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Cyclophosphorylation of *tert*-Butyldimethylsilyl Derivatives of Cyclodextrins

A. A. Sutyagin, A. E. Glazyrin, M. K. Grachev, G. I. Kurochkina, and E. E. Nifant'ev

Moscow Pedagogical State University, Moscow, Russia

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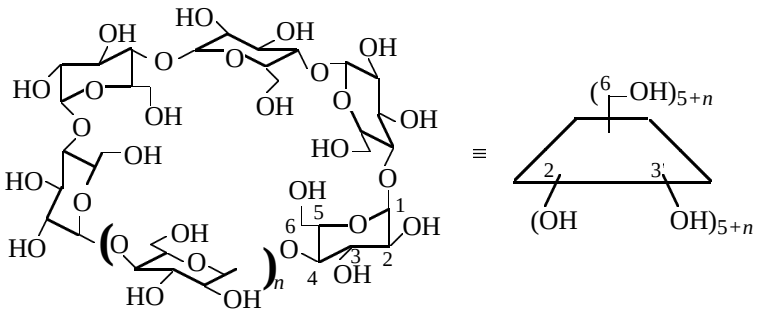
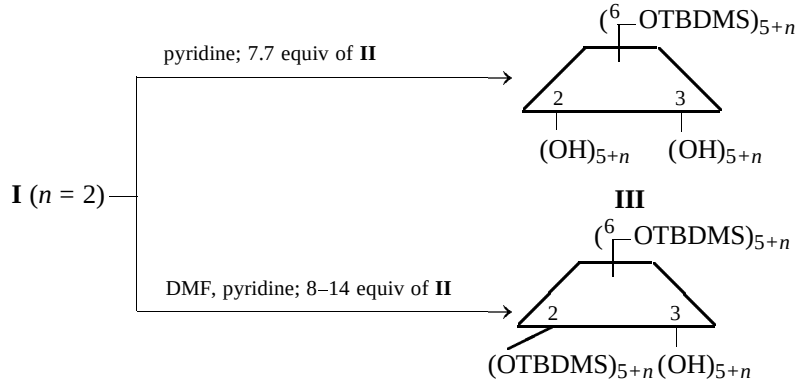
Abstract — A convenient method for preparing interglucoside 2,3'-cyclophosphorylated derivatives of cyclodextrins, based on the possibility of incomplete silylation of cyclodextrins by the 6 position of the glucoside units is offered.

It is known that regiodirected functionalization of cyclodextrins **I** (α, β, and γ-cyclodextrins, where n = 1–3, respectively) is an experimentally complicated task [1]. Of special interest is introduction of the *tert*-butyldimethylsilyl (TBDMS) protective groups, because it opens up strong possibilities for further directed functionalization. In this case the regiodirected silylation of β-cyclodextrin **I** (n = 2) by the 6-OH groups of glucoside units with *tert*-butyldimethylsilyl chloride (**II**) proceeds only in pyridine which plays the role of solvent and HCl acceptor [2], while in DMF–pyridine [3] or dimethylaminopyridine [4] the silylation proceeds also by the secondary 2-OH groups. In the presence of deprotonating agents (NaH), cyclodextrins are silylated by the secondary 2-OH groups [5]. The secondary 3-OH groups, being much less reactive and sterically shielded, remain intact under these conditions.



I, n = 1–3.



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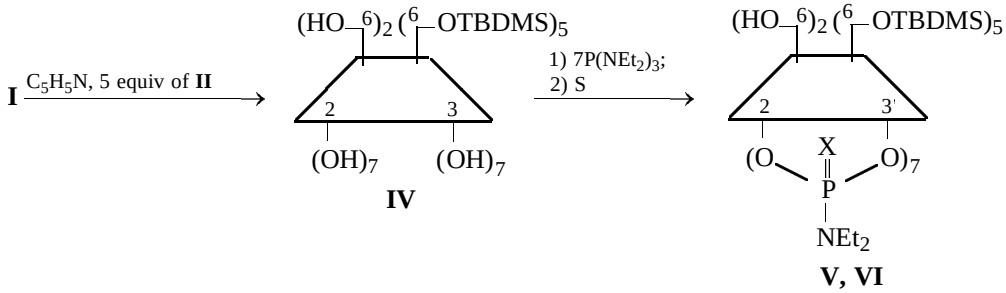
At the same time, even in the silylation in pyridine, part of the silylating agent is consumed for reaction with secondary hydroxy groups, and thus part of primary hydroxyls remains free. This fact considerably complicates isolation of the target 6-per-*O*-*tert*-butyldimethylsilyl cyclodextrin derivative **III** and reduces its yield. Using excess silylating agent will not only favor more complete substitution by the 6 position, but also further substitution by the 2 positions of the glucoside units. Improved procedures of regiodirected silylation and product isolation [6], too, fail to ensure exhaustive silylation, and the reported yields of products are much dependent on the required purity of the latter. This fact reflects the specific feature of regiodirected functionalization of cyclodextrins. First groups are introduced easily but further silylation is complicated by growing steric hindrance (so-called "statistical" factor [7]).

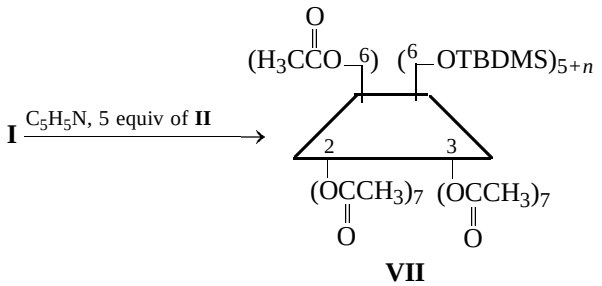
Previously we studied this problem in terms of further perphosphorylation [8] and interglucoside 2,3' cyclophosphorylation [9] of silylated β-cyclodextrin **III** (n = 2). The yields of compound **III** was as low as 57%, and considerable experimental efforts were needed to separate partly 6- and 2-silylated drivatives. Certain difficulties arose on the removal of the silyl protecting groups under standard conditions, on account of the overload of the 6 positions by the silyl groups.

Proceeding with our search for optimal conditions for preparing silyl derivatives **III** for their subsequent 2,3' cyclophosphorylation [10], we turned to alternative approaches. In the present work we showed that the silylation of as little as 5 equiv of compound **II** in pyridine occurs much more readily and highly regioselectively in the 6 positions.



X = lone electrone pair (**V**), S (**VI**).

The exclusive pentasilylation of the 6 positions was proved by the ^{1}H NMR spectra of derivative **IV** (the 2- and 6-silyl groups of the glucoside units are clearly distinguished by the $Si(CH_3)_2$ and $Si(CH_3)_3$ proton signals [4]) and also by the exhaustive acylation of silyl derivative **IV** with excess acetyl chloride under standard conditions (see Experimental). The ^{1}H NMR spectrum of compound **VII** contains 3 groups of signals of methyl protons of the 2-, 3-, and 6-acyl groups with the intensity ratio 7:7:2.



It is important that the two remaining free 6-OH groups in compound **IV** are sufficiently shielded and undergo no phosphorylation under standard conditions. Further treatment of penta-6-*O*-silyl derivative **IV** with 7 equiv of hexaethylphosphorous triamide produces complete interglucoside 2,3' cyclophosphorylation: The ^{31}P NMR spectrum of the reaction mixture contains a single signal at δ_P 148 ppm, as we reported previously [9]. Both remaining free primary 6-OH groups are not phosphorylated under the experimental conditions (otherwise, signals of phosphorodiamidites at δ_P 135 ppm would appear in the ^{31}P NMR spectra). The structure and individuality of cyclophosphorylated derivative **VI** and acyl derivative **VII** were established by means of ^{1}H and ^{31}P NMR spectroscopy, TLC, and elemental analysis.

Hence, we offer a more convenient procedure for preparing the target interglucoside 2,3'-cyclophosphorylated derivatives of cyclodextrins, based on the possibility of incomplete silylation of cyclodextrins by the 6 positions of the glucoside units.

EXPERIMENTAL

The ^1H and ^{31}P NMR spectra were registered on Bruker WP-250 (250 MHz) and Bruker WP-80 (32.4 MHz) spectrometers against external TMS and 85% phosphoric acid, respectively.

All experiments with trivalent phosphorus compounds were carried out under dry argon and in thoroughly dried solvents. Thin-layer chromatography was performed on aluminum plates with fixed silica gel layer, eluents 7:1 $CHCl_3$–MeOH (A) and 3:1 hexane—3:1.

Pentakis[6-*O*-(*tert*-butyldimethylsilyl)]-β-cyclodextrin (IV). To a solution of 3.41 g of β-cyclodextrin in 40 ml of pyridine, 2.26 g of *tert*-butyldimethylsilyl chloride was added in portions with stirring at °C. The reaction mixture was stirred for 4 h at 0°C, then kept for 15 h at 20°C, and the pyridine hydrochloride precipitate was filtered off. The filtrate was evaporated in a vacuum, and the residue was extracted with 100 ml of chloroform. The chloroform extract was washed with water (5 × 8 ml) and dried over calcined $CaCl_2$. The solution was filtered, the chloroform was distilled off, and the residue was purified on a column with calcined Al_2O_3, eluent methylene chloride. The solvent was removed, and the residue was dried in a vacuum dessicator over P_2O_5 to obtain 3.69 g (72%) of compound **IV**, mp 290–292°C (decomp.), R_f 0.95 (A). ^1H NMR spectrum ($CDCl_3$), δ, ppm: –0.06 to 0.00 m [30H, $Si(CH_3)_2$], 0.77–0.83 m [45H, $SiC(CH_3)_3$], 3.38–4.11 m (44H, C^2H–C^5H, C^6H_2, and C^6OH), 4.76–4.94 m (7H, C^1H), 5.25 br.s, 6.50 br.s (14H, C^2OH, C^3OH). Found, %: C 50.65; H 8.28; Si 8.22, $C_{72}H_{140}O_{35}Si_5$. Calculated, %: C 50.58; H 8.27, Si 8.23.

β-Cyclodextrin-pentakis[6-*O*-(*tert*-butyldimethylsilyl)]heptakis[2,3'-*O*,*O*-cyclo(diethylphosphoramidothioate] (VI). A solution of 1.70 g of silyl derivative **IV** and 1.73 g of hexaethylphosphorous triamide in 10 ml of benzene was stirred for 10 h at 80–90°C under a slight flow of argon. ^{31}P NMR spectrum of the reaction mixture: δ_P 148 ppm [P(III) derivative **V**]. Finely powdered sulfur, 0.22 g, was added to the reaction mixture which was then stirred for 1 h at 70°C. The solvent was evaporated in a vacuum, the residue was washed with hexane, dried in a vacuum dessicator over P_2O_5, and crystallized twice from 10 ml of ethanol to obtain 2.19 g (83%) of compound **VI**, mp 225–227°C (decomp.), R_f 0.93 (A). ^{31}P NMR spectrum (C_6H_6), δ_P, ppm: 87 br.s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.01–0.07 m [30H, $Si(CH_3)_2$], 0.80–0.87 m [45H, $SiC(CH_3)_3$], 1.06–1.28 m [42H, $N(CH_2CH_3)_2$], 3.11–3.42 m [28H, $N(CH_2CH_3)_2$], 3.65–4.25 m (44H; C^2H–C^5H, C^6H_2, and C^6OH), 5.25–5.45 m (7H, C^1H). Found, %: C 45.55; H 7.48; N 3.65; P 8.23. $C_{100}H_{196}N_7O_{35}P_7S_7Si_5$. Calculated, %: C 45.52; H 7.49; N 3.72; P 8.22.

Pentakis[6-*O*-(*tert*-butyldimethylsilyl)]hexadecakis(2,3,6-*O*-acetyl)-β-cyclodextrin (VII). To a solution of 1.37 g of silyl derivative **IV** and 1.42 g of triethylamine in 35 ml of benzene, a solution of 1 g of acetyl chloride in 5 ml of benzene was added with stirring in 40 min at 20°C. The resulting mixture was left to stand for 15 h at 20°C, and the triethylamine hydrochloride precipitate was filtered off. The solvent was removed, and the residue was dried in a vacuum dessicator over P_2O_5 to obtain 1.64 g (86%) of compound **VII**, mp 182–183°C (decomp.), R_f 0.4 (B). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.02–0.08 m [30H, $Si(CH_3)_2$], 0.85–0.93 m [45H, $SiC(CH_3)_3$], 1.26 s [6H, $CH_3C(O)OC^6$], 2.08 br.s, 2.15 br.s [42H; $CH_3C(O)\cdot OC^2$ and $CH_3C(O)OC^3$], 3.50–4.21 m (42H; C^2H–C^5 and C^6H_2), 4.82–5.14 m (7H, C^1H). Found, %: C 52.56; H 7.25; Si 5.87. $C_{104}H_{172}O_{51}Si_5$. Calculated, %: C 52.51; H 7.29; Si 5.90.

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