

THEORETICAL STUDY OF THE *TRANS* 3,6-DIMETHOXY-1,2 DIOXANE MOLECULE

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(Received October 5, 2001)

ABSTRACT. We present a theoretical study of the electronic structure and conformational stability of the title compound. We resort to the semiempirical AM1 and PM3 molecular orbital methods and the relative energetic stability of the different isomers is discussed in terms of the several steric and electronic factors determining the equilibrium molecular structure. Results are analyzed in a comparative fashion with other similar molecules previously studied theoretically and experimentally.

INTRODUCTION

Although there are not available data for this sort of substituted dioxanes there is information about 1,3 and 1,4-dioxanes. The importance of the conformational analysis of dioxanes with their substituents at the *axial-axial* (*trans*) position rests upon the fact the need to study the stereoelectronic effect, which is responsible of the most energetically stable structure with respect to the *equatorial-equatorial* isomers.

Experimental data arising from X rays and Nuclear Magnetic Resonance (NMR) spectroscopy of some substituted 1,3 and 1,4-dioxanes show that they reach a *chair* conformation and they seem to demonstrate that the *trans* isomer is the most energetically stable one [1-5]. Previous theoretical studies [6-8] have demonstrated that although cyclic six-membered systems adopt preferentially the *chair* conformation, some of them choose the *twist* conformation [6-8].

The *ab initio* calculation of the 1,2-dioxane predicts the *chair* conformation as the most stable, and some semiempirical calculations via AM1, MNDO and PM3 methods agree with those more refined results [9]. Theoretical studies of the *trans* isomers of the di- and tetra-halogenated 1,2-dioxanes resorting to the AM1 [10,11] and MNDO-PM3 methods [11] have shown that the *trans axial-axial* isomers in the *chair* conformation are the most stable ones for the disubstituted molecules. When substituents do not possess free electron pairs, the *trans equatorial-equatorial* isomer is the most stable one. It is necessary to point out that there is not experimental evidence on this sort of chemical compounds.

The purpose of this paper is to report the results of the molecular electronic structure for the *cis* and *trans* isomers of the title compound, comparing closely with a related peroxide family (*cis* and *trans* 3,5-dimethoxy-1,2,4,5-tetroxane molecules) where there exist significative anomeric effects. Since there are a real scarcity of conformational information about this molecule, we present here a

theoretical study of both isomers resorting to the semiempirical AM1 and PM3 molecular orbital methods to determine the molecular electronic structures and to discuss the different electronic and structural factors determining the molecular stability.

RESULTS AND DISCUSSION

We have examined the *trans a-a* and *e-e* isomers as well as the *cis a-e* and *e-a* isomers. We discuss their stability and the closely related stereoelectronic effects (anomeric and exoanomeric) and their relevant role in the stabilization of the *trans* isomer where both methoxyl groups occupy the *axial* position.

The theoretical study with both theoretical methods show that the *trans diaxial* isomer is more energetically stable than the *cis* isomer, and this result is in agreement with those data found for tetroxanes [12]. There is a conformational equilibrium for the former isomer between the synclinal and periplanar forms. We present the results for the rotation barriers of the methoxyl group, computed with both methods and then we discuss the greater stability of one isomer with respect to the other one, in terms of the interactions depending on the alignment of the free electron pairs of the exocyclic oxygen, regarding the C-O_{endo} bond/antibonds.

The stability of the *trans axial-axial* isomers when the substituent has free electron pairs may be attributable to the existence of interactions involving those free electron pairs belonging to the substituent [12], in addition to the specific interactions of the free pairs of the oxygen atoms located within the ring. The importance of the stereoelectronic effect of the substituent has not been taken into account in previous studies [6,8].

We display in Table 1 the heats of formation (ΔH_f°) for the *trans a-a* and *cis a-e* in the *chair* and *twist* conformations of the 3,6-dimethoxy-1,2-dioxane. After examining the energy data we see that the most energetically stable isomer is the *trans axial-axial* one with the *chair* geometry. The most stable geometries optimized through the AM1 and PM3 methods are shown in Figures 1 and 2.

We give in Table 2 the geometrical parameters (*i.e.* bond lengths, bond-angles and dihedral angles) obtained from the AM1 and PM3 methods for the 3,6-dimethoxy-1,2,4,5-tetroxane molecule in its *chair* and *twist* geometries. The stability order of this molecule is analyzed taking into consideration the four main factors considered in our previous publication on this issue [12] plus two additional stereoelectronic features:

- The interaction between the adjacent free electron pairs [4], localized on the oxygen atoms. Assuming that the oxygen atom located within the ring has a tetrahedral hybridation, the repulsion between the free electron pairs is weaker for the *twist* than for the *chair* geometry. Regarding this particular effect, the repulsion between two electrons is considered to decrease in the following order: free pair–free pair > σ - σ , and it reveals through anomalous bond angles, specially with deviations from three center lineal bonds which generally are attributed to repulsions free pair - σ .
- The torsion angle around of the O-O favours the *twist* geometry, since this is the less strained conformation. Results are displayed in Table 2.
- The steric effect, according to the location of the methoxyl group at the *equatorial* or *axial* position [6].
- The anomeric effect of the free pairs of the endocyclic oxygens exerting on the C-O_{endo} bond and upon the C-O_{exo} bonds, when the methoxyl group is at a *axial* position.
- The exoanomeric effect that the free pairs of the substituting oxygen put forth on the C-O_{endo} bonds in the synclinal and antiperiplanar conformations.

The rotation barrier of the methoxyl group around the C(ring)-O(methoxyl) bond must be low (1-3 kcal/mol [13]) and the exoanomeric effect have to increase this barrier height by an additional quantity of 2 kcal/mol. In fact, in Table 3 we show the energetic minima found by rotation of the methoxyl group around the C-O_{exo} bond, according to both semiempirical methods. The PM3 calculation indicates the synclinal conformer with two anomeric effects and one exo-anomeric effect to be the most energetically stable one, with a energy difference for both conformers equal to 5.6 kcal/mol. The corresponding theoretical result arising from the AM1 method is similar to that found with the PM3 method, but the energy differences between both conformations are somewhat minor.

The semiempirical AM1 method indicates a shortening of the C-O_{exo} bond, which is larger in the anti conformer than in the synclinal and it makes evident the studied stereoelectronic interactions. The lengthened C-O_{endo} bond corresponds to the situation where the free pair belonging to the oxygen atom of the methoxyl group is located at an antiperiplanar position. This situation corresponds to the synclinal conformer and it is shown in Figure 3. In the antiperiplanar conformer, the free electron pairs corresponding to the oxygen atom of the methoxyl group are located at an antiperiplanar position with respect to each C-O_{endo} bond. The consequence of this fact is that all the C-O_{endo} distances are quite similar. The PM3 semiempirical method predicts the same general results, but the differences in the bond lengths between both conformers are rather lower.

For this sort of chemical compounds we can propose that the secondary stereoelectronic effect of the type n→σ* produced by the free electron pairs belonging to the peroxidic oxygen atoms on the C-O antibond of the methoxyl group, located at an *axial* position, furnishes an important stabilization contribution for the *trans diaxial* conformation.

Although the AM1 describes poorly the O-O bond distance with respect to the PM3 procedure, results show that changes in the C-O_{endo} and C-O_{exo} bonds are described in a more suitable way by means of the AM1 method.

At the same time, the PM3 method describes in a better way the energy differences between the synclinal and antiperiplanar conformers of the *trans a-a* isomers, while the AM1 method underestimates this quantity. Regarding the equilibrium between these conformers, although there is some experimental evidences in quite similar compounds with five membered rings (2-methoxy-1,3-dioxolane) that the synclinal ⇌ antiperiplanar equilibrium in solution prefers the antiperiplanar form, in this compound the most energetically stable conformer is the synclinal one. This result is similar to that found for the 3,6-dimethoxy-1,2,4,5-tetroxane molecule. We give the geometrical parameters of both conformers in Table 4.

The theoretical calculations predict that the synclinal isomer is the most stable structure of the 3,6-dimethoxy-1,2-dioxane since in spite the anti conformer is the most electronically favored due to two exoanomic interactions that free electron pairs corresponding to the oxygen atom located in the methoxyl group exert on the C-O ring antibonds, the steric repulsion produced when the methyl group of the methoxy moiety is located at an antiperiplanar position with respect to the C-H bond and they yield the synclinal conformer as the most stable isomer.

The most prominent feature on this issue is that the stability of the *trans axial-axial* conformers when the substituents have free electron pairs, can be ascribed to the existence of stereoelectronic interactions involving the substituent free electron pairs, besides the specific interactions of the free pairs of the ring oxygen atoms.

Table 1: Heats of formation (kcal/mol) of the 3,6-dimethoxy-1,2-dioxane isomers.

ISOMERS		CHAIR		TWIST	
		AM1	PM3	AM1	PM3
TRANS	A-A	-123.25	-115.67	-118.52	-111.06
CIS	A-E	-128.11	-132.24	-132.68	-130.59
TRANS	E-E	-118.99	-112.58	-118.52	-111.06

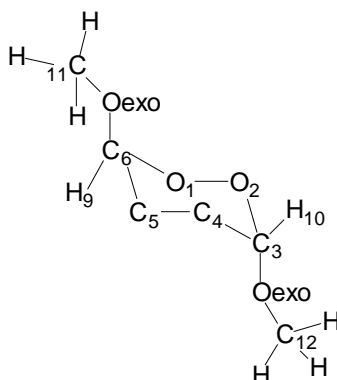
$$\Delta(\Delta H_f^\circ) (aa-ee) = 4.26 \text{ kcal/mol } axial \rightarrow equatorial \text{ conversion (AM1).}$$

$$\Delta(\Delta H_f^\circ) (aa-ee) = 3.09 \text{ kcal/mol } axial \rightarrow equatorial \text{ conversion (PM3).}$$

This energy difference reveals the anomeric effect since it stabilizes the isomer with the methoxyl group at the *axial* position.

The interconversion barrier *chair(aa)* → *chair(ee)* would pass through an *twist* intermediate conformation, and the *chair-twist* energy interconversion is equal to 4.73 kcal/mol, according to the AM1 method and 4.61 kcal/mol according to the PM3 method (for the sake of comparative purposes, it is useful to point out that the corresponding cyclohexane interconversion barrier value is 5.5 kcal/mol).

Table 2: Geometrical parameters for *trans* 3,6-dimethoxy-1,2-dioxane molecule, calculated with the AM1 and MNDO-PM3 methods.



	AM1		PM3	
	<i>TWIST</i>	<i>CHAIR</i>	<i>TWIST</i>	<i>CHAIR</i>
<i>Bond Length (Å)</i>				
O ₁ -O ₂	1.281	1.289	1.538	1.575
C ₃ -O ₂	1.456	1.440	1.403	1.385
C ₃ -C ₄	1.526	1.525	1.542	1.540
C ₃ -O _{exo}	1.390	1.390	1.419	1.419
O _{exo} -C ₁₂	1.410	1.410	1.410	1.405
C ₃ -H ₁₀	1.121	1.124	1.117	1.118
<i>Bond Angle (degrees)</i>				
C ₃ -O ₂ -O ₁	113.71	114.51	110.09	111.79
O ₂ -C ₃ -C ₄	112.09	111.62	115.09	114.60
C ₄ -C ₃ -O _{exo}	108.52	108.57	112.67	108.11
O ₂ -C ₃ -O _{exo}	101.43	106.94	93.58	108.68
C ₃ -O _{exo} -C ₁₂	113.89	113.96	114.81	115.37
<i>Torsion Angle (degrees)</i>				
C ₆ -O ₁ -O ₂ -C ₃	68.43	60.50	69.65	55.55
O ₂ -C ₃ -C ₄ -C ₅	-21.64	-47.29	-24.35	-49.64
O ₂ -C ₃ -O _{exo} -C ₁₂	65.53	-64.82	-147.39	-73.77
C ₄ -C ₃ -O _{exo} -C ₁₂	-173.69	-174.21	93.49	161.08
C ₅ -C ₄ -C ₃ -O _{exo}	75.74	57.48	55.74	77.48
C ₅ -C ₄ -C ₃ -H ₁₀	95.77	-163.04	-150.65	-162.96
H ₁₀ -C ₃ -O _{exo} -C ₁₂	-47.16	48.06	-33.67	36.10
C ₆ -C ₅ -C ₄ -C ₃	52.67	44.00	52.23	43.90

Table 3: Heats of formation (kcal/mol) of *trans* -conformer diaxial 3,6-dimethoxy-1,2-dioxane molecule.

<i>Trans</i> conformer	AM1	PM3	ΔH_f° (AM1)*	ΔH_f° (PM3)*
Synclinal	-123.98	-115.67	-119.02	-108.97
Antiperiplanar	-118.96	-114.70		

* Activation enthalpies of the conversion synclinal-antiperiplanar.

The energy barrier height corresponding to the methoxy group rotation around the $C_{\text{ring}}-O_{\text{methoxy}}$, calculated with the AM1 method is equal to 4.96 kcal/mol, which is lower (1-3 kcal/mol [13]) than that value given by the PM3 method (6,70 kcal/mol).

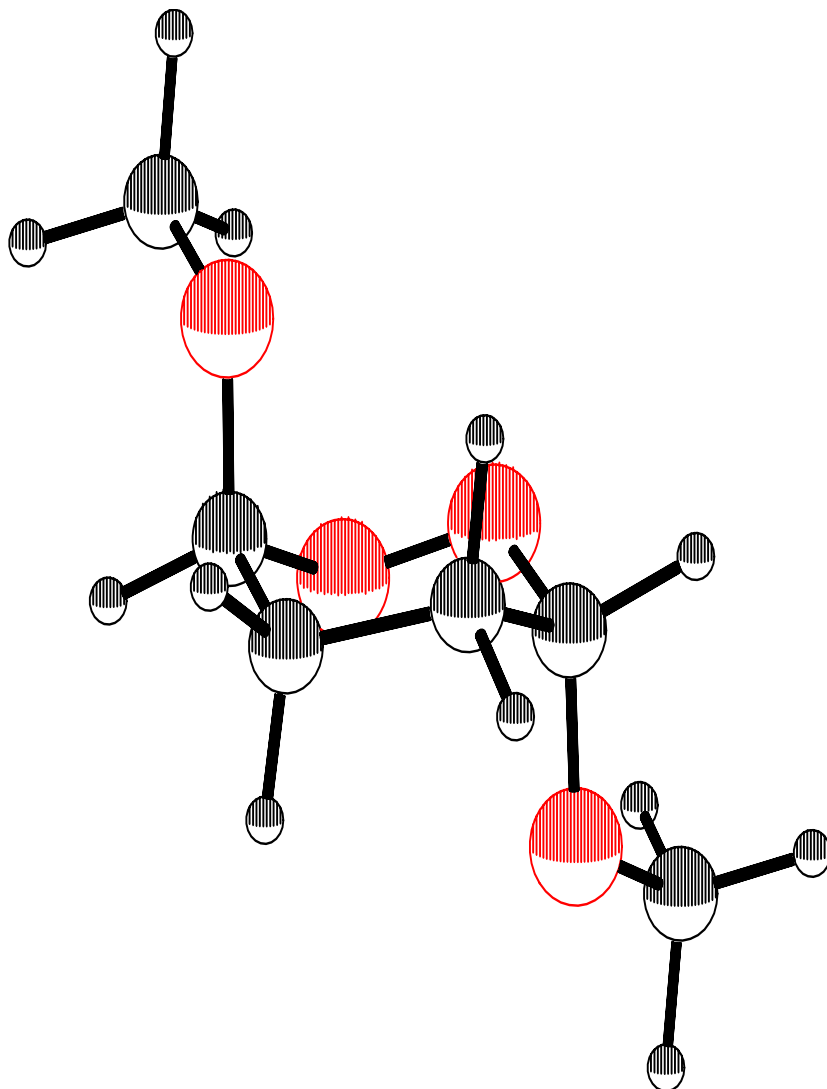


Figure 1. Chair conformation of *trans* diaxial isomer of 3,6-dimethoxy-1,2-dioxane molecule via the AM1 method.

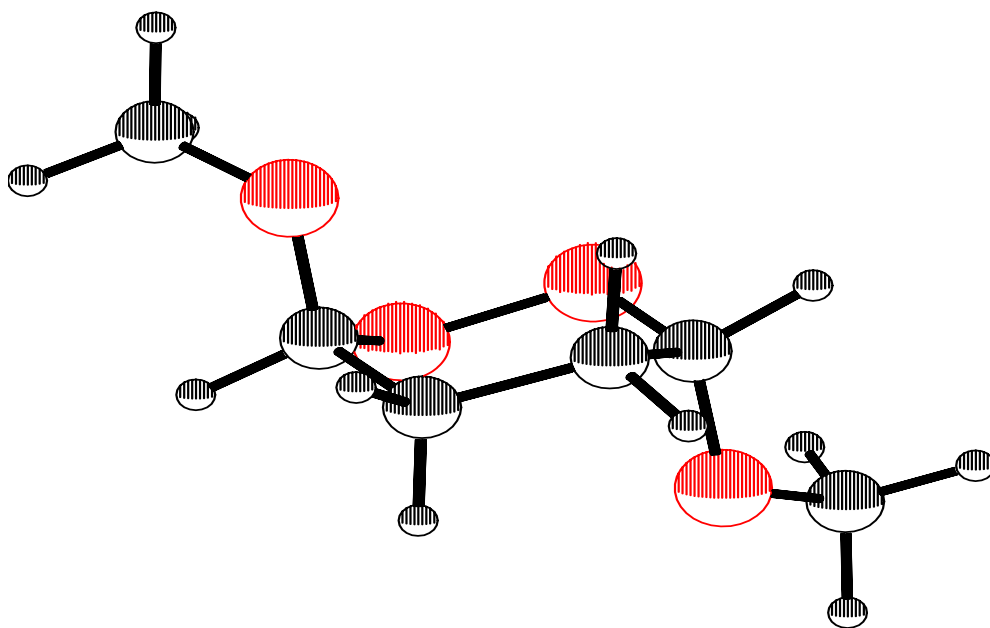


Figure 2. Chair conformation of *trans* diaxial isomer of the 3,6-dimethoxy-1,2-dioxane molecule via the PM3 method.

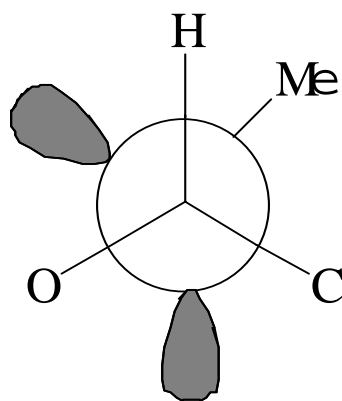


Figure 3. Synclinal conformer.

Table 4: Geometrical parameters of the *trans* diaxial 3,6-dimethoxy-1,2-dioxane (chair structure) molecule, obtained from the AM1 method for the synclinal and antiperiplanar conformers.

	Synclinal	Antiperiplanar
<i>Bond length (Å)</i>		
O ₁ -O ₂	1.289	1.295
C ₃ -O ₂	1.440	1.426
C ₃ -C ₄	1.525	1.426
C ₃ -O _{exo}	1.410	1.378
O _{exo} -C _{Me}	-	1.423
C ₃ -H ₁₀	1.124	1.125
<i>Bond angle (degrees)</i>		
O ₂ -C ₃ -O ₄	114.51	105.99
C ₅ -C ₆ -O ₁	111.93	106.03
C ₅ -C ₄ -C ₃	111.05	114.95
O ₂ -O ₁ -C ₆	114.63	114.96
O _{exo} -C ₃ -C ₄	108.57	113.43
O _{exo} -C ₃ -O ₂	106.94	113.43
C ₃ -O _{exo} -C _{Me}	113.96	119.22
C ₆ -O _{exo} -C _{Me}	113.95	119.20
<i>Torsion angle (degrees)</i>		
C _{Me} -O _{exo} -C ₃ -O ₂	-64.82	60.50
C ₆ -C ₅ -C ₄ -C ₃	44.00	56.50
C ₆ -O ₁ -O ₂ -C ₃	60.50	-56.53
C ₅ -C ₄ -C ₃ -O ₂	-47.29	-51.94
O ₂ -O ₁ -C ₆ -O ₅	55.47	51.84
C _{Me} -O _{exo} -C ₃ -H ₁₀	48.06	-180.00
C _{Me} -O _{exo} -C ₃ -C ₄	174.21	-60.50
C ₄ -C ₅ -C ₃ -H ₁₀	-172.26	-166.96

CONCLUSIONS

The anomeric effect reveals itself in the chemical system in the following ways:

- 1- In the structure: from the shortening of the anomeric C-O bond.
- 2- In the energy: through the stabilization of the gauche (*axial*) geometry with respect to the anti (*equatorial*) geometry.
- 3- In the chemical reactivity: by the variation in the attack rate on the anomeric center.

In the 1,3- and 1,4-dioxane molecules prevail the *diaxial* conformations for the substituted compounds at the *trans* position and $\Delta G > 2$ kcal/mol for the *diaxial* \leftrightarrow *diequatorial* equilibrium. The main conclusion is that energetic behaviour in 1,2-dioxane molecules with polar substituents and having free electron pairs are determined (mainly) by the anomeric and (secondarily) steric effects. There is an energy difference of 2 kcal/mol between these two *trans diaxial* and *diequatorial* conformations.

There are first order effects in the C-O bond lengths, R-C-O bond angles and R-O-C-O torsion angles in the gauche *diaxial* conformation as well as a shortening of the C-O bonds, lengthening of the underlying C-O bond and a growth of the R-C-O angles. Apparently, these parameters are not affected in the *anti* conformation and this feature follows from the shortening of the CX₂ geminal bond with X = strongly electronegative atom. Since the anomeric effect defines quite well the preference of the electronegative substituent or that one having free electron pairs lying at the *axial* positions when it is located on the anomeric center, now the free energy difference corresponding to the *axial* \leftrightarrow *equatorial* equilibrium must be nearly equal to 2 kcal/mol.

In the cyclic system, while the anomeric effect represents the predominance of the *axial* form over the *equatorial* one, both of them show a clear preference for the substituent in the methoxyl group in the synclinal form with respect to the antiperiplanar form. This feature is known as the exoanomeric effect. This effect competes with the anomeric effect, since apparently the free rotation of the methoxyl group substituent reaches the optimum geometry in each case. Here we have seen that the studied cyclic systems exhibit both effects, pointing out that the exoanomeric effect is present in the two conformations (*axial* and *equatorial*).

The explanation in terms of the molecular orbital framework rests upon the accepting property of the (C-OMe) σ^* antibond, relative to the (C-H) antibonding orbital, together with the donor property of the (MeO-C) n_p free electron pair. That is to say there should be an effective interaction between the lowest antibonding orbital of the C-O_{exo} bond and the higher level corresponding to the n_p free electron pair, and we can speculate that the anomeric effect should increase the ΔH°_f . Thus, the more electronegative substituent corresponds with a lower antibonding orbital. When substituents are rather bulky, the steric effect exceeds the anomeric effect and the most stable conformations are the *diequatorial* ones. The possible explanation of this feature can be ascribed to the change of the R-C-O-O torsion angle, which can prevent the anomeric effect, destabilizing the *diaxial* form with respect to the *diequatorial* structure.

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