

Theoretical Study of the *trans*-3,6-Dimethoxy-1,2,4-trioxane Molecule¹

N. L. Jorge, M. Gomez-Vara, L. F. R. Cafferata, and E. A. Castro

Facultad de Ciencias Exactas, Universidad Nacional del Nordeste, Corrientes, Argentina

Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata, Argentina

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Abstract—The molecule of *trans*-3,6-dimethoxy-1,2,4-trioxane has been studied by the semiempirical molecular orbital AM1 and PM3 methods. The numerical results of the structural study have been analyzed in terms of several stereoelectronic effects and compared with available experimental data. Theoretical predictions derived from both methods are in a good agreement with each other.

The integral study of organic peroxides encompasses a very large thematic field covering from biological aspects, such as metabolic oxidation processes, up to important industrial applications, such as initiation of polymerization reactions, painting production, etc. [1–3]. Within the realm of biologically active compounds, they have a significant relevance since they take part of cellular degradation transformations caused by enzymatic self-oxidation due to intermediate peroxide species. An important peroxide belonging to the 1,2,4-trioxane family is a natural product obtained from *Artemisia annua* [4, 5], which is a very potent antimalarial drug having a low human toxicity effect [6]. This compound is denominated *Qinghaosu* (*Artemisine* or *Arteannuin*) and comes from research on the Chinese traditional medicinal practice [7–10]. The antimalarial activity of the *Artemisia annua* extract is associated with the presence of the 1,2,4-trioxane ring in molecules forming these compounds. For that reason, several efforts were made to synthesize some compounds having a 1,2,4-trioxane ring by means of different methods [11]. Since there is a real scarcity of structural information about this class of molecules, we have deemed suitable and necessary to perform a conformational study of both 3,6-dimethoxy-1,2,4-trioxane isomers, resorting to the semiempirical AM1 and PM3 methods.

We have examined the diaxial (*aa*), diequatorial (*ee*), axial–equatorial (*ae*), and equatorial–axial (*ea*) isomers, analyzed their energetic stabilities, and discussed the stereoelectronic (anomeric and exoanomeric) effects and their relevant role in the stability of the *trans* isomer where both methoxy groups are

located at the axial positions. The results of theoretical study by the two molecular orbital methods show the preference of the *trans*-diaxial isomer over the *cis* isomer, in agreement with the experimental data. There exists a conformational equilibrium between the *synclinal* and *antiperiplanar* forms for the first isomer. Below are given the barriers for rotation of the methoxy groups, calculated by both methods, and the stabilization preference of one isomer with respect to the other is discussed in terms of interactions depending on the orientation of free electron pairs belonging to the exocyclic oxygen atom relative to the C–O_{endo} bonds–antibonds.

When the substituent has free electron pairs, the energetic stability of the *trans*-diaxial isomer can be attributed to interactions involving free electron pairs of the substituent [12, 13], in addition to characteristic interactions of free electron pairs of the ring oxygen atoms. The importance of stereoelectronic effect on the substituent has not been taken into account before [12]. Table 1 lists the heats of formation of the *trans-aa* and *cis-ae* isomers of 3,6-dimethoxy-1,2,4-trioxane in the *chair* and *twist* conformations. The barriers to conversion of the diaxial isomer into diequatorial $\Delta(\Delta H(aa-ee))$ are 8.61 (AM1) and 3.52 kcal/mol (PM3). This energy difference reveals the anomeric effect since it stabilizes the isomer with the axial methoxy group. The *chair-aa-chair-ee* interconversion should pass through an intermediate *twist* conformation, and the barrier to the *chair-twist* interconversion is equal to 5.08 kcal/mol, according to the AM1 method (for comparison, the corresponding barrier for the cyclohexane molecule is 5.5 kcal/mol). The value calculated with the PM3 method is 4.05 kcal/mol. Analysis of the data in Table 1 shows

¹ This article was submitted by the authors in English.

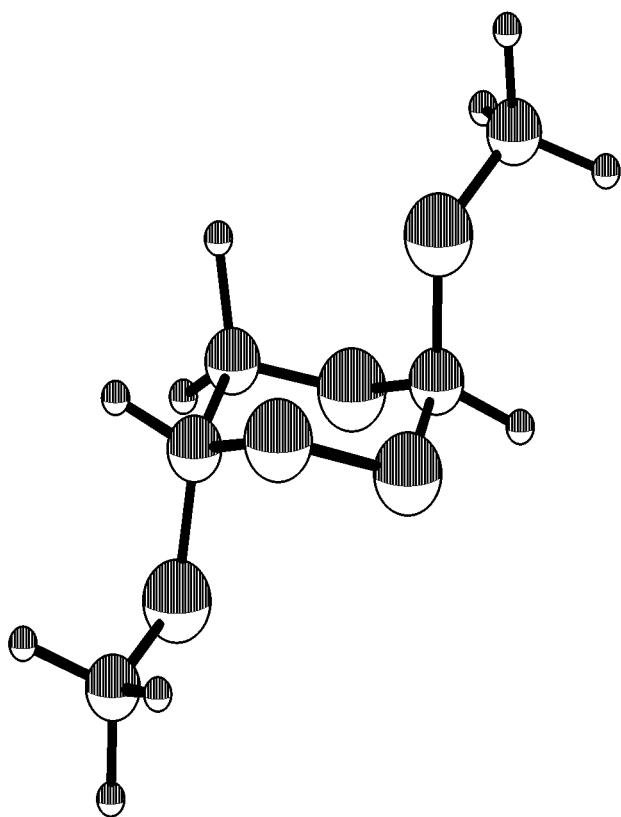


Fig. 1. Chair conformation of the *trans*-diaxial isomer of 3,6-dimethoxy-1,2,4-trioxane according to the AM1 calculations.

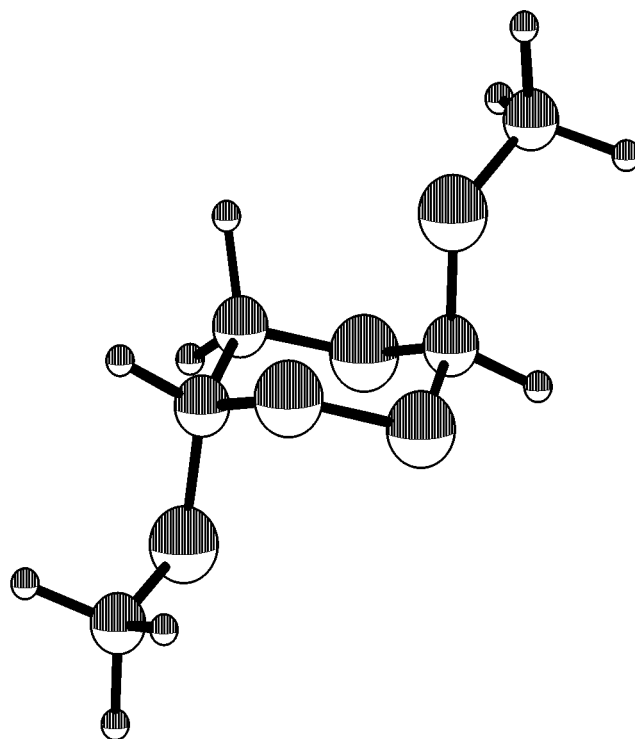


Fig. 2. Chair conformation of the *trans*-diaxial isomer of 3,6-dimethoxy-1,2,4-trioxane according to the PM3 calculations.

that the most stable is the *trans*-diaxial conformer in the chair form.

The molecular geometries optimized by the AM1 and PM3 molecular orbital methods are shown in Figs. 1 and 2. Table 2 contains the geometric parameters obtained by the AM1 and PM3 methods: bond lengths, bond angles, and dihedral angles for the *trans*-diaxial isomer of the title compound in the *chair* and *twist* conformations. The stability order of this molecule has been analyzed taking into consideration four main factors chosen in previous papers on this topic [12–14] plus two additional stereoelectronic effects:

(1) The *syn-axial* effect arising from nonbonding repulsions between free electron pairs located at the nonadjacent oxygen atoms. Assuming that the ring oxygen atom has a tetrahedral hybridization, the repulsion between the 1,5-*syn-axial* free electron pairs are weaker in the *twist* form than in the *chair* form due to the fact that free electron pair momenta in the first of these are less parallel. This effect is enhanced as the OCO bond angle decreases and the XCX' bond angle increases (X = MeO, X' = H).

(2) The torsion angle around the O=O bond favors the *twist* form which is less strained. The results are presented in Table 2.

(3) Steric effect corresponding to the equatorial or axial position of the methoxy group [8].

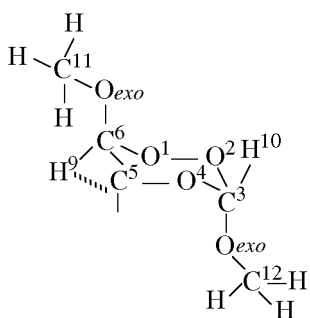
(4) Anomeric effect produced by free electron pairs of the endocyclic oxygen atoms on the C–O_{endo} and C–O_{exo} bonds, when the methoxy group occupies the axial position.

(5) Exoanomeric effect produced by free electron pairs of the substituent oxygen atom on the C–O_{endo}

Table 1. Heats of formation (kcal/mol) of 3,6-dimethoxy-1,2,4-trioxane isomers

Isomer	Chair		Twist	
	AM1	PM3	AM1	PM3
<i>trans-aa</i>	–161.22	–150.36	–156.14	–146.31
<i>cis-ae</i>	–153.73	–147.53	–158.49	–148.82
<i>trans-ee</i>	–152.61	–146.84	–156.14	–146.31

Table 2. Geometric parameters of the *trans*-diaxial isomer of 3,6-dimethoxy-1,2,4-trioxane, calculated by the AM1^a and PM3 methods



Parameter	AM1		PM3	
	<i>twist</i>	<i>chair</i>	<i>twist</i>	<i>chair</i>
Bond lengths, Å				
O ¹ –O ²	1.283	1.291	1.545	1.576
C ³ –O ²	1.443	1.428	1.396	1.373
C ³ –O ⁴	1.397	1.397	1.405	1.408
C ³ –O _{exo}	1.404	1.401	1.403	1.403
O _{exo} –C ¹²	1.422	1.422	1.405	1.405
C ³ –H ¹⁰	1.117	1.120	1.114	1.112
Bond angles, deg				
C ³ O ⁴ C ⁵	114.96	114.86	116.10	116.54
O ² C ³ O ⁴	110.33	109.45	113.77	111.91
O ¹ C ⁶ C ⁵	109.75	110.25	112.97	112.83
O ⁴ C ³ O _{exo}	104.87	105.28	108.15	110.59
O ⁴ C ³ H ¹⁰	109.62	109.07	105.34	105.99
O ² C ³ O _{exo}	102.02	108.43	95.73	105.12
O ² C ³ H ¹⁰	113.09	107.30	115.70	105.58
C ³ O _{exo} C ¹²	113.78	113.92	115.49	115.30
Torsion angle, deg				
C ⁶ O ¹ O ² C ³	65.09	–58.85	63.68	–54.86
C ⁶ C ⁵ O ⁴ C ³	59.39	48.62	57.21	47.60
O ² C ³ O ⁴ C ⁵	–30.63	–53.80	–27.01	–55.52
O ² C ³ O _{exo} C ¹²	–81.07	–73.81	–143.75	–152.82
O ⁴ C ³ O _{exo} C ¹²	163.84	169.13	98.91	86.21
C ⁵ O ⁴ C ³ O _{exo}	78.53	62.55	78.01	61.32
O ¹ O ² C ³ O _{exo}	–143.67	–55.63	–145.21	–64.57
O ¹ O ² C ³ O ⁴	–32.65	58.71	–32.49	55.42

^a The AM1 method well describes stereoelectronic effects, but the theoretical conformation differs appreciably from the experimental one in bond lengths and bond angles. The theoretical difference in the C³–O² and C³–O⁴ bonds is 0.031 Å; the corresponding experimental value is 0.011 Å. The difference between the O⁴C³O_{exo} and O²C³O_{exo} bond angles is 3.15° (AM1) and 1.9° (experimental).

bonds in the *synclinal* and *antiperiplanar* conformations. As stated above, the barrier to rotation of the methoxy group about the C(ring)–O(MeO) bond must be low (i.e., 1–3 kcal/mol [15]), and the exoanomeric effect must increase the height of this barrier by about 2 kcal/mol [16].

Below are given the energy minima (kcal/mol) found for rotation of the methoxy group around the C–O_{exo} bond according to both methods.

<i>trans</i> Conformer	<i>synclinal</i>	<i>antiperiplanar</i>
AM1	–161.22	–158.62
RM3	–150.36	–147.92
$\Delta H^\ddagger(\text{AM1})^2$	–158.55	
$\Delta H^\ddagger(\text{PM3})^2$	–146.72	

The AM1 results indicate that the *synclinal* conformer with two anomeric effects and one exoanomeric effect has the lowest energy, the energy difference between both conformers being equal to 2.6 kcal/mol. The PM3 results coincide with those obtained by the AM1 method, but the energy difference between these conformations is 2.3 kcal/mol. According to the AM1 calculations, the C–C_{exo} bond is shorter in the *anti* conformer than in the *synclinal* form, which supports the existence of the above stereoelectronic interactions. The longer C–O_{endo} bond corresponds to a structure in which the methoxy group is located at the *antiperiplanar* position, i.e., to the *synclinal* conformer shown in Fig. 3. The free electron pairs belonging to the oxygen atoms of the methoxy groups occupy antiperiplanar positions with respect to each C–O_{endo} bond in the *antiperiplanar* conformer.

Thus, the semiempirical PM3 method predicts the same general results as AM1 does, but the differences between the bond lengths of both conformers, calculated by the PM3 method, are lower than those obtained by the AM1 method. We can state that the secondary stereoelectronic effect like *n*→ σ produced by free electron pairs of the peroxide oxygen atoms on the C–O antibonding orbital of the axial methoxy group is responsible for significant stabilization of the *trans*-diaxial isomer. Although the AM1 method poorly describes the O–O bond distance, as compared

² Given are the enthalpies of activation for the conversion of the *synclinal* conformer to *antiperiplanar*. The barrier to rotation of the methoxyl group about the C_{ring}–C_{MeO} bond, calculated by the AM1 method is 2.67 kcal/mol; the corresponding PM3 value is 3.64 kcal/mol.

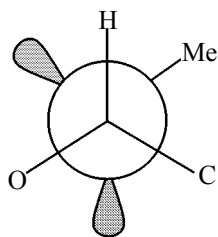


Fig. 3. *Synclinal* conformer of 3,6-dimethoxy-1,2,4-trioxane.

to PM3, our results show that variations in the C–O_{endo} and C–O_{exo} bonds are better reproduced by the AM1 method, which is also the case of the other peroxide derivatives. Despite some experimental evidences for similar compounds with five-membered rings (i.e., the *synclinal*–*antiperiplanar* equilibrium of 2-methoxy-1,3-dioxolane in solution favors the *antiperiplanar* form), the *synclinal* conformer of 3,6-dimethoxy-1,2,4-trioxane is the most energetically stable form.

According to the calculations, the *anti* conformer of the title compound is electronically preferred due to two exoanomeric effects of free electron pairs of the methoxy oxygen atoms on the C–O antibonds of the ring. On the other hand, steric repulsion produced by the methyl group of the methoxy substituent located in the *antiperiplanar* position with respect

Table 3. Geometric parameters of the *trans*-diaxial isomer of 3,6-dimethoxy-1,2,4-trioxane (*chair* conformation, *synclinal* and *antiperiplanar*), calculated by the AM1 method and found experimentally

Parameter	Experiment	<i>Synclinal</i>	<i>Antiperiplanar</i>
Bond lengths, Å			
O ¹ –O ²	1.467	1.291	1.292
C ³ –O ²	1.412	1.422	1.425
C ³ –O ⁴	1.401	1.397	1.398
Bond angles, deg			
O ² C ³ O ⁴	110.10	109.45	111.79
C ⁵ C ⁶ O ¹	107.90	110.25	109.21
C ⁵ O ⁴ C ³	115.00	114.83	118.14
O ² O ¹ C ⁶	107.31	114.10	113.31
O _{exo} C ³ O ⁴	111.60	105.28	112.48
O _{exo} C ³ O ²	109.91	108.43	111.49
C ³ O _{exo} C _{Me}	110.20	113.92	120.00
C ⁶ O _{exo} C _{Me}		114.05	114.05
Torsion angles, deg			
C ⁶ C ⁵ O ⁴ C ³	–45.90	48.62	37.58
C ⁶ O ¹ O ² C ³	71.50	–58.85	–60.65
C ⁵ O ⁴ C ³ O ²	54.80	–53.80	–39.38
O ² O ¹ C ⁶ C ⁵	–62.31	50.63	54.25

to the C–H bond makes the *synclinal* conformer the most stable form. The most important conclusion of this study is as follows. When the substituent has free electron pairs, the stability of the *trans*-diaxial isomer can be attributed to the existence of stereoelectronic interactions involving those free pairs, in addition to interactions of the free electron pairs of the ring oxygen atoms.

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