Theoretical density functional study of substituted dioxanes: *trans*-3,6-dimethoxy-1,2-dioxane

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Abstract
A theoretical Density Functional study of the *trans*-3,6-dimethoxy-1,2-dioxane molecule is performed with the purpose to analyze different conformational features.The energetic stability of the different isomers is discussed in terms of several electronic factors. Results are compared with previous semiempirical studies and they are discussed in a comparative fashion. Final results show that *ab initio* studies allow one to overcome some drawbacks derived from the semiempirical techniques.

Keywords*:* *trans*-3,6-Dimethoxy-1,2-dioxane, density functional methods, substituted dioxanes

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Introduction

Although the standard literature does not register any data related to the title compound, there exists information about 1,3- and 1,4-dioxanes and the importance of the dioxane molecules with substituents at the *axial-axial (trans)* position. The relevance of these substituents arises from the fact that stereoelectronic effects take place, which implies they are more stable than their *equatorial-equatorial* isomers.[1]

X-Rays and Nuclear Magnetic Resonance (NMR) experimental data of some substituted 1,3- and 1,4-dioxanes show they adopt a *chair* conformation, and it is suggested that the most stable isomer is the *trans* one.[2-5] Some previous theoretical studies have shown that although cyclic six-membered systems preferentially adopt the *chair* conformation, some of them can choose the *twist* conformation.[6-8]

Ab initio molecular orbital calculations on 1,2-dioxane predict the *chair* conformation as the most stable conformation and complementary semiempirical AM1 and MNDO-PM3 calculations are in agreement with this prediction.[9]

Other theoretical studies of the *trans* isomers of the di and tetrahalogenated isomers of 1,2-dioxane employing AM1[10,11] and MNDO-PM3 methods[11] have demonstrated that within disubstituted molecules isomers *trans axial-axial* corresponding to the *chair* conformation are the most stable ones. When substituents have not free electron pairs, the *trans equatorial-equatorial* isomer is the most stable structure. Thus, there is not experimental available evidence about this sort of compounds.

Since there is practically no information about the geometrical conformation of the title compound, we present the results of analyzing its electronic molecular structure by means of the Density Functional Theory (DFT) methods, comparing the results with a closely related molecule, *i.e. cis* and *trans* 3,6-dimethoxy-1,2,4,5-tetroxane, where it seems to play important anomeric effects.

Calculation procedure

The DFT calculations were performed in order to find the most stable geometrical conformation. We used the GAUSSIAN 94 package to perform the calculations.[13] When one tries to optimize molecular geometries it is necessary to locate the absolute minimum point over the potential energy hypersurface which gives the corresponding equilibrium structure. The optimization is complete when the numerical process converges, that is to say, when forces are zero. Geometry optimization was made without any restriction for DFT with B3LYP method, using the 3-21+G and 6-311+G basis sets.

Results and Discussion

We examine the *a-a* and *e-e trans* isomers, studying their relative stabilities and discussing the stereoeletronic (anomeric and exoanomeric) effects and their significant roles in the stabilization of the *trans* isomer, where both methoxyl groups are located at the *axial* position.

DFT sstudy reveals that the *trans diaxial* isomer is more stable than the *cis* one, in agreement with theoretical results found for tetroxane derivatives[12] and semiempirical methods.[1] In the first isomer exists a conformational equilibrium between synclinal and antiperiplanar structures. We inform about the rotation barriers of the methoxyl group calculated by both methods and then we analyse the stabilization of a conformer over the other one in terms of interactions depending on the orientation of the free electron pairs belonging to the exocyclic oxygen atom with respect to the C-O endo bonds and antibonds.

The stability of the *trans axial-axial* isomers when the substituent has free electron pairs can be attributed to the existence of interactions involving the free electron pair belonging to the substitutent,[12] besides the interactions of the free electron pairs of the cyclic oxygen atoms. The importance of the substituent stereoelectronic effect has not been studied in previous studies.[6,8]

In Table 1 we present the electronics energy for the *trans a-a* and *e-e* and *cis a-e* isomers for the *chair* and *twist* geometries of 3,6-dimethoxy-1,2-dioxane. We can verify from the energy results that the most stable conformer is the *tans axial-axial* in the *chair* geometry.

Figure 1 shows the the most stable isomer (*chair trans axial-axial* conformer) obtained from the *B3LYP* calculation at the 3-21+G basis set level.

In Table 2 we display the geometrical parameters obtained from the B3LYP methods: bond lengths, bond angles and dihedral angles for the *trans axial-axial* isomer of the 3,6-dimethoxy-1,2,4,5-tetroxane molecule corresponding to the *chair* and *twist* geometries, respectively.

The stability order of 3,6-dimethoxy-1,2-dioxane is analyzed taking into account the following four factors analyzed in previous similar works,[12] and two additional stereoelectronic effects:
a) Interactions between adjacent free electron pairs,[4] located at the oxygen atoms. Assuming that cyclic oxygen atom presents a tetrahedral hybridization, repulsions between free electron pairs are lower in the *twist* form than in the *chair* form. Regarding this effect, the repulsion between both electrons is considered that it decreases in the following order: free-pair – free-pair > free-pair - σ > σ - σ and it reveals itself through anomalous bond angles, with deviations of linear three center bonds which are usually attributable to free-pair - σ repulsions.
b) The torsion angle around the O-O bond favours the *twist* conformation, since it is the less strained geometry. Results are presented in Table 2.
c) The steric effect, according the methoxyl group is located at the *equatorial* or *axial* position.[6]
d) The anomeric effect that oxygen endocyclic free-electron pairs exert on the endo C-O bond and on exo C-O bonds when the methoxyl group is located at the *axial* position.
e) The exoanomeric effect that free-electron pairs attached to the substituent oxygen atom exerts on the endo C-O bonds at the synclinal and antiperiplanar conformations.

The rotation barrier of the methoxyl group around the C(ring) – O(methoxyl) must be low (~1 – 3 kcal/mol)[13] and the exoanomeric effect must rise this barrier height in additional 2 kcal/mol.

Table 3 display the energy minima found via rotation of the methoxyl group around the C-Oexo bond, according to both basis set level.. The synclinal conformer with two anomeric effects and one exo-anomeric effect has the lowest energy, and the difference between both conformers is 4.45 kcal/mol and 1.13 kcal/mol for the AM1 and PM3 semiempirical methods, respectively. The results for DFT methods lie between 12.42 kcal/mol (B3LYP/3-21+G) and 8.9 kcal/mol (B3LYP/6-3111+G).

Semiempirical AM1 and DFT methods show a shortening of the exo C-O bond, which is greater in the anti conformer than in the synclinal one, and it reveals the studied stereoelectronic interactions. The lengthened endo C-O bond corresponds to the situation where the oxygen free electron pair is located at a antiperiplanar position with respect to this specific bond. This particular situation corresponds to the synclinal conformer and it is shown in Figure 2.

In the antiperiplanar conformer, the oxygen free-electron pairs corresponding to the methoxyl group are located at an antiperiplanar position with respect to each endo C-O bond. Consequently, the endo C-O distances are quite similar.

Semiempirical PM3 method predicts the same general results, although differences in the bond lengths between both conformers are lower.

The stereoelectronic secondary effect of the n → σ* type, produced by the peroxydic oxygen free-electron pairs on the C-O antibond belonging to the methoxyl group and located at the *axial* position, yields an important stabilization effect of the *trans diaxial* form for this sort of compounds.

Although AM1 method describes poorly the O-O bond distance with respect to the PM3 procedure, results show that changes in the endo C-O and exo C-O bond lengths are described in a better way via AM1 method. DFT method overestimates the O-O distance regarding experimental data.

At the same time, PM3 method describes in a more satisfactory manner the energy differences between synclinal and antiperiplanar conformers corresponding to the *a-a trans* isomer, while AM1 method underestimates them. Regarding the equilibrium between the synclinal and antiperiplanar conformers, although there exists experimental evidence in similar compounds with five-membered rings (*i.e.* 2-methoxy-1,3-dioxolane) that in solution the antiperiplanar conformation is the preferred one, here we find that the synclinal isomer is the most stable form, and this result is similar to that found for the 3,6-dimethoxy-1,2,4,5-tetroxane. DFT meted describes in a better way the energy differences between synclicnal and antiperiplanar conformers.

In Table 4 we present the geometrical parameters corresponding to both conformers calculated via DFT methods using B3LYP/3-21+G basis set.

Regarding 3,6-dimethoxy-1,2-dioxane, theoretical calculations show that synclinal isomer is the most stable one since although the anti conformer is electronically favoured by two exoanomeric interactions arising between the free electron pairs of the methoxy oxygen atom and the cyclic C-O antibonds, the steric repulsion taking place when the methyl group of the methoxyl group is located at an antiperiplanar position with respect to the C-H bond makes the synclinal conformer the most stable isomer.

The most remarkable issue is that stability of the *trans axial-axial* isomers when the substituent has free electron pairs can be attributable to the existence of stereoelectronic interactions involving the substituent free electron pairs, in addition to the proper interactions of the free electron pairs of the cyclic oxygen atoms.

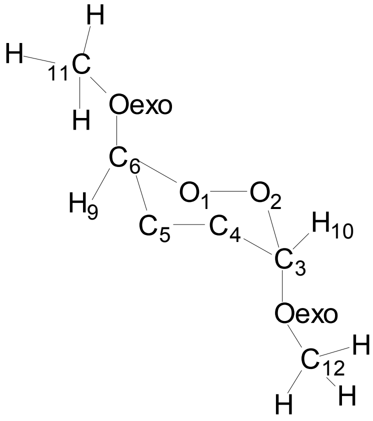
Table 1. Electronic Energy (hartrees) of 3,6-dimethoxy-1,2-dioxane isomers

Isomers		AM1		PM3		B3LYP/3-21+G		B3LYP/6-311+G	
		Chair	Twist	Chair	Twist	Chair	Twist	Chair	Twist
TRANS	a-a	-0.1967	-0.1962	-0.1846	-0.1825	-533.8207	-533.8180	-536.6411	-536.6395
CIS	a-e	-0.1922	-0.1908	-0.1793	-0.1814	-533.8172	-533.8133	-536.6382	-536.6345
TRANS	e-e	-0.1899	-0.1892	-0.1797	-0.1772	-533.8153	-533.8097	-536.6369	-536.6306

$\Delta(\Delta H)$(aa-ee)= 4.27 kcal/mol conversion *axial* $\rightarrow$ *equatorial* (AM1).
$\Delta(\Delta H)$(aa-ee)= 3.07 kcal/mol conversion *axial* $\rightarrow$ *equatorial* (PM3).
$\Delta(\Delta H)$(aa-ee)=3.39 kcal/mol conversion *axial* $\rightarrow$ *equatorial* (B3LYP/3-21+G).
$\Delta(\Delta H)$(aa-ee)=2.63 kcal/mol conversion *axial* $\rightarrow$ *equatorial* (B3LYP/6-311+G).

This energy difference reveals the anomeric effect, since the most stable isomer is that one with the methoxyl group at *axial* position, since in case of existing this effect there must be 2 kcal/mol difference between the *trans diaxial – diequatorial* conformations.[14] Semiempirical and *ab initio* methods show this effect since numerical values are larger than 2 kcal/mol. The most large value obtained within *ab initio* techniques is obtained from the employment of the 3-21+G basis set.

Table 2. Geometrical parameters for *trans* 3,6-dimethoxy-1,2-dioxane, calculated with the *B3LYP* methods



	B3LYP 3-21+G basis set		B3LYP 6-311+G basis set	
	CHAIR	*TWIST*	*CHAIR*	*TWIST*
Bond Length (Å)				
O_1-O_2	1.5362	1.5317	1.5221	1.5164
C_3-O_2	1.4893	1.4882	1.4723	1.4739
C_3-C_4	1.5239	1.5315	1.5368	1.5370
C_3-O_{exo}	1.4332	1.4325	1.4230	1.4210
O_{exo}-C_{12}	1.4804	1.4800	1.4608	1.4634
C_3-H_{10}	1.1004	1.1008	1.0967	1.0975
Bond Angle (degrees)				
C_3-C_4-C_5	110.47	109.74	111.04	110.51
O_2-C_3-C_4	110.84	110.87	110.84	110.83
C_4-C_3-O_{exo}	108.30	107.85	108.61	108.15
O_2-C_3-O_{exo}	112.50	112.91	112.94	113.14
C_3-O_{exo}-C_{12}	114.58	114.54	115.57	115.44
Torsion Angle (degrees)				
C_6-O_1-O_2-C_3	-62.53	78.59	-61.95	77.30
O_2-C_3-C_4-C_5	-56.33	-26.52	-54.69	-25.55
O_2-C_3-O_{exo}-C_{12}	-53.27	57.60	-54.65	59.58
C_4-C_3-O_{exo}-C_{12}	-176.13	-179.54	-178.03	-177.25
C_5-C_4-C_3-O_{exo}	67.53	-150.61	69.95	-150.11
C_5-C_4-C_3-H_{10}	-167.62	85.30	-165.88	86.18
H_{10}-C_3-O_{exo}-C_{12}	57.91	-53.96	56.51	-51.74
C_6-C_5-C_4-C_3	53.11	62.76	51.48	60.87

Table 3. Electronic Energy (hartrees) of *trans* -conformer diaxial 3,6-dimethoxy-1,2-dioxane

	AM1	**PM3**	**B3LYP/3-21+G**	**B3LYP/6-311+G**
Synclinal	-0.1967	-0.1846	-533.8207	-536.6411
Anti-periplanar	-0.1896	-0.1828	-533.8009	-536.6220

The rotation barrier of the methoxyl group around the $C_{(ring)}$-$O_{(mehtoxyl)}$ bond, calculated with the AM1 method is 4.96 kcal/mol, a lower value (1-3 kcal/mol **[13]**) than the result arising from the PM3 method, which gives a difference of 6.7 kcal/mol.

The energy difference between both conformations oscillates between 12.42 kcal/mol (B3LYP/3-21+G basis set level) up to 11.99 kcal/mol (B3LYP/6-311+G basis set level).

Table 4. Geometrical parameters of *trans* diaxial 3,6-dimethoxy-1,2-dioxane (*chair*), obtained from B3LYP/3-21+G method from the synclinal and antiperiplanar conformers

	Synclinal	Antiperiplanar
Bond length (Å)		
O_1-O_2	1.5362	1.5377
C_3-O_2	1.4893	1.4863
C_3-C_4	1.5239	1.5426
C_3-O_{exo}	1.4332	1.4327
O_{exo}-C_{Me}	1.4804	1.4812
C_3-H_{10}	1.1004	1.1009
Bond angle(degrees)		
O_2-C_{3-}-C_4	110.84	109.45
C_5-C_6-O_1	110.84	109.60
C_5-C_4-C_3	110.47	115.44
O_2-O_1-C_6	109.05	108.96
O_{exo}-C_3-C_4	108.30	117.29
O_{exo}-C_3-O_2	112.50	113.92
C_3-O_{exo}-C_{Me}	114.58	120.02
C_6-O_{exo}-C_{Me}	114.58	119.95
Torsion angle (degrees)		
C_{Me}-O_{exo}-C_3-O_2	-53.27	72.88
C_6-C_5-C_4-C_3	-53.11	35.59
C_6-O_1-O_2-C_3	-62.53	-72.05
C_5-C_4-C_3-O_2	-56.33	-43.44
O_2-O_1-C_6-C_5	60.52	60.71
C_{Me}-O_{exo}-C_3-H_{10}	57.91	-179.15
C_{Me}-O_{exo}-C_3-C_4	-176.13	-57.05
C_5-C_4-C_3-H_{10}	-167.62	-153.33

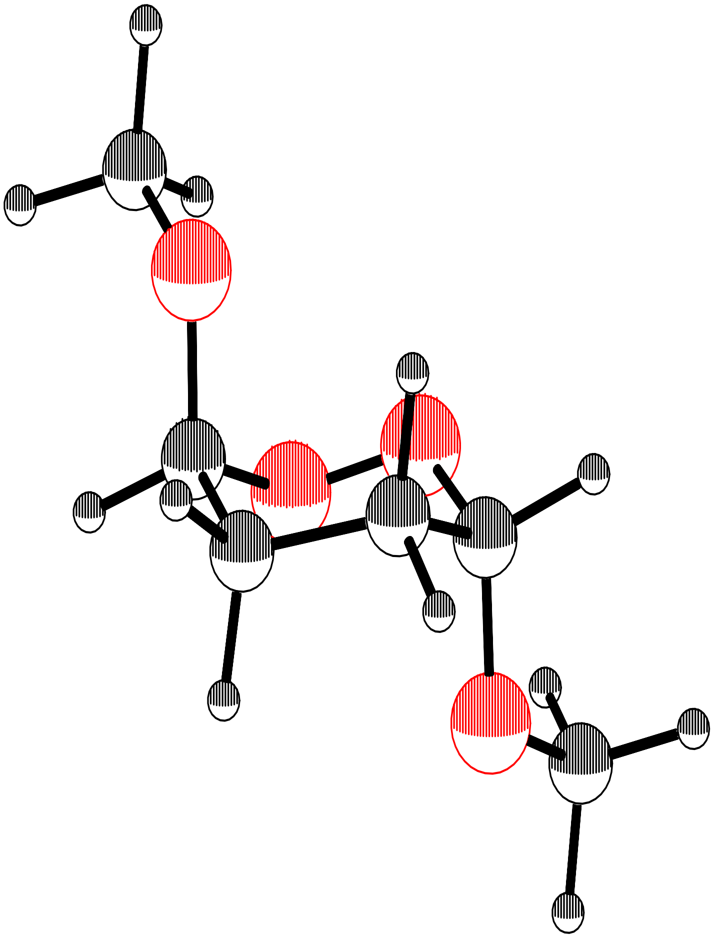


Figure 1. Chair conformation of *trans* diaxial via the *B3LYP* method with basic 3-21+G.

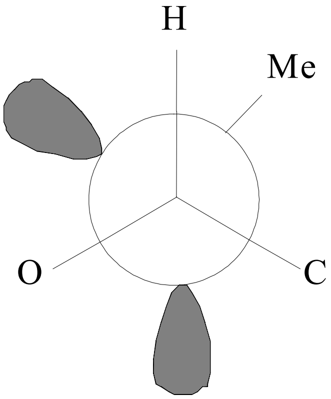


Figure 2. Synclinal conformer.

Conclusions

The anomeric effect is revealed in the molecular system in the following way:

1- In the geometrical structure: from a shortening of the anomeric C-O bond.

2- In the energy: it stabilizes the gauche (*axial)* form with respect to the anti (*equatorial*) form.

3- In the chemical reactivity: there is a rate change in the attack around the anomeric center.

In 1,3- and 1,4-dioxanes prevail the *diaxial* conformations for the disubstituted molecules at the *trans* position and $\Delta G > 2$ kcal/mol for the *diaxial-diequatorial* equilibrium.

The main conclusion is that the energetic behaviour in 1,2-dioxanes with polar substituents and free electron pairs is mainly determined by the anomeric effect and to a lesser extent by the steric effect. Energy difference between the *trans diaxial – diequatorial* is equal to 2 kcal/mol.

In the gauche *diaxial* conformation there are first order effects on the C-O bond length, on the R-C-O bond angle and the torsion angle R-O-C-O, as well a shortening of the C-O bond and a lengthening of the underlying C-O bond and an increase of the R-C-O angle.

Apparently, these parameters are not modified in the anti conformation and it follows on the basis that it takes place a shortening in the geminal CX_2 bond (X = electronegative atom).

Since the anomeric effect defines quite well the preference of the electronegative substituent having free electron pairs located at the *axial* position when it is in the anomeric centre, the free energy difference for the *axial – equatorial* equilibrium must be approximatively equal to 2 kcal/mol.

While the anomeric effect represents the prevalence of the *axial* form with respect to the *equatorial* form in the cycic system, both show a clear preference of the substituent, for example, in the methoxyl group in the synclinal form with respect to the antiperiplanar geometry. This is known as an exoanomeric effect. This effect competes with the anomeric effect since apparently the free rotation of the methoxyl substituent reaches the optimum geometry in each case.

Here we have shown that cyclic systems exhibit both effects, making clear that exoanomeric effects is presented by *axial* and *equatorial* conformations.

The theoretical explanation in terms of molecular orbital concepts is based on the acceptor behaviour of the σ^* (C-OMe) antibond with respect to the antibond C-H bond together with the donor property of the n_p (MeO-C) free electron pair. That is to say, the effect should take place between the lowest antibond orbital associated to the C-O_{exo} bond and the higher level of the n_p free electron pair and we can speculate that the anomeric effect increases the ΔH value. Consequently, for the more electronegative substituent corresponds a lower antibonding orbital.

When substituents are rather bulky, the steric effect overcomes the anomeric effect and the most stable conformations are the *diequatorial*s. The explanation can be based on the change of the torsion angle R-C-O-O, which can prevent the anomeric effect, which, on his turn, destabilizes the *diaxial* form with regard to the *diequatorial*.

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