of the twist-boat conformation to a boat is accompanied by drastic changes in the energy of

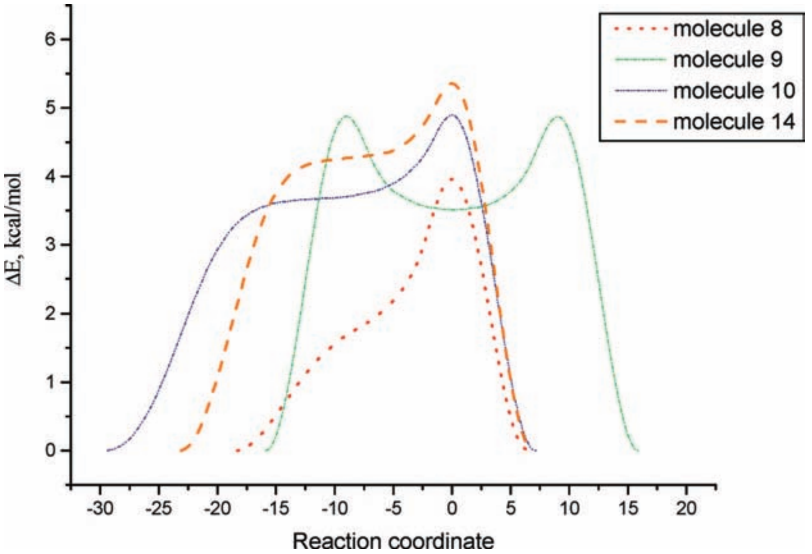


Figure 3. Energy profile for ring inversion of molecules **8**, **9**, **10**, and **14**.

hypeconjugation interactions. The energy of the interaction of the exocyclic double bond with the $C(5)H_2$ methylene group becomes 2−5 kcal/mol higher as compared to the $C(3)H_2$ group. Further transformation of the ring to the other twist−boat conformation at the saddle point is again accompanied by a decrease of the differences in the energy of the hypreconjugation interactions with participation of two methylene groups. Transition from the saddle point to the second equilibrium half-chair conformation results in back inversion of energy of hyperconjugation interactions. Taking into account remarkable inversion of character of hyperconjugative interactions within the plateau on the ring-inversion profile it is possible to assume that small energy changes within this plateau may be associated with characteristics of hyperconjugation. One can suggest that the increase of the energy of the molecule during ring inversion is caused by classic factors (for example, barriers of rotation around C−C bonds, repulsion between hydrogen atoms in boat conformation, etc.). If the higher hypeconjugation interactions with the $C(5)H_2$ methylene group, as compared the $C(3)H_2$ one, are more favorable, it is possible to assume that within the plateau an increase of the energy of a molecule due to unfavorable classic steric interactions may be at least partially compensated by a decrease of the energy due to the appearance of more favorable hyperconjugation interactions.

Investigation of the potential-energy surface for **9** demonstrates the existence of an additional minimum on the potential-energy surface corresponding to the boat conformation (Figure 3, Table 2). Accordingly, the ring-inversion process has two transition states corresponding to different twist-boat conformations (Table 4), and it can be described as a four-stage process similar to that observed earlier in tetrahydroheterocycles with the heteroatom and double bond separated by a methylene group.[8] It should be noted that the energy profile for the ring inversion in **9** is very symmetric (with some flattening around the additional minimum).

The total energy of the interactions of the exocyclic double bond with two neighboring methylene groups according to the results of NBO analysis is very close in both transition states of ring inversion in **9**. The hyperconjugation interactions of the exocyclic double bond with the $C(5)H_2$ methylene group are greater in the transition states, in contrast to the equilibrium geometry. The difference in the total energy of the interactions with neighboring methylene groups is about 3−4 kcal/mol. In the third minimum this difference becomes smaller (Table 3). This probably results in the flattening of the potential-energy surface around the additional minimum.

It should be noted that the value of the ring-inversion barrier in **8**−**10** and **14** is smaller as compared with cyclohexene. It is very interesting that the value of the ring-inversion barrier increases in the order O−S−Se. Analysis of the value of the ring-inversion barrier in the tetrahydroheterocycles[8] demonstrates an opposite trend. Earlier it was suggested[8] that the ring-inversion barrier in the tetrahydroheterocycles containing a heteroatom nonconjugated with a double bond correlates with the energy of rotation around the $C(sp^3)-X$ bond and does not depend on the hyperconjugation interactions of the lone pairs of the heteroatom with neighboring methylene groups. In **8**−**10** the change of the value of the ring-inversion barrier (Table 4) is in a good agreement with the variation of the interaction energy of the lone pairs with antibonding orbitals of the $C(sp^2)-C(sp^3)$ bonds (Table 3). Weakening of the interactions leads to an increase of the value of the ring-inversion barrier. The highest value of the ring-inversion barrier is observed in **14**, where there are no lone pairs. It should be noted that the transition of the ring from half-chair to twist-boat and boat conformations only slightly effects the energy of such $n \rightarrow \sigma^*$ interactions. Therefore, this allows suggesting that the interactions of the lone pairs with the antibonding orbital of the $C(sp^2)-C(sp^3)$ bond destabilize mainly the equilibrium conformation of ring.

Molecules **11**−**13** differ from **8**−**10** by the presence of the hydrogen atom attached to the heteroatom. The results of calculations demonstrate that the conformational characteristics of the ring depend on the orientation of the X−H bond with respect to the C3−C4 bond.

Investigation of the potential-energy surface for **11**−**13** with a trans orientation of the X−H bond relative the C3−C4 bond demonstrates the existence of an additional minimum (Figure 4) corresponding to a boat conformation. One can assume that stabilization of the third stationary point on the potential-energy surface is caused by the minimal repulsion between the hydrogen atom attached to the heteroatom and the hydrogen atoms of the C(5) methylene group. The relative energy of the additional minimum increases in the order N−P−As (Table 2).

The existence of the additional minimum on the potential-energy surface results in the appearance of two saddle points

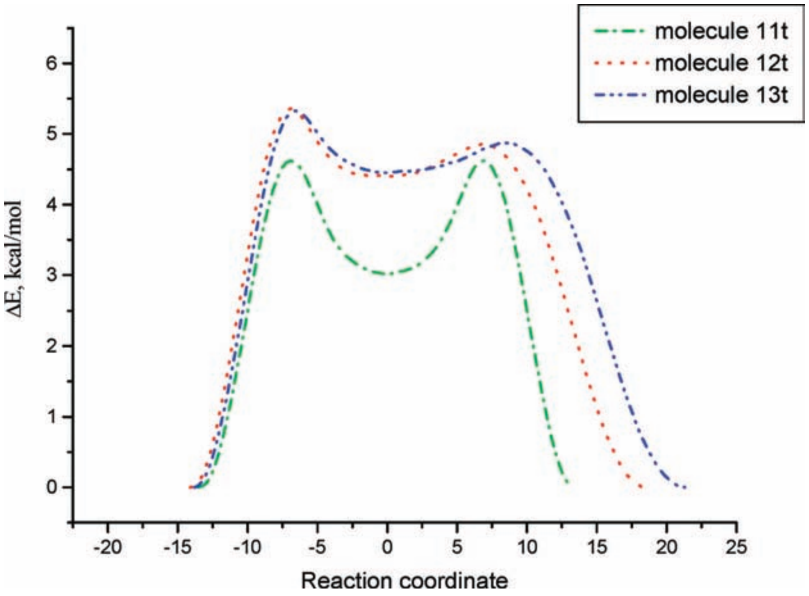


Figure 4. Energy profile for ring inversion of molecules **11t**, **12t**, and **13t** and cyclohexene.

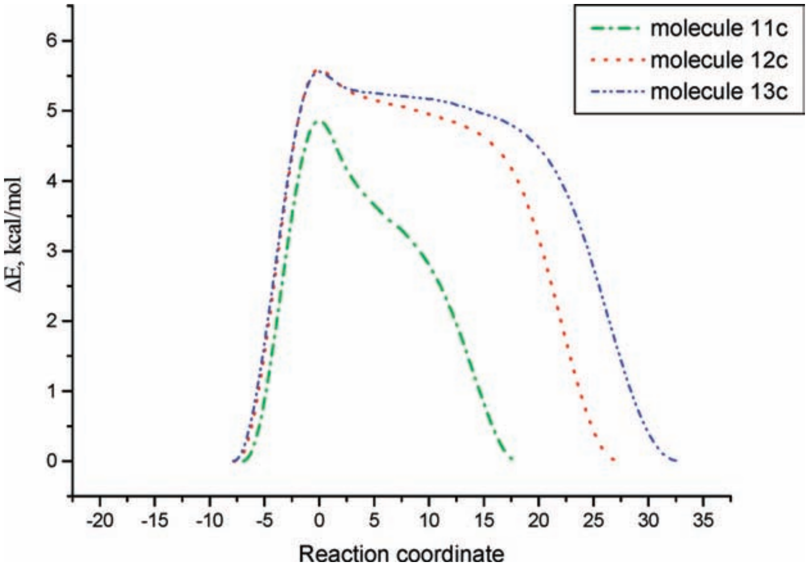


Figure 5. Energy profile for ring inversion of molecules **11c**, **12c**, and **13c** and cyclohexene.

corresponding to twist-boat conformations. Therefore, the ring-inversion process in **11**−**13** has four-stage character, similar to **9**. In both saddle points the tetrahydrocycle adopts a twist-boat conformation (Table 4). The energies of the transition states are equal for **11** and very close for **12** and **13**.

NBO analysis demonstrates that the total energy of the hyperconjugation interactions of the exocyclic double bond with the C(5)H_2 methylene group is higher as compared with the C(3)H_2 methylene group for both transition states and the additional minimum of **11**. Presumably, the symmetry of the hyperconjugation interactions in all extreme points leads to the symmetry of the energy profile of the ring-inversion process for **11**. On the contrary, some asymmetry of the hyperconjugation interactions in extreme points is observed in **12** and **13**. The total energy of the interactions with the C(5)H_2 methylene group is higher as compared with C(3)H_2 in TS1 and additional minimum; however, the difference is minimal in TS2. This asymmetry of intramolecular interactions results in asymmetry of the energy profile for the ring inversion in **12** and **13**.

Investigation of the potential-energy surface demonstrates the existence of only one saddle point for **11**−**13** with a cis orientation of the X−H bond (Figure 5). The tetrahydrocycle adopts a twist-boat conformation in this transition state (Table 4). The energy of the transition states for the molecules with a cis orientation of the hydrogen atoms is slightly higher as compared with the trans isomers.

Investigation of the energy profile for the ring-inversion process in cis isomers of **11**−**13** reveals the existence of the flattened area around the point on the potential-energy surface which corresponds to a boat conformation (Figure 4). A similar energy profile was observed for **8**, **10**, and **14**. The size of this plateau on the potential-energy surface in terms of the C(sp^3)−C(sp^2)−C(sp^3)−C(sp^3) torsion angle is about 59° for **11**−**13**. This corresponds to an energy change about 0.9 kcal/mol for **11**, 0.6 kcal/mol for **12**, and 0.8 kcal/mol for **13**. Thus, the ring-inversion process in **11**−**13** with a cis orientation of the X−H bond relative to the C(3)−C(4) bond can be described as a four-stage process as observed for molecules **8**, **10**, and **14**.

NBO analysis of the hyperconjugation interactions during ring inversion for the cis isomers of **11**−**13** demonstrates the same features as observed for **8**, **10**, and **14** (Table 3). Hyperconjugation interactions of the double bond with the $C(3)H_2$ methylene group are higher in the equilibrium conformation. The transition state and a boat conformation are characterized by the stronger interactions with the $C(5)H_2$ methylene group. The twist-boat conformation which is not a stationary point on the potential-energy surface reveals the very close total energy of the interactions of the exocyclic double bond with neighboring methylene groups. The plateau on the potential-energy surface corresponds to the area of inversion of hyperconjugation interactions with two methylene groups.

Conclusions

The results of the calculations demonstrate that replacement of one methylene group in cyclohexene by an exocyclic double bond leads to a significant asymmetry in the equilibrium conformation and a change in the ring-inversion profile compared to cyclohexene. Conformational characteristics of all tetrahydrocycles depend on the presence or absence of conjugation between the endocyclic and the exocyclic double bonds.

Geometrical parameters of molecules containing conjugated double bonds are determined by two opposite effects, namely, $\pi-\pi$ conjugation between double bonds and $n \rightarrow \sigma^*$ hyperconjugation between the lone pair of the heteroatom of the exocyclic double bond and σ-antibonding orbitals of neighboring endocyclic C−C bonds. The latter interactions are responsible for elongation of the $C(sp^2)-C(sp^2)$ bond in oxygen- and nitrogen-containing molecules despite stronger $\pi-\pi$ interactions between two double bonds.

However, the equilibrium conformation and ring-inversion barriers of molecules with conjugated double bonds depend mainly on the strength of the $\pi-\pi$ interactions. An increase of conjugation results in flattening of the ring and an increase of the ring-inversion barrier in oxygen- and nitrogen-containing tetrahydrocycles.

Investigation of the ring-inversion process demonstrates the presence of a heterobutadiene fragment in derivatives of cyclohexene with conjugated double bonds results in complete loss of the top-flattened character of the potential-energy surface around the saddle point compared to cyclohexene. The ring-inversion process has conventional two-stage character with a twist-boat conformation as the transition state.

Geometrical parameters of tetrahydrocycles with double bonds separated by methylene groups significantly depend on $\pi \rightarrow \sigma^*$ hyperconjugation interactions between the exocyclic double bond and neighboring methylene groups and the $n \rightarrow \sigma^*$ interactions between lone pairs of the heteroatom and σ-antibonding orbitals of the $C(sp^2)-C(sp^3)$ bonds. A balance between these two interactions is responsible for variations in bond lengths, change of the equilibrium conformation of the ring, and significant asymmetry of the ring-inversion profile. As a result, an additional minimum and accordingly two transition states or the flattened region appear on the potential-energy surface for the molecules containing the heteroatom of the VI group of the periodic table.

The character of the ring-inversion process in the molecules with nonconjugated exocyclic and endocyclic double bonds depends on the orientation of the hydrogen atom attached to the heteroatom. The trans orientation of the hydrogen atom relative to the C(3)−C(4) bond leads to the appearance of the additional minimum and two saddle points on the potential-energy surface. The cis orientation of the hydrogen atom results only in the appearance of the flattened region around a boat conformation which is not a stationary point on the potential-energy surface.

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