KINETICS OF THE THERMAL DECOMPOSITION OF SUBSTITUTED CYCLIC ORGANIC PEROXIDES IN TOLUENE SOLUTION: SUBSTITUENT EFFECTS ON THE REACTION RATES AND THE ACTIVATION PARAMETERS OF THE UNIMOLECULAR REACTIONS

Adriana I. Cañizo,[*] Gladys N. Eyler, Carmen M. Mateo, Elida E. Alvarez, and Rosa K. Nesprías

Department of Chemistry Engineering, Engineering Faculty, National University of the Center of Buenos Aires Province, del Valle Avenue Nº 5737 (B7400JWI) Olavarria, Buenos Aires, Argentine

Abstract - Thermal decomposition reactions of substituted cyclic organic di- and triperoxides have been carried out in toluene solution in order to investigate substituent effects on homolytic scission of the O-O bond in those compounds. A comparative analysis of the reactivities at 145 ℃ and the activation parameters for unimolecular reactions of molecules of this type were interpreted in terms of substituent effects and ring size. An isokinetic relationship was established to validate the existence of a genuine substituent effect for the unimolecular homolysis reaction of the substances considered. Cyclic organic peroxides of very high reactivity and sterically hindered deviated from correlation's. It appears to be possible to determine whether a peroxy group is part of a six or nine membered ring on the basis of the activation parameters values.
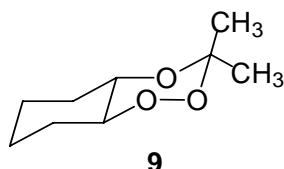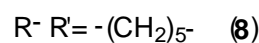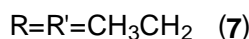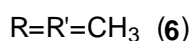
INTRODUCTION

Organic peroxides have reached a great importance through the years because of the unusual reactivity of the O-O bond linkage whose decomposition in free radicals make them applicable in polymerization, essential operation in the synthetic polymer fabrication. Actually, the effects of the nature of some cyclic organic peroxides (COPs) are being evaluated[1] as initiators in polymerization of styrene because using these compounds it is possible to produce polymers with high molecular weights and narrow

---
• To whom correspondence should be adressed. Tel: 54-2284-451055/056. Fax:54-2284-450628. E-mail: acanizo@fio.unicen.edu.ar

polydispersities at high reaction rates. The COPs used as polyfunctional initiator can be added to the reaction system in solid state (bulk polymerization) or in solution (styrene/organic solvent, 1:1, V/V), being toluene, chlorobenzene[1b] or ethylbenzene the organic solvent commonly employed.

On the other hand, the importance of synthetic 1,2,4-trioxanes has grown considerably in recent years[2,3] and some of its derivatives achieved prominence as potent antimalarial agents. Thus, the 1,2,4-trioxane heterocycle has been identified as the critical pharmacophore in antimalarial activity. Other authors,[4] confirm in vitro activity against *Plasmodium falciparum* of dispiro-1,2,4,5-tetroxanes as a new class of peroxide antimalarial drugs.
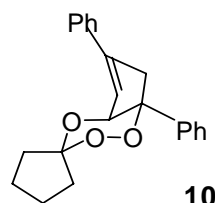
In previous works kinetic data[5-11] and solvent effect[5,6,8,10] analysis of the thermal decomposition reactions of cyclic peroxides of the families of substituted 1,2,4,5-tetroxanes,[5-7] 1,2,4-trioxanes[8] and 1,2,4,5,7,8-hexaoxacyclononanes[6,9-11] have been evaluated. An evident substituent effect on the O-O homolytic rupture on the thermolysis of 1,2,4,5-tetroxanes was found in benzene solution.[7] In this work, the effects of substituents and of the ring size on the O-O bond homolysis of various cyclic organic peroxides have been investigated. All available kinetic data of the thermal decomposition reaction of a series of substituted COPs (scheme) in toluene solution were shown and correlated.

R=R'=CH₃ **(1)**
R=R'=CH₃(CH₂)₂ **(2)**
R‑R'=‑(CH₂)₅‑ **(3)**
R= CH₃, R'=(CH₃)₃C **(4)**
R=CH₃, R'=C₆H₅ **(5)**

R=R'=CH₃ **(6)**
R=R'=CH₃CH₂ **(7)**
R‑R'=‑(CH₂)₅‑ **(8)**

9
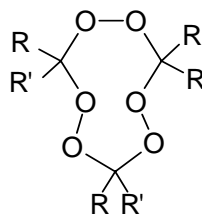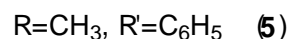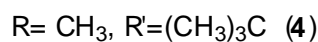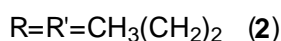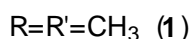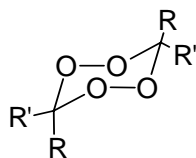
trans-3,3-dimethyl-5,6-tetramethylene-1,2,4-trioxacyclohexane

10

cis-6-phenyl-5,6-(2-phenyl-propylidene)-3,3-tetramethylene-1,2,4-trioxacyclohexane

Scheme

RESULTS AND DISCUSSION

The thermal decomposition reaction of cyclic organic peroxides (**2**, **4**, **5** and **10**) was studied in toluene at the temperature ranges indicated in Table 1 and initial concentrations *ca.* 2 x 10^{-2} M. It was demonstrated that the kinetic behavior of the different systems is according to a first order kinetic law up to at least *ca.* 50 % of COPs conversions, although many runs show that type of behavior for more higher decomposition of peroxides.

Table 1. Pseudo First-Order Rate Constant Values for the Thermal Decomposition Reaction of Different Cyclic Organic Peroxides (COP) in toluene solution.

COP	t (°C)	k_{exp} x 10^5 (s^{-1})	r [a]
2 [b]	130.0	1.16	
	141.4	5.63	
	145.0	5.90	0.998
	151.0	16.8	
	166.0	65.1	
4 [b]	120.0	4.36	
	130.0	12.2	0.994
	140.0	29.6	
	150.0	115	
5 [c]	155.0	0.433	
	165.0	1.32	0.995
	175.0	2.66	
	186.0	5.93	
10 [d]	100.0	1.00	
	110.0	3.17	0.998
	122.0	9.50	
	130.0	26.8	

[a] - Correlation coefficient according to the Arrhenius equation, [b] - Initial concentration (2x10^{-2} M), [c] - Initial concentration (1x10^{-2} M), [d] - Initial concentration (1.5x10^{-2} M).

Experiments carried out with **2**, **4**, **5** and **10** showed that the reaction follows first-order kinetic laws up to at least *ca.* three half lives of COP conversion. It seems that there are no contributions from second-order processes inducing the decomposition at higher conversions. On the other hand, toluene is a well known radical scavenger and its large excess should inhibit radical chains. At the experimental conditions of this work it is possible to assume that induced decomposition pathways in the thermolysis were absent, so the rate constant values (Table 1) could be associated with the cleavage of an O-O bond (the weakest bond) leading to a biradical. Thus, the first step in the thermolysis mechanism of these COPs in solution is initiated by a process of the type represented in equation 1 for a generic molecule of a substituted tetraoxacyclohexane (eq. 1).

(1)
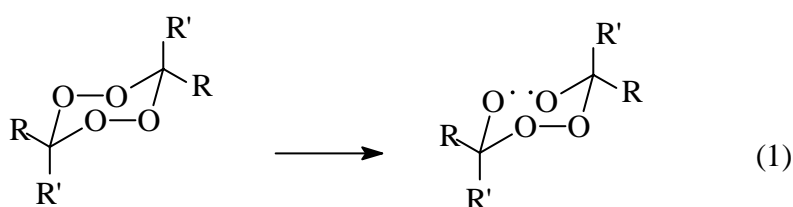
The principal organic product derived from the thermal decomposition of the biradical is the starting ketone (Table 2).

Table 2. Main Products of the Thermal Decomposition of COPs (2, 4 and 5) in Toluene Solution at 150 °C

COP	Product	Yield [a]
2	4-heptanone	0.26
	propane, bibenzyl	[b]
4	3,3-dimethyl-2-butanone	0.28
	methane, bibenzyl, 2-methylpropane	[b]
5	acetophenone	1.2 [c]
	methane, benzene, bibenzyl, benzoic acid	[b]

[a] - Moles of product per mole of COP decomposed, [b] - Qualitative determination,

[c] - yield up to at least 85 % COP 5 conversion

Other products only qualitatively detected are those coming from the reaction between free radicals and the solvent or by radical combination. For example, the presence of methane, propane, 2-metylpropane and benzene can be explained by a hydrogen atom abstraction reaction (eqs. 2-5) between free radicals derived from C-C bond rupture of **2**, **4** or **5**.

$$CH_3^{\bullet} + PhCH_3 \longrightarrow CH_4 + PhCH_2^{\bullet} \qquad\qquad (2)$$

$$CH_3CH_2CH_2^{\bullet} + PhCH_3 \longrightarrow (CH_3)_2CH_2 + PHCH_2^{\bullet} \qquad (3)$$

$$(CH_3)_3C^{\bullet} + PhCH_3 \longrightarrow (CH_3)_3CH + PhCH_2^{\bullet} \qquad (4)$$

$$Ph^{\bullet} + PhCH_3 \longrightarrow PhH + PhCH_2^{\bullet} \qquad\qquad (5)$$
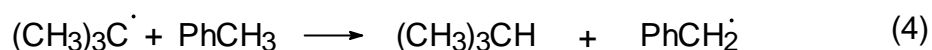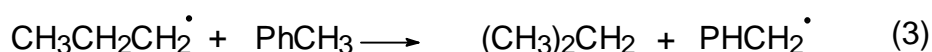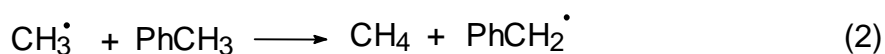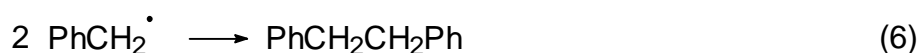
The formation of the other reaction products can be interpreted by coupling of benzyl radicals (eq. 6).

$$2\ PhCH_2^{\bullet} \longrightarrow PhCH_2CH_2Ph \qquad\qquad (6)$$

Probably molecular oxygen and CO_2 are produced in the reaction media caused by C-O and C-C ruptures from the biradical generated in eq. 1, but there are no experimental evidence about their formation.

The effect of the temperature on the k_{exp} values can be evaluated through the linearity of the Arrhenius equations (Table 1) over a relatively large temperature ranges which suggest that the thermal decomposition reaction of **2**, **4**, **5** and **10** belong to a single process, which could be its unimolecular thermal cleavage of the O-O bond as the initial bond breaking step.

The activation enthalpy and entropy values according to Eyring equation and corresponding to the unimolecular thermal decomposition reaction can be compared with already reported data for analogous homolysis of others COPs in toluene (Table 3). It is recognized that rate constant should be determined over a large temperature range for obtaining exact activation parameters (in this work $\Delta t \geq 30\ ^{\circ}C$).   The ranges of $\Delta H^{\#}$ and $\Delta S^{\#}$ values ($\Delta\Delta H^{\#} = 19.3\ kcal\ mol^{-1}$ and $\Delta\Delta S^{\#} = 50.9\ cal\ mol^{-1}K^{-1}$) corresponding to the unimolecular thermal decomposition reaction are large compared to the probable errors of those parameters.

The rate constant values at 145 ºC (Table 3) showed that **1, 5, 6** and **9** are approximately 10-30 times less reactive than **2**, **3** and **7**, where both substituents are alkyl or cycloalkyl groups but not a methyl group. On the other hand, we found that the k_{exp} values of **4** and **10**, where steric hindrance is predominant, actually correspond to the highest values. This is probably due to qualitatively different ground or transition states for their unimolecular reactions. This fact is in line with conclusions of the solvent effect study[13] on the homolytic rupture of **4** where it was demonstrated that changes in the reaction solvent practically do not affect the kinetic parameters obtained in solution.

The linear dependence between activation enthalpy and activation entropy[14] in a series of related reactions is called the "compensation effect". The proportionality constant β represents a temperature (isokinetic temperature) at which all reactions should proceed at the same rate.

$$\Delta H^{\#} = \Delta H^{0} + \beta \, \Delta S^{\#} \qquad (7)$$

Figure 1 shows the relationship according to eq. 7, between the activation entalpies and entropies in the decomposition of cyclic substituted peroxides in toluene.

Table 3. Activation Parameters for the Unimolecular Thermal Decomposition Reaction of COPs and the Corresponding Rate Constant Values at 145 °C in Toluene Solution

COP	Δt, °C	$\Delta H^{\#}$,[a] kcal mol^{-1}	$\Delta S^{\#}$,[a] cal mol^{-1} K^{-1}	$\Delta G^{\#}$,[a] kcal mol^{-1}	$k_{145°C}$ x 10^{-5} s^{-1}	Ref
1	25.0	28.9±0.4	-13.7±1.0	34.6±0.4	0.28	5
2	36.0	39.8 ±1.2	17.0 ±2.9	32.7 ±1.2	5.9	This work
3	16.0	40.0±0.3	16.9±0.8	32.9±0.3	5.5	6
4	30.0	34.6±1.2	8.8±3.0	31.0±1.2	56	This work
5	35.0	32.6 ±1.1	-7.6±2.4	33.0 ±1.1	0.22	This work
6	36.0	41.8±1.6	18.5±3.8	34.1±1.6	0.49	9
7	45.0	48.2±1.7	37.2±4.2	32.5±1.7	6.6	10
8	16.0	46.3±2.9	34.1±6.9	32.0±2.9	14.3	6
9	36.2	34.9±1.0	1.1±1.0	34.4±1.0	0.40 [b]	8
10	30.0	31.2±0.7	1.7±1.9	30.5±0.7	117	This work

[a] - Errors calculated as in reference 12; [b] - k_{exp} value at 147 ºC

Anomalous behavior of peroxides of very high reactivity may lead to error in slope and hence in isokinetic temperature. The linearity of the free-energy relationship (Figure 1, correlation coefficient, r= 0.971; r=0.995, if the activation parameters of COP **4** and **10** are excluded) suggests that, both families of peroxides of six or nine membered ring, decompose by a single interaction mechanism. The values of $\Delta G^{\#}$ within the series are approximately constant in comparison with the variations of $\Delta H^{\#}$ ($\Delta\Delta G^{\#} = 4.1$, or 2.8 kcal mol^{-1} when COPs **4** and **10** are excluded). The "isokinetic temperature" value ($\beta= 358$ K, 85 °C) is near to the lowest experimental temperatures selected to run the kinetic experiments (100.0 °C). With the limited data available here it appears as if each class of cyclic peroxides containing a six or nine membered ring has a characteristic range of O-O activation parameters values. So, triperoxides (**6-8**) (nine membered rings, also called hexaoxacyclononanes) show higher enthalpies and entropies of activation values than those obtained in the thermolysis of diperoxides (**1-5**) and trioxane (**10**) where the O-O bond is part of a six membered ring. This ring size effect is specially marked with cyclic triperoxides (**7**) and (**8**), where the substituents are CH$_3$CH$_2$ - or -(CH$_2$)$_5$-.
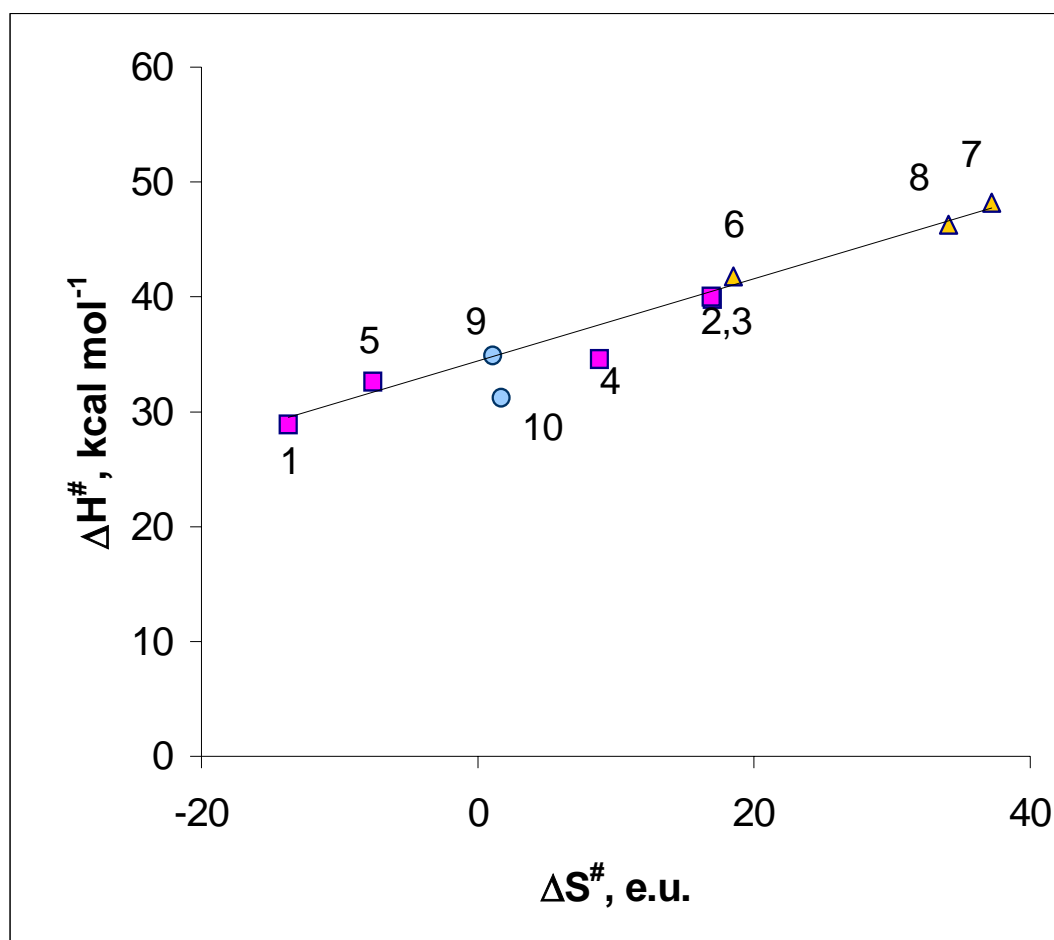

Figure 1: "Isokinetic Relationship" According to Leffler for the Thermal Decomposition Reaction of COPs in Toluene.

The relationship showed in Figure 1 is to be viewed with scepticism as these parameters are mutually interdependent. But existence of Exner[15,16] relationship (Figure 2), who proposed an appropriate statistical technique for finding the isokinetic temperature, confirms the isokinetic relationship.
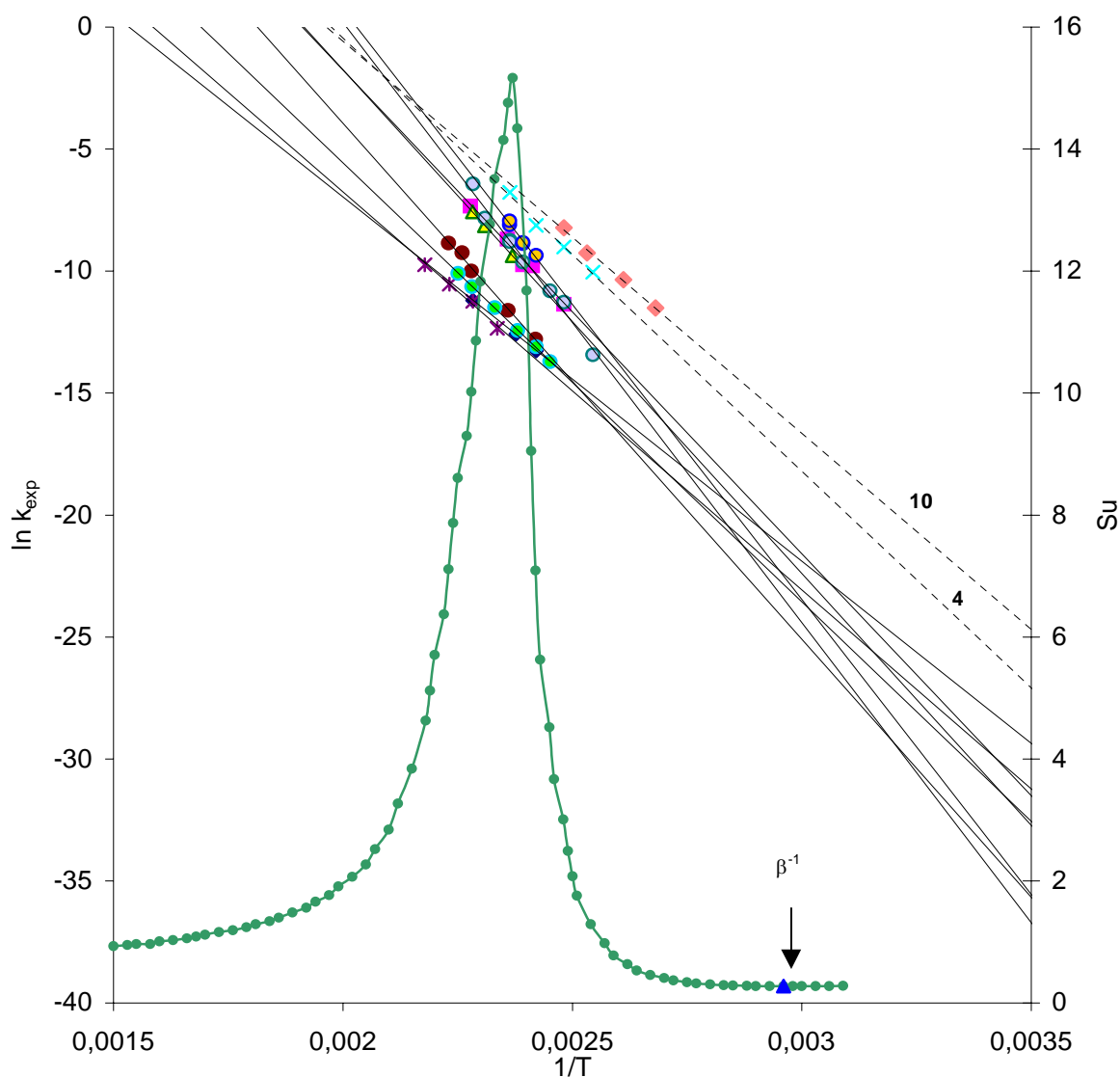

Figure 2: Dependence of the Residual Sum of Squares S_u on the Supposed Isokinetic Temperature β for COPs Unimolecular Thermolysis in Toluene.

When the temperature dependence of the rate constants is represented in the coordinates $x \equiv T^{-1}$ and $y \equiv \ln k_{exp}$, the plot for each reaction must be linear according to the Arrhenius equation. If eq. 7 is valid, all lines intersect in one point, the abscissa of which gives the isokinetic temperature (Figure 2). Thus, to estimate the β values, the residual sum of squares (S_u) are given and β is then defined by the minimum of the S_u when varying the abscissa of the intersection point along the T^{-1} axis.[17] The corresponding

isokinetic temperature determined by this method is 338 K (65 ºC) when COPs (**4**) and (**10**) are excluded. This value is in reasonable agreement with the β value obtained according to eq. 7, taking in consideration that both values are lower than the experimental temperatures. Both graphical treatment support the postulation that some of the reactions considered in this work constitute a genuine isokinetic relationship for the reaction which represent the unimolecular homolysis of COPs (**1**, **2**, **3**, **5**, **6**, **7**, **8**, and **9**). Peroxides (**4**) and (**10**) can be considered to decompose by different interaction mechanism at higher reaction rates. Both molecules experience important steric hindrance in comparison with those COPs where the substituents of the ring are methyl, ethyl or another alkyl or cycloalkyl group.

The ground state steric interactions are not so important to talk about of a substituents effect within the serie of COPs which obey eq. 7, but do become important to evaluate the behavior of COPs (**4**) and (**10**) which can be discarded in both treatments represented in Figures 1 and 2, because these peroxides showed very high reactivity and they are very sterically hindered peroxides.

CONCLUSIONS

- The analysis of the reaction products and the kinetics parameters of the thermolysis of some substituted COPs in toluene solution support a general homolytic stepwise mechanism.
- An important substituent effect is operative on the thermal decomposition reaction of several COPs (**1**, **2**, **3**, **5**, **6**, **7**, **8** and **9**) studied in this work in contrast to the behaviour of sterically hindered COPs (**4**) and (**10**).
- It appears to be possible to determine whether a peroxy group is part of a six or nine membered ring on the basis of the activation parameters values.

EXPERIMENTAL

Materials: COPs (**2**)[18], (**4**)[19] and (**5**)[19] were prepared by methods described in the literature. COP (**10**) was provided by Professor Charles W. Jefford (University of Geneva, Switzerland) and was synthesized according to literature procedures.[20] The toluene solvent for the kinetic experiments was purified by standard methods[21] (bp.: 110.0-111.0 °C) and its purity shown to be suitable for this type of work by GC analysis. Sublimated naphthalene (Mallinckrodt, A. R.) was employed as internal standard in quantitative determinations of COP concentration.

Kinetic Methods: Pyrex glass tubes (4-6 mm id., 100 mm length) half filled with the appropriate COP solution and spiked with the suitable internal standard were thoroughly degassed under vacuum at -196.0 °C and then sealed with a flame torch. To perform the runs, the ampoules were immersed in a thermostatic oil bath (± 0.1 °C) and withdrawn after selected times, stopping the reaction by cooling at

0 °C. The corresponding concentrations of COPs (**5**) and (**10**) remaining in the solution was determined by quantitative HPLC analysis in a Hewlett-Packard 1050 instrument with ODS Hypersil RP-C18 column (4.6 μm, 4 mm id. X 100 mm long), UV detection (λ=254 nm) and gradient elution. The starting mobile phase employed to analyse COP (**5**) was methanol/H_2O 70:30 and the linear gradient is run over 7 min to a final proportion of methanol/H_2O/acetonitrile 40:40:20 with a 0.8 mL/min flow-rate and *ca.* 65 bar pressure. Under this condition the retention time of **5** was *ca.* 11 min. The mobile phase employed to analyse **10** was methanol/H_2O/acetonitrile 45:30:25 with a 0.8-mL/min flow-rate and ca. 65 bar pressure. Under this condition the retention time of **10** was *ca.* 14 min.

The corresponding concentrations of COPs (**2**) and (**4**) remaining in the solution was determined by quantitative GC analysis using a methyl silicone gum rubber packed column installed in a Konik 2000C instrument with nitrogen gas as the carrier gas, injector at 125 ºC and FID detection (250 °C). The temperature program used with **2** was the following: 60 °C for 3 min, followed by a temperature increase of 3 °C/min up to 160 °C for 40 min. Under this condition retention time of **2** was *ca.* 44 min. With COP **4** the temperature program was: 50 ºC for 12 min, followed by a temperature increase of 10°C/min up to 160°C for 30 minutes. Under this condition the retention time of **4** was *ca.* 30 min.

The activation parameters were calculated according to the Eyring equation, and the errors were worked out by the Arrhenius equation methods using a least-means-square data treatment.[12]

ACKNOWLEDGEMENT

REFERENCES

1- J. R. Cerna, G. Morales, G. N. Eyler, and A. I. Cañizo, *J. App. Polym. Sci.*, 2002, **83**, 1; J. R Cerna, G. Morales, G. N. Eyler, and A. I. Cañizo, *J. Phys. Org. Chem.*, 2004, **17,** 1.

2- C. W. Jefford, 'Comprehensive Heterocyclic Chemistry', Vol 6, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford, 1996, pp. 861-899.

3- C. W. Jefford, 'Advances in Drug Research', Vol 29, ed. by B. Testa and A. U. Meyer, Academic Press, New York, 1997, pp. 271-325.

4- J. L. Vennerstrom, H. N. Fu, W. Y. Ellis, A. L. Ager Jr., J. K. Wood, S. L. Andersen, L. Gerena, and W. Milhous, *J. Med. Chem.,* 1992*,* **35**, 3023.

5- L. F. R. Cafferata, G. N. Eyler, E. L. Svartman, A. I. Cañizo, and E. E. Alvarez, *J. Org. Chem.*, 1991, **56**, 411.

6- J. R. Sanderson and P. R. Story, *J. Org. Chem.*, 1974, **39**, 3463.

7- L. F. R. Cafferata, G. N. Eyler, E. L. Svartman, A. I. Cañizo, and E. J. Borkowski, *J. Org. Chem.*, 1990, **55**, 1061.

8- G. N. Eyler, A. I. Cañizo, C. M. Mateo, E. E. Alvarez, and L. F. R. Cafferata, *J. Org. Chem.*, 1999*, **64***, 8457.

9- G. N. Eyler, C. M. Mateo, E. E. Alvarez, and A. I. Cañizo, *J. Org. Chem.,* 2000, **65**, 2319.

10- G. N. Eyler, A. I. Cañizo, E. E. Alvarez, and L. F. R. Cafferata, *An. Asoc. Quím. Argent.*, 1994, **82** 175.

11- C. M. Mateo, G. N. Eyler, E. E. Alvarez, and A. I. Cañizo, *Información Tecnológica,*1998**, 9**, 19.

12- S. Huyberechts, A. Halleux, and P. Kruys, *Bull. Soc. Chim. Belg.*, 1955, **64,** 203.

13- G. N. Eyler, A. I. Cañizo, and R. K. Nesprías, Quimica Nova, 2002, **25**, 364.

14- J. E. Leffler, *J. Org. Chem.,* 1955, **20**, 1202.

15- O. Exner, *J. Phys. Org. Chem.,* 1997, **10**, 797.

16- O. Exner, *Nature,* 1970, **227**, 366.

17- W. Linert and R. F.Jameson, *Chem. Soc. Rev*., 1989, **18**, 477.

18- W. Dilthey, M. Inkel, and H. Stephan, *J. Prakt. Chem.,* 1940, **154**, 219.

19- K. J. McCullough, A. R. Morgan, D. C. Nonhebel, P. L. Pauson, and C. J. White, *J. Chem. Res. Synop.*, 1980, **2**, 34.

20- C. W. Jefford, S. Kohmoto, D. Jaggi, G. Timári, J. C. Rossier, M. Rudaz, O. Barbuzzi, D. Gérard, U. Burger, L. M. Kamaloprija, J. Mareda, G. Bernardinelli, I. Manzanares, C. J. Canfield, S. L. Fleck, B. Robinson, and W. Peters, *Helv. Chim. Acta,* 1995, **78**, 647.

21- J. A. Riddick and W. B. Bunger, "Organic Solvent", ed. by A. Weissberger,Wiley Interscience, New York, 1970.