CATALYZED CARBON SKELETON
REARRANGEMENT OF BASIC CARBOHYDRATES

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The essentials of a remarkable carbon skeleton rearrangement of aldoses catalyzed with molybdic acid and known as the Bílik reaction are introduced. The extension of the reaction to a mutual interconversion of 2-ketoses and 2-C-(hydroxymethyl)-aldoses is also described. Finally, the molybdic acid catalysis is briefly compared with other known systems catalyzing similar transformations.

Introduction

For a long time carbohydrates have been considered important natural compounds but their significance has been restricted mostly to building and storage materials of living organisms. A research boom in the field in the last two decades has changed the view dramatically. Due to their participation in all both normal and pathological life processes, carbohydrates are as much biologically important as proteins, which
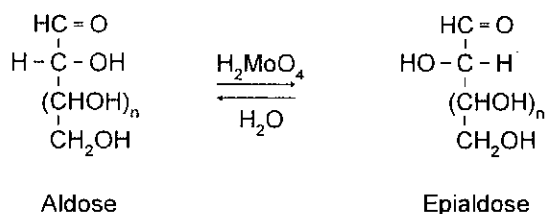
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have been considered to be the most important natural compounds since the beginning of the modern life sciences.

The basic carbohydrates are monosaccharides with two most important subgroups of compounds, aldoses and 2-ketoses (of respective general formulae $HOCH_2-(CHOH)_n-CHO$ and $HOCH_2-(CHOH)_{n-1}-CO-CH_2OH$). While the latter sugars are easily prepared from common aldoses by the application of the Lobry de Bruyn–Alberda van Ekenstein reaction [1], known for more than a century, several aldoses have been rather scarcely available (and therefore called rare aldoses) since the procedures of their preparation were very demanding.

Molybdic Acid-Catalysis

A revolutionary change that certainly has facilitated the carbohydrate research boom was the discovery of the epimerization of aldoses catalyzed with molybdic acid. It is a general reaction of an at least four-carbon aldose that gives a thermodynamic equilibrium of the aldose and its epimer (epialdose) as the only product of the transformation [2]. The reaction was discovered and published 26 years ago by a great Slovak chemist Vojtech Bilik, Ph.D., D.Sc. (1929 – 1994) who joined his career with the Institute of Chemistry of the Slovak Academy of Sciences where he developed the topic of reactions of carbohydrate catalyzed by molybdate ions. (V. Bilik contributed to the development in carbohydrate chemistry also by his discoveries of three other molybdate-catalyzed reactions of preparation of aldoses, *viz.* stereoselective hydroxylation of glycals [3], oxidative decomposition of 1-deoxyalditol-1-nitronates [4], and oxidative degradation of aldose phenylhydrazones [5]. In literature the epimerization of aldoses catalyzed by molybdic acid is referred to as the Bílik reaction [6]

$$
\begin{array}{ccc}
\begin{array}{l}
HC=O \\
\mid \\
H-C-OH \\
\mid \\
(CHOH)_n \\
\mid \\
CH_2OH
\end{array}
&
\underset{H_2O}{\overset{H_2MoO_4}{\rightleftharpoons}}
&
\begin{array}{l}
HC=O \\
\mid \\
HO-C-H \\
\mid \\
(CHOH)_n \\
\mid \\
CH_2OH
\end{array}
\\
\text{Aldose} & & \text{Epialdose}
\end{array}
$$

Treatment of an aldose in a mild acidic solution in the presence of molybdate ions (usually heating of aqueous solution containing 10–20% of starting aldose and 0.1 – 0.2% molybdic acid for 2 – 6 h at 70 – 80 °C) gives rise to an equilibrium mixture of epimeric aldoses without formation of the complementary 2-ketose, irrespective of which aldose was adopted. As out of every epimeric pair, one aldose

is usually more easily available, either directly isolated from its natural source or in combination with chain extension by one-carbon atom, the application of the Bílik reaction makes it possible to obtain the other, rarer aldose and the following equilibria can be obtained

D-Threose	:	D-Erythrose	4 : 3	[7]
D-Xylose	:	D-Lyxose	7 : 5	[8]
L-Arabinose	:	L-Ribose	2 : 1	[9]
D-Glucose	:	D-Mannose	3 : 1	[2]
D-Galactose	:	D-Talose	4 : 1	[10]
D-Allose	:	D-Altrose	3 : 2	[11]
L-Quinovose	:	L-Rhammose	3 : 2	[12]
L-Fucose	:	6-Deoxy-L-Talose	4 : 1	[13]
D-*glycero*- -L-*gluco*-Heptose	:	-L-*manno*-Heptose	4 : 1	[14]
D-*glycero*- -D-*gulo*-Heptose	:	-D-*ido*-Heptose	4 : 1	[15]
D-*glycero*- -D-*galacto*-Heptose	:	-D-*talo*-Heptose	4 : 1	[15]
7-Deoxy-L-*glycero*- -L-*galacto*-Heptose	:	-L-*talo*-Heptose	4 : 1	[14]
D-*threo*- -L-*galacto*-Octose	:	-L-*talo*-Octose	4 : 1	[16]

The reaction is of great significance. Several institutions and companies have commercialized it; many basic aldoses available on the market, e.g., D-mannose, D-talose, D- and L-lyxose, or L-ribose are prepared with the use of the Bílik reaction

The mechanism, of the Bílik reaction was explained later. Soon after the discovery of the reaction and using at that time available [2]H- and ^{3}H-isotopic methods it was found that the formation of a catalytically efficient complex of aldose with molybdic acid causing the epimerization results in the intramolecular hydrogen atom exchange at the carbon atoms C-1 and C-2, i.e., the hydrogen atom H-1 of the

starting aldose becomes the hydrogen atom H-2 of the epimeric aldose and *vice versa* [17]. When also regiospecifically ^{13}C-enriched aldoses became available, the ^{13}C NMR spectroscopy proved that the Bílik reaction is accompanied by a remarkable carbon skeleton rearrangement of the participating aldoses C-1–C-2–C-3–C-4–... $\rightleftharpoons$ C-2–C-1–C-3–C-4–... [18]. It means that the carbon atoms C-1 and C-2 exchange their positions together with the attached hydrogen atoms.

The existence of complexes considered to be catalytically active was proved by ^{1}H, ^{13}C and [95]Mo NMR spectroscopy [19,20]. Different amounts of binuclear tetradentate molybdate complexes, involving the hydrated aldehyde group and three adjacent hydroxyl groups of the hydrate, i.e., HO-2, HO-3, and HO-4, were detected for all the aldoses investigated. The complexing site of aldoses with *threo* configuration at the carbon atoms C-2 and C-3 enters these complexes in zig-zag conformation while the conformation of the complexing site of aldoses with *erythro* configuration at the same carbon atoms in these complexes is sickle. The zig-zag and sickle conformations of interconverting aldoses in their acyclic aldehyde forms was used to mechanistically elucidate the results of the study with regiospecifically ^{13}C-enriched aldoses [18]. However, to fulfil the strict stereochemical rules valid for all the molybdenum(VI) complexes of known structure, e.g., [21–23], it is very likely that just the afore-mentioned complexes of hydrated acyclic forms of aldoses participate in the mutual interconversion of epimeric aldoses catalyzed by molybdic acid.

Based on these results and considerations, the mechanism of the Bílik reaction is depicted in Scheme 1. Hydrated acyclic form of an aldose by its four adjacent hydroxyl groups HO-1, HO-2, HO-3, and HO-4 enters a tetradentate binuclear molybdate complex I, in which the aldose probably undergoes a rearrangement to give the transition state II. At this point both bonds C-2–C-3 and C-1–C-3, the former one being split while the latter is newly formed, are equivalent. Moreover, the process is accompanied by simultaneous dehydration and hydration of the respective carbon atoms C-1 and C-2. Thus, the process results in the formation of the molybdate complex of epimeric aldose III. The epialdose, however, in comparison with the starting aldose has mutually exchanged its carbon atoms C-1 and C-2 including their substituents (hydrogen atoms and hydroxyl groups). Therefore, the process when strictly classified should not be denoted as an epimerization, i.e., the process including the configuration change only at one (C-2) carbon atom, but a carbon skeleton rearrangement that, in a special case when the skeletal carbon atoms are not labelled, results in the epimerization of unsubstituted aldoses. As the Bílik reaction utilizes only catalytic amounts of the catalyst (mole ratio of molybdic acid expressed as dimolybdate to aldose is usually 1 : 100 – 200), it results in establishing thermodynamic equilibrium of epimeric aldoses.

Even more dramatic structural changes are observed when the Bílik reaction is extended to 2-ketoses or 2-C-(hydroxymethyl)aldoses. In accordance with the

R = H, CH$_2$OH, or (CHOH)$_n$-CH$_2$OH
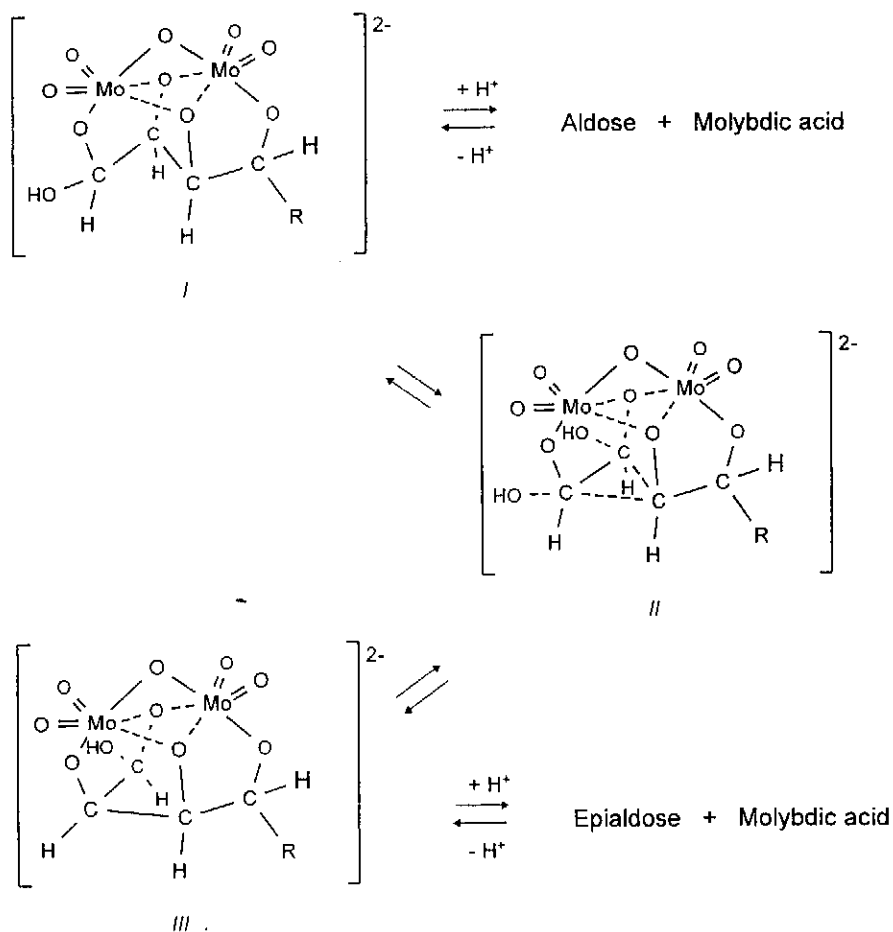
Scheme 1

mechanism suggested for the reaction both these groups of monosaccharides are mutually intercovertible at the conditions of the Bílik reaction and following thermodynamic equilibria of isomeric sugars have so far been obtained

D-Fructose	: D-Hamamelose	14 : 1	[24]
D-gluco-Hept-2-ulose	: 2-C-(Hydroxymethyl)-D-mannose	12 : 1	[25]
D-manno-Hept-2-ulose	: 2-C-(Hydroxymethyl)-D-glucose	28 : 2	[25]

Thus, D-hamamelose (2-C-(hydroxymethyl)-D-ribose) can easily be obtained in one step in 6.5% yiels by molybdic acid treatment of D-fructose [24]. Even more efficient is the synthesis of 2-ketoses from 2-C-(hydroxymethyl) branched chain aldoses [25,26].

The expected mechanism of transformation has been verified similarly as for the analogous interconversion of empiric aldoses. D-(2-^{13}C)Fructose treated with a catalytic amount of molybdic acid was transformed to D-(2-^{13}C)hamamelose, which was proved by ^{1}H and ^{13}C NMR spectroscopy [24].

Other Catalytic Systems

Mechanistically related transformations of carbohydrates including the carbon skeleton also are epimerizations of aldoses catalyzed with nickel(II)-ethylenediamine [27] and cobalt(II)-ethylenediamine complexes [28] as well as with calcium(II), strontium(II), and lanthanum(III) cations in aqueous or alcoholic alkaline solutions [29,30]. In all the cases, however, not catalytic but equimolar amounts of catalysts are necessary to achieve the transformations so that not thermodynamic equilibria of aldoses but those of their complexes are the result. Moreover, the epimerizations catalyzed with the calcium(II), strontium(II), and lanthanum(III) cations are not universal, as these cations catalyze the carbon skeleton rearrangement of aldoses with *threo* configuration at the carbon atoms C-3 and C-4 only. Nickel(II)-ethylenediamine complexes have been utilized also for the isomerization of hex-2-uloses to 2-C-(hydroxymethyl)pentoses [31]. Due to different application restrictions or difficulties, all these catalyzed transformations are rather of a theoretical significance only.

Acknowledgements

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