Physical Chemistry

Conformational mobility of the six-membered ring in 5-oxo-1,3-cyclohexadiene and its derivatives

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Molecular mechanics and MNDO calculations showed that the six-membered ring in the molecule of 5-oxo-1,3-cyclohexadiene possesses high conformational mobility. The transition from a planar equilibrium conformation to a distorted sofa conformation in which the $C(sp^2)—C(=O)—C(sp^3)—C(sp^2)$ torsion angle is equal to ±30° increases the energy of the molecule by less than 1 kcal mol^{-1}. The influence of steric (R = Me, Et, Pr^i, Bu^t) and electronic (R = NH_2, NO_2) effects of substituents R on the equilibrium conformation and mobility of the carbocycle has been analyzed. Both types of substituents at unsaturated C atoms do not change the equlibrium conformation or flexibility of the six-membered ring. Substituents at saturated C atoms cause the transition of the carbocycle to the distorted sofa conformation and significantly restrict its mobility. The electronic structures of 5-oxo-1,3-cyclohexadiene and its amino and nitro derivatives have been analyzed.

Key words: conformational analysis, molecular mechanics, MNDO method; electronic structure; conformational mobility; 5-oxo-1,3-cyclohexadiene, alkyl, amino, and nitro derivatives.

The classical conformational analysis of cyclic systems involves determination of stable conformers and barriers of their interconversion.[1] However, these data make it possible to obtain information of mostly static character. The dynamic properties of the rings can be judged only from the inversion barriers. The equilibrium conformation determined from the experimental data is the result, to a greater or lesser extent, of averaging over the region of the potential energy minimum. At the same time, this minimum itself can be rather flattened. In this case, conformations that are close to the equilibrium conformation in energy, but differ substantially from it in the geometric parameters, have noticeable populations. Consequently, the rings can possess great conformational mobilities, which is of great importance if the molecules incorporating these rings participate in intermolecular interactions of the receptor—substrate type, for example, in biological systems. In these cases, the conformation of a molecule can readily change, thus providing the most favorable conditions for the interaction.

1,3-Cyclohexadiene derivatives possessing biological activity[2,3] and acting as ligands in the formation of complexes with metals[4,5] can serve as an example of these compounds. Previously[6] we have shown that the molecule of 1,3-cyclohexadiene is not conformationally

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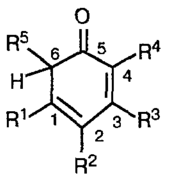
rigid, in spite of the small effect of substituents on the equilibrium conformation of the carbocycle. In this molecule, the possibility of relatively easy flattening of the twisted π-system (the torsion angle between the double bonds is 15—18°, according to various publications[6—8]) with almost no change in the geometry of the saturated moiety exists. The equilibrium conformation and the inversion barrier are mainly determined by the latter.[7] It was of interest to verify this by replacing one of the methylene groups of the molecule by an exocyclic double bond. The present paper is devoted to the study of conformational characteristics and flexibility of the dihydro ring in molecules of 5-oxo-1,3-cyclohexadiene (**1**) and its alkyl, amino, and nitro derivatives.



1—6

1: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
2: $R^2 = R^3 = R^4 = R^5 = H$; R^1 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**), NH_2 (**e**), NO_2 (**f**)
3: $R^1 = R^3 = R^4 = R^5 = H$; R^2 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**), NH_2 (**e**), NO_2 (**f**)
4: $R^1 = R^2 = R^4 = R^5 = H$; R^3 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**), NH_2 (**e**), NO_2 (**f**)
5: $R^1 = R^2 = R^3 = R^5 = H$; R^4 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**), NH_2 (**e**), NO_2 (**f**)
6: $R^1 = R^2 = R^3 = R^4 = H$; R^5 = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**)

Procedure of Calculations

The equilibrium conformations of the molecules **1** and **2(a—d)**—**6(a—d)** were calculated by molecular mechanics method[8] with the MMX[9] force field using the PCMODEL program.[10] The spatial structures of molecules **2e,f**—**5e,f** were determined by semiempirical MNDO calculations[11] with full optimization of the geometry. The conformational mobility of the 1,3-cyclohexadiene ring was studied by scanning over the C(1)—C(6)—C(5)—C(4) torsion angle over the range of ±30° at 5° intervals. The influence of steric effects of the substituents on the conformational mobility of the ring was estimated by molecular mechanics using the dihedral driver technique,[8] and the action of electronic effects was estimated in the MNDO approximation[11] using the method of the reaction coordinate.[12] The equilibrium conformation of the ring was characterized by folding parameters S, θ, and ψ (S is the degree of folding of the ring, and θ and ψ are polar angles describing the type of conformation).[13]

Results and Discussion

The equilibrium conformation of 5-oxo-1,3-cyclohexadiene (**1**) is mostly determined by two opposing groups of factors: (1) conjugation between the double bonds and 1,2-allylic interaction between the H atoms of the methylene group and the neighboring olefinic H atom (as in 1,4-cyclohexadiene[14]), which tend to make the molecule planar; (2) the angular strain resulting from the deformation of the endocyclic bond angle at the saturated C atom, which is maximum in the planar conformation. One more complex factor reflects the tendency to fix the eclipsed configuration of the C—H bonds of the methylene group and the exocyclic C=O double bond. As applied to each separate H atom at the saturated C atom, this arrangement is only possible when the molecule is nonplanar. However, due to the fact that the *syn*-periplanar conformation with respect to the carbonyl group for each of the C—H bonds is associated with the deviation of the C(6) atom (in the opposite direction) from the plane of the C=C double bonds, a planar conformation proves to be the optimum. Thus, the overall effect favors flattening.

The predominance of the factors that tend to flatten the ring in molecule **1** over the tendencies for the disruption of the planarity results in the planar equilibrium conformation of the ring in molecule **1** (the data of MNDO and molecular mechanics calculations). The alkyl substituents at unsaturated C atoms have no effect on the factors determining the conformation of the dihydro ring. Consequently, the 1,3-cyclohexadiene ring in compounds **2**—**5** remains planar.

The substituents at the saturated C atom in compounds **6a**—**d** break the symmetry of the 1,2-allylic interactions with respect to the mean plane of the ring as in similar 1,4-cyclohexadiene derivatives.[14] This results in the transition of the dihydro ring to a distorted sofa conformation (Table 1) whose characteristics (except for the degree of folding) are close to those of the conformation of the carbocycle in other derivatives of 1,3-cyclohexadiene.[6,7] The degree of folding of the 1,3-cyclohexadiene ring in compounds **6a**—**d** depends on the size of the substituent introduced, which is also typical, in particular, for 1,4-cyclohexadiene derivatives.[14,15]

As has been shown for 1,4-cyclohexadiene,[14—16] 1,3-cyclohexadiene,[6,7] and 1,4-dihydropyridine,[17] the existence of the two oppositely directed factors, which determine the equilibrium conformation of the molecule, may result in high conformational mobility of the dihydro ring. Molecular mechanics and MNDO calculations showed that molecule **1** also possesses high conformational mobility (Fig. 1). The transition from the planar equilibrium conformation to the distorted sofa conformation with a C(1)—C(6)—C(5)—C(4) torsion angle of ±30° is associated with an increase in energy of less than 1 kcal mol^{-1}.

Thus, the conformational mobility of the ring in molecule **1** is intermediate between those exhibited by 1,3- and 1,4-cyclohexadienes. On the one hand, the planar equilibrium conformation is the reference conformation, as in the case of 1,4-cyclohexadiene, and, on the other hand, when the planarity is broken, the dihydro ring assumes a conformation with disrupted

Table 1. Conformational characteristics of the dihydro ring in the molecules of 6-alkyl derivatives of 5-oxo-1,3-cyclohexadiene

Compound	R	Torsion angle/deg		The parameters of folding		
		C(1)—C(2)—C(3)—C(4)	C(1)—C(6)—C(5)—C(4)	S	θ	ψ
6a	Me	3.3	9.0	0.12	35.1	20.1
6b	Et	3.6	9.5	0.13	35.0	20.3
6c	Pr^i	5.5	14.8	0.19	34.2	19.0
6d	Bu^t	9.7	26.3	0.33	34.7	21.0

planarity of the π-system typical of 1,3-cyclohexadiene. It should also be noted that the results obtained by molecular mechanics method are in good agreement with those obtained by MNDO.

As would be expected, bulky *tert*-butyl substituents at the C(2), C(3), and C(4) atoms (compounds **3d—5d**) exert no substantial effect on the conformational mobility of the dihydro ring (Fig. 2). However, the same dependence is observed for compound **2d**, which is at variance with the data obtained previously for 1,4-cyclohexadienes[18] and 1,4-dihydropyridines.[17] The increase in the nonvalence interactions of the 1,2-allylic type between an alkyl substituent and the H atoms of the methylene group in this compound would have resulted in the restriction of the conformational mobility of the dihydro ring. The result observed can probably be explained by the increase in the angular strain at the saturated C atom due to the higher rigidity of the C—C—C bond angles compared with the C—C—H angles.

Alkyl substituents at the saturated C atom cause substantial restriction of the mobility of the dihydro ring (see Fig. 2). This results from intensification of nonvalence interactions (of the 1,2-allylic type) between the alkyl group with the neighboring olefinic H atom and the O atom of the exocyclic C=O double bond as well as from the trend of the molecule towards an eclipsed conformation between the C—H bond at the C(6) atom and the carbonyl group.

Thus, the conformational mobility of the carbocycle in alkyl derivatives of 5-oxo-1,3-cyclohexadiene does not depend on the steric effects of substituents. However, molecule **1** also contains a conjugated system, whose planarity is broken as the conformation of the dihydro ring varies. Therefore, we have considered the influence of electronic effects of the substituents on the flexibility of the 1,3-cyclohexadiene ring. A strong π-donor (the amino group) and a π-acceptor (the nitro group) were chosen as the substituents.

According to the data of MNDO calculations, these substituents at unsaturated C atoms of the dihydro ring have no substantial effect on the equilibrium conformation of the molecule. Since the carboxylic group possesses pronounced π-acceptor properties, one might expect that the introduction of an electron-donating substituent would decrease the conformational mobility of the dihydro ring, and the introduction of an electron-withdrawing substituent would increase it. However, the results of quantum-chemical calculations (Table 2) indi-

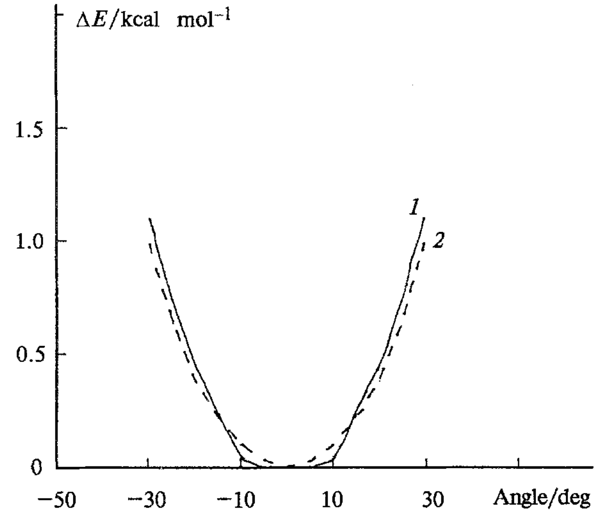


Fig. 1. The dependence of the energy of molecule **1** on the magnitude of the C(1)—C(6)—C(5)—C(4) torsion angle according to molecular mechanics (*1*) and MNDO (*2*) calculations.

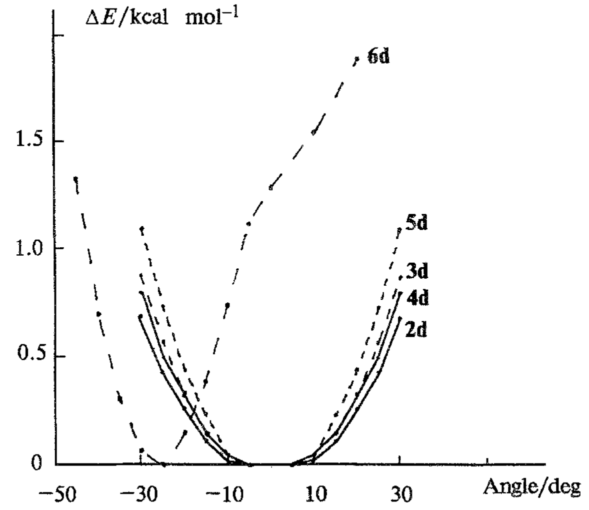


Fig. 2. The dependence of the energies of molecules on the magnitude of the C(1)—C(6)—C(5)—C(4) torsion angle for molecules **2d—6d**.

Table 2. The energy variation (ΔE) on bending of the rings in the molecules of amino and nitro derivatives of 5-oxo-1,3-cyclohexadiene calculated by MNDO method

Compound	R	ΔE/kcal mol^{-1}						
		0°*	5°*	10°*	15°*	20°*	25°*	30°*
1	—	0	0.03	0.10	0.12	0.38	0.60	0.85
2c	1-NO_2	0	0.03	0.08	0.14	0.34	0.53	0.76
2f	1-NH_2	0	0.03	0.09	0.17	0.36	0.49	0.71
3e	2-NO_2	0	0.03	0.07	0.18	0.34	0.51	0.81
3f	2-NH_2	0	0.03	0.06	0.15	0.32	0.49	0.71
4e	3-NO_2	0	0.03	0.07	0.17	0.33	0.52	0.75
4f	3-NH_2	0	0.03	0.09	0.19	0.36	0.54	0.73
5e	4-NO_2	0	0.03	0.08	0.16	0.34	0.51	0.74
5f	4-NH_2	0	0.03	0.07	0.15	0.33	0.52	0.72

* The values of the C(1)—C(6)—C(5)—C(4) torsion angle.

cate that the presence of substituents of both types in any position of the dihydro ring virtually does not change its mobility. To elucidate the causes of this fact, we analyzed the electronic structure of **1** and of its amino and nitro derivatives (Fig. 3, Tables 3—5).

First, five π-MOs are distinguished in the molecule of 5-oxo-1,3-cyclohexadiene (see Fig. 3). The three upper MOs are actually "pure" π-MOs, and the two orbitals with lower energies contain substantial contributions of the pseudo-π-orbital of the methylene group; this is evidence for hyperconjugation. Bending of the molecule has almost no effect on the energies of π-MOs, which is in agreement with the low sensitivity of the conformational mobility of the carbocycle to the electronic effects of substituents.

As should be expected, the electron-donating substituent increases the energies of π-MOs, and the electron-withdrawing substituent decreases these energies. In the latter case, this effect is much more pronounced (see Table 5). The amino group has a greater effect on the distribution of charges in the molecule than the nitro group, especially for the atoms of the C=C double bond to which it is attached (see Table 3).

Since the interactions between p_z-orbitals exert the greatest effect on the conformational mobility of the ring, we will consider the orders of the bonds between these particular AOs. As follows from the data given in Table 4, the endocyclic double bonds are noticeably nonequivalent with respect to the electronic effects of substituents. In fact, the order of the C(1)=C(2) π-bond varies over somewhat narrower limits (0.04) than that of

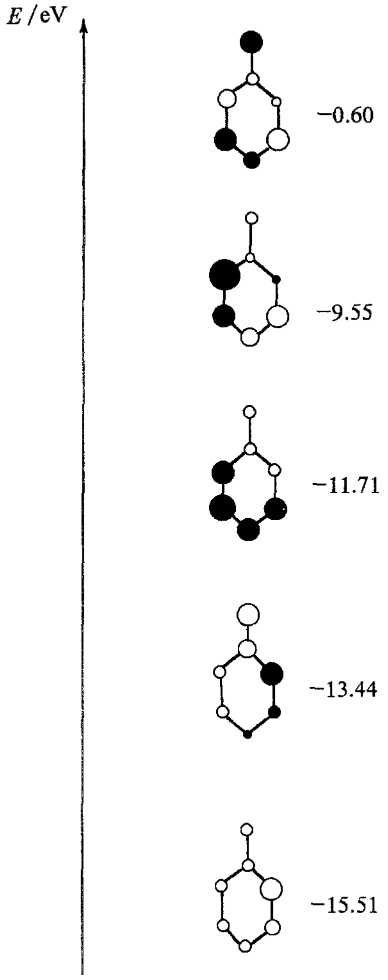


Fig. 3. The scheme of the π-MOs of 5-oxo-1,3-cyclohexadiene.

Table 3. The charges (q) on the atoms in the molecules of nitro and amino derivatives of 5-oxo-1,3-cyclohexadiene

Compound	R	q/e^-						
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	O
1	—	−0.07	−0.06	0	−0.14	0.25	−0.02	0.29
2e	1-NO_2	−0.05	−0.06	0	−0.12	0.25	−0.02	−0.28
2f	1-NH_2	0.02	−0.14	0	−0.13	0.25	−0.03	−0.28
3e	2-NO_2	0	−0.06	0	−0.11	0.24	−0.03	−0.27
3f	2-NH_2	−0.13	0.01	0	−0.14	0.25	0	−0.29
4e	3-NO_2	−0.05	−0.07	0.01	−0.06	0.24	−0.02	−0.25
4f	3-NH_2	−0.06	−0.08	0.10	−0.21	0.26	−0.02	−0.30
5e	4-NO_2	−0.03	−0.10	0.09	−0.16	0.28	−0.02	−0.25
5f	4-NH_2	−0.10	−0.05	−0.07	−0.04	0.26	0	−0.29

Table 4. The orders of bonds (n) between p_z-AO in the molecules of nitro and amino derivatives of 5-oxo-1,3-cyclohexadiene

Com-pound	R	n				
		C(1)=C(2)	C(2)—C(3)	C(3)=C(4)	C(4)—C(5)	C(5)=O
1	—	0.95	0.29	0.93	0.23	0.92
2e	1-NO_2	0.94	0.29	0.94	0.22	0.93
2f	1-NH_2	0.92	0.28	0.94	0.23	0.92
3e	2-NO_2	0.94	0.29	0.94	0.22	0.93
3f	2-NH_2	0.91	0.27	0.94	0.23	0.92
4e	3-NO_2	0.94	0.29	0.93	0.21	0.93
4f	3-NH_2	0.95	0.27	0.88	0.26	0.91
5e	4-NO_2	0.94	0.31	0.91	0.22	0.91
5f	4-NH_2	0.94	0.30	0.89	0.21	0.70

Table 5. The energies of π-MOs (E_π) in the molecules of nitro and amino derivatives of 5-oxo-1,3-cyclohexadiene

Com-pound	R	E_π/eV				
		π_1	π_2	π_3	π_4	π_5
1	—	−0.60	−9.55	−11.71	−13.44	−15.51
2e	1-NO_2	−1.50	−10.44	−12.34	−14.11	−16.22
2f	1-NH_2	−0.56	−9.16	−10.78	−13.40	−15.51
3e	2-NO_2	−1.52	−10.49	−12.38	−14.15	−16.26
3f	2-NH_2	−0.63	−9.19	−10.81	−13.43	−15.54
4e	3-NO_2	−1.61	−10.44	−12.39	−14.20	−16.24
4f	3-NH2	−0.57	−9.20	−10.72	−13.08	−15.56
5e	4-NO_2	−1.62	−10.49	−12.20	−14.21	−16.25
5f	4-NH_2	−0.58	−8.86	−11.03	−13.57	−15.62

the C(3)=C(4) π-bond (0.06), which is due to the effect of the carbonyl group. The latter is most sensitive to the introduction of the amino group into position 4 of the ring: the order of the C=O π-bond in compound **5f** is 0.22 smaller than that in the unsubstituted molecule.

The change in the conformation of the molecule results in the unflattening of the π-electronic system due to rotations about the C(2)—C(3) and C(4)—C(5) bonds. The energy required for these rotations depends on the orders of the above-mentioned bonds. The analysis of these values for various nitro and amino derivatives of **1** (see Table 4) shows that the introduction of these substituents leads to slight variations of the orders of C(2)—C(3) and C(4)—C(5) bonds (they increase by no more than 0.03 with respect to the unsubstituted molecule). The orders of the C(3)=C(4) and C(5)=O π-bonds vary much more significantly (by up to 0.22).

From the aforementioned, one can conclude that the NH_2 and NO_2 groups have no substantial effect on the conjugation between the double bonds in the 5-oxo-1,3-cyclohexadiene moiety, and, therefore, they do not change the conformational mobility of the dihydro ring. This means that the conformational characteristics of 5-oxo-1,3-cyclohexadiene and its derivatives exhibit unique insensitivity to steric and electronic effects of substituents at the C=C double bonds. These compounds occupy an intermediate position between 1,3- and 1,4-cyclohexadiene, which confirms the previously drawn conclusion[6,7] that the saturated moiety plays a decisive role in the conformational behavior of 1,3-cyclohexadiene.

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