

Molecular Recognition Ability of a Nickel(II) Complex: Effect of Chirality of Diamine Ligand in Aldose Epimerization

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The complex composed of nickel(II) and the optically active *N,N'*-diethylcyclohexane-1,2-diamine (chxn) showed ability to recognize the shape of molecules in terms of the configuration of the various OH groups in aldoses during the epimerization of D-glucose to D-mannose.

During our studies on the epimerization at C-2 of aldohexoses and aldopentoses by nickel(II)-diamine systems, it became apparent that during the reaction, (1-¹³C)-D-glucose (1*-Glc) changed into (2-¹³C)-D-mannose (2*-Man) not *via* the so-called ene-diol rearrangement (Lobry de Bruyn, Alberta van Ekenstein rearrangement) but *via* stereospecific rearrangement of the carbon skeleton.¹ It was also elucidated that the coordination state of the complex consisting of three units, the metal, diamine and sugar, played an important role in this reaction. Based on these findings, a large number of approaches were comprehensively studied to clarify the influence of conditions on the epimerization processes.²⁻⁴

This C-2 epimerization is known to take place very readily and rapidly at 65 °C in methanol. When this reaction was carried out at low temperature, the equilibrium state of the epimerization was controlled successfully. The most significant result of this work is that the reaction system in this study showed molecular recognition ability, that is, the composition of the mixture of the two epimers could be regulated by nickel complex systems having an appropriate ligand.

We studied the epimerization efficiency using the optically active *N,N'*-diethylcyclohexane-1,2-diamine (chxn) as a ligand at different temperatures. The influence of the chirality of the ligand in the nickel(II) complex upon epimerization is discussed in this paper. The object of this report is to clarify how this difference in optical isomerism affects the equilibrium between two epimers, glucose and mannose. In addition, the influences of ligand structure, reaction temperature and reaction time on the kinetics and thermodynamics of the reaction have been studied.

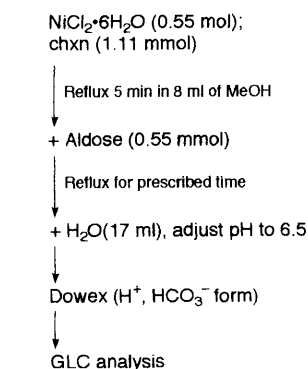
Epimerization and analysis of the reaction mixture were conducted in a manner similar to that described previously,⁴ except for the reaction temperature and time. The procedures shown in Scheme 1 were applied.

A cyclohexane-1,2-diamine (chxn) derivative was chosen as the ligand because of its structural similarity with ethylenediamine (en) which showed the highest epimerizing ability in previous studies. The optically active chxn was obtained by resolution of the diastereoisomers obtained by the reaction of L-tartaric acid and the primary diamine.⁵ *N,N'*-Diethylated chxn was prepared by *N*-acetylation of the optically resolved chxn, followed by reduction of acetyl groups. The optical

purity of chxn samples was confirmed by comparison of their specific rotations with literature data. They were in good agreement with reference values.⁶

The progress of the epimerization of glucose and mannose with time at 0 °C is shown in Fig. 1, and results at 65, 30 and 0 °C are summarized in Table 1. As shown in Fig. 1, the final solution compositions were almost identical (equilibrium) when either glucose or mannose was used as the starting sugar. The equilibrium was attained smoothly within 5 min at 65 and 30 °C. When *N,N'*-dialkylcyclohexanediamine was used as a ligand the corresponding ketose, fructose, was not obtained from the starting glucose or mannose. This means that the product solution consisted of only the starting and epimerized aldoses.

As shown in Table 1, it was confirmed that at 65 °C the chirality of the ligand diamine employed had no significant effect on the epimerizations. At 30 °C there were small differences, but the influence of chirality was not readily apparent. When the reaction was carried out at 0 °C, the



Scheme 1 Epimerization sequence

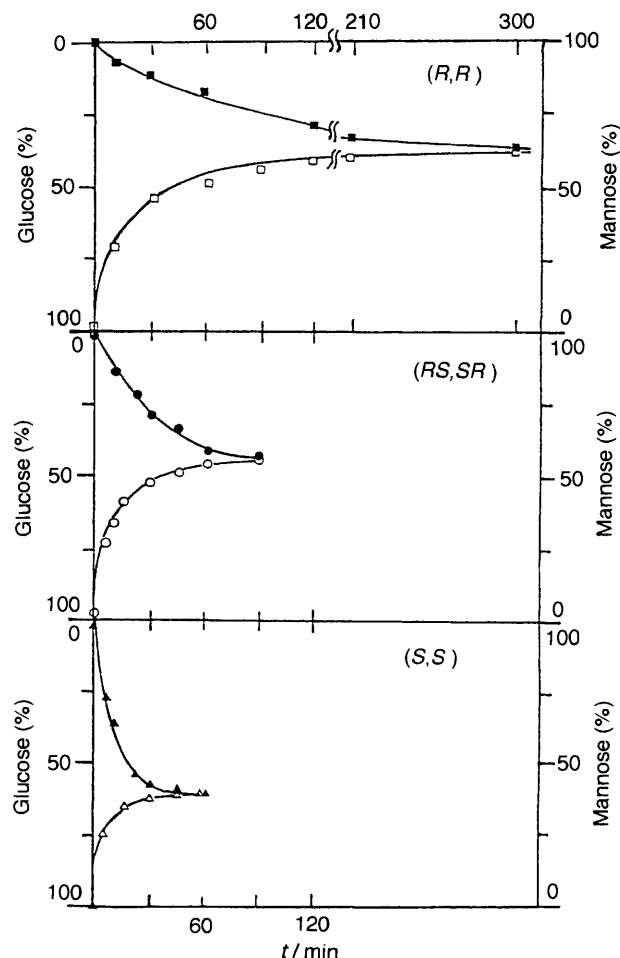


Fig. 1 Time course of the epimerization of 0 °C for Glc (□, ○, △) and Man (■, ●, ▲) with chxn ligands possessing (*R,R*), (*RS,RS*) and (*S,S*) absolute configurations

Table 1 Epimerization of glucose and mannose at various temperatures using racemic and optically active chxn ligands

Chirality of chxn	T/°C	t/min	Glc. ^a to		Man. ^a to	
			Glc.	Man. ^b	Glc.	Man. ^b
<i>R,R</i>	65	5	55.3	44.7	52.5	47.5
Racemate	65	5	54.2	45.8	57.5	42.5
<i>S,S</i>	65	5	53.3	46.7	51.7	48.3
<i>R,R</i>	30	5	52.6	47.4	46.8	53.2
Racemate	30	5	54.3	45.7	49.1	50.9
<i>S,S</i>	30	5	58.4	41.6	53.3	46.7
<i>R,R</i>	0	300	37.5	62.5	36.0	64.0
Racemate	0	90	45.4	54.6	44.7	55.3
<i>S,S</i>	0	60	60.4	39.6	60.0	40.0

^a Glucose and mannose were epimerized as starting substrates.

^b Composition of product (%). The corresponding ketose, fructose, was not observed in any experiments.

differences in the rate of epimerization and equilibrium became more distinct.

The epimerization of glucose at 0 °C using chxn with the (*R,R*)-absolute configuration was found to give a greater yield of the mannose epimer, although a longer time was required to reach equilibrium. When we ran the epimerization with the (*S,S*)-isomer, a smaller proportion of mannose was formed and the reaction required a shorter time to reach the equilibrium. On the other hand, with mannose as starting compound, the epimerizing activity of the reaction system was specifically stimulated by the (*S,S*)-isomer. The largest

amount of epimer was obtained in the shorter time. The racemic ligand showed intermediate properties between those of the optically active ones.

The equilibrium of the reaction system shifted in accordance with the chirality of the diamine ligand employed. This is the first example of the observation of the molecular recognition ability of a complex which depends on the effect of the chirality of the ligand upon the epimerization of aldoses. The recognition of such steric effects in the coordination of these complexes could be obtained in a relatively straightforward manner because of the unique geometry of the six-membered ring. The existence of two axial or equatorial positions, which are fixed by the ring structure, is a prime requisite for molecular recognition.

Received, 25th February 1991; Com. 1/00903F

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