Preparation of Sugar Phosphates by Displacement of Primary Sulfonyloxy Groups

ASISH K. CHATTERJEE AND DONALD L. MACDONALD[1]

Department of Biochemistry and Biophysics, Oregon State University, Corvallis, Oregon 97331

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A primary *p*-tolylsulfonyl group in certain otherwise acetylated sugars and glycosides can be displaced by diphenyl phosphate ion in refluxing dimethylformamide. Subsequent removal of protecting groups gives the phosphorylated sugar or glycoside. In this way D-glucose 6-phosphate was prepared in low yield and the anomeric methyl α- and β-D-glucopyranoside 6-phosphates in moderate yield (about 35%). In the last-mentioned case, methyl β-D-glucopyranoside 6-(monophenyl phosphate) was isolated as an intermediate.

The displacement of a sulfonyloxy group on primary as well as on secondary hydroxyl groups in carbohydrates has led to the formation of a variety of substituted sugars, and the versatility of this general synthetic route is continually being exploited. As yet, however, the successful introduction of phosphate groups by this method does not appear to have been described. The present report records modest success in this direction, with the displacement of a primary *p*-tolylsulfonyloxy group in otherwise acetylated derivatives of β-D-glucopyranose, methyl β-D-glucopyranoside, and methyl α-D-glucopyranoside.

The analogous preparation of phosphorylated sugars by displacement of a primary halogen has met with varying degrees of success. Silver dibenzyl phosphate has been used to prepare a derivative of uridine 5′-phosphate from 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine[2] and the same reagent has been used to prepare phosphatidic acid derivatives from diacylglycerol α-iodohydrins.[3] On the other hand, methyl 3,4-di-*O*-acetyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside react only very slowly with silver diphenyl phosphate[4] at 80°. (The products of these reactions were not described.) The unacetylated compounds readily undergo reaction, but the product is not the result of a simple displacement. Thus, methyl 6-deoxy-6-iodo-α-D-glucopyranoside and methyl 2,6-dideoxy-6-iodo-α-D-glucopyranoside readily yield the corresponding 3,6-anhydro derivatives when treated with silver diphenyl phosphate.[4,5] In the work described herein, we have used the fully acetylated derivatives in order to avoid this anhydride formation, and have carried out the reactions at higher temperatures.

When a sample of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose was refluxed in dimethylformamide with an excess of lithium diphenyl phosphate considerable decomposition took place. The product which contained esterified phosphate[6] in a yield of 34%, was subjected to hydrogenolysis and hydrolysis and yielded D-glucose 6-phosphate as the sparingly soluble hydrated barium salt in a yield of only 3 to 4%. The other products of the reaction were not investigated. The reaction of methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside with lithium diphenyl phosphate proceeded more smoothly. The crude material, containing esterified phosphate in 58% yield, was converted into the cyclohexylammonium salt of methyl α-D-glucopyranoside 6-phosphate mp 195–205°, $[\alpha]^{20}D$ +60°, in 35% yield. Szabó and Szabó[7] reported mp 157–159° and $[\alpha]^{25}D$ +61° for their anhydrous material. In our laboratory, this compound was hydrated, whether prepared by displacement as above or by phosphorylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside following the directions of Szabó and Szabó.[7]

In a similar manner, after the action of lithium diphenyl phosphate on methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside, hydrogenolysis and hydrolysis gave a crystalline cyclohexylammonium salt in 38% yield. However, this proved to be a salt of methyl β-D-glucopyranoside 6-(monophenyl phosphate). The removal of both phenyl groups is prevented presumably either by steric factors or by poisoning of the platinum catalyst. Charcoal treatment and repetitive addition of fresh catalyst did not effect the desired hydrogenolysis, suggesting that the inhibition may be steric. Furthermore, phosphorylation of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside with diphenyl phosphorochloridate followed by hydrogenolysis led to the same phospho diester. In contrast to this behavior of the acetylated material, the purified deacetylated product readily underwent hydrogenolysis of the sole remaining phenyl group to produce methyl β-D-glucopyranoside 6-phosphate, isolated as its cyclohexylammonium salt in 87% yield.

Experimental Section

Thin layer chromatography was run on Avicel plates[8] using ethyl acetate–acetic acid–water (3:3:1) as irrigating solvent and the Hanes–Isherwood spray[9] for spot detection. The R_f values found were as follows: methyl β-D-glucopyranoside 6-(monophenyl phosphate), 0.75; methyl β-D-glucopyranoside 6-phosphate and methyl α-D-glucopyranoside 6-phosphate, 0.53; D-glucose 6-phosphate, 0.28; and inorganic phosphate, 0.60.

Lithium Diphenyl Phosphate.—Diphenyl phosphoric acid (25 g) in water (40 ml) was neutralized (pH 7) with 2 *N* lithium hydroxide and the solution was evaporated *in vacuo*. The resulting white solid was air dried and used without further purification.

D-Glucose 6-(Barium phosphate).—A mixture of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[10] (4 g) and lithium diphenyl phosphate (6 g, *ca.* 3 molar equiv) in dry dimethylformamide (10 ml) was heated under reflux. The solids rapidly dissolved and after 3 hr the dark mixture was concen-

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trated at reduced pressure. The residual solids were partitioned between chloroform and water and the organic layer was washed several times with water and then dried with anhydrous sodium sulfate. The chloroform was evaporated and the residual syrup dissolved in methanol; this solution was treated with charcoal and filtered and the charcoal treatment was repeated giving after removal of solvent, a bright yellow syrup. This was dissolved in 30 ml of 95% ethanol, 2 drops of concentrated hydrochloric acid was added, and the material was hydrogenated overnight at room temperature and 45 psi using 400 mg of Adams catalyst. The catalyst was removed by centrifugation and the solution was treated with charcoal and filtered; the hydrogenation was repeated with a second portion of catalyst. To the filtered solution (75 ml), 4 ml of concentrated ammonium hydroxide was added and the solution left overnight. The solution was then concentrated *in vacuo* and the residue dissolved in water, treated batchwise with Dowex 50 H^+ (50 ml), and filtered and 1.2 g of barium acetate added. This solution was then evaporated to a small volume and seeded with authentic D-glucose 6-(barium phosphate) heptahydrate to yield 160 mg (3.8%).

Methyl β-D-Glucopyranoside 6-(Cyclohexylammonium Monophenyl Phosphate). A. By *p*-Tolylsulfonyl Displacement.—Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside[11] (2 g) and lithium diphenyl phosphate (3.1 g, *ca.* 3 molar equiv) were refluxed in DMF (6 ml) for 2 hr and the mixture was worked up with chloroform as described above. Dissolution of the syrup in ethyl acetate and addition of petroleum ether resulted in the recovery of 200 mg of starting glycoside. The mother liquor remaining was concentrated *in vacuo* and the residue dissolved in ethanol the solution was treated thrice with charcoal and filtered. This was then shaken overnight with hydrogen at room temperture and 3 atm of pressure in the presence of 200 mg of Adams catalyst and 2 drops of concentrated hydrochloric acid. The catalyst was removed by filtration and the hydrogenation was repeated three times, each time with fresh catalyst. Acetyl groups were then removed by addition of ammonium hydroxide and heating on a steam bath and the residue, in aqueous solution, was passed through a column of Dowex 50W H^+ and then treated with excess cyclohexylamine. The solution was evaporated and the product crystallized from water by the addition of acetone. The yield of air-dried product was 650 mg (38%): mp 228° dec, $[\alpha]^{20}D$ −21.6° (*c* 1, H_2O).

Anal. Calcd for $C_{19}H_{32}NO_9P$ (449.4) C, 50.77; H, 7.18; N, 3.12; P, 6.89. Found:[12] C, 50.55; H, 7.25; N, 3.16; P, 6.74.

B. By Phosphorylation with Diphenyl Phosphorochloridate Diphenyl phosphorochloridate (1.5 g) was added to dry pyridine (14 ml) containing methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside[13] (1.6 g) and the solution was left 2 days at room temperature. Water (2 ml) was then added and after 0.5 hr the solvent was removed *in vacuo*. The residue was dissolved in chloroform and the solution was washed with water, 1 *N* sulfuric acid, and then again with water and dried (sodium sulfate). The syrup (2.8 g) which remained after removal of solvent was dissolved in ethanol and shaken overnight with hydrogen at room temperature and 3 atm of pressure in the presence of 0.2 g of Adams catalyst. The acetyl groups were removed and the product isolated as described above to yield 500 mg (22%): mp 225°, $[\alpha]^{20}D$ −21.2° (*c* 1, H_2O). This material is chromatographically identical with the above-described substance.

Methyl β-D-Glucopyranoside 6-(Dicyclohexylammonium phosphate).—A 0.4-g sample of methyl β-D-glucopyranoside 6-(cyclohexylammonium monophenyl phosphate) in water was converted into the free acid using a small column of Dowex 50W H^+. The resulting solution was concentrated *in vacuo* and the residue dissolved in ethanol (30 ml) and hydrogenated overnight at room temperature and 3 atm of pressure using 200 mg of platinum oxide. The resulting filtered solution was made alkaline with cyclohexylamine and concentrated at reduced pressure and the residue was crystallized from water by the addition of acetone. The air-dried product weighed 375 mg (87%): mp 185°, $[\alpha]^{20}D$ −25.6° (*c* 1, H_2O)

Anal. Calcd for $C_{19}H_{41}N_2O_9P \cdot {}^1/_2H_2O$ (481.5): C, 47.39; H, 8.79; N, 5.82; P, 6.43. Found: C, 47.14; H, 8.77; N, 5.49; P, 6.24.

Methyl α-D-Glucopyranoside 6-(Dicyclohexylammonium Phosphate).—Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[14] (0.85 g) and lithium diphenyl phosphate (1.25 g) were refluxed in dimethylformamide (9 ml) for 10 hr. The product was worked up as described in the displacement reaction on the α anomer, except that no starting material was recovered. The final air-dried product weighed 300 mg (35%) after crystallization from water–acetone, and showed mp 195–205°, $[\alpha]^{20}D$ +60° (*c* 1, H_2O).

The compound was also prepared by phosphorylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside with diphenyl phosphorochloridate following the procedure of Szabó and Szabó,[7] except that the hydrogenation was performed at 3 atm rather than 1 atm of pressure. The product was obtained in 66% yield and had melting point and rotation identical with those of the product obtained by tosyl displacement. Szabó and Szabó obtained anhydrous material with mp 157–159° and $[\alpha]^{25}D$ +61°.

Anal. Calcd for $C_{19}H_{41}N_2O_9P \cdot {}^1/_2H_2O$ (481.5) C, 47.39; H, 8.79; N, 5.82; P, 6.43. Found: C, 47.19; H, 8.80; N, 5.64; P, 6.05.

Registry No.—$C_{19}H_{32}NO_9P$, 15764-86-0; $C_{19}H_{41}N_2O_9P$ (β-D), 15764-87-1; $C_{19}H_{41}N_2O_9P$(α-D), 15764-88-2.

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