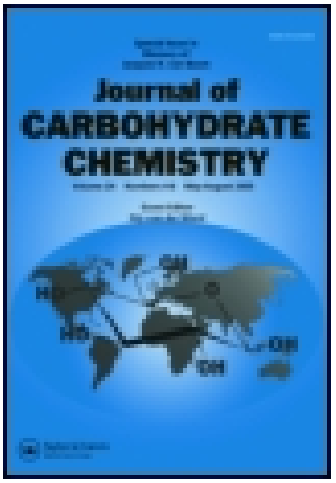

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Gas Chromatographic Investigation of the Boron Trifluoride Etherate-Induced Formation and Anomerization of Glucopyranosides

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GAS CHROMATOGRAPHIC INVESTIGATION OF THE BORON TRIFLUORIDE ETHERATE-INDUCED FORMATION AND ANOMERIZATION OF GLUCOPYRANOSIDES[1]

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ABSTRACT

Boron trifluoride etherate-induced glucosylation of methanol, 1-propanol, 2-propanol, 2-bromoethanol, and 3-bromo-2-(bromomethyl)propan-1-ol, using 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose as donor, gave the corresponding β-glucopyranosides. The α-glucosides and 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose were formed as byproducts in varying amounts, according to GLC analysis. The propensity of the different glucopyranosides to anomerize was determined in separate experiments.

INTRODUCTION

Glycosylation of simple alcohols with the fully acetylated derivatives of common and inexpensive monosaccharides can often be performed by Lewis acid-promotion in a suitable solvent.[2] Such glycosylations normally proceed in only moderate yield (50-60%) but the simplicity of the method and avoidance of toxic and/or expensive heavy metal catalysts make such procedures attractive.

It was pointed out by Paulsen and Paal[3] that the sugar β-acetates (1,2-*trans* configuration) are the preferred glycosyl donors in Lewis-acid-induced glycosylations and we have confirmed here that the corresponding α-acetates are practically inert under the conditions used. The participating nature of the 2-*O*-acetyl group causes initial

formation of a β-glycoside but prolonged treatment with boron trifluoride leads to partial anomerization to the corresponding α-glycoside. Anomerization with boron trifluoride etherate was developed into a preparatively useful procedure by Lindberg.[4]

RESULTS AND DISCUSSION

In order to obtain some information about the relative rates of Lewis acid-promoted anomerization and glycosylation, we undertook a limited rate study where some simple alcohols were glucosylated by 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**1β**) in solvents of different polarity, using boron trifluoride etherate (BF_3OEt_2) as promoter. The compounds used in the investigation, and a probable reaction scheme, are depicted in Figs. 1 and 2, respectively.

The rate of anomerization of the resulting β-glucosides was investigated separately. Quantitation of the β- and α-acetates (**1β** and **1α**) as well as the β- and α-glucosides (**2β-6β** and **2α-6α**) was performed by gas chromatography, which assures a reasonable accuracy in the measurements (Figs. 3 and 4). Possible byproducts (such as β- and α-glucosides having a free hydroxyl group in the 2-position; cf. Fig. 2) were not volatile enough for GLC-detection. The BF_3OEt_2-mediated synthesis of allyl glycosides with a free 2-OH group was recently reported.[5]

The simple alcohols (2 equiv) methanol, 1-propanol, 2-propanol, 2-bromoethanol, and 3-bromo-2-(bromomethyl)propan-1-ol were glucosylated by β-D-glucose pentaacetate (**1β**, 1 equiv) under BF_3OEt_2-promotion[6] (3 equiv) in solvents of different polarity. As seen in Fig. 3, the main part of **1β** was consumed within a few hours of reaction and the corresponding β-glucoside (**2β-6β**) was formed at approximately the same rate. In all experiments, only a small amount of **1α** was formed, which showed that glycosylation of **1β** was more rapid than its anomerization. The rates of anomerization of the initially formed β-glucosides were similar to the anomerization rates determined in a separate set of experiments (Fig. 4). The small discrepancies might well depend on the fact that the glucosylation mixtures, in contrast to the anomerization mixtures, contained ~1 equiv of unreacted alcohol, which would affect *inter alia* the polarity of the solvent, which in turn might affect anomerization rates and equilibria.

When reaction times were kept below 3 h, the β-glucosides **2β-6β** could be obtained by this simple procedure. Compounds **5β** and **6β** were most easily prepared, partly due to the high reaction rates and exceptional stability against anomerization (see below).

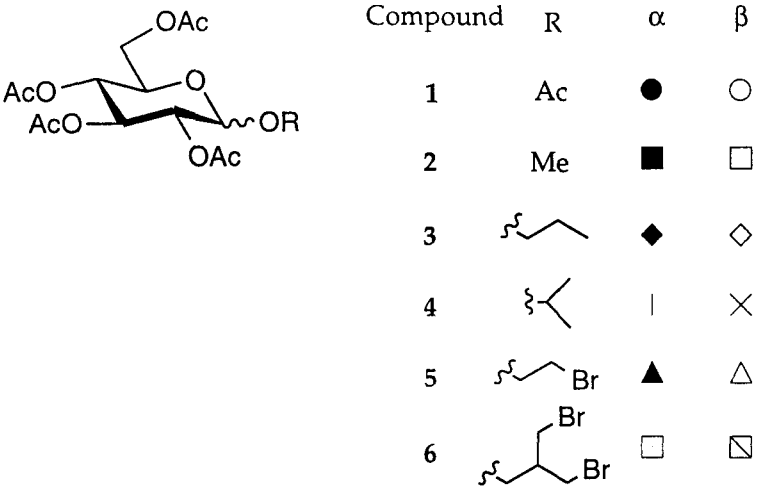

Figure 1. The glucopyranose derivatives used in this investigation. The symbols for α and β derivatives were used in Figs. 3 and 4.

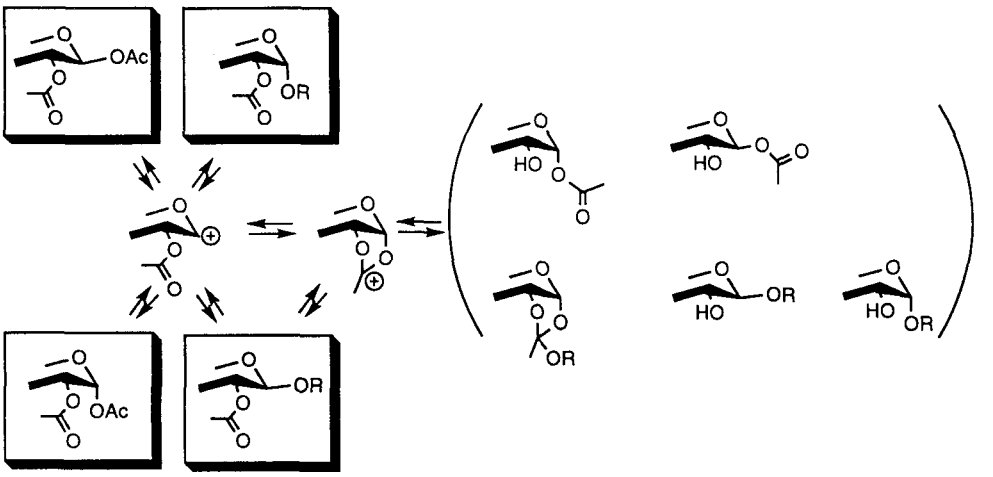

Figure 2. Reaction scheme for glycosylation with 1-*O*-acetyl donors and anomerization of the resulting glycosides. Compound types in frames were quantitated by GLC (cf. Experimental section and Figs. 3 and 4).

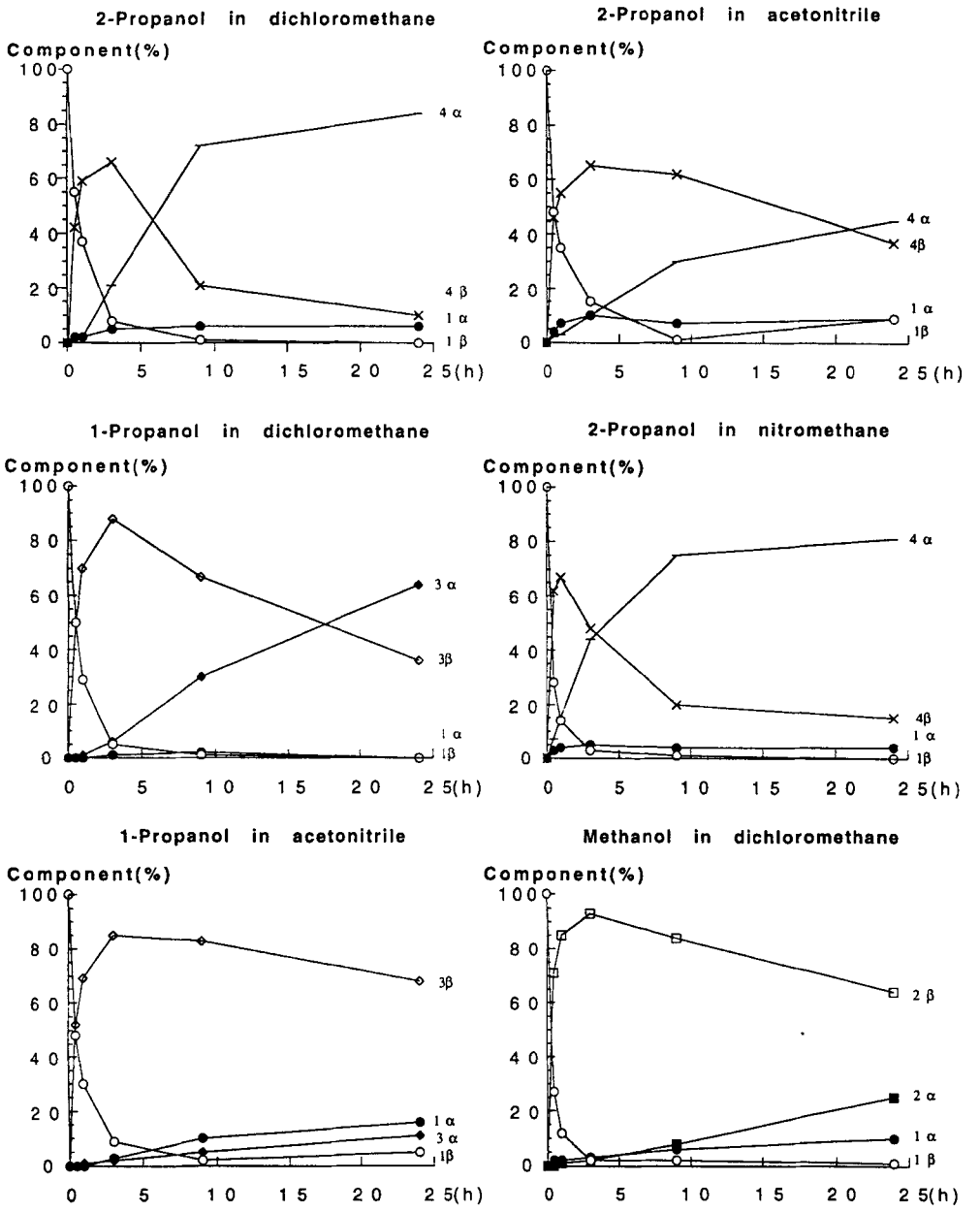

Figure 3. GLC-quantitation of the BF_3OEt_2-induced glucosylation of alcohols by the glucose pentaacetate **1β** in various aprotic solvents. Glucosides with a free 2-OH group were detected by TLC but not by GLC. The graphs show [i] the rapid disappearance of the starting material **1β**, [ii] the appearance of small amounts of **1α**, [iii] the rapid appearance of the β-glucosides **2β-6β**, [iv] the variously rapid appearance of the α-glucosides **2α-6α** at the expense of the corresponding **2β-6β**.

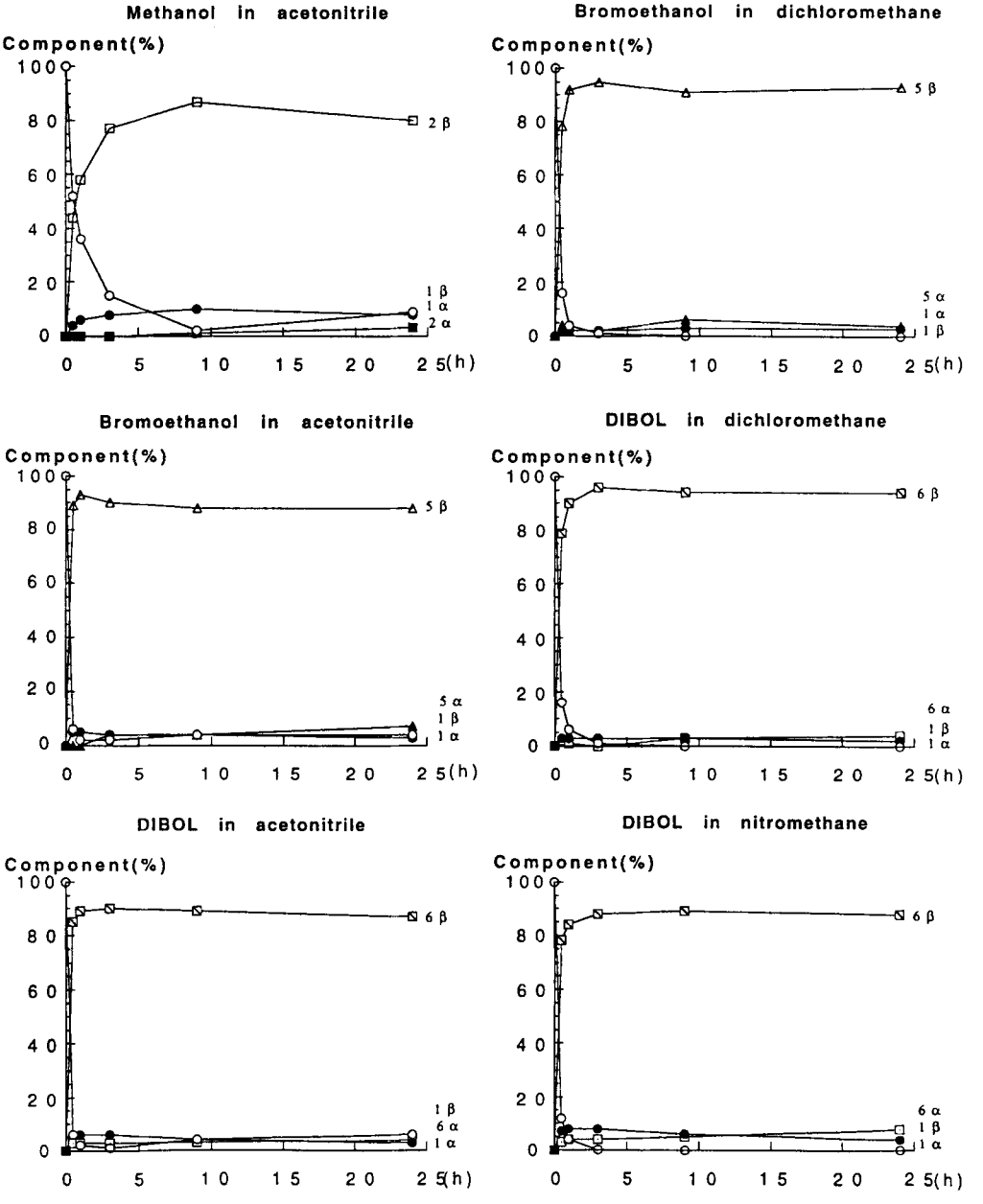

Figure 3. continued.

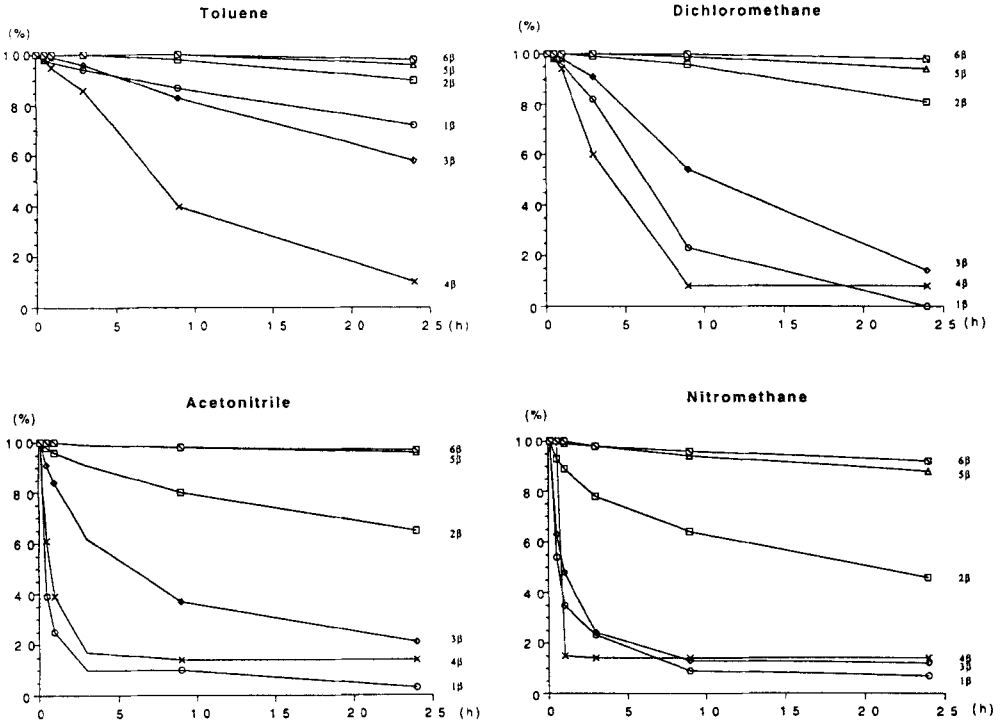

Figure 4. GLC-quantitation of the BF_3OEt_2-induced anomerization of compounds **1β-6β**. The graphs show that anomerization is more rapid in the polar solvents acetonitrile and nitromethane than in the less polar solvents toluene and dichloromethane. The bromine-containing glycosides **5β** and **6β** were practically inert against anomerization.

The pure β-glucosides were submitted to the anomerization conditions and the rate of anomerization was determined. As shown in Fig. 4, the 1-propyl and 2-propyl glucosides **3β** and **4β** underwent rapid anomerization in the polar solvents acetonitrile and nitromethane and somewhat slower anomerization in the less polar solvents toluene and dichloromethane. The methyl glucoside **2β** was more stable against anomerization. The bromine-containing glucosides **5β** and **6β** were practically unaffected by the anomerization conditions and the corresponding α-glucosides were barely detectable in the reaction mixtures. The reason for the relative stability of **5β** and **6β** requires further investigation. We have used 2-bromoethyl and 3-bromo-2-(bromomethyl)propan-1-yl (dibromoisobutyl or DIB) glycosides in stepwise syntheses of neoglycolipids, neoglycoproteins, and neoglycoparticles.[7,8]

EXPERIMENTAL

General methods. Boron trifluoride etherate (BF_3OEt_2) was distilled (60 mmHg, bp approx. 68 °C) and stored in a sealed ampoule at 22 °C. Starting materials were dried (0.01 mmHg, 22 °C, 15 min) in the reaction flask before each experiment. Dichloromethane and acetonitrile were dried by passing through a bed of alumina (Neutral, activity grade I). Analyses were performed on a Shimadzu GC-9A gas chromatograph equipped with a semi-polar DB-17+ capillary column (J&W Scientific) and a Hewlett Packard 3390 A electronic integrator. The relative amounts of **1β**, **1α**, and the corresponding glucosides **2β-6β** and **2α-6α** were determined by integration of the respective peaks on the gas chromatograms. Suitable sampling intervals were determined initially by TLC on Kieselgel 60 F254 plates (Merck). The TLC-plates were developed by spraying with 50% sulfuric acid and charring on a hot (~160 °C) plate. Charring without sulfuric acid caused development of the spots of **1β** and **1α** only; the glucosides **2-6** were not developed under these conditions.[4] The glucosides **2-6** have been reported: **2β**,[9] **2α**,[9] **3β**,[9] **3α**,[9]**4β**,[9]**4α**,[10]**5β**,[11]and **6β**.[12] The identity of **5α** and **6α** were inferred from the GLC patterns.

Investigation of the Rate of Glucosylation of Various Alcohols by 1β (cf. Fig. 3). Compound **1β** (39 mg, 0.1 mmol) was dissolved in the appropriate solvent (0.7 mL), the alcohol (0.2 mmol) and BF_3OEt_2 (0.039 mL, 0.3 mmol) were added, and the mixture was stirred at room temperature. Samples (0.050 mL) were collected after 0.5, 1.0, 3.0, 9.0, and 24.0 h and partitioned between saturated aqueous sodium hydrogencarbonate (0.5 mL) and diethyl ether (0.2 mL). Aliquots were taken from the ether solution for TLC and GLC analysis. The results of the GLC-analyses are presented in Fig. 3.

The following alcohol–solvent combinations were used: methanol in dichloromethane or acetonitrile; 1-propanol in dichloromethane or acetonitrile; 2-propanol in dichloromethane, acetonitrile, or nitromethane; 2-bromoethanol in dichloromethane or acetonitrile; 3-bromo-2-(bromomethyl)propan-1-ol in dichloromethane, acetonitrile, or nitromethane.

Attempted Glucosylation of 1-Propanol by 1α. Compound **1α** (39 mg, 0.1 mmol) was dissolved in dichloromethane (0.7 mL), 1-propanol (0.015 mL, 0.2 mmol) and BF_3Et_2O (0.039 mL, 0.3 mmol) were added, and the mixture was stirred at room temperature. Samples were collected and treated as above. The 1-propyl glucosides **3β** and **3α** could not be detected by TLC or GLC analysis.

Investigation of the Rate of Anomerization of the Glucosides 2β-6β (cf. Fig. 4). The glucoside (**2β-6β**, 0.1 mmol) was dissolved in the appropriate solvent (0.7 mL),

BF_3Et_2O (0.039 mL, 0.3 mmol) was added, and the mixture was stirred at room temperature. Samples (0.050 mL) were collected after 0.5, 1.0, 3.0, 9.0, and 24.0 h and partitioned between saturated aqueous sodium hydrogencarbonate (0.5 mL) and diethyl ether (0.2 mL). As above, aliquots were taken from the ether solution for TLC and GLC analysis. The results of the GLC-analyses are presented in Fig. 4.

ACKNOWLEDGMENT

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