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The influence of microwave irradiation on stereospecific Mo(VI)-catalyzed transformation of deoxysugars

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Dedicated to the memory of
Professor V. Bílik (1929–1994)

ABSTRACT

The stereospecific mutual isomerization of 5-, 6-, and 7-deoxysugars in a microwave field with Mo(VI) as a catalyst is reported. The reaction cycle allows the use of catalytic amounts of molybdate ions to form highly reactive catalytically active dimolybdate complexes that create conditions for stereospecific intramolecular rearrangement. The microwave-enhanced Mo(VI)-catalyzed transformation of deoxyaldoses occurred with full stereospecificity resulting in the formation of the corresponding *epi*-deoxyaldoses in very good yields. The microwave field has a substantial effect on the transformation studied.

1. Introduction

Naturally occurring deoxysugars are essential biological molecules that play a number of roles in many physiologically significant processes such as cell signaling, immuno-stimulation, target recognition of microorganisms and antibiotics. They occur frequently as components of glycoproteins, glycolipids, and polysaccharides and have received an increased interest as they were shown to be substantial cell wall components of several human pathogens.[1] 6-Deoxy-L-hexoses, as constituents of the surface polysaccharide structures of gram-positive and gram-negative human pathogenic bacteria are involved in host–pathogen interactions, and a deficiency in the production of these surface molecules results in a significant decrease in bacterial virulence. L-Fucose (6-deoxy-L-galactose) has been investigated as a potential agent to prevent tumor cell growth[2] and as an anti-inflammatory drug to alleviate rheumatoid arthritis.[3] L-Fucose, D-rhamnose (6-deoxy-D-mannose), and L-pneumose (6-deoxy-L-talose), are, respectively, components of the cell surface lipopolysaccharides of *Helicobacter pylori, Pseudomonas aeruginosa*, and *Actinobacillus actinomycetemcomitans serotype a*.[4,5] L-Rhamnose and L-qiunovose are also found as constituents of extracellular, gram-negative bacterial polysaccharides, such as the *Salmonella* and *Escherichia coli* O-antigen. L-Qiunovose (6-deoxy-L-glucose) is the part of disaccharide in digitalin which is a powerful cardiac stimulant.[6,7] 6-Deoxyheptoses (6-deoxy-L-*galacto*-heptose, 6-deoxy-L-*talo*-heptose, 6-deoxy-D-*altro*-heptose, and 6-deoxy-D-*manno*-heptose) are rare components of bacterial lipopolysaccharides.[8,9] Deoxysugars occur in very small amounts and their isolation from natural sources is rather difficult. However, sufficient amounts of these compounds could be useful for the study of their biosynthetic pathways and novel interventions in antibacterial chemotherapy.

The synthesis of rare carbohydrates with biological activity, which are applicable mainly in medicinal chemistry, is an attractive problem. Carbohydrate chemistry is currently dealing with the development of efficient methods for the conversion of carbohydrates into more valuable, enantiomerically pure products. Transition metal-catalyzed reactions belong to the powerful tools of contemporary organic synthesis.[10] The interaction of carbohydrates with metal ions has been extensively studied for a long time.[11] The formation of molybdate complexes with saccharides and unusual epimerization of aldoses have been studied in detail.[12–14] Such reactions allow a considerable increase in molecular complexity in a single step and usually proceed with excellent stereoselectivity. Furthermore, the use of microwave radiation in organic synthesis has become more common and is very useful as an alternative heat source in chemistry. It is increasingly being studied due to its better yields, cleaner products, reduction of reaction time and side reactions.[15–17]

Recently, we have developed the stereochemical transformation of reducing saccharides in a microwave field by using molybdate ions as a catalyst. This approach appears to be an ideal reaction for the isomerization of a carbohydrate carbon skeleton with high stereospecificity. The procedure led to efficient preparation of aldoses,[18] 2-*C*-(hydroxymethyl)-aldoses, ketoses,[19] and (1→6)-linked disaccharides.[20] As a part of our research program aimed at the study of saccharide–molybdate complexes, Mo(VI)-catalyzed rearrangement of reducing sugars and the development of facile and straightforward synthetic routes to various sugar derivatives, we herein report the preparation of several 5-, 6-, and 7-deoxyaldoses by direct skeletal isomerization in microwave field.

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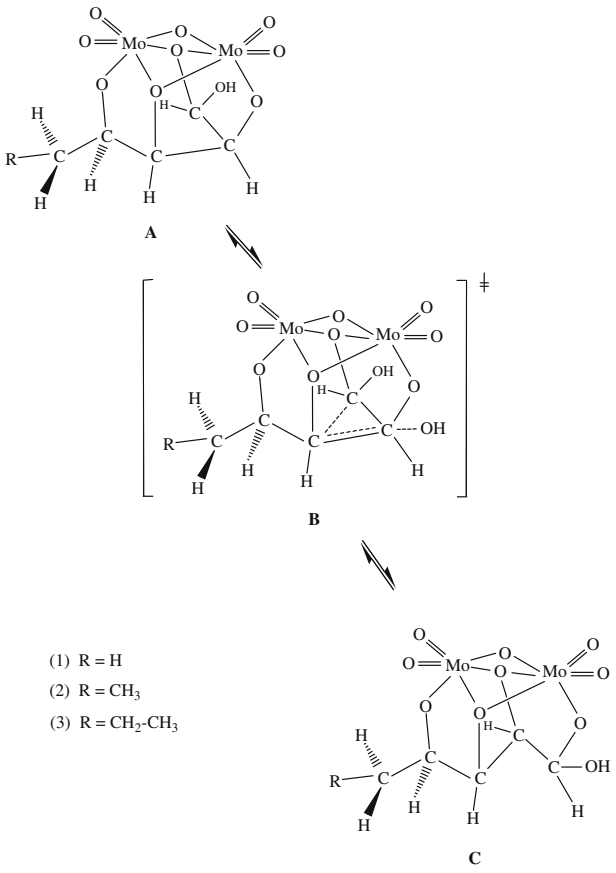
2. Results and discussion

The knowledge of the structure of saccharide–Mo(VI) complexes[21–24] and mechanism of the highly stereospecific isomerization reaction[14] lead us to the idea that microwave irradiation might have a considerable effect also on the isomerization of deoxysugars. The influence of a microwave irradiation on the stereoselective transformation of eight representative deoxysugars was studied. It was observed that the isomerizations of selected deoxyaldoses in the presence of molybdate ions in microwave field were more effective than those using conventional heating.[25] Aqueous solutions of sugars containing molybdate ions generated in microwave field gave thermodynamically equilibrated mixtures of epimeric deoxyaldoses in a few minutes. The transformation is proposed to involve the formation of a dimolybdate species of the corresponding saccharides. The reaction cycle allows the use of a catalytic amount of molybdate ions to form highly reactive catalytically active Mo(VI) complexes that create conditions for stereospecific intramolecular rearrangement producing desired epimeric deoxyaldose. All the deoxyaldoses examined reacted similarly, producing equilibrium mixtures of two C-2 epimers. It was determined that the microwave irradiation had a substantial effect on the yield of the corresponding *epi*-deoxyaldoses. Scheme 1 shows the one-pot synthetic preparation of various deoxyaldoses. The transformation proceeds via an acyclic dimolybdate–saccharide complexes. The formation of the dimolybdate complex with the carbonyl-oxygen atom C-1 and the adjacent three hydroxylic oxygen atoms at C-2, C-3, and C-4 of the deoxyaldose in acyclic-hydrated form (Scheme 1A), leads to the transition state (Scheme 1B) in which the rearrangement occurs. The saccharide functions as a bidentate ligand bound to the metal center. The critical C-2–C-3 and new C-1–C-3 bond are formed stereospecifically. Effective stereospecific transformation occurs in the case of deoxyaldoses with C-2–C-3 bond cleavage and transposition. Dissociation of the complex produces the epimeric deoxyaldose as shown in Scheme 1C. The thermodynamic equilibrium favours the saccharide with a lower value of conformational instability. The ratio of deoxyaldose and *epi*-deoxyaldose in an equilibrium reaction mixture was comparable regardless of the starting sugar. These results matched well with our previous observations[18] and are also in agreement with NMR experiments analyzing the mechanism of this transformation with ^{13}C-enriched saccharides.[13,14,26,27] It was determined that this transformation could be sped up by applying microwave irradiation. The reaction time decreased from hours to minutes and is 60 to 120-fold shorter than in the case of conventional oil-bath heating, in addition to obtaining the better yields and cleaner products.



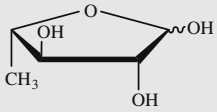
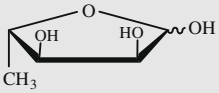
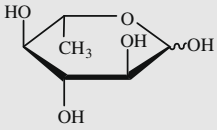
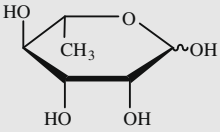
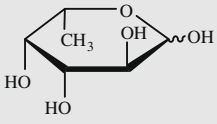
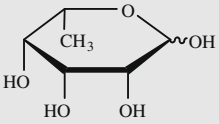
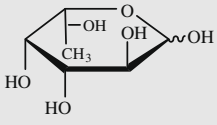
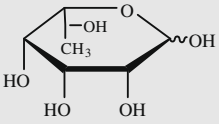
Scheme 1.

Thermal effects result from dipolar polarization as a consequence of dipole–dipole interactions between polar molecules and the electromagnetic field. They originate from the dissipation of energy into heat as a result of intermolecular friction when the dipoles change their mutual orientation at each alternation of the electric field at a high frequency. As carbohydrates have permanent dipole moments they are suitable chemical substances for microwave irradiation. Accordingly, controlled microwave irradiation can be used to transfer significant amounts of energy into the reaction and satisfy the high energy demands required for the monomolecular C–C bond rearrangement. Thus, the rearrangement process can be completed in a very short time. Selective absorption of microwave energy is able to shift the reaction equilibrium and product distribution is affected by the structure of ligand. The best yields were obtained with the microwave irradiation power of 600 W. Table 1 shows the results of Mo(VI)-catalyzed isomerization of the selected deoxyaldoses in both cases. The isomerization reaction progressed smoothly in microwave field and reached thermodynamic equilibrium within 3–5 min compared to the 3–10 h required for conventional conditions. The results suggest that the ability of molybdate ions to form catalytically active complexes with deoxyaldoses and to promote the isomerization process during microwave irradiation is improved. The rate enhancement may be attributed to the absorption of more energy by the polar media, which generates sufficient heat energy to promote the demanding isomerization reaction.

Different final concentrations of 2-epimers were obtained under different reaction conditions (Table 1). This is in agreement with epimerizations of aldoses where final product concentrations also vary.[18] Examination of the data suggested that final concentrations depended upon the stereochemistry of starting compounds, namely *cis*- or *trans*-configurations at C-3 and C-4 carbons. If deoxyaldoses have *cis* configuration of hydroxyl groups at C-3 and C-4, for example, 6-deoxy-L-galactose and 6-deoxy-L-talose, the reaction does not proceed to true equilibrium. In the case of the *trans*-configuration, for example, 6-deoxy-L-mannose/6-deoxy-L-glucose interconversion, the true equilibrium was reached. It thus appears, that the configuration at C-3 and C-4 carbons is an important factor that influences the final equilibria of the products obtained under microwave conditions. The reason for this behavior is not fully understood at present, but might originate in a lower stability of the *cis*-configured aldoses due to steric effects.

The primary reaction produces the 2-epimers. However, in case of longer conventional heating, secondary products are also formed in addition to the 2-epimers.[25,27] Such a secondary reaction produces a certain amount of 3-epimer of the starting deoxyaldose, which immediately equilibrates with its 2-epimer. The presence of 3-epimers complicates product separation. This problem can simply be solved by a microwave approach since the energy absorption is different from the conventional mode of heating. NMR anal-

Table 1
Mo(VI)-catalyzed isomerizations of deoxyaldoses under conventional heating and microwave irradiation.

Deoxyaldose	*epi*-Deoxyaldose	Conventional heating		Microwave field		
		Time (min)	Deoxyaldose /*Epi*-deoxyaldose	Time (min)	Deoxyaldose /*epi*-deoxyaldose (%)	Yield[c]
5-Deoxy-L-arabinose[28]	5-Deoxy-L-ribose[28]	240	3:1[a]	3	2.2:1	66/30
						
5-Deoxy-L-ribose	5-Deoxy-L-arabinose	240	1:3[a]	3	1:2	30/60
6-Deoxy-L-glucose[29]	6-Deoxy-L-mannose[29]	180	1.5:1[b]	3	2.3:1	64/29
						
6-Deoxy-L-mannose	6-Deoxy-L-glucose	180	1:1.5[b]	3	1:2.3	30/62
6-Deoxy-L-galactose[29]	6-Deoxy-L-talose[29]	480	4:1[a]	5	3.1:1	70/20
						
6-Deoxy-L-talose	6-Deoxy-L-galactose	480	1:4 [a]	5	1:2.1	26/61
7-Deoxy-L-galactoheptose[30]	7-Deoxy-L-taloheptose[30]	600	9:1[a]	5	6.5:1	81/10
						
7-Deoxy-L-taloheptose	7-Deoxy-L-galactoheptose	600	1:9[a]	5	1:4.5	10/77

[a] Ref. 25.
[b] Ref. 13.
[c] Semi-preparative scale.

ysis clearly showed that only insignificant amounts of 3-epimers (up to 3%) are present in equilibrated reaction mixtures obtained under microwave conditions. The differences in the composition of the reaction mixtures can be rationalized by these effects and the tendency of microwave irradiations to prevent secondary reactions. The relative energies that are necessary for the creation of dominant and secondary products are different and a selective absorption of microwave energy in a system increases the proportion of primary product and decreases the proportion of secondary product compared to a conventional approach.

The transformation was also studied with one deoxyketose, 6-deoxy-L-fructose. The preliminary ^{1}H NMR investigation of the reaction mixture obtained from the treatment of 6-deoxy-L-fructose[31] with Mo(VI) in a microwave field revealed the presence of two singlets 5.22 and 5.12 ppm, in the anomeric reagion of the spectra with a prevalence for the β-furanose form. A comparison of the signals with the published data[32] suggests that they correspond to two tautomeric forms of 2-*C*-(hydroxymethyl)-5-deoxy-L-ribose. The new compound is of high purity due to its significant retention on a strongly acidic cation-exchange resin in the Ba^{2+} form. In this case formation of the dimolybdate complex with the carbonyl-oxygen atom C-2 and the adjacent three hydroxyl groups at C-3, C-4 and C-5 of 6-deoxy-L-fructose leads to the transition state in which the critical C-3–C-4 and new C-2–C-4 bond is formed stereospecifically. Similar evidence was seen during the interconversion of (1→6)-linked disaccharides, where the terminal fructose unit of D-palatinose was isomerized to 2-*C*-(hydroxymethyl)-D-ribose.[20] Dissociation of the complex produces the starting deoxyketose and the isomeric product generated by the stereospecific rearrangement. Examination of the NMR spectra showed that the conversion reached its equilibrium in 5 min. The mechanism of the rearrangement is in accordance with our previous observations[32] but the reaction equilibrium is strongly shifted to the starting compound (10:1).

In terms of application, microwave radiation enables rapid synthetic transformations and offers significant improvements with regard to yield, reaction time, and simplicity of the operation. The method is suitable for preparative purposes, as the epimers can be effectively obtained by chromatography. Identical experiments were conducted according to the literature.[25] Isomeric products were also obtained by this conventional way, but the yields were markedly lower. Comparison of these results clearly shows that microwave irradiation considerably accelerated the isomerization process and that the fast and homogeneous transfer of energy can minimize the side reactions. Microwave chemistry thus opens up new possibilities for effective preparation of various carbohydrates.

3. Conclusion

In conclusion, we have demonstrated an easy approach toward the stereoselective mutual transformation of terminal deoxysugars

by using Mo(VI) as a catalyst in a microwave field. The transformation studied involves reactive, catalytically active dimolybdate complexes as intermediates, which enable the stereospecific rearrangement in the catalytic cycle. The present reaction may provide insight into the development of other stereoselective transformations in carbohydrate synthesis.

4. Experimental

4.1. General and experimental methods

Saccharides 5-deoxy-L-arabinose, 5-deoxy-L-ribose, 7-deoxy-L-*glycero*-L-*galacto*-heptose, 7-deoxy-L-*glycero*-L-*talo*-heptose were prepared according to the literature.[25] 6-Deoxy-L-mannose (L-rhamnose) was purchased from Fluka, 6-deoxy-L-galactose (L-fucose) was purchased from Sigma–Aldrich. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 and Varian Unity 600 spectrometer. The experiments were carried out in aqueous solution at 25 °C and 40 °C. The chemical shifts were referenced to internal TSP (D_2O). A 5 mm QNP probe was used for the measurements of the 1D ^{13}C NMR spectra. Two-dimensional techniques (2D), COSY, HMBC, and HSQC were used to determine the ^{1}H and ^{13}C chemical shifts; the 2D HSQC experiment was performed in phase-sensitive pure-absorption mode. HRMS (high-resolution mass spectra) were taken with a MALDI-TOF-MS. Melting points were measured on a Kofler hostage microscope. Optical rotations were determined with an automatic polarimeter Perkin–Elmer Model 141 using a 10 cm, 1-mL cell. Experiments were conducted using domestic microwave oven producing continuous irradiation at 2450 MHz. Separations of the free sugars were accomplished by column chromatography on a Dowex 50W X8 resin (Sigma–Aldrich) in the Ca^{2+} or Ba^{2+} form (200–400 mesh). Paper chromatography was performed by the descending method on the Whatman No. 1 paper using ethyl acetate–pyridine–water (8:2:1) as the mobile phase. The chromatograms were made visible by means of alkaline silver nitrate. All concentrations were carried out under reduced pressure at a bath temperature not exceeding 50 °C.

4.2. Representative procedure

The deoxyaldose (200 mg, 0.6 mmol) in 0.5% molybdic acid (10 mg, 0.0617 mmol) in D_2O (2 ml) was exposed to microwave irradiation using a microwave oven operated at 600 W for an appropriate time. The composition of the reaction mixture was determined by ^{1}H NMR spectroscopy to determine the ratio of the epimers present in the thermodynamic equilibrium mixture (Table 1). The ion-exchange resin Amberlite IRA-400 in the HCO_3^- form was used to remove the catalyst. The reaction mixture was fractionated by column chromatography on Dowex 50W X8 in Ba^{2+} form with water as eluent. In the case of 5-deoxy-L-Ara/5-deoxy-L-Rib the Dowex 50W X8 in Ca^{2+} form and aqueous 0.001 M TEA as eluent was used. The yields of products are listed in Table 1. Branched deoxyaldose, 2-*C*-(hydroxymethyl)-5-deoxy-L-ribose, was separated on Dowex 50W X8 in Ba^{2+} form with water as the eluent. δ_C (D_2O, 600 MHz): 101.90 (C-1), 78.45 (C-2), 78.17 (C-5), 75.70 (C-4), 70.85 (C-3), 64.05 (*C*H_2(C-2)). HRMS *m/z* calcd for $C_6H_{12}O_5$ 164.1565; found 187.1543 $[M+Na]^+$.

Acknowledgments

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