

CONFORMATIONAL EQUILIBRIUM OF THE THERMAL UNIMOLECULAR DECOMPOSITION REACTIONS OF SUBSTITUTED 4-FLUOROPHENYL 1,2,4-TRIOXANES

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Dedicated to the memory of the late Prof. Hans J. Schumacher on the occasion of his 100th birthday

Abstract

The unimolecular fragmentations of two fluorine substituted 1,2,4-trioxanes molecules had been interpreted considering the experimental activation parameters of the thermal decomposition reactions in solution. The kinetic data can be rationalized through the postulation of conformational equilibrium of each of the *cis*-6-(4-fluorophenyl)-5,6-[2-(4-fluorophenyl)-propyliden-3,3-tetramethylene-1,2,4-trioxacyclohexane (**I**) and *cis*-6-(4-fluorophenyl)-5,6-[2-(4-fluorophenyl)]-3-hydroxypropyliden-3,3-tetramethylene-1,2,4-trioxacyclohexane (**II**) molecules, which would originate intermediate diradicals in their thermolysis in methanol and in *n*-hexane solutions. The kinetics data and spectroscopic (UV) studies already reported are in close agreement with an *ab-initio* DFT level calculation performed on those molecules.

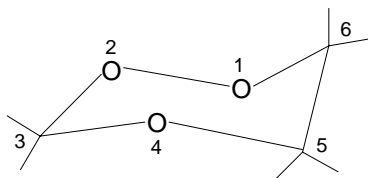
Resumen

Las fragmentaciones moleculares de dos 1,2,4-trioxanos flúor-sustituídos han sido interpretadas considerando los valores experimentales de los parámetros de activación obtenidos en sus reacciones de descomposición térmica unimolecular en solución. Los datos cinéticos correspondientes pueden racionalizarse a través de la postulación de

equilibrios conformacionales de las moléculas del *cis*-6-(4-fluorfenil)-5,6-[2-(4-fluorfenil)-propiliden-3,3-tetrametilen-1,2,4-trioxaciclohexano (**I**) y *cis*-6-(4-fluorfenil)-5,6-[2-(4-fluorfenil)]-3-hidroxi-propiliden-3,3-tetrametilen-1,2,4-trioxaciclohexano (**II**), que originarían el biradical intermediario correspondiente en sus termólisis en soluciones de metanol y de *n*-hexano. Los datos de la cinética de las reacciones estudiadas y de estudios espectroscópicos (UV) ya informados están perfectamente de acuerdo con los de un cálculo *ab-initio* (DFT) realizado en esas moléculas.

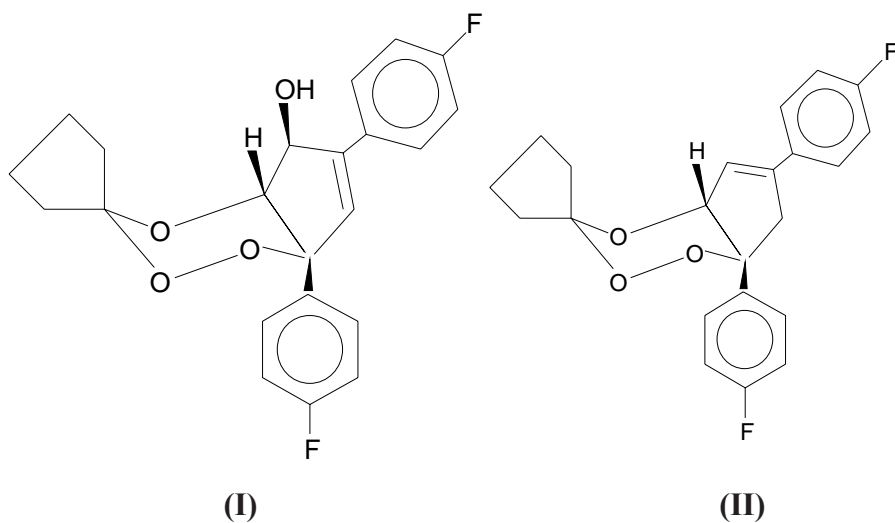
Introduction

The rapid growth of knowledge both related to the synthesis and chemical reactivity of cyclic peroxides as the substituted 1,2,4,5-tetroxanes and 1,2,4-trioxanes has been achieved by several groups of researchers [1-5]. Furthermore, the particular set of substituted 1,2,4-trioxacyclohexane molecules (**A**), constitute an interesting and large family of compounds with therapeutic applications [5-7].



(A)

Thus, most of those compounds are employed as antimalarial agents whose synthesis and pharmacological activities are now investigated in different laboratories [6,7]. However, the heteroatomic A ring is not a useful chromophore group and therefore renders difficult the quantitative evaluation of 1,2,4-trioxanes in solution for medicinal applications. Hence, a suitable choice of substituent groups attached to the A ring would allow the quantitative analysis of these compounds by means of RP-HPLC techniques [8] or electronic spectroscopy [9,10].

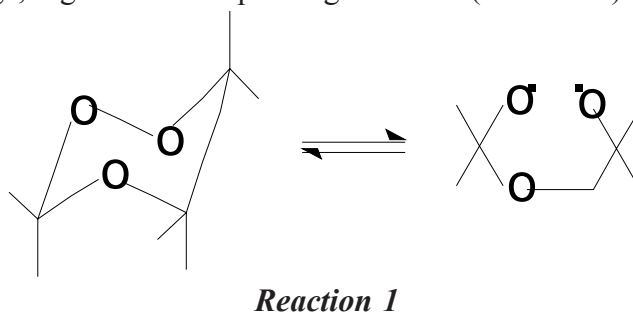


(I)

(II)

The geometries for **I** and **II** molecules, scanned using dynamic simulations were characterized through *boat* and *chair* conformations of their trioxacyclohexane ring. However, the *chair* conformation, a recognized rigid structure with lower energy instead of the flexible *boat* form higher energy, can easily convert into a somewhat more stable form known as the *twist* conformation. In the vast majority of compounds containing a 1,2,4-trioxacyclohexane ring, their molecules exist almost entirely in the *chair* conformation. Moreover, there must be a rapid interconversion of one *chair* form to another and this is only possible through an intermediate *boat* or *twist* conformation. Conversion of one *chair* form to another would include an important activation energy, a change that, however, should be very rapid at room temperature. Nevertheless, when the temperature of those molecules in solution is increased, this equilibrium could be modified.

The thermal stabilities in methanol and in *n*-hexane solutions of both compounds **1** and **II** have already been determined using kinetic methods [11, 12] and the corresponding temperature effect evaluated through the Arrhenius equations. Furthermore, it is accepted that the first stage in the mechanism of **I** and **II** thermolysis is the homolytic cleavage of the peroxydic bond, occurring into the reaction cage, to give the corresponding diradicals (*Reaction 1*).



Moreover, those intermediate diradicals subsequently undergo further stepwise decomposition yielding the already observed reaction products [11, 12]. It is worth recalling that the unimolecular homolyses, studied by kinetic methods and products analysis, in both cases presents significant effects of the initial concentrations of the reactants and solvents employed [13].

In this work, **I** and **II** molecules were further studied in order to report the optimized parameters of an *ab-initio* DFT level calculation, to contribute to the knowledge of their structures since there are no X-ray data available in the literature.

Experimental

The trioxanes **I** and **II** were obtained by methods described elsewhere [5]. The purities of these substances were checked by an appropriate RP-HPLC analytical method [8]. The activation parameters corresponding to the unimolecular reactions investigated were obtained applying the Eyring equation ($k = k_B T / h \exp(-\Delta H^\ddagger / RT) \exp(\Delta S^\ddagger / R)$, where $(k_B / h) = 2.084 \times 10^{10} \text{ K}^{-1} \text{ s}^{-1}$ and $R = 1.986 \text{ cal mol}^{-1} \text{ K}^{-1}$). Error limits were determined by a computational data treatment and using a reliable literature method [14].

Computational Details

The conformation of **I** and **II** molecules was studied using the molecular dynamics (MD) module of the *HyperChem* package [15]. Several simulations were accomplished with the aid of

the MM+ force field. The starting geometries were characterized by different conformations of the peroxydic ring heating from 0 to 600 K in 0.1 ps. Then, the temperature was kept constant by coupling the system to a simulated 0.5 ps bath relaxation time with a 0.5 fs time step. After an equilibration period of 1 ps a 500 ps-long simulation was run saving the coordinates every 1 ps. Those geometries were then optimized to a less than 0.001 kcal mol⁻¹ Å⁻¹ energy gradient using the MM+ force field. The energy values of the molecular conformers were selected against 1 kcal energies intervals between the highest and lowest values of the collection and their selected optimized geometries by means of the MNDO module of the *Hyperchem*. Geometry optimizations were performed using the Becke's three-parameter hybrid functional [16] with the Lee-Yang-Parr correlation functional [17], a combination that gives rise to the well-known B3LYP method. The 6-31G** basis set was used for all the atoms of both trioxanes.

Results and Discussion

The experimental activation parameters values for the unimolecular thermal decomposition reactions of **I** and **II** trioxanes in methanol and in *n*-hexane solutions are shown, respectively, in Table 1 and Table 2.

Table 1. Activation parameter values^a for the unimolecular thermal decomposition reactions of trioxane I in methanol and in *n*-hexane solutions

Reaction Solvent	Initial conc. x 10 ⁵ M	ΔH [#] kcal mol ⁻¹	ΔG [#] kcal mol ⁻¹	ΔS [#] cal mol ⁻¹ K ⁻¹
methanol	2.7	28.7 ± 0.6	29.4 ± 0,7	1.8 ± 1.3
methanol	54.0	29.0 ± 0.8	29.6 ± 0,8	1.1 ± 1.2
<i>n</i> -hexane	13.5	31.1 ± 0.9	30.9 ± 0.9	0.4 ± 2.1
<i>n</i> -hexane	263	37.7 ± 1.2	36.1 ± 1.1	3.7 ± 3.0

^a Values calculated at the middle of the experimental temperature range (423 K) through a least means square data treatment and error limits as in ref. [14].

Table 2. Activation parameter values^a for the unimolecular thermal decomposition reactions of trioxane II in methanol and in *n*-hexane solutions

Reaction Solvent	Initial conc. x 10 ⁵ M	ΔH [#] kcal mol ⁻¹	ΔG [#] kcal mol ⁻¹	ΔS [#] cal mol ⁻¹ K ⁻¹
Methanol	1.05	29.1 ± 0.8	29.7 ± 0.8	-1.5 ± 1.8
Methanol	13.0	30.1 ± 0.7	29.6 ± 0.7	0.9 ± 1.8
<i>n</i> -hexane	14.5	31.7 ± 0.7	31.4 ± 0.7	0.65 ± 1.7
<i>n</i> -hexane	82.0	38.5 ± 0.5	35.1 ± 0.5	8.1 ± 1.2

^a Values calculated at the middle of the experimental temperature range (410.7 K) through a least means square data treatment and error limits as in ref. [14].

The nearly similar values of ΔG^\ddagger found for **I** and **II** reactions in methanol solutions (Table 1 and Table 2), in spite of their different molecular structures apart from the corresponding trioxane ring, indicate that analogous types of qualitative interactions between both substrates and solvent molecules are playing in their thermolysis. Furthermore, the corresponding activation enthalpies of the homolytic reactions are almost compensated by the entropies of activation, yielding practically constant free energies of activation for both molecules. Thus, the analogous values of the activation enthalpies for both trioxanes reactions indicate that the substituent atomic groups in the respective molecules do not interact significantly with the peroxydic O-O bond, whose cleavage constitutes the rate-determining step of the whole reactions.

On the other hand, the ΔH^\ddagger and ΔG^\ddagger values for **I** and **II** reactions in *n*-hexane solutions at two different concentrations (Table 1 and Table 2), turn to be significantly dissimilar. Thus, an influence of the initial concentrations of the trioxanes in the *n*-hexane solutions is noticed, along with a relevant solvent effect when those values are compared for the same molecules in methanol solutions. The behavior at different initial concentrations in hydrocarbon solutions, points out that dissimilar quantitative interactions take place in the unimolecular thermolysis either between the substrate and the solvent or among the trioxane molecules themselves. Considering that electrostatic effects between the *n*-hexane molecules are practically negligible, some kind of interaction between the 1,2,4-trioxane molecules themselves could be responsible of the difference found between the activation parameters values for the **I** and **II** reactions. Then, it could be tentatively postulated that this effect is due to different conformational changes in both trioxanes molecules during the initial stage of their thermal decompositions in solution. To draw this conclusion the average experimental activation energies had been taken for comparison at a given temperature.

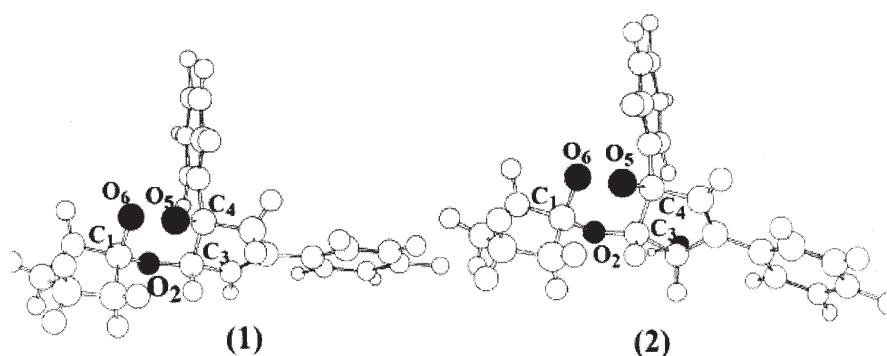


Figure 1. Representation of the conformational equilibrium corresponding to the initial diradical postulated in the thermolysis of trioxane **I** in solution.

In Figure 1 are represented as an example the conformers (shown as 1 and 2) corresponding to the lowest energy of the diradical postulated for the trioxane **I** reaction, using the density functional theory as implemented in the Gaussian 98 package [18]. The picture is in line with the reported finding (9, 10) of more than eighteen conformational species of analogous molecules of 1,2,4-trioxanes existing in equilibrium at room temperature, as result of calculation and spectroscopic (UV) studies performed in *n*-hexane solution.

Actually, as the temperature of **I** and **II** thermolysis in solution increase, their conformational equilibrium in the initial states would turn to be more rapid. Furthermore, *it can be assumed that*

at ambient temperature the difference between the concentrations of the most stable conformers (*chair*) may be larger than the concentration of the less stable ones. Moreover, with the change of the reaction temperature the position of the equilibrium certainly can be modified, which in turn would change the average activation parameters of the unimolecular reactions, as it is in fact observed (Table 1 and Table 2).

The results of calculations performed for the **I** and **II** molecules by the B3LYP method (see Experimental) are shown in Table 3.

Table 3. Relevant geometrical optimized parameters for the lowest energy of the conformers of **I** and **II** trioxanes calculated at B3LYP/6-31G** level.

Optimized Parameters	Trioxane I	Trioxane II	Experimental values [5]
C ₁ O ₂	1.43	1.44	1.439
C ₁ O ₆	1.44	1.44	1.443
C ₃ O ₂	1.42	1.41	1.413
C ₃ C ₄	1.53	1.54	1.548
C ₄ O ₅	1.44	1.45	1.447
O ₅ O ₆	1.48	1.49	1.477
C ₁ O ₆ O ₅	105.6	112.3	105.6
O ₆ O ₅ C ₄	107.0	102.5	107.0
C ₁ O ₂ C ₃	114.7	107.2	114.7
O ₆ C ₁ O ₂	108.8	111.4	108.8
O ₂ C ₃ C ₄	113.7	112.4	113.7
C ₃ C ₄ O ₅	102.7	101.8	102.7
C ₁ O ₆ O ₅ C ₄	66.1	67.4	-74.9
O ₆ O ₅ O ₄ C ₃	-65.5	-67.5	61.6
O ₅ C ₄ C ₃ O ₂	67.1	71.2	-46.5
C ₄ C ₃ O ₂ C ₁	-58.2	-60.6	42.9
C ₃ O ₂ C ₁ O ₆	54.5	52.4	53.6
O ₂ C ₁ O ₆ O ₅	29.8	28.9	68.1

It is evident that the calculated values for **I** and **II** molecules (Table 3) represent quite well the C-O, C-C y O-O bond length changes, compared to those of an analogous 1,2,4-trioxane

already investigated by X-ray analysis [5]. The compounds studied in this report (as also the indicated as **7** in the referenced article) show a slightly flatted chair conformation in the peroxydic ring. However, the most remarkable difference with the ent-**7** molecule is the dihedral angle formed by the trioxane ring respect to the cyclopentene ring and the dihedral angles obtained here for the 1,2,4-trioxane ring.

Conclusions

The kinetic results obtained for **I** and **II** thermolysis in n-hexane solutions demonstrate that the physicochemical characteristics of this solvent promote a bigger energy requirement to perform the rupture of the peroxydic bond in the 1,2,4-trioxane ring. This is more important when the initial concentration of those compounds is increased in the solution. On the other hand, in methanol solutions, once the postulated initial diradical is formed, the free interconversion of the different conformers would be less affected by the strong electrostatic interactions of this solvent with the **I** and **II** species. Therefore, a considerable increase of the initial concentration of those trioxanes would not significantly influence the kinetics of the respective unimolecular thermolysis, as is experimentally observed. A reasonable good agreement was found between the reaction kinetics, spectroscopic (UV) and calculated data for the **I** and **II** molecules. The procedure followed in this work demonstrates once again it is a valid alternative to relate theoretical calculations with experimental results.

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References

- [1] Cafferata, L. F. R.; Furlong, J. J. *Advances in Oxygenated Processes*. A. L. Baumstark (Ed.). Vol. 4, 81-105, JAI Press, USA, **1995**.
- [2] Hawkins, E. G. E. *Organic Peroxides*. Their Formation and Reactions, E. and F. F. Spon Ltd, London. **1961**.
- [3] *Organic Peroxides*, Swern, D. (Ed.), Wiley. Interscience, New York, **1971**.
- [4] Cafferata, L. F. R. *Trends in Organic Chemistry*. L. Menon (Ed.), Chapter 4, 773-795, Council of Scientific Research Integration, Trivandrum, India, **1993**.
- [5] Jefford, C. W.; Kohmoto, S.; Joggi, D.; Rossier, J. C.; Timarí, G.; Ruday, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G.; Manzanares, J.; Canfield, C. J.; Fleck, S. L.; Robinson, B. L.; Peters. W. *Helv. Chim. Acta*, **1995**, 78, 647.
- [6] Jefford, C. W. *Eur. Pat. Appl.* **1988**, EP 286.
- [7] Jeandupeux, R.; Cafferata, L. F. R. *Acta Farm. Bonaerense*, **1995**, 14, 91.
- [8] Rimada, R. S.; Cafferata, L. F. R.; Allegretti, P. J. Furlong. *J. J. High Resol Chromatogr.* **1999**, 22, 67.

- [9] Jubert, A. H. ; Castro, E. A.; Cafferata, L. F. R. *J. Mol. Struct. (Theochem)* **2000**, *503*, 165.
- [10] Jubert, A. H.; Pis Diez, R.; Cafferata, L. F. R. *J. Mol. Struct. (Theochem)* **2001**, *545*, 167.
- [11] Cafferata, L. F. R.; Jefford, C.W.; Rimada, R. S. *Int. J. Chem. Kinetics*, **2000**, *32*, 523.
- [12] Rimada, R. S.; Cafferata, L. F. R. *Afinidad*, **2002**, *59*, 684.
- [13] Rimada, R. S.; Cafferata, L. F. R. *Molecules*, **2003**, *8*, 655.
- [14] Huyberegts, S.; Halleux, A., Kruys, P., *Bull. Chim. Belg.*, **1955**, *64*, 203.
- [15] *HyperChem*, Release 7.5 for Windows , Hypercube Inc., USA.
- [16] Becke, A. D. *J. Chem. Phys.*, **1993**, *98*, 5648.
- [17] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **37**, **1988**, *37*, 785.
- [18] *Gaussian 98*, Revision A 7, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K.N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; González, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; González, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, USA, **1998**.