Epimerization of Aldoses Catalysed by Self-organized Metallomicelles in an Aqueous Solution

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Nickel(II) complexes coordinated with long chain *N*-alkylated ethylenediamine ligands were synthesized. It was found that the complexes possessed a marked C-2 epimerization activity for aldoses in aqueous media. In contrast, a short chain diamine nickel(II) complex had little activity. The agreement between the formation of micelles and the enhancement of epimerization was clearly recognized. Amphiphilic complexes formed 'metallomicelles' which coordinated the aldoses and produced a new ternary complex composed of nickel, diamine and sugar. The stereospecific epimerization occurred in this aggregate accompanied by carbon skeleton rearrangement. One explanation for the high epimerizing ability of the amphiphilic nickel complex is the accumulation effect of nickel ion and ethylenediamine at the micelle surface.

Since the epimerizing ability of Ni-diamine complexes was first recognized, this reaction has been extensively investigated. It was proven that the epimerization of aldose at C-2 proceeded *via* stereospecific rearrangement of the carbon skeleton, that is, from $[1-^{13}C]$-D-glucose into $[2-^{13}C]$-D-mannose and *vice versa*. It was distinctly different from the so-called Lobry Alberda rearrangement by reversible enolization (LA rearrangement or enediol rearrangement).[1] Based on this finding, a number of experiments were carried out to clarify the influence of the reaction conditions, such as the structure of ligand and the chirality of the diamine.[2-4]

In recent years, reactions carried out in a micellar solution have attracted increasing interest, as organized molecular aggregates can act as mimics of biological systems. Such reactions as hydroxylation of benzene,[5] debromination of bromocarboxylic acid[6] and phosphate ester hydrolysis,[7] have been carried out in molecular aggregates.

In this study, we have prepared a homologous series of Ni-ethylenediamine complexes of various *N*-alkyl chain length, and discuss the influence of the hydrophobicity of the complex ligand upon the epimerization in aqueous media.

Results and Discussion

Progress of the Epimerization.—Analytical results and yields of the epimer are given in Table 1. For the epimerization of aldohexoses, fructose was produced as a sole by-product. For the aldopentoses, the product contained corresponding ketose, other complicated sugars, and decomposed compounds, which were impossible to identify, in addition to original raw materials and the epimerized aldoses.

The results are also illustrated graphically in Fig. 1. They show the degree of epimerization at 80 °C for 20 min as a function of alkyl group chain length of *N,N*-dimethyl-*N'*-alkylated ethylenediamine (1,1,*n'*-en)* at a nickel complex concentration of 67 mmol dm⁻³.

An equilibrium between the C-2 epimers, where the final solution composition was almost identical whether D-glucose or D-mannose was used as a starting sugar, was smoothly attained as longer chain length *N*-alkylated ethylenediamines such as 1,1,16'-en or 1,1,18'-en were used as ligands of the Ni complex.
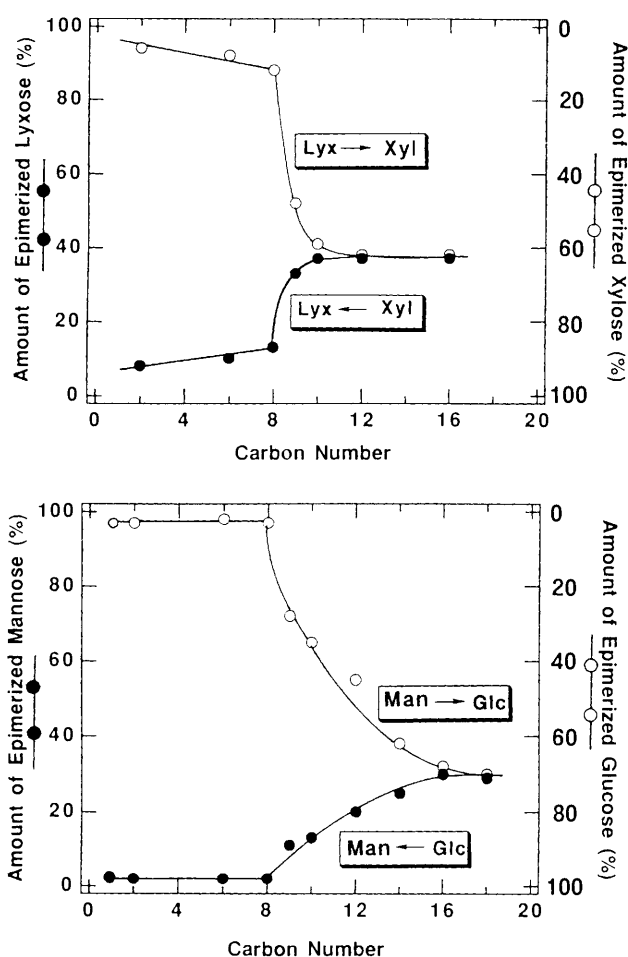

Fig. 1 Influences of the carbon number in Ni-1,1,*n'*-en complex on the epimerization between glucose and mannose (bottom) and between xylose and lyxose (top)

As Fig. 1 shows, the yield of C-2 epimer increased with the carbon chain length of the diamine irrespective of which aldose was subjected to the reaction conditions. The epimerization increased critically when the *N'*-alkyl group became longer than octyl (1,1,8'-en) and the epimerization curves shifted to higher values to attain equilibrium with increasing alkyl chain length. A dramatic difference was observed between the yields

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* 1,1-refers to *N,N*-dimethyl, *n'* refers to the carbon number of the *N'*-alkyl chain.

Table 1 Epimerization products from glucose, mannose, xylose and lyxose

Ligands	Substrate	Products (%)			Substrate	Products (%)			
		Glc	Man	Fru		Xyl	Lyx	Xylu^a	Others
1,1,1'-en	Glucose	95	2	3					
	Mannose	3	90	7					
1,1,2'-en	Glucose	97	2	1	Xylose	84	7	5	4
	Mannose	2	95	3	Lyxose	5	75	10	10
1,1,6'-en	Glucose	97	2	1	Xylose	82	9	6	3
	Mannose	2	95	3	Lyxose	7	76	12	5
1,1,8'-en	Glucose	97	2	1	Xylose	75	11	6	8
	Mannose	3	95	2	Lyxose	10	75	9	6
1,1,9'-en	Glucose	87	11	2	Xylose	58	29	6	7
	Mannose	27	69	4	Lyxose	42	45	8	5
1,1,10'-en	Glucose	87	13	0	Xylose	55	33	5	7
	Mannose	34	63	3	Lysose	53	37	3	7
1,1,12'-en	Glucose	80	20	0	Xylose	56	33	5	6
	Mannose	45	55	0	Lyxose	54	33	7	6
1,1,14'-en	Glucose	75	25	0					
	Mannose	61	37	2					
1,1,16'-en	Glucose	69	29	2	Xylose	56	33	5	6
	Mannose	67	32	1	Lyxose	57	35	4	4
1,1,18'-en	Glucose	71	29	0					
	Mannose	69	29	2					

^{a} Xylulose.

R: —CH(OH)CH(OH)CH₂OH, —CH(OH)CH₂OH
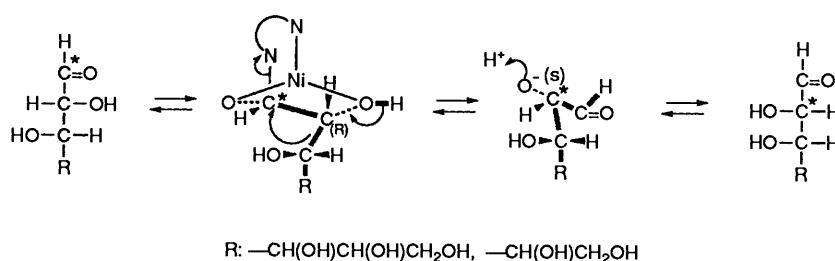
Scheme 1 Mechanism of the epimerization by the amphiphilic Nickel complex

[1-¹³C]-Glc

[2-¹³C]-Man

100   80   60

δ
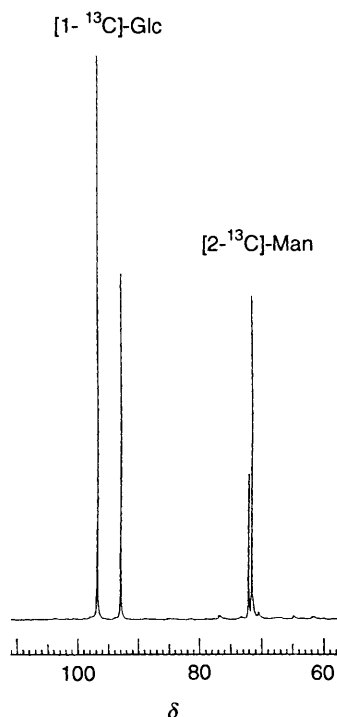
Fig. 2 ¹³C-NMR spectrum of the reaction product derived from [1-¹³C]-glucose

of epimers, depending on the hydrophobicity of the diamine complex applied. Epimerization was observed in the hydropho-

bic complex system (ligands 1,1,9'-en–1,1,18'-en) with yields of 30–70%, approximately 15–35 fold greater than that observed in the hydrophilic complex system (ligands 1,1,1'-en and 1,1,2'-en), both in aldohexoses and aldopentoses.

The influence of pH of the medium on the extent of epimerization was investigated. The pH of the aqueous solutions containing prescribed nickel chloride and ethylenediamine derivative was measured at 25 °C with a TOA HM-30S pH meter, and the results were as follows: 1,1,2'-en, pH 9.1; 1,1,8'-en, 8.6; 1,1,9'-en, 8.0; 1,1,12'-en, 7.4. The pH of the solution decreased as the alkyl chain length increased. A clear relationship between the rate of the epimerization and pH of the system could not be recognized.

According to the stereospecific epimerization mechanism, which was introduced and demonstrated in the previous paper,[1] the coordination of aldose to a Ni²⁺-diamine complex is crucial to this reaction. The stereospecific rearrangement occurred in the ternary complex system (Scheme 1) composed of Ni²⁺, diamine and sugar. It was demonstrated that the epimerization in aqueous media proceeded via a similar mechanism in methanol solution. The rearrangement may take place via a Ni²⁺-chelated five membered intermediate, where the migration occurs with an antiperiplaner alignment to the leaving diamine ligand giving inversion of configuration at C-2.

Fig. 2 shows the ¹³C NMR spectrum of the product mixture derived from [1-¹³C]-Glc. The peaks at 92.7 and 96.9 ppm were assigned to C-1 of α- and β-glucose, and 72.0 and 72.6 ppm to C-2 of α- and β-mannose, respectively. Epimerized mannose possesses carbon labelled at C-2, showing that the carbon sequence of aldose was rearranged between C-1 and C-2.

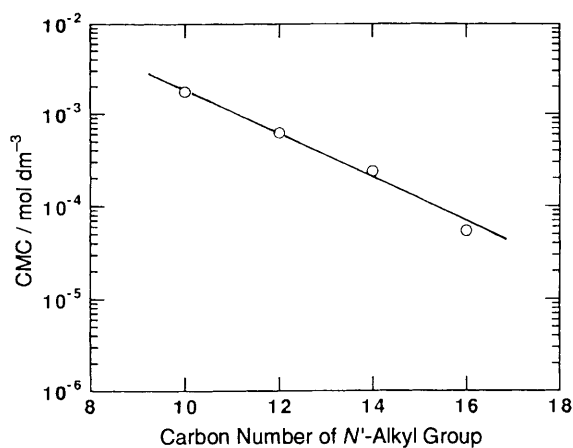The introduction of hydrophobicity into the aqueous

Fig. 3 Effect of length of the hydrophobic N'-alkyl group on the critical micelle concentration on the carbon number in ligands, $1,1,n'$-en
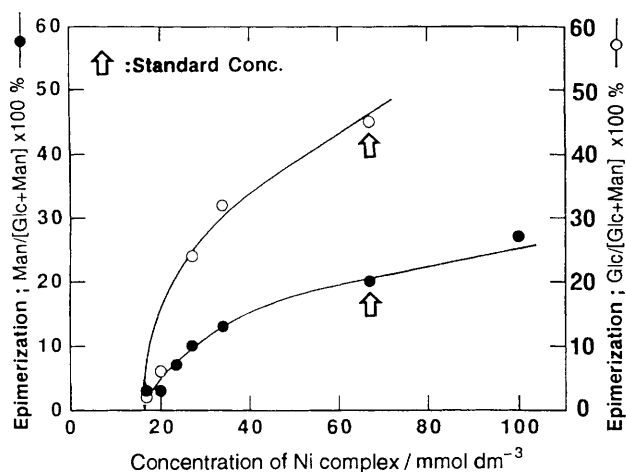

Fig. 4 Influences of the concentration of the Ni complex on the epimerization

reaction system seemed to be important to attain effective epimerization. Aggregation of complex and hydrophobic interaction due to their amphiphilic properties played a key role for the coordination of aldose. Possible reasons for the high epimerizing ability of amphiphilic nickel complex include enhanced concentration of nickel ion and ethylenediamine by a metal complex core structure on the micelle surface, which would strengthen the coordination of aldose to nickel complex. The integrated effect of an active site was responsible for the pronounced epimerization.

In contrast, the nickel complex coordinating shorter chain alkylated diamines showed less epimerization, although they allowed the substrate sugar to attain equilibrium in methanol.[2] They would be homogeneously dissolved in the matrix, and be strongly hydrated. The coordination of substrate sugar to the complex, which is a key process in epimerization, was inhibited by hydration.

Formation of Metallomicelles.—It was suggested that significant enhancement of the epimerization was attributable to the formation of metallomicelles in the reaction system. To confirm the existence of the micelles, the surface tension of the reaction system was measured. It was confirmed that the hydrophobic Ni-diamine complex containing alkyl chains longer than decyl formed micelles, whereas Ni-diamine complex containing alkyl chains shorter than nonyl formed no micelles. It should be emphasized that such formation of micelles was in accordance with the progress of epimerization. The fact that a nickel
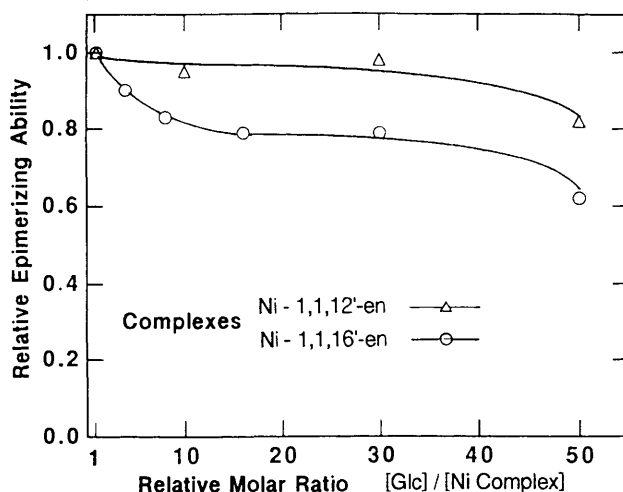

Fig. 5 Catalytic epimerization by amphiphilic Ni complex

complex which can aggregate to form metallomicelles shows an excellent epimerizing ability is the most noteworthy point.

The dependence of the critical micellization concentration (c.m.c.) on the chain length was also investigated. The results are shown in Fig. 3. In general, the c.m.c. of amphiphiles in aqueous media decreases as the hydrophobic character of the amphiphile increases, and the relationships between the c.m.c. and the number of carbon atoms (N) in the hydrophobic group can be expressed by the following equation; where A and B are

$$\log C_{cmc} = A - BN$$

constants reflecting the free energy changes involved in transferring the hydrophilic group and a methylene unit of the hydrophobic group, respectively, from an aqueous environment to the micelle. The value of A and B for the micelle of this metallic complex were -0.43 and 0.24, respectively. They were compatible with those for the approved commercial anionic and cationic surfactant.[8]

Concentration Effect and Catalytic Activity.—The hydrophobic nickel complexes facilitate the epimerization by the assembly of the Ni^{2+} ion and diamine on the micelle. The effect of concentration of Ni-diamine complex on the epimerization of aldoses was investigated. Fig. 4 shows the results for addition of $NiCl_2 \cdot 6H_2O$ and N,N-dimethyl-N'-dodecylethylenediamine to give the concentration of nickel complex indicated. Where the concentration of the nickel complex was 67 mmol dm^{-3}, glucose (Glc) and mannose (Man) were epimerized smoothly into their corresponding epimers, whereas no epimerization took place with concentration below 20 mmol dm^{-3}.

A simple comparison between two results may not be ideal, since the surface tension and epimerization were measured at different temperatures (the former at 25 and the latter at 80 °C). However, it is interesting that the results are consistent with the interpretation of the formation of aggregates, suggesting further evidence for the existence of metallomicelle.

Catalytic Activity of the Complex System.—Rate of the epimerization in aqueous media was studied. The catalytic activity is presented as relative activity against changing molar ratio of glucose to nickel complex. The epimerization of glucose under the standard condition was used as a reference. The results are summarized in Fig. 5.

When hydrophobic ligand was used, the epimerizing ability of nickel complex was not significantly reduced even in the presence of a relatively large amount of aldose. The Ni^{2+}-$1,1,12'$en complex especially showed excellent epimerization

even when the molar ratio of glucose to complex was increased by a factor of about 30. This would suggest the interconversion between free aldose in a bulk aqueous phase and aldose coordinated to the nickel complex, and that the interconversion is accompanied during the epimerization by the skeletal rearrangement of the two epimers. In contrast, the hydrophilic nickel complex showed no catalytic epimerizing ability as under standard conditions.

Experimental

Materials.—Water used for the epimerization of aldoses was purified in the following manner to remove any colloidal and common impurities. Deionized water was further distilled by the quartz distillation apparatus (WG-200, Yamato). Conductivity and surface tension of the water used were less than 1 μS cm^{-1} and more than 71 mN m^{-1}, respectively. In order to remove dissolved oxygen, pure nitrogen gas was bubbled through distilled water for half an hour prior to preparing sample solutions.[2]

Various types of higher *N*-alkylated diamine derivative ligands were prepared according to the reactions shown in Scheme 2. *N,N*-Dimethylethylendiamine was treated with the
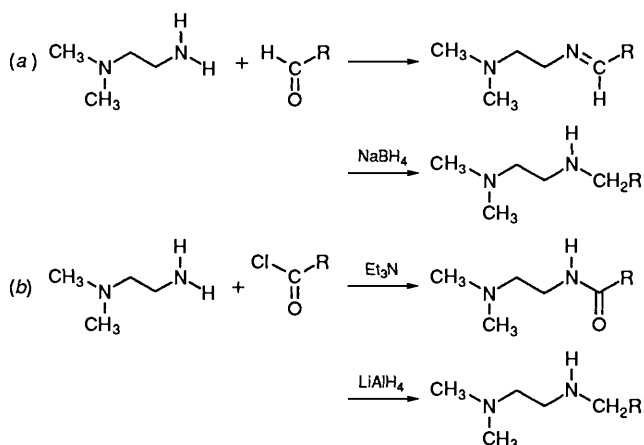
Scheme 2 Preparation of *N,N*-dimethyl-*N'*-alkylethylenediamine

corresponding higher aldehyde, and the resulting Schiff base was reduced with sodium borohydride. *N*-Higher-acylated dimethylethylenediamine, which was prepared from the corresponding acid chloride, was reduced with lithium aluminium hydride. The product was purified by distillation *in vacuo*. Boiling point data are as follows: (°C/mmHg); 1,1,8'-en, 87–88/0.05; 1,1,9'-en, 100–104/0.1; 1,1,10'-en, 109–112/0.7; 1,1,12'-en, 146–148/1.4; 1,1,14'-en, 149–150/0.5; 1,1,16'-en, 147–149/0.3; 1,1,18'-en, 185–188/0.6. Product structure and purity was established on the basis of elementary analysis, IR and NMR spectra in addition to TLC and physical constant measurements. ^{1}H NMR spectrum of 1,1,12'-en (90 MHz; 20 mg/0.35 cm^3 CDCl$_3$, Me$_4$Si) is shown here as an example. δ 0.89 [3 H, t, N-(CH$_2$)$_{11}$CH_3], 1.25 [18 H, br s, N-CH$_2$CH$_2$-(CH_2)$_9$-CH$_3$], 1.51 [2 H, m, N-CH$_2$CH_2(CH$_2$)$_9$-CH$_3$], 2.14 (1 H, br s, amino proton), 2.23 [6 H, s, N(CH_3)$_2$], 2.42, 2.69 [2 H × 2, 2 t, -N-(CH_2)$_2$N-], 2.61 [2 H, t, N-CH_2-(CH$_2$)$_{10}$-CH$_3$]. Other spectra were in fair agreement with the theoretical spectra. Lower homologues such as 1,1,1'-en and 1,1,2'-en were

purchased from Tokyo Kasei Chemicals Co., Tokyo. Commercial sugars of the highest quality available were used. D-Glucose, D-mannose, D-xylose and D-lyxose were examined. The ^{13}C-enriched glucose at C-1, [1-^{13}C]-Glc, was purchased from ISOEC Inc., Ohio and used to confirm the mechanism of the reaction. All other reagents employed were the highest commercial grade, and were used without further purification.

Epimerization and Product Analysis.—In a typical experiment, NiCl$_2$·6H$_2$O (1 mmol) and diamine (2 mmol) were mixed in a round bottom flask containing water (15 cm^3). The solution was incubated for 5 min at 80 °C. After the addition of aldose (1 mmol), the reaction mixture was maintained at 80 °C for 20 min with stirring. The reaction temperature, time and the amount of substrates were varied according to the reaction condition. The product solution was treated with Dowex 50W × 2 (H$^+$ type) and Dowex 2 × 8 (HCO$_3^-$-type) ion exchange resins to deionize the reactant solutions. Work-up of the eluate, and subsequent qualitative and quantitative analysis of the resulting sugars were carried out in a similar manner as previously described.[3] The trimethylsilyl ethers of both epimerized and unchanged residual sugars were formed in a conventional manner, and assayed.

GLC analysis was carried out isothermally at 200 °C with a capillary column (OV-1 Bonded, 0.25 mm id, 25 m length) using flame ionization detector.

Surface Tension and CMC Measurements.—Amphiphilic complex solutions were prepared by serial dilution. The surface was aged for 0.5 h at an experimental temperature prior to each measurement. Surface tension was measured with Model A3 Tensiometer, Kyowa Kagaku Co. by Wilhelmy's vertical plate method at 25 °C. Critical micelle concentration was determined from the breaking point on a surface tension *vs.* concentration curve.

References

1 T. Tanase, T. Shimizu, M. Kuse, S. Yano, M. Hidai and S. Yoshikawa, *Inorg. Chem.*, 1988, **27**, 4085.
2 K. Fukushima, M. Takahashi, H. Nagano, S. Osanai and S. Yoshikawa, *Nippon Kagaku Kaishi*, 1988, 585.
3 K. Inaba, S. Osanai and S. Yoshikawa, *Carbohydr. Res.*, 1990, **209**, 289.
4 K. Hataya, R. Yanagihara, S. Osanai and S. Yoshikawa, *J. Chem. Soc., Chem. Commun.*, 1991, 1246.
5 S. Tamagaki, K. Fukuda and W. Tagaki, *Chem. Express*, 1992, 7 (11), 869.
6 K. Takagi, N. Miyake, E. Nakamura, H. Usami and Y. Sawaki, *J. Chem. Soc., Faraday Trans. 1*, 1988, **84**, 3475.
7 F. M. Menger, L. H. Gan, E. Johnson and D. H. Durst, *J. Am. Chem. Soc.*, 1987, **109**, 2800.
8 M. J. Rosen, *Surfactants and Interfacial Phenomena*, John Wiley and Sons, New York, 1978.