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Thermal decomposition of trioxanes in solution of 1,4-dioxane

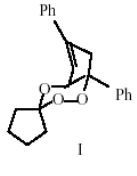
Carmen M. Mateo[1], Karina Nesprias[1,2], Adriana I. Cañizo[1] and Nora Eyler[1]

Facultad de Ingeniería [1] and Facultad de Agronomía [2], Universidad Nacional del Centro de la Provincia de Buenos Aires, Avda. Del Valle 5737, B7400JWI Olavarría, Buenos Aires, Argentina.
e-mail: cmateo@fio.unicen.edu.ar

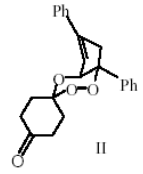
Introduction

Substituted 1,2,4-trioxanes are a family of compounds with interesting pharmacological properties. Over the past few years have been studied intensively by various research groups (Borstnik *et al.*, 2002; Ploypradith, 2004) due to the proved antimalarial activity shown by these molecules. Their structures possess the 1,2,4-trioxacyclohexane ring, similar to that of artemisinin, which is a natural drug from the plant extract of *Artemisia annua*, used to combat malaria.

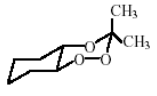
In this work the thermal decomposition kinetic study of two trioxanes, *cis*-6-phenyl-5,6-(2-phenylpropiliden)-3,3-tetramethylene-1,2,4-trioxacyclohexane (**I**) and *cis*-6-phenyl-5,6-(2-phenylpropiliden)-3,3-(pentan-3-one)-1,2,4-trioxacyclohexane (**II**) in solution of 1,4-dioxane at different temperatures was carried out. Results were compared with those of *trans*-3,3-dimethyl-5,6-tetramethylene-1,2,4-trioxacyclohexane (**III**) (Eyler *et al.,* 1999).



I



II



III

Methodology

Pyrex glass ampoules (7 cm length x 6 mm ext. diam.) were filled with *ca.* 1 ml of the corresponding peroxide solution in 1,4-dioxane, cooled with liquid nitrogen (-196 ºC), 3 times degassed in vacuum line, and heat-sealed with a propane-oxygen torch. Ampules were placed in a silicone oil bath at a selected temperature (± 0.1 ºC) and removed at properly determined times based on the kinetic available data, stopping peroxide decomposition in an ice/water bath at 0 ºC.

The quantitative remaining peroxide determination in the pyrolized solutions of the respective trioxanes in 1,4-dioxane solution was carried out by high-performance liquid chromatography (HPLC) on a Hewlett-Packard equipment, 1050 C series, using a reversed-phase column (ODS Hypersil, 5 μm., 100 x 4.6 mm) and variable wavelength UV-Visible detector ($\lambda = 254$ nm).

Methanol/acetonitrile/agua (40:30:30) was used as mobile phase, with a flow of 0.5 ml/min for the analysis of **I**, and methanol/acetonitrile/water (40:40:20), with a flow of 0.8 ml/min for the analysis of **II**. HPLC quality solvents were used.

Solvents

1,4-Dioxane, used as solvent, was purified by distillation on sodium according to previously reported techniques (Riddick, 1970). Purity was controlled by GLC and HPLC.

Synthesis de Peroxides

Trioxanes **I** and **II** used in this study were prepared and purified according to techniques described in the literature (Jefford *et al.,* 1995).

Results

Thermal decomposition of the trioxanes **I** and **II** has been studied in solution of 1,4-dioxane in a range of temperatures between 100 and 140 ºC for initial concentrations of the order of 10^{-4} M (Table 1).

In both cases the thermolysis reaction of the trioxans in 1,4-dioxane follows a *pseudo*-first order kinetics law until *ca.* 80% peroxide conversions. This shows that there are no effects of second-order induced reactions that accelerate their thermal decomposition. The effect of temperature on the rate constants can be represented by equations (1-3), where activation energies are expressed in cal/mol, and the errors account for the standard deviations derived from a kinetic data treatment by the least squares method (Huyberetch *et al.,*1955).

ln kexp **I** (s-1) = (31,5 ± 0,8) - (31747 ± 339)/RT (1) ln kexp **II** (s-1) = (32,96 ± 4,8) - (33226 ± 1961)/RT (2) ln kexp **III** (s-1) = (19,9 ± 2,6) - (24900 ± 1107)/RT (3)

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The linearity of Arrhenius equations in a relatively wide range of temperatures (30 ºC) suggested that the activation parameters calculated for trioxanes in solution of 1,4-dioxane can be assigned to a simple process such as O-O bond homolytic rupture.

According to the values of the rate constants (Table 1), trioxane **III** shows higher reactivity than **I** and **II** probably due to an effect of substituents. Compounds **I** and **II** have similar structures, and show a similar kinetic behaviour.

Upon evaluation of the activation parameters (Table 2) it can be observed that a modification of the activation enthalpy value ($\Delta H^{\#}$) is accompanied by a change in the same sense of the corresponding activation entropy ($\Delta S^{\#}$), determining a *compensation effect* that results in a variation of activation free energy ($\Delta G^{\#}$) that is almost negligible ($\Delta\Delta G^{\#}$ = 2 kcal/mol). Further it should be noted that this value is in the order of the calculated experimental error for this parameter.

On the other hand, the fact that the values of free energy are similar in all cases allow to establish that thermal decomposition occurs in the three studied trioxanes *via* the same stepwise-type mechanism, and is initiated by the O-O bond homolytic rupture of the trioxane molecule.

The observed differences in activation parameters can be explained taking into account that the activated complex of **III** (trioxane with smaller substituents) is more polar that its initial state, and in turn, more polar than the activated complexes of **I** and **II**, so that solvation of **III** is higher at that point. Therefore, the value of activation enthalpy decreases as a result of that solvation, thus lowering the energy barrier that trioxane **III** must overcome to be transformed into products. The association forces then lead to a highly ordered activated complex, which gives rise to a significant decrease in the values of activation entropy for **III**, as shown in Table 2.

Conclusions

Large amount of research has demostrated that those substances that possess a substituted 1,2,4-trioxane ring show antimalarial activity to some extent. In this work the cycle opening kinetics by the O-O bond homolytic rupture is affected by the size of the substituents, as has been observed for organic cyclic diperoxides o triperoxides. Therefore, it should not be ruled out the possibility that this biological activity may also depend on substituents. However, so far kinetic and thermodynamic results obtained for the three trioxanes referenced in this work are insufficient to obtain a definitive conclusion on the matter.

Table 1: Values of the rate constants for trioxanes **I**, **II** and **III** at different temperatures.

Trioxane	Temperature [ºC]	$10^4 k_{exp}$ [s^{-1}]	r[a]	References
I	110	0.39	0.999	This work
	120	1.17		
	130	3.29		
	140	7.87		
II	120	0.65	0.982	This work
	130	2.16		
	140	7.51		
	150	11.1		
III	135	19.8	0.988	(Eyler *et al.*, 1999)
	143	41.1		
	143	31.9		
	150	70.7		
	150	72.0		
	165	158		

[a] Correlation coefficient according to Arrhenius equation obtained by treatment of least squares.

Table 2: Values of the activation parameters of trioxanes **I**, **II** and **III** in solution of 1,4-dioxane.

Trioxane	Δt [ºC]	$\Delta H^{\#}$ [kcal mol^{-1}]	$\Delta S^{\#}$ [cal $mol^{-1}K^{-1}$]	$\Delta G^{\#}$[a] [kcal mol^{-1}]	Ref.
I	30	31.0 ± 0.8	1.7 ± 0.3	30.1 ± 0.8	This work
II	30	32.3 ± 4.8	4.1 ± 1.96	30.6 ± 4.8	This work
III	30	24.0 ± 1.1	-19.8 ± 2. 6	32.6 ± 1.1	Eyler, 1999

[a] Calculated at the mean experimental temperature.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

References

- Borstnik K., Paik I., Shapiro T. A. and Posner G. H. (2002) Antimalarial chemotherapeutic peroxides: artemisinin, yingzhaosu A and related compounds. *Int. J. Parasitol.* **32**, 1661-1667.

-Eyler G. N., Cañizo A. I., Mateo C. M., Alvarez E. E. and Cafferata L. F. R. (1999) Solvent effect in the thermal decomposition reaction of *trans*-3,3-dimethyl-5,6-tetramethylene-1,2,4-trioxacyclohexane. *J. Org. Chem*. **64**, 8457-8460.

- Huyberetch S., Halleux A. and Kruys P. (1955) Une application de calcul statistique a le cinétique chimique. *Bull. Soc. Chim. Belg*. **64**, 203-209.

- Jefford C. W., Kohmoto S., Jaggi D., Timári G., Rosier J.C., Rudaz M., Barbuzzi O., Gérard D., Burger U., Kamalaprija P., Mareda J., Bernardinelli G., Manzanares I., Canfield C. J., Fleck S. L., Robinson B. L. and Peters W. (1995) Synthesis, structure, and antimalarial activity of some enantiomerically pure *cis*-fused cyclopentene-1,2,4-trioxanes. *Helv. Chim. Acta* **78**, 647-662.

- Ploypradith P. (2004) Development of artemisinin and its structurally simplified trioxane derivatives as antimalarial drugs. *Acta Tropica* **89,** 329-342.

- Riddick J. A. Y. and Bunger W. B. (1970) *Organic Solvents.* Vol II, A., Weissberger Ed., Wiley Interscience, N. Y.