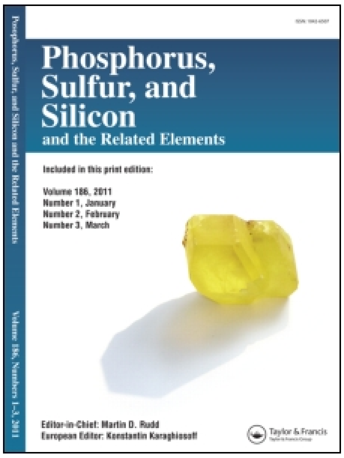

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REACTION OF PHOSPHOROTHIOIC ACIDS WITH SUGAR OXIRANES. EXPERIMENTAL EVIDENCE OF THE PENTACOORDINATE PHOSPHORUS INTERMEDIATE IN TRANSPHOSPHORYLATION REACTIONS IN THE 1,2-HYDROXYTHIOLO SYSTEM

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REACTION OF PHOSPHOROTHIOIC ACIDS WITH SUGAR OXIRANES. EXPERIMENTAL EVIDENCE OF THE PENTACOORDINATE PHOSPHORUS INTERMEDIATE IN TRANSPHOSPHORYLATION REACTIONS IN THE 1,2-HYDROXYTHIOLO SYSTEM

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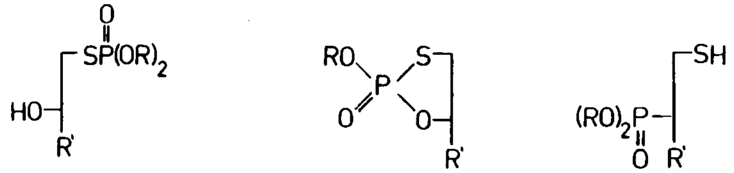
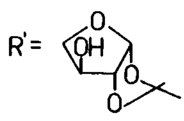
Our present work is a continuation of the investigations devoted to the synthesis of sugar thiiranes.[1] We found that careful monitoring of the reaction of monothio acids of phosphorus with 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose **1** allows deeper insights into the mechanism of that reaction. It affords new, convincing arguments for the participation of the pentacoordinate intermediate **8** in the transphosphorylation step **3** → **4**.

Thorough investigations of the reaction of the model oxirane **1** with monothioacids of phosphorus **2** were performed on three model acids: O,O-diethylphosphorothioic acid **2a**, O,O-diphenylphosphorothioic acid **2b** and O,O-isopropylphosphorothioic acid **2c**. The reactions were carried out with free acids in inert solvents. The temperature ranges were adjusted so that the formation of intermediate products could be followed by ^{31}P NMR spectroscopy. The advantage of performing the reaction with free acids in non-aqueous solvents is that one can avoid complications connected with the hydrolytic process. In this way it was possible to demonstrate that intermediate products represented in Scheme 1 were formed.

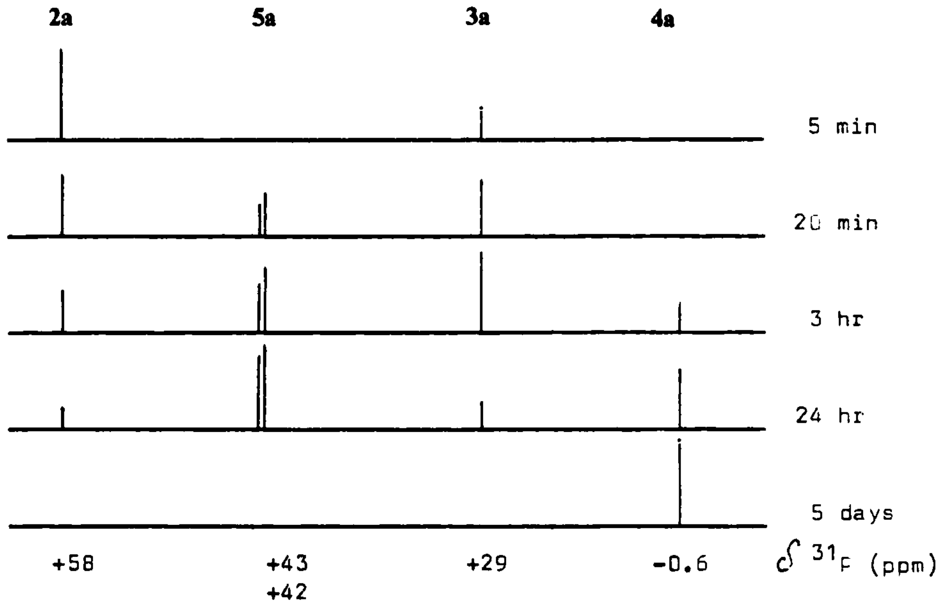
In the course of investigations which are not included in this paper, we have been able to isolate the product **3** when using the acid **2** (R = ^{t}Bu)[2] and also products of type **4**.[3]



3 **5** **4**



SCHEME 1



SCHEME 2

The reaction of the oxirane **1** with the acid **2a** (R = Et) was performed in toluene solution, at 18°C using stoichiometric amounts of reagents. The progress of the reaction in course of time, as viewed by ^{31}P NMR spectroscopy is represented in Scheme 2. The appearance of a signal characterized by chemical shift δ ^{31}P = +26 ppm was observed after a few minutes. Twenty minutes later two new signals appeared, δ ^{31}P = +42 and +41 ppm. During the next few hours the intensity of the signals at δ = +26, +42 and +41 ppm increased, and after ca. 3 hrs a new signal at −0.6 ppm appeared. The signals at +42 and +41 ppm showed maximum intensity after 24 hrs, during which time the signal at +26 ppm diminished and the signal at −0.6 ppm considerably increased. After 5 days all signals including the signal corresponding to the starting O,O-diethylphosphorothioic acid (δ ^{31}P = +54 ppm) had disappeared and only the signal at −0.6 ppm was observed.

The signal at +26 ppm can be ascribed to the adduct **3a** by comparison with the δ ^{31}P value found for the product **3** (R = ^{t}Bu)[2] as well as with the adducts described by Russian workers.[4] The signal at δ = −0.6 ppm corresponds to the isomerization product **4a**. This is confirmed by the IR spectra of the isolated product. The signals at +42 and +41 ppm occur in the region characteristic of chemical shifts ascribed to the oxathiaphospholanes **5**.[4] Additional evidence for the structure **5** is the presence of two signals which correspond to two diastereoisomers.

The reaction of **1** with **2a** can be steered towards the formation of the product **5a** (R = Et) by removing ethyl alcohol from the reaction medium. Equimolar amounts of **2a** and **1** were dissolved in toluene and allowed to react at room temperature until the signal corresponding to the starting thioacid **2a** (R = Et) disappeared. During that time, ethyl alcohol formed was continuously removed under vacuo. It was found that under these conditions the post-reaction mixture contained, besides diastereomeric oxathiaphospholanes **5a** (δ ^{31}P = +42 and +41 ppm), only minute amounts of the mercaptophosphate **4** (δ ^{31}P = −0.6 ppm).

In the same reaction carried out with excess ethyl alcohol, however, no oxathiaphospholanes were observed, at least, in amounts detectable by the spectroscopic method used.

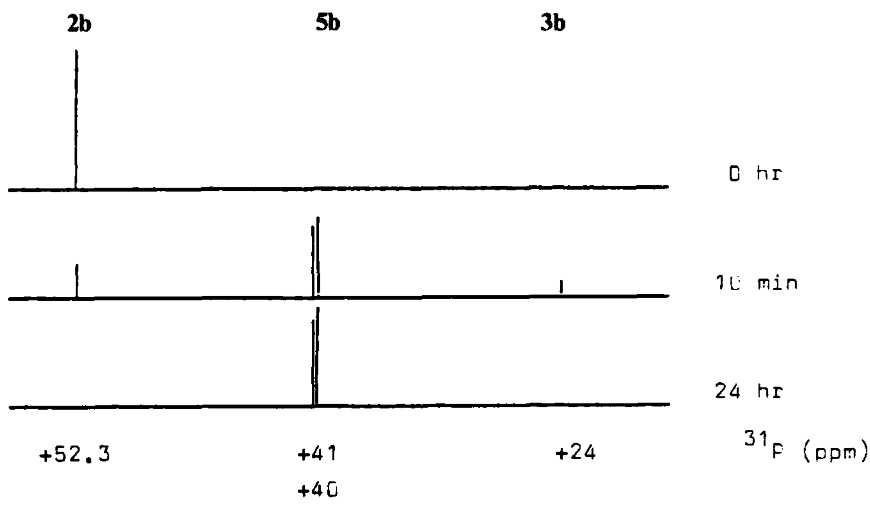
The reaction of **1** with O,O-diphenylphosphorothioic acid **2b** proceeds with high selectivity towards the diastereoisomeric oxathiaphospholanes **5b** (δ ^{31}P = +40.6 and +40.0 ppm) in 1 : 2 ratio, respectively. (Scheme 3)

The question is, what role do the oxathiaphospholanes play in the mechanism of the reaction between alkene oxides and phosphorothioic acids? In other words, are the oxathiaphospholanes intermediate products in the isomerisation **3** → **4** or not? The fact that oxathiaphospholanes are formed on elimination of alcohol strongly suggests the existence of equilibria between **3**, **4** and **5**.

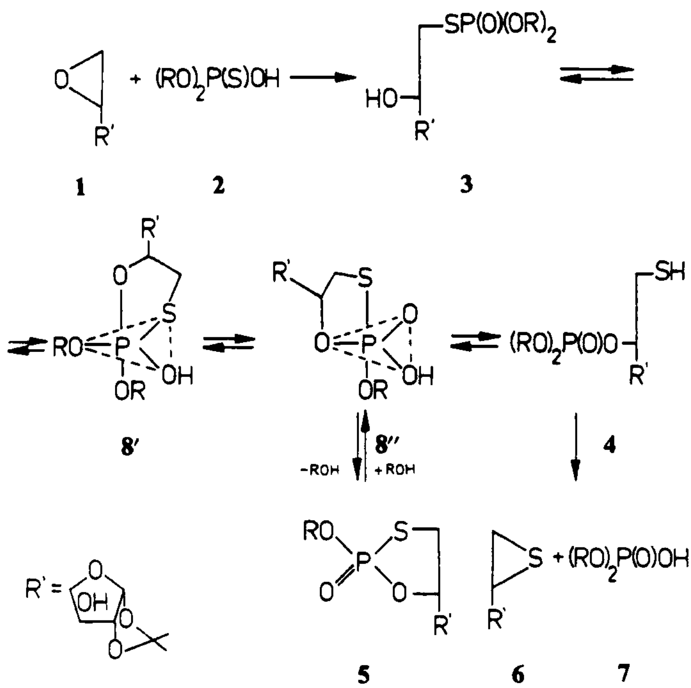
The intramolecular nucleophilic substitution at phosphorus results from the attack of the hydroxyl group on phosphorus in the phosphoryl group of compound **3** and leads to the formation of the pentacoordinate system **8**.

All these experimental facts give strong support for the existence of the pentacoordinate intermediate **8** (Scheme 4) common for both products **5** and **4**. According to Westheimer[5] pentacoordinate compounds like **8** should be stabilized by the presence of the five-membered ring.

In order to fulfill the rule of apical entry and apical departure, the ligand rearrangement **8′**—**8″** is required, with the OH group as a pivot. The pentacovalent system exists in equilibrium with its protonated forms, e.g.: **8‴**. The proton source can be internal, from the OH group which on deprotonation increases its equatoriality, or external, from the monothiophosphoric acid. The V-coordinate phosphorus intermediate **8″** or its protonated form **8‴** can disintegrate in two ways: through rupture either of the P—O bond, or of the P—S bond. The first route leads to an oxathiaphospholane **5**, the second to the product **4** containing a free thiolo group.



SCHEME 3

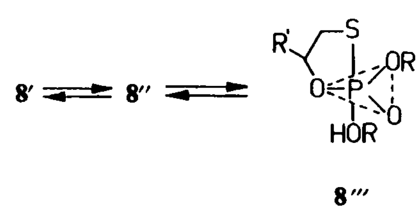


SCHEME 4

The exocyclic elimination affording oxathiaphospholane is a reaction leading to a chiral system **5**. The process of formation of compound **5** proceeds, according to the experimental data, with stereochemical selection.

In the case of R = Phenyl, the equilibrium is shifted towards oxathiaphospholanes because phenoxide ion is a good leaving group. When R = Et, it is possible to shift the equilibrium towards the oxathiaphospholanes by removal of ethyl alcohol. It is obvious that in the case of further transformation of compound **4** into episulphide **6** the equilibrium is shifted towards **6** due to the irreversible character of the reaction.

Returning to the question of the role of compound **5** in the reaction under consideration, it should be emphasized that **5** cannot be the intermediate product in the isomerization process **3**–**4**. The pentacoordinate system **8** is the true intermediate product in this transformation. The oxathiaphospholanes **5** are formed through the same intermediate **8** in a parallel elimination reaction of alcohol or phenol. They are



SCHEME 5

in equilibrium with the product **3** as well as with **4** through the pentacoordinate system **8**. The formation of **5** seems to be kinetically controlled. When the eliminated alcohol is not removed, **5** undergoes transformation into **4** (which is thermodynamically the more stable product) or, under more drastic conditions, into the final reaction product which has the episulphide structure **6**. This final reaction step is accompanied by the elimination of the corresponding phosphoric acid **7**. In this sense it can be considered as the end of the oxygenation process of the starting phosphorothioic acid.

The ease of exocyclic elimination of alcohol or phenol from the pentacoordinate system **8** is worth emphasizing. In spite of the fact that the P—S bond in the apical position is likely to undergo an easier fission than the analogous P—O bond, the dominating factor in the reaction is the leaving group ability of the alkoxy or aryloxy group in its protonated form.

Our results provide strong support for mechanistic schemes proposed by other authors for the transphosphorylation reaction in 1,2-cis-diol systems[6] and analogous systems containing sulphur,[7] selenium[8] and tellurium.[9] They demonstrate the importance of pentacoordinate phosphorus intermediates in nucleophilic displacement at tetracoordinate phosphorus atom according to Westheimer's[5] conceptions.

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