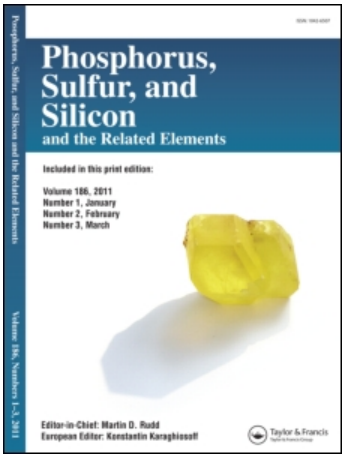

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Aksnes, Gunnar and Frøyen, Paul(1991) 'DISPLACEMENT RATE OF ARYLOXY SUBSTITUENTS IN CYCLIC AND ACYCLIC TRIPHOSPHITES BY METHOXIDE IONS, AND WATER', Phosphorus, Sulfur, and Silicon and the Related Elements, 63: 1, 45 — 50
To link to this Article: DOI: 10.1080/10426509108029425
URL: http://dx.doi.org/10.1080/10426509108029425

Phosphorus, Sulfur, and Silicon, 1991, Vol. 63, pp. 45–50
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DISPLACEMENT RATE OF ARYLOXY SUBSTITUENTS IN CYCLIC AND ACYCLIC TRIPHOSPHITES BY METHOXIDE IONS, AND WATER

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(Received May 31, 1991; in final form June 6, 1991)

The displacement rate of aryloxy substituents by methoxide ions in the following triphosphites: 2-phenoxy-1,3,2-dioxaphospholane (**I**), 2-methoxy-benz-1,3,2-dioxaphospholene (**II**), and dimethyl phenylphosphite (**III**), is for each phosphite higher in methanol than in dichloromethane. On the other hand, dichloromethane discriminates much more strongly between five-membered cyclic and acyclic phosphites than methanol, as shown by the following rate ratios cyclic/acyclic in CH_3OH: **I/III** = 13, **II/III** = 2; and in CH_2Cl_2: **I/III** = 1.8×10^3, **II/III** = 1.1×10^3.

Water, as nucleophile towards the same phosphites in deuteroacetone, appears to exhibit somewhat similar magnitude of discrimination as methoxide in methanol.

Key words: Cyclic and acyclic triphosphites; displacement rate of aryloxy substituents.

Nucleophilic displacement at phosphorus in organic phosphoryl and phosphonium compounds are well documented to proceed through pentacovalent intermediates or transition states.[1–4] The rate of displacement by hard nucleophiles (RO^-, HO^-) of various leaving groups are found to be 10^3–10^7 times faster in four- and five-membered cyclic phosphoryl and phosphonium compounds than in corresponding acyclic compounds.[2–5] The effect is rationalized as arising from the small ring angle at phosphorus when it is part of four- and five-membered cyclic compounds. The angle (89–97°) is assumed to facilitate the formation of a bipyramidal intermediate, or transition state. The effect is expressed by two main rules[4]:

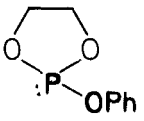
1. Four- and five-membered cyclic systems give rise to trigonal structures where the atoms adjacent to phosphorus span axial-equatorial positions (90° angles).
2. The most electronegative ligands occupy preferentially axial sites, and during substitution the leaving group is displaced from the axial position.

When the rules are applied to trivalent phosphorus compounds the results are more dubious. The presence of the lone electron pair makes the phosphorus atom less electrophilic, at the same time as the lone electron pair constitutes a strong nucleophilic reaction center. However, towards hard nucleophiles (HO^-, RO^-) it is assumed that organic triphosphites primarily utilize the electrophilicity of phosphorus in displacement processes, forming an unstable trigonal bipyramidal

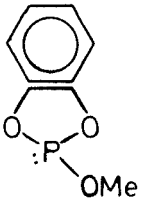
intermediate, or transition state where the lone electron pair on phosphorus occupies one of the equatorial positions.

Alkaline hydrolysis of five-membered cyclic triphosphite esters is claimed to proceed some 10^3 times faster than corresponding acyclic ones.[6] Brown and Hudson have also reported several substitution reactions towards triphosphites where cyclic derivatives are considerably accelerated in comparison with acyclic ones.[7,8]

The mechanistic uncertainty connected with substitution in tricoordinated phosphorus compounds prompted us to study in some detail the rate of displacement of aryloxy substituents (phenoxy and catecholate) in the following cyclic and acyclic triphosphites by CH_3O^-, HO^-, and H_2O:



I



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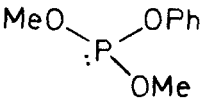


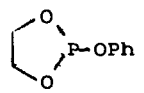
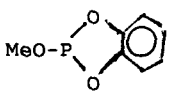
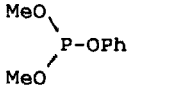
III

RESULTS AND DISCUSSION

Rate data of the nucleophilic displacement of phenolate and catecholate groups in cyclic and acyclic triphosphites, **I**, **II**, and **III**, by $NaOH_3$ and NaOH in dichloromethane and methanol are recorded in Table I. The rate constants for $NaOCH_3$

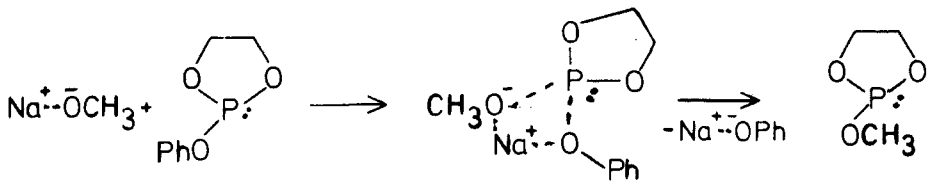
TABLE I

Rate constants of displacement of phenolate and catecholate ions from aromatic phosphite esters by $NaOCH_3$ in CH_2Cl_2, and by $NaOCH_3$, resp NaOH in CH_3OH

Phosphite	Temp.	Rate constant, $k(l\ mol^{-1}s^{-1})$		
		$NaOCH_3(CH_2Cl_2)$	$NaOCH_3(CH_3OH)$	$NaOH(CH_3OH)$
	20	4.1	50.5	52.5
	20	2.6	7.6	12.4
	25	0.0023	3.9	3.7

in CH_2Cl_2 are seen to be $1-2 \times 10^3$ times faster towards cyclic than acyclic triphosphites. On the other hand, the effect of the five-membered ring is much smaller when the same reactions take place in methanol, although the substitution rates for the three phosphites are several times faster in this medium. Apparently, different effects are involved in aprotic and protic solvents.

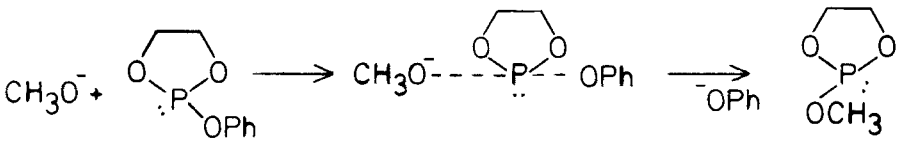
Sodium methoxide exist as tight ion-pair aggregations in dichloromethane. It is thus to be expected that the methoxide reacts as an ion-pair towards the triphosphite:



SCHEME I

In Scheme I an unstable bipyramidal intermediate, or transition state, is assumed to be formed directly during the approach of the ion-pair towards the triphosphite. In the cyclic phosphite its five-membered ring can obtain the favourable axial-equatorial placement of the oxygen atoms, at the same time as the incoming methoxy group and the axial leaving phenolate ion form a 4-membered ring of similar favourable placement. The diffuse, and electropositive electron pair, will according to the selection rule occupy an equatorial position in the intermediate, or transition state.

In methanol sodium methoxide, in the low concentration used in the reactions ($10^{-3}-10^{-4}$ mol/l) is expected to be entirely dissociated. Therefore, assistance from Na^+, as in dichloromethane, is much less likely since this will require a termolecular reaction. This means that the transition state most likely constitutes a very unstable negatively charged complex giving rise to a S_N2-P mechanism where the transition state of cyclic phosphites cannot profit in the same way by axial-equatorial placement of the ring:



SCHEME II

If the displacement reactions in dichloromethane and methanol are correctly described by Schemes I and II, the displacements ought to give retention in CH_2Cl_2 and inversion in CH_3OH. It should, therefore, in principle be possible to obtain proof for the mechanisms by using an enantiomer of a cyclic ester as substrate. However, we know from earlier trials that such isomers, as 2-ethoxy-4-methyl-1,3,2-dioxaphospholane, isomerize so fast that they are impossible (or extremely difficult) to obtain in pure forms.[12]

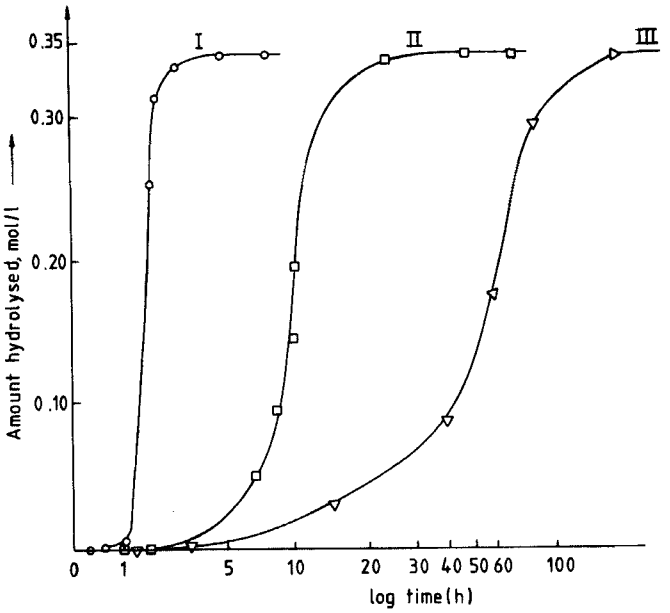
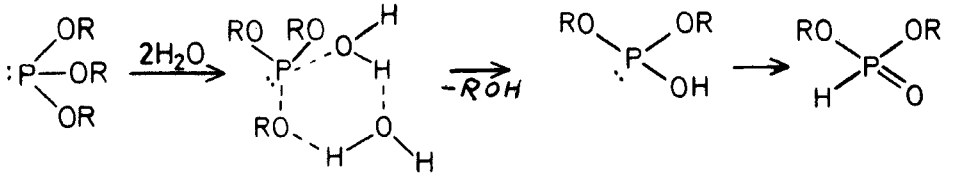


FIGURE 1 Rate curves for the hydrolysis of the triphosphites **I**, **II**, and **III** by water in denteroacetone using equimolecular start concentrations (0.35 mol/1).

It is seen from Table I that the displacement rates of sodium methoxide and hydroxide towards the triphosphites in CH_3OH is of the same magnitude, in accordance with their comparable basicity and nucleophilicity.[17]

When water functions as nucleophile towards triphosphites in aprotic medium the kinetics of the reaction are more complex since the primary product, diphosphite, hydrolyze further to the acidic monophosphite (pK ≈ 2), which has a strong proton catalytic effect on the hydrolysis of triphosphite. The overall reaction shows an autocatalytic course as seen from Figure 1, where the triphosphites **I**, **II**, and **III**, are hydrolyzed by equimolecular amount of water in deuteroacetone.

In an earlier study[13] of the hydrolysis of tripropylphosphite by water in acetonitrile, we have shown that during the first few percent of hydrolysis, before acid catalysis starts to dominate the process, the reaction obeys overall third order kinetics, first order in phosphite, and second order in water. From the kinetics, together with results from ^{18}O-exchange studies, the reaction Scheme III was postulated:



SCHEME III

Recently, similar kinetics were observed for the reaction of water with sulphite esters.[14]

The loose transition state in Scheme III will hardly be able to profit fully from axial-equatorial placements of the ring oxygens in cyclic phosphites, in the same way as substitution reactions passing through a real intermediate. This view is supported by the rate ratios between cyclic (**I** and **II**) and acyclic (**III**) triphosphites: **I/III** ≈ 33, and **II/III** ≈ 5, which are only 2.5 times the corresponding rate ratios of the same phosphites towards CH_3O^- in CH_3OH. The rate ratios by water are approximate since the rapid proton catalysis from monophosphite produced in the second step, obscures the first step, the slow substitution by water.

Applying the ring-effect as mechanistic guide, it appears that nucleophilic displacement reactions towards phosphorus in trivalent phosphorus primarily go through a transition state, or a very unstable intermediate. Reactions in this category are utilized in the coupling of nucleosides to nucleotides in the synthesis of RNA and DNA. Caruthers[15] and coworkers used phosphoramidites, $ROP(NR_2)_2$, since amino groups are even more easily displaced than alkoxy and phenoxy groups in aprotic solvent. No mechanistic details of coupling reactions are reported.[16] The present study might stimulate to look more carefully into these very important reactions with regard to cyclic versus acyclic P-**III**-compounds, as well as the choice of solvent.

EXPERIMENTAL

Materials. The triphosphites, **I, II, III** were prepared by standard methods from phosphorus trichloride and methanol, phenol, and catechol.

I, prepared by transesterfication of triphenylphosphite with ethylene glycol had boiling point: 62–63°C/0.2. Lit.[9] 73°C/0.3, ^{1}H, NMR (200 MHz, in acetone-d_6) δ: 4.02–4.28 (m, 4H), 7.00–7.19 (m, 3H), 7.29–7.41 (m, 2H).

II, prepared from methyldichlorophosphite and equivalent amount of the Pb-**II** salt of catechol in toluene had boiling point. 77–78°C/12. ^{1}H, NMR (200 MHz in acetone-d_6) δ: 3.27 (d, J 8.6 Hz, 3H), 7.01–7.10 (m, 2H), 7.12–7.22 (m, 2H).

III, prepared according to literature[10] had boiling point: 60–61°C/0.3. Lit.[10] 62–63°C/0.25. ^{1}H, NMR (60 MHz in acetone-d_6) ∂: 3.60 (d, J 10.2 Hz, 6H), 7.2 (m, 5H).

Kinetic measurements. The substitution rates of aryloxy groups (phenolate and catecholate) of **I, II,** and **III** by $NaOCH_3$ in CH_2Cl_2, and with NaOH and $NaOCH_3$ in CH_3OH, where followed by measuring the UV-absorption of the phenolate ions at 294 nm, and catecholate ions at 317 nm.

Concentrations of triphosphites were in the range of 10^{-4}–10^{-5} mole/l and that of the nucleophile (CH_3O^-, HO^-) between 10^{-3} and 10^{-4} mole/l, sufficiently high to obtain pseudo 1. order rate dependence.

The reaction of the same triphosphites, **I, II, III**, with H_2O were performed in acetone-d_6 using equimolecular concentrations of triphosphite and water (approximately 0.35 mol/l). The reaction was followed by NMR (200 MHz). The rate of **I** was calculated from the phenol multiplets (δ 6.84 and 7.19), and also by the decrease of **I** at δ 7.00–7.18, and 7.30–7.40. The rate of **II** was followed by the methyl protons of its product of hydrolysis, centered at δ 3.30, and the rate of **III** by the methyl protons of its product of hydrolysis at δ 3.73.

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