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Phosphorylation of β-Cyclodextrin with Substituted Secondary Hydroxy Groups Using Phosphorous Acid Diamide

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Abstract—Phosphorylation of β-cyclodextin with substituted secondary hydroxy groups using 1,2-*O,O'*-isopropylideneglyceryl phosphorous diamide as a phosphorylating agent, in contrast to phosphorylation with trivalent phosphorus acid chlorides, is found to proceeds under mild conditions, but only in homogenous medium, and to afford acyclic diesteroamidophosphite derivatives of β-cyclodextin.

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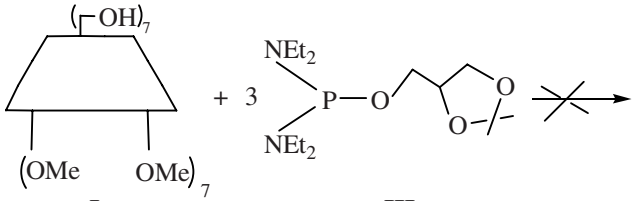
A regioselective functionalization of cyclodextin is known to be a complicated experimental problem due to the presence in the cyclodextin molecules of a large number of hydroxy groups belonging to two different by their nature kinds: primary and secondary [1]. Meanwhile, for majority of applications a special attention attract just the selectively substituted cyclodextrins allowing a solution of several practical problems (e.g., see [2]). For preparation of phosphorus-containing cyclodextrins are commonly used highly reactive (but of low selectivity) P(III) acid chlorides affording mainly perphosphorylated cyclodextrin derivatives [3, 4]. Another important class of phosphorylating agents, the P(III) acid amides, possesses better experimental performance, but, unfortunately, requires elevated temperature in the application to "ordinary" alcohols and oligohydroxy compounds, that decreases the regioselectivity of the phosphorylation [5].

Continuing our investigation on developing effective and selective phosphorylating agents for cyclodextins, we recently found that phosphorylation of unprotected β-cyclodextin using phosphorous amides in pyridine unexpectedly proceeds under mild conditions (20°C) and selectively at the primary hydroxy groups [6, 7]. It is significant that mild conditions of phosphorylation are defined by supramolecular influence of cyclodextin cavity (that is, by primarily inclusion of P(III) reagent into the cavity of the "host" cyclodextin), similarly to the behavior of some cyclodextin derivatives observed by us earlier [8].

In this connection it is interesting from the practical viewpoint to study phosphorylation by phosphorous acid diamide of β-cyclodextin containing free primary hydroxy groups while secondary groups are protected. Among such derivatives we chose per-(2,3-di-*O*-methyl)- (**I**) and per-(2,3-di-*O*-acetyl-β-cyclodextins (**II**). For a phosphorylating agent we selected 1,2-*O*,*O'*-isopropylideneglyceryl diamidophosphite (**III**) that we had studied earlier in the phosphorylation of free β-cyclodextin [6]. It was interesting to elucidate structure of final compounds, because phosphorous diamidophosphites at the phosphorylation of the cyclodextin oligohydroxy system were capable of both mono- and diphosphorylation, leading to formation, respectively, of diesteroamido- or cylophosphitotriester fragments.

Unfortunately, compound **I** is practically insoluble in the solvents ordinary used for this reaction [pyridine (Py) and dimethylformamide (DMF)] and is well soluble only in water and simple alcohols. Attempted phosphorylation of **I** in heterogenous medium (Py, DMF, dioxane, benzene) with three molar equivalents of diamidophosphite **III** failed even at heating to 70–80°C as shown by the presence of a

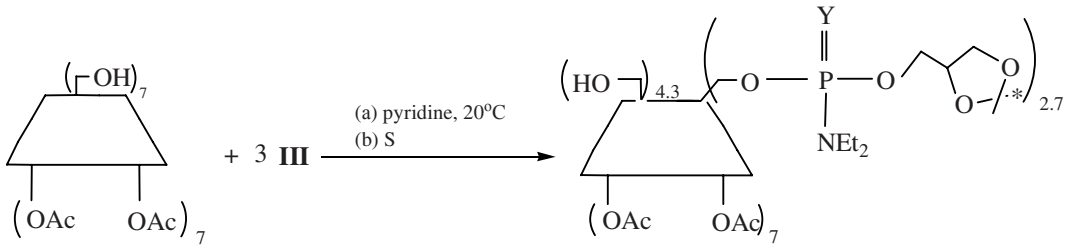
single signal at 136 ppm in the ^{31}P NMR spectrum of the reaction mixture corresponding to the parent phosphite **III**.



I **III**

In this connection note that with P(III) acid chlorides the phosphorylation can be carried out in heterogenous medium (in dioxane) because the product formed in the course of phosphorylation becomes soluble, and phosphorylation is competed in homogenous medium [4].

On the contrary, derivative **II** turned to be well soluble in pyridine and its phosphorylation was carried out under mild conditions (20°C, 12 h) with intermediate formation of diesteramidophosphite-containing β-cyclodextin (**IV**), as we judged from the disappearance in the ^{31}P NMR spectrum of the signal of parent diamidophosphite **III** and appearance of typical signal of the product **IV** at 148 ppm.



II **IV, V**

IV: Y= lone electron pair; **V**: Y=S

After addition of sulfur the β-cyclodextin diesteramidothionophosphate derivative (**V**) was isolated and characterized by the ^{1}H and ^{31}P NMR spectroscopy.

In the ^{1}H NMR spectrum the integral intensity of the signals of methyl protons at 1.35 and 1.40 ppm of isopropylidene fragment were equal to that of the methyl protons of amide fragment at the prhosphorus atom located at 1.09 ppm. From the comparison of integral intensities of the signals of methyl protons in the isopropylidene fragment and the sum of integral intensities of the protons at the cyclodextrin backbone follows that average degree of substitution by the phosphorus-containing fragment equals 2.7, more than at phosphorylation of free β-cyclodextin where the average degree of substitution was equal to 2 [6]. In the ^{31}P NMR spectrum the diesteramidodithionophosphate fragment gave rise to a signal at 76 ppm. The product **V** was also characterized by the data of TLC and elemental analysis.

Thus, phosphorylation with phosphorous acid diamide of the β-cyclodextin with protected secondary hydroxy groups like the phosphorylation of unprotected β-cyclodextin occurs under mild conditions, but unlike the phosphorylation with the P(III) acid chlorides proceeds only in homogenous medium and leads to acyclic β-cyclodextin diesteramidophosphite derivatives.

EXPERIMENTAL

All experiments with the trivalent phosphorus derivatives were carried out under inert atmosphere using anhydrous solvents purified by common procedures.

The ^{1}H NMR spectra were registered on a Bruker AC-200 instrument with operating frequency 200.13 MHz, external reference TMS. The ^{31}P NMR spectra were registered on a Bruker WP-80 instrumet, frequency 32.4 MHz, external reference 85% H_3PO_4.

For the thin layer chromatography were used aluminum plates with fixed silica gel layer (Silufol UV–254), eluent acetonitrile–water–25% aqueous ammonia in the ratio 6 : 3 : 2.

β-Cyclodextin from "Wacker" (USA) was worked up additionally for very careful removal of the residual water. Compounds **I**–**III** were obtained along procedures described, respectively, in [9–11].

2,3-Di-*O*-peracetyl-6-*O*-(1,2-*O*,*O*′-isopropylideno-glycerodiethylamidothionophosphato)$_{2.7}$-β-cyclodextin (V). To a solution of 0.20 g of β-cyclodextrin derivative **II** in 1 ml of pyridine at stirring was added 0.11 g of diamidophosphite **III** at 20°C. The reaction mixture was stirred for 12 h at 20°C. ^{31}P NMR spectrum of the reaction mixture (compound **IV**), δ_P, ppm: 148. To the reaction mixture was added 0.01 g of fine sulfur powder and stirring was continued for 2 h at 20°C. Then unreacted sulfur was filtered off, to the filtrate was added 2 ml of diethyl ether, the mixture was stirred, the precipitate formed was filtered off and washed with diethyl ether (2 × 3 ml). Powdery product was kept for 4 h at 70°C in a vacuum (1 mm Hg). Yield 0.17 g (60 %), decomp. 159–161°C, R_f 0.85. ^{1}H (DMSO-d_6), δ, ppm: 0.88–1.30 m [16.2H, N(CH_2CH_3)$_2$], 1.35 s [8.1H, C(CH_3)$_2$], 1.40 s [8.1H, C(CH_3)$_2$], 2.05 br.s [42H, C(O)CH_3], 2.95–3.32 m [10.8H, N(CH_2·CH_3)$_2$], 3.86–4.30 m [55.5H, C^2H–C^5H, C^6H_2, $POCH_2CH(O)CH_2O$], 4.71 br.s (4.3H, C^6OH), 5.10–5.30 m (7H, C^1H). ^{31}P NMR spectrum (pyridine), δ_P, ppm: 76. Found, %: C 49.15; H 6.16; P 3.40. $C_{97}H_{152}O_{57.1}N_{2.7}P_{2.7}S_{2.7}$. Calculated, %: C 47.75; H 6.28; P 3.43.

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