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Alkaline Hydrolysis of the *cis* and *trans* Isomers of the Cyclic Phosphinate: 1-Oxo-1-ethoxy-2,2,3,4,4-pentamethyl-phospha-cyclobutan

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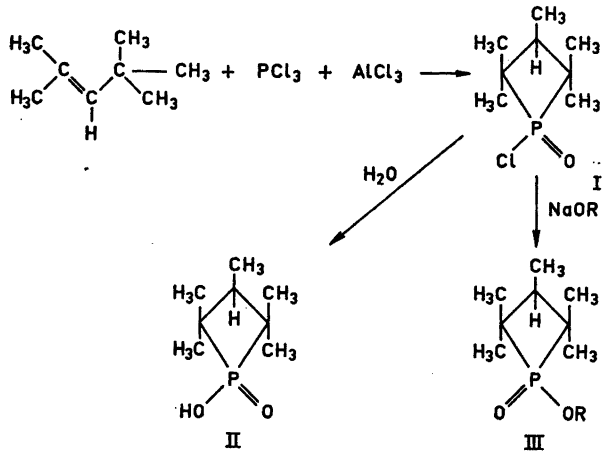
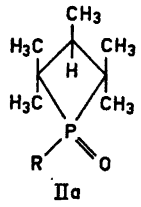
The rates of the alkaline hydrolysis of the *cis* and *trans* isomers of the four-membered cyclic ethyl phosphinate, 1-oxo-1-ethoxy-2,2,3,4,4-pentamethyl-phospha-cyclobutan, have been determined at 4 different temperatures. From the rates the activation parameters have been calculated. The approximately 7 times greater rate of hydrolysis of the *cis* isomer as compared with the *trans* isomer, is due to a more favourable entropy of activation of the *cis* isomer.

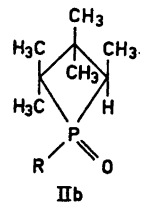
McBride and co-workers[1] have reported the synthesis of a cyclic four-membered phosphorus compound by the reaction of 2,4,4-trimethyl-2-pentene with phosphorus trichloride and aluminium trichloride in methylene chloride:



Theoretically, this reaction can lead to two alternative cyclic structures IIa and IIb, which differ in the position of a methyl group.



IIa



IIb

From the NMR spectrum of the acids (IIa and IIb, R = OH) McBride *et al.*[1] were not able to distinguish between these two structures. The choice of structure IIa for the isolated compound was based on mechanistic arguments. They also pointed out that the esters of both acids (R = OMe) will give rise to *cis-trans* isomers, and the presence of two isomers in the ratio 1:4 was indeed confirmed by high resolution analytical gas chromatography.

In the present study the rates of alkaline hydrolysis of the above-mentioned *cis* and *trans* esters were measured. The isomers were separated through partial hydrolysis of the 1:4 mixture of ester isomers. This was possible since the *cis* ester hydrolysed faster than the *trans* ester. The position of the ring carbon atom, singly substituted with a methyl group (2- or 3-position), is discussed on the basis of the NMR spectra of the *cis* and *trans* acids.

EXPERIMENTAL

The NMR spectra were recorded on a Varian A-60-A spectrometer operating at 60 Mc, and a JEOL JNM-4H-100, 100 Mc spectrometer.

1-Oxo-1-chloro-2,2,3,4,4-pentamethyl-phospha-cyclobutan (I) was synthesized according to the method of McBride and coworkers.[1] M.p. 73.5°, reported [1] 72–75°.

1-Oxo-1-ethoxy-2,2,3,4,4-pentamethyl-phospha-cyclobutan (III) (mixed isomers). A solution of the acid chloride (I) (95 g) in 250 ml ethanol was added dropwise with stirring to a solution of sodium (18.0 g) in 450 ml ethanol. After standing for 30 h the ethanol was stripped off *in vacuo*. The solid residue was taken up in water and extracted several times with methylene chloride. The extract was dried and after removal of solvent, the remaining ester mixture was fractionated twice *in vacuo* in a heated jacketed column to give 90 % yield of the mixed ester isomers (III), b.p.$_1$ 72°, b.p.$_{10}$ 112°, n_D^{20} 1.4575. (Found: C 58.59; H 10.12. Calc. for $C_{10}H_{21}O_2P$: C 58.78; H 10.29.) GLC purity > 99 %.

Preparation of pure ester isomers. The *trans* ester was obtained by partial hydrolysis of the ester mixture followed by acidification and extraction with methylene chloride. *Trans* ester: b.p.$_{10}$ 112°, n_D^{20} 1.4570. The *cis* acid obtained by partial hydrolysis of the ester mixture was converted to the acid chloride by refluxing with thionyl chloride in benzene. The acid chloride was then converted to the *cis* ester with sodium ethoxide in ethanol. *Cis* ester: b.p.$_{10}$ 112°, n_D^{20} 1.4620.

Preparation of pure acid isomers. Saponification of the pure *cis* and *trans* esters with aqueous base, followed by acidification, gave the corresponding acids as their dihydrates. The anhydrated acids were obtained on drying in vacuum over P_2O_5 at temperatures above their melting points. *Cis* acid: m.p. 74.1°, pK_a 2.69, *trans* acid: m.p. 74.6°, pK_a 2.95.

Kinetic measurements were performed in a 50 % (v/v) water-ethanol mixture using an ordinary back-titration method. The degree of ester hydrolysis was determined at eight

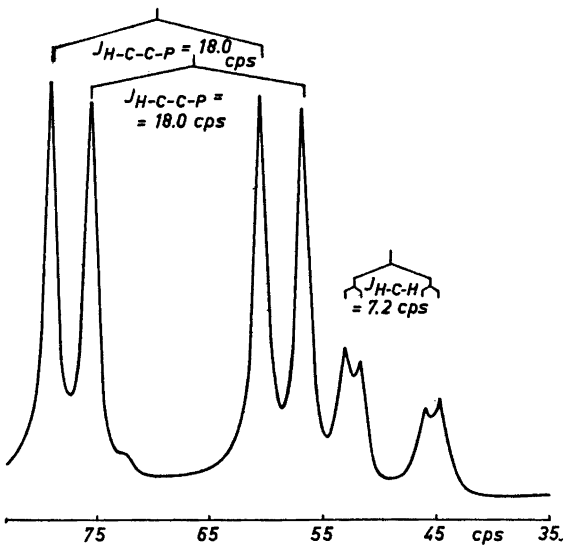


Fig. 1. Spectrum at 60 Mc of the *cis* acid isomer in CCl_4 solution with TMS as internal standard.

intervals up to approximately 70 % of completion. Measurements were made at 3 and 4 separate temperatures, each kept constant within ± 0.01°C. The average error of the calculated rate constants is estimated to ± 1 %.

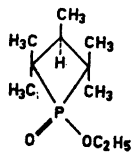
RESULT AND DISCUSSION

The 60 Mc NMR spectra (Fig. 1) of the pure acid isomers both show three different methyl signals, integrating to 6:6:3 protons. The methyl signals occur at 79.2 cps and 63.0 cps from TMS and are split to the same extent (18.0 cps) evidently owing to an H—C—C—P coupling since the same splitting (18.0 cps) is observed in the spectra recorded on a 100 Mc spectrometer. The third methyl signal (49.5 cps) gives a double doublet due to vicinal H—H coupling (7.2 cps) and H—C—C—C—P coupling (1.6 cps). The only structure which is compatible with these observations is the symmetrical structure (IIa), which has four methyl groups near phosphorus and a fifth farther away. This assumption is supported by additional NMR evidences: The two methyl groups in the 2- (or 4-) position will not be magnetically equivalent due to the influence of the phosphoryl group. Thus, the lower doublet (79.2 cps) which in both isomers integrate to two CH_3 groups, must be ascribed to the two α,α'-methyl groups which lie nearest to the deshielding phosphoryl group. In the alternative structure (IIb) the *cis* and *trans* isomers would show one, respectively two methyl groups at low field. Further, the NMR spectra of the two acid isomers are very similar in the methyl and methine regions, indicating

that the methyl group and the methine hydrogen occur at the same position (3-position in both isomers).

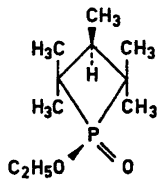
Refractive indexes, densities and P=O frequencies of the isomeric ethyl esters are given in Table 1.

Table 1. Physical data of the (III) isomers.

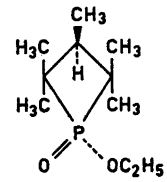
Compound	Isomer	n_D^{20}	d_4^{20}	P=O cm^{-1}	Tentative conformation
	A	1.4620	1.098	1213 1250	*cis*
	B	1.4570	1.053	1215 1255	*trans*

The isomers (A) and (B) probably exist in a puckered ring configuration characteristic for cyclobutane derivatives.[2-4] They might therefore be expected to obey the conformational rule which states that *cis* isomers of 1,3-disubstituted cyclobutanes have the higher refractive index and the higher density.[5,6] Accordingly, the data (Table 1) indicate a *cis* structure for isomer (A) and a *trans* structure for isomer (B).

The alkaline hydrolysis of the geometric isomers (A) and (B) show second order kinetics in accordance with earlier findings for cyclic phosphinates, phosphonates and phosphates.[7] Isomer (A) is hydrolysed about 7 times more rapidly than isomer (B). This fits well with the *cis* configuration (IIIa) for isomer (A), since in the *trans* form (IIIb) three methyl groups block the access of the hydroxyl ion, against only two in the case of the *cis* form.



IIIa, *cis*



IIIb, *trans*

This explanation is also in agreement with the entropies of activation found for the isomers (Table 2). The entropy is approximately 4 *e.u.* more favourable for the *cis* isomer, indicating a lesser degree of steric hindrance during the substitution reaction in the *cis* isomer.

Table 2. Rate constant and activation parameters for the alkaline hydrolysis of the ester isomers IIIa and IIIb in 0.1 N sodium hydroxide in 50 % (v/v) aqueous ethanol.

Ester isomer	Rate constant, l mole^{-1} sec^{-1} × 10^4				E	ΔS^*
	30°	40°	50°	60°	kcal/mole	
cis (IIIa)	0.742	1.703	3.880		16.0 ± 0.3	−26.5
trans (IIIb)	0.106	0.245	0.561	1.225	16.0 ± 0.3	−30.6

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