Novel C-2 Epimerization of Aldoses and Stereoselective Uptake of One of the Epimeric Aldoses by Nickel(II) Complexes

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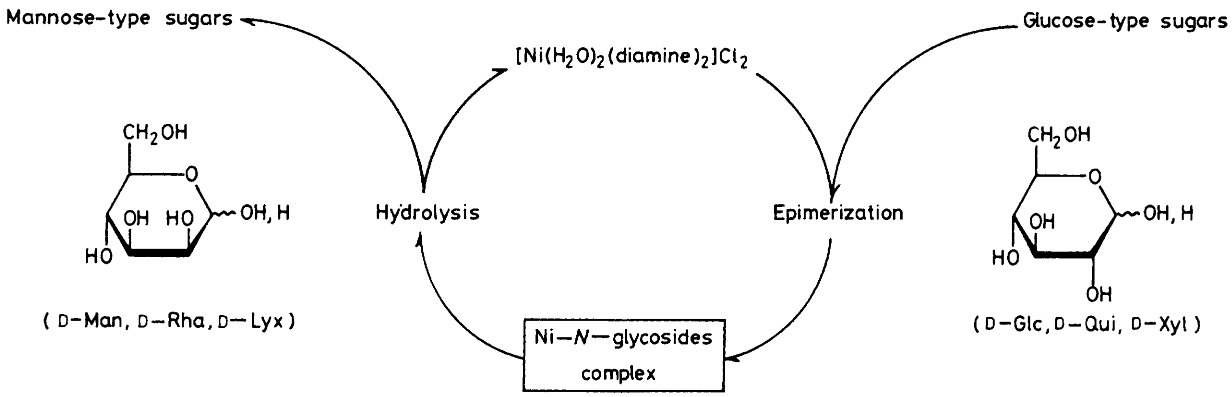
Aldoses are rapidly epimerized at C-2 in the presence of $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = *N,N,N'*-trimethylethylenediamine) and, of the two C-2 epimers, nickel(II) ions form complexes with only the mannose-type epimers (D-mannose, D-lyxose, and D- or L-rhamnose) stereoselectively.

It is of interest to develop methods whereby metals promote transformations of sugars. In order to elucidate carbohydrate–transition metal interactions, we have extensively studied the synthesis and characterization of transition metal complexes containing *N*-glycosides derived from the reaction of sugars and diamines.[1] Previously, when we used *N,N'*-dimethylethylenediamine (*N,N'*-Me_2en) as the diamine component, of many natural aldoses, only D-mannose gave a binuclear nickel(II) complex containing *N*-glycosides and we determined its crystal structure by *X*-ray crystallography.[2] These studies showed that the complex cation contains three mannose residues forming *N*-glycosides with *N,N'*-Me_2en.



Scheme 1. An aldose transformation cyclic system involving the process of C-2 epimerization of sugars and the stereospecific co-ordination of one of the C-2 epimeric aldoses from which the mannose-type sugars are recovered by hydrolysis. The diamine is *N*,*N*,*N*′-trimethylethylenediamine (tmen).

Two of these adopt the β-$^4C_1$-pyranose form and the other mannose residue adopts the unusual furanose form and links the two nickel atoms with an oxygen bridge *via* the C-3 hydroxy group. We think that the key to this stereoselective complexation lies in the bridging part of the mannofuranoside residue which seems to have a strong affinity for nickel(II) ions. In addition, when we used D-glucose as a starting sugar instead of D-mannose, a nickel(II) complex containing D-mannose was unexpectedly obtained although its yield was very low. Prompted by this knowledge, we have investigated the reactions of natural aldoses and nickel(II) complexes of diamines in order to develop suitable complexes for metal-assisted epimerization of monosaccharides and establish the stereoselective complexation of various aldoses. Simplifying the reaction between aldoses and diamines in the hope of abstracting the bridging part of the *N*-mannofuranoside residue as observed in the previous case,[2] we chose *N*,*N*,*N*′-trimethylethylenediamine (tmen) as the diamine component, which has one reaction point (secondary amino group) in the molecule.

To a methanolic solution of $[Ni(H_2O)_2(tmen)_2]Cl_2$† (1 equiv.) was added D-glucose (D-Glc‡) or D-mannose (D-Man‡) (1 equiv.). The solution was incubated at 60 °C for 3—4 min with stirring. Then the reaction mixture was loaded on an LH-20 gel permeation column. In both cases, the same green complex (**1**)§ was obtained as the only product containing sugar moieties. D-Mannose was the only sugar component in the product by h.p.l.c.¶[3] The green complex (**1**) is too hygroscopic to isolate as powder suitable for elemental analysis, but the results of our preliminary EXAFS study[4] suggest a nickel polynuclear complex with *N*-mannofuranoside bridging. From the complex (**1**) (after a few purification runs on LH-20 gel) D-mannose was easily obtained by hydrolysis¶[3] in 45—50% yield. When L-Rha, D-Qui, D-Lyx, and D-Xyl were used as the starting sugar, green complexes (**2**) and (**3**),§ containing only L(or D)-Rha and D-Lyx respectively, were obtained as purified solutions. These results implied the extensive occurrence of C-2 epimerization of aldoses during the reaction, so we investigated the ratios of C-2 epimers in the reaction mixtures¶[3] (Table 1), and it was revealed that the nickel(II) complexes of tmen promote C-2 epimerization of aldoses to provide a near-equilibrium mixture of C-2 epimeric aldoses rapidly and then nickel(II) ions form complexes only with the mannose-type C-2 epimers (D-Man, D-Lyx, and D,L-Rha) stereoselectively. The present epimerization proceeds without forming any detectable side reaction products including ketoses, and without any C–H proton exchange in a deuterium labelled solvent (CH_3OD). These observations indicate that the mechanism of this transformation is significantly different from the typical base-catalysed aldose–ketose isomerization.[5] The results of several blank tests|| suggest that a certain complex of Ni^{2+}, tmen, and aldose is the reactive species in this C-2 epimerization reaction, but details are not clear.

'Ni-tmen–D-Man'	'Ni-tmen–L (or D)-Rha'	'Ni-tmen–D-Lyx'
(**1**)	(**2**)	(**3**)

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† Satisfactory elemental analysis for the Ni^{II}-tmen complex was obtained.

‡ The following abbreviations are used; D-Glc, D-glucose; D-Man, D-mannose; D-Xyl, D-xylose; D-Lyx, D-lyxose; D-Qui, D-quinovose (6-deoxy-D-glucose); L-Rha, L-rhamnose (6-deoxy-L-mannose); D-Gal, D-galactose; D-Tal, D-talose; D-Rib, D-ribose; D-Ara, D-arabinose.

§ The concentrations of nickel ions in the methanolic solution of complex (**1**) were determined by atomic absorption spectra and monosaccharides were determined by h.p.l.c. (the ratio of nickel ions and monosaccharides in the solution is 3 : 2). Near-i.r., visible, and c.d. spectra of the complex (**1**) from D-glucose and from D-mannose in methanol and the ratios of monosaccharide contained in the two complexes are identical. The same facts were observed in the case of complexes (**2**) and (**3**).

¶ The green complexes or reaction mixtures were dissolved in 50 ml of water and were kept at pH 6.5 with 2 M H_2SO_4 for an hour at room temperature. Then the solutions were treated with excess of Dowex 50-X8 (H^+) and Dowex 1-X2 (HCO_3^-), and were assayed for monosaccharides with h.p.l.c.

Sugar analyses were performed with a TSK HLC-803D h.p.l.c. system using a column of anion exchange resin (TSK). Sugar components were eluted with 0.5 M borate buffer adjusted to pH 8.5 and fluorimetrically detected by the reaction with 2-cyanoacetamide.

|| Several blank tests were run as follows. Aldoses were treated with Ni^{2+} (1 equiv.); tmen (2 equiv.); NaOH (2 equiv.); Ni^{2+} (1 equiv.) + NaOH (2 equiv.); H_2SO_4 (1 equiv.) + tmen (2 equiv.), under the same reaction conditions described above. In no cases were the starting aldoses epimerized.

Table 1. Ratios of C-2 epimeric aldoses in the reaction mixtures and monosaccharides obtained from the nickel(II) complexes.

		Aldoses in the reaction mixtures		Monosaccharides obtained from the nickel(II) complexes (%)[d]	
Aldoses[a]	Conditions	Ratios of C-2 epimers[b] (%)[c]			
		Glc : Man			
D-Glc	60 °C 4 min	45 : 55	(94)	D-Man	(~45)
D-Man	60 °C 4 min	34 : 66	(93)	D-Man	(~50)
		Qui : Rha			
D-Qui	60 °C 4 min	55 : 45	(85)	D-Rha	(~30)
L-Rha	60 °C 4 min	55 : 45	(91)	L-Rha	(~30)
		Xyl : Lyx			
D-Xyl	60 °C 3 min	49 : 51	(79)	D-Lyx	(~30)
D-Lyx	60 °C 3 min	50 : 50	(72)	D-Lyx	(~30)

[a] Starting aldoses (1 equiv.) were treated with $[Ni(H_2O)_2(tmen)_2]Cl_2$ (1 equiv.) in methanol. [b] Ratios of C-2 epimers based on aldoses obtained from the reaction mixtures. [c] Yields of aldoses based on the starting sugars. [d] Yields of aldoses obtained from the nickel(II) complex (**1**), (**2**), or (**3**) based on the starting sugars.

Bilik and Haynes *et al.* reported the closely related reactions[6,7] in which, in mildly acidic solutions of molybdate, aldoses epimerize at C-2 over a long reaction time (90 °C, 2—13 h) with the formation of a thermodynamic equilibrium mixture of the two epimers. Contrary to this, the present reaction is very fast in mild basic conditions and involves the stereoselective uptake of the mannose-type C-2 epimers (depicted in Scheme 1). So this reaction has much potential for the synthesis of expensive and naturally rare aldoses including acid-unstable oligosaccharides from their C-2 epimers, as well as being of theoretical importance.

We are now trying to improve the stereospecific co-ordination of other aldoses** employing polyamines and metals and to clarify the detailed mechanism of this C-2 epimerization reaction.

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** When D-Gal, D-Tal, D-Ara, and D-Rib were used as the starting sugar, they were partially epimerized but gave two kinds of complex and the stereoselective complexation was not realized.

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