

Reactions of Saccharides Catalyzed by Molybdate Ions. II.* Epimerization of D-Glucose and D-Mannose

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In acidified water solutions of molybdate, aldoses epimerize under the formation of equilibrium mixtures in which the epimer having *trans* relationship of the hydroxyl groups at C-2 and C-3 predominates. The epimerization of both D-glucose and D-mannose gives the equilibrium mixture of D-glucose and D-mannose in the ratio 75 : 25. A tentative mechanism for this reaction is suggested and the preparation of D-mannose from D-glucose is described.

The existence of molybdate complexes of saccharides in acidified water media has been recently confirmed by electrophoresis [1–3], polarimetry [4, 5], potentiometry [5], optical rotatory dispersion [6] and circular dichroism [7]. Particularly the electrophoretic data suggested that the complexing with molybdate occurs only with polyols having a *cis-cis* (1 ax, 2 eq, 3 ax) arrangement of the hydroxyl groups in a six-membered ring. It has been shown in more recent papers [5–7] that the *cis-cis*-triol system of hydroxyl groups does not comprehend all possibilities of saccharide complexing with molybdate because all aldoses with free hydroxyl groups at C-1 and C-3 form molybdate complexes. Qualitative differences in the molybdate complexes of saccharides were the basis for a distribution of the basic aldoses into two groups. The first group includes those having *cis-cis* arrangement of the hydroxyl groups. Their molybdate complexes migrate during electrophoresis [1–3]. The second group includes the aldoses having *trans-trans* arrangement of the hydroxyl groups, molybdate complexes of which do not migrate evidently.

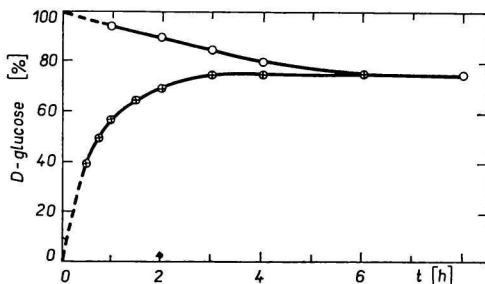


Fig. 1. The epimerization of D-glucose (O) and D-mannose (⊕) as a function of time.

* For Part I. see Ref. [8].

Molybdate complexes of the aldoses of the second group show only two Cotton effects while the complexes of the aldoses belonging to the first group show 3 to 4 Cotton effects [6, 7].

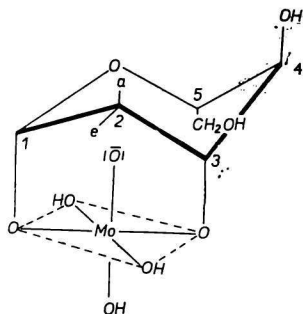
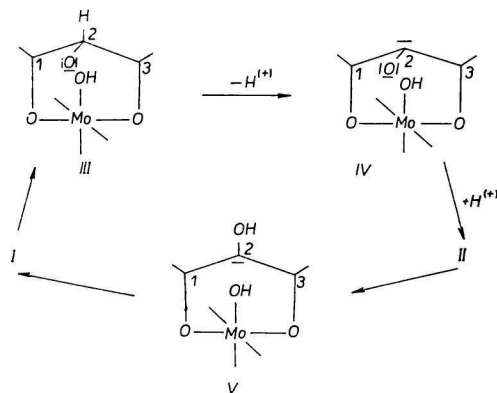


Fig. 2. Molybdate complex of β ,D-mannose (I) ($a = \text{H}$, $e = \text{OH}$, 1C) and β ,D-glucose (II) ($a = \text{OH}$, $e = \text{H}$, 1C).

We found that the C-2 hydroxyl group of aldoses undergoes inversion in acidified solution of molybdate. The reaction leads to the equilibrium of epimeric aldoses in which such epimer predominates which possesses *trans* relationship of the hydroxyl groups at C-2 and C-3. The epimerization of D-glucose or D-mannose catalyzed by molybdate ions gives the equilibrium mixture of D-glucose and D-mannose in the ratio 75 : 25. When the reaction is carried out at 90°C the equilibrium is reached within 3 hours with D-mannose and within 6 hours with D-glucose (Fig. 1). On the basis of the conception of the molybdate complexes of aldoses suggested by Bayer and Voelter [5], the following mechanism of the epimerization of D-mannose (I) and D-glucose (II) (both being in the 1C conformation) may be proposed (Fig. 2 and Scheme 1).



Scheme 1

The C-2 hydroxyl group of D-mannose (I and III) is, for spatial reasons, in a direct interaction with the octahedral molybdate ion bound through the hydroxyl groups at C-1 and C-3. Similarly as with other aldoses of the first group, the molybdate complex of D-mannose is apparently charged more negatively than the complex of D-glucose. From the internal complex of D-mannose (I and III) a proton may be split off (II), which leads consequently to the inversion of the C-2 hydroxyl group under the formation

Table 1

Epimerization of D-mannose in the presence of various catalysts

Catalyst	Ratio of aldoses in solution after the epimerization of D-mannose (90°C, 3 hours)			
	in water		in 0.1 N-HCl	
	D-glucose	D-mannose	D-glucose	D-mannose
H ₂ MoO ₄ · H ₂ O	75	25	75	25
H ₃ PO ₄ · 12MoO ₃ · 12H ₂ O	75	25	75	25
Na ₂ MoO ₄ · 2H ₂ O	—	100	75	25
H ₂ WO ₄	—	100	—	100
Na ₂ WO ₄ · 2H ₂ O	—	100	—	100

of D-glucose (II). The inversion of the hydroxyl group of D-glucose proceeds at slower rate and probably intramolecularly, involving a transitory state V in D-mannose (I).

Contrary to the epimerization of D-mannose by molybdate ions leading to the equilibrium of the epimers (Table 1), no epimerization of D-mannose occurs in the presence of tungstate ions under the same conditions, in spite of the fact that the complexing of D-mannose with tungstate has been demonstrated by electrophoresis [3].

The epimerization of D-glucose into D-mannose has a preparative significance. After D-glucose is partially removed from the epimerization mixture by crystallization, D-mannose can be isolated as its phenylhydrazone and subsequently liberated in 40% yield based on the amount of the unrecovered D-glucose.

Molybdate complexes of saccharides can be practically utilized both in the stereoselective hydroxylation of glycals [8] giving *cis* 2,3-substituted aldoses and in the epimerization of aldoses giving preponderately the epimer having *trans* 2,3-arrangement of the hydroxyl groups.

Experimental

The epimerization of D-glucose and D-mannose was followed by chromatography of the reaction mixtures on Whatman No. 1 paper with butanol—ethanol—water (5 : 1 : 4 v/v). The chromatograms were detected by diphenylamine reagent [9] and scanned with an ERI-10 densitometer (Zeiss, Jena). Water solutions were deionized on a column (50 × 3 cm) of Amberlite 405 (OH⁻).

Time dependence of the epimerization of D-glucose and D-mannose

A mixture of D-glucose or D-mannose (5 g) and molybdenic acid (50 mg) in water (25 ml) was heated at 90°C. At appropriate time intervals aliquots of the reaction mixture were examined by paper chromatography to determine the ratio of epimeric aldoses (Fig. 1).

Effect of different catalysts on the epimerization of D-mannose

A mixture of D-mannose (1 g) and a catalyst (10–15 mg) in water or 0.1 N-HCl (5 ml) was heated at 90°C for 3 hours. The results of the chromatographic estimation of the ratio of epimers are presented in Table 1.

Preparation of D-mannose by epimerization of D-glucose

A solution of D-glucose (200 g) and molybdenic acid (2 g) in water (1000 ml) was kept for 8 hours at 95°C. The reaction mixture was then evaporated *in vacuo*. The syrupy residue was dissolved in methanol (200 ml), ethanol (500 ml) was added under heating and the solution, seeded with D-glucose, was crystallized at room temperature for 48 hours. Crystalline D-glucose (104 g) was filtered off, the filtrate was evaporated to a syrup which was dissolved in water and deionized on a column of the ion exchanger. The effluent was made up to 2000 ml with water followed by addition of phenylhydrazine (53 ml) in acetic acid (220 ml) and the mixture was left to stand for 10–20 hours at room temperature. D-Mannose phenylhydrazone (76 g) was filtered off, washed with water and ethanol and finally dried.

A mixture of D-mannose phenylhydrazone (76 g), water (760 ml), ethanol (75 ml), benzaldehyde (57 ml), and pyridine (25 ml) was heated for 2 1/2 hours at 100°C. After cooling the mixture was filtered and the insoluble portion was washed twice with 50 ml of water. The filtrates were combined, extracted with ethyl acetate (4 × 150 ml) and treated with charcoal. The filtered solution was evaporated *in vacuo* to a syrupy residue which was dissolved in methanol (20 ml). Ethanol (120 ml) was added and the solution was seeded with D-mannose and crystallized for 48 hours at room temperature to give crystalline D-mannose (39–40 g) which represented 80% yield based on D-mannose phenylhydrazone and 40% yield based on the unrecovered D-glucose.

Recrystallization from ethanol gave D-mannose; $[\alpha]_D^{24} + 25.9^\circ$ (3 min) $\rightarrow +14.3 \pm 0.5$ (24 hours, *c* 4, water). Ref. [10] gives $[\alpha]_D^{20} + 14.8^\circ$ (water).

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