

Reactions of saccharides catalyzed by molybdate ions

XL.* Inhibition of the epimerization of aldoses

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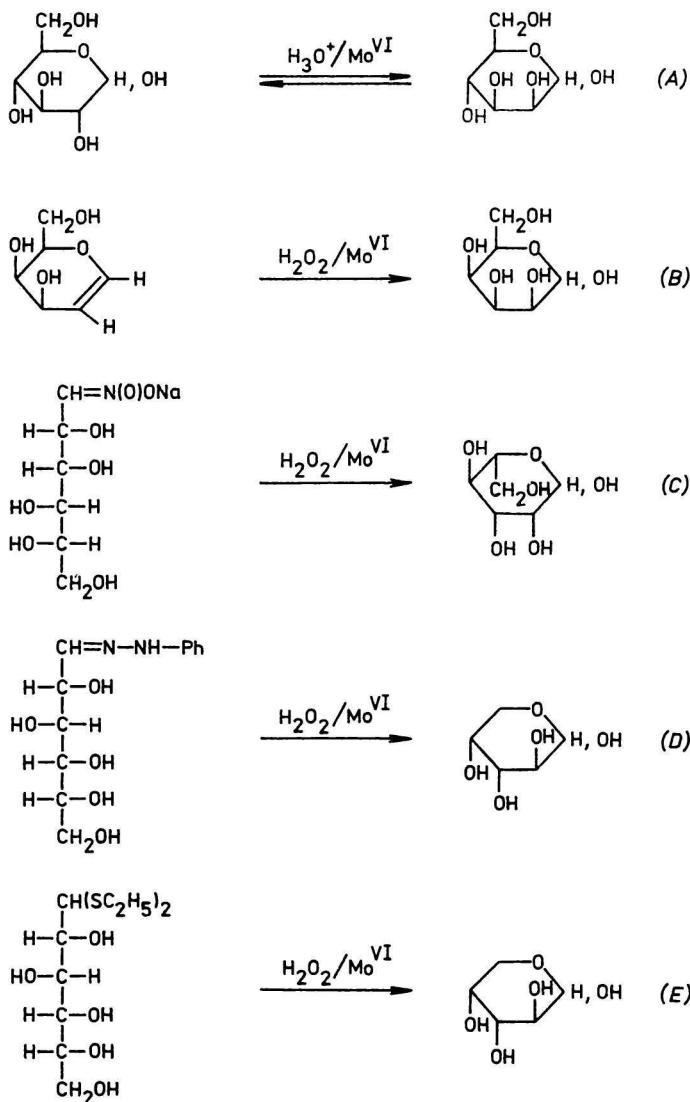
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The molybdate-catalyzed epimerization of aldoses is completely inhibited by oxalic acid at the mole ratio $\text{Mo}^{\text{VI}} : (\text{COOH})_2 = 1 : 2$ in the reaction medium. The inhibitory effect is not so strong with citric acid, α -hydroxydicarboxylic acids, alditols, and aldonic acids. The epimerization of aldoses does not proceed at $\text{pH} < 0.1$ and $\text{pH} > 7$. Optimum pH for the reaction lies between pH 1.5 and 3.

Щавелевая кислота полностью ингибирует эпимеризацию альдоз, катализируемую молибденат-ионами, если в реакционной среде молярное соотношение $\text{Mo}^{\text{VI}} : (\text{COOH})_2$ составляет 1 : 2. Более слабое ингибирующее действие проявляет лимонная кислота, α -гидроксидикарбоновые кислоты, альдитолы и альдоновые кислоты. Эпимеризация альдоз не протекает при $\text{pH} < 0,1$ и $\text{pH} > 7$. Оптимальное pH для реакции находится между pH 1,5 и 3.

In a series of papers devoted to reactions of saccharides catalyzed by molybdate ions we have reported on three types of reactions. A wide application has found the epimerization of aldoses leading to an equilibrium mixture of C-2 epimeric aldoses (reaction *A*, Scheme 1). The hydroxylation of glycals by hydrogen peroxide gives stereospecifically aldoses having the *cis* arrangement of the hydroxyl groups on carbon atoms C-2 and C-3 (reaction *B*). On numerous examples we have also demonstrated that sodium salts of 1-deoxy-1-nitroal-ditols can be decomposed with hydrogen peroxide to the corresponding aldoses (reaction *C*). We have modified the oxidative degradation of phenylhydrazones of aldoses to aldoses by one carbon atom shorter by using hydrogen peroxide (reaction *D*) [1] instead of oxygen as described by *Schulz* and *Somogyi* [2]. Molybdate ions were used as a catalytic agent also in the oxidation of dithioacetals of aldoses to the corresponding sulfones which are decomposed in ammoniacal medium to give aldoses by one carbon atom shorter (reaction *E*)

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Scheme 1

[3]. Application of the reactions *A* through *E* to easily available aldoses may afford rare aldoses, going from tetroses to octoses. In spite of the fact that reactions *B*—*E* are irreversible, the reversible epimerization of the newly formed aldoses must be prevented before their isolation by removing the molybdate ions from the reaction mixtures.

In the present paper the epimerization reaction was studied in the pre-

sence of several compounds which form complexes with molybdate ions. X-Ray analysis of complexes of molybdate ions with oxalic acid ($\text{NH}_4\text{NaMoO}_3(\text{C}_2\text{O}_4) \cdot 2\text{H}_2\text{O}$, $\text{K}_2\{[\text{MoO}_2(\text{C}_2\text{O}_4)\text{H}_2\text{O}]_2\text{O}\}$ and $\{[\text{MoO}_3(\text{C}_2\text{O}_4)]^{2-}\}_\infty$) showed that each central molybdenum binds one molecule of oxalic acid [4]. It was proved by NMR spectroscopy that alditols having four vicinal hydroxyl groups form complexes with molybdate [5]. Complexing of Mo^{VI} [6] and Mo^{V} [7] with α -hydroxycarboxylic acids was demonstrated by methods of circular dichroism. The values of the Cotton effects of the complexes were found to be pH-dependent [6, 7].

The molybdate-catalyzed epimerization of aldoses does not proceed in strongly acidic medium ($\text{pH} < 0.1$) and in alkaline medium. The epimerization of D-glucose carried out at 90°C for 3 h and in pH range 0.5—4 led to an equilibrium mixture of D-glucose and D-mannose in the ratio 3 : 1 (Fig. 1). Regarding the rate of the reaction the most convenient pH of the medium lies between pH 1.5 and 3 (Fig. 1). The rate of D-glucose epimerization was eight times more rapid at pH 2.1 than at pH 4.5 (Fig. 2).

The epimerization of D-glucose to D-mannose catalyzed by molybdate ions was examined in the presence of oxalic acid, citric acid, α -hydroxycarboxylic acids, and alditols (Tables 1 and 2). Medium pH was in some cases adjusted to

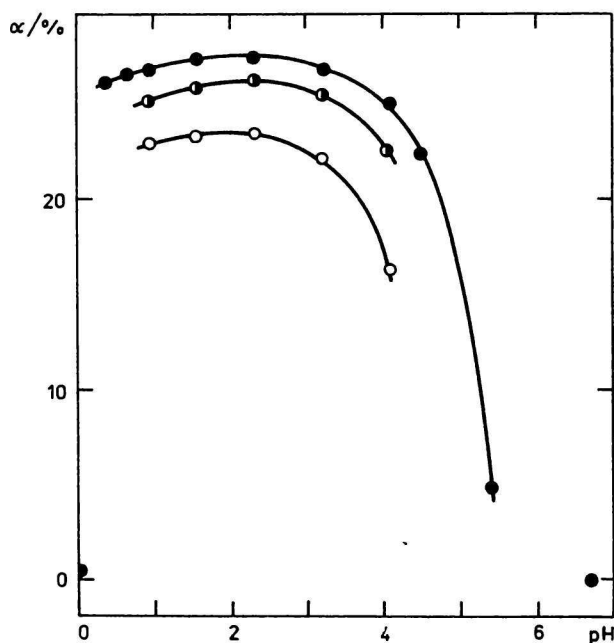


Fig. 1. Degree of D-glucose conversion to D-mannose during molybdate-catalyzed epimerization of D-glucose as a function of pH and time (○ 0.5 h, ◐ 1 h, ● 3 h).

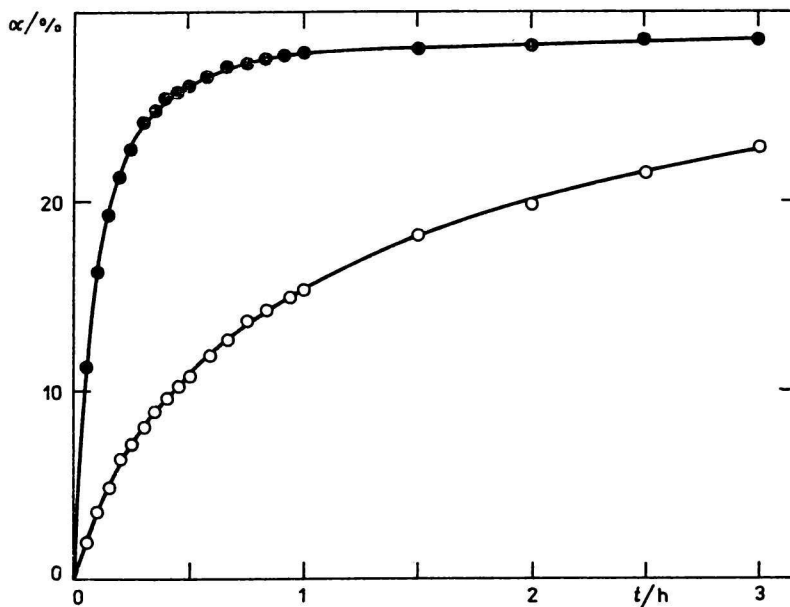


Fig. 2. Degree of D-glucose conversion to D-mannose during molybdate-catalyzed epimerization of D-glucose at pH 2.1 (●) and pH 4.5 (○) as a function of time.

a suitable value by acetic acid. Oxalic acid blocked the epimerization completely at the mole ratio $\text{Mo}^{\text{VI}} : (\text{COOH})_2 = 1 : 2$ (Table 1). A similar inhibitory effect was exhibited by citric acid, however, at the mole ratio $\text{Mo}^{\text{VI}} : \text{citric acid} = 1 : 8$ (Table 2). The epimerization was significantly inhibited also by alditols. The

Table 1

Effect of oxalic acid on molybdate-catalyzed epimerization of D-glucose (3 h, 90 °C)

Mole ratio			pH ^a	Yield of D-mannose/% ^b
Mo ^{VI} : oxalic acid : acetic acid				
1	0.5	2.5	2.8	25.4
1	1	2	2.4	22.0
1	1.3	1.7	2.2	9.5
1	1.6	1.4	2.0	1.3
1	2	1	1.8	0
1	0	3	3.8	28.6
1	0	0.1 M-HCl	1.0	27.0

a) Solution after epimerization; b) isolated as its phenylhydrazone.

Table 2

Effect of alditols and acids on molybdate-catalyzed epimerization of D-glucose (3 h, 90 °C)

Compound	Mole ratio Mo ^{VI} : alditol and Mo ^{VI} : acid							
	1 : 2		1 : 4		1 : 6		1 : 8	
	Yield of D-mannose/% ^a	pH	Yield of D-mannose/% ^a	pH	Yield of D-mannose/% ^a	pH	Yield of D-mannose/% ^a	pH
Glycerol			27.9	3.5 ^b			27.9	3.5 ^b
Adonitol			27.5	3.6 ^b			25.6	3.6 ^b
D-Arabinitol	26.8	3.6 ^b	18.1	3.7 ^b				
D-Mannitol	15.5	3.5 ^b	7.5	3.5 ^b				
Dulcitol	13.6	3.3 ^b	7.7	3.2 ^b				
Perseitol	9.1	3.5 ^b	4.5	3.5 ^b				
Acid								
glycolic			28.1	2.0			27.0	1.7
lactic			27.6	1.8			26.0	1.6
D-gluconic	26.5	2.1 ^c	17.6	1.8	10.1	1.5		
D-gulonic	24.6	2.5 ^c	18.5	2.3	13.6	2.0		
D-glycero-D-guloheptonic	24.1	2.6 ^c	16.9	2.3	11.3	2.0		
mucic	22.8	1.8 ^c	11.3	1.6				
tartaric	24.6	1.5 ^c	10.5	1.3	4.2	1.1		
malic	27.2	2.0 ^c	24.1	1.8	17.6	1.5		
succinic							28.6	2.7
malonic							27.5	1.6
oxalic	0	1.8 ^c						
citric	14.8	2.3 ^c	2.9	2.0			0	1.7

a) D-Mannose as its phenylhydrazone.

pH adjusted by addition of 6.3 mmol (b) and 2.1 mmol (c) of acetic acid.

inhibitory effect was proportional to the number of hydroxyl groups in an alditol. Glycerol was without any effect since it does not complex with molybdate [5].

Aliphatic dicarboxylic acids, except of oxalic acid, do not form complexes with molybdate ions and, consequently, they do not inhibit the epimerization. On the contrary, dicarboxylic acids with an α -hydroxyl group(s) inhibited strongly the reaction. Aldonic acids were found less inhibitory than alditols or α -hydroxydicarboxylic acids (Table 2).

The inhibitory effect of oxalic or citric acid on molybdate-catalyzed epimerization of aldoses can be used in preparative and analytical chemistry of saccharides. During isolation of aldoses in the course of reactions *A*—*E*, subsequent epimerization decreasing the product yields can be prevented by addition of oxalic or citric acid. The epimerization of D-glucose affords an equilibrium mixture of D-glucose and D-mannose from which a portion of the starting D-glucose is isolated by crystallization ($\approx 40\%$). The regenerated D-glucose contains 0.8—3.6 % of the original amount of the molybdate catalyst. D-Mannose is separated from the mother liquor in the form of *N*-phenyl-D-mannosylamine which also contains some of the molybdate catalyst (0.2—0.3 %). Analogous situation occurs during preparation of C-2 epimeric aldoses of the homomorphous series of D- or L-xylose and during preparation of D- or L-ribose from D- or L-arabinose. Aldoses can be released from *N*-phenylglycosylamines by formaldehyde [8], benzaldehyde [9], by hydrolysis during water vapour distillation [10] or by hydrolysis with a strongly acidic ion exchanger [11]. These methods can be used also in the presence of large amounts of the molybdate catalyst if appropriate amount of oxalic or citric acid is added to reaction mixtures [12, 13].

The examples presented in the paper demonstrate only partially the effect and application of the compounds that are inhibitory to the epimerization reaction. Thus the reaction rate is dependent on the amount of the molybdate catalyst, pH of the reaction mixture, temperature and on the presence of compounds that form stable complexes with molybdate.

Experimental

Specific rotations of saccharides were measured with an automatic Perkin—Elmer polarimeter, type 241. pH was measured with a Standard pH-Meter, type PHM-82 (Radiometer, Copenhagen). Molybdenum was determined by atomic absorption spectroscopy using an AAS Perkin—Elmer spectrometer, model 403.

Monitoring of D-glucose epimerization at various pH

D-Glucose monohydrate (19.8 g; 0.1 mol) was dissolved in 100 cm³ of solutions of various pH: diluted hydrochloric acid, diluted acetic acid, acetate or phosphate buffers.

The solutions heated to 90 °C (± 0.5 °C) were mixed with 4.1 cm³ of 6 % solution of ammonium molybdate ((NH₄)₆Mo₇O₂₄ · 4H₂O, 2×10^{-4} mol) and at time intervals 1 cm³ samples were taken and diluted to adjust molybdate concentration to 4 g dm⁻³ and aldose concentration to 1.5 g dm⁻³. In such a solution D-glucose shows $[\alpha](D, 23^\circ C) = +56^\circ$ and D-mannose $[\alpha](D, 23^\circ C) = -35^\circ$. After 20–24 h standing at room temperature specific rotation of samples was measured. The values give the proportion of D-glucose and D-mannose in the reaction mixtures (Figs. 1 and 2).

Inhibition of D-glucose epimerization by selected alditols and acids

D-Glucose monohydrate (29.7 g; 0.15 mol), ammonium molybdate (0.37 g; 3×10^{-4} mol corresponding to 2.1×10^{-3} mol of Mo^{VI}) and a tested alditol or acid (Tables 1 and 2) were dissolved in 150 cm³ of water and heated at 90 °C for 3 h. After cooling the solution was mixed with 50 cm³ of ethanol and 16.3 cm³ of phenylhydrazine (0.165 mol). After standing at 23 °C for 20 h separated D-mannose phenylhydrazone was filtered off and washed with methanol (Tables 1 and 2).

Preparation of D-mannose from D-glucose

D-Glucose monohydrate (250 g) was dissolved in a solution of ammonium molybdate (3 g) and acetic acid (2 cm³) in water (25 cm³). The solution was heated at 90 °C for 50 min, then mixed with methanol (120 cm³) and ethanol (120 cm³) and left to crystallize (2–3 days). Crystalline D-glucose was filtered off (98–105 g, *i.e.* 39–42 % of the starting D-glucose). The filtrate was diluted to 500 cm³ with a mixture methanol–ethanol ($\phi_r = 1 : 1$), mixed with aniline (100 cm³) and left to stand for 20 h. Crystalline *N*-phenyl-D-mannosylamine was separated by filtration (77–80 g, *i.e.* 24–25 % yield of D-mannose, or 39–45 % yield when referred to regenerated D-glucose).

Of the total amount of ammonium molybdate used in the reaction (3 g, *i.e.* 1.63 g of Mo^{VI}), the regenerated D-glucose contained 12.5–58.3 mg of Mo^{VI} and *N*-phenyl-D-mannosylamine 3.7–4.2 mg of Mo^{VI}.

A solution of *N*-phenyl-D-mannosylamine (80 g), oxalic acid dihydrate (0.5 g), 35 % aqueous solution of formaldehyde (50 cm³), water (600 cm³), and ethanol (100 cm³) was heated at 90 °C for 3 h. The solution was then filtered and evaporated to a sirupy residue which was dissolved in 150 cm³ of methanol and left to crystallize for 20–24 h. Crystalline D-mannose was separated by filtration (47.5 g, *i.e.* 84 %), the mother liquor evaporated and the residue crystallized from 30 cm³ of methanol to give the second crop of D-mannose (7.5 g, 13 %). Recrystallization from methanol gave D-mannose, m.p. = 124–126 °C and $[\alpha](D, 20^\circ C, \rho = 20 \text{ g dm}^{-3}, \text{water}) = +13.5^\circ$.

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