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The Orthoester Glycosylation Method. Part II.* Variation in the Anomeric Composition of the Product with Aglycone Basicity and Steric Accessibility

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The previously observed influence of aglycone basicity on the steric outcome of the two-step orthoester glycosylation procedure is further substantiated by the observation that 2-nitroethanol yields anomeric D-glucopyranosides in an $\alpha:\beta$ ratio of 44:56. Fluoroethanol yields the β-D-glucopyranoside only; this is ascribed to the *gauche* effect. A comparison of the products of glycosylation of cyclohexanol and 2,2,6,6-tetramethylcyclohexanol shows that steric hindrance may inhibit catalysis by electrophilic attack at the alkoxyl group, leading to an increase in the α-D-glucopyranoside produced.

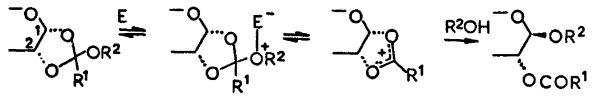
In the orthoester glycosylation method, developed by Kochetkov and co-workers for the synthesis of glycosides with 1,2-*trans*-configuration,[2–6] the usual procedure is to treat a 1,2-orthoester in which the alkoxyl residue is the desired aglycone, with a Lewis acid, in the presence of the alcohol. The 1,2-dioxolonium ions thus formed react with the alcohol producing a 1,2-*trans*-glycoside.

Other products may, however, be produced if the electrophile instead attacks O-1 or O-2. This possibility was studied in a previous investigation,[1] in which we demonstrated that the product composition varies with the basicity of the aglycone oxygen (R^2OH in Scheme 1). Low electron density rendering the oxygen less susceptible to electrophilic attack, gave rise to competing attack at O-1 and consequently other products, *e.g.* 1,2-*cis*-glycosides, were also formed. Competing attack at O-2 should lead to glycosides with an unsubstituted hydroxyl group in the 2-position. This, however, was not observed.

We now report some studies on the influence of steric factors in the choice of reaction paths. The stereospecific formation of 1,2-*trans*-glycosides depends on the electrophile attacking the alkoxyl oxygen only and the resulting formation of the required acyloxonium ion (Scheme 1). One might therefore anticipate that bulky substituents on the α-carbon atom(s) of the alkoxyl residue would direct the electrophile to O-1 (or, possibly O-2) with concomitant loss of stereospecificity.

The various orthoesters required for the study (*1*–*4*) were made as previously described. Only one stereoisomeric form, presumably the *exo* isomer was obtained for each orthoester. The glycosylations were carried out by allowing the various orthoesters to react with the appropriate alcohol, in nitromethane, in the presence of mercury(II) bromide.

* Part I, Ref. 1.



Scheme 1.

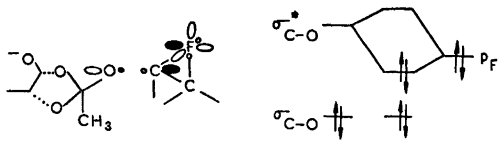


Fig. 1. Gauche effect in 2′-fluoroethyl orthoesters.

In order to investigate a possible steric effect on the reaction, the products of glycosylation of 2,2,6,6-tetramethylcyclohexanol were examined and compared to those obtained from cyclohexanol. Studies on the proton catalyzed glycosylation of the cyclohexyl orthoester *1* with cyclohexanol have shown that a mixture of anomeric glycopyranosides with extensive deacetylation in the 2-position are obtained.[7,8] Under the conditions used in the present study, the following products and yields were obtained: Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (*5*, 62 %), cyclohexyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (*6*, 16 %) and cyclohexyl 3,4,6-tri-*O*-acetyl-*β*-D-glucopyranoside (*7*, 15 %). The position of the free hydroxyl group in *6* and *7* was demonstrated by methylation analysis. Cyclohexyl acetate in an amount corresponding to *6* and *7* was found present in the original reaction mixture. Glycosylation of the 2′,2′,6′,6′-tetramethylcyclohexyl orthoester *2* afforded a 40 % yield of a mixture of the α-D-anomer *8* and the *β*-D-anomer *9* in a ratio of 26:74 by optical rotation of the mixture and 22:78 by weighing the separated components. Products with a free hydroxyl group in the 2-position were not observed. A comparison of the ratio of α-D-glucopyranoside to *β*-D-glucopyranoside obtained in this latter reaction to that obtained in the corresponding glycosylation of cyclohexanol (17:83) would implicate steric hindrance as a factor in these reactions. The effect, however, seems to be smaller than that obtained by varying the aglycone basicity.

Secondly, as a continuation of our previous investigation on the effect of polar substituent in the alcohol component (R^2OH, Scheme 1), we have examined the products obtained using 2-fluoroethanol and 2-nitroethanol. The former gave rise to an 85 % yield of the *β*-D-glucopyranoside *10*. The corresponding α-anomer was not detected in the reaction mixture. This result contrasts strikingly with those previously obtained with 2-chloroethanols. For these, the polar chlorine substituents gave rise to α-D- as well as to *β*-D-glucopyranosides.[1] A possible explanation for this apparent anomaly is provided by the more pronounced *gauche* effect expected for the fluoro substituent.[9–11] A *gauche* arrangement of the alkoxyl oxygen and the adjacent fluoro *p* orbital involves the mixing of an occupied fluorine *p* orbital and the carbon-oxygen antibonding orbital as depicted in Fig. 1 [11] (and additionally the corresponding mixing of an occupied *p* orbital on the alkoxyl oxygen and the antibonding carbon-fluorine orbital, not shown in Fig. 1). This orbital mixing results in a lower-lying highest occupied

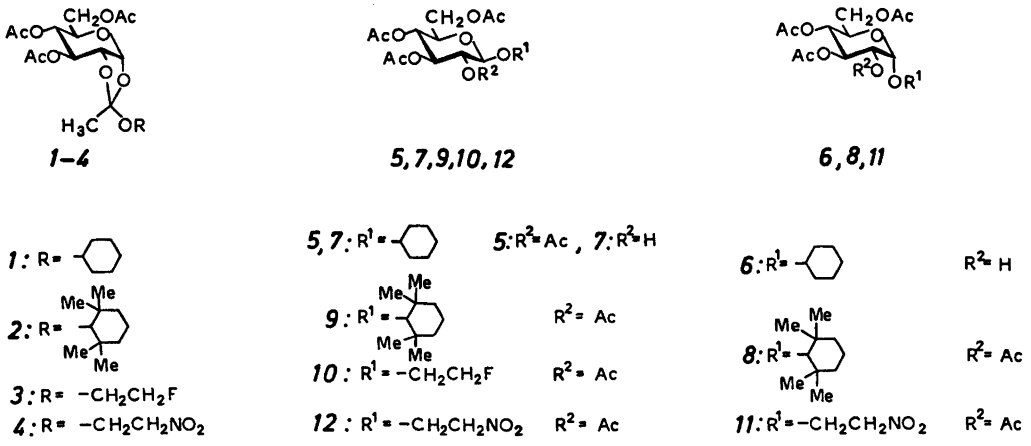


Fig. 2. Orthoesters and glycosides obtained.

molecular orbital for the electrophile to attack and thereby a lower-energy transition state.

For 2-nitroethanol this orbital effect is precluded. As anticipated, this alcohol gave rise to a mixture of anomeric 2′-nitroethyl D-glucopyranosides (*11* and *12*), in which the ratio of α- to β-D-pyranoside was 44:56. Deacetylation at the 2-position [7,8] was not observed in the above two examples.

EXPERIMENTAL

General methods were the same as those described before.[1]

Preparation of orthoesters. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (10 mmol) in dry nitromethane (10 ml) was treated with the appropriate alcohol (20 mmol) in the presence of 2,6-lutidine (20 mmol) at 37 °C for 20 h with respectively cyclohexanol, 2-fluoroethanol or 2-nitroethanol and for 96 h with 2,2,6,6-tetramethylcyclohexanol as the alcohol component. Aqueous silver nitrate (7.5 ml 2 M), water (12.5 ml) and acetone (25 ml) were added with stirring. The mixture was filtered and the filtrate extracted three times with chloroform (25 ml). The chloroform extract was shaken three times with water (25 ml), dried over magnesium sulfate, filtered and concentrated.

*3,4,6,-Tri-*O*-acetyl-1,2-*O*-(cyclohexyloxyethylidene)-α-D-glucopyranose* (*1*) was obtained in pure form by means of chromatography on a silica gel column (toluene–ethyl acetate 2:1) and then recrystallized from diethyl ether–light petroleum to yield 3.0 g (70 %), m.p. 83–84 °C, $[\alpha]_D$ +26° (*c*, 1.0, $CHCl_3$), (lit.[7] m.p. 83 °C, $[\alpha]_D$ +25° ($CHCl_3$).

*3,4,6-Tri-*O*-acetyl-1,2-*O*-(2′,2′,6′,6′-tetramethylcyclohexyloxyethylidene)-α-D-glucopyranose* (*2*) was obtained in pure form by means of chromatography on a silica gel column (toluene–ethyl acetate 4:1) in a yield of 2.2 g (45 %), $[\alpha]_D$ +24° (*c* 1.0, $CHCl_3$). Anal. $C_{24}H_{38}O_{10}$: C, H. NMR ($CDCl_3$): δ 0.88, 0.91 and 0.97 (12 H, s, cyclohexyl CH_3), 1.0–1.8 (6 H, cyclohexyl H), 1.76 (3 H, s, O–C(=O)–CH_3), 2.10 and 2.12 (9 H, s, OAc), 3.11 (1 H, s, cyclohexyl-O-C-H), 4.00 (1 H, m, H-5), 4.19 and 4.23 (1 H each, H-6, H-6′), 4.42 (1 H, dd, $J_{1,2}$ 5 Hz, $J_{2,3}$ 3 Hz, H-2), 4.92 (1 H, dd, $J_{3,4}$ 3 Hz, $J_{4,5}$ 9 Hz, H-4), 5.20 (1 H, t, *J* 3 Hz, H-3), 5.76 (1 H, d, *J* 5 Hz, H-1).

*3,4,6-Tri-*O*-acetyl-1,2-*O*-(2′-fluoroethoxyethylidene)-α-D-glucopyranose* (*3*) was recrystallized from ethanol to yield 2.8 g (71 %) m.p. 115–116 °C $[\alpha]_D$ +30° (*c* 1.0 $CHCl_3$). Anal. $C_{16}H_{23}O_{10}F$: C, H. NMR ($CDCl_3$): δ 1.76 (3 H, s, CCH_3), 2.12 and 2.14 (9 H, s, OAc), 3.64 and 3.94 (1 H each, OCH_2CH_2F), 4.00 (1 H, m, H-5), 4.2–4.3 (2 H, m, H-6, H-6′), 4.36 and 4.80 (1 H each, OCH_2CH_2F), 4.40 (1 H, dd, $J_{1,2}$ 5 Hz, $J_{2,3}$ 3 Hz, H-2), 4.94 (1 H, dd, $J_{3,4}$ 3 Hz, $J_{4,5}$ 9 Hz, H-4) 5.20 (1 H, t, *J* 3 Hz, H-3), 5.77 (d, *J* 5 Hz, H-1).

*3,4,6-Tri-*O*-acetyl-1,2-*O*-(2′-nitroethoxyethylidene)-α-D-glucopyranose* (*4*) was recrystallized from ethanol to yield 3.0 g (71 %), m.p. 119.5–120.5 °C, $[\alpha]_D$ +32° (*c* 1.1, $CHCl_3$). Anal. $C_{16}H_{23}NO_{12}$: C, H, NMR ($CDCl_3$): δ 1.76 (3 H, s, CCH_3), 2.12 and 2.14 (9 H, s, OAc), 4.00 (1 H, m, H-5), 4.10 (2 H, $OCH_2CH_2NO_2$). 4.24 and 4.28 (1 H each, H-6, H-6′), 4.34 (1 H, dd, $J_{1,2}$ 5 Hz, $J_{2,3}$ 3 Hz, H-2) 4.60 (2 H, $OCH_2CH_2NO_2$), 4.96 (1 H, dd, $J_{3,4}$ 3 Hz, $J_{4,5}$ 9 Hz, H-4), 5.24 (1 H, t, *J* 3 Hz, H-3), 5.78 (1 H, d, *J* 5 Hz H-1).

Preparation of glycosides. The appropriate orthoester (3 mmol), the corresponding alcohol (6 mmol) and mercury(II) bromide (1 mmol) in dry nitromethane (12 ml) was refluxed for 15 min. The various products were obtained as described below.

*Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (*5*). Chromatographic separation by means of silica gel column chromatography (toluene–ethyl acetate 1:1) of the product of glycosylation of 3,4,6-tri-*O*-acetyl-1,2-*O*-(cyclohexyloxyethylidene)-α-D-glucopyranose (*1*) and crystallisation from diethyl ether–light petroleum afforded 0.80 g of *5* (62 %), m.p. 119–120 °C $[\alpha]_D$ −24° (*c* 1.0, $CHCl_3$) in agreement with literature values.[13]

*Cyclohexyl 3,4,6-tri-*O*-acetyl-α- and β-D-glucopyranosides* (*6*, *7*). A slower-moving fraction, 0.37 g (32 %) containing the two anomers *6* and *7* was also obtained from the above separation. The optical rotation, $[\alpha]_D$ +66° (*c* 1.0, $CHCl_3$) indicated a ratio of 50:50 of *6* and *7* in the mixture. Further separation by means of silica gel column chromatography (toluene–ethyl acetate 4:1) afforded the pure anomers. Cyclohexyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (*6*), 0.18 g (16 %) had $[\alpha]_D$ +133° (*c* 0.9, $CHCl_3$). Anal. $C_{18}H_{28}O_9$: C, H. NMR ($CDCl_3$): δ 1.1–2.0 (10 H, m, cyclohexyl H) 2.06 and 2.10 (9 H, s, OAc), 2.30 (1 H, OH), 3.5–3.9 (2 H, m, H-5 and cyclohexyl O-C-H), 4.0–4.4 (3 H, m, H-2, H-6 and H-6′), 5.02 (1 H, t, $J_{3,4}$ and $J_{4,5}$ 9 Hz, H-4), 5.10 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.28 (1 H, t, $J_{2,3}$ 9 Hz, H-3). Cyclohexyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (*7*) was recrystallized from diethyl ether–light petroleum to yield 0.17 g (15 %), m.p. 108–109 °C $[\alpha]_D$ −2° (*c* 1.0, $CHCl_3$). Anal. $C_{18}H_{28}O_9$: C, H. NMR ($CDCl_3$): δ 1.1–2.0 (10 H, cyclohexyl H), 2.06 and 2.10 (9 H, s, OAc), 2.9 (1 H, OH), 3.5–3.9 (3 H, m, H-2, H-5 and cyclohexyl O-C-H), 4.14 (1 H, dd, $J_{5,6}$ 3 Hz, $J_{6,6'}$ 12 Hz, H-6), 4.35 (1 H, dd, $J_{5,6}$ 5 Hz, H-6′), 4.54 (1 H, d, $J_{1,2}$ 8 Hz, H-1), 4.9–5.3 (2 H, m, H-3, H-4).

The position of the free hydroxyl group in the above two anomers was demonstrated by methylation with methyl triflate [14,15] followed

by deacetylation (sodium methoxide in methanol), acidic hydrolysis (0.25 M H_2SO_4 at 100 °C overnight), reduction with sodium borohydride and acetylation.[16] The two products were examined by GLC-MS and were in both instances identical to 1,3,4,5,6-penta-*O*-acetyl-2-*O*-methyl-D-glucitol. Examination of the original reaction mixture by GLC and comparison to authentic material revealed the presence of cyclohexyl acetate. The amount was related to that of the cyclohexanol present. A known amount of authentic cyclohexyl acetate was added and the new ratio of cyclohexanol to cyclohexyl acetate was determined. From these results the amount of cyclohexyl acetate produced in the reaction was calculated and found to correspond stoichiometrically to *6* and *7*.

2',2',6',6'-Tetramethylcyclohexyl 2,3,4,6-tetra-O-acetyl-α-D- and -β-D-glucopyranosides (8, 9). Chromatographic separation by means of silica gel column chromatography (toluene–ethyl acetate 2:1) of the product of glycosylation of 3,4,6-tri-*O*-acetyl-1,2,*O*-(2',2',6',6'-tetramethylcyclohexyloxyethylidene)-α-D-glucopyranose (*2*) afforded a mixture of the anomeric glycosides *11* and *12*, 0.58 g (40 %). The optical rotation $[\alpha]_D$ +2° (*c* 1.2, $CHCl_3$), indicated a ratio of 26:74 of the α-D- and β-D-anomers, *11* and *12*, respectively. Further separations on a silica gel column (toluene–ethyl acetate 2:1) afforded each of the two anomers in pure form. 2',2',6',6'-Tetramethylcyclohexyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside, 0.12 g (8 %) was obtained, m.p. 113.5–114.5 °C, $[\alpha]_D$ +66° (*c* 0.9, $CHCl_3$). Anal. $C_{24}H_{38}O_{10}$: C, H. NMR ($CDCl_3$): δ 0.95, 0.98 and 1.02 (12 H, s, cyclohexyl CH_3), 1.0–1.6 (6 H, m, cyclohexyl H), 2.00, 2.04 and 2.06 (12 H, s, OAc), 3.00 (1 H, s, cyclohexyl O–Ċ–H), 4.0–4.4 (3 H, m, H-5, H-6, H-6'), 4.9–5.2 (3 H, m, H-1, H-2, H-4), 5.48 (1 H, t, *J* 9 Hz H-3). 2',2',6',6'-Tetramethylcyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, 0.43 g (30 %) was obtained, m.p. 141–142 °C, $[\alpha]_D$ −21° (*c* 1.0, $CHCl_3$). Anal. $C_{24}H_{38}O_{10}$: C, H. NMR ($CDCl_3$): δ 0.87, 0.94 and 1.00 (12 H, s, cyclohexyl CH_3), 1.0–1.6 (6 H, m, cyclohexyl H), 2.00, 2.02 and 2.06 (12 H, s, OAc), 2.98 (1 H, s, cyclohexyl O–Ċ–H), 3.66 (1 H, m, H-5), 4.16 (2 H, m, H-6 and H-6'), 4.62 (1 H, d, $J_{1,2}$ 8 Hz, H-1), 4.9–5.3 (3 H, m, H-2, H-3, H-4).

2'-Fluoroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (10). Chromatographic purification by means of silica gel column chromatography (toluene–ethyl acetate 1:1) of the product of glycosylation of 3,4,6-tri-*O*-acetyl-(2'-fluoroethoxyethylidene)-α-D-glucopyranose (*3*) and crystallization from diethyl ether afforded 1.0 g (85 %), m.p. 108.5–109.5 °C, $[\alpha]_D$ −16° (c 1.0, $CHCl_3$). Anal. $C_{16}H_{23}O_{10}F$: C, H. NMR ($CDCl_3$): δ 2.03, 2.05, 2.07 and 2.11 (12 H, s, OAc), 3.6–4.0 (2 H, m, H-5 and O*C*HCH_2F), 4.10 (1 H, m, −*C*HCH_2F), 4.2–4.4 (3 H, m, H-6, H-6' and OCH_2*C*HF), 4.66 (d, $J_{1,2}$ 8 Hz, H-1), 4.82 (1 H, m, OCH_2*C*HF), 4.9–5.2 (3 H, m, H-2, H-3 and H-4). The corresponding α-anomer was not detected in the reaction mixture.

2'-Nitroethyl 2,3,4,6-tetra-O-acetyl-α-D and β-D-glucopyranosides (11, 12). Chromatographic separation by means of silica gel column chromatography (toluene-ethyl acetate 1:1) of the product of glycosylation of 3,4,6-tri-*O*-acetyl-1,2-*O*-(2'-nitroethoxyethylidene)-α-D-glucopyranose (*4*) afforded 0.94 g (75 %) of an anomeric mixture which from the optical rotation, $[\alpha]_D$ +35° (*c* 1.0, $CHCl_3$), was calculated to contain the α-D- and the β-D-anomer in a ratio of 44:56. The anomers could be distinguished by TLC on silica gel plates impregnated with dimethyl sulfoxide using diethyl ether saturated with dimethyl sulfoxide as solvent. The chromatographically pure anomers were obtained by crystallization of the β-anomer from a diethyl ether–light petroleum solution. 2'-Nitroethyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (*11*), 0.40 g (32 %) was obtained, $[\alpha]_D$ +100° (*c* 1.0, $CHCl_3$). Anal. $C_{16}H_{23}NO_{12}$: C, H. NMR ($CDCl_3$): δ 2.02, 2.04, 2.07 and 2.12 (12 H, s, OAc), 4.04 (1 H, m, H-5), 4.1–4.3 (4 H, H-6, H-6', $OCH_2CH_2NO_2$), 4.63 (2 H, m, $OCH_2CH_2NO_2$), 4.86 (1 H, dd, $J_{1,2}$ 4 Hz, $J_{2,3}$ 9.5 Hz, H-2), 5.06 (1 H, t, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 5.16 (1 H, d, H-1), 5.41 (1 H, t, H-3). 2'-Nitroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (*12*), 0.50 g (40 %) was obtained, m.p. 114–115 °C, $[\alpha]_D$ −16° (*c* 1.1, $CHCl_3$) (lit.[12] m.p. 119–120 °C $[\alpha]_D$ −16° $CHCl_3$). NMR ($CDCl_3$): δ 2.02, 2.05 and 2.11 (12 H, s, OAc), 3.76 (1 H, m, H-5), 4.2–4.3 (4 H, m, H-6, H-6' and $OCH_2CH_2NO_2$), 4.58 (2 H, $OCH_2CH_2NO_2$), 4.60 (1 H, d, $J_{1,2}$ 8 Hz), 4.9–5.4 (3 H, m, H-2, H-3 and H-4).

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