THEORETICAL STUDY OF SUBSTITUTED TRIOXANES: *trans*-3,6-DIMETHOXY-1,2,4-TRIOXANE

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Abstract

We report the calculation of a theoretical study of the *trans*-3,6-dimethoxy-1,2,4-trioxane molecule through the employment of the AM1 and PM3 semiempirical methods in order to determine the geometrical structure of the *trans a-a* and *e-e* and *cis a-e* and *e-a* isomers. The relative energetic stabilities are discussed on the basis of several purely electronic and stereoelectronic effects. Predictions derived from both methods are quite similar.

Introduction

The all encompassing study of organic peroxides comprehends a large number of chemical issues, from biological like themes (involving, for example, the metabolic oxidation processes), up to disinfection action and pigment manufacture.[1-3] In biological systems organic peroxides are specially important, since they take part in cellular decaying transformations caused by an enzymatic self-oxidation due to intermediate peroxidic chemical species.

An important peroxide within family of 1,2,4-trioxanes is natural product derived from *Artemisia annua,*[4,5] which is a very powerful antimalarial drug with a rather low human toxicity[6]. This compound is the so called Qinghaosu (Artemisinina or Arteannuin) and it was derived from research on chinese medical traditional practices.[7-10] The antimalarial activity of the *Artemisia annua* extract can be associated to the presence of the ring in 1,2,4-trioxane within the molecules of these compounds. The specific antimalarial action of these compounds is discussed in the previous references.

Owing to this reason during these last years several research groups have synthetized many new compounds having a ring of 1,2,4-trioxane by way of different methods.[11(a)-(d)]

Since there exists a real scarcity of structural information about this sort of chemical compounds, in the following we present the results of a conformational study of both isomers resorting to the semiempirical AM1 and PM3 molecular orbital methods.

Results and Discussion

Calculations were made resorting to the HYPERCHEM® package and computations were run in a PENTIUM 4 of 1Ghz and 512 Mbytes of RAM. Although some critics have arisen regarding the predictive capabilities of the PM3 and AM1 methods to reproduce the energetics of internal rotations, this seems not to be the case for the present calculations.

We have not included results derived from the action of environmental effects since some previous calculations using explicit solvent models do not change significantly the results obtained from the isolated molecule model.

We examine the *trans a-a* and *e-e*, and *cis a-e* and *e-a* isomers, analyzing their relative stabilities. The stereoelectronic (anomeric and exoanomeric) effects are discussed as well as their their significant roles in the stabilization of the *trans* isomer, where both methoxyl groups are located at the *axial* position.

The theoretical analysis derived from both methods shows that *trans diaxial* isomer is the preferred one with respect to the *cis* isomer, in close agreement with experimental results. In fact, there is a conformational equilibrium between the synclinal and antiperiplanar forms in the *trans diaxial* isomer. We present results on the rotational barriers of the methoxyl group calculated via both methods and we discuss the stabilization of one conformer with respect the other one, in terms of interactions depending on the orientation of the free electron pairs attached to the exocyclic oxygen atom on the C-O endo bonds/antibonds.

The stability of the *trans axial-axial* isomers when the substituent has free electron pairs can be attributable to the existence of interactions involving free electron pairs located at the substituent,[12,13] besides the proper interactions of the free electron

pairs of the ring oxygen atoms. The importance of the stereoelectronic effect exerted by the substituent has not been taking into account in previous papers.[12]

We give in Table 1 the heats of formation of the *trans a-a* and *e-e* and *cis a-e* isomers in the *chair* and *twist* forms of the 3,6-dimethoxy-1,2,4-trioxane. From the examination of the energetic results we verify that the most stable conformer is the *trans axial - axial* with the *chair* geometry.

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

Isomers		*Chair*		*Twist*	
		AM1	PM3	AM1	PM3
TRANS	*a-a*	-161.22	-150.36	-156.14	-146.31
CIS	*a-e*	-153.73	-147.53	-158.49	-148.82
TRANS	*e-e*	-152.61	-146.84	-156.14	-146.31

$\Delta(\Delta H)$ (*aa-ee*)= 8.61 kcal/mol conversion *axial-equatorial* (AM1).

$\Delta(\Delta H)$ (*aa-ee*)= 3.52 kcal/mol conversion *axial-equatorial* (PM3).

This energy difference reveals the anomeric effect since it stabilizes the isomer having the metoxyl group at the *axial* position. The effect is more noticeable from AM1 calculations.

The interconversion barrier *chair (aa) – chair (ee)* should pass through an intermediate *twist* conformation and the interconversion *chair/twist* is equal to 5.08 kcal/mol, according to the AM1 method (for comparison purposes it is suitable to point out that the value corresponding to cyclohexane is equal to 5.5 kcal/mol). The energy barrier calculated with PM3 method is 4.05 kcal/mol.

The most stable geometries calculated with the AM1 and PM3 methods are shown in Figures 1 and 2. The rather similar appearance of the equilibrium geometries must be considered carefully. In fact, although the general pattern in nearly the same, specific figures associated with the bond lengths and bond angles present some significant differences. These details can be seen in Table 2 where we display the geometrical parameters derived from the AM1 method: bond lengths, bond angles and dihedral angles, for the *trans axial - axial* of the title compound in the *chair* and *twist* geometries, together with the geometrical parameters obtained from the PM3 method.

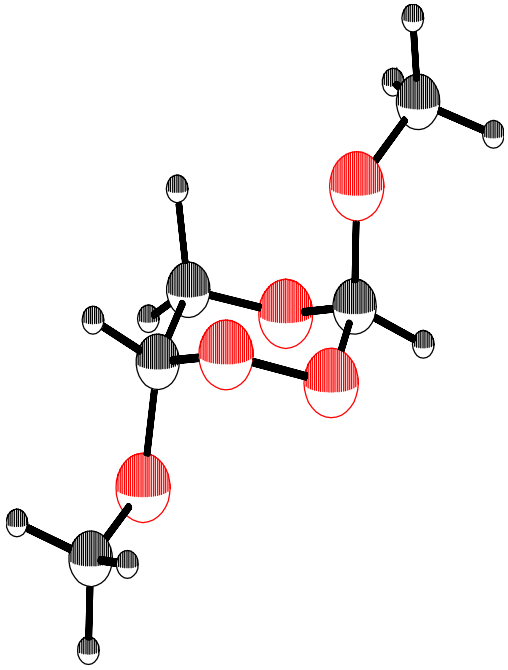

Figure 1. Chair conformation of *trans* diaxial isomer via the AM1 method.

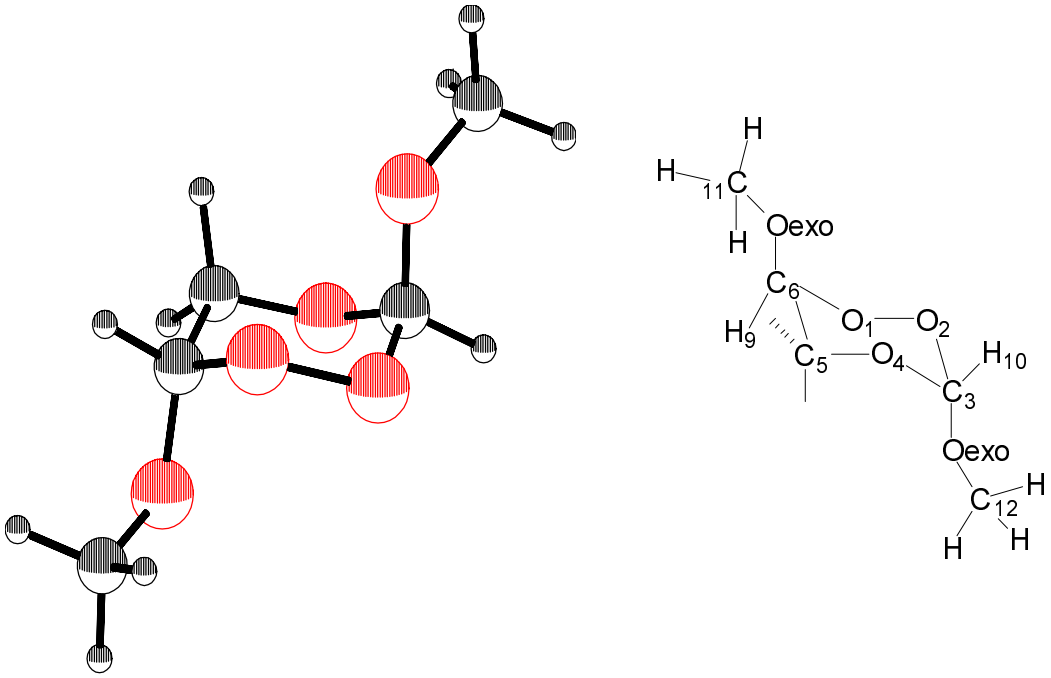

Figure 2. Chair conformation of *trans* diaxial isomer via the PM3 method.

Table 2. Geometrical parameters of *trans diaxial* 3,6-dimethoxy-1,2,4-trioxane obtained for AM1 and PM3 methods.

	AM1		MNDO-PM3	
	Twist	*Chair*	*Twist*	*Chair*
Bond length (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 angle (degrees)				
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 (degrees)				
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

AM1 method describes quite well stereoelectronic effects, but predicted conformation differs from the experimental data, since there are some differences in bond lengths and bond angles.

Δ bond angle (C_3-O_2-C_3-O_4) = 0.031Å

Exp Δ bond angle (C_3-O_2-C_3-O_4) = 0.011Å

Δbond angle (O_4-C_3-O_{exo})-(O_2-C_3-O_{exo}) = 3.15°

ΔExp.bond angle (O_4-C_3-O_{exo})-(O_2-C_3-O_{exo}) = 1.90°

The stability order of the isomers of 3,6-dimethoxy-1,2,4-trioxane is analyzed taking into consideration the four factor chosen previously in similar works[12-14] plus two additional stereoelectronic properties:

a) The *syn-axial* effect arising from the nonbonding repulsion between the free electron pairs located on the non-adjacent oxygen atoms. Assuming a tetrahedrical hibridization for the oxygen atom belonging to the ring, the repulsions between 1,5 *syn-axial* free electron pairs are smaller in the *twist* than in the *chair* form, because the free electron pairs momenta are less parallel in the first than in the second structure. This effect is magnified with the decrease of the O-C-O bond angle and the increase of the X-C-X′ bond angle, where X ≡ methoxyl and X′ ≡ hydrogen.

b) The torsion angle around the O-O bond favours the *twist* form, since this the less strained conformation. Results are given in Table 2.

c) The steric effect, according the methoxyl group is located at the *equatorial* or *axial* position[8].

d) The anomeric effect that free electron pairs of the endocyclic oxygen atoms exert on the C-Oendo and C-Oexo bonds when the methoxyl group is at the *axial* position.

e) The exoanomeric effect that oxygen free electron pairs of the substituent exert on the C-Oendo in the synclinal and antiperiplanar conformations. As stated before, the methoxyl group rotational barrier around the C(ring) – O(methoxyl) bond must be rather low (*i.e.* 1-3 kcal/mol[15]) and the exoanomeric effect must increase this barrier height in around additional 2 kcal/mol[16].

We present in Table 3 the energy minima corresponding to the methoxyl group rotation around the C-Oexo bond calculated by the AM1 and PM3 methods. Regarding the first procedure the synclinal conformer with two anomeric effects and one anomeric effect is the most stable isomer, and the difference is 2.6 kcal/mol. The PM3 results is quite similar to this because the energy difference is 2.3 kcal/mol.

Table 3. Heats of formation (kcal/mol) of *trans*–conformer diaxial 3,6-dimethoxy-1,2,4-trioxane.

Conformer *trans*	AM1	PM3	$\Delta H^{\#(a)}_{AM1}$	$\Delta H^{\#(b)}_{PM3}$
Synclinal	-161.22	-150.36	-158,55	-146,72
Antiperiplanar	-158.62	-147.92		

(a) and (b) activation enthalpies of the conversion synclinal-antiperiplanar.

The rotation barrier of the methoxyl group around the $C_{(ring)} - O_{(methoxyl)}$, calculated via AM1 method is a rather small value: 2.67 kcal/mol. PM3 prediction is equal to 3.64 kcal/mol.

The AM1 semiempirical method reveals a shortening of the C-Oexo bond, which is larger in the anti conformer than in the synclinal isomer, which makes evident the studied stereoelectronic interactions. The lengthened C-Oendo bond corres-

ponds to a state of affairs where the methoxyl oxygen free electron pairs locate at a antiperiplanar position with respect to such atom. This situation is associated to the synclinal conformer and it is shown in the Figure 3. In the antiperiplanar conformer the methoxyl oxygen free electron pairs ar located at an antiperiplanar position with respect to each C-Oendo bond. Geometrical parameters of *trans* diaxial 3,6-dimethoxy-1,2,4-trioxane with a *chair* conformation obtained from AM1 method for antiperiplanar and synclinical geometries are given in Table 4 together with available experimental data.

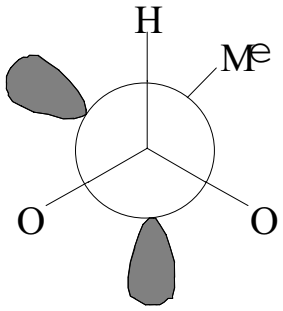

Figure 3. Synclinal conformer.

Table 4. Geometrical parameters of *trans* diaxial 3,6-dimethoxy-1,2,4-trioxano (chair) obtained from AM1 method from conformers synclinal, antiperiplanar and experimental values.

	Experimental	Synclinal	Antiperiplanar
Bond length (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 angle (degrees)			
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 angle (degrees)			
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

Conclusions

PM3 semiempirical method predicts the same general results as AM1 does, but the difference among bond lengths between both conformers are lower and it is due to the deficient description of the C-O bond lengths arising from this method.

For this sort of compounds we can state that the secondary stereoelectronic effect of $n \rightarrow \sigma^*$ type generated by the free electron pairs belonging to the peroxidic oxygen atoms on the methoxyl group C-O antibond, located at *axial* position, yields an important stabilization effect on the *trans diaxial* form.

Although AM1 method describes incorrectly the O-O bond distances with respect to the PM3 method, numerical results show that variations in C-Oendo and C-Oexo bond lengths are given quite well from the first method, which also happens with the remaining peroxides molecules.

Regarding the equilibrium between synclinal and antiperiplanar conformers, although there is some experimental evidence in similar compounds with five-membered rings (for example, 2-methoxy-1,3-dioxolane) that synclynal $\Leftrightarrow$ antiperiplanar

equilibrium in solution favours the antiperiplanar form, in this compound it is found the lower energy form corresponds to the synclinal isomer.

Theoretical calculations show that for the title compound although the anti conformer is electronically favoured from two exoanomeric interactions that methoxyl oxygen free electron pairs exert on the C-O ring antibonds, steric repulsion arising when the methoxyl methyl group is located at an antiperiplanar position with respect to the C-H bond, and consequently the synclinal conformer is the most stable isomer.

The most remarkable fact is the stability of *trans axial-axial* isomers when the substituent possesses free electron pairs, can be attributable to the existence of stereoelectronic interactions which are specific of the free electron pairs attached to the oxygen atoms located into the ring.

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Povzetek

Z uporabo AM1 in PM3 semiempiričnih metod smo študirali *trans*-3,6-dimetoksi-1,2,4-trioksansko molekulo z namenom določiti prostorske strukture *trans a-a* in *e-e* ter *cis a-e* in *e-a* izomerov. Relativno stabilnost smo poskusili določiti z upoštevanjem čistih elektronskih in stereoelektronskih efektov. Obe metodi dasta približno enake rezultate.