Reactions of saccharides catalyzed by molybdate ions XLII.* Epimerization and the molybdate complexes of the aldoses

V. BÍLIK and M. MATULOVÁ

Institute of Chemistry, Centre for Chemical Research, Slovak Academy of Sciences, CS-842 38 Bratislava

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Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday

Epimerization of D-[2,3,4,5,6-^{13}C]mannose catalyzed by the molybdate ions results in formation of D-[1,3,4,5,6-^{13}C]glucose. In aqueous solutions of ammonium molybdate D-mannose, D-lyxose, D-glucose, and D-xylose in acyclic forms produce binuclear tetradentate molybdate complexes involving the hydrated carbonyl group as well as hydroxyl groups attached to carbon atoms C-2, C-3, and C-4. In the molybdate complexes D-glucose and D-xylose have an arrangement of the carbon chain close to the zig-zag one, while D-mannose and D-lyxose have sickle arrangement. At the same time D-mannose and D-lyxose produce in greater extent tridentate molybdate complex involving β-anomeric hydroxyl group and the hydroxyl groups bound to carbon atoms C-2 and C-3 of the pyranoid structure of the aldose.

В результате катализированной молибдатными ионами эпимеризации из D-[2,3,4,5,6-^{13}C]маннозы образуется D-[1,3,4,5,6-^{13}C]глюкоза. В водных растворах молибдата аммония D-манноза, D-ликсоза, D--глюкоза и D-ксилоза в ациклических формах образуют двухъядерные тетрадентатные молибдатные комплексы с участием гидратированной карбонильной группы и гидроксильных групп на атомах углерода C-2, C-3 и C-4. В молибдатном комплексе углеродная цепь D-глюкозы и D--ксилозы имеет конформацию, близкую зигзагообразной, а у D--маннозы и D-ликсозы наблюдается серпообразное расположение. У D-маннозы и D-ликсозы к тому же в большей мере образуется тридентатный молибдатный комплекс, включающий β-аномерную гидроксильную группу и гидроксильные группы, присоединенные к атомам углерода C-2 и C-3 пираноидной структуры альдозы.

Epimerization of the aldoses catalyzed by molybdate ions leads to formation of an equilibrium mixture of C-2 epimeric aldoses. General validity of the reaction was proved for the series of aldoses [1]. Basing on investigation of the aldoses labelled on purpose with the isotopes of carbon and hydrogen one can suggest a mechanism of epimerization reaction. By means of chemical methods

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and by measuring radioactivity of the respective reaction products we have proved that by epimerization of D-[1-^{3}H]glucose D-[2-^{3}H]mannose was formed and *vice versa*, D-[2-^{3}H]mannose gave rise to D-[1-^{3}H]glucose [2]. These results made us suppose that epimerization occurred with the cyclic structure of aldose and migration of hydrogen atoms took place from C-1 to C-2 and simultaneously in the reverse direction [2]. *Barker et al.* [3, 4] studied by means of NMR spectroscopy epimerization of the aldoses specifically labelled with carbon and hydrogen isotopes ^{13}C and ^{2}H at the carbon atoms C-1, C-2 or C-3 catalyzed by molybdate ions. By analysis of the NMR spectra they proved that during this epimerization a recombination of the carbons C-1 and C-2 took place, *i.e.* they mutually exchanged their position together with the attached hydrogen atoms. It was assumed that in the transition molybdate complex the aldose occurred in acyclic form, while a linkage between the carbons C-2 and C-3 was splitted and simultaneously a linkage was formed between carbons C-3 and C-1 of the aldose [3—5].

It was proved by means of NMR spectroscopy that the aldoses of arabinose homomorphous series joined molybdate complexes exclusively in acyclic structures and formed binuclear tetradentate molybdate complexes. Preferable molybdate complexes involve in the complexation hydroxyl groups at carbon atoms C-2, C-3, C-4, and C-5 [6]. It was found that the aldoses of lyxose or ribose homomorphous series joined molybdate complexes in pyranoid structures with the donor hydroxyl groups bound to C-1, C-2, and C-3, or C-2, C-3, and C-4, respectively [6—9]. *Verchere* and *Chapelle* [10] ascribe to D-lyxose, D-mannose, and L-rhamnose an ability to form binuclear tetradentate molybdate complexes with donor hydroxyl groups attached to the carbons C-1, C-2, C-3, and C-4 of the pyranoid structure of the aldoses.

In this paper we deal with the investigation of epimerization of ^{13}C-labelled D-mannose and the molybdate complexes of D-mannose, D-lyxose, D-glucose, and D-xylose by means of NMR spectroscopy.

Epimerization of D-[2,3,4,5,6-^{13}C]mannose enriched with ^{13}C up to 55% content, catalyzed by the molybdate ions leads to formation of D-[1,3,4,5,6-^{13}C]glucose. ^{13}C NMR spectra of these aldohexoses unambiguously prove that nonlabelled carbon atom C-1 of the ^{13}C-labelled D-mannose after the epimerization is transferred to the position C-2 of ^{13}C-labelled D-glucose (Table 1). This experiment confirms finding of *Barker et al.* [3, 4] that during epimerization of the aldose catalyzed by molybdate ions the recombination of the carbons C-1 and C-2 of the aldose takes place (Scheme 1).

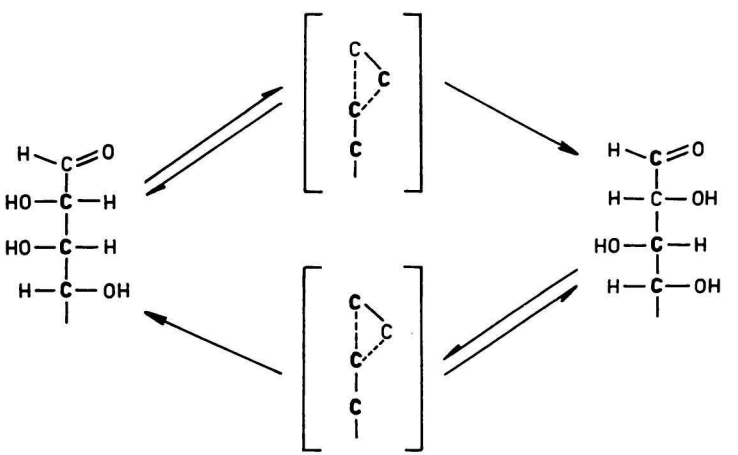
Alditols do not isomerize under the conditions of the epimerization reaction of the aldoses catalyzed by molybdate ions [11]. It implies at the same time that for occurring of epimerization on the carbon C-2 it is necessary for C-1 carbon to bear a carbonyl group. Epimerization also requires hydroxyl group at C-3

Table 1

^{13}C NMR data for the carbon atoms C-1 to C-4 of the initial D-[2,3,4,5,6-^{13}C]mannose and of D-[1,3,4,5,6-^{13}C]glucose isolated after its epimerization

Saccharide	Form	Chemical shift/ppm			
		C-1	C-2	C-3	C-4
D-Mannose	α-Pyranose	—	71.9	71.6	68.1
	β-Pyranose	—	72.5	74.3	67.8
D-Glucose	α-Pyranose	93.2	—	73.9	70.9
	β-Pyranose	97.1	—	76.9	70.9

carbon of the aldose. In the presence of the molybdate ions, 3-deoxy-D-*ribo*--hexose and 3-deoxy-D-*arabino*-hexose do not epimerize but irreversibly isomerize to give 3-deoxy-D-*erythro*-hexulose [12]. The presence of the hydroxyl group at C-4 carbon is not essential for epimerization to occur, but its presence or blocking with substituent, or its absence significantly influence the rate of epimerization reaction and/or formation of side products. Aldotetroses to aldooctoses epimerize very readily with formation of the equilibrium mixture of C-2 epimeric aldoses without any significant amount of the side products [1]. Disaccharides with $1 \rightarrow 4$ linkage (lactose, epilactose, maltose, epimaltose) under mild conditions of epimerization do not epimerize. Only in the presence of the increased amount of molybdic acid, trace amounts of epilactose were formed from lactose [13]. Epimerization of 4-deoxy-D-*xylo*-hexose gives rise to 4-deoxy-



Scheme 1

The course of epimerization reaction. ^{13}C-Enriched carbon atoms of the aldose are graphically emphasized.

-D-*lyxo*-hexose (14 %) and simultaneously large amount of the side products (33 %) is formed. Similarly, epimerization of D,L-[1-^{13}C]glyceraldehyde leads to the formation of only small amount of D,L-[2-^{13}C]glyceraldehyde, while as the main product [1-^{13}C]dihydroxyacetone is formed [3]. These results imply that successful processing of epimerization reactions of the aldoses requires presence of the carbonyl group and hydroxyl groups at the carbon atoms C-2, C-3, and C-4 of the aldose.

The aldoses of lyxose homomorphous series in the presence of molybdate ions at pH 5.5—5.9 preferably form molybdate complexes involving β-anomeric hydroxyl group and the hydroxyl groups bound to C-2 and C-3 carbons of the pyranoid structure of the aldose [7—9]. We have found that along with the preferable molybdate complex of the cyclic structure of D-mannose or D--lyxose, another type of the molybdate complex was formed in which these aldoses occurred in acyclic structure. On the basis of NMR data for the molybdate complexes of D-lyxose (*III*) and D-mannose (*IV*), and comparison of these data with those of the corresponding alditols *VII*, *VIII* [14] one can assume that these complexes involve the hydrated carbonyl group as well as hydroxyl groups bound to the carbon atoms C-2, C-3, and C-4 (Tables 2 and 3).

Differences in the chemical shift and coupling constant values between the complexed and free form of the alditols established during the NMR investigation of the molybdate complexes of the alditols imply that alditols produce binuclear molybdate complexes in which they occur as tetradentate donors with four vicinal hydroxyl groups [14]. In aqueous solutions of erythrose and threose the proton of the hydrated carbonyl group (aldehydrol form) has in ^{1}H NMR spectra a signal with $\delta = 5.08$, resp. 5.01, while the proton of the aldehydic group (aldehydo form) reveals it at $\delta = 9.71$, resp. 9.69 [15]. Proton H-1 attached to carbon atom C-1 with the hydrated carbonyl group which is involved in molybdate complex formation has in D-mannose and D-lyxose the signal shifted downfield ($\delta = 5.45$, resp. 5.50) (Table 3). In the case of D-mannose in the semiselective INEPT experiment after irradiation of this H-1 proton, the signal of C-2 carbon became visible in the ^{13}C NMR spectrum, while that of C-5 was not present. This fact implies also that D-mannose in this molybdate complex possesses an acyclic structure. At higher temperatures (60 °C) a total amount of the molybdate complexes of D-mannose does not change ($\approx$ 55 %) but an amount of the molybdate complex of the acyclic structure decreases by 10 % in favour of the cyclic structure complex.

In the case of D-xylose (*I*) and D-glucose (*II*) similarly as with the aldoses of arabinose homomorphous series, molybdate complexes of their acyclic structures are exclusively formed. NMR data of the molybdate complexes of D-xylose and D-glucose are in good accordance with the respective data for the molybdate complexes of xylitol (*V*) and D-glucitol (*VI*) (Table 2). This can imply that the

Table 2

^{13}C NMR data for the molybdate complexes of the aldoses and corresponding alditols

Saccharide in the complex	Chemical shift/ppm						Hydroxyl groups in the complex	Content of the molybdate complex/%
	C-1	C-2	C-3	C-4	C-5	C-6		
D-Xylose (*I*)	99.7	86.9*	81.0*	85.6*	63.2	—	1,2,3,4	15
Xylitol (*V*)	76.1	83.4*	82.5*	85.7*	63.9	—	1,2,3,4**	—
D-Glucose (*II*)	99.7	86.8*	80.8*	85.1*	71.2	64.4	1,2,3,4	10
D-Glucitol (*VI*)	76.1	83.3*	82.2*	84.8*	71.1	64.4	1,2,3,4**	—
D-Lyxose (*III*)	95.4	93.4	82.0	81.9	63.8	—	1,2,3,4	10
(*IIIa*)	112.7	84.6	88.2	81.7	68.4	—	1,2,3***	70
L-Lyxitol (*VII*)	70.2	91.5	82.9	82.8	63.8	—	1,2,3,4**	—
D-Mannose (*IV*)	95.4	94.0	81.9	81.2	71.8	64.4	1,2,3,4	15
(*IVa*)	112.7	84.4	88.5	79.5	80.0	65.2	1,2,3***	40
D-Mannitol (*VIII*)	70.1	91.8	82.8	82.0	71.7	64.4	1,2,3,4**	—

* Chemical shift values can be interchanged; ** see Ref. [13]; *** cyclic structures with the conformation $^1S_5$, see Ref. [7, 8].

Table 3

^{1}H NMR data for the molybdate complexes of the aldoses and corresponding alditols

Saccharide in the complex	Chemical shift/ppm								
	H-1	H-1′	H-2	H-3	H-4	H-5	H-5′	H-6	H-6′
III	5.50	—	4.71	4.71	4.58	4.01	*	—	—
IIIa	6.18	—	4.97	5.36	4.41	4.27	4.04	—	—
VII	4.35	4.07	4.75	4.65	4.54	3.88	3.73	—	—
IV	5.45	—	4.71	5.01	4.33	3.98	—	*	*
IVa	6.21	—	5.01	5.40	4.34	4.48	—	3.85	3.73
VIII	4.32	4.07	4.76	4.95	4.29	3.98	—	3.83	3.60
Saccharide in the complex	Coupling constants J/Hz								
	$J_{1,2}$	$J_{1',2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
III	< 0.2	—	*	< 0.2	7.5	5.0	−11.2	—	—	—
IIIa	4.4	—	6.8	7.8	< 0.2	2.8	−12.8	—	—	—
VII	< 0.2	2.6	4.4	0.8	8.2	5.3	−11.6	—	—	—
IV	< 0.2	—	4.4	< 0.2	8.7	—	—	*	*	*
IVa	4.4	—	6.9	7.5	< 0.2	—	—	6.7	6.9	*
VIII	< 0.2	2.7	4.1	0.0	9.5	—	—	6.8	2.7	−10.1

* Not assigned or not resolved.

molybdate complexes are formed involving the hydrated carbonyl group and hydroxyl groups bound to carbon atoms C-2, C-3, and C-4. Chemical shift value of H-1 proton of the hydrated carbonyl group involved in the molybdate complex is $\delta = 5.44$, resp. 5.48.

Arrangement of the hydroxyl groups attached to carbon atoms C-2 and C-3 (*threo* or *erythro* arrangement) is a decisive factor influencing spatial conformation of the carbon chain of the produced molybdate complex of the acyclic structure of the aldoses. Aldoses of the homomorphous series of arabinose and xylose [6] in the molybdate complexes, in which as the donor hydroxyl groups participate hydroxyl group of the hydrated carbonyl group and hydroxyl groups at the carbon atoms C-2, C-3, and C-4, have carbon chains shaped close to zig-zag arrangement. Molybdate complexes with acyclic structure of aldoses of the lyxose homomorphous series have sickle arrangement of the carbon chains (Fig. 1). In the case of the aldoses of ribose homomorphous series we were not

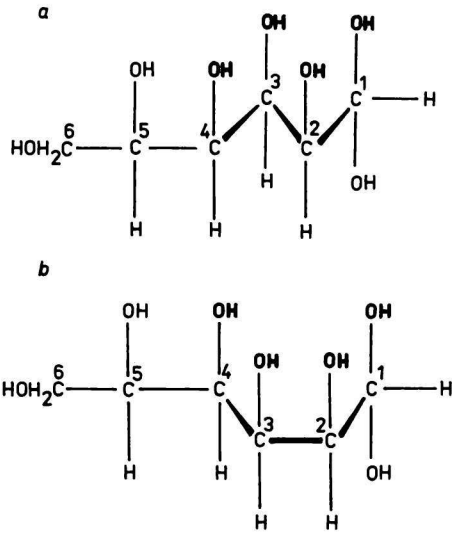


Fig. 1. Hydrated forms of the acyclic structure of D-glucose (*a*) and D-mannose (*b*) in the molybdate complex. Hydroxyl groups of the aldoses involved in the molybdate complex are graphically emphasized.

able to identify unambiguously from the spectral data the molybdate complexes of their acyclic structures [6]. For all investigated aldoses, *i.e.* D-ribose, D-talose, D-*glycero*-D- and D-*glycero*-L-*talo*-heptose, in ^{1}H NMR spectra a signal was registered with $\delta = 5.50$—5.65 (D-ribose 5.50; D-talose 5.59; D-*glycero*-D- and D-*glycero*-L-*talo*-heptose 5.60, resp. 5.65) and the coupling constant lower than

0.2 Hz, which could be ascribed to the proton at C-1 carbon with the hydrated carbonyl group involved in the molybdate complex. This could imply that also aldoses of the ribose homomorphous series form along with the preferable molybdate complex of the cyclic structure also the molybdate complexes with acyclic structures. From this point of view, during epimerization catalyzed by the molybdate ions, an aldose with *threo* configuration at the carbon atoms C-2 and C-3 transforms into aldose with *erythro* configuration, or *vice versa* (Fig. 2).

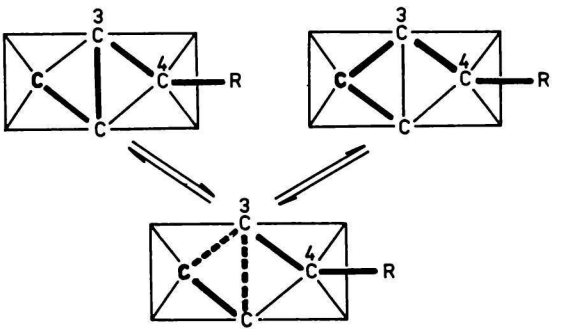


Fig. 2. Schematic illustration of the epimerization of the aldoses depicted as binuclear tetradentate molybdate complexes with acyclic structure of the aldoses. Two molybdate octahedra are joined by the common face under the figure plane. An arrangement of the aldose carbon chain in the site of complexation of its hydrated carbonyl group and three adjacent vicinal hydroxyl groups is graphically emphasized.

According to present considerations, epimerization proceeds through the transition molybdate complex with the acyclic structure of the aldose [3—5]. Acyclic structures of the aldoses in the molybdate complexes, that were established by means of NMR spectroscopy, involve hydrated carbonyl group and hydroxyl groups bound to the carbon atoms C-2, C-3, or C-4 of the aldoses from the homomorphous series of arabinose and ribose [6]. Their structure as well as the structure of the molybdate complexes with acyclic structures of the aldoses from the homomorphous series of lyxose and xylose, is probably close to the transition complexes which are responsible for epimerization of the aldoses (Fig. 2).

Experimental

^{13}C-Labelled D-[2,3,4,5,6-^{13}C]mannose and D-[1,3,4,5,6-^{13}C]glucose were obtained by application of the methods developed for synthesis of ^{14}C-labelled aldoses. Water-soluble

α-D-[U-^{13}C]glucan (800 mg) enriched up to 55 % content of ^{13}C (purchased from the Institute for Development, Production and Application of Radioisotopes, Prague) was subjected to acid hydrolysis. Thereupon D-[U-^{13}C]glucose (620 mg) was isolated [16]. From ^{13}C-labelled D-glucose through 4-nitrophenylhydrazone of D-[U-^{13}C]glucose and its oxidative degradation D-[U-^{13}C]arabinose (210 mg) was prepared [17]. Applying nitromethane synthesis to ^{13}C-labelled D-arabinose with the subsequent oxidative decomposition of 1-deoxy-1-nitrohexitols, D-[2,3,4,5,6-^{13}C]mannose (90 mg) was prepared [16]. Epimerization of D-[2,3,4,5,6-^{13}C]mannose (90 mg) was carried out in 1 % aqueous solution of molybdic acid (2 cm^3) at 90 °C for 3 h. By means of the paper chromatography (Whatman No. 3, 1-butanol—ethanol—water (φ_r = 5 : 1 : 4), flow time 45 h, 23 °C, elution of the glucose zone with water) D-[1,3,4,5,6-^{13}C]glucose (50 mg) was isolated from the reaction mixture.

NMR spectra of the aqueous solutions of ^{13}C-labelled aldoses were registered. For the investigation of the molybdate complexes of the aldoses, aqueous solutions containing aldose and ammonium molybdate in mass ratio 1 : 2 were used.

^{1}H NMR spectra were registered using FT NMR spectrometer Bruker AM-300 (300.13 MHz) at 298 K in deuterium oxide. Sodium 3-(trimethylsilyl)propionate was used as an internal standard. The digital resolution was 0.12 Hz per point.

^{13}C NMR spectra (75.46 MHz) were registered at the same conditions as ^{1}H NMR spectra using methanol (δ = 50.15) as internal standard. Digital resolution was 1.5 Hz per point. Assignment of the signals in NMR spectra was carried out using homocorrelated COSY-45 and COSYLR with emphasized long-range couplings and heterocorrelated CH HETCOR spectroscopy.

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