Mechanistic and Synthetic Aspects of Intramolecular Base-Catalyzed Migration of the Thiophosphoryl Group from Sulfur to Oxygen in Sugar β-Hydroxyphosphorodithioate Systems†

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Abstract: β-Hydroxyphosphorodithioates of suitably substituted hexopyranoses undergo pyridine-catalyzed transphosphorylation to give the corresponding β-mercaptophosphorothioates in high yields. The propensity of the thiophosphoryl group to migrate from sulfur to oxygen is correlated with the steric arrangement of substituents involved in the transphosphorylation process. The formation of transient oxathiaphospholanes, indicated by ^{31}P NMR, allowed us to propose the mechanistic scheme for intramolecular thiophosphoryl group transfer from sulfur to oxygen, involving pentacovalent phosphorus intermediates. In the case of methyl 2-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (**15**), pyridine-catalyzed migration took an unusual course, affording methyl 4-*O*-(5′,5′-dimethyl-1′,3′,2′-dioxaphosphorinan-2′-yl)-2,3-dithiolo-α-D-altropyranoside (**18**). Isolation of the key intermediate **19** and transient appearance of several other intermediates characterized by ^{31}P NMR analysis allowed the reaction pathway to be constructed, showing that also this transformation occurs as a result of intramolecular rearrangements through pentacovalent phosphorus intermediates.

Introduction

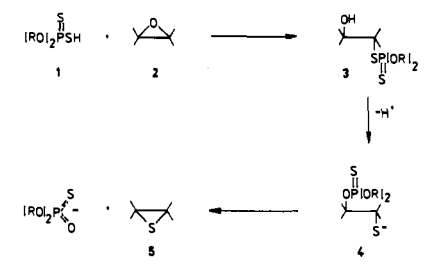
The search for potent antimetabolites, analogues of naturally occurring nucleic acids and oligosaccharides of biological importance, justifies the expansion of synthetic methods concerned with modifications of the carbohydrate components.[1] Another important factor that has intensified the research in this field is the elucidation of the structure of several antibiotics containing "unusual" sugar components.[2] Among various modified carbohydrates, derivatives containing the thiolo function are most interesting.[3] Replacement of oxygen by sulfur undoubtedly affects the physical, chemical, and biological properties of the biomolecule, for example, the substrate specificity with respect to enzymic reactions.[4] Modification of a sugar molecule by addition of a chemically reactive group could provide a biochemical handle unique to a specific location in the molecule.

The aim of these investigations was to elaborate efficient synthesis of sugar *vic*-thiolophosphorothioates by transphosphorylation of the corresponding *vic*-hydroxyphosphorodithioates.

Phosphoryl group transfer reactions in *vic*-diol systems, which occur in many biological processes, have long been at the focus of extensive studies in many laboratories.[5] A similar migration of the phosphoryl group from sulfur to oxygen has been observed in synthetic procedures leading to episulfides or alkenes, e.g., in reactions of oxiranes with monothio-[6] and monoselenoacids of phosphorus[7] and reactions of carbonyl compounds with carbanions containing the thiophosphoryl group[8] or with alkoxyanions generated from *S*-(β-oxoalkyl)thio- and selenophosphates.[9] The reaction of styrene ^{18}O oxide with ribonucleoside P-chiral 3′,5′-phosphorothioates has been explored in the stereospecific conversion into corresponding chiral [^{18}O]phosphates.[10] Mechanistic proposals for the transphosphorylation step from sulfur to oxygen involving the formation of pentacovalent phosphorus intermediates,[11] put forward by Hamer,[12] found experimental support in our studies on oxirane ring opening by *O,O*-dialkylphosphorothioic acids in the case of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose.[13]

Free dithioacids of phosphorus (**1**) react with sugar oxiranes **2** to give the stable adduct **3** whereas the reaction with dithioacid salts leads to the corresponding episulfides (**5**).[14] (Scheme I). Our previous efforts to stop the reaction at the stage of β-mercaptophosphorothioates **4** were not successful. The growing interest in thiolosugars stimulated us to reinvestigate our previous work.

Scheme I



† Dedicated to Professor Frank Westheimer on the occasion of his 80th birthday.

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(10) (a) Guga, P.; Okruszek, A. *Tetrahedron Lett.* **1984**, *25*, 2897-2900. (b) Okruszek, A.; Guga, P.; Stec, W. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1225-26. (c) Okruszek, A.; Guga, P.; Stec, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 594-595.

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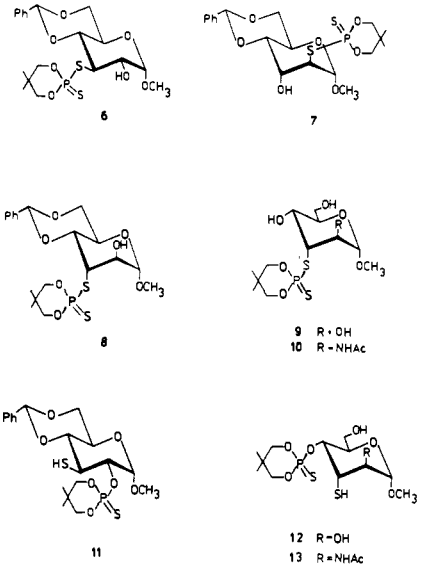
Chart I. Model Sugar β-Hydroxyphosphorodithioates **6–10** and Products of Their Rearrangement **11–13**



Through systematic studies of the reaction of sugar oxiranes with dithiophosphoric acids in the present work, we have found conditions under which the β-mercaptophosphorothioates can be obtained as stable, readily isolated compounds in high yields. Employing appropriate model sugar β-hydroxyphosphorodithioates, we have been able to correlate the propensity of the thiophosphoryl group to migrate from S to O with the steric arrangement of groups involved in the transphosphorylation process **3** → **4**. Monitoring the progress of the reaction **3** → **4** by ^{31}P NMR spectroscopy allowed us to propose the mechanistic scheme of thiophosphoryl group transfer, consistent with our previous investigations.

The present paper is also concerned with elucidation of an unusual course of transphosphorylation caused by just such stereochemical factors and leading to a sugar phosphate containing two thiolo groups in trans-diaxial arrangement.

Results and Discussion

Employing the diequatorial, axial–equatorial, and diaxial β-hydroxyphosphorodithioates **6–10** (Chart I), allowed the relative rates of migration of the thiophosphoryl group within the sugar molecule to be measured. Pyridine was found to be the reaction medium of choice for the quantitative conversion of β-hydroxyphosphorodithioates into β-mercaptophosphorothioates. The transphosphorylation proceeded at ambient temperature, and the reaction progress was followed by ^{31}P NMR spectroscopy. The β-mercaptophosphorothioates **11–13** were isolated with high yields and their structures confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.

Thus, in the case of diequatorial arrangement of the reacting centers in β-hydroxyphosphorodithioate **6**, transphosphorylation S → O proceeded smoothly and was accomplished within 5 min, affording the β-mercaptophosphorothioate **11** in quantitative yield. The transdiequatorial arrangement seems to be particularly favorable for the formation of the pentacoordinate phosphorus intermediate. The spectroscopic data for compound **11** and its acetyl derivative (**11a**) (see Experimental Section) confirm the presence of the thiolo function as well as the position of the OP(S) substituent at C-2.

Compound **7** with its diaxial geometry of OH and SP(S)$(OR)_2$ failed to undergo migration of the thiophosphoryl group. Even after 30 days, the ^{31}P NMR spectrum continued to show only one signal corresponding to the starting β-hydroxyphosphorodithioate **7**. This lack of reactivity was not surprising, in view of the distance

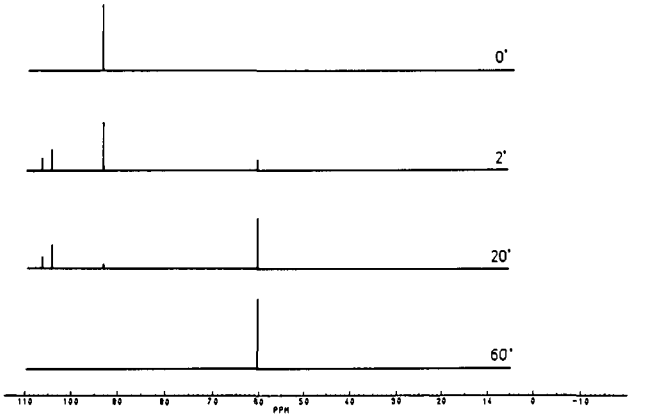
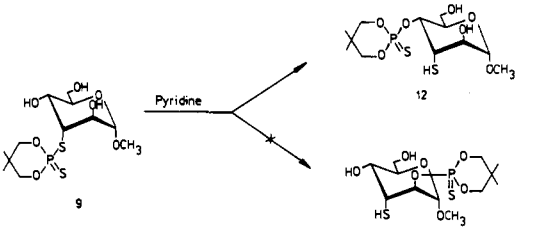


Figure 1. Time course of the rearrangement of **9** in pyridine solution at room temperature, as observed by ^{31}P NMR spectroscopy.

Scheme II. Preferential Route of Transphosphorylation of **9**



between the substituents involved in transphosphorylation and the context of a rigid bicyclic structure that does not allow the conformational changes necessary for the formation of the pentacoordinate phosphorus intermediate.

A similar unfavorable situation for the formation of the pentacoordinate phosphorus intermediate occurs in the case of the diaxially substituted β-hydroxyphosphorodithioate **8**. Compound **8** also failed to show transphosphorylation under the applied conditions, even after 1 month.

Debenzylidenation of the dithiophosphate **8**, however, dramatically changed the situation. The formation of compound **9** opened two possibilities for the thiophosphoryl group transfer from the axially oriented dithiophosphate substituent: either to the adjacent equatorial group at C-4 or to the axial hydroxyl group at C-2. Rearrangement of **9** proved to be fully regioselective with preference for the equatorially oriented hydroxyl group and afforded β-mercaptophosphorothioate **12**. (Scheme II).

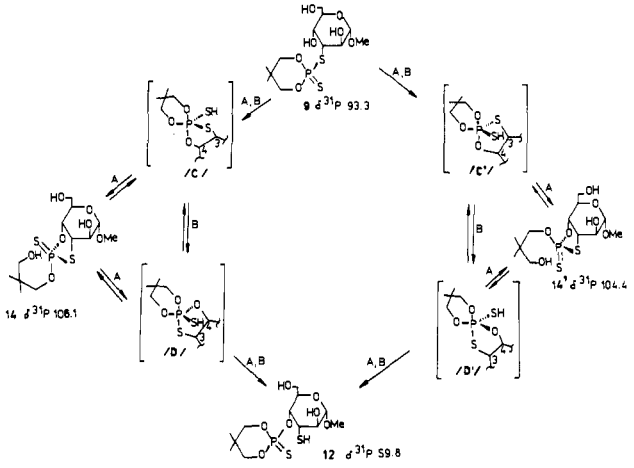
^{31}P NMR data confirmed the presence of the phosphorothioate group at carbon C-4. The undecoupled ^{31}P NMR signal at 59.8 ppm is a double triplet of triplets due to the coupling with the two axial ($^{3}J_{P,a}$ = 5.5 Hz, t) and two equatorial protons ($^{3}J_{P,e}$ = 21.0 Hz, t) of the phosphorinane ring and with the axial proton at C-4 ($^{3}J_{P,4}$ = 11.4 Hz, d). The same coupling constants were observed in the ^{1}H NMR spectrum for the H-4 proton at 5.05 ppm. Additional proof for the migration toward C-4 OH is given by ^{13}C NMR. The doublet signals corresponding to C-3, C-5, and C-4 are due to coupling with the ^{31}P nucleus through three and two linkages, respectively. Axial–equatorial migration leading to the phosphorothioate **12** containing a free SH group at C-3 was accomplished within 1 h and in quantitative yield. ^{31}P NMR studies of the transphosphorylation **9** → **12** revealed the formation of two intermediate diastereoisomeric oxathiaphospholanes (**14** and **14'**) at 106.1 and 104.4 ppm[15] (Figure 1).

On this basis, a mechanistic scheme for the transphosphorylation **9** → **12** is proposed. (Scheme III). Previous studies[13] suggest that the phospholanes **14** and **14'** are involved in complex equilibria on the way from the substrate **9** to the product **12**. Although it is most likely that transphosphorylation **9** → **12** occurs through

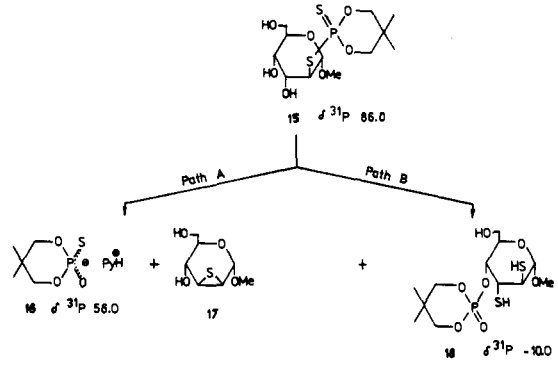
(13) Kudelska, W.; Michalska, M. *Tetrahedron* **1986**, *42*, 629–636.
(14) (a) Kudelska, W.; Michalska, M. *Carbohydr. Res.* **1980**, *83*, 43–49. (b) Kudelska, W.; Michalska, M.; Swiatek, A. *Carbohydr. Res.* **1981**, *90*, 1–6.

(15) The ^{31}P NMR signals for diastereoisomeric phospholanes were ascribed to isomers "trans" and "cis" on the basis of the results obtained by Mikołajczyk and Witczak: *J. Chem. Soc., Perkin Trans. 1* **1977**, 2213–2222.

Scheme III. Mechanistic Scheme for Transphosphorylation **9** → **12**



Scheme IV



the intermediate formation of these oxathiaphospholanes, the possibility of a parallel process involving a direct route (**9** → C → D → **12** or **9** → C′ → D′ → **12**) cannot be excluded.

The diequatorial β-hydroxyphosphorodithioate **6** can be expected to follow the analogous reaction path as shown in Scheme II, but in this case it was not possible to register ^{31}P NMR signals corresponding to the intermediate oxathiaphospholanes due presumably to the short reaction time (5 min).

Another example of thiophosphoryl group transfer is shown with the model sugar dithiophosphate **10**, which was obtained by ring opening of the sugar aziridine and subsequent debenzylidenation.[16] Axial–equatorial arrangement of the groups involved in transphosphorylation allowed smooth transfer of the thiophosphoryl group. Thus, methyl 2-*N*-acetyl-3-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-α-D-altropyranoside (**10**) was converted into 2-*N*-acetyl-3-mercapto-4-thionophosphate **13** within 1 h. Acetylation of the mercaptosugar **13** gave compound **13a**, identified as the *N*,*O*,*S*-triacetyl derivative. Transphosphorylation **10** → **13** offers a convenient route to the synthesis of β-aminomercaptosugars.

An unusual course of transphosphorylation was observed on methyl 2-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (**15**).[14b] The following course of events was observed when **15** was allowed to rearrange at room temperature in pyridine solution. (Scheme IV). The reaction was completed within 48 h at ambient temperature, and the ^{31}P NMR spectrum showed that two phosphorus-containing products were formed. In addition, TLC revealed the presence of a third product that did not contain phosphorus. The ^{31}P NMR spectrum showed no change over a period of 3 weeks. The values of chemical shifts suggested that compound **16** ($\delta(^{31}P)$ = 56.0 ppm) contained one less sulfur atom than **15** and that **18** contained a phosphorus atom completely surrounded by oxygen atoms. The products were

(16) Brzezińska, E.; Michalska, M. *J. Carbohydr. Chem.* **1990**, *9*, 451–460.

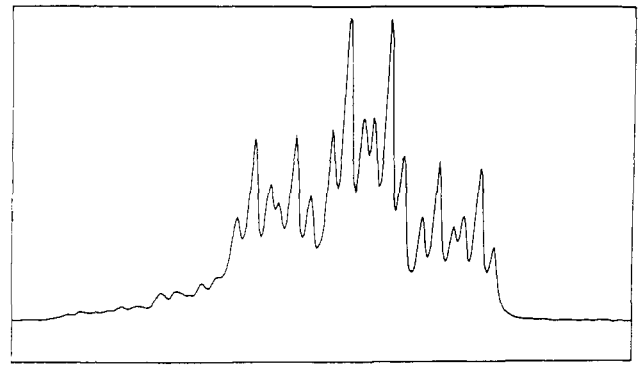


Figure 2. Undecoupled ^{31}P NMR signal at −10 ppm, corresponding to **18**.

separated by partition between water and chloroform. The water-soluble compound **16** was identified as the pyridinium 5,5-dimethyl-1,3,2-dioxaphosphorinanylthioate by comparison with an authentic sample obtained independently. The aqueous layer also contained product **17**, which was isolated as the acetyl derivative **17a** and identified as methyl 4,6-di-*O*-acetyl-2,3-epithio-α-D-mannopyranoside. The chloroform layer contained product **18** ($\delta(^{31}P)$ = −10 ppm), which was identified as methyl 4-*O*-(2′-oxo-5′,5′-dimethyl-1′,3′,2′-dioxaphosphorinan-2′-yl)-2,3-dithiolo-α-D-altropyranoside.

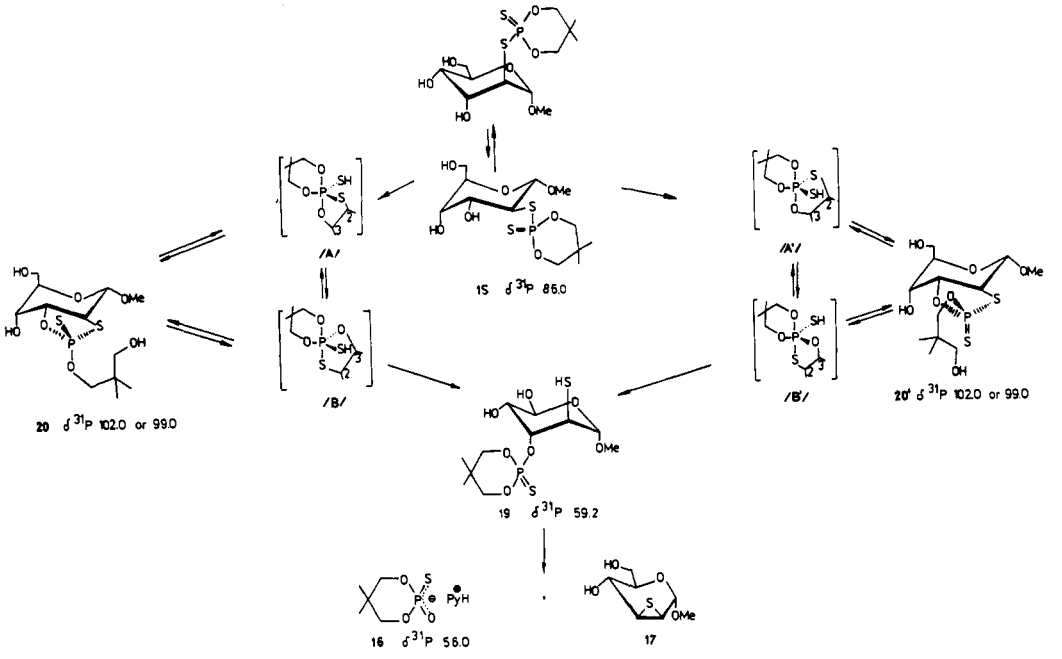
This somewhat unexpected structure got strong support from spectroscopic investigations, in particular, from the pattern of the undecoupled ^{31}P NMR signal at −10.0 ppm corresponding to **18** (Figure 2). This signal is a double triplet of triplets, due to the coupling with the two axial ($^3J_{P,a}$ = 3.5 Hz) and two equatorial protons of the phosphorinane ring ($^3J_{P,e}$ = 20.6 Hz) and with the axial H-4 proton ($J_{P,4}$ = 9.0 Hz). The doublet signal characterized by the coupling value 9.0 Hz proves that the phosphate group is connected to a secondary carbon atom. The same coupling constant is observed for the ^1H NMR signal corresponding to the H-4 proton at 4.88 ppm, which is a double triplet with $^3J_{P,4}$ = $^3J_{4,5}$ = 9.0 Hz and $^3J_{3,4}$ = 4.5 Hz. The two thiolo functions were ascribed the doublet signals at 2.38 and 2.55 ppm with coupling constants $^3J_{2,SH}$ = $^3J_{3,SH}$ = 9.4 Hz. The characteristic doublet signal of the anomeric proton at 4.73 ppm and $^3J_{1,2}$ = 1.2 Hz confirms the α-configuration of the MeO–glycoside. The position of the *O*-phosphate group at C-4 was further confirmed by the values of chemical shifts and ^{31}P–^{13}C coupling constants corresponding to carbon atoms C-3, C-5, and C-4, respectively: 44.71 ppm ($^3J_{P,3}$ = 3.8 Hz), 68.25 ppm ($^3J_{P,5}$ = 5.6 Hz), and 69.30 ppm ($^3J_{P,4}$ = 3.8 Hz).

An additional proof of the ascribed structure is provided by ^1H, ^{13}C, and ^{31}P NMR spectra of the acetyl derivative of compound **18**. In the ^1H NMR spectrum, three singlet signals of 1:1:1 intensity, at 2.40, 2.37, and 2.12 ppm, indicate the presence of the two SAc groups and one OAc group, respectively. The ^{13}C NMR spectrum is complementary to the results of ^1H NMR. Three ^{13}C signals at 193.40, 192.70, and 170.72 ppm confirm the character and number of the $SCOCH_3$ and $OCOCH_3$ groups present in the molecule of compound **18a**. The undecoupled ^{31}P signal shows the same pattern and coupling constants as the signal corresponding to the non-acetylated compound **18**.

Monitoring of the reaction progress by high-resolution ^{31}P NMR spectroscopy and precise analysis of ^{31}P NMR and $^{31}P\{^1H\}$ NMR spectra allowed us to observe the intermediates on the reaction pathways to products **16**, **17**, and **18**. The progress of the transphosphorylation in the course of time is represented by the Figure 3. Although the registered signals reflected the parallel occurence of two reactions, we were able to identify the ^{31}P signals corresponding to the intermediates on path A or B, respectively, of Scheme IV. From analysis of the present results, in conjunction with those of our earlier investigations,[13] we can precisely define the path A (**15** → **16** + **17**) in Scheme V.

The first step depicted in Scheme V consists of the formation of two diastereoisomeric pentacovalent trigonal-bipyramidal in-

Scheme V. Mechanistic Scheme for Path A



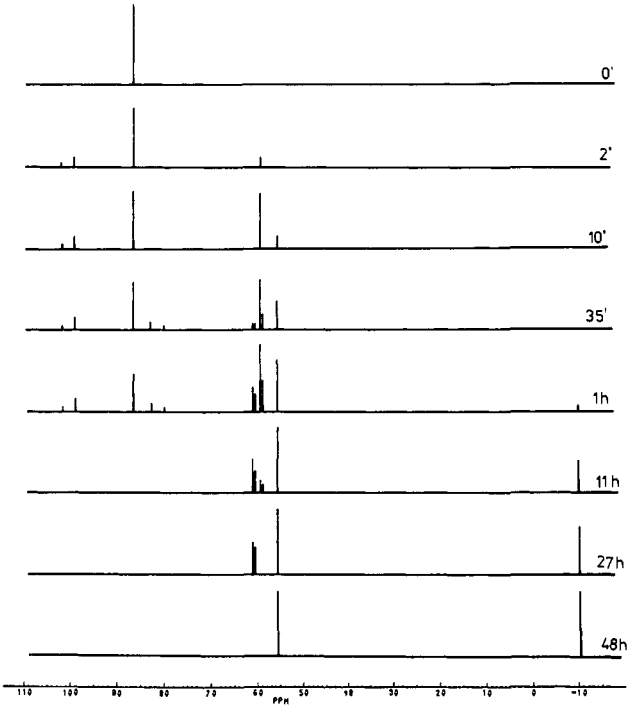


Figure 3. Progress of transphosphorylation in the course of time.

termediates (TBP)[17] by nucleophilic attack of the neighboring oxygen atom on the prochiral phosphorus atom. The formation of the TBP A and A′ is possible only under one condition, namely, if the hexopyranose ring changes its conformation from $^4C_1$ to $^1C_4$. The intermediates A and A′ are in equilibrium with the TBP B and B′ as the result of a pseudorotation process.[17] Breaking of the apical P–O bonds in the TBP A or A′ leads to diastereoisomeric oxathiaphospholanes **20** and **20′** characterized by $\delta(^{31}P)$ chemical shifts[18] at 102.0 and 99.0 ppm. We were not able to ascribe with certainty the chemical shifts to the particular diastereoisomer. The oxathiaphospholanes **20** and **20′** can, in turn, undergo transformation into the TBP B and B′ in which the P–S bond is in the apical position. It is not certain whether the TBP B nd B′ derive from the transformation of oxathiaphospholanes, or from pseudorotation of the TBP A and A′.

All these intermediates are in equilibrium. The P–S bond breaking in the TBP B and B′ is a more favorable process than P–O bond breaking in the TBP A and A′ because it leads, via elimination of a better leaving group ($^-$SR), to the thionophosphate **19** ($\delta(^{31}P)$ = 59.2 ppm) in which the hexopyranose ring returns to its privileged $^4C_1$ conformation. The data collected in Figure 3 show clearly the intensification of the 59.2 ppm signal and parallel decrease of signals at 102.0 and 99.0 ppm, ascribed to the oxathiaphospholanes **20** and **20′**. The thionophosphate **19** is converted into episulfide **17** and the phosphorothioate anion **16** by nucleophilic attack of the sulfur atom (in compound **19**) at C-2 on the carbon atom C-3 bearing the phosphorothioate substituent. The ease of episulfide formation under mild conditions (pyridine, ambient temperature) can best be explained in terms of the favorable transdiaxial arrangement of the reacting centers, which facilitates the intramolecular nucleophilic attack by sulfur and subsequent departure of the monothioacid anion.

A more difficult task was to find a rational explanation for the unusual course of transphosphorylation **15** → **19** → **18** via path B. It has already been suggested that the thionophosphate **19** is the crucial intermediate for products **16**, **17**, and **18**. In contrast to the relatively obvious reaction course leading to **16** and **17**, step **19** → **18** seems to be more complex. On the way from **19** to **18**, two pairs of signals (at 83.0 and 80.0 ppm and 60.5 and 60.2 ppm) appeared in the ^{31}P NMR spectrum in addition to the signal at 59.0 ppm. The signal corresponding to **18** (at −10.0 ppm) appeared after a few hours. The mechanistic scheme shown in Scheme VI consistent with the observed ^{31}P NMR spectral data is proposed.

The thionophosphate **19** undergoes a nucleophilic attack at phosphorus by the neighboring oxygen atom at C-4. The pentacoordinate phosphorus intermediates C and C′ thus formed are in equilibrium with the two diastereoisomeric 1,3,2-dioxaphospholanes **24** and **24′** ($\delta(^{31}P)$ = 80.0 and 83.0 ppm, respectively[15]) and the newly formed thionophosphate **21** ($\delta(^{31}P)$ = 59.0 ppm), via the TBP D and D′.

The dioxaphospholanes **24** and **24′** undergo nucleophilic attack by sulfur on carbon atom C-3, resulting in the rupture of the C–O bond in the five-membered ring and formation of two diastereoisomeric structures (**22** and **22′**) ($\delta(^{31}P)$ = 60.5 and 60.2 ppm). The signal at −10.0 ppm corresponding to methyl 2,3-dithiolo-4-*O*-(2′-oxo-5′,5′-dimethyl-1′,3′,2′-dioxaphosphorinan-2′-yl)-α-D-altropyranoside, **18**, gains in intensity as the signals at 60.5 and

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(18) Gorenstein, D. G. *J. Am. Chem. Soc.* **1975**, *97*, 898–900.

Scheme VI. Mechanistic Scheme for Path B

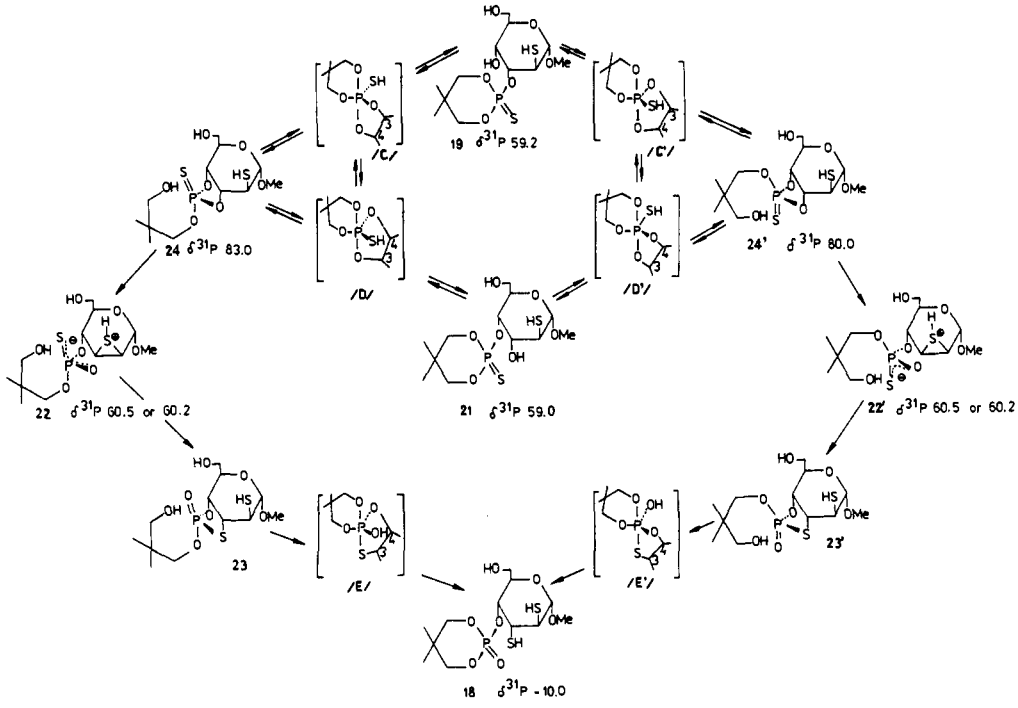

Table I

compd	δ(31P) (ppm)	31P–1H coupling constants (Hz)
19	59.2 (dtq)	$^3J_{P,a} = {}^4J_{P,4} = 3.0$, $^3J_{P,e} = 22.3$, $^3J_{P,3} = 11.1$
20 and **20'**	102.0 (t)	$^3J_{P,CH} = 7.2$, $^3J_{P,3} = {}^3J_{P,2} = 0$
	99.0 (t)	
16	56.0 (tt)	$J_{P,e} = 22.7$, $J_{P,a} = 6.4$
22 and **22'**	60.2 (dt)	$^3J_{P,CH} = 11.5$, $^3J_{P,4} = 7.0$
	60.5 (dt)	

60.2 ppm disappear. Formation of the new carbon–sulfur bond at C-3 is initiated by the attack of the sulfur atom in the ambident thiophosphate anions **22** and **22'** on carbon C-3. It is worth mentioning here that opening of the thiirane ring is facilitated by the fact that the attacking nucleophile is situated at the neighboring carbon atom in a rather favorable geometrical arrangement. The reaction presumably proceeds further via the oxathiaphospholanes **23** and **23'** (undetected by ^{31}P NMR spectroscopy) followed by the formation of TBP E and E' to yield 2,3-dithiolohexopyranose-4-phosphate **18**. The isomerization **24** → **23** via **22** and **24'** → **23'** via **22'**, respectively, is an example of the thiono–thiolo rearrangement in cyclic thionophosphates, leading in this case, to the formation of the endocyclic thiolophosphate. The thiono–thiolo isomerization of organophosphorus thionoesters is known to be effected thermally as well as by the influence of catalysts.[19] The rearrangement observed in our case was possible due to participation by a neighboring sulfur atom.[20]

The structures of the proposed intermediates **19–22** are confirmed by the chemical shifts of the ^{31}P nucleus, typical for this kind of thiophosphorus compounds. The undecoupled ^{31}P NMR spectra, registered in the course of the rearrangement, allowed us to find coupling constants between the phosphorus nucleus and protons. The values of coupling constants were in agreement with the proposed structures (Table I). The observed value of long-range coupling $^3J_{P,4}$ in compound **19** results from the zigzag "W" arrangement acquired by the phosphorus atom and H-4 atom, lying in the same plane. In the case of oxathiaphospholanes **20** and **20'**, where the hexopyranose ring and the five-membered oxathiaphospholane ring are trans-fused, the P–O–C–H2 and P–O–C–H3 torsion angles are close to 90°. Accordingly, the $^3J_{P,3}$ and $^3J_{P,2}$ values are close to 0 Hz, which is in full agreement with the Karplus curve.[21]

Being aware of the crucial role of the thionophosphate **19** in the formation of compounds **16**, **17**, and **18**, we undertook the task to isolate **19** prior to its further transformations. This was possible at the point of highest concentration of **19** in the reaction mixture, established by ^{31}P NMR monitoring. The thionophosphate **19** was characterized as its *O,O,S*-triacetyl derivative (**19a**) (δ(^{31}P) = 61.1 ppm). The structure of **19a** was unambiguously proved by the results of elemental analysis, IR, and ^1H and ^{13}C NMR spectroscopy.

Summarizing, evidence obtained from ^{31}P NMR spectroscopy gives a convincing picture of the reaction path B, which involves the formation of dioxaphospholanes at 80.0 and 83.0 ppm, and of the diastereoisomeric phosphorothioate anions at 60.5 and 60.2 ppm.

Conclusions

The present work has demonstrated that pyridine-catalyzed thiophosphoryl group transfer from the sulfur atom to the neighboring oxygen atom in β-hydroxyphosphorodithioate systems involves intermediate formation of the pentacoordinate phosphorus species and oxathiaphospholanes. The relative rate of migration is dependent upon the steric arrangement of the groups involved in transphosphorylation. The specific steric arrangement of the reacting centers in the case of compound **15** induced further transformations of the primarily formed thionophosphate **19**, leading to the *trans*-2,3-dimercapto-4-*O*-phosphate **18** via intramolecular thiono–thiolo-type rearrangement.

The synthetic aspect of these investigations is the easy generation of the mercapto function in monosaccharide systems under mild reaction conditions.

Experimental Section

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. Optical rotations were determined in chloroform with a Polamat A polarimeter. IR spectra were obtained by using a

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Unicam SP-200G spectrophotometer. ^{31}P NMR spectra were measured in pyridine or $CHCl_3$ with H_3PO_4 as external standard (Varian 300, Bruker 300, Jeol 60 MHz FT). ^1H NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standard (with Bruker 300-MHz or Varian 60-MHz spectrometers). ^{13}C NMR spectra were determined on solutions in $CDCl_3$ with a Tesla BS 567A spectrometer operating at 25.2 MHz. Chemical shifts are given in parts per million. Elemental analyses were performed by the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies of the Polish Academy of Sciences, Łódź. Column chromatography was performed on E. Merck Silica Gel 60 (63–200 μm).

Methyl 4,6-*O*-benzylidene-3-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-glucopyranoside (**6**), methyl 4,6-*O*-benzylidene-2-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (**7**), methyl 4,6-*O*-benzylidene-3-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-altropyranoside (**8**), methyl 3-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-altropyranoside (**9**), and methyl 2-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (**15**) were prepared from the corresponding 2,3-oxiranes according to the procedure described by Kudelska and Michalska.[14b] Methyl 2-acetamido-2-deoxy-3-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-altropyranoside (**10**) was obtained according to the procedure described by Brzezińska and Michalska.[16]

Isomerization of β-Hydroxyphosphorodithioates 6–10 in Pyridine Solution. General Procedure. The appropriate sugar β-hydroxyphosphorodithioate was dissolved in a minimum amount of dry pyridine and allowed to react at room temperature. The progress of the isomerization was monitored by the ^{31}P NMR spectroscopic method. When the reaction was completed, the solvent was removed under reduced pressure and the residue subjected to codistillation with heptane to remove traces of pyridine. Crystallization from chloroform–diethyl ether gave the corresponding β-mercaptophosphorothioate.

Methyl 4,6-*O*-Benzylidene-2-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thiolo-α-D-glucopyranoside (11). **11** was prepared from phosphorodithioate **6** (0.93 g, 2 mmol) and pyridine (5 mL). Reaction time: 5 min at 20 °C. Yield: 0.84 g (90%) (colorless crystals). Mp: 166–167 °C $[\alpha]_{578}^{20}$: +24 (*c* 1.9). IR: ν_{max} 2520 (SH) and 690 cm^{-1} (P═S); ^{31}P NMR ($CDCl_3$): δ 58.9. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3 H, CCH_3 (e)), 1.21 (s, 3 H, CCH_3(a)), 2.05 (d, 1 H, SH, $^3J_{SH,3}$ = 3.5 Hz), 3.38 (s, 3 H, OCH_3), 3.55 (dt, 1 H, H-3, $^3J_{SH,3}$ = 3.5 Hz, $^3J_{2,3}$ = $^3J_{3,4}$ = 10.5 Hz), 3.64 (t, 1 H, H-4, $^3J_{3,4}$ = $^3J_{4,5}$ = 10.5 Hz), 3.72–3.92 (m, 4 H, H-5, H-6, 2 × OCH_2(e)), 4.19–4.33 (m, 3 H, H-6, 2 × OCH_2(a)), 4.45 (dt, 1 H, H-2, $^3J_{1,2}$ = 3.5 Hz, $^3J_{P,2}$ = $^3J_{2,3}$ = 10.5 Hz), 4.97 (d, 1 H, H-1, $^3J_{1,2}$ = 3.5 Hz), 5.48 (s, 1 H, CHC_6H_5), 7.15–7.55 (m, 5 H, H(Ar)). ^{13}C NMR ($CDCl_3$): δ 20.82 (CCH_3(e)), 21.94 (CCH_3(a)), 32.10 (d, $^3J_{P,C}$ = 5.6 Hz, $C(CH_3)_2$), 40.50 (d, $^3J_{P,C}$ = 9.4 Hz, C-3), 55.31 (OCH_3), 63.90 (C-5), 68.83 (C-6), 75.77 (C-2), 81.67 (C-4), 97.64 (C-1), 101.90 (CC_6H_5), 126.16, 128.25, 129.15, 136.99 (C(Ar)). Anal. Calcd for $C_{19}H_{27}O_7S_2P$: C, 49.33; H, 5.88. Found: C, 49.13; H, 5.97.

Methyl 3-*S*-Acetyl-4,6-*O*-benzylidene-2-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-glucopyranoside (11a). Compound **11** was acetylated to give **11a** as colorless crystals. Mp: 108–109 °C (methanol–water). $[\alpha]_{578}^{20}$: +58 (*c* 1.8). IR: ν_{max} 1670 (SAc) and 710 cm^{-1} (P═S); ^{31}P NMR ($CDCl_3$): δ 59.0. ^1H NMR ($CDCl_3$): δ 0.80 (s, 3 H, CCH_3(e)), 1.20 (s, 3 H, CCH_3(a)), 2.26 (s, 3 H, SAc), 3.39 (s, 3 H, OCH_3), 3.49 (dd, 1 H, H-3, $^3J_{2,3}$ = 11.5 Hz, $^3J_{3,4}$ = 10.5 Hz), 3.64 (t, 1 H, H-4, $^3J_{3,4}$ = $^3J_{4,5}$ = 10.5 Hz), 3.68–3.90 (m, 3 H, H-5, 2 × OCH_2(e)), 4.11–4.27 (m, 4 H, H-6, H-6′, 2 × OCH_2(a)), 4.52 (dt, 1 H, H-2, $^3J_{1,2}$ = 3.5 Hz, $^3J_{P,2}$ = $^3J_{2,3}$ = 11.5 Hz), 4.91 (d, 1 H, H-1, $^3J_{1,2}$ = 3.5 Hz), 5.43 (s, 1 H, CHC_6H_5), 7.15–7.50 (m, 5 H, H(Ar)); ^{13}C NMR ($CDCl_3$): δ 20.67 (CCH_3(e)), 22.02 (CCH_3(a)), 30.90 (SAc), 31.40 (d, $^3J_{P,C}$ = 5.6 Hz, $C(CH_3)_2$), 44.72 (d, $^3J_{P,C}$ = 9.4 Hz, (C-3), 55.17 (OCH_3), 64.35 (C-5), 68.90 (C-6), 77.04 (C-2), 78.30 (C-4), 97.94 (C-1), 101.90 (CC_6H_5), 126.16, 128.18, 129.04, 136.99 (C(Ar)), 194.00 (SAc). Anal. Calcd for $C_{21}H_{29}O_8S_2P$: C, 50.06; H, 5.75; S, 12.71. Found: C, 49.95; H, 6.02; S, 12.84.

Methyl 4-*O*-(5′,5′-Dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thiolo-α-D-altropyranoside (12). **12** was prepared from phosphorodithioate **9** (0.75 g, 2 mmol) and pyridine (4 mL). Reaction time: 1 h at 20 °C. Yield: 0.71 g (91%) (colorless crystals). Mp: 143–144 °C. $[\alpha]_{578}^{20}$: +94 (*c* 2.4). IR: ν_{max} 2530 (SH) and 690 cm^{-1} (P═S). ^{31}P NMR ($CDCl_3$): proton decoupled δ 59.8 (s); undecoupled (dtt, $^3J_{P,a}$ = 5.5 Hz, $^3J_{P,e}$ = 21.0 Hz, $^3J_{P,4}$ = 11.4 Hz). ^1H NMR ($CDCl_3$): δ 0.94 (s, 3 H, CCH_3(e)), 1.23 (s, 3 H, CCH_3(a)), 2.49 (d, 1 H, SH, $^3J_{SH,3}$ = 10.2 Hz), 3.05 (br s, 2 H, 2 × OH), 3.42 (s, 3 H, OCH_3), 3.61 (dt, 1 H, H-3, $^3J_{2,3}$ = 4.2 Hz, $^3J_{SH,2}$ = 10.2 Hz), 3.80–4.08 (m, 6 H, H-5, H-6, 2 × OCH_2(e), 2 × OCH_2(a)), 4.20–4.34 (m, 2 H, H-2, H-6), 4.71 (d, 1 H, H-1, $^3J_{1,2}$ = 4.2 Hz), 5.05 (ddd, 1 H, H-4, $^3J_{3,4}$ = 4.7 Hz, $^3J_{4,5}$ = 9.1 Hz, $^3J_{P,4}$ = 11.4 Hz). ^{13}C NMR ($CDCl_3$): δ 20.97 (CCH_3(e)), 21.72 (CCH_3(a)), 32.30 (d, $^3J_{P,C}$ = 7.5 Hz, $C(CH_3)_2$), 42.55 (d, $^3J_{P,C}$ = 3.7 Hz, C-3), 55.54 (OCH_3), 61.14 (C-6), 67.70 (d, $^3J_{P,C}$ = 7.6 Hz, C-5), 71.10 (d, $^2J_{P,C}$ = 5.7 Hz, C-4), 72.71 (C-2), 101.97 (C-1). Anal. Calcd for $C_{12}H_{23}O_7S_2P$: C, 38.49; H, 6.19; S, 17.12. Found: C, 38.37; H, 6.25; S, 16.87.

Methyl 2-Acetamido-2-deoxy-4-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thiolo-α-D-altropyranoside (13). **13** was prepared from phosphorodithioate **10** (0.83 g, 2 mmol) and pyridine (4 mL). Reaction time: 1 h at 20 °C. Yield: 0.78 g (94%) (colorless crystals). Mp: 139–140 °C. $[\alpha]_{578}^{20}$: +26 (*c* 1.9). IR: ν_{max} 3450 (OH), 3300 (NH), 2520 (SH), 1655 and 1530 (amide) and 690 cm^{-1} (P═S). ^{31}P NMR ($CDCl_3$): δ 60.15. ^1H NMR ($CDCl_3$): δ 0.95 (s, 3 H, CCH_3(e)), 1.25 (s, 3 H, CCH_3(a)), 2.02 (s, 3 H, NAc), 2.50 (d, 1 H, SH, $^3J_{SH,3}$ = 10.0 Hz), 2.95 (br s, 1 H, OH), 3.43 (s, 3 H, OCH_3), 3.55–4.60 (m, 9 H, H-2, H-3, H-5, H-6, H-6′, 2 × CH_2(e), 2 × CH_2(a)), 4.66 (d, 1 H, H-1, $^3J_{1,2} \approx 1$ Hz), 6.90 (br d, 1 H, NH, $^3J_{NH,2}$ = 10.0 Hz). Anal. Calcd for $C_{14}H_{26}O_7NPS_2$: C, 40.47; H, 6.32; H, 3.37. Found: C, 40.58; H, 6.16; N, 3.42.

Methyl 2-Acetamido-6-*O*-acetyl-3-*S*-acetyl-2-deoxy-4,6-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-3-thio-α-D-altropyranoside (13a). Treatment of **13** with Ac_2O in pyridine afforded **13a** as colorless crystals. Mp: 159–160 °C. $[\alpha]_{578}^{20}$: +52 (*c* 1.8). IR: ν_{max} 3300 (NH), 1750 (OAc), 1710 (SAc), 1655 and 1530 (amide) and 680 cm^{-1} (P═S). ^{31}P NMR ($CDCl_3$): δ 58.9. ^1H NMR ($CDCl_3$): δ 0.90 (s, 3 H, CCH_3(e)), 1.22 (s, 3 H, CCH_3(a)), 2.00 (s, 3 H, NAc), 2.10 (s, 3 H, OAc), 2.35 (s, 3 H, SAc), 3.40 (s, 3 H, OCH_3), 3.45–4.50 (m, 9 H, H-2, H-3, H-5, H-6, H-6′, 2 × OCH_2(a)), 4.60 (d, 1 H, H-1, $^3J_{1,2} \approx 1$ Hz), 4.75–5.25 (m, 1 H, H-4), 6.40 (br d, 1 H, NH, $^3J_{NH,2}$ = 10.0 Hz). Anal. Calcd for $C_{18}H_{30}O_9NPS_2$: c, 43.27; H, 6.06; N, 2.87. Found: C, 42.98; H, 6.26; N, 2.77.

Pyridine-Catalyzed Rearrangement of Methyl 2-*S*-(5′,5′-Dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (15). Methyl 2-*S*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (**15**) (3.0 g, 8 mmol) was dissolved in dry pyridine (20 mL). The mixture was left at room temperature for 48 h. At this point, the ^{31}P NMR spectrum of the reaction mixture showed two signals: at δ 56.0 ppm and δ −10.0 ppm in a 55:45 ratio. Pyridine was removed under reduced pressure and coevaporation with heptane. The residue was partitioned between chloroform (50 mL) and water (50 mL). The aqueous layer was extracted with chloroform (1 × 15 mL). The combined organic layers were washed with water. The ^{31}P NMR spectrum showed one signal at −10.0 ppm for the organic layer and one signal at 56.0 ppm for the aqueous layer. The products were isolated by the following procedure.

The chloroform solution was dried over anhydrous $MgSO_4$ and filtered and the solvent removed by rotary evaporation in vacuo. The colorless oil thus obtained (1.3 g, 43.3%) was purified by silica gel column chromatography and crystallized from methanol–water to afford methyl 2,3-dimercapto-4-*O*-(5′,5′-dimethyl-2′-oxo-1′,3′,2′-dioxaphosphorinan-2′-yl)-α-D-altropyranoside (**18**) (1.1 g, 36.8%). Mp: 109–110 °C. $[\alpha]_{578}^{20}$: +45 (*c* 1.6). IR: ν_{max} 3250 (OH), 2530 (SH) and 1250 cm^{-1} (P═O). ^{31}P NMR ($CDCl_3$): proton decoupled δ −10.0 (s); undecoupled (dtt, $^3J_{P,a}$ = 3.5 Hz, $^3J_{P,e}$ = 20.6 Hz, $^3J_{P,4}$ = 9.0 Hz). ^1H NMR ($CDCl_3$): δ 0.85 (s, 3 H, CCH_3 (e)), 1.21 (s, 3 H, CCH_3 (a)), 2.38 (d, 1 H, $^3J_{H,SH}$ = 9.4 Hz, SH), 2.55 (d, 1 H, $^3J_{H,SH}$ = 9.4 Hz, SH), 3.29–3.40 (m, 1 H, H-2), 3.33 (s, 3 H, OCH_3), 3.57 (dt, 1 H, $^3J_{3,SH}$ = $^3J_{3,2}$ = 9.4 Hz, $^3J_{3,4}$ = 4.5 Hz, H-3), 3.75–4.75 (m, 7 H, 2 × OCH_2 (a), 2 × OCH_2 (e), H-5, H-6,6′), 4.73 (d, 1 H, $^3J_{1,2}$ = 1.2 Hz, H-1), 4.88 (dt, 1 H, $^3J_{P,4}$ = $^3J_{4,5}$ = 9.0 Hz, $^3J_{4,3}$ = 4.5 Hz, H-4). ^{13}C NMR ($CDCl_3$): δ 20.23 (CCH_3 (e)), 21.57 (CCH_3 (a)), 32.12 (d, $^3J_{P,C}$ = 5.6 Hz, $C(CH_3)_2$), 44.34 (C-2), 44.71 (d, $^3J_{P,C}$ = 3.8 Hz, C-3), 55.54 (OCH_3), 61.07 (C-6), 68.25 (d, $^3J_{P,C}$ = 5.6 Hz, C-5), 69.30 (d, $^2J_{P,C}$ = 3.8 Hz (C-4), 103.02 (C-1). Anal. Calcd for $C_{12}H_{23}O_7S_2P$: C, 38.49; H, 6.19; S, 17.12. Found: C, 38.21; H, 6.27; S, 17.38.

Compound **18** was acetylated (Ac_2O/Py) to give syrupy methyl 6-*O*-acetyl-2,3-di-*S*-acetyl-4-*O*-(5′,5′-dimethyl-2′-oxo-1′,3′,2′-dioxaphosphorinan-2′-yl)-α-D-altropyranoside (**18a**). $[\alpha]_{578}^{20}$: +75 (*c* 1.6). IR (film): ν_{max} 1730 (OAc), 1680 (SAc) and 1250 cm^{-1} (P═O). ^{31}P NMR ($CDCl_3$): proton decoupled δ −10.0 (s); undecoupled (dtt, $^3J_{P,a}$ = 3.5 Hz, $^3J_{P,e}$ = 20.6 Hz, $^3J_{P,4}$ = 9.0 Hz). ^1H NMR ($CDCl_3$): δ 0.89 (s, 3 H, CCH_3 (e)), 1.22 (s, 3 H, CCH_3 (a)), 2.12 (s, 3 H, OAc), 2.37 (s, 3 H, SAc), 2.40 (s, 3 H, SAc), 3.40 (s, 3 H, OCH_3), 3.90 (dd, 2 H, $^2J_{a,e}$ = 11.1 Hz, $^3J_{P,e}$ = 20.6 Hz, 2 × OCH_2 (e)), 4.00–4.15 (m, 4 H, 2 × OCH_2 (a), H-2, H-5), 4.30–4.35 (m, 3 H, H-3, H-6,6′), 4.67 (d, 1 H, $^3J_{1,2}$ = 1.7 Hz, H-1), 4.80 (dt, 1 H, $^3J_{P,4}$ = $^3J_{4,5}$ = 9.0 Hz, $^3J_{3,4}$ = 4.5 Hz, H-4). ^{13}C NMR ($CDCl_3$): δ 20.33 (CCH_3 (e)), 20.80 (OAc), 21.60 (CCH_3 (a)), 30.20 and 30.53 (2 × SAc), 32.15 (d, $^3J_{C,P}$ = 5.7 Hz, $C(CH_3)_2$), 45.45 (d, $^3J_{C,P}$ = 3.8 Hz, C-3), 46.92 (C-2), 55.4 (OCH_3), 62.90 (C-6), 67.9 (d, $^3J_{C,P}$ = 5.6 Hz, C-5), 70.75 (d, $^2J_{C-P}$ = 3.8 Hz, C-4), 100.4

(C-1), 170.72 (OAc), 192.70, 193.40 (2 × SAc). Anal. Calcd for $C_{18}H_{29}O_{10}SP$: C, 43.23; H, 5.79; S, 12.82. Found: C, 43.30; H, 5.89; S, 12.79.

The aqueous layer (56.0 ppm) was evaporated to dryness. Examination of the resulting syrup (1.5 g) by TLC (R_f 0.05 and 0.20, ethyl acetate–chloroform, 1:1, v/v) showed that it was composed of two products. The phosphorus-containing product was identified as the pyridinium 5,5-dimethyl-1,3,2-dioxaphosphorinanylthioate **16**. The ^{31}P NMR spectrum did not change when an authentic sample of the salt **16**, obtained independently, was added to the reaction mixture. The syrup was acetylated (15 mL Ac_2O/8 mL Py, 24 h), and the acetyl derivative was isolated by dilution of the reaction mixture with water (0 °C, 50 mL) and extraction with chloroform (3 × 20 mL). The aqueous layer contained the pyridinium salt **16** ($\delta(^{31}P)$ = 56.0 ppm). The combined chloroform extracts were washed successively with 1 N HCl, saturated aqueous $NaHCO_3$, and water. The chloroform solution was dried ($MgSO_4$) and filtered and the solvent removed to yield a colorless oil (0.8 g). Purification of the product by silica gel column chromatography gave the syrupy methyl 4,6-di-*O*-acetyl-2,3-dideoxy-2,3-epithio-α-D-mannopyranoside (**17a**). $[\alpha]^{20}_{578}$: +107 (*c* 2.06). IR (film): ν_{max} 1720 and 1700 cm^{-1} (OAc). ^1H NMR ($CDCl_3$): δ 2.05 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 3.03 (s, 2 H, H-2, H-3), 3.42 (s, 3 H, OCH_3), 3.70–3.95 (m, 1 H, H-5), 3.95–4.20 (m, 2 H, H-6,6′), 4.95 (d, 1 H, $^3J_{4,5}$ = 10.0 Hz, H-4), 5.00 (s, 1 H, H-1). ^{13}C NMR ($CDCl_3$): δ 20.67 and 20.82 (2 × –OAc), 33.07 and 35.08 (C-2 and C-3), 63.38 (C-6), 65.54 (C-4 and C-5), 97.64 (C-1), 169.68 and 170.51 (2 × OAc). Anal. Calcd for $C_{11}H_{15}O_6S$: C, 47.85; H, 5.76; S, 11.6. Found: C, 47.89; H, 5.99; S, 11.8.

Methyl 4,6-Di-*O*-acetyl-2-*S*-acetyl-3-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (19a). In order to isolate the thionophosphate **19**, the following procedure was applied on the basis of the results of ^{31}P NMR monitoring of the reaction progress. The altropyranoside **15** (1.5 g) was dissolved in dry pyridine (10 mL). After 0.5–1.0 h at ambient temperature when the signal corresponding to the thionophosphate **19** ($\delta(^{31}P)$ = 59.2 ppm) reached its highest intensity, acetic anhydride (5 mL) was added. After 24 h at 20 °C, the reaction mixture was worked up by a standard procedure. On evaporation of the chloroform extracts to the volume of 5 mL, colorless crystals precipitated and were filtered off. The precipitate (0.3 g), mp 136–137 °C, was identified (IR, ^1H, ^{13}C, and ^{31}P NMR) as the tri-*O*-acetyl derivative of **15**. The mother liquors were evaporated under vacuo. Silica gel column chromatography (eluent, benzene–acetone–chloroform, 3:1:1, v/v) of the residual oil gave the triacetyl derivative of **19** as colorless hexagonal crystals (0.3 g). Mp 95–96 °C (chloroform–diethyl ether). $[\alpha]^{20}_{578}$: +83 (*c* 1.9). IR: ν_{max} 1740 and 1730 (OAc), 1700 (SAc) and 690 cm^{-1} (P=S). ^{31}P NMR ($CHCl_3$): δ 61.08. ^1H NMR ($CDCl_3$): δ 0.90 (s, 3 H, CCH_3 (e)), 1.28 (s, 3 H, CCH_3 (a)), 2.12 (s, 6 H, 2 × OAc), 2.40 (s, 3 H, SAc), 3.40 (s, 3 H, OCH_3), 3.60–4.5 (m, 8 H, H-2, H-6,6′, 2 × OCH_2 (a), 2 × OCH_2 (e)), 4.72 (d, 1 H, $^3J_{1,2}$ = 1 Hz, H-1), 4.83–5.41 (m, 2 H, H-3, H-4). ^{13}C NMR ($CDCl_3$): δ 20.90 (CCH_3 (e)), 21.94 (CCH_3 (a)), 32.23 (d, $^3J_{P,C}$ = 7.6 Hz, $C(CH_3)_2$), 45.39 (C-2), 55.69 (OCH_3), 62.56 (C-6), 65.22 (d, $^3J_{P,C}$ = 5.7 Hz, C-4), 73.40 (d, $^2J_{P,C}$ = 5.6 Hz, C-3), 100.8 (C-1). Anal. Calcd for $C_{18}H_{29}O_{10}S_2P$: C, 43.23; H, 5.79; S, 12.82. Found: C, 43.20; H, 5.69; S, 12.69.

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Reactions of Anionic Nucleophiles with α-D-Glucopyranosyl Fluoride in Aqueous Solution through a Concerted, A_ND_N (S_N2) Mechanism[1]

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Abstract: The first-order rate constants for the disappearance of α-D-glucopyranosyl fluoride in the presence of anionic nucleophiles show a linear dependence on the concentration of the nucleophile in water at 30.0 °C and ionic strength 2.0 M, maintained with KCl. The products from the reactions with azide and acetate anions, identified by ^1H NMR, show complete inversion of stereochemistry. These results provide evidence for a concerted bimolecular S_N2 (or A_ND_N) reaction of anionic nucleophiles at the anomeric carbon atom of α-D-glucosyl fluoride. The second-order rate constants for the nucleophiles follow the Swain–Scott correlation with a slope of s = 0.18, indicating a small sensitivity of the displacement reaction to the nature of the nucleophile. No reaction is observed with uncharged amine nucleophiles, which do not provide electrostatic stabilization to the carbocation-like transition state for substitution. The solvolysis of α-D-glucosyl fluoride in mixtures of H_2O, EtOH, and CF_3CH_2OH, and in H_2O and MeOH, has a high selectivity for reaction with water. The lifetime of the glucosyl cation is probably too short to allow diffusion, so that this suggests that the rate of formation of the unstable glucosyl oxocarbenium ion is increased in the presence of water molecules that stabilize the cationic transition state. These results are consistent with the conclusion that the glucosyl oxocarbenium ion exists for a short time in water but has no significant lifetime when it is in contact with a strong nucleophile, so that the reaction mechanism is forced to become concerted. They also suggest that glycosides may undergo concerted displacement reactions by anionic groups at the active sites of enzymes.

Introduction

The stereochemistry of the products from the solvolysis of α- and β-glucose derivatives in methanol and in 1:1 ethanol–2,2,2-trifluoroethanol is consistent with a mechanism of hydrolysis of the pyranose ring through rate-determining formation of a short-lived oxocarbenium ion intermediate, followed by rapid trapping by a solvent molecule to give products with both inversion and retention of configuration (eq 1). Different product ratios are observed with different leaving groups, which shows that the lifetime of the cation is too short to allow diffusional equilibration with the bulk solvent, and the increased yield of the trifluoroethyl glycoside in the reaction with retention of configuration when

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