Solvent and Substituent Effects on the Thermolysis of Antimalarial Fluorophenyl Substituted 1,2,4-Trioxanes

Lazaro F. R. Cafferata* and Ruben S. Rimada

Laboratorio LADECOR (UNLP) and CINDECA (CONICET), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Calles 47 Y 115, (1900) La Plata, República Argentina.

* Author to whom correspondence should be addressed: caferata@quimica.unlp.edu.ar

Abstract: The kinetics and mechanism of the thermal decomposition reaction of *cis*-6-(4-fluoropheny1)-5,6-[2-(4-fluorophenyl)-propylidene]-3,3-tetramethylene-l,2,4-trioxacyclo-hexane (**I**) were investigated separately in *n*-hexane and in methanol solutions over the temperature and concentration ranges of 393.2-443.2 K and 2.7-54 x 10^{-5} M, respectively. The values of the activation parameters for both reactions were compared with the corresponding ones for the thermolysis of *cis*-6-(4-fluorophenyl-5,6-[2-(4-fluorophenyl)-3-hydroxypropylidene]-3,3-tetramethylene-1,2,4-trioxacyclohexane (**II**), investigated in the same solvents and temperature range. Substituent and solvent effects on the initial homolytic rupture of the O-O peroxydic bonds of those molecules were evaluated.

Keywords: Peroxides – Thermolysis - Fluorophenyl Substituted 1,2,4-trioxanes - Thermal decomposition Reactions - Solvent and Substituents Effects - Antimalarial Compounds

Introduction

Cyclic peroxides of the substituted 1,2,4-trioxane type are structurally related to the six-member ring 1,2,4,5-tetroxanes and 1,2,4,5-trioxazines already investigated by kinetic methods [1,2]. Examples of those compounds, which are available through new synthetic methods, are related to the antimalarial activity of molecules with a 1,2,4-trioxane ring as in artemisinin and their derivatives [3]. Furthermore, the activation parameters values for the unimolecular thermolysis of acyclic organic peroxides [4,5] and cyclic diperoxides [6-8] depend significantly on the reaction media. On the other hand, mass spectrometric evidence for the analysis of the products of thermolysis of other 1,2,4-trioxanes in solution have been reported [9]. The kinetics of all the cases cited constitute genuine "reaction series" [7] where the decomposition of those molecules is controlled by their O-O bond homolysis.

Herein, the kinetic data on the thermolysis of molecules **I** and **II** in methanol solution [10] is compared with that obtained in *n*-hexane solution [11], to examine possible solvent effects in their thermolyses.

(I)   **(II)**
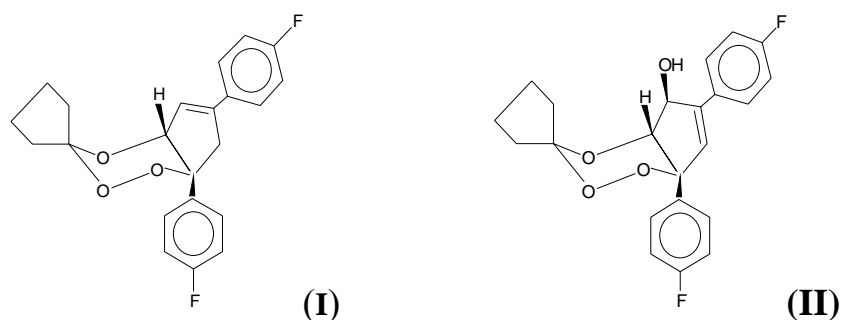
Results and Discussion

Rate measurements on the thermal decomposition reactions of **I** and **II** in *n*-hexane and methanol solutions in the 10^{-4} - 10^{-5} M initial concentration and 393.2- 443.2 K temperature range show first-order kinetic law behavior up to *ca*. 98% conversions of both trioxanes (Table I).

Table I. First-Order Rate Constant Values for the Thermal Decomposition Reactions of Trioxanes **I** and **II** in *n*-Hexane and Methanol Solutions.

Temp K	Reaction Solvent	$10^5 \cdot [I]^a$ M	$10^5 \cdot k_{obs}$ s^{-1}	$10^5 \cdot [II]^a$ M	$10^5 \cdot k_{obs}$ s^{-1}
393.2	*n*-hexane	13.5	5.1 ± 0.5	82	2.7 ± 0.2
393.2	methanol	2.7	38.2 ± 0.4	1.05	27.6 ± 3.0
403.2	*n*-hexane	13.5	14 ± 1.5	82	4.2 ± 0.4

Table 1. *Cont.*

403.2	methanol	2.7	90.3 ± 0.8	26	73.6 ± 7.0
413.2	*n*-hexane	13.5	37.0 ± 3.0	14.5	29.4 ± 3.5
413.2	methanol	2.7	232 ± 9	26	180 ± 13
423.2	*n*-hexane	13.5	87 ± 6.5	14.5	67.3 ±3.5
423.2	methanol	2.7	546 ± 21	26	405 ± 10
433.2	*n*-hexane	13.5	222 ± 18	14.5	141 ± 4
433.2	methanol	54.0	697 ± 8	13.0	706 ± 47
443.2	*n*-hexane	13.5	532 ± 25	14.5	277 ± 18

Note: [a] trioxane initial concentrations.

Figure 1. Arrhenius Equation Plots for the Thermolysis of Trioxanes **I** (...) and **II** (−) in Solution.
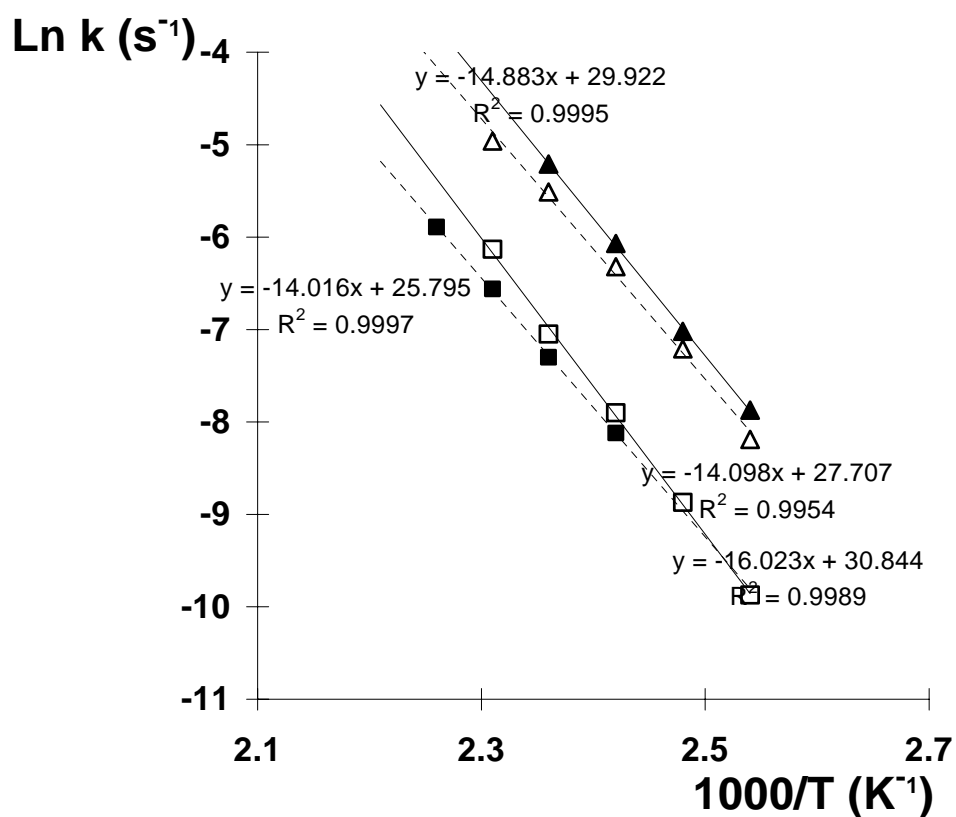
Symbols: □, *n*-hexane, (13.5x10^{-5} M); ■, *n*-hexane, (14.5x10^{-5} M); Δ, methanol, (13x10^{-5} M); ▲, methanol, (54x10^{-5} M).

From the data a kinetic solvent effect in the thermolysis of **I** and **II** is evident, as the reaction rates, at the same temperature, are faster in methanol than in *n*-hexane. Furthermore, the temperature effect on the experimental rate constant values (k_{obs}) in the solvents investigated can be represented by an Arrhenius equation (Figure 1), where the error limits indicated are standard deviations from a least mean-squares data treatment.

The linearity of these plots ($R^2 \geq 0.9954$) over a relatively large temperature range suggests that the calculated activation parameters for **I** and **II** reactions (Table II) correspond to single processes.

Table II. Activation Parameters Values[a] for the Unimolecular Thermolysis in Solution of Trioxanes **I** and **II**.

Trioxane	Reaction Solvent	$\Delta H^{\#}$ kcal mol^{-1}	$\Delta S^{\#}$ cal mol^{-1} K^{-1}	$\Delta G^{\#}$ kcal mol^{-1}
I	methanol	28.2 ± 0.7	- 3.0 ± 1.3	28.9 ± 0.7
I	*n*-hexane	31.1 ± 0.9	0.4 ± 2.1	30.9 ± 0.9
II	methanol	29.0 ± 0.7	- 1.5 ± 1.8	29.6 ± 0.7
II	*n*-hexane	31.7 ± 0.6	0.7 ± 1.7	31.4 ± 0.6

Note: [a] calculated at the middle of the experimental temperature range (see Table I).

These activation parameters can be assigned to the "in cage" unimolecular thermal cleavage of the O-O bonds of **I** and **II** molecules as initial stages of their mechanisms of reaction (eq. 1).

(1)
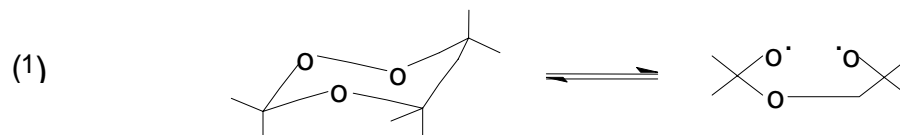
Moreover, if the unimolecular thermolyses of those molecules involve concerted bond breaking and formation, the experimentally observed activation entropies (Table II) should be very negative. Hence, it can be supposed that the activation parameters for the decomposition reactions of **I** and **II** in *n*-hexane and methanol solutions correspond to their unimolecular homolysis, because alternative reaction pathways can not be reasonably postulated. The $\Delta G^{\#}$ values for both trioxane reactions (Table II) support similar interactions between substrate and the solvent molecules in each thermolysis. Furthermore, the corresponding activation enthalpies of the reactions are almost compensated by the entropies of activation, yielding practically the same values of the free energies of activation. Also the analogous $\Delta H^{\#}$ values for both trioxane reactions (Table II) reflect that the unsaturated cyclopentene rings of **I** and **II** molecules and the hydroxyl atomic group at the C-3 position of the latter, do not influence the peroxydic bond strength of the trioxanes as already advanced [12].

Thus, the first step in the reactions of **I** and **II** is their unimolecular homolysis to give the corresponding substituted diradical (eq. 1), which undergoes subsequently further decompositions to finally yield the observed reaction products (Table III).

Table III. Products Molar Yields[a] Arising from the Thermolysis of **I** and **II** in Different Solvents.

Trioxane	Solvent	Reaction Products
I	*n*-hexane	Cyclopentanone (5%); 1,3-di-(4-fluorophenyl)-3-cyclopenten-1-ol (18 %) ; 1,4-di-(4-fluorophenyl)-3-cyclopenten-1,2-diol (39 %).
I	methanol	Cyclopentanone (7%); 3-(4-fluorophenyl)-4-(4-fluorobenzoyl)-2-buthenal (6%); 3,5-di-(4-fluorophenyl)-5-methoxy-2-cyclopenten-1-ol (3%); 1,4-di-(4-fluorophenyl)-2-methoxy-3-cyclopenten-1-ol (3%); 1,4-di-(4-fluorophenyl)-3,4-dimethoxy-cyclopentene (2.5%); 1,1-methyl-methoxy-cyclopentane (8%); 4-fluorobenzoic acid (5%)
II	*n*-hexane	Cyclopentanone (6%); 4-(4-fluorobenzoyl)-3-(4-fluorophenyl)-2-hydroxy-3-butenal (13%); 1,3-di-(4-fluorophenyl)-2-cyclo-penten-1,4-diol (10 %).
II	methanol	Cyclopentanone (10%); 4-(4-fluorobenzoyl)-3-(4-fluorophenyl)-2-hydroxy-3-butenal (10%); 2,4-di-(4-fluorophenyl)-5-methyl-4-methoxy-2-cyclopeten-1-ol (3%); 2,4-di-(4-fluorophenyl)-4-methoxy-2-cyclopenten-1-ol (5%); 2,4-(4-fluorophenyl)-4,5-dimethoxy-2-cyclopenten-2-ol (3%); 1,1-methyl-methoxy-cyclopentane (10%); 1,3-di-(4-fluorophenyl)-5-methyl-2-cyclopenten-1,4-diol (2%).

Note: [a] expressed in parenthesis as % of total GC-MS peak areas (MSD in TIC mode) of all products observed.

However, the decomposition of **I** differs from the reaction of **II** in some aspects. Not only is the kinetic solvent effect on the unimolecular homolysis quantitatively different, but the main products of the whole reactions are different too. In both solvents the trioxanes investigated furnished cyclopentanone in nearly molar yields (Table III), providing good evidence for the scission of the postulated initial diradical (eq. 1). Thus, the thermolyses of molecules **I** and **II** are similarly governed by the extrusion of stable fragments as cyclopentanone and other methoxy-substituted products, these evidently coming in the case of methanol solution, from the reaction of intermediate species with the molecules of the solvent (Table III).

Conclusions

Analysis of the kinetics and product distributions for the thermolysis of trioxanes **I** and **II** support the hypothesis of a solvent effect on the initial homolytic rupture of their O-O peroxydic bonds, which constitutes the rate determining step of both reactions. Substituent effects appear to have little influence on the decomposition kinetics. Furthermore, the present results parallel those obtained for the thermolysis of substituted 1,2,4,5-tetroxanes in solution [1], which also decompose by an unimolecular homolysis in a step-wise mechanism of reaction.

Experimental

General

The trioxanes *cis*-6-(4-fluorophenyl)-5,6-[2-(4-fluorophenyl)-propylidene]-3,3-tetramethylene-1,2,4-trioxacyclohexane (**I**) and *cis*-6-(4-fluorophenyl)-5,6-[2-(4-fluorophenyl)-3-hydroxy-propylidene]-3,3-tetramethylene-1,2,4-trioxacyclohexane (**II**) were obtained by methods mentioned elsewhere [13]. The purity of these substances was checked by appropriate RP-HPLC methods already reported [14]. The methanol and *n*-hexane employed were commercial analytical reagents purified by standard techniques [15] and further distillation from saturated solutions of ethylenediamine tetraacetic acid (EDTA). This treatment was carried out to remove traces of metallic ions, which might accelerate the thermolyses according to a previous report [2] for other cyclic peroxide reactions.

Kinetics and analytical methods

Pyrex glass tubes (6 cm length, 6 mm o.d., and *ca.* 1 mm wall thickness) half filled (*ca.* 0.4 mL) with the corresponding cyclic peroxide solutions, were thoroughly degassed under vacuum at 83 K and then sealed with a flame torch. To perform the kinetic runs the ampoules were immersed in a thermostated silicone oil bath (± 0.1 K) and withdrawn after selected times, stopping the reactions by cooling to 273 K. For monitoring the concentrations of the remaining 1,2,4-trioxanes in the solutions, as well as the organic reaction products, a RP-HPLC technique of analysis was employed [14] using a Pharmacia LKB instrument with a Spherisorb SuperPack RP-C18 column (ODS, 2.5 μm, 4.0 mm i.d., 100 mm length) at room temperature. In the present work mixtures of methanol 85%-water (v/v) were employed as mobile phases at 0.5 mL/min flow-rate (inlet pressure *ca* 9.0 mPa) for the analysis of the products of I reactions and methanol 75 %-water (v/v) for the analysis of II reactions, respectively.

Samples (20 μL) or the standards dissolved in the same mixture of solvents were injected, using UV detection at 254 nm wavelength, for both monitoring the peak areas of **I** and **II**. The identification of the products of the thermolyses was performed by GC-MS analyses in a 5890 model, Series II Plus, Hewlett-Packard instrument, with helium as carrier gas, conveniently coupled to a 5972 A model, Hewlett-Packard MSD at 179 ºC, using a HP5 (cross-linked 5% phenyl methylsilicone) capillary silica

fused column (30 m length, 0.25 mm i.d., 0.25 μm film thickness) programmed at 10°C/min rate from 50°C to 200 °C with the injector port temperature at 120°C (split mode).

The first-order rate constants values for the thermolysis of **I** and **II** were calculated by a least means square data treatment by plotting ln [trioxane concentration] *vs.* reaction time. The corresponding correlation factors obtained (r > 0.9950) were satisfactory considering the several experimental steps involved to get the final analytical data. The activation parameters values for the unimolecular reactions investigated were obtained applying the Eyring equation (k = k_B T / h exp (-ΔH$^{\#}$ / RT) exp (ΔS$^{\#}$ / R), where (k_B /h) = 2.084 x 10^{10} degree^{-1} s^{-1} and R = 1.986 cal mol^{-1} K^{-1}. Error limits were determined by a computational treatment of the data and using a reliable literature method [16].

References

1. Cafferata, L. F. R.; Furlong, J. J. "Thermolysis of Tetroxanes", in *Advances in Oxygenated Processes*, Baumstark, A. L.; Ed.; JAI Press Inc.: USA, **1995**; Volume IV, 81-105.

2. Cafferata, L. F. R.; Nojima**,** M.; Yamakoshi, H. Kinetics and Mechanism of the Thermal Decomposition Reaction of Dyhydro-3,6-Diphenyl-5-Benzyl-1,2,4,5-Trioxazine. *Int. J. Chem. Kin.* **1995**, *28*, 21-25.

3. Jefford, C. W.; Rossier, J. C.; Boukouvalas; J. C. *J. Chem. Soc., Chem. Commun.*, **1987**, 713-716.

4. Cafferata, L. F. R.; Mirífico, M. V. Efectos de Solventes en la Cinética de la Descomposición Unimolecular del Peróxido de Benzoílo, *An. Asoc. Quím. Argentina,* **1982**, *70***,** 29-42.

5. Cafferata, L. F. R.; Quintáns, M. T. *An. Asoc. Quím. Argentina,* **1987**, *75***,** 461-474.

6. Cafferata, L. F. R.; Eyler, G. N.; Svartman, E. L.; Cañizo, A.; Alvarez, E. Solvent effects in the Thermal Decomposition Reactions of Cyclic Ketone Diperoxides, *J. Org. Chem.*, **1991**, *56*, 411-414.

7. Eyler, G. N.; Cañizo, A.; Alvarez, E.; Mateo, C.; Cafferata, L. F. R. Induced Decomposition Reaction in Solution of Acetone Derived Cyclic Peroxides, *Afinidad*, **2002**, *59* (502), 684-687.

8. Leiva, L.; Castellanos, M. G.; Gómez Vara, M.; Cafferata' L. F. R. Thermolysis of Benzaldehyde and Acetone Cyclic Diperoxide in Tetrahydrofurane Solution, *Afinidad*, **2002**, *59* (502), 676-683.

9. Allegretti, P.; Rimada, R. S.; Furlong, J. J.; Cafferata, L. F. R. Mass Spectrometric Evidence for the Reaction Mechanism of Thermolysis of 1,2,4-trioxanes in Solution, *Asian J. Spectrosc.,* **1998,** *2*, 165-172.

10. Cafferata, L. F. R.; Jefford, C. W.; Rimada, R. S. Kinetics and Mechanism of Thermolysis of Fluorine Substituted 1,2,4-trioxanes in Methanol Solution, *Int. J. Chem. Kin.,* **2000**, *32*, 523-528.

11. Cafferata, L. F. R.; Jefford, C. W.; Rimada, R. S. Kinetics and Mechanism of Thermolysis of 1,2,4-trioxanes in *n*-hexane Solution, *Afinidad,* **2002**, *59* (502), 670-675.

12. Cafferata, L. F. R.; Jefford, C. W. Solvent and Substituent Effects on the Kinetics of Thermolysis of *cis*-fused 1,2,4-Trioxanes, *Molecules*, **2001**, *6*, 699-709.

13. Jefford, C. W.; Kohmoto, S.; Joggi, D.; Rossier, J. C.; Timarí, G.; Ruday, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Bernardinelli, G.; Canfield, C.; Fleck, B. I.; Robinson, R.;

Peters, W. Synthesis, Structure and Antimalarial Activity of Some Enantiomerically Pure *cis*-fused Cyclopentene-1,2,4-trioxanes. *Helv., Chim. Acta,* **1995**, *78*, 647-655.

14. Cafferata, L. F. R.; Rimada, R. S.; Furlong, J. J.; Allegretti, P. RP-HPLC and GC-MS Techniques for the Quantitative Analysis of Substituted 1,2,4-trioxanes and their Thermolysis Products in Solution, *J. High Resol. Chrom.*, **1999**, *22*, 67-70.

15. Bunnet. J. "Investigation of Rates and Mechanism of Reaction", in *Techniques of Chemistry*, Weissberger, A., Ed.; Wiley: New York, **1974**; Part I, Vol. VI, Chapter VIII.

16. Huyberechts, S.; Halleux, A.; Kruys, P. Une Aplication de Calcule Statistique a la Cinetique Chimique, *Bull. Chim. Belg..* **1955**, *64*, 203-209.

Sample availability: Samples of compounds **I** and **II** are available from the authors.