Methoxy group migrations in the reaction of some methyl-pyranoside chlorosulfate ester derivatives with aluminum chloride[1]

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Received March 25, 1970

The treatment of methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) with aluminum chloride yielded a mixture of two major components identified as methyl α-D-xylopyranoside 2,3,4-tri(chlorosulfate) and 4-*O*-methyl-α-L-arabinopyranosyl chloride 2,3-di(chlorosulfate). The latter compound constituted about 25% of the mixture and was formed as a result of the preferential migration of the anomeric methoxy group to C-4 of the pyran ring. Similar treatment of methyl α-D-glucopyranoside 2,3,4,6-tetra(chlorosulfate) with aluminum chloride yielded crystalline 6-*O*-methyl-α-D-glucopyranosyl chloride 2,3,4-tri(chlorosulfate) as the only major methoxy migration product. This methoxy migration occurred to the extent of 66% and in contrast to the results obtained with methyl pentapyranoside derivative the anomeric methoxy group migrated preferentially to C-6 in this case. The factors controlling these highly selective methoxy migrations are discussed.

Canadian Journal of Chemistry, **48**, 2735 (1970)

Introduction

The ability of the methoxy group to participate in solvolytic displacement reactions was first established by Winstein and Henderson (1), and significant participation has been observed in reactions where the methoxy group participates through the formation of a three-membered (MeO-3 participation), five-membered (MeO-5 participation), and a six-membered (MeO-6 participation) oxonium ion (2). In the carbohydrate field a number of examples of methoxy group participation have also been established. The solvolysis of both methyl 5-*O*-*p*-bromobenzenesulfonyl-6-deoxy-2,3-*O*-isopropylidene-β-L-allofuranoside (3) and methyl 4-*O*-nitrobenzene-*p*-sulfonyl-β-D-xylopyranoside (4) resulted in MeO-5 participation with the subsequent migration of the glycosidic methoxy group. Similarly the benzoate displacement of 2,3,5-tri-*O*-benzyl-4-*O*-toluene-*p*-sulfonyl-D-ribose dimethyl acetal resulted in MeO-5 participation with the subsequent migration of one of the acetal methoxy groups (5). Evidence for the MeO-5 participation of a methoxy group not situated at the hemi-acetal position has also been obtained when the solvolysis of methyl 2,3-di-*O*-benzyl-6-*O*-methanesulfonyl-β-D-galactopyranoside yielded 3,6-anhydro-2-*O*-methyl-β-D-galactopyranoside as one of the products (6). One incidence of MeO-3 participation has been reported where the brominolysis of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside in acetic acid yielded as one of the products 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-D-glucopyranose (7).

In all the above reactions, competitive methoxy participation involving the possibility of the simultaneous formation of oxonium ions of differing ring sizes was avoided by the introduction of only one leaving group in each molecule. We would now like to report a series of methoxy group migrations carried out by treating fully chlorosulfated methylglycopyranosides with aluminum chloride. These migrations occurred almost exclusively as a result of MeO-5 participation despite the possibility of MeO-3 and MeO-4 participation. This work was prompted by a previous observation that the treatment of β-D-xylopyranosyl chloride 2,3,4-tri(chlorosulfate) and its α-D-lyxopyranosyl analogue with aluminum chloride resulted in predominant Cl-3 participation (8) and it was hoped to determine some of the factors responsible for this selective migration by varying the nature of the migrating group.

Discussion

Methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) when treated with aluminum chloride yielded a syrupy mixture containing two major components, subsequently identified as methyl α-D-xylopyranoside 2,3,4-tri(chlorosulfate) (anomerization product) and methyl 4-*O*-methyl-α-L-arabinopyranosyl chloride 2,3-di(chlorosulfate) (**4**) (methoxy migration product). The

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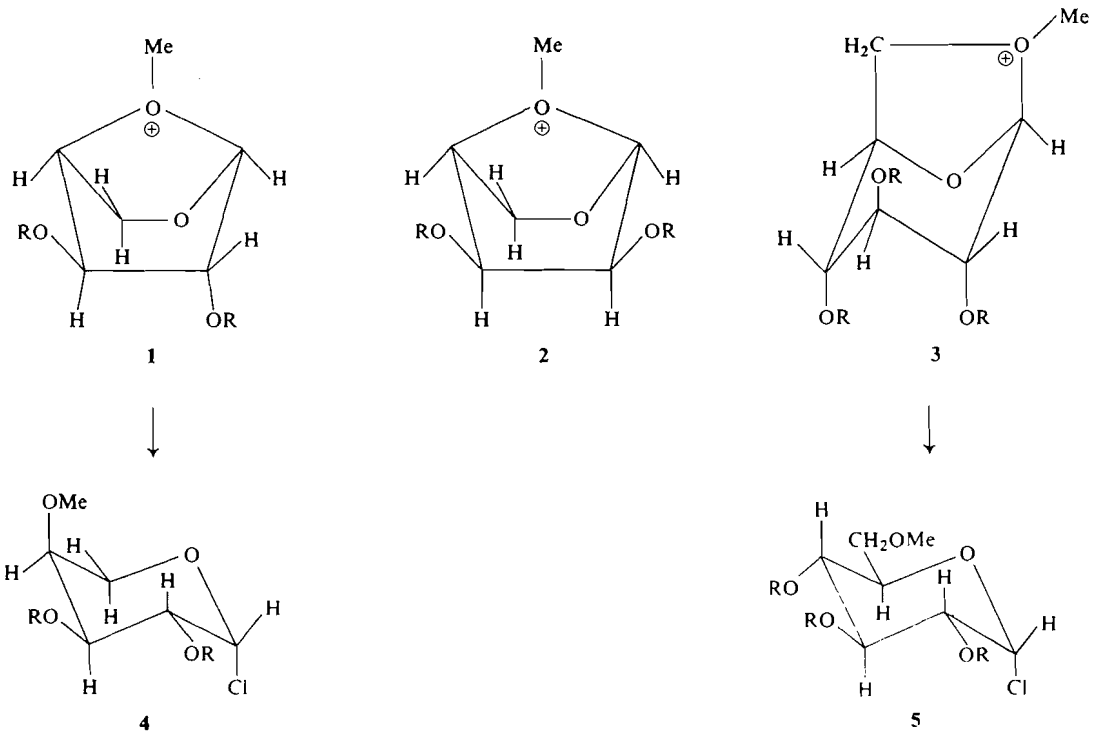

migration was easily followed using proton magnetic resonance (p.m.r.) spectroscopy by the distinguishable methoxy signals of the compounds above in the crude reaction product and also, in the case of **4**, by the appearance of a characteristic low-field anomeric doublet, due to the introduction of the more electronegative chloro-group at the anomeric position. The extent of migration was estimated as 25% by comparison of the integrated areas of the above p.m.r. signals and this was confirmed by the subsequent isolation of the dechlorosulfated products of the reaction. Dechlorosulfation of the syrupy mixture above yielded two major components (paper chromatography) which were separated by cellulose column chromatography. The individual components were identified as syrupy 4-*O*-methyl-L-arabinopyranose and crystalline methyl α-D-xylopyranoside, the former component constituting 28% of the mixture. The isolation of only one major monomethylpentose from the reaction mixture indicates a distinct preference for the anomeric methoxy group of methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) to migrate to C-4 rather than to C-2 or -3 of the pyran ring. This preferential methoxy migration probably involves the formation of the intermediate bicyclic oxonium ion (1), despite the high energy requirement of this ion (1) due to the unfavorable non-bonded steric interactions which would occur in its boat conformation. Related ions in the boat conformation have been encountered in the acetolysis of *trans* 4-methoxycyclohexyl tosylate (9) and more recently in the hydrolysis of methyl 4-*O*-nitrobenzene-*p*-sulfonyl-β-D-xylopyranoside (4).

Methyl α-D-lyxopyranoside 2,3,4-tri(chlorosulfate) when treated with aluminum chloride yielded no detectable quantity of methoxy migration product even after an extended period of reaction. This was determined by the absence of any new methoxy singlet or the appearance of any low-field anomeric signal in the p.m.r. spectrum of the reaction product. The failure of the anomeric methoxy group to migrate to C-4 in the lyxopyranoside derivative can probably be attributed to the higher energy required to form the oxonium ion **2** compared with that necessary to form **1** because of the greater non-bonded interactions. Oxonium ion **2** has an

unfavorable eclipsed (*cis*) orientation of the C-2 and -3 chlorosulfate groups whereas **1** has the more favorable *trans*-orientation of these groups.

Methyl α-D-glucopyranoside 2,3,4,6-tetra-(chlorosulfate) when treated with aluminum chloride gave a good yield of methoxy migration product (**5**). This was determined by the appearance in the p.m.r. spectrum of the syrupy reaction product of an additional methoxy signal (τ 6.58) to the methoxy signal of the original reactant (τ 6.42), plus a low-field anomeric doublet (τ 3.53), characteristic of a methoxy migration product. The amount of **5** present in the mixture was estimated at approximately 66% by the integration of these signals in the p.m.r. spectrum of the syrupy reaction product. The migration product (**5**) was isolated crystalline from the syrupy mixture and the p.m.r. spectrum of crystalline **5** confirmed the assignments made previously on the p.m.r. spectrum of the syrupy reaction product. The elemental analysis of **5** was consistent with the structure assigned to it and this structure was confirmed when the dechlorosulfation of **5** yielded crystalline 6-*O*-methyl-D-glucose. That only one major methoxy migration product was formed in the reaction was determined by dechlorosulfation, and acid hydrolysis of the product of the mother liquors obtained from the recrystallization of **5**. This yielded two reducing components which were identified as D-glucose and a faster running monomethyl-glycopyranose derivative (paper chromatography). The faster running component was isolated by cellulose column chromatography and was characterized as crystalline 6-*O*-methyl-D-glucose. Methoxy migration in this case probably occurs via oxonium ion **3** which requires for its formation that the glycosidic methoxy group have the β-D-configuration. This is obviously readily achieved by the continual equilibration of the methoxy group of the original reactant (α-D-anomer) in the presence of aluminum chloride. Once more the preference for MeO-5 participation is established but this time the anomeric methoxy group migrates to the exocyclic C-6 position, a route not available in the pentopyranoside derivatives. This is readily explained by the lower energy requirement of the chair conformation of **3** in comparison with the ion in the boat conformation that would be required for the alternative MeO-5 participation. The lower energy requirement of the ion in the chair conformation is also reflected in the higher yield of methoxy migration product resulting from **4** in comparison with that resulting from **1**. A related ion in the same chair conformation has been encountered in the solvolysis of methyl 1-thio-6-*O*-toluene-*p*-sulfonyl-β-D-glucopyranoside (10).

Although energy factors do exert an influence on the route of methoxy migration in these pyranoside derivatives (c.f. **1** and **3**) they do not seem to affect the overall preference for MeO-5 participation. This preference is in accord with the results of kinetic studies carried out by Winstein *et al.* on the solvolysis of the acyclic ω-methoxyalkyl *p*-bromobenzenesulfonates, where methoxy participation was the most favorable when it occurred via a monocyclic five-membered oxonium ion (11). Also this preference for MeO-5 participation is in direct contrast to the results obtained using the analogous pentapyranosyl chloride derivatives, as these exhibited a distinct preference for Cl-3 participation using identical conditions (8). Thus the nature of the participating group is a dominant factor in determining the ring-size of the intermediate ion even to the extent of overcoming the substantial energy-requirements involved in the formation of **1**. To our knowledge, no kinetic data is available to establish a preference for Cl-3 participation but the results obtained using the pentapyranosyl chloride derivatives would seem to indicate that this would prove to be the case.

It is interesting to note that in all the reactions carried out no significant MeO-3 participation was observed, whereas MeO-3 participations have been reported by Winstein and Henderson (1) and Lemieux and Fraser–Reid (7). The latter example is particularly relevant to our work as it does involve MeO-3 participation of the anomeric methoxy group in a pyranose ring structure. Although the factors controlling migration are complex, nevertheless, for neighboring group participation the electronic effects (inductive) of the participating group and the leaving group on each other are of some consequence (2). Thus the more electronegative chlorosulfate group might tend to inhibit MeO-3 participation to a greater extent than the less electronegative iodo group used by Lemieux and Fraser–Reid (7) as a leaving group. Certainly, the chlorosulfate group is more electronegative than iodine as it is also more electronegative than chlorine. This can be

ascertained from chemical shift data obtained from the p.m.r. spectra of configurational analogues, where the substitution of a chlorosulfate group by chlorine caused a considerable upfield shift ($\simeq 1.0$ p.p.m.) in the α-proton signal (8). It has been established that a qualitative comparison of the degree of electronegativity of substituent groups can be obtained from the relative positions of the resonance frequencies of their α-protons (12).

Experimental

Melting points were determined on a Kofler hot stage and are uncorrected, and optical rotations were measured at 21 ± 3°. Paper chromatograms were run by the descending method using butan-1-ol – ethanol – water (3:1:1) (v/v) as the solvent. Sugars were located on paper chromatograms by *p*-anisidine hydrochloride (13) or by periodate–permanganate (14) spray reagents. Column chromatography was performed using Whatman cellulose powder (CF11) with butan-1-ol half saturated with water as the eluant. The p.m.r. spectra were obtained from a Varian A60A spectrometer using deuteriochloroform as the solvent and tetramethylsilane ($\tau = 10.0$) as the internal standard.

Methyl α- and β-D-Xylopyranoside 2,3,4-Tri(chlorosulfate)

Crystalline methyl α-D-xylopyranoside 2,3,4-tri(chlorosulfate) was prepared by the methanolysis of β-D-xylopyranosyl chloride 2,3,4-tri(chlorosulfate) as previously described (15) and the p.m.r. spectrum of the crystalline product indicated one methoxy singlet at τ 6.46. Crystalline methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) was also prepared as previously described by treating methyl β-D-xylopyranoside with sulfuryl chloride and the p.m.r. spectrum of the crystalline product indicated one methoxy-singlet at τ 6.38.

Reaction of Aluminum Chloride with Methyl β-D-Xylopyranoside 2,3,4-Tri(chlorosulfate)

Methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) (10 g, 0.022 mole) was dissolved in absolute chloroform (750 ml) and the solution was heated to 60°. The large volume of chloroform was found to be advantageous in reducing decomposition in these reactions. Finely divided aluminum chloride (4.3 g, 0.032 mole) was added to the solution with vigorous stirring and the stirring was maintained for 3 h. The optimum time of reaction which yielded the maximum amount of methoxy migration product was determined by examination of the methoxy signals of the p.m.r. spectra of a number of preliminary reactions carried out using a time variable. The chloroform solution was then washed with water, saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Following clarification with charcoal, the solution was filtered and concentrated to a syrup (7 g). Examination of the p.m.r. spectrum of the syrup indicated two major methoxy signals at τ 5.89 (assigned to compound **4**) and τ 6.46 (assigned to the methyl α-D-anomer of the original reactant) in the ratio of 1:3. A small methoxy signal at τ 6.38 (assigned to the original reactant) was also detected. The spectrum also indicated a low field doublet at τ 3.56 ($J_{1,2}$ 3.1 Hz) which was assigned to the anomeric proton of **4**.

4-O-Methyl-L-arabinose

The syrup above was dechlorosulfated with sodium iodide in aqueous-acetone in the presence of barium carbonate (16). The solution was filtered free of insoluble salts and deionized by passage through Amberlite IR120 and Duolite A4 ion-exchange resins. Concentration of the solution gave a syrup (2.6 g) which was shown by paper chromatography to contain two major components; one reducing component and a faster running non-reducing component. The two components were separated by cellulose column chromatography and the non-reducing component was obtained as a syrup (1.8 g, 50%) which on crystallization from ethyl acetate gave crystals of m.p. 85–87°, undepressed on admixture with an authentic sample of methyl α-D-xylopyranoside. The chromatographically pure reducing component was obtained as a syrup (0.5 g, 14%) which resisted crystallization and had $[\alpha]_D$ + 130° (*c*, 1.0 in water); literature reports $[\alpha]_D$ + 132 ± 2° for 4-*O*-methyl-L-arabinose (17). The syrup gave a crystalline phenylosazone derivative of m.p. 174–176° undepressed on admixture with an authentic sample of the phenylosazone of 4-*O*-methyl-L-arabinose (17) and methanolysis of the syrup with methanolic hydrogen chloride (17) yielded a crystalline methyl glycoside of $[\alpha]_D$ + 240° (*c*, 0.15 in methanol) of m.p. 112–114° undepressed on admixture with authentic methyl 4-*O*-methyl-α-L-arabinopyranoside (17).

Methyl α-D-Lyxopyranoside 2,3,4-Tri(chlorosulfate)

Methyl α-D-lyxopyranoside (5 g) (18) was treated with sulfuryl chloride (13 ml) and pyridine (20 ml) in chloroform solution using identical conditions to those used in the synthesis of methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate) (13). The chloroform soluble product was crystallized from chloroform – light petroleum (b.p. 30–60°) and gave crystals (4.2 g, 30%) of m.p. 135–137° and $[\alpha]_D$ −9° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_6H_9Cl_3S_3O_{11}$: C, 15.68; H, 1.97; Cl, 23.15; S, 20.92. Found: C, 15.90; H, 2.30; Cl, 23.24; S, 20.34.

The p.m.r. spectrum of the above crystals indicated one methoxy singlet at τ 6.47.

Reaction of Aluminum Chloride with Methyl α-D-Lyxopyranoside 2,3,4-Tri(chlorosulfate)

The tri-chlorosulfate derivative above (4 g) was treated with aluminum chloride and the chloroform soluble product was obtained using identical procedures to those described previously for methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate). The chloroform soluble product (2.5 g) gave an almost identical p.m.r. spectrum to that of the starting material. No significant quantity of methoxy migration product could be detected in the p.m.r. spectrum of the product by either the appearance of any other methoxy signal or a low-field anomeric signal. This latter signal has been shown to be a characteristic feature of the migration of an anomeric methoxy group in this type of reaction. Prolongation of the reaction for a further 2 h also produced negligible changes in the p.m.r. spectrum of the product.

6-O-Methyl α-D-Glucopyranosyl Chloride 2,3,4-Tri(chlorosulfate)

Crystalline methyl α-D-glucopyranoside 2,3,4,6-tetra-(chlorosulfate) (6.5 g) (14) was treated with aluminum chloride in absolute chloroform (450 ml) using identical conditions to those previously described for methyl β-D-xylopyranoside 2,3,4-tri(chlorosulfate). The chloroform solution was also washed, dried, and clarified as described previously. Concentration of the chloroform solution yielded a syrup (4.0 g), the p.m.r. spectrum of which indicated two major methoxy singlets at τ 6.42 (identical chemical shift to that of the methoxy signal of the original reactant) and at τ 6.58 (assigned to **5**), in the ratio of 1:2 respectively. The spectrum also gave a low-field doublet at τ 3.53 ($J_{1,2}$ 3.8 Hz) which was assigned to the anomeric proton of **5**. The syrup slowly crystallized and recrystallization from propan-2-ol gave crystals (0.9 g, 16%) of m.p. 143–145° and $[\alpha]_D$ + 130° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_7H_{10}O_{11}S_3Cl_4$: C, 16.54; H, 1.98; Cl, 27.90; S, 18.92. Found: C, 16.63; H, 2.14; Cl, 28.20; S, 18.64. An examination of the p.m.r. spectrum of crystalline **5** confirmed the assignments made previously for **5** in the crude reaction product above.

6-O-Methyl-D-glucose

Crystalline **5** (0.4 g) was dechlorosulfated with sodium iodide in aqueous acetone in the presence of barium carbonate (16). The solution was filtered free of insoluble salts and deionized by passage through Amberlite IR120 (H^+) and Duolite A4 (OH^-) ion exchange resins. Concentration of the solution gave a syrup (0.17 g) which was shown to be homogeneous by paper chromatographic analysis. The syrup slowly crystallized and recrystallization from benzene–ethanol gave crystals (0.032 g, 20%) of m.p. 143–144° and $[\alpha]_D$ + 104° → + 55° (equilibrium) (*c*, 0.8 in water); literature reports m.p. 142–143° and $[\alpha]_D$ + 56° (equilibrium in water) for 6-*O*-methyl-D-glucose (19). The syrupy product obtained by concentrating the mother liquors of the recrystallization above gave a crystalline phenylosazone derivative which when recrystallized from methanol had m.p. 186–188° and $[\alpha]_D$ −72° → −47° (equilibrium) (*c*, 0.4 in ethanol). These physical constants are consistent with those reported in the literature for the phenylosazone of 6-*O*-methyl-D-glucose (20).

The mother liquors obtained from the crystallization of **5** were concentrated to a syrup which was dechlorosulfated and deionized by the same procedure used for the dechlorosulfation of **5**. The syrupy dechlorosulfated product was then hydrolyzed with normal sulfuric acid and the neutralized hydrolyzate was concentrated to a syrup which was shown to contain only two major components (paper chromatography). These components had identical R_F values to those of D-glucose and 6-*O*-methyl-D-glucose and the latter component was isolated by cellulose column chromatography. The crystalline product thus obtained had m.p. 143–144° undepressed on admixture with authentic 6-*O*-methyl-D-glucose isolated previously from **5**.

We wish to thank Mrs. A. Martin for technical assistance and Mr. A. E. Castagne for determination of the microanalyses and the 60 MHz p.m.r. spectra. The authentic crystalline 4-*O*-methyl-L-arabinose derivatives were kindly provided by Dr. C. T. Bishop.

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