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Microwave-assisted stereospecific intramolecular rearrangement of (1→6)-linked disaccharides catalyzed by Mo(VI)

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ABSTRACT

Three (1→6)-linked disaccharides, melibiose, isomaltose and palatinose, were converted into their isomers via intramolecular rearrangement catalyzed by Mo(VI). The reaction proceeded with excellent stereoselectivity. Product disaccharides, α-D-galactopyranosyl-(1→6)-D-mannose, α-D-glucopyranosyl-(1→6)-D-mannose and α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose were structurally characterized by NMR and MS spectroscopy. This contribution highlights the remarkable advantages of Mo(VI) catalysis and beneficial effects of microwave irradiation in oligosaccharide synthesis.

1. Introduction

It is well known that many oligosaccharides and glycoconjugates play important roles in fundamental biological systems.[1,2] They are involved in metabolic processes, signal transduction and the immune response.[3] The rapidly growing development of glycobiology and carbohydrate-based pharmaceuticals[4,5] sets demands for the increased development and methodological advances for the selective construction of natural and unnatural carbohydrates. There is need for access to reasonable quantities of natural oligosaccharides in their pure form. However, the isolation and purification of these materials from natural sources is often quite laborious. The same need exists for unnatural analogues that may be used in structure–activity relationship studies. Great effort has been undertaken to develop alternative methods. Part of the solution to these problems is the invention of new approaches in carbohydrate synthesis. Catalysis with transition metals allows stereospecific access to a wide range of organic molecules. In our previous studies, molybdate ions were investigated as catalysts for the isomerization of reducing sugars and it was shown that in a microwave field transformations proceed very efficiently.[6,7]

Microwave energy offers numerous benefits when performing synthesis, including increased reaction rates, yield enhancements and cleaner products. Microwave radiation provides an alternative to conventional oil-bath heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The absorption and transmission of the energy is completely different from the conventional mode of heating.[8–10] Microwave thermal effects are based on dielectric heating, that is, molecules exhibiting a permanent dipole moment tend to align to the applied electromagnetic field resulting in molecular rotations and collisions and thus in heat generation. As water and carbohydrates are polar molecules, having high dielectric losses, oligosaccharides dissolved in water are suitable chemical systems for microwave irradiation. Consequently, high demands in activation energy in the isomerization process can be completed in a very short time.

The interaction of metal ions with carbohydrates has been extensively studied for a long time.[11,12] One of the significant achievements in this field is the discovery of the isomerization of the carbohydrate carbon skeleton upon formation of molybdate complexes.[13–15] The selective *Bilik's* epimerization reaction[16] is preceded by the formation of complexes between aldoses and molybdate anions. Systematic studies of these molybdate complexes in aqueous solutions include a variety of monosaccharides, their derivatives as well as alditols.[17–21] General stereospecificity trends, as analyzed by aldose/epialdose[22] or 2-*C*-(hydroxymethyl)-aldose/2-ketose[23–25] mutual isomerizations promoted by Mo(VI), together with the knowledge of the structure of carbohydrate molybdate complexes, suggest that (1→6)-linked oligosaccharides could yield the corresponding isomers. Indeed, epimelibiose has been prepared from raffinose in a small yield.[26] This evidence, as well as our previous experiences with Mo(VI)-catalyzed reactions prompted us to study the transformations of (1→6)-linked disaccharides in detail especially under the conditions of a microwave field. Herein, we report the improved method on the microwave-accelerated transformation of disaccharides as well as examination of rare disaccharide preparation on a semipreparative scale using this approach. The benefits of stereospecific rearrangement as well as the behaviour of (1→2), (1→3) and (1→4)-linked disaccharides under identical conditions are discussed.

2. Results and discussion

Three (1→6)-linked disaccharides, melibiose, isomaltose and palatinose were chosen as substrates for comparison of

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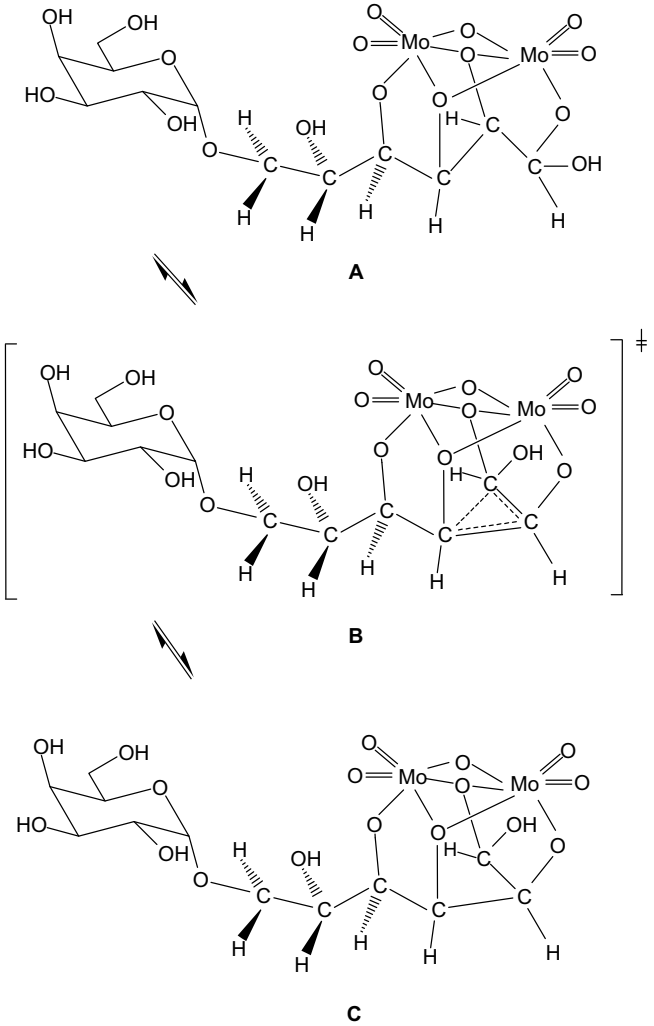
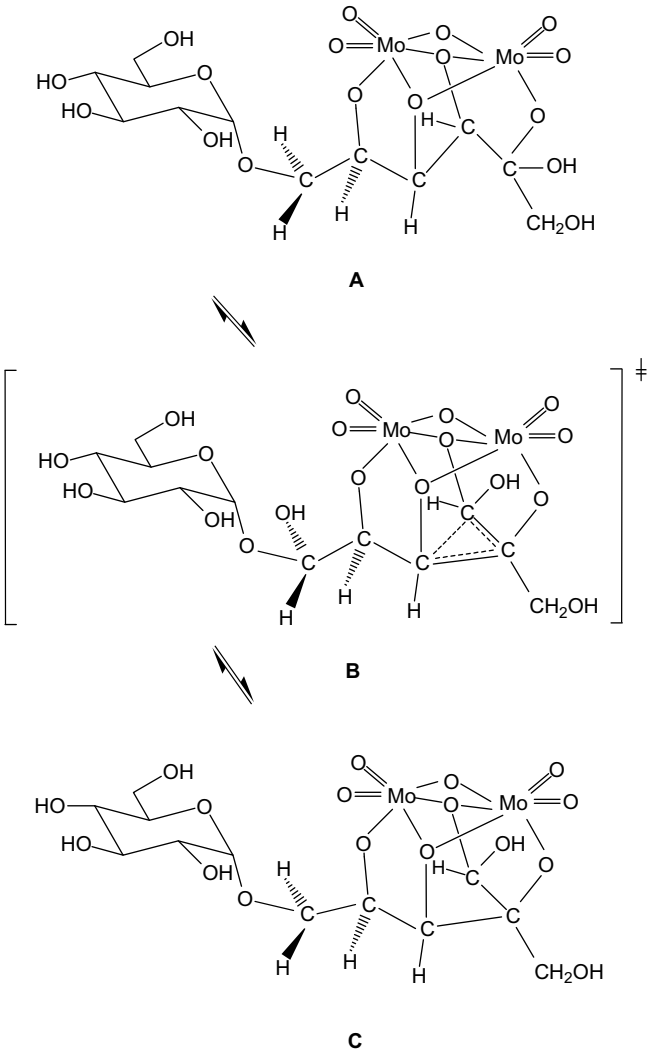
microwave-assisted reactions to conventionally oil-heated reactions. The reactions were performed under identical reaction conditions in order to make the comparison of the stereo/chemoselectivity, as well as isomerization process, more rigorous. The disaccharides studied were treated with the catalytic amount of molybdic acid in aqueous solution until the thermodynamic equilibrium mixtures of the two isomers were obtained. It was observed that melibiose (α-D-galactopyranosyl-(1→6)-D-glucose) and isomaltose (α-D-glucopyranosyl-(1→6)-D-glucose), disaccharides having D-glucose on the terminal, isomerize at C-2 of the reducing unit to afford epimelibiose (α-D-galactopyranosyl-(1→6)-D-mannose) and epiisomaltose (α-D-glucopyranosyl-(1→6)-D-mannose), respectively.

It is known that molybdate ions can form highly reactive catalytically active complexes with carbohydrates that promote an unusual stereospecific transformation. In the case of disaccharides, isomerization takes pace only in the reducing unit of the disaccharide molecule. Mutual interconversion of the OH groups at C-2 and C-3 of the terminal glucose unit is a consequence of the highly stereospecific carbon skeleton rearrangement that is taking place during the chelation of the sugar in the tetradentate dimolybdate complex. In the present case, the complexation of melibiose and isomaltose proceeds through the catalytically active dimolybdate complexes, which require four hydroxyl groups (C-1, C-2, C-3 and C-4) of the acyclic hydrated form of the terminal glucose unit (Scheme 1). In the dimolybdate complex of melibiose (Scheme 1A), rearrangement occurs through a transition state (Scheme 1B) in which C-1 and C-2 are enantiomeric. The bond formation between C-2 and C-3 regenerates the starting terminal aldose, while the bond formation between C-1 and C-3 produces the 2-epimer (Scheme 1C). The configuration at C-3 is maintained since bond breaking and bond formation occur on the same face of this carbon. Carbons C-1 and C-2 have the same hybridization in the transition state and form a transitory tricentric bond with C-3. We observed that this transformation proceeds efficiently in a microwave field yielding the desired isomers, epimelibiose (31%) and epiisomaltose (30%). We have suggested a possible mechanism for the isomerization of melibiose into epimelibiose on the basis of our experimental results (Scheme 1). The proposed mechanism could explain the transformation of melibiose and isomaltose to its isomeric analogues, epimelibiose and epiisomaltose, respectively.

Another example is palatinose (α-D-glucopyranosyl-(1→6)-D-fructose), having D-fructose as the reducing unit. This disaccharide isomerizes to a 2-*C*-branched disaccharide, α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose. The mechanism of this transformation is depicted in Scheme 2. The formation of the dimolybdate complex with the carbonyl-oxygen atom C-2 and the adjacent three hydroxylic oxygen atoms at C-3, C-4 and C-5 of the terminal fructose unit (Scheme 2A) leads to the transition state



Scheme 1.



Scheme 2.

Table 1
Mo(VI)-catalyzed isomerization of (1→6)-linked disaccharides in a microwave field and under conventional conditions

	Starting disaccharide	Product disaccharide	MW filed		Conventional heating	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	Melibiose α-D-Gal-(1→6)-D-Glc	Epimelibiose α-D-Gal-(1→6)-D-Man	5	31	600	16
2	Isomaltose α-D-Glc-(1→6)-D-Glc	Epiisomaltose α-D-Glc-(1→6)-D-Man	5	30	600	14
3	Palatinose α-D-Glc-(1→6)-D-Fru	α-D-Glc-(1→6)- 2-*C*-(HMe)-D-Rib	5	19	600	8

(Scheme 2B) in which the terminal saccharide functions as a bidentate ligand bound to the metal centre. The design of the ligand is a key issue for the catalytic process. The critical C-3—C-4 and new C-2—C-4 bond is formed stereospecifically. Dissociation of the complex produces either the starting palatinose or the isomeric α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose (Scheme 2C) generated by the stereospecific rearrangement. We observed that this transformation also afforded the desired α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose in good yield (19%).

Both transformations studied proceeded without any significant side reactions such as decomposition into monosaccharide components or formation of ketoses. The isomerization reaction progressed smoothly in a microwave field and reached thermodynamic equilibrium within 5 min (compared to 10 h required under conventional conditions, Table 1). The results suggest that the ability of molybdate ions to form complexes with a reducing unit of (1→6)-disaccharides and to promote the isomerization processes during microwave irradiation is improved. Fast complex formation, subsequent intramolecular rearrangement and release of the product disaccharide form the complex in good yields.

The identical experiments were conducted at 90 °C, for 10 h. using conventional oil-bath heating. Isomeric products were also obtained by this conventional method, however, the yields were markedly lower. The yield of epimelibiose was 16%, which is in accordance with the data already published.[26] The yield of epiisomaltose was 14% and the yield of α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose was only 8%.

As indicated from the data in Table 1, the methods have provided different yields of the products. The effect of microwave irradiation increases the yields of products up to 50%. In addition, the beneficial effect of microwaves is significant from a reaction kinetic point of view. The reaction time decreased from hours to minutes, which is about 120-fold shorter than in the case of conventional oil-bath heating. All these observations strongly suggest that the C-2 isomerization in the case of (1→6)-linked disaccharides proceeds through an intermediate dinuclear tetradentate molybdate complexes, where the reducing unit in an open-chain form is isomerized at C-2 through a stereospecific rearrangement of the carbon skeleton. This fact was confirmed during the study of the mechanism of mutual epimerization of aldoses[27] and isomerization of 2-*C*-branched aldoses and ketoses with isotopically labelled sugars.[28,29]

Intramolecular isomerization does not take place in the case of (1→2), (1→3) and (1→4)-linked disaccharides. Reaction mixtures obtained after treatment of saccharose (α-D-glucopyranosyl-(1→2)-β-D-fructose), turanose (α-D-glucopyranosyl-(1→3)-D-fructose), maltose (α-D-glucopyranosyl-(1→4)-D-glucose), lactose (β-D-galactopyranosyl-(1→4)-D-glucose) and cellobiose, (β-D-glucopyranosyl-(1→4)-D-glucose) with an aqueous solution of molybdic acid at elevated temperatures or in a microwave field consist only of corresponding monosaccharides and their epimers. This fact is clear due to known isomerization conditions. Only partial hydrolysis of glycosidic bonds is observed while subsequent epimerization of aldoses to the corresponding epialdoses takes place. Product distribution is in accordance with the current knowledge about the mechanism of this transformation. These disaccharides do not have a free hydroxyl group at C-2, C-3 or C-4 that is required for the complex formation and subsequent stereospecific rearrangement. As four *subsequent* hydroxylic groups of the sugar moiety are essential for complexation with the dinuclear tetradentate molybdate anion, in the case of (1→2), (1→3) and (1→4)-linked disaccharides the proper complex formation is precluded.

The microwave-assisted selective isomerization in (1→6)-linked disaccharide molecules readily provides access to its valuable isomers. This approach is of synthetic interest, providing biologically active sugars in a very simple manner. The particular attraction of this approach is that carbohydrates are used without any protection and no significant byproducts are present in the reaction mixtures. The product disaccharides were readily isolated from the reaction mixtures by ion-exchange chromatography. Further studies on the use of this approach are currently in progress and the results will be reported in due course.

3. Conclusion

We have demonstrated that (1→6)-linked disaccharides can be easily synthesized using the effect of Mo(VI) ions and a microwave field via the intramolecular isomerization of the carbon skeleton. Examples of chemical transformations producing higher yields in considerably (two orders) shorter reaction times, compared to traditional methods, are presented. The method was tested on the preparations of epimelibiose (α-D-galactopyranosyl-(1→6)-D-mannose), epiisomaltose (α-D-glucopyranosyl-(1→6)-D-mannose) and α-D-glucopyranosyl-(1→6)-2-*C*-(hydroxymethyl)-D-ribose from melibiose, isomaltose and palatinose, respectively. The method is straightforward and leads to rare disaccharides in a single step. This approach provides an excellent alternative to the classical methods in the chemical synthesis of rare carbohydrates.

4. Experimental

4.1. General experimental methods

Disaccharides, melibiose, isomaltose and palatinose were purchased from Fluka. 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 40 °C. The chemical shifts were referenced to internal TSP (D_2O). Presaturation of the residual HDO resonance was achieved by low-power irradiation and typically 8–16 scans were collected to achieve a good signal/noise ratio in the one-dimensional ^{1}H spectra. 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 hotstage microscope. Optical rotations were determined with an automatic polarimeter Perkin–Elmer Model 141 using a 10 cm, 1-mL cell. Experiments were carried out 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. Reaction of the (1→6)-linked disaccharide with Mo(VI) ions under microwave irradiation

The disaccharide (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 (Table 1). The composition of the reaction mixture was determined by ^1H NMR spectroscopy to determine the ratio of disaccharides present in the equilibrium mixture. The ion-exchange resin Amberlite IRA-400 in the $(HCO)_3^-$ form was used to remove the catalyst. The reaction mixture of melibiose/epimelibiose was fractionated by column chromatography on a Dowex 50W X8 in Ba^{2+} form with water as eluent. In the case of isomaltose and palatinose, the Dowex 50W X8 column in Ca^{2+} form and aqueous 0.001 M TEA as eluent were used. The yields of products are listed in Table 1.

4.3. Reaction of the (1→6)-linked disaccharide with Mo(VI) ions with conventional heating

The disaccharide (200 mg, 0.6 mmol) was dissolved in D_2O (2 mL) and molybdic acid (10 mg, 0.0617 mmol) was added. The reaction mixture was heated in an oil-bath at 90 °C for 10 h. The composition of the reaction mixture was analyzed by NMR spectroscopy measurements and ratio of disaccharide/epidisaccharide was determined by integration of selected resonances in ^1H NMR spectra. The reaction mixture was worked up as mentioned in the typical procedure. The yields of products are listed in Table 1.

4.4. Epimelibiose (α-D-galactopyranosyl-(1→6)-D-mannose)

Yield 31%; mp 200 °C; $[\alpha]_D$ = +121→+122 (*c* 1, H_2O), 24 h, that is in accordance with the literature.[30] δ_C (D_2O, 75.45 MHz): 99.11 (C-1′), 95.18 (C-1α), 94.83 (C-1β), 75.36 (C-5β), 74.13 (C-3β), 72.12 (C-2β), 71.84 (C-5′), 71.75 (C-5α), 71.57 (C-2α), 71.36 (C-3α), 70.41 (C-3′), 70.15 (C-4′), 69.39 (C-2′), 67.53 (C-4α), 67.27 (C-4β), 66.91 (C-6α, β), 62.06 (C-6′). HRMS *m/z* calcd for $C_{12}H_{22}O_{11}$, 342.2965; found, 365.2947 $[M+Na]^+$.

4.5. Epiisomaltose (α-D-glucopyranosyl-(1→6)-D-mannose)

Yield 30%; $[\alpha]_D$ = +90→+92 (*c* 1, H_2O), 24 h, that is in accordance with literature.[30] δ_C (D_2O, 75.45 MHz): 98.87 (C-1′), 97.00 (C-1β) 93.12 (C-1α), 76.88 (C-3β), 75.22 (C-5β), 74.98 (C-2β), 73.99 (C-3α), 73.99 (C-3′), 72.70 (C-2α), 72.40 (C-2′), 70.96 (C-5α), 70.44 (C-4′), 70.44 (C-5′), 70.44 (C-4β), 70.34 (C-4α), 66.62 (C-6α, β), 61.39 (C-6′). HRMS *m/z* calcd for $C_{12}H_{22}O_{11}$, 342.2965; found, 365.2945 $[M+Na]^+$.

4.6. α-D-Glucopyranosyl-(1→6)-2-*C*′-(hydroxymethyl)-D-ribose

Yield 19%; $[\alpha]_D$ = +100→+102 (*c* 1, H_2O), 24 h; δ_C (D_2O, 75.45 MHz): 102.12 (C-1α), 99.15 (C-1′) 98.30 (C-1β), 81.65 (C-2β), 81.05 (C-4β), 80.56 (C-4α), 78.62 (C-2α), 73.98 (C-3′β), 73.90 (C-3′α), 72.92 (C-2′β), 72.78 (C-2′α), 72.33 (C-5′), 72.03 (C-3β), 71.01 (C-3α), 70.46 (C-4′) 68.89 (C-6β), 67.26 (C-6α), 63.64 (*C*H_2(C-2)α), 63.31 (*C*H_2(C-2)β), 61.43 (C-6′). HRMS *m/z* calcd for $C_{12}H_{22}O_{11}$, 342.2965; found, 365.2943 $[M+Na]^+$.

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