COMPLEXES OF CARBOHYDRATES WITH METAL CATIONS

PART II[1]. GLYCOSIDATIONS OF D-ALLOSE IN THE PRESENCE OF STRONTIUM AND CALCIUM IONS

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ABSTRACT

Any of the four methyl glycosides of D-allose can be prepared in good yield by Fischer glycosidation in the presence or absence of calcium chloride or, preferably, strontium chloride. Complexing with the cation shifts the equilibrium in favour of the α-anomers.

INTRODUCTION

The previous paper[1] in this series dealt with complexing between metal ions and hydroxyl groups of carbohydrates. We now report the first of a series of applications of this complexing in influencing the course of synthetic reactions.

Alkaline-earth metal ions complex with three hydroxyl groups in an axial–equatorial–axial arrangement on successive carbon atoms of a cyclohexane or tetrahydropyran ring, or in a *cis–cis* relationship on successive carbon atoms of a tetrahydrofuran (and presumably of a cyclopentane) ring[2]. D-Allose serves as an example: in aqueous solution, it exists mainly as the β-pyranose, due to destabilisation of the α-pyranose by a 1,3-diaxial interaction between HO-1 and HO-3. However, when the solution is made 0.85M in calcium chloride, the proportion of α-pyranose rises from 14% to 37%, due to complexing of calcium ions with HO-1, HO-2, and HO-3 in this isomer. Similar complexing occurs when one of the hydroxyl groups is methylated (*e.g.*, in 3-*O*-methyl-D-gulose[1]). This suggested to us that, with suitable sugars, the course of Fischer glycosidation might be influenced by the presence of alkaline-earth metal ions.

We chose β-D-allose for our investigations as it is readily available[3] and can complex in the α-furanoid and α-pyranoid forms[1].

RESULTS AND DISCUSSION

Addition of calcium or strontium chlorides to Fischer glycosidations slows the reaction rate considerably, and it was found necessary to increase the acid concentra-

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tion to ten times that used in the absence of added salt in order to obtain similar reaction rates. Fig. 1 shows the results of reaction of β-D-allose with 5mM hydrogen chloride in boiling methanol, and Fig. 2 shows the results of a similar experiment using 50mM hydrogen chloride. Figs. 3 and 4 show the results of reaction of β-D-allose with 50mM hydrogen chloride in boiling methanol that was 0.56M in calcium chloride and 0.56M in strontium chloride, respectively. β-D-Allose was allowed to react for 72 h with 0.5M hydrogen chloride and 0.56M calcium chloride in boiling methanol, to determine the position of final equilibrium; a similar experiment was carried out using strontium chloride in place of calcium chloride. These results are shown in Table I.

TABLE I

COMPOSITION OF EQUILIBRIUM MIXTURE OF METHYL D-ALLOSIDES IN METHANOL

Conditions	*Composition* (%)			
	α-Pyranoside	*β-Pyranoside*	*α-Furanoside*	*β-Furanoside*
0.5M HCl, 0.56M $CaCl_2$, 72 h	40.5	17.5	23.0	9.3
0.5M HCl, 0.56M $SrCl_2$, 72 h	47.0	11.8	29.7	5.4

Comparison of Figs. 1a–d shows a dramatic increase in the proportion of methyl α-D-allofuranoside formed when calcium or strontium chloride is included in the reaction mixture. It was found that increasing the concentration of calcium chloride tenfold resulted in only a 3–4% further increase in the maximum concentration of the α-furanoside, and slowed down the reaction greatly. Comparison of Fig. 1b and Table I shows a marked increase in the proportion of methyl α-D-allopyranoside present at long reaction times when calcium or strontium chloride is added to the glycosidation.

In all cases, the complexing is a little stronger with strontium chloride than with calcium chloride; because of this, we used the strontium salt in our preparative experiments. It has the additional advantage of being dried more easily than calcium chloride.

It is interesting to note that calcium chloride had been used once before in a glycosidation. Scattergood and Pacsu[4] were preparing methyl β-D-mannofuranoside which is best isolated as its calcium chloride complex. In one experiment, they added calcium chloride at the beginning of the Fischer glycosidation of D-mannose and obtained a better yield of the β-furanoside than in the absence of the salt. They did not comment on this fact, and apparently did not follow it up.

The amount of methyl α-D-allofuranoside remaining at long reaction times is remarkable, indicating that it forms stronger complexes than does the α-pyranoside. By contrast, in aqueous solutions of D-allose, the α-pyranoside complexes better than the α-furanoside, and calcium forms stronger complexes than strontium[1].

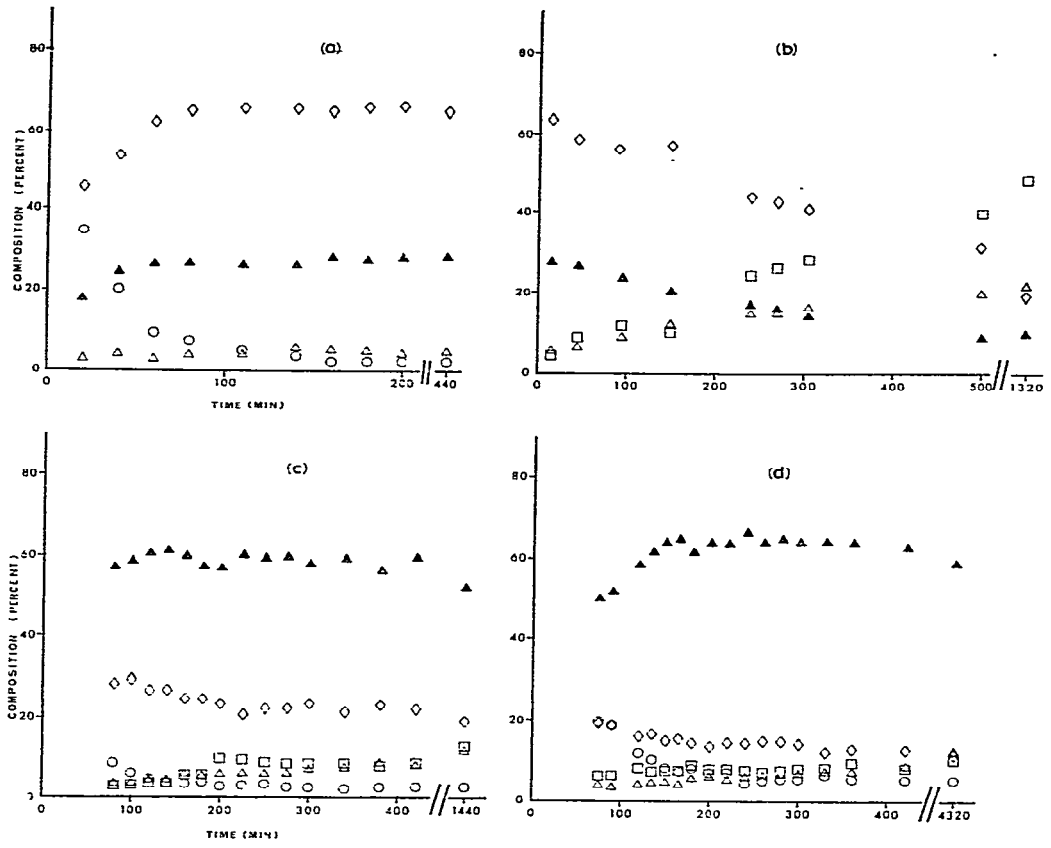

Fig. 1. Reactions of D-allose with methanol in (a), 5mM HCl; (b), 50mM HCl; (c), 50mM HCl+0.56M $CaCl_2$; and (d) 50mM HCl+0.56M $SrCl_2$. ▲, Methyl α-D-allofuranoside; △, methyl α-D-allopyranoside; ◇, methyl β-D-allofuranoside; □, methyl β-D-allopyranoside; and ○, D-allose.

The addition to the reaction of one molecular proportion of methyl orthoformate per mole of allose was investigated; the results were indistiguishable from those obtained without this addition.

From Figs. 1b and 1d, conditions were selected for preparation of methyl β-D-allofuranoside and α-D-allofuranoside, and these compounds were obtained in yields of 61% and 68%, respectively; previously, they have been reported[5] only as minor products of the methanolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. The di-*O*-isopropylidene derivatives of the methyl allofuranosides can also be prepared by the method developed by Randall[6] for the corresponding mannosides. Kuhn methylation of 2,3:5,6-di-*O*-isopropylidene-D-allofuranose gives mainly methyl 2,3:5,6-di-*O*-isopropylidene-α-D-allofuranoside, whereas treatment of its sodio derivative with methyl iodide gives mainly the β-anomer[7].

Use of strontium chloride with Fischer glycosidation offers a practical synthesis of the α-pyranoside in 47% yield; it was obtained crystalline for the first time. It has

also been obtained[5] by methanolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose and by treatment of methyl 2,4,6-tri-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-α-D-glucoside with sodium benzoate in boiling *N*,*N*-dimethylformamide[8]. However, the best route to this compound is probably by modification[9–11] of the procedure[12] of Baker and Buss, involving oxidation and reduction of methyl 4,6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α-D-glucoside, followed by removal of the blocking groups, although none of the published syntheses[13–15] of this compound appears satisfactory.

Methyl β-D-allopyranoside may be prepared by Fischer glycosidation of D-allose[16] or by treatment of methyl 2,4,6-tri-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-β-D-glucoside with sodium benzoate in boiling *N*,*N*-dimethylformamide[8].

The method here described provides a synthesis, by varying the conditions of the reaction, of any of the four methyl D-allosides in one reaction step from D-allose. It appears general for sugars which can form complexes with metal cations, and its applications are being studied.

EXPERIMENTAL

General methods. — β-D-Allose was prepared according to Stevens[3]. Calcium chloride was dried for 16 h at 220°, and strontium chloride for 16 h at 120°. Methanol was dried by the magnesium Grignard complex. Gas–liquid chromatography (g.l.c.) was carried out with a custom-built instrument, using nitrogen carrier-gas, and a hydrogen flame-ionisation detector. A column (1/8 × 48 in.) of 2% LAC-1R-296 on Chromosorb W at 230° resolved the tetra-acetate of methyl α-D-allopyranoside from those of the other three allosides which all emerged as a single peak. A column of 1.5% QF1 silicone gum on Chromosorb W at 200° resolved the α-anomers, which emerged as one peak, from the β-anomers which emerged as two overlapping peaks. Because of this, the percentages calculated for β-allosides are rather less-accurate than those for the α-allosides. Acetylated D-allose was well-separated from the methyl allosides on both columns. Peaks were cut out and weighed to determine the composition of mixtures. It was shown that acetylated, equimolar quantities of β-D-allose and methyl β-D-allopyranoside gave equal peak weights; it was assumed that all of the allosides gave equivalent peak weights. Excellent agreement was obtained between figures from g.l.c. analysis and isolated yields of allosides.

Solutions were concentrated under reduced pressure. Syringes (10, 30, or 100 μl) were used to measure acetyl chloride.

Reaction of β-D-allose with 5mM hydrogen chloride in methanol. — β-D-Allose (0.25 g) was added to methanol (5 ml) in which acetyl chloride (1.8 μl) had been dissolved, and the mixture was boiled under reflux; the joints were greased and the condenser was sealed with a drying tube filled with silica gel. At intervals, samples (0.1 ml) were removed and added to anhydrous sodium acetate (~0.5 g), acetic anhydride (2 ml) was added, and the mixture was boiled for 40 sec. The mixture was cooled, diluted with water (15 ml), and stirred for 15 min, chloroform (1.5 ml) was then added and stirring was continued for 10 min. The chloroform layer was removed, filtered through a small plug of cotton-wool, evaporated, and kept for 1 h at 0.01 torr.

The residue was dissolved in ethyl acetate (0.15 ml) and examined by g.l.c. The results are shown in Fig. 1a.

Reaction of β-D-allose with 50mM hydrogen chloride in methanol. — The above experiment was repeated using ten times the quantity of acetyl chloride. The results are shown in Fig. 1b.

Reaction of β-D-allose with 0.05M hydrogen chloride and 0.56M calcium chloride in methanol. — Calcium chloride (0.308 g) was dissolved in methanol (5 ml) in which acetyl chloride (0.018 ml) had been dissolved. β-D-Allose (0.25 g) was added, and the mixture was boiled, sampled, and analysed as described above. The results are shown in Fig. 1c.

Reaction of β-D-allose with 0.05M hydrogen chloride and 0.56M strontium chloride in methanol. — The previous experiment was repeated using strontium chloride (0.444 g) in place of calcium chloride. The results are shown in Fig. 1d.

Methyl α-D-allopyranoside. — Strontium chloride (1.776 g) and methyl orthoformate (0.605 ml) were dissolved in methanol (20 ml) in which acetyl chloride (0.72 ml) had been dissolved. β-D-Allose (1 g) was added, and the mixture was boiled for 72 h under reflux. Sodium acetate (2 g) was added to the cooled solution, and the methanol was evaporated at 40°/30 torr. Acetic anhydride (15 ml) was added, and the mixture was boiled gently until the lumpy solid became a fine powder. The cooled mixture was diluted with water (30 ml), stirred for 30 min, and extracted with chloroform (10 ml and 2 × 5 ml). The extracts were combined, washed by stirring with water (2 × 30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), dried ($MgSO_4$), and evaporated. A solution of the residue in 20mM methanolic sodium methoxide was left for 16 h at 25° and then evaporated. The product was eluted with water from a column (2.4 × 43 cm) of Bio Rad AG-1-x 2 resin (OH^- form, 200–400 mesh), collecting 25-ml fractions which were monitored polarimetrically.

Fractions 11–15 had positive rotations and were combined and evaporated to give methyl α-D-allopyranoside (0.506 g, 47.0%) which crystallised on standing (it was found subsequently that crystallisation occurs readily on trituration of the syrup with ethyl acetate). A sample was acetylated and examined by g.l.c. and shown to contain ~1% of the β-pyranoside as the only impurity. Recrystallisation from a mixture of methanol (0.45 ml) and ethyl acetate (1 ml) gave pure α-pyranoside (0.451 g, 42%), m.p. 118–119°, $[\alpha]_D$ +152.8° (*c* 0.82, water); lit. +134° (water)[8] and +154° (water)[9] (Found: C, 43.17; H, 7.32. $C_7H_{14}O_6$ calc.: C, 43.30; H, 7.22%).

Fractions 16–18 had negative rotations, and were combined and evaporated to give methyl β-D-allopyranoside (0.127 g, 11.8%). Fractions 19–29 had positive rotations, and were combined and evaporated to give methyl α-D-allofuranoside (0.321 g, 29.7%). Fractions 51–59 had negative rotations, and were combined and evaporated to give methyl β-D-allofuranoside (58 mg, 5.4%). Acetylation and examination by g.l.c. showed that each of these compounds was essentially pure.

Repetition of this experiment, using calcium chloride (1.23 g) in place of strontium chloride, gave the allosides in yields of 40.5% (α-P), 17.5% (β-P), 23% (α-F), and 9.3% (β-F).

Methyl α-D-allofuranoside. — Strontium chloride (1.776 g) was dissolved in methanol (20 ml) in which acetyl chloride (0.072 ml) had been dissolved. β-D-Allose (1.0 g) was added, and the mixture was boiled under reflux for 200 min, and then cooled, neutralised with sodium acetate (2.0 g), and worked up and fractionated as in the previous experiment. Fractions 10–12 gave the α-pyranoside (68 mg, 6.3%), fractions 13–14 gave the β-pyranoside (85 mg, 7.9%); fractions 15–30 gave methyl α-D-allofuranoside (0.730 g, 67.6%), m.p. 103.5–104.5°. Recrystallisation from a mixture of methanol (0.8 ml) and ethyl acetate (6 ml) gave the alloside, m.p. 105–105.5° (unchanged on recrystallisation), $[\alpha]_D$ +127.5° (*c* 0.57, water); lit.[5] m.p. 108–109°, $[\alpha]_D$ +131° (water). Fractions 41–55 gave the β-furanoside (0.148 g, 13.7%).

Methyl β-D-allofuranoside. — β-D-Allose (1.0 g) was added to methanol (20 ml) in which acetyl chloride (7.2 μl) had been dissolved. The mixture was boiled under reflux for 180 min, cooled, neutralised with Amberlite IRA-400 resin (1 ml, OH^- form, methanol-washed), and evaporated. The residue was fractionated as described in the previous two experiments. Fractions 12–15 gave the α-pyranoside (49 mg, 4.5%); fractions 16–18 gave the β-pyranoside (54 mg, 5.0%); fractions 20–30 gave the α-furanoside (0.283 g, 26.2%), m.p. 103–105°; fractions 41–68 gave methyl β-D-allofuranoside (0.656 g, 61%), m.p. 83–85°. Recrystallisation from a mixture of methanol (0.16 ml) and ethyl acetate (1.6 ml), with slow cooling, gave the alloside (0.525 g), m.p. 83.5–85° (unchanged by recrystallisation), $[\alpha]_D$ −55.3° (*c* 0.50, water); lit.[5] m.p. 86–88°, $[\alpha]_D$ −57.5° (water).

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REFERENCES

1 Part I: S. J. ANGYAL, *Aust. J. Chem.*, 25 (1972) in the press.
2 S. J. ANGYAL AND K. P. DAVIES, *Chem. Commun.*, (1971) 500.
3 J. D. STEVENS, *Methods Carbohyd. Chem.*, 6 (1972) 123.
4 A. SCATTERGOOD AND E. PACSU, *J. Amer. Chem. Soc.*, 62 (1940) 903.
5 J. M. WILLIAMS, *Carbohyd. Res.*, 13 (1970) 281.
6 M. H. RANDALL, *Carbohyd. Res.*, 11 (1969) 173.
7 S. J. ANGYAL AND G. M. GILMORE, unpublished results.
8 R. AHLUWAHLIA, S. J. ANGYAL, AND M. H. RANDALL, *Carbohyd. Res.*, 4 (1967) 478.
9 J. S. BRIMACOMBE AND A. HUSAIN, *Carbohyd. Res.*, 6 (1968) 491.
10 K. ONODERA, S. HIRANO, AND N. KASHIMURA, *Carbohyd. Res.*, 6 (1968) 276.
11 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *Carbohyd. Res.*, 10 (1969) 456.
12 B. R. BAKER AND D. H. BUSS, *J. Org. Chem.*, 30 (1965) 2304.
13 G. J. ROBERTSON AND C. F. GRIFFITH, *J. Chem. Soc.*, (1935) 1193.
14 H. R. BOLLIGER AND D. A. PRINS, *Helv. Chim. Acta*, 28 (1945) 465.
15 R. W. JEANLOZ AND D. A. JEANLOZ, *J. Amer. Chem. Soc.*, 79 (1957) 2579.
16 S. J. ANGYAL AND K. JAMES, *Aust. J. Chem.*, 23 (1970) 1209.