

Reactions of saccharides catalyzed by molybdate ions. XIII.* Preparation of D-allose and D-altrose and their epimerization

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Epimeric aldoses were prepared by oxidative decomposition of a mixture of sodium salts of nitrohexitols obtained from D-ribose. Allose or altrose epimerize in acidic water solution under catalytic action of molybdate ions giving an equilibrium mixture of allose and altrose in the ratio 3 : 2. From the equilibrium mixture of epimeric aldoses, allose can simply be isolated by crystallization.

Cyanohydrine synthesis is one of the oldest methods for preparation of D-allose and D-altrose [1, 2]. There are some other routes to synthesis of D-altrose starting from D-glucose or its suitable derivatives. Alkaline hydrolysis of methyl 2,3-anhydro-4,6-O-benzylidene- α -D-allopyranoside preferentially affords the corresponding derivative of D-altrose [2, 3]; penta-O-acetyl- β -D-glucopyranose is transformed into D-mannose and D-altrose in liquid hydrogen fluoride [4] and hydrolysis of neolactose (obtained from octaacetyllactose by inversion with aluminium chloride and phosphorus pentachloride) gives D-altrose and D-galactose [5]. Reduction of methyl β -D-ribohexopyranosid-3-ulose with Raney nickel or borohydride leads to formation of the corresponding derivative of D-altrose [6]. Analogous reaction was reported with 1,2:5,6-di-O-isopropylidene- α -D-ribohexulofuranose reduced with lithium aluminium hydride [7]. Acetolysis of 1,2:5,6-di-O-isopropylidene- α -D-allofuranose (treatment with acetic acid, acetic anhydride, and sulfuric acid) gives D-altrose in 45% yield; unsubstituted D-allose does not epimerize under these conditions [8]. There are only few routes to the synthesis of D-allose. In addition to the cyanohydrine synthesis, it can be obtained from 1,2,4,6-tetra-O-benzoyl-3-O-toluene-*p*-sulfonyl- β -D-glucopyranose by nucleophilic substitution of the tosyl group by sodium benzoate *via* penta-O-benzoyl- β -D-allopyranose [9]. We have concentrated on the preparation of the above rare aldoses either by nitromethane synthesis with D-ribose followed by oxidative decomposition of the nitrohexitols formed into aldoses, or by interconversion of D-allose and D-altrose in the molybdate catalyzed epimerization.

Nitromethane synthesis with D-ribose was used for preparation of 2-deoxy-D-ribohexose by Zorbach and Ollapally [10]. The reaction mixture of nitrohexitols was acetylated and crystallization afforded penta-O-acetyl-1-deoxy-1-nitro-D-altritol. Applying the Nef reaction they obtained D-allose and D-altrose as syrupy compounds. In this paper, the mixture of sodium salts of nitrohexitols prepared from D-ribose was converted by oxidative decomposition [11] to D-allose and D-altrose (in the ratio 45 : 55) in 42% yield. This reaction also obeyed the Maltby rule, since the allose

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possessing the *trans* arrangement of hydroxyl groups at C-2 and C-4 predominates. In the course of the oxidative decomposition of nitrohexitols the pH of the reaction medium decreases from 11 (starting pH) to 6. No evidence has been obtained that this change in the pH values causes transformation of altrose or allose into psicose but it significantly accelerates the parallel elimination reaction to D-ribose (16% based on the starting amount of D-ribose). Similar elimination reaction was observed during oxidative decomposition of nitroheptitols prepared from L-mannose [12], but not with nitrohexitols derived from L-arabinose and L-lyxose [11].

In acidic water solutions under catalytic action of molybdate ions, allose or altrose epimerizes to form an equilibrium mixture of epimeric aldoses, allose and altrose, in the ratio 3 : 2. The equilibrium established is on the side of the aldose having *cis* substituents at positions C-2 and C-3. A comparison of the epimerization equilibria of different aldopentoses and aldohexoses shows that in all previous cases the aldose having *trans* arrangement of the hydroxyl groups at C-2 and C-3 was formed predominantly. This is shown in the following homotropic order demonstrating also the effect of the substituent at C-5:

glucose	:	mannose	3	1	[13],
chinovose	:	rhamnose	3	2	[14],
xylose		lyxose	10	9	[15],
galactose	:	talose	4	1	[16],
arabinose	:	ribose	2	1	[15].

The flexibility of the pyranoid ring and the preferred conformation depend on the magnitude of the C-5 substituent. However, the thermodynamic equilibria of epimeric aldoses are also influenced by other factors of conformational instability as

Table 1

Characterization of the instability of D-allose and D-altrose

Aldose	*Instability factors of conformers		*Preferred conformation	**Amount present in the equilibrium mixture at 40°C [%]	**Free energy [kcal mol ⁻¹]		
	C1	1C			C1	1C	
D-Allose	α -pyr.	2	6.5 ⁺	C1	18	3.9	5.35
	β -pyr.	1	5.5 ^H	C1	70	2.95	6.05
	α -fur.				5		
	β -fur.				7		
D-Altrose	α -pyr.	3	3	C1 \rightleftharpoons 1C	27	3.65	3.85
	β -pyr.	4.5 ⁺	4.5 ^H	C1 \rightleftharpoons 1C	40	3.35	5.35
	α -fur.				20		
	β -fur.				13		

*Ref. [17]; **Ref. [18].

+ = Δ 2 effect.

H = Hassel—Ottar effect.

well as by the effect of the reaction medium on the ratio of tautomeric and anomeric forms. D-Allose, contrary to D-altrose, possesses less factors of conformational instability; β -D-allopyranose is its preferred form in water solution and this form comprises the lowest free energy of all pyranoid forms of allose and altrose (Table 1). Unfavourable energy state of altrose in comparison with allose is also reflected in a considerable number of furanoid forms of this sugar in water solutions. The above-quoted factors are apparently the main reasons why allose predominates in the epimerization mixture at the equilibrium.

The results of the epimerization of aldopentoses and aldohexoses catalyzed by molybdate ions can be summarized in the following rule: "In acidic water solutions under catalytic action of molybdate ions individual aldopentoses and aldohexoses epimerize to an equilibrium of epimeric aldoses with that aldose predominating which, in the preferred conformation, possesses a lower value of conformational instability." In contrast to transformation of aldoses in alkaline medium (reaction of Lobry de Bruyn—Alberda van Ekenstein), molybdate catalyzed epimerization is not accompanied by transformation to ketoses.

Kinetics of the epimerization of D-allose and D-altrose was followed as a system of two reversible equations of the first order. Such a calculation gave the following average values of the rate constants: for D-allose 0.70 hr^{-1} , for D-altrose 0.37 hr^{-1} ; graphical method gave 0.61 hr^{-1} and 0.39 hr^{-1} respectively (Table 2). The reaction is particularly suitable for preparation of D-allose from D-altrose. D-Allose (36%) is directly crystallized from the deionized epimerization mixture of aldoses and the repeated epimerization with the filtrate yields further (22%) of D-allose. The residue of the second epimerization does not contain other saccharides or destruction products and is therefore suitable for succeeding epimerizations.

Table 2

Epimerization rate constants of 4% water solutions of D-allose and D-altrose in 0.2% molybdenic acid at 90°C and pH 3.6

Time [hrs]	D-Allose [%]	D-Altrose [%]	$\ln \frac{x_e}{x_e - x}$	k [hr^{-1}]
Epimerization of D-allose				
0.5	86	14	0.460	0.35
1.0	78	22	0.865	0.33
1.5	72	28	1.335	0.34
2.0	67	33	2.028	0.38
2.5	64	36	2.944	0.45
Epimerization of D-altrose				
1.0	47	53	1.419	0.87
1.5	52	48	1.826	0.76
2.0	54	46	2.048	0.63
2.5	57	43	2.518	0.63
3.0	59	41	3.029	0.63

To the equilibrium (x_e) 38% of D-allose and 62% of D-altrose had reacted of the starting amount of D-allose (100%, α).

Experimental

Specific rotation of saccharides was measured with a Perkin-Elmer polarimeter, type 141, melting points were determined on a Kofler stage and pH of solutions with a Titrator, type TTT2 (Radiometer, Copenhagen) equipment. Saccharide mixtures obtained after oxidative decomposition of nitrohexitols were fractionated on a column (3.5×120 cm) of Dowex 50 W (X-8, 100–200 mesh in Ba^{2+} cycle) using elution with water at a rate of 45 ml/hr. Epimerization and purity of saccharides were followed by chromatography on Whatman No. 1 paper in *n*-butanol-ethanol-water (5 : 1 : 4, v/v) and sugars were visualized with the aniline-hydrogen phthalate reagent (mobilities relative to ribose R_R 1.00; allose 0.63, altrose 0.76, psicose 0.90). For kinetic purposes, detected chromatograms were scanned with a densitometer ERI-10 (Zeiss, Jena).

Nitromethane synthesis of D-allose and D-altrose

D-Ribose (25 g) dissolved in methanol (100 ml) was mixed with nitromethane (50 ml) and a solution of sodium methoxide (6.5 g of sodium in 200 ml of methanol) was added under stirring during 1 hr. The reaction mixture was left to stand at room temperature for 6 hrs, then *n*-propanol (100 ml) was added followed by additional 1-hr standing. Sodium salts of nitrohexitols were filtered off, washed with cold methanol (2×25 ml) and dissolved in 0.05 N-NaOH (250 ml). To this solution, sodium molybdate (1 g) and 15% hydrogen peroxide (40 ml) were added at a rate to keep the temperature of the reaction mixture below 30°C. The pH of solution equal to 11 decreased to pH 6 on addition of hydrogen peroxide. After 20-hr standing at room temperature, the solution was treated with 5% Pd/C (0.1 g) for 24 hrs and finally filtered. The filtrate was mixed with acetic acid (10 ml), concentrated under reduced pressure to a half volume and deionized on ion-exchange columns in the order: anion exchanger SBW in acetate form (3.5×50 cm), cation-exchanger KPS in H^+ cycle (4×65 cm) and again SBW in acetate form (3×80 cm). Deionized solution (4.5 l) was evaporated to syrup which was fractionated on a Dowex 50 W column (Ba^{2+} cycle). Fraction 1 (11.9 g collected in the volume 780–1040 ml) contained a mixture of D-allose and D-altrose, fraction 2 (collected in the volume 1040–1370 ml) represented D-allose (3.2 g), and fraction 3 (1370–1980 ml) contained D-ribose (4.1 g). Refractionation of the fraction 1 gave D-altrose (6.7 g) and further (2.9 g) of D-allose. D-Altrose was crystallized from anhydrous ethanol, m.p. 104–107°C, $[\alpha]_D^{23} + 31.5^\circ$ (c 2, water) without mutarotation. D-Allose crystallized from methanol, m.p. 129–131°C, $[\alpha]_D^{23} + 1.8^\circ$ (2 min) $\rightarrow +14.1^\circ$ (equil.) (c 2, water).

Ref. [19] gives for β -D-allose m.p. 128–128.5°C, $[\alpha]_D^{20} + 0.6^\circ$ (2 min) $\rightarrow +14.4^\circ$ (equil.) (c 1.3, water). Ref. [20] gives for D-altrose m.p. 103–105°C, $[\alpha]_D + 32.6^\circ$ (c 7.6, water) no mutarotation.

Kinetic study of D-allose and D-altrose epimerization

Water solution of D-allose or D-altrose (100 mg in 2.5 ml) containing 2% molybdenic acid was kept at 90°C. In time intervals up to the epimerization equilibrium, samples of the reaction mixture were taken and chromatographed to determine the ratio D-allose : D-altrose.

The rate constants of the epimerization were calculated as a system of two reversible reactions of the first order approaching equilibrium [21]. This was always done only for one aldose present at a starting concentration a . In case the symbol x designates the amount of aldose transformed in time t and x_e its amount at equilibrium, the following equation is valid for the epimerization rate constant k

$$k = \frac{x_e}{a t} \ln \frac{x_e}{x_e - x}$$

The rate constants were determined also graphically using the angular coefficient of the function of $\ln \frac{x_e}{x_e - x}$ on time and concentration ratios $\frac{x_e}{a}$.

Preparation of D-allose by D-altrose epimerization

A solution of D-altrose (10 g) and molybdenic acid (0.5 g) in water (250 ml) was heated to 90°C for 4 hrs. The reaction mixture was deionized on an anion-exchange column (SBW in acetate form, 2.5 × 50 cm). The water eluate (3.5 l) was concentrated in a vacuum to syrup which was dissolved in methanol (50 ml) and let crystallize at room temperature for 20 hrs. Crystalline D-allose (3.6 g) was filtered off and the filtrate evaporated to syrup which was dissolved in water (60 ml) and, after addition of molybdenic acid (0.3 g), treated as described above to give further crop of crystalline D-allose (2.2 g).

Recrystallization from methanol gave chromatographically homogeneous β-D-allose, m.p. 130–132°C, $[\alpha]_D^{25} +1.3^\circ$ (1 min) → +2.3° (3 min) → +3.3° (5 min) → +5.6° (10 min) → +10.4° (20 min) → +13.1° (30 min) → +14.1° (45 min) → +14.1° (24 hrs) (c 2, water).

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