

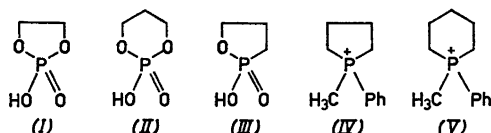
Rate Studies of the Michaelis-Arbuzov Reaction between Ethyl Iodide and Cyclic Phosphites

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The rates of the Michaelis-Arbuzov reaction between ethyl iodide and five- and six-membered cyclic phosphites are somewhat lower than the rates of the corresponding reaction of open chain phosphites. The high reactivity, characteristic for displacement reactions on phosphorus in five-membered phospholan derivatives, seems therefore to be limited to compounds containing quadruply linked phosphorus.

The rate of nucleophilic substitution on phosphorus in quadruply linked phosphorus compounds is often unusually high when the phosphorus atom is part of a five-membered ring. The effect is greatest in 1,3,2-dioxaphospholan systems; thus the ester acid (I) is hydrolyzed 10^8 times more rapidly than its six-membered analog (II) and corresponding open chain diester acids.^{1,2} The rate ratio is approximately 10^5 between the 1,2-oxaphospholan acid (III) and the corresponding six-membered or open chain analogs.³ The same is true for the corresponding ethyl esters.⁴ The high reactivity of phospholan systems

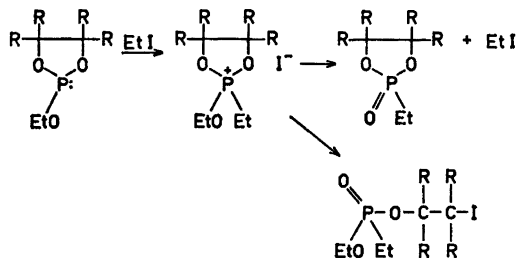


is not restricted to ring cleavage reactions, as shown by the fact that the product from the very rapid acid catalysed hydrolysis of 2-methoxy-2-oxo-1,3,2-dioxaphospholan contains approximately 30 % of the ring preserved phospholan acid.⁵ In the same way, the rate of the nucleophilic reaction between hydroxyl ions and the five-membered phosphonium compound (IV) is more than 1300 times faster than the corresponding reaction of the six-membered phosphonium compound (V), even though both rings containing the phosphorus atom are preserved during the decomposition.⁶

The influence of ring size in cyclic phosphites upon electrophilic substitution on phosphorus is less known. Westheimer *et al.*⁷ have reported that the rate of acid hydrolysis of five-membered cyclic phosphites seems to be considerably higher than the rate of six-membered and open chain analogs. The present paper reports rate data for the Michaelis-Arbuzov reaction of five-membered, respectively six-membered cyclic phosphites with ethyl iodide in acetonitrile.

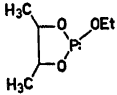
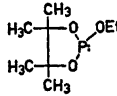
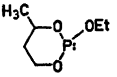
RESULT AND DISCUSSION

Previous investigations of Michaelis-Arbuzov reactions in open chain compounds have shown that the first step, the formation of the phosphonium intermediate, is rate determining.^{8,9} The present results indicate that tertiary phospholans and phosphorinans react with ethyl iodide by the same mechanism, *i.e.* with the first step rate determining:



The rate data in Table 1 show that the presence of a phospholan ring in the phosphite has a small retarding effect on the substitution as compared with the reactions of open chain phosphites and the six-membered phosphorinan derivative. Alkylation of the phospholan ring causes a small rate increase which most certainly is due to the electron releasing effect of the alkyl groups. A corresponding rate increase is also observed for triisopropyl phosphite as compared with triethyl phosphite (Table 1).⁹ Whereas the rate is little affected by methyl substitution in the phospholan ring (Table 1), the product composition is, however, drastically changed, the unsubstituted phospholan giving rise only to ring cleavage product and the tetramethylsubstituted derivative to ring-preserved product only. Monomethyl-phospholans are intermediate in behaviour.^{10,11} The above reaction scheme for the Michaelis-Arbuzov reaction nicely explains these observations. The product composition depends on the second step: the nucleophilic attack of the iodide ion on one of the three carbon atoms linked to oxygen in the phosphonium intermediate. The change of primary ring carbon atoms to secondary or tertiary on methyl substitution, make the ring increasingly indifferent towards nucleophilic attack from the iodide ion. The ring stabilization effect on alkyl substitution in the ring is a common phenomenon for various cyclic compounds as for example in the hydrolysis of cyclic anhydrides,¹² sultones,¹³ lactones,¹⁴ and cyclic phosphate esters.¹⁵ Bordwell *et al.*¹³ believe that the effect is due to restricted rotation of the ring atoms in the moment of ring opening. This assumption seems

Table 1. Rate of Michaelis-Arbuzov reaction of ethyl iodide with cyclic and open chain phosphites in acetonitrile.

Compound	Conc. (mole/l)		Temp. °C	2nd order rate constant l/mole sec $\times 10^6$
	phosphite	ethyl iodide		
	0.296	0.246	70.0	0.7 ± 0.2
	0.121	0.356	70.0	1.1 ± 0.3
	0.187	0.206	70.0	2.7 ± 0.4
	0.229	0.247	65.0	1.5 ± 0.4
	0.273	0.287	60.0	0.9 ± 0.2
Triethyl phosphite ⁷	0.1996	0.7296	69.9	4.80
Triisopropyl phosphite ⁸	0.139	0.139	69.9	7.96

plausible since atoms formerly linked to each other in a ring cannot separate linearly, as is true in open chain systems, but must rotate away from each other.

The fact that tertiary phospholan compounds undergo alkyl substitution on phosphorus with approximately the same rate as do phosphorinane and open chain analogs (Table 1) points to the conclusion that the unusually high rate of substitution on phosphorus observed for some phospholan systems ¹⁻⁶ is restricted to phospholan compounds with quadruply linked phosphorus. From a reaction kinetic view these findings are not surprising since different transition states must be involved for electrophilic substitution on phosphorus in trivalent phosphites and nucleophilic substitution on phosphorus in quadrivalent phosphorus compounds: The rate determining step of the Michaelis-Arbuzov reaction proceeds through a sp^3 -hybridized phosphonium intermediate, whereas the rate determining step of the hydrolysis of phosphate esters and alkaline decomposition of phosphonium salts proceeds through a sp^3d -hybridized state. The steric requirements as well as the energy differences

between bond breaking and bond forming processes during the substitutions must be expected to vary considerably and may in no way be comparable in triply and quadruply linked phosphorus compounds.

EXPERIMENTAL

The cyclic phosphites in Table 1 were synthesized from the corresponding chloro compounds and ethanol in the presence of triethylamine or N,N-dimethylamine. The chloro phosphites were made from phosphorus trichloride and the appropriate glycols.¹⁶⁻¹⁸

2-Ethoxy-4-methyl-1,3,2-dioxaphospholan, b.p.₁₄ 55.3°, $n_D^{19.5}$ 1.4349 (reported:¹⁶ b.p.₂₃ 70.4–70.7, n_D^{25} 1.4330).

2-Ethoxy-4,5-tetramethyl-1,3,2-dioxaphospholan, b.p.₁₆ 76°, n_D^{20} 1.4422 (reported:¹⁷ b.p.₁₄ 75–76°, n_D^{20} 1.4392).

2-Ethoxy-4-methyl-1,3,2-dioxaphosphorinan, b.p.₁₀ 68–69°, n_D^{20} 1.4460 (reported:¹⁸ b.p.₈ 63–64°, n_D^{20} 1.4410).

Rate measurements. The rates of the Michaelis-Arbuzov reaction between the cyclic phosphites (Table 1) and ethyl iodide were studied in acetonitrile. The concentrations of both reactants were in the region 0.1–0.4 M. The reaction was followed quantitatively by measuring the intensity of the P=O band of the product formed.⁸ The rate of the Michaelis-Arbuzov reaction of the unsubstituted and monomethyl substituted five-membered ring phosphite is not reported due to a disturbing side reaction in acetonitrile solution, most reasonably caused by small amounts of oxygen. Semi-quantitative data showed, however, that the Michaelis-Arbuzov reaction was slower than for the di- and tetrasubstituted phosphites. The relative high error of the quoted rate constants for all ring phosphites is also due to this side reaction.

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