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Solvent and Substituent Effects on the Kinetics of Thermolysis of *cis*-Fused 1,2,4-Trioxanes

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Abstract: The kinetics of the thermal decomposition reaction of *cis*-6-phenyl-5,6-(2-phenylpropyliden)-3,3-pentamethylene-1,2,4-trioxacyclohexane (**Ia**) were investigated in benzene and methanol solutions in the temperature and concentration ranges of 353.3 – 413.2 K and $(1.1 - 13.1) \times 10^{-3}$ M, respectively. First-order rate constant values were obtained for up to at least ca. 20% conversions of that cyclic peroxide. The activation parameter values for the initial unimolecular homolysis of that molecule, results supported by the effect of the addition of di-*tert*-butyl-*p*-cresol as a free radical scavenger, indicate a stepwise reaction mechanism which is in keeping with the reaction products analysis. The corresponding activation parameters for the reaction of **Ia** in methanol ($\Delta H^\ddagger = 20.2 \pm 0.6$ kcal mol⁻¹; $\Delta S^\ddagger = 0.1 \pm 1.6$ cal mol⁻¹ K⁻¹; $\Delta G^\ddagger = 20.2 \pm 0.6$ kcal mol⁻¹) and in benzene ($\Delta H^\ddagger = 15.4 \pm 0.2$ kcal mol⁻¹; $\Delta S^\ddagger = -13.2 \pm 0.5$ cal mol⁻¹ K⁻¹; $\Delta G^\ddagger = 20.5 \pm 0.2$ kcal mol⁻¹) solutions are compared with values obtained for *cis*-6-phenyl-5,6-(2-phenylpropyliden)-3,3-tetramethylene-1,2,4-trioxacyclohexane (**Ib**) thermolysis in the same solvents. The thermolysis kinetics of **Ia** are less sensitive to solvent changes compared to the behaviour already reported for the analogous reactions of **Ib**. Because both molecules in solution are flexible structures due to their configurations, the

relatively small solvent effect found on the former trioxane reaction is attributed to the extent of the chain of methylene groups attached on C-3 of the corresponding molecular rings. Furthermore, the pertinent substituent effect on the peroxidic bond strength of those molecules in solution was evaluated.

Keywords: *cis*-Substituted 1,2,4-trioxanes; Kinetics; Stepwise Reaction Mechanism; Solvent and Substituent Effects

Introduction

Cyclic peroxides such as the substituted 1,2,4,5-tetroxanes undergo thermolysis, both in the gas [1] and solution phase [2] by a stepwise mechanism, where the activation parameters values of the initial unimolecular homolysis fall within a limited range, although significant steric [3] and solvent effects [4] have also been observed. Moreover, the experimental activation energies for their thermolyses are usually in good agreement with calculated values based on a peroxidic bond homolysis of the corresponding molecular rings [5]. The first step in the mechanism of thermolysis of *cis*-fused 1,2,4-trioxanes seems to be the rupture of their molecular peroxidic bond [6] with looser transition states. Because the *cis*-6-phenyl-5,6-(2-phenylpropyliden)-3,3-pentamethylene-1,2,4-trioxacyclohexane (**Ia**) and the *cis*-6-phenyl-5,6-(2-phenylpropyliden)-3,3-tetramethylene-1,2,4-trioxacyclohexane (**Ib**) molecules (Scheme 1) have different cyclic atomic groups on the corresponding C-3 atoms it is relevant to report the activation parameters for both thermolyses and also to compare the effects of the reaction solvents.

Scheme 1

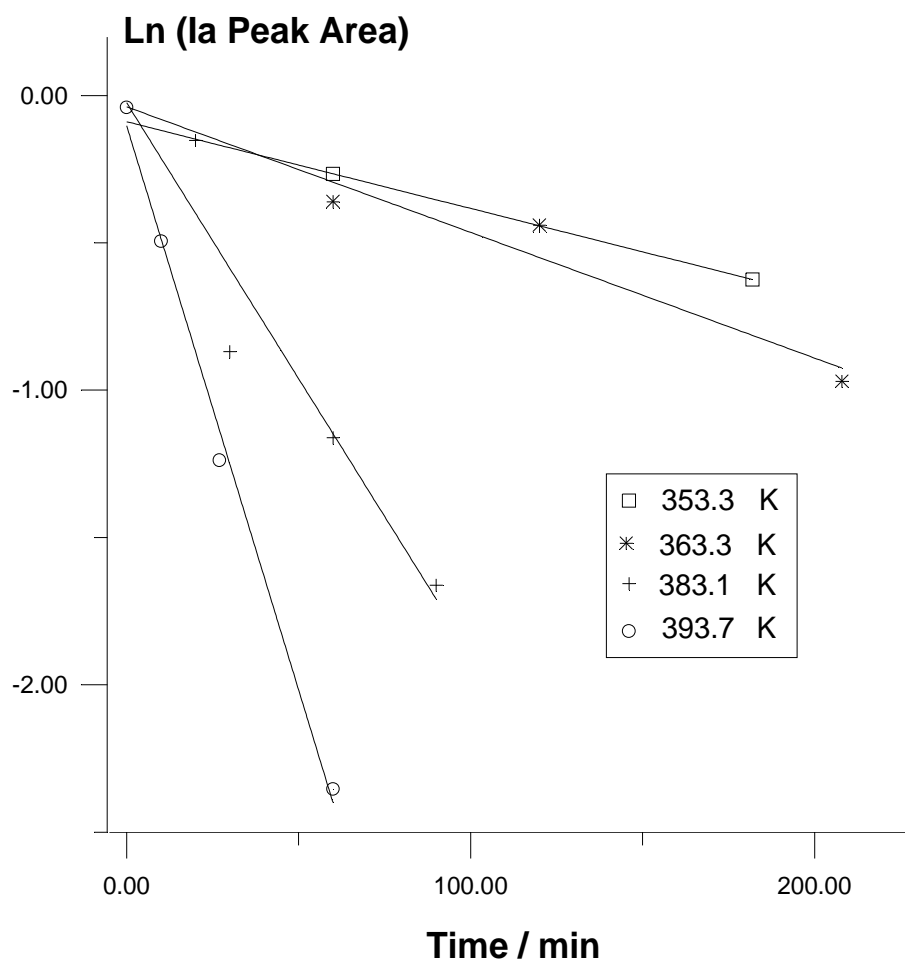


Consequently the decomposition reactions of **Ia** in methanol and benzene solutions have now been investigated to learn about on the thermal stability in solution of this cyclic peroxide, which is related to the chemotherapy with *Qinghaosu* and other synthetic drugs of the same type.

Results and discussion

Rate measurements of the thermal decomposition reactions of **Ia** in benzene and in methanol solutions indicate that at each temperature the thermolyses follow first-order kinetic laws up to at least ca. 20% conversions (Figure1).

Figure 1. Representation through First-order Kinetic Plots of the Data of Typical Runs of **Ia** Thermolysis in Methanol Solutions at Different Temperatures.



Moreover, many runs, including those without a previous Na₂EDTA treatment of the methanol solvent, showed that type of behaviour for higher conversions of the trioxane. In the thermolysis

kinetics of substituted 1,2,4,5-tetroxanes the observed rate constant values show significant increases with the initial concentrations in the solutions [2]. This seems to be a general behaviour in the thermolysis of cyclic peroxides because of bimolecular induced decomposition processes. However, this is not the case for reactions of **Ia**, probably due to the rather low initial concentrations used (Table I).

Table I. First-Order Rate Constant Values for the Thermal Decomposition Reactions of **Ia** in Solution.

Temp (K)	Reaction solvent	$10^3 \cdot [\text{Trioxane}]^a$ (moles.dm ⁻³)	$10^6 \cdot k_{\text{obs}} \text{ s}^{-1}$
353.3	methanol	1.1	4.5±0.2
353.3	methanol ^b	1.1	2.0±0.1
353.3	methanol ^b	1.1	2.5±0.1
353.3	benzene	13.1	4.6±0.3
363.3	methanol	4.8 ^c	10.4±0.5
363.3	methanol ^b	1.1	7.8±0.4
363.3	benzene	4.8 ^c	6.9±0.3
363.3	benzene ^b	12.4	5.4±0.3
375.9	benzene	13.1	11.5±0.6
375.9	benzene ^b	13.1	10.2±0.5
383.1	methanol	4.8 ^c	26.6±1.1
383.1	methanol ^b	4.8 ^c	24.1±1.0
393.7	methanol	1.1	44.8±2.0
393.7	methanol ^b	1.1	50.5±2.0
393.7	benzene	13.1	25.6±1.1
393.7	benzene	13.1	28.6±1.0
413.2	methanol	1.1	114±5.0
413.2	benzene	1.1	69.6±2.1
413.2	benzene ^b	13.1	77.7±3.1

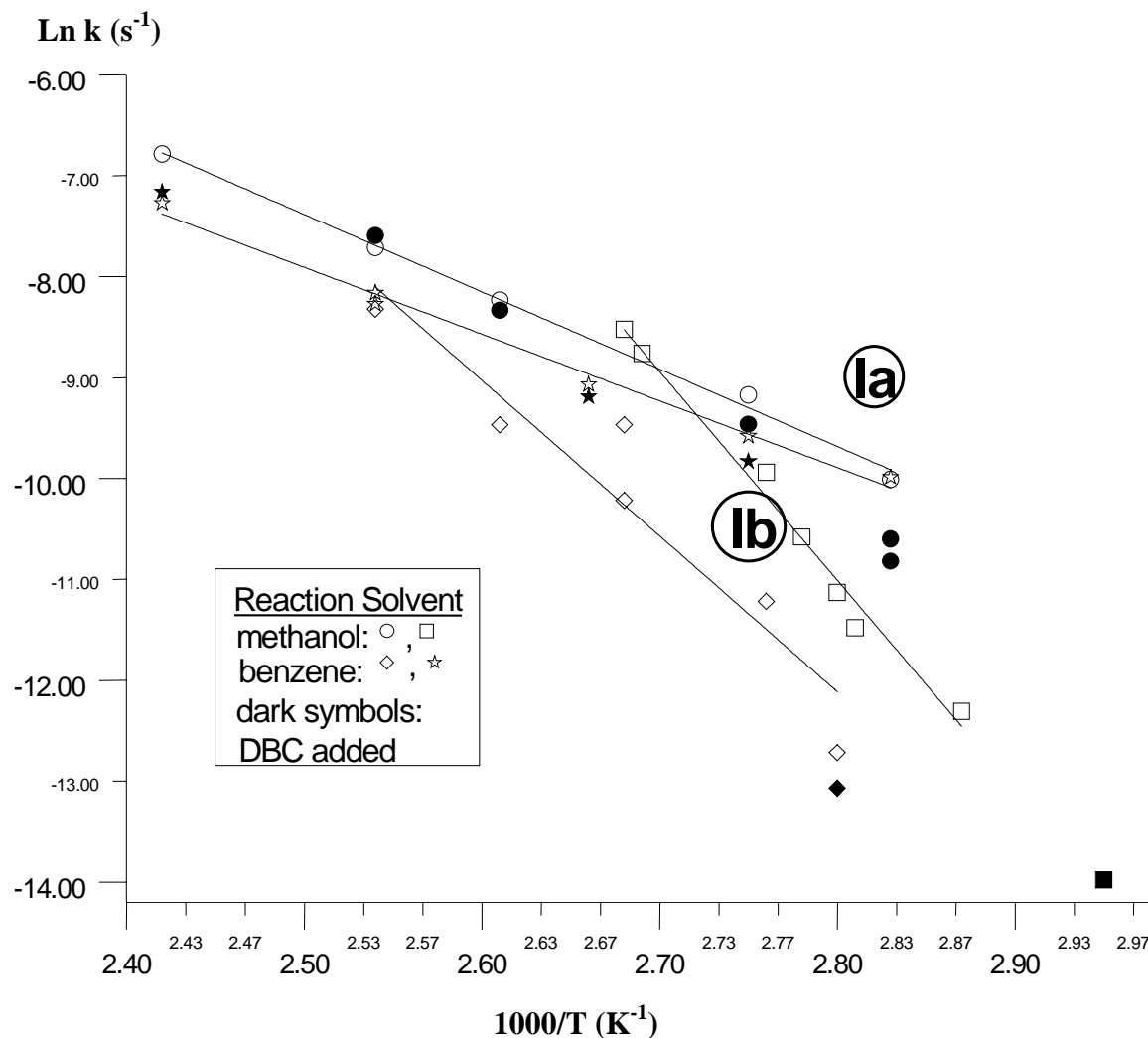
Notes: ^a trioxane initial concentrations; ^b 2,6-di-*tert*-butyl-*p*-cresol added (0.02 M);

^c maximum allowable concentration in methanol solution at 298 K.

Nevertheless, a kinetic solvent effect on **Ia** thermolysis is evident (Table I) as the reaction rates are significantly faster in methanol than in benzene. Under comparable experimental conditions, the rate constant values turn to be ca. 1.6 times greater in methanol, except at the lowest temperature where they are very similar. Besides, the kinetics of **Ia** thermolysis in the temperature range investigated and

in the same solvent turn out to be faster (Figure 2) compared with the corresponding **Ib** reaction [6]. Furthermore, in general the experiments performed in the solvents with added DBC show k_{obs} values similar to those found without that scavenger. However, it is apparent in both solvents at the lower experimental temperatures a kinetic lowering effect of the added cresol, probably related to the change of the physicochemical properties (e.g. polarity) of the reaction solvents.

Figure 2. Arrhenius Equation Plots for the Thermolysis of Trioxanes **Ia** and **Ib** in Solution.



The temperature effects on **Ia** thermolyses in methanol and in benzene solutions, evaluated through the Arrhenius equation method, show plots (Figure 2) which are linear (Table II) over relatively large temperature intervals (> 55 K). This supports the fact that the corresponding activation parameters for **Ia** (Table II) and **Ib** thermolyses belong to simple processes.

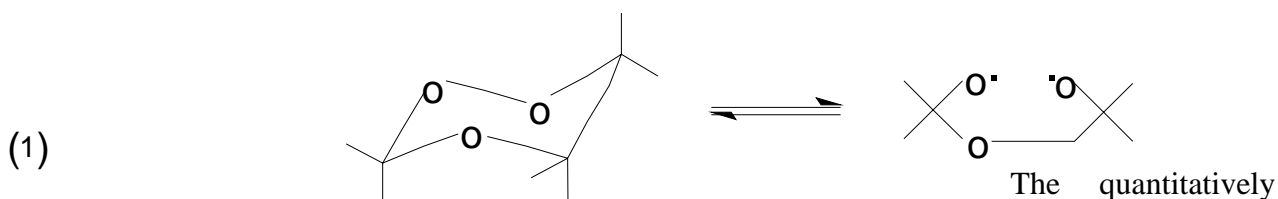
Table II. Activation Parameters^a for the Unimolecular Thermolysis in Solution of Substituted 1,2,4-trioxanes.

Trioxane	Reaction Solvent	ΔH^\ddagger kcal mol ⁻¹	ΔS^\ddagger cal mol ⁻¹ K ⁻¹	ΔG^\ddagger kcal mol ⁻¹	r ^b	Reference
Ia	methanol	20.2 ± 0.6	0.1 ± 1.6	20.2 ± 0.6	0.9902	this work
Ia	benzene	15.4 ± 0.2	-13.2 ± 0.5	20.5 ± 0.2	0.9992	this work
Ib	methanol	39.6 ± 0.6	30.2 ± 1.6	28.8 ± 0.7	0.9961	[6]
Ib	benzene	30.9 ± 1.7	3.8 ± 4.3	29.5 ± 1.7	0.9479	[6]

Notes: ^a values calculated at 383.2 K by the Eyring equation method and error limits obtained as in ref. [7]; ^b correlation coefficient values in the corresponding Eyring equation plots.

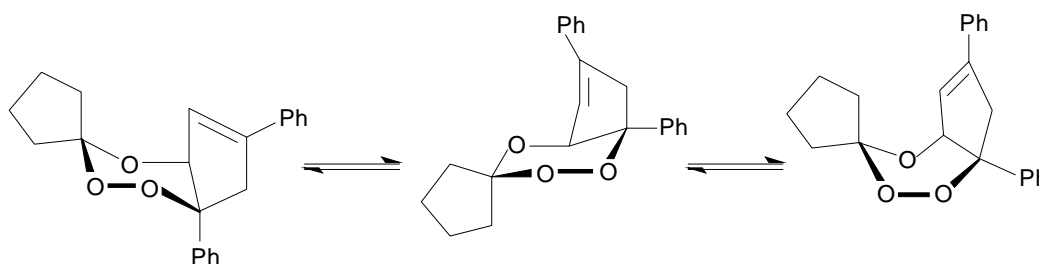
It is not likely that both the unimolecular homolytic reaction and the alternative concerted process (in that case corresponding to a pericyclic reaction) for the thermal decomposition of **Ia** have identical activation parameters. Moreover, if the thermolyses were of the latter type, where the bond breaking at the transition state is partly compensated by bond making, the experimentally found activation entropies would turn to very negative values. Hence, the experimental activation parameters for the decomposition reactions of **Ia** in methanol and benzene solutions (Table II) correspond to their unimolecular homolysis because alternative reaction pathways can not be reasonably postulated.

The very similar values of ΔG^\ddagger for both trioxane's reactions (Table II) support an analogous type of interactions between substrate and the solvent molecules in each unimolecular thermolysis. This means that the corresponding activation enthalpies of the reactions are almost compensated by the entropies of activation, yielding practically constant free energies of activation for each trioxane. The passage of the **Ia** initial stage in solution to the corresponding diradical transition state would engender many degrees of freedom. Moreover, the reaction transition state in methanol would have relatively more degree of freedom reflected in the observed ΔS^\ddagger value (Table II) than those achieved in the hydrocarbon solvent. Although it is accepted that activation enthalpies near 33 kcal mol⁻¹ correspond to peroxidic ruptures in most organic molecules [8] the rather low values found (Table II) for **Ia** thermolysis can be ascribed to its particular kinetic behaviour in the solvents investigated. Thus, the first step in the rupture of the peroxidic ring in the **Ia** thermolysis would be the unimolecular homolysis to give the corresponding diradical which undergoes subsequently further decompositions to yield the observed reaction products (Equation 1).



different solvent effects noted for **Ia** and **Ib** homolysis (Figure 2) may be ascribed to the structures, conformations and reaction environments of those cyclic peroxide molecules. Although in the *cis*-fused bicyclic trioxanes considered both the α and β faces of the corresponding molecules should be equally accessible, the solvation of the transition state arising from **Ia** seems to be less effective due to the more bulky substituent on C-3. Referring to that it is worth noting that the *cis*-fused bicyclic rings of the analogous **Ib** molecule (Scheme 2) would invert rapidly between chair and non-chair conformations allowing relatively more easy its interaction with the reaction solvent.

Scheme 2. Inversion of Chair and Boat-like Conformers of the **Ib** Molecule



Similar solvent effects have been shown to operate for other cyclic peroxides of the substituted 1,2,4,5-tetroxane family [4]. The decomposition of **Ia** differs from the reaction of **Ib** in some aspects. Not only are the solvent effects quantitatively different but the main products are different too (Table III).

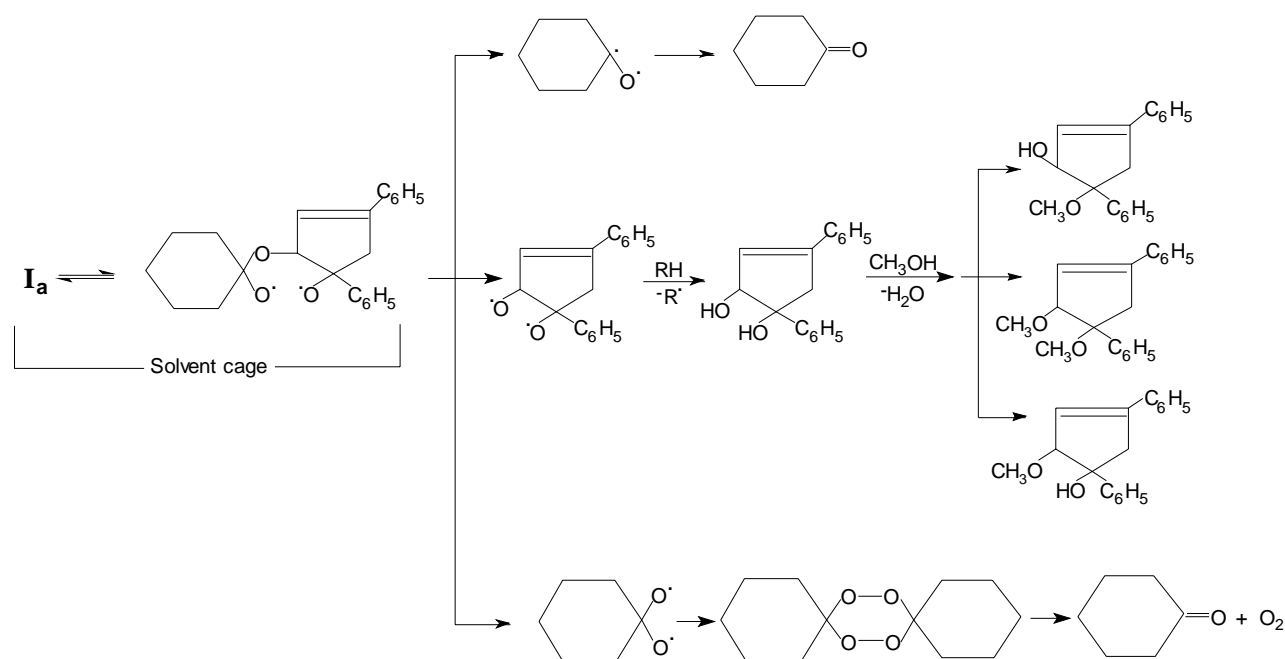
Table III. Products Arising from the Thermolyses^a of **Ia** and **Ib** in Different Solvents

Trioxane ^b	Solvent	Reaction Products ^c	References
Ia (0.013)	benzene	cyclohexanone (68 %), 1,4-diphenyl-3,4-cyclopentenediol (3 %), cyclohexanone diperoxide (10 %) ^d .	This work
Ia (0.001)	methanol	cyclohexanone (63 %), 1,4-diphenyl-3,4-cyclopentenediol (6 %), 1,4-diphenyl-3,4-dimethoxycyclopentene (0.5%), 1,4-diphenyl-3-methoxy-cyclopentene-4-ol (1 %), cyclohexanone diperoxide (2 %) ^d .	This work
Ib (0.003)	benzene	cyclopentanone (70 %), 1,4-diphenyl-3,4-cyclopentenediol (8 %), cyclopentanone diperoxide (9 %) ^d .	[9]
Ib (0.002)	methanol	cyclopentanone (60 %), 1,4-diphenyl-3,4-cyclopentenediol (7 %), cyclopentanone diperoxide (9 %) ^d .	[9]

Notes: ^a At 413.2 K; ^b trioxane initial molar concentrations; ^c yields expressed as % of total GC-MS peak areas (MSD in TIC mode) of all products observed; ^d See text.

However, in methanol or benzene solutions both trioxanes furnish the corresponding ketones in nearly the same molar yields (Table III), providing good evidence for the scission of the initial diradical (Equation 1). Then, the second step of **Ia** and **Ib** thermolysis is similarly governed by the extrusion of stable fragments. Loss of ketone is also the main event in the thermal decomposition of related *cis*-fused bicyclic 1,2,4-trioxanes in the solid state [10]. Yet another similarity is seen for the thermolysis of both trioxanes: the formation of the diperoxide of the cyclic ketone. That diperoxide formation might be rationalised by recombination in the solvent cage of the corresponding 1,3-dioxy-diradical (Scheme 3). In the **Ia** thermal decomposition in methanol solution the cyclohexanone, the methoxy-substituted 1,4-diphenyl-cyclopentenyl derivatives and the 3,6-bis-pentamethylene-1,2,4,5-tetroxacyclohexane (cyclohexanone diperoxide) observed support the following reaction pathways (Scheme 3).

Scheme 3. Reaction Pathways for the Initial Diradical Decomposition of **Ia**
Thermolysis at 413.2 K of in Methanol Solution.



Clearly an alternative avenue in both trioxanes reactions is competing with a non-radical elimination of the corresponding ketone, but this can be discarded considering the kinetic parameter values and the other products of their decompositions (Table III). Then, in both solvents the initial diradical (Equation 1) would break down into a 1,3-dioxy-diradical and cyclopentenyl-diphenyl-substituted diradicals. The former may originate the corresponding ketones by hydrogen abstraction from the methanol solvent molecules or other sources of hydrogen atoms, through a thermally labile gem-diol intermediate. On the other hand, the 3,4-dihydroxy-diphenyl substituted derivative must necessarily arise from a competitive C-O bond rupture in the initially formed diradical (Equation 1).

That hydroxylated product, evidently coming from the remainder of the trioxane molecules, would react further with methanol molecules yielding the secondary methoxy-substituted compounds only observed in this solvent. It is also evident that during the thermolyses of each trioxane the cyclohexanone or cyclopentanone diperoxides [9] gradually decompose, most probably yielding additional ketone. For both trioxane reactions the overall mass balance (Table III) may indicate further thermal decompositions of the final reaction products with probably some loss of volatile substances during the analytical procedures employed.

Conclusions

On the whole, the low values of the observed rate constant values for **Ia** thermolysis confirm the stability of the *cis*-fused 1,2,4-trioxanes. Moreover, the decomposition products, especially those formed in methanol solution, are typical of those originating from stepwise radical processes. The diradical initially released upon thermolysis of **Ia/Ib** is not trapped by DBC addition to the solutions. Furthermore, although the *cis*-fused bicyclic skeleton of **Ia** and **Ib** exposes both sides of the peroxidic bond, a less marked solvent effect is observed for the former reaction owing to greater shielding of that bond by the C-3 substituent atomic group. The present results parallel those obtained for the thermolysis of substituted 1,2,4,5-tetroxanes which also decompose by unimolecular homolysis of the O-O bond in a stepwise mechanism. Furthermore, the diradical initiated mechanisms of thermolyses in the two solvents investigated, which are also supported by the analysis of the reactions products, are in keeping with those advanced for other *cis*-fused bicyclic 1,2,4-trioxanes both in the solid state [10] and in solution [11].

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Experimental

Materials

cis-6-Phenyl-5,6-(2-phenylpropyliden)-3,3-pentamethylene-1,2,4-trioxacyclohexane (**Ia**) was obtained by a method described elsewhere [12]. The organic solvents employed in the kinetic runs were commercial analytical grade reagents purified by standard techniques and further distilled from saturated solutions of the sodium salt of ethylenediaminetetracetic acid (Na₂EDTA). This preventive treatment allowed removing traces of metallic ions that might otherwise accelerate the thermolyses.

Analytical reagent grade (Fluka) di-*tert*-butyl-*p*-cresol (DBC) was employed as a free radical scavenger.

Kinetics and analytical methods

Pyrex glass tubes (6 cm long x 6 mm o.d. x ca. 1 mm wall thickness), half filled (ca. 0.4 mL) with solutions of **Ia** were thoroughly degassed under vacuum at 83 K and then sealed with a flame torch. To perform the kinetics runs these ampoules were immersed in a thermostated silicone oil bath (± 0.1 K), then withdrawn after selected times and the reactions stopped by cooling to 273 K. Monitoring of the concentrations of the trioxane remaining in solution, as well as the organic reaction products, was performed by GC analysis in a HP 5890, series II Plus instrument, using a megabore AT1 (Alltech Assoc., Inc.) silica fused column impregnated with polydimethylsiloxane (12 m length, 0.53 mm i.d., 1.2 μm film thickness), programmed from 130° C (2 min) to 200° C (30 min) at a rate of 20° C/min with the injector port temperature at 180° C; 4 μL of the solutions were injected using a 7:1 split ratio and nitrogen carrier gas with FID detection (280° C). For the measurement of the concentrations of **Ia** in the solutions, a chromatographic peak area normalisation method was employed with a setting of 2000 in the HP 3395 model recording integrator area rejection. The corresponding first-order rate constant values (k_{obs}) for **Ia** thermolysis were worked-out by a least mean squares data treatment plotting Ln of the trioxane peak areas data vs. the reaction time (Figure 1). It is worth noting that preliminary experiments performed in the reaction solvents without the Na₂EDTA treatment showed anomalously high rate constant values and with poor reproducibility in general. Although it is recognized that simple distillation of the reaction solvents from Na₂EDTA does not necessarily remove all kinds of metal ions, the kinetic data here is considered to be sufficiently reliable, based, first, on their reproducibility (e.g. see error limits in the rate constant values of Table I) and, second, because there is no evidence of products resulting from scission of the cyclohexane or cyclopentane rings of the trioxanes considered in the product analysis. The activation parameters were obtained by application of the Eyring equation method to the k_{obs} values and the corresponding error limits worked out from a computational least means square data treatment considering a literature method [7].

Product analysis

Solutions of trioxane **Ia** in benzene (0.013 M) and in methanol (0.001 M) were decomposed in sealed ampoules for ca. 2 h at 413.2 K. Identification of the main GC peaks in the corresponding analyses was performed by comparison of retention time values with those of authentic samples: **Ia** (ca. 12.1 min); 3,6-bis-pentamethylene-1,2,4,5-tetroxacyclohexane ‘cyclohexanone diperoxide’ (ca. 10.0 min); cyclohexanone, (ca. 0.8 min). For the identification of some of the other peaks, a HP model 5972A quadrupolar MSD was interfaced to the chromatograph using a similar oven temperature program on a HP5 capillary quartz fused bonded phase 5% phenylmethylsilicone column. In some

cases both mass spectral data and GC retention times evaluations were necessary to identify the unknown reaction products.

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Sample availability: Samples of compounds **Ia** and **Ib** are available from the authors