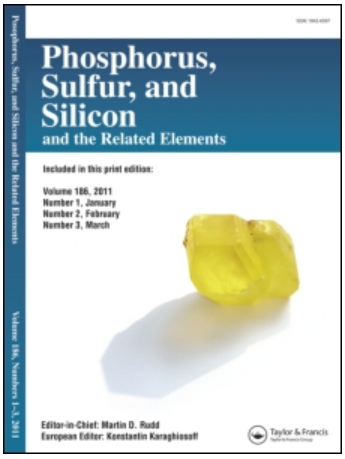

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THIONOPHOSPHATES OF CYCLODEXTRINS

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THIONOPHOSPHATES OF CYCLODEXTRINS

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The preparation of thionophosphates of cyclodextrins by using P(III)-reagents has been investigated.

Keywords: Cyclodextrin; phosphorylation; dioxophosphorinane; regioselectivity

INTRODUCTION

Cyclodextrins (α-, β-, γ-: n = 1–3, see Figure R = R^1 = R^2 = H) are available natural cyclic oligosaccharides having high potentiality for the synthesis of fine organic chemicals. The cyclodextrin rings form a torso with the primary hydroxyl groups (OR) of the glucose residues lying on the narrow end of the torso. The secondary glucopyranose hydroxyl groups are located on the wider end and are connected each other by strong hydrogen bonds,[1] so the main structural peculiarity of cyclodextrines is *spatial isolation* the primary and the secondary hydroxyl groups. Due to that cyclodextrins can be regiodirectly alkylated, acylated[2,3] and silylated.[4] However, up to the present other electrophilic reactions were restrictively investigated. There are only few papers on phosphorylated cyclodextrins mainly obtained by monophosphorylation with P(V)-reagents for the purpose of biomimetic investigations.[5] In another paper the direction of the cyclodextrin phosphorylation by chlorophosphite using ^{31}P NMR spectroscopy was investigated, but, unfortunately, reaction products were not isolated.[6] In the present paper the first results on phosphorylation of α- and β-cyclodextrins **1** (n = 1) and **2** (n = 2) by the reagents of trivalent phosphorus **3–6** which previously have been widely used for the synthesis of phosphocontaining mon-

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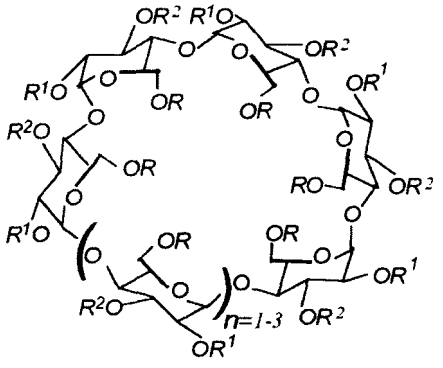

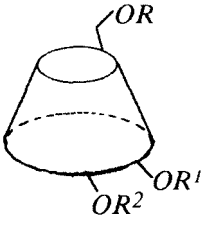

1,**7**,**10**: n = 1; **2**,**8**,**9**,**11-18**: n = 2;

X = -P(O)(O)X , (S)X = -(S)P(O)(O)X ; Y = -P(O)(O)Y , (S)Y = -(S)P(O)(O)Y

1,**2**: R=R^1=R^2=H; **3**: Cl-X ; **4**: Cl-Y; **5**: X-N(N)= ; **6**: X-N(N)=N ;

7,**8**: R=R^1=R^2=X; **9**: R=R^1=R^2=Y; **10**,**11**: R=R^1=R^2=(S)X;

12: R=R^1=R^2=(S)Y; **13**: R=X, R^1=R^2=H; **14**: R=R^1=X, R^2=H;

15: R=(S)X, R^1=R^2=H; **16**: R=R^1= (S)X,R^2=H; **17**: R=R^1=(S)X, R^2=Y;

18: R=R^1=(S)X, R^2=(S)Y

osaccharides, cellulose, chitozane and for some other natural hydroxylcontaining compounds are given.[7]

RESULTS AND DISCUSSION

The main difficulty we faced during the phosphorylation of cyclodextrins consisted in their essentially different organosolubility: α-cyclodextrin **1** turned out to be practically insoluble in such solvents as benzene, dioxane, pyridine, while β-cyclodextrin **2** showed good solubility in pyridine. Therefore, to conform with α-cyclodextrin **1**, we studied only *per*phosphorylation (compound **7**) in *hetero-phase* conditions (in dioxane), i.e. with excess of phosphorylating agent **3**. On the contrary, β-cyclodextrin **2** was *per*phosphorylated in *homogeneous* phase (in pyridine) by chlorophosphites **3**,**4** (method *a*) and azolophosphites **5**,**6** (method

b) with the formation of perphosphorylated β-cyclodextrins **8,9**. Attempts of perphosphorylation of α-cyclodextrin **1** by **4–6** led only to partial phosphorylation (by 30–50%) even at 20 °C for 48 hrs. The phosphorylation degree was monitored by ^{31}P NMR.

Perphosphorylated compounds **7–9** add sulfur forming cyclodextrins perthionophosphates **10–12** which were isolated in a pure state and investigated by ^{1}H and ^{31}P NMR. Unfortunately, because of the extreme complexity of such perphosphorylated cyclodextrins, their NMR spectra present broadened signals that make difficulties in their fine reference. Nevertheless, on the basis of NMR spectra, within the limits of the accuracy of this method, one can draw a conclusion on the quantity of phosphocontaining residues introduced into a molecule of cyclodextrin. Thus there are 2 broadened signals (~0.89 and 1.23 p.p.m.) in the ^{1}H NMR spectra of **7–9** which refer to equatorial and axial methyl protons (relative to the phosphorinane or phospholane ring) and broadened multiplets (~3.00–5.33 p.p.m.) of cyclodextrin frame protons and phosphorinane methylene protons (for **10,11**). The ratio of integral intensities corresponded to the perphosphorylated structures **10–12**. It is important that ^{31}P NMR spectra of α-cyclodextrin derivatives **7** and **10** show only one broadened signal whereas P(III)-derivatives of β-cyclodextrin **8** and **9** show two broadened signals with a ratio of 1:2. On the basis of known data[3,8] and on consideration of the less reactive hydroxyls of positions 3 (OR^2), compared to the ones of positions 2 (OR^1) and 6 (OR), one may expect that the downfield signal refers to the phosphorus atoms in positions 3 and the upfield signal refers to the phosphorus atoms in positions 2 and 6.

For the verification of this supposition we studied phosphorylation of 6-OH, 2-OH and 3-OH hydroxyls of β-cyclodextrin in steps under ^{31}P NMR control. Indeed, hepta-6-O-phosphorylated β-cyclodextrin **13** having signals at 121 p.p.m was formed on treatment with 7 equivalents of chlorophosphite **3**. Further treatment by another 7 equivalents of **3** led to tetradeca-2,6-phosphorylated β-cyclodextrin **14**, ^{31}P NMR signals of which have the same chemical shift (121 p.p.m.) as the upfield group of ^{31}P signals of compound **7**. Finally, further treatment by another 7 equivalents of **3** led to the appearance of the second broadened signal at 124 p.p.m. corresponding to the downfield signal of perphosphorylated compound **7** in expected integral ratio 1:2. Hepta-(**13**) and tetradeca-(**14**)-phosphorylated β-cyclodextrins add sulfur with the formation of thionophosphates **15,16** which were isolated in a pure state. The indicated regiodirection of phosphorylation was additionally confirmed by introduction of different phosphocontaining residues in the β-cyclodextrin molecule. Thus, tetradeca-2,6-O-thionophosphite β-cyclodextrin **16** was treated by 7 equivalents of **4** and the phosphorus atom signals in the phospholane residues of the com-

pound **17** coincided in chemical shift (148 p.p.m.) with the ones of the downfield group signals of perphosphorylated **9**. This observation additionally confirms that at the last step only the hydroxyls of position 3 of the glucose fragments have been phosphorylated. After sulfur addition the corresponding "hetero" perphosphorylated compound **18** was isolated in a pure state. According to the ^{1}H and ^{31}P NMR data the integral ratio of the methyl protons of the phosphorinane rings to the methyl protons of the phospholane rings and their ratios to the protons of the cyclodextrin framework and to the methylene protons of the phosphorinane rings, as well as the ratio of the phosphorinane phosphorus atom signals to the signals of the phospholane phosphorus atoms corresponded to the expected values.

Still more obvious results on the stepwise phosphorylation of hydroxyls in positions 6,2 and 3 were obtained during perphosphorylation of β-cyclodextrin by triazolophosphite **6** (method *b*), which was previously shown by us as a mild and highly selective phosphorylating agent.[9] According to the ^{31}P NMR data the phosphorylation of the *primary* hydroxyl groups in positions 6 was completed after 20 min, of *secondary* hydroxyl groups in positions 2 after 45 min, and of *secondary* hydroxyl groups in positions 3 after 18 hrs. These findings are in accordance with the published data on the essentially distinct reactivity of these hydroxyl groups.[2,3] It is also in accordance with our data on the essentially different rates of phosphorylation of distinct hydroxyl groups by azolophosphites.[9]

Thus, this investigation opens a new way for obtaining functionalized cyclodextrins containing different phosphorus residues.

EXPERIMENTAL

All the experiments with the P(III)-derivatives were performed in an atmosphere of dry argon and in dried solvents. The systems A (benzene-dioxane 5:1), B (chloroform-methanol 10:1), C (benzene-aceton-dioxane-petroleum ether 1:2:4:1), D (chloroform-aceton-methanol 1:2:1), E (chloroform-*i*-butanol 4:1), F (chloroform-aceton-methanol 3:1:2) were used for TLC on silica gel pre-coated aluminum plates.

General procedure of α- and β-cyclodextrins phosphorylation

Method *a*. Stoichiometric quantities of chlorophosphites **3** or **4** were added under stirring at 20°C to the suspension of α-c.d. **1** (0.0010 mol) and triethylamine (0.020 mol) in 10 ml of dioxane or to the solution of β-c.d. **2** (0.0010 mol) in

5 ml of pyridine and the reaction mixture was kept at 20°C approx. 1 hr.[10]

Method *b*. Stoichiometric quantities of azolophosphites **5** or **6** were added under stirring to the solution of β-c.d. **2** (0.00011 mol) in 2 ml of pyridine and the reaction mixture was kept at 20°C.[10]

General procedure of sulfur addition

Stoichiometric quantities of fine grained sulfur were added under stirring to the reaction mixture with the P(III)-derivative (**7–9,13,14** or **17**), kept at 80°C approx. 1 hr,[10] and filtered off.

Hexakis[2,3,6-tri-O-(2-thio-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)]-α-cyclodextrin 10

After sulfur addition hexane (10 ml) was added with stirring to the reaction mixture. The precipitate was filtered off, washed with hexane, diethyl ether and purified by flash chromatography over Al_2O_3 with eluent chloroform-methanol-hexane (7:1:1). The soluton was evaporated under reduced pressure and the residue was recrystallized from dioxane and methanol to obtain **10** (71%). m.p. 214–220°C (dec.), Rf 0.7(A). ^{31}P NMR (dioxane): 60 p.p.m. Found, %: C 38.90, H 5.55, P 13.83. Calcd. for $(C_{21}H_{37}O_{11}P_3S_3)_6$,%: C 38.53, H 5.70, P 14.19.

Heptakis[2,3,6-tri-O-(2-thio-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)]-β-cyclodextrin 11

After sulfur addition the reaction mixture was poured into 200 ml ice water, and stirred for 1 hr. The precipitate was filtered off, washed with ice water, dried in a vacuum desiccator over P_2O_5 and twice recrystallized from ethanol to obtain **11** (90%), m.p. 214–215°C (dec.), Rf 0.6(A), 0.9(B). ^{31}P NMR (dioxane): 59 p.p.m. Found, %: C 38.85, H 5.65, P 13.93. Calcd. for $(C_{21}H_{37}O_{11}P_3S_3)_7$,%: C 38.53, H 5.70, P 14.19.

Heptakis[2,3,6-tri-O-(2-thio-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane-2-yl)]-β-cyclodextrin 12

By analogy with **11** perthionophosphate of β-c.d. **12** (90%) was obtained, m.p. 210–213°C (dec.), Rf 0.6(A), 0.9(B). ^{31}P NMR (dioxane): 78 p.p.m. Found, %: C 40.85, H 7.72, P 13.02. Calcd. for $(C_{24}H_{53}O_{11}P_3S_3)_7$,%: C 40.79, H 7.56, P 13.15.

Heptakis[6-O-(2-thio-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)]-β-cyclodextrin 15

After sulfur addition the solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to obtain **15** (85%), m.p. 250–255°C (dec.), Rf 0.8(C), 0.9(D). ^{31}P NMR (chloroform): 60 p.p.m. Found, %: C 40.35, H 5.70, P 9.63. Calcd. for $(C_{11}H_{19}O_7PS)_7$,%: C 40.49, H 5.87, P 9.50.

Heptakis[2,6-di-O-(2-thio-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)]-β-cyclodextrin 16

After sulfur addition the solvent was evaporated under reduced pressure, the residue was dissolved in 10 ml benzene and mixed with 5 ml pentane. The precipitate was filtered off and washed with pentane to obtain **16** (70%), m.p. 230–233°C (dec.), Rf 0.7(E), 0.9(F). ^{31}P NMR (benzene): 60 p.p.m. Found, %: C 39.32, H 5.76, P 12.36. Calcd. for $(C_{16}H_{28}O_9P_2S_2)_7$,%: C 39.18, H 5.75, P 12.63.

Heptakis[2,6-di-O-(2-thio-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)]-heptakis[3-O-(2-thio-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane-2-yl)]-β-cyclodextrin 18

By analogy with **11** "hetero" perthionophosphate of β-c.d. **18** (60%) was obtained, m.p. 218–220°C (dec.), Rf 0.5(A), 0.8(B). ^{31}P NMR (dioxane): 60 and 78 p.p.m. in an integral ratio 2:1. Found, %: C 39.52, H 6.15, P 13.60. Calcd. for $(C_{22}H_{39}O_{11}P_3S_3)_7$,%: C 39.51, H 5.88, P 13.90.

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[10] The exact time of the reaction end was monitored by ^{31}P NMR spectroscopy with a Bruker WP-80 spectrometer at a frequency of 32.4 MHz.