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C-2 Epimerization of Aldoses Promoted by Combination of Monoamines and Alkaline Earth or Rare Earth Metal Ions, Involving a Rearrangement of the Carbon Skeleton

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Aldoses are rapidly epimerized at C-2 by combination of alkaline earth or rare earth metal ions (Ca^{2+}, Sr^{2+}, Pr^{3+}, or Ce^{3+}) and monoamines (triethylamine etc.). ^{13}C NMR studies using [1-^{13}C]-D-glucose of the Ca^{2+} system revealed that this reaction proceeds via the stereospecific rearrangement of carbon skeleton.

We have recently reported the novel C-2 epimerization of aldoses promoted by combination of various metal ions (Ni^{2+}, Co^{2+}, Ca^{2+}, or Sr^{2+}) and diamines, which proceeds rapidly under the mild basic conditions like biological reactions.[1,2] The ^{13}C NMR studies of the nickel(II)-diamine system (diamine = N,N,N'-trimethylethylenediamine (tmen) and N,N,N',N'-tetramethylethylenediamine (tetmen)) using ^{13}C enriched D-glucose surprisingly revealed that the C-2 epimerization involves the novel stereospecific rearrangement of carbon skeleton or 1,2-carbon shift,[2,3] and we proposed a possible mechanism involving the nickel(II)-diamine-aldose intermediate complex (Fig. 1).[2] In the proposed intermediate complex, diamines are thought to play two important roles; (a) anchoring aldoses to metal centers (because aldoses have little affinity to nickel(II) ions by themselves[4]), and (b) activation of carbonyl carbon with the nucleophilic addition. From all these considerations it can be expected that combination of certain metal ions having significant affinity for aldoses and nucleophilic reagents will promote the similar C-2 epimerization.

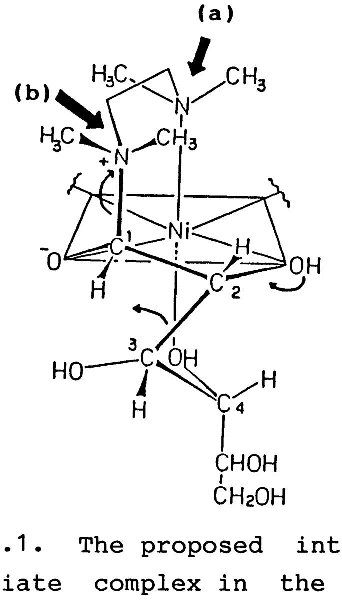


Fig.1. The proposed intermediate complex in the C-2 epimerization promoted by nickel(II) diamine complexes.

Table 1. Yields of C-2 Epimeric Aldoses Obtained from the Reaction by Metal Ions and Nucleophilic Reagents

No	Metal ion[a)]	Nucleophilic reagent[a)]	D-Glucose(substrate)[a)]		D-Mannose(substrate)[a)]	
			D-Man(%)[b)]	D-Glc(%)[c)]	D-Glc(%)[b)]	D-Man(%)[c)]
1	Ni^{2+}	Et_3N	trace	99	0	100
2	Ca^{2+}	Et_3N	38	32[d)]	10	74
3	Ca^{2+}	Et_2NH	38	25[d)]	17	66
4	Ca^{2+}	$(i\text{-}Pr)_2NH$	37	33[d)]	17	62
5	Ca^{2+}	$(CH_3)_2NCH_2CH_2OH$	18	66	trace	86
6	Ca^{2+}	$NH_2CH_2CH_2OH$	14	63	6	78
7	Sr^{2+}	Et_3N	15	65	12	71
8	Pr^{3+}	Et_3N	7	70	2	78
9	Pr^{3+}	$(CH_3)_2NCH_2CH_2OH$	5	78	2	72
10	Ce^{3+}	Et_3N	5	74	2	74

a) Starting aldoses were treated with metal ions (1 equiv.) and nucleophilic reagents (2 equiv.) in methanol at 60 °C for 5 min. b) Yields of C-2 epimers based on the starting aldoses. D-Man = D-mannose, D-Glc = D-glucose. c) Yields of recovered starting aldoses. d) D-Fructose was also detected (see Ref. 7).

In this study, we examined the C-2 epimerization of aldoses using some alkaline earth and rare earth metal ions which have much more affinity for carbohydrates than nickel(II) ions,[4,5)] and monoamines and their derivatives.

Aldoses (D-glucoses and D-mannose) (1 equiv.) were treated with metal chlorides (1 equiv.)[6)] and various nucleophlic reagents (2 equiv.)[6)] in methanol at 60 °C for 5 min with stirring. Then the reaction mixture was dissolved in water and the pH of the solution was adjusted to be 6.5 with 1 M HCl. The solution was kept at room temperature for an hour. Monosaccharides contained in the solution were analysed by HPLC[1,2)] after deionization, and the results worth noting are listed in Table 1.[6)] Among some alkaline earth and rare earth metal ions, only Ca^{2+}, Sr^{2+}, Pr^{3+}, and Ce^{3+} proved to be effective with monoamines and aminoalcohols. These results interestingly reflect the characteristics of metal centers in contrast with the fact that no C-2 epimerization was observed in the Ni^{2+} -monoamine or -aminoalcohol systems. Especially, Ca^{2+}-Et_3N (triethylamine) system has much advantage for the practical use, although some defects were observed; low yields of C-2 epimeric aldoses compared with those in Ni(II)-diamine systems, and ketose (D-fructose) formations as by-products.[7)]

To confirm the detailed paths in the present reaction, we used [1-^{13}C]-D-glucose as a starting sugar and analysed the products in the reaction mixture. [1-^{13}C]-D-Glucose was treated with $CaCl_2 \cdot 2H_2O$ (1 equiv.) and Et_3N (2 equiv.) for 5 min at 60 °C, and purified by the same method described above. The 100 MHz ^{13}C NMR spectrum of the purified reaction mixture is given in Fig. 2. Besides the peaks at 97.4 and 93.6 ppm (β, and α-D-glucopyranose), four new resonances appeared at 72.7, 72.2, 65.4, and 64.4 ppm, and no other significant peak was observed.[8)] Large two peaks at 72.7 and 72.2 ppm were assigned to those for C-2

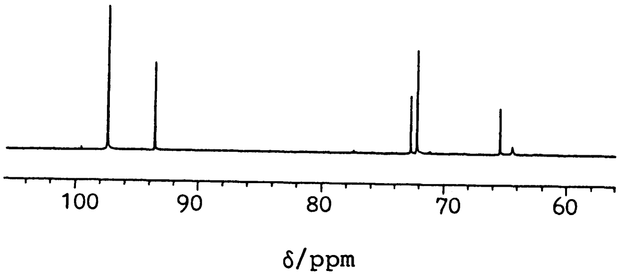
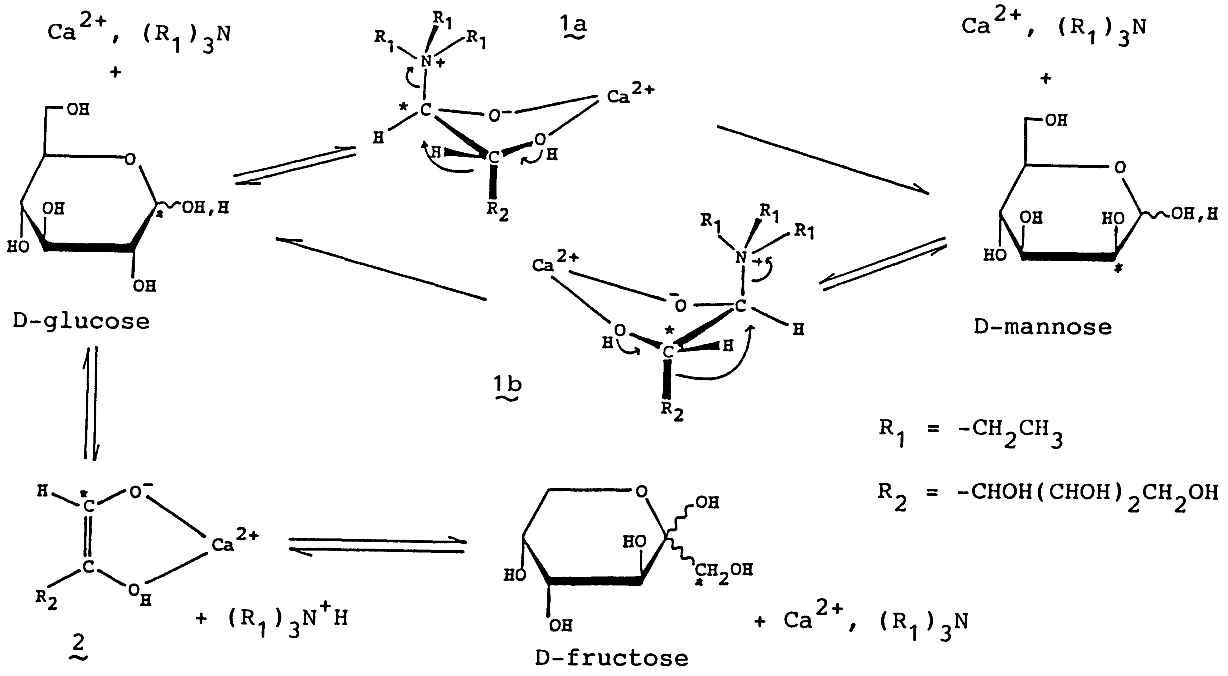


Fig.2. 100 MHz ^{13}C NMR spectrum of the product mixture obtained from the reaction of [1-^{13}C]-D-glucose with Ca^{2+} and Et_3N.

of β- and α-D-mannopyranose and small peaks at 65.4 and 64.4 ppm were assigned to those for C-1 of β-D-fructopyranose and β-D-fructofuranose, respectively,[8)] which were consistent with the results of HPLC analyses. This observation indicates that in the Ca^{2+}-Et_3N-D-glucose reaction system, a novel C-2 epimerization of aldoses involving the exchange of C-1 and C-2 atoms by inversion of the C-1-C-2 aldose fragment and a ketose formation without rearrangement of carbon skeleton exclusively occurred at this stage. The former is the same type rearrangement as observed in the case of nickel(II)-diamine complex[2)] and molybdate.[3)] On the basis of these results, we propose a plausible mechanism for the C-2 epimerization and the aldose-ketose isomerization (Scheme 1). Aldoses are epimerized through intermediate complexes (**1**) in which starting aldoses might attach to Ca^{2+} ions in an open chain form and could be fixed their conformations suitable for the stereospecific rearrangement. As for the ketose formation (by product), it proceeds via an ene-diol intermediate forming a chelate with Ca^{2+} (**2**) promoted by the monoamine which acts as a base catalyst.[9)]



Scheme 1.

In this study, it was revealed that aldoses are epimerized at C-2 under mild conditions by combination of alkaline earth or rare earth metal ions and monoamines through the stereospecific rearrangement of carbon skeleton. Analogous C-2 epimerization might occur in biological systems, since Ca^{2+} ions and simple amine residues are often observed in such systems. In addition, the Ca^{2+}-Et_3N system is expected to have much potential for the syntheses of naturally rare mannose-type aldoses and alditols from the industrial point of view.

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6) Metal ions and ligands used are as follows; (metal) $CaCl_2 \cdot 2H_2O$, $SrCl_2 \cdot 6H_2O$, $BaCl_2 \cdot 2H_2O$, $MgCl_2 \cdot 6H_2O$, $PrCl_3 \cdot 7H_2O$, $CeCl_3 \cdot 7H_2O$, $LaCl_3 \cdot xH_2O$; (nucleophilic reagents) Et_3N, Et_2NH, $(i\text{-}Pr)_2NH$, $(CH_3)_2NCH_2CH_2OH$, $(CH_3)NHCH_2CH_2OH$, $NH_2CH_2CH_2OH$, $SHCH_2CH_2OH$, $SHCH_2CH_2SH$, $HOCH_2CH_2OH$, and $HOCH_2CH_2OCH_2CH_2OH$. When $SHCH_2CH_2OH$, $SHCH_2CH_2SH$, $HOCH_2CH_2OH$, and $HOCH_2CH_2OCH_2CH_2OH$ were used, no epimerization of aldoses was observed.
7) The yields of D-fructose obtained from the reaction of D-glucose with Ca^{2+}-Et_3N, Et_2NH, and $(i\text{-}Pr)_2NH$ were 18, 23, and 23%, which were determined by HPLC with an electrochemical detector (N. Watanabe, G. Toda, and Y. Ikeda, Bunseki Kagaku, 33, E241 (1984)).
8) Carbon-13 NMR spectra were obtained at 100 MHz with a Jeol GX-400 superconducting FT spectrometer and chemical shifts are given relative internal TMS by setting spectral parameter to give the anomeric resonance of β-[1-^{13}C]-D-glucopyranose at 97.4 ppm. T. E. Walker, R. E. London, T. W. Whaley, R. Barker, and N. A. Matwiyoff, J. Am. Chem. Soc., 98, 5807 (1976); G. A. Morris and L. D. Hall, ibid., 103, 4703 (1981).
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