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Mild Regioselective Phosphorylation of β-Cyclodextrin with Trivalent Phosphorus Acid Amides

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Abstract — Phosphorylation of β-cyclodextrin with trivalent phosphorus acid diamides in pyridine is found to proceed selectively at primary hydroxy groups under mild conditions (20°C) due to the supramolecular effect of the cyclodextrin cavity. The compounds obtained are of practical interest for further synthesis on their basis of amphiphilic glycophospholipids immobilized on the cyclodextrin matrix.
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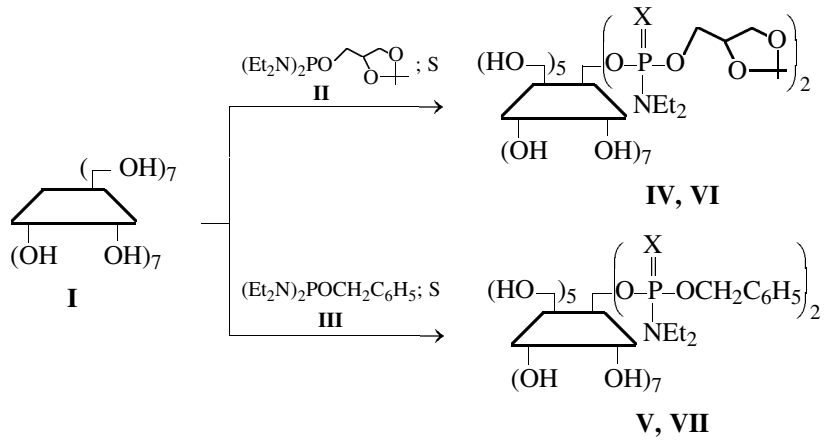
Dialkylamides of trivalent phosphorus acids are known to be capable of phosphorylating hydroxyl-containing compounds only at elevated temperatures (above 70–80°C) with distilling off the liberated dialkylamine [1]. Unfortunately, phosphorylation by this method of complex oligohydroxyl-containing compounds proceeds with a low selectivity at hydroxy groups of different nature, e.g., primary and secondary. In such cases, more reactive P(III) acid azolides which phosphorylate already at room temperature and preferably at primary hydroxy groups, even when the latter are present together with secondary hydroxyls [2], are commonly used. However, P(III) acid azolides are often hardly available and easily hydrolyzed, which restricts their practical application. Still more challenging problems arise on attempted phosphorylation with P(III) acid dialkylamides under ordinary conditions, i.e. on heating, of such a complex oligohydroxy compound as β-cyclodextrin (**I**) containing 7 primary and 14 secondary hydroxy groups. It is known that regioselective functionalization of β-cyclodextrin is generally quite an intricate problem which could only be successfully solved in selected cases [3]. β-Cyclodextrin is most frequently phosporylated with nonselective P(III) acid chlorides to obtain, as a rule, perphosphorylated β-cyclodextrin derivatives [4]. For regioselective phosphorylation selectively protected β-cyclodextrins are commonly used, but this method is complicated by the necessity of introducing and subsequently removing protective groups. As to functionalization of β-cyclodextrin, it was noted that the nature of the solvent [5] and even temperature, as, for example, in silylation [6], can strongly affect the regioselectivity of substitution of cyclodextrin hydroxy groups. With β-cyclodextrin, an additional problem arises due to its re- stricted solubility in most solvents used for this reaction, except for pyridine and DMF. On the other hand, we previously showed that phosphorylation of free β-cyclodextrin by the simplest phosphorous triamide unexpectedly proceeds under mild conditions (20°C) selectively by primary hydroxy groups [7].

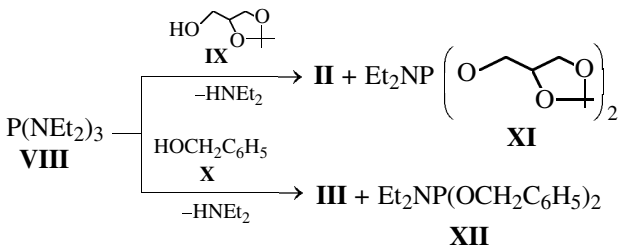
Accounting for the importance of selective phosphorylation of free (unprotected) β-cyclodextrin, we set ourselves the task to find conditions for mild regioselective phosphorylation with more complex phosphorylating agents, phosphorous diamidoesters: 1,2-*O*-isopropylideneglycerol tetraethylphosphorodiamidite (**II**) and benzyl tetraethylphosphorodiamidite (**III**). The choice of these phosporylating agents was motivated by the possibility of their further use as starting materials in the synthesis of complex natural compounds, e.g., glycophospholipids, using known experimental approaches [8]. Such glycophospholipids immobilized on a cyclodextrin matrix are ampiphilic compounds and present considerable practical interest, combining in one molecule specific properties of the cyclodextrin cavity as a host and transport functions of phospholipids in biological membranes [9]. In view of the above-mentioned data [7], phosphorylation was performed in pyridine, and the reaction progress was monitored by ^{31}P NMR spectroscopy. We found that the reaction of β-cyclodextrin **I** with 3 mol of phosphorylating agents **II** or **III** proceeds under mild conditions (20°C) and leads to P(III)-containing products **IV** or **V**, respectively, which have the structure of

phosphorous amidodiesters and show a typical ^{31}P chemical shift of 148 ppm. Therewith, under these prosphorylation conditions, only 2 mol of phosphorylating agent **II** or **III** entered reaction and no possible cyclophosphorylated compounds with expected ^{31}P chemical shifts of 152 ppm [7] were detected.



IV, V: X = lone electron pair, **VI, VII**: X = S.

β-Cyclodextrin phosphorus amidodiester derivatives **IV** and **V** were treated with sulfur in situ to obtain the corresponding thiophosphoric derivatives **VI** and **VII** which were isolated as individual compounds and analyzed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and TLC. In the ^{1}H NMR spectrum of derivative **VI**, 1,2-*O*-isopropylideneglycerol methyl protons give signals in the region of 1.27–1.33 ppm with the integral intensity equal to that of amido methyl protons (δ_P 1.01–1.08 ppm), indicating the absence of phosphocyclization due to the possible reaction of the second amide function at P(III) with one of the residual primary hydroxy groups in the course of phosphorylation. The number of introduced phosphorus substituents was judged about from a comparison of the integral intensities of the 1,2-*O*-isopropylideneglycerol methyl and cyclodextrin frame proton signals. The average degree of substitution in this case was equal to two. In the ^{13}C NMR spectrum of derivative **VI**, the cyclodextrin C^5 and C^6 signals were shifted, implying substitution by primary hydroxy groups. The ^{1}H NMR spectrum of derivative **VII** contained signals of methyl protons in the region of 1.01–1.08 ppm and amido methylene protons in the region of 2.89–2.96 ppm. The presence of the amido group, too, implies the absence of phosphocyclization under the experimental conditions. From a comparison of the integral intensities of the aromatic benzyl and cyclodextrin frame proton signals we concluded that here, too, the degree of substitution of β-cyclodextrin hydroxyls is equal to two. It can be assumed that the mild and specific influence of pyridine as a solvent on the phosphorylation course and regioselectivity is defined by the supramolecular effect of the cyclodextrin cavity, like we observed previously in certain cases [10]. To provide evidence for this assumption, we investigated the possibility and features of the synthesis of diamidoesters **II** and **III** in pyridine. Note that the synthesis of these compounds was described long ago, but the reaction of phosphorous hexaethyltriamide (**VIII**) with 1,2-*O*-isopropylideneglycerol (**IX**) or benzyl alcohol (**X**), was performed, as a rule, without solvent with distilling off the liberated diethylamine [11].



We found that in our case alcohols **IX** and **X** do not enter phosphorylation in pyridine at 20°C at all. The reaction starts at 70°C and is complete in 3 h. The ^{31}P NMR spectrum of the reaction mixture contained, along with expected compounds **II** and **III** (δ_P 136 ppm), up to 15–20 mol% of phosphorous amidodiesters **XI** and **XII** (δ_P 148 ppm). It is important to note that on introduction to this reaction mixture of the corresponding quantity of β-cyclodextrin diamidoesters **II** and **III** react with it even at 20°C to form phosphorous amidodiesters **IV** and **V**, respectively, as noted above for the reaction of individual diamidoesters **II** and **III** with β-cyclodextrin. Noteworthy, amidodiesters **XI** and **XII** formed by side reactions do not react with β-cyclodextrin under these conditions, due, probably, to steric hindrances from their bulky substituents. This observation gives further evidence for our assumption that it is the cyclodextrin cavity that is responsible for the mild phosphorylation conditions of β-cyclodextrin with P(III) acid diamides.

Thus, our present research opens up new possibilities for mild regioselective synthesis of such practically important compounds as phosphorylated β-cyclodextrins.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on a Bruker AC-200 instrument at 200 and 50.32 MHz, respectively. The chemical shifts are given relatively to internal TMS.

The ^{31}P NMR spectra were registered on a Bruker WP-80 instrument at 32.4 MHz, external reference 85% H_3PO_4.

All syntheses with trivalent phosphorus compounds were performed under dry argon in an anhydrous solvent purified by a conventional procedure.

Thin-layer chromatography was performed on Silufol UV-254 plates in the system acetonitrile–water–25% ammonia, 6:3:2.

6^I,6^{II}-Bis-*O*-[(diethylamino)(2,2-dimethyl-1,3-dioxolan-4-yloxy)phosphinothioyl]-β-cyclodextrin (VI). To a solution of 1.8 g of β-cyclodextrin in 10 ml of pyridine, 1.44 g of 1,2-*O*-isopropylideneglycerol tetraethylphosphorodiamidite was added dropwise with stirring 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 148 ppm. Finely ground sulfur, 0.15 g, was then added to the reaction mixture, and stirring was continued for 2 h at 20°C. The residual sulfur was filtered off, the solvent was distilled off in a vacuum, and the oily residue was triturated with 5 ml of diethyl ether. Compound **VI** was filtered off and washed with ether (2 × 5 ml). The solvents were removed in a vacuum, and the powder-like yellowish product was kept for 4 h at 70°C in a vacuum (1.5 mm Hg). Yield 1.74 g (78 %), decomp. point 208–210°C, R_f 0.75. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.12 t [12 H, N(CH_2CH_3)$_2$; $^3J_{HCCH}$ 7.2 Hz], 1.27 s (12H), 1.33 s (12H) [C(CH_3)$_2$], 2.91 q [8H, N(CH_2CH_3)$_2$; $^3J_{HCCH}$ 7.5 Hz], 3.1–4.3 m (42H; C^2H–C^5H, C^6H_2), 4.50 br.s (5H, C^6OH), 4.84 d (7H, C^1H), 5.75 br.s (14H; C^2OH, C^3OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 11.1–14.1 [(CH_3CH_2)$_2$N], 25.3, 26.6 [C(CH_3)$_2$], 41.3 [(CH_3CH_2)$_2$N], 59.6 (C^6OH), 63.1 (POCH_2CHCH_2O), 65.4 (C^6OP), 66.5 (POCH_2CHCH_2O), 70.0 (C^5C^6OP), 72.5–73.6 (C^2, C^3, C^5, POCH_2CHCH_2O), 81.5 (C^4), 101.9 (C^1), 108.8 [C(CH_3)$_2$]. ^{31}P NMR spectrum (pyridine): δ_P 76 ppm. Found, %: C 44.26; H 6.59; P 3.74. $C_{62}H_{110}O_{41}N_2 \cdot P_2S_2$. Calculated, %: C 44.71; H 6.66; P 3.72.

6^I,6^{II}-Bis-*O*-[(benzyloxy)(diethylamino)phosphinothioyl]-β-cyclodextrin (VII). To a solution of 1.8 g of β-cyclodextrin in 10 ml of pyridine, 1.33 g of benzyl tetraethylphosphorodiamidite was added dropwise with stirring at 20°C. The reaction mixture was stirred for 12 h at 20°C. ^{31}P NMR spectrum of the reaction mixture (compound **V**): δ_P 148 ppm. Finely ground sulfur, 0.15 g, was then added to the reaction mixture, and stirring was continued for 2 h at 20°C. The residual sulfur was filtered off, the solvent was distilled off in a vacuum, and the oily residue was triturated with 5ml of diethyl ether. Compound **VII** was filtered off and washed with ether (2 × 5 ml). The solvents were removed in a vacuum, and the powder-like light brown product was dried at 70°C in a vacuum (1.5 mm Hg) for 4 h. Yield 1.61 g (78 %), decomp. point 210–212°C, R_f 0.71. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.20–4.30 m (42H; C^2H–C^5H, C^6H_2), 4.50 br.s (5H, C^6OH), 4.84 br.s (7H, C^1H), 5.75 br.s (14H; C^2OH, C^3OH), 7.37 s (10H, C_6H_5). ^{31}P NMR spectrum (pyridine): δ_P 76 ppm. Found, %: C 44.04; H 6.30; P 3.85. $C_{64}H_{102}O_{37}N_2P_2S_2$. Calculated, %: C 47.52; H 6.36; P 3.83.

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