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LETTERS

The Nonexistence of Repulsive 1,3-Diaxial Interactions in Monosubstituted Cyclohexanes

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Hydrogen atoms directly involved in the so-called 1,3-*syn*-diaxial repulsion in the monosubstituted cyclohexanes studied here gain stabilization, giving evidence that this interaction is of an attractive nature and is not the origin of the generally observed equatorial preference that is usually accepted. Hydrogen and chlorine atoms and methyl and *tert*-butyl groups are more stable when they adopt the axial position in cyclohexane but produce the destabilization of the cyclohexyl ring. It is possible to conclude this from the analysis of the contribution of the atomic to the molecular energy determined in the frame of the theory of atoms in molecules. Electron transfer is responsible for this behavior as the charge distribution proves.

Introduction

A half-century has passed since Barton's seminar paper relating cyclohexane conformation to the physical and chemical properties of cyclohexanoid systems.[1] Since those years, the conformational behavior of a large number of monosubstituted cyclohexanes has been investigated and the subject has been extensively reviewed.[2−4] Several computational studies to describe the conformational behavior of monosubtituted cyclohexanes have also been conducted.[5] It has been generally accepted that 1,3-syn-diaxial repulsion is the origin of the conformational preference of monosubstituted cyclohexanes.[6] This intuitive idea is based on experimental conformational energies, $-\Delta G$ (A value), which are related with the substituent volume, but there are no direct experimental or computational evidences of the repulsive origin of the interaction between the substituent and the syn-axial hydrogen atoms. Recently, Wiberg et al.[7] suggested that there is no evidence of the 1,3-syn-diaxial repulsion, and their geometrical analysis of monosubstituted cyclohexanes shows the local change at the carbon atom bonded to the substituent.

Only a few systematic studies have addressed conformational analysis through the energetic change of each of the atoms or groups within a molecule.[8] The energy of an atom within a molecule not only depends on connectivity but also on conformation as is described here. Herein we present the study of the atomic and group contributions to molecular energy and atomic charge to establish the origin of the conformational preferences in cyclohexane derivatives. (Scheme 1).

Atomic Energies. From the atomic statement of the virial theorem it is possible to define the energy of an atom in a molecule $E(\Omega)$,in such way that the sum of all the contributions yield the total electronic energy of the molecule, eq 1.[9]

$$E = \sum_{\Omega} E(\Omega) \tag{1}$$

The virial theorem gives the following relationships between the kinetic ($T(\Omega)$), potential ($V(\Omega)$), and electronic ($E(\Omega)$) energies of an atom in a molecule: $E(\Omega) = - T(\Omega)$; $2T(\Omega) = - V(\Omega)$, where $E(\Omega) = T(\Omega) + V(\Omega)$. For a molecule in an equilibrium geometry, the energy $V(\Omega)$, which is the virial of the forces acting on the electrons (the virial of the Ehrenfest force), equals the total potential energy as it is usually defined,

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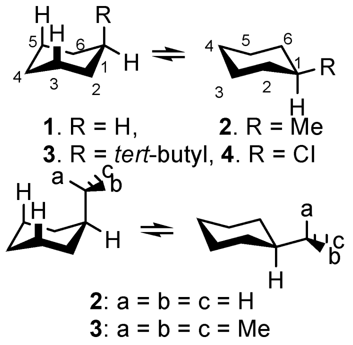
SCHEME 1



that is, the sum of the electron−nuclear energy, the electron−electron energy, and the nuclear−nuclear energy. Under these conditions the sum of the electronic energies, $E(\Omega)$, equals the total energy of the molecule.[9]

The rigorous definition of an atom in a molecule provided by the theory of atoms in molecules (AIM)[9,10] allows one to estimate fundamental atomic properties and to establish that every property of a molecule is given by the sum of the contributions from each of its constituent atoms or groups.[11] Group additivity played a fundamental role in the development of the concept of functional group as a bonded group of atoms that exhibits a set of characteristic and measurable properties.[12] The idea that the molecular value of some property could be obtained as a sum of group contribution has been applied in chemistry since 1855 when Kopp showed that the volumes of the normal alkanes were additive.[13] Rossini[14] demonstrated that the heat of formation of hydrocarbons follows a group additivity scheme. These observations can be reproduced with the AIM theory, and here we give three examples. (1) The identification of the energy of the standard methylene group, $E(CH_2)$, obtained by the linear regression of the total energies of experimental heats of formation ($E_{mol} = 2E(CH_3) + mE(CH_2)$) with that of calculated by the AIM. (2) This same standard energy, when compared with the AIM energy of a methylene group in cyclopropane, yields one-third of the difference in the experimentally determined group energy that is ascribed as “strain energy”.[15] (3) If one compares the AIM energy of a C−H group in *cis*-1,3-butadiene with that of a C−H group in benzene, one finds that they differ by one-sixth of the energy ascribed to resonance energy.[16]

Computational Methods

Full geometry optimization of all molecules discussed herein was performed at HF/6-311++G(2d, 2p) and B3LYP/6-311++G(2d,2p) levels of theory using Gaussian 94.[17] Because both levels of theory show a similar trend, only results determined with the B3LYP functional are presented here. Wave functions were used to compute AIM atomic energies using the AIMPAC[18] set of programs and are shown in Table 1. The atomic coordinates at the level of theory described are presented in the Supporting Information.

Results and Discussion

In cyclohexane (**1**), atomic energy contributions are as follows: −38.03610 au for the carbon atom, −0.64583 au for the axial hydrogen atom, and −0.64440 au for the equatorial. Hax is stabilized by 0.90 kcal/mol with respect to Heq. The energy of the methylene group is −39.32633 au. After the addition of the contribution of each methylene, the total energy is −235.95798 au. The difference with the total energy determined is 0.07 kcal/mol; this disparity is caused by the error in the numeric integration of the atomic energy, and indicates that comparisons are reliable. The densities at the corresponding bond critical points are C−C = 0.252, C−Hax = 0.290 and C−Heq = 0.293 au; the atomic charge is 0.070 e, for the carbon atom and −0.038 and −0.032 for Hax and Heq, respectively. The bond length relation is C−Hax > C−Heq (1.095 vs 1.092 Å). These data can be used to establish that the increase of charge in the axial hydrogen atom is accompanied by electron transfer and stabilization and explains the chemical shift of Hax with respect to Heq observed in ^{1}H NMR, and the relative magnitude of one-bond C−H coupling constants determined experimentally and theoretically. It has been suggested that this charge transfer is originated by $\sigma_{C-Hax} \rightarrow \sigma^*_{C-Hax}$ hyperconjugative interaction.[19] Additional support to this statement was found in the experimental equatorial preference of the hydrogen isotopes, deuterium and tritium, ($\Delta G° = 6.3$ and 11.2 cal/mol respectively) that are the result of the larger stretching force constant for the equatorial bond. The presence of an isotopic effect on the conformational equilibrium in cyclohexane indicates the weakening of axial bond.[20]

In agreement with the experimental behavior and previous B3LYP reports, **2**-eq, is more stable than **2**-ax, the energy difference being of 2.2 kcal/mol in the present work.[21] The methyl group is more stable in the axial conformer by 3.80 kcal/mol. However, the ring is 6.53 kcal/mol more stable when the methyl group is at the equatorial position. This sharply contrasts with the general idea that this group should be more stable at the equatorial position. The introduction of the methyl group in cyclohexane causes the destabilization of carbon C1, being 6.19 kcal/mol higher in the axial conformer. Carbons C2 and C6 are more stable in the equatorial by 3.28 kcal/mol. The geometric changes determined by Wiberg et al.[7] could be responsible for these changes in energy.

It has been suggested that the 1,3-syn diaxial repulsion with the axial protons at positions 3 and 5 explains the observed conformational preference, but this cannot justify the fact that the methyl group is more stable at the axial rather than the equatorial conformer. The axial protons at positions 3 and 5 of **2**-ax are the most stable of the methylene protons, and H3-ax of **2**-ax is 1.4 kcal/mol more stable than in **2**-eq. The hydrogen atom of the methyl group that points toward the center of the ring (a, Scheme 1) is more stable by 2.37 kcal/mol than the two other hydrogen atoms of the group and 3.12 kcal/mol more stable than the hydrogen atom of the methyl group that assumes the equatorial position. The stabilization of this proton cannot be due to a hyperconjugative interaction of the $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ type[22] with the geminal hydrogen atom because this interaction is also possible in the equatorial isomer. However, the stabilization of the hydrogen atom at position a (Scheme 1) and the axial hydrogen atoms in positions 3 and 5 supports the existence of a stabilizing rather than the generally accepted destabilizing interaction, despite no interatomic surface and bond path which indicate interaction is present.

Equatorial *tert*-butylcyclohexane, **3**-eq, is 5.36 kcal/mol more stable than **3**-ax as previously described.[22] Juaristi et al.[23] reported that in **3**-ax the methyl group pointing toward the ring does not arrange itself on the plane that goes through R, C1, and C4. The hydrogen atoms of this group are arranged in such a way that two of them point toward the hydrogen atoms at positions 3 and 5. The substituent is more stable in **3**-ax by 3.94 kcal/mol but the ring is more stable in **3**-eq by 9.13 kcal/mol. In the axial conformer C1, C2, and C6 are the main source

TABLE 1: Atomic and Molecular Energies of Molecules 1 to 4 in au and Differences in kcal/mol at the B3LYP/6-311++G(2d,2p) Level of Theory

	2-ax	**2**-eq	Δ	**3**-ax	**3**-eq	Δ	**4**-ax	**4**-eq	Δ
C1	−38.02771	−38.03758	6.19	−38.02584	−38.04016	8.99	−37.89893	−37.90497	3.79
C2	−38.04277	−38.04799	3.28	−38.03693	−38.04905	7.61	−37.97146	−37.97432	1.79
C3	−38.03635	−38.03652	0.11	−38.0389	−38.03718	−1.08	−37.95935	−37.95637	−1.87
C4	−38.03596	−38.03734	0.87	−38.04019	−38.04023	0.03	−37.95621	−37.95810	1.19
C5	−38.03636	−38.03639	0.02	−38.03957	−38.03718	−1.50	−37.95935	−37.95640	−1.85
C6	−38.04280	−38.04794	3.23	−38.04139	−38.04897	4.76	−37.97145	−37.97432	1.80
H	−0.65492	−0.65316	−1.10	−0.66081	−0.65580	−3.14	−0.63357	−0.63387	0.19
H2ax	−0.64696	−0.64529	−1.05	−0.64815	−0.64876	0.38	−0.63778	−0.63570	−1.31
H2eq	−0.64513	−0.64485	−0.18	−0.64925	−0.65028	0.65	−0.63377	−0.63481	0.65
H3ax	−0.64820	−0.64596	−1.41	−0.65152	−0.64639	−3.22	−0.63770	−0.64260	3.07
H3eq	−0.64456	−0.64418	−0.24	−0.64564	−0.64477	−0.55	−0.64091	−0.63844	−1.55
H4ax	−0.64613	−0.64581	−0.20	−0.64643	−0.64588	−0.35	−0.64496	−0.64236	−1.63
H4eq	−0.64449	−0.64416	−0.21	−0.64498	−0.64438	−0.38	−0.64069	−0.64013	−0.35
H5ax	−0.64807	−0.64599	−1.31	−0.6514	−0.64642	−3.12	−0.63764	−0.64263	3.13
H5eq	−0.64457	−0.64418	−0.24	−0.64541	−0.64478	−0.40	−0.64092	−0.63843	−1.56
H6ax	−0.64696	−0.64532	−1.03	−0.64882	−0.64854	−0.18	−0.63775	−0.63572	−1.27
H6eq	−0.64515	−0.64485	−0.19	−0.64936	−0.65037	0.63	−0.63378	−0.63480	0.64
C7	−38.03114	−38.03146	0.20	−37.99570	−38.00124	3.48			
A	−0.64076	−0.63578	−3.12	−39.96549	−39.95716	−5.23			
B	−0.63637	−0.63563	−0.46	−39.96355	−39.96114	−1.51			
C	−0.63637	−0.63563	−0.46	−39.96249	−39.96141	−0.68			
$\Sigma_\Omega E(\Omega)$	−275.28173	−275.28610	2.74	−393.25182	−393.26009	5.19	−695.58730	−695.58865	0.85
SCF energy	−275.28262	−275.28611	2.19	−393.24935	−393.25789	5.36	−695.58756	−695.58883	0.80
$\Sigma_\Omega E(\Omega) - \mathrm{SCF}$	0.56	0.006	0.55	1.55	1.38	−0.17		0.11	0.05
ring	−235.33708	−235.34749	6.54	−235.36459	−235.37914	9.13	−234.73622	−234.74397	4.86
R	−39.94464	−39.93859	−3.80	−157.88723	−157.88095	−3.94	−460.85110	−460.84468	−4.03

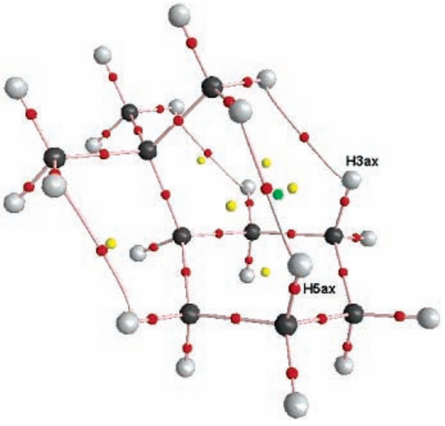


Figure 1. Molecular graph of axial-*tert*-butylcyclohexane.

of ring destabilization by 8.99, 7.61, and 4.76 kcal/mol, respectively.

The methyl group that points toward the ring is the most stable of all the methyls of the *tert*-butyl group (a, in **3**, Scheme 1) and is 5.23 kcal/mol more stable than the associated methyl group of **3**-eq. Hydrogen atoms labeled H3ax and H5ax are more stable in the axial conformer by 3.22 and 3.13 kcal/mol, respectively. Under these conditions, an intense repulsion could be expected; however, the atoms involved are surprisingly stabilized. The behavior of **2**-ax and **3**-ax cannot support the generally accepted repulsion model. The molecular graph of **3**-ax is shown in Figure 1. In **3**-ax two H−H bond trajectories are present between two of the hydrogen atoms of the *tert*-butyl group and the axial hydrogen atoms of the cyclohexyl group. There are two additional H−H bond paths between H2eq and H6eq and two hydrogen atoms of the *tert*-butyl group, but trajectories similar to the latter are also present in the equatorial conformer. Each H−H bond forms a new ring with the corresponding ring critical point. The H−H interactions exhibit the characteristics of closed-shell interaction.[24] A low value for the density at the bond critical point ($\rho_b = 0.0093$ and $\rho_b = 0.01$ au), relative small positive values for the Laplacian ($\nabla^2\rho_b = 0.027$, $\nabla^2\rho_b = 0.0313$) and a positive value for the energy density that is close to zero ($H_b = 0.0009$, $H_b = 0.0012$). Recently, H−H bonding has been described for a number of systems where nearly equivalent hydrogen atoms bearing a slightly negative charge share a bond path.[25] The fact that **3**-ax is a stationary state means that there are not net forces acting on the hydrogen atoms linked by the H−H bond path.[25]

Chlorocyclohexane (**4**) shows a lower preference ($\Delta E = 0.80$ kcal/mol) to assume the equatorial position than the systems previously described. On **4**-ax the chlorine atom is more stable respect to **4**-eq by 4.04 kcal/mol, but the ring is destabilized by 4.86 kcal/mol, just as in the previous cases. The introduction of a chlorine atom in cyclohexane produces the destabilization of the carbon atom where it is linked (C1) in relation to the equatorial ($\Delta E = 3.79$ kcal/mol). In this case, H3ax and H5ax atoms are more stable in the equatorial rather than the axial conformer by 3.1 kcal/mol. If a repulsive interaction would be present in the axial conformer, both, the axial hydrogen and the chlorine atoms must be destabilized in the conformer, but this is not the case.

An important geometrical change between axial and equatorial conformers of **2**−**4** is the C1−R bond distance. C1−R is larger in the axial conformer than in the equatorial: The differences are 0.005, 0.006, and 0.013 Å, respectively. On the other hand the analysis of the accumulated charges can be used to conclude that axial substituents in cyclohexane gain charge (population) Hax = −0.038, Heq = −0.032; Me-ax = −0.030, Me-eq = −0.021; the *tert*-butyl-ax = −0.026, *tert*-butyl-eq = −0.025; and Cl-ax = −0.307, Cl-eq = −0.300. From this information one can confirm that charge transfer is the mechanism that explains the conformational preference of monosusbtituted cyclohexanes. In the axial conformer, electron transfer from the ring to the substituent occurs in a process that produces ring destabilization, the main contribution of which being that of the C1 atom.

Conclusion

In general, the ring is more stable when substituted at the equatorial position and the substituent is more stable when axially oriented. The observed conformation is consequence of the energetic balance between the ring and the substituent. The results show that the hydrogen atoms directly involved in the so-called 1,3-*syn*-diaxial repulsion are stabilized, providing evidence that this interaction is not the origin of the observed equatorial preference of the monosubstituted cyclohexane derivatives studied here. The equatorial preference follows the order Cl < Me < *tert*-bu, which is the order observed experimentally. Finally, the stabilization of the axial substituent is associated with charge transfer from the ring to the substituent.

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Supporting Information Available: Tables giving energy and atomic coordinates of compounds **1**−**4** and geometry and energy (au) and energy of the tertbutyl group of **4**-ax and the structure of **3**-ax. This material is available free of charge via the Internet at http://pubs.acs.org.

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