C-2 Epimerization of Aldoses promoted by Combinations of Metals and Diamines involving a Novel Rearrangement of the Carbon Skeleton

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Aldoses are epimerized at C-2 by combinations of certain metals (Ni^{2+}, Co^{2+}, Ca^{2+}, and Sr^{2+}) and diamines (*N,N,N'*-trimethylethylenediamine and *N,N,N',N'*-tetramethylethylenediamine), and a ^{13}C n.m.r. study reveals that a novel rearrangement of the carbon skeleton, the exchange of C-1 and C-2 atoms by inversion of the C-1–C-2 aldose fragment, is involved in this reaction.

Much attention has recently been focused on rare naturally occurring carbohydrates, with the elucidation of the biological functions of carbohydrates contained in glycoproteins, glycolipids, nucleic acids, and antibiotics. It is thus desirable to develop methods whereby metals promote transformation of sugars. Bilik *et al.* have shown that in mildly acidic solutions of molybdate, aldoses epimerize at C-2 with the formation of a thermodynamic equilibrium mixture of the two epimers.[1] However, the reaction proceeds slowly, with careful control of conditions (90 °C, 2—13 h, pH 4.5) being necessary, and yields of the mannose-type C-2 epimers (Man, Lyx, Rha, Tal, and Rib)† are comparatively low owing to their thermodynamic instability. Previously, we reported that aldoses are epimerized at C-2 in a very short time (60 °C, 3—4 min) with the nickel(II)–tmen complex, $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = *N,N,N'*-trimethylethylenediamine) and, of the two C-2 epi-

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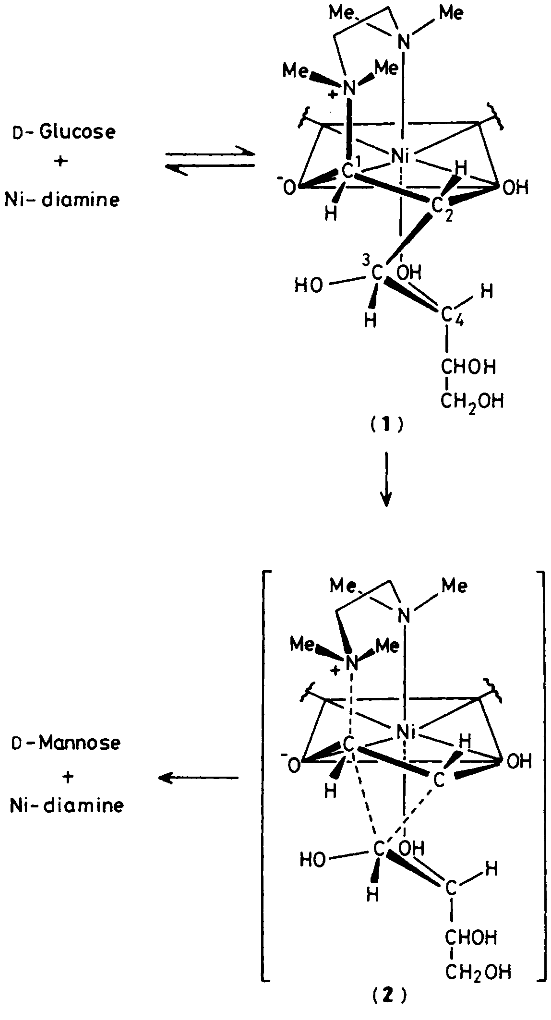
† The following abbreviations are used: D-Glc, D-glucose; D-Man, D-mannose; D-Xyl, D-xylose; D-Lyx, D-lyxose; L-Rha, L-rhamnose (6-deoxy-L-mannose); D-Tal, D-talose; D-Rib, D-ribose; D-Ara, D-arabinose.

Table 1. Results of C-2 epimerization of aldoses promoted by metals and diamines.

		D-Glucose (substrate)[a]		D-Mannose (substrate)[a]	
Metal ion[a]	Diamine[a]	Glc : Man[b]	(Aldoses, %)[c]	Glc: Man[b]	(Aldoses, %)[c]
Ni^{2+}	tmen	62 : 38	(91)	42 : 58	(86)
Ni^{2+}	tetmen	44 : 56	(98)	44 : 56	(94)
Co^{2+}	tmen	63 : 37	(75)	32 : 68	(72)
Co^{2+}	tetmen	80 : 20	(84)	7 : 93	(95)
Ca^{2+}	tmen	67 : 33	(86)	8 : 92	(87)
Ca^{2+}	tetmen	81 : 19	(91)	2 : 98	(95)
Sr^{2+}	tmen	81 : 19	(83)	14 : 86	(95)
Sr^{2+}	tetmen	97 : 3	(89)	2 : 98	(99)

[a] Substrates (1 equiv.) were treated with metal ions (1 equiv.) and diamines (2 equiv.) at 60 °C, for 5 min in methanol. [b] Ratios of C-2 epimers based on the aldoses obtained from the reaction mixtures. [c] Yields of aldoses obtained from reaction mixtures based on the starting aldoses.



Scheme 1

mers, nickel(II) ions form complexes with only the mannose-type epimers (Man, Lyx, and Rha) stereoselectively.[2] In this study, we report the C-2 epimerization of carbohydrates using various metal ions and *N*-substituted diamines, in order to elucidate the role of the metal centre and the diamine component.

Aldoses (D-Glc and D-Man) (1 equiv.) were treated with a metal chloride‡ (1 equiv.) and tmen (2 equiv.) in methanol, 60 °C, 5 min with stirring. The reaction mixture was dissolved in water and kept at pH 6.5 with 0.5 M H_2SO_4 or 1 M HCl for an hour at room temperature, and was assayed for monosaccharides with h.p.l.c.[2,3] after deionization. Of the metal ions used,‡ only Ni^{2+}, Co^{2+}, Ca^{2+}, and Sr^{2+} promote C-2 epimerization of aldoses (Table 1).§ Even when H_2MoO_4 (1 equiv.) was used as the metal centre, C-2 epimerization did not occur in this short reaction time. The reaction using Ca^{2+} proceeds slowly compared with that using Ni^{2+} ions, but this has advantages for practical use. The metal ions Ni^{2+}, Co^{2+}, Ca^{2+}, and Sr^{2+} are known to have a strong affinity for carbohydrates,[4] so it is assumed that a certain interaction or complexation between metal ions and aldoses is indispensable to the present epimerization. We then used *N,N,N',N'*-tetramethylethylenediamine (tetmen), *N,N,N',N'*-tetramethyltrimethylenediamine (tetmtn), and triethylamine as the amine component. Although aldoses do not form *N*-glycosides with these tertiary amines, the starting aldose was epimerized at C-2 with various combinations of metal ions (Ni^{2+}, Co^{2+}, Ca^{2+}, or Sr^{2+}) and tetmen (Table 1). In contrast, almost no epimerization occurred with Ni^{2+} (1 equiv.)–tetmtn (2 equiv.) and Ni^{2+} (1 equiv.)–triethylamine (4 equiv.), indicating that the length of the methylene carbon chain of the diamine is extremely important.

D-[1-^{13}C]Glucose was used as a starting sugar to clarify the mechanism of this C-2 epimerization, and the ^{13}C n.m.r. spectrum¶ of the reaction mixture shows two peaks at δ 97.4 and 93.6 for C-1 of β- and α-D-glucopyranose (substrate), respectively; two new resonances also appeared at δ 72.7 and 72.2 which were assigned to C-2 of β- and α-D-

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‡ Metal ions used are as follows: $NiCl_2\cdot 6H_2O$, $CoCl_2\cdot 6H_2O$, $CuCl_2\cdot 2H_2O$, $FeCl_2\cdot 4H_2O$, K_2PdCl_4, K_2PtCl_4, $MnCl_2\cdot 4H_2O$, $CrCl_3\cdot 6H_2O$, $RhCl_3\cdot 3H_2O$, $RuCl_3\cdot 3H_2O$, NaCl, KCl, RbCl, CsCl, $MgCl_2\cdot 6H_2O$, $CaCl_2\cdot 2H_2O$, $SrCl_2\cdot 6H_2O$, $BaCl_2\cdot 2H_2O$, $ZnCl_2$, $AlCl_3$.

§ Other aldoses (Xyl, Lyx, Rib, Ara, and Rha) were also epimerized at C-2 under these conditions, the results of which will be listed in our subsequent full report.

¶ ^{13}C N.m.r. spectra were obtained at 100 MHz with a JEOL GX-400 superconducting Fourier transform spectrometer and chemical shifts are given relative to internal Me_4Si by setting spectral parameters to the anomeric resonance of β-D-[1-^{13}C]glucopyranose at δ 97.4.[5] The C-1 resonances of β- and α-mannopyranose show large one-bond C–C coupling constants (42.7 and 46.4 Hz, respectively), as expected for a 2-^{13}C-enriched aldose.

mannopyranose, respectively.[5] This observation demonstrates that the present reaction involves a novel exchange of C-1 and C-2 atoms by inversion of the C-1–C-2 fragment. In the light of these results, we propose a possible mechanism for the epimerization in the Ni^{2+}–diamine–D-glucose system in Scheme 1: *i.e.* D-glucose (substrate) reacts with the diamine to give the carbinol–ammonium-like adduct (not *N*-glycoside[6]) which forms the reactive complex (**1**)** with Ni^{2+}. In this complex, C-2 epimerization can occur through a transition state (**2**), in which C-2–C-3 bond breaking and C-1–C-3 bond formation take place simultaneously, accompanied by elimination of the diamine residue. The product D-mannose is then disconnected from the reactive complex. Although this novel rearrangement was observed in the C-2 epimerization by molybdate,[7] the present reactions provide the first example of its occurrence using metals and nucleophilic diamines under mild basic conditions; this method might be developed to provide a general 1,2 carbon shift reaction of carbohydrates with metal complexes.

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Related work is reported in the following communication.[8]

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** The detailed structure of the reactive complex (**1**), *e.g.* whether it is mononuclear or binuclear, is unknown. However, as far as the aldose–diamine part is concerned, the mechanism is consistent with the experimental observations. D-Mannose is also transformed to D-glucose through a similar path, and the reactive complex containing D-mannose residue is thought to be diastereoisomeric to that of D-glucose (**1**).