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Cyclophosphorylation of Per-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin

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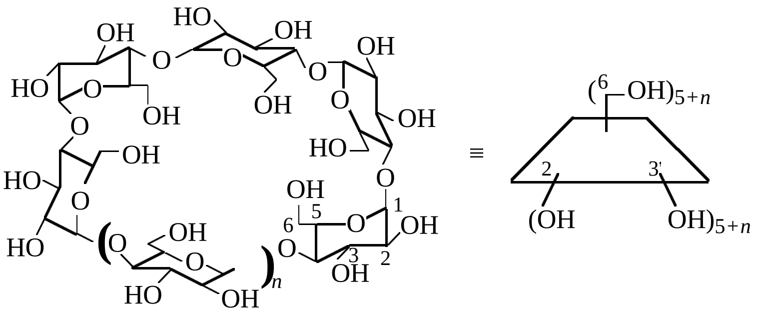
Abstract—Treatment of per-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin with hexaalkylphosphorous triamides gave interglucoside 2,3'-cyclophosphorylated derivatives with rigid carcasses and large chiral bowl-like cavities.

Cyclodextrins **I** are accessible natural oligosaccharides and present great interest as molecular containers and reagents for fine organic synthesis (see, for example, recent rewiews [1, 2]). Cyclodextrin molecules can be represented as a truncated cone with primary hydroxy groups located at the smaller rim's torus and secondary hydroxyls, at the wider rim's torus [3]. Such structural organization of cyclodextrins predetermines steric isolation of their primary and secondary hydroxy groups, which allowed them to be introduced in regioselective processes: alkylation, acylation, and silylation [1].

Moreover, investigations on reactions of cyclodextrins with other reagents have been initiated. Thus, for instance, there have been some information on the phosphorylation of cyclodextrins with P(V) reagents, aiming at preparing substances for biomimetic studies [4]. The phosphorylation of cyclodextrins with phosphorochloridites has also been reported [5]; note that the reaction products have not been isolated pure, and their structure has been assessed from ^{31}P NMR evidence only.

In our recent studies on reactions of cyclodextrins with P(III) reagents we observed perphosphorylation and regioselective phosphorylation of α- and β-cyclodextrins [6], per-6-deoxy-per-6-bromo-β-cyclodextrin [7], and per-6-(*tert*-butyldimethylsilyl)-β-cyclodextrin [8]. As a result, original phosphorus-containing cyclodextrins of different chemical nature could be prepared. In the present communication we report first results of phosphorylation of cyclodextrin derivatives with P(III) reagents, such as phosphorous triamides which are known to be capable of cyclophosphorylating polyol systems. The interest in cyclic derivatives was defined by the intention to build on the cyclodextrin carcass a further rim by binding two secondary hydoxy groups in the 2 and 3' positions of neighboring glucoside units in cyclodextrin molecules. Had success been acheived, a bulky rigid structure would have been created, highly interesting for supramolecular and biomimetic chemistry.

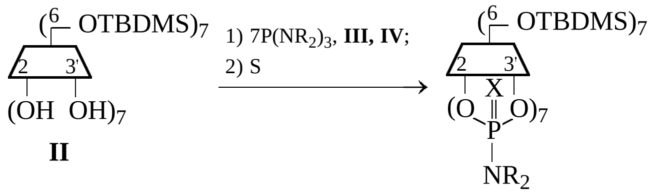
Designing the experiment, we relied on the available information on the structure of β-cyclodextrin **I** (n = 2). Thus, it was known that the 2-OH and 3'-OH



I

n = 1–3.

groups of the glucopyranoside units are beoud with each other by strong interglucoside hydrogen bonds [$HO^2\cdots HO^{3'}$]. This followed from the X-ray data for β-cyclodextrin [9, 10]: the O^2–$O^{3'}$ interglucoside bonds were found to be 2.73–2.88 Å, which were optimal O–O distances for phosphocyclization (2.70–3.00 Å) [11]. Furthermore, the possibility of phosphocyclization followed from the data of Sukairi and Kuzuhara [12], who reported the preparation of an interglucoside 2,3'-benzylidene-β-cyclodextrin derivative by treatment of β-cyclodextrin **I** with α,α-dimethoxytoluene. Note that some authors postulated interglucoside 2,3 cyclostannylation of β-cyclodextrin **I** (with subsequent ring opening) [13] and 2→3 migration of the silyl protection [14], but their conclusions on the reaction pathway were based on the structure of the final products only, which cannot be considered sufficient evidence for the postulated interglucoside mechanism.



III, V, VII, R = Me; **IV, VI, VIII**; R = Et; **V, VI,** X = lone electron pair; **VII, VIII**, X = S.

It view of the aforesaid, in the first stage of our investigation we have protected all primary hydroxy groups in β-cyclodextrin **I** with *tert*-butyldiethylsilyl groups by treatment with *tert*-butyldimethylsilyl chloride in pyridine according to [15]. The key stage of the synthesis was cyclophosphorylation of silyl derivative **II** with hexamethyl- (**III**) and hexaethylphosphorous triamides (**IV**) using 1 mol of amide **III, IV** per one glucoside unit of the cyclodextrin derivative. The reactions were performed at 80–90°C for 10 h with distillation of the dimethyl- or diethylamine formed. The reaction progress was controlled by ^{31}P NMR spectroscopy. The phosphorus signals of the reaction mixture change as follows. After 4-h heating, signals at 138 and 135 ppm are observed, relating respectively to intermediate tetramethyl or tetraethyl phosphoramidite derivatives [16]. On further heating, broadened singlets at 145 and 148 ppm appear, belonging to 2,3'-cyclophosphorylated derivatives **V** and **VI**, respectively, which are single final reaction products. Probably, initially phosphorylation involves the 2-OH groups of the glucoside units, as much more active [17], followed by interglucoside cyclophosphorylation involving the 3'-OH groups. Thus we showed that the polyhydroxyl system of per-6-silylated β-cyclodextrin **II** can be subjected to directed cyclophosphorylation to form regular 2,3'-cyclized systems (2,3 cyclization is unlikely [18]). It is important to know that good results could be achieved with soft phosphorylating agents, phosphorous triamides **III, IV**.

For stabilization P(III) derivatives **V, VI** were coverted to phosphorothioates **VII, VIII**. The sulfur addition was controlled by ^{31}P NMR spectroscopy. The signals of phosphorothioates **VII, VIII** were observed at 88 and 87 ppm, respectively, which is characteristic of cyclic phosphoramidothioate derivatives.

Compounds **VII** and **VIII** were isolated pure as white amorphous substances melting with decomposition. They were characterized by ^1H NMR and TLC data, specific optical rotations, and elemental analyses. Unfortunately, because of the very complex structure of cyclodextrin derivatives **VII** and **VIII**, their NMR spectra display broadened signals and thus are difficult to assign. Nevertheless, by the integral intensity ratios of ^1H NMR signals of nonoverlapping signals whose assignment casts no doubts and within accuracy limits of the method used we can judje about the number of phosphorus-containing residues in the cyclodextrin molecule. Thus, the ^1H NMR spectrum of compound **VII** (in $CDCl_3$) contains nonoverlapping broadened multiplets at 0.02–0.08, 0.85–0.91, 2.50–3.00, and 3.64–5.40 ppm, relating to the $Si(CH_3)_2$, $SiC(CH_3)_3$, and $N(CH_3)_2$ groups and the cyclodextrin frame, respectively, in a 6 : 9 : 6 : 7 ratio, which is consistent with structure **VII**. Similarly, the ^1H NMR spectrum of compound **VIII** (in $CDCl_3$) contains nonoverlapping broadened multiplets at 0.01–0.10, 0.82–0.94, 1.04–1.26, 3.09–3.39, and 3.61–5.47 ppm, relating to the $Si(CH_3)_2$, $SiC(CH_3)_3$, $N(CH_2C\mathit{H}_3)_2$, and $N(C\mathit{H}_2CH_3)_2$ groups and the cyclodextrin frame, respectively, in the 6 : 9 : 6 : 4 : 7 ratio expected for structure **VIII**.

Thus, the results of our study open up new ways to preparing 2,3'-cyclophosphorylated cyclodextrin derivatives, prospective macromolecules with large bowl-like chiral cavities and highly reactive P(III)–N bonds (compounds **V** and **VI**), which can be functionalized for solving some problems of supramolecular and biomimetic chemistry.

EXPERIMENTAL

All experiments with P(III) compounds were performed in dry argon with thoroughly dried solvents. Thin-layer chromatography was performed on aluminum plates with fixed silica gel layer, eluents $CHCl_3$–CH_3COCH_3–MeOH, 3 : 1 : 2 (A) and $CHCl_3$–

MeOH, 5 : 4 (B). The ^1H and ^{31}P NMR spectra were obtained on Bruker WP-250 and Bruker WP-80 instruments at 250 and 32.4 MHz, external references TMS and 85% H_3PO_4, respectively.

β-Cyclodextrin-heptakis[6-*O*-(*tert*-butyldimetilsilyl)]heptakis[2,3'-*O,O*-cyclo(dimethylphosphoramidothioate)] (VII). A solution of 1.99 g of silylated β-cyclodextrin **II** and 1.18 g of phosphorous triamide **III** in 10 ml of benzene was stirred at 80–90°C for 10 h under a slow stream of argon. Finely ground sulfur, 0.24 g, was then added, the mixture was stirred at 70°C for 1 h, the solvent was removed in a vacuum, the residue was washed with hexane, dried in a vacuum dessicator over P_2O_5, and recrystallized twice from 10 ml of methanol to obtain 2.34 g (85%) of compound **VII**, mp 223–225°C (decomp.), $[\alpha]_D^{21}$ +22.0 (*c* 1.00, $CHCl_3$), R_f 0.8 (A), 0.5 (B). Found, %: C 44.24; H 7.42; N 3.65; P 8.10. $(C_{14}H_{28} \cdot NO_5PSSi)_7$. Calculated, %: C 44.08; H 7.40; N 3.67; P 8.13.

β-Cyclodextrin-heptakis[6-*O*-(*tert*-butyldimetilsilyl)]heptakis[2,3'-*O,O*-cyclo(diethylphosphoramidothioate)] (VIII) was obtained similarly to compound **VII** from 1.99 g of silylated β-cyclodextrin **II**, 1.83 g of phosphorous triamide **IV**, and 0.24 g of sulfur in 10 ml of benzene. Yield 2.25 g (81%), mp 214–215°C (decomp.), $[\alpha]_D^{21}$ +18.7 (*c* 1.00, $CHCl_3$), R_f 0.8 (A), 0.6 (B). Found, %: C 46.71; H 7.85; N 3.41; P 7.55. $(C_{16}H_{32}NO_5PSSi)_7$. Calculated, %: C 46.93; H 7.48; N 3.42; P 7.57.

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