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Note

Aldose epimerization by Ni(II): effect of ether-containing alkylenediamine ligands

Shuichi Osanai*, Kiyoshi Inaba, and Sadao Yoshikawa
Faculty of Science & Technology, Keio University 3-14-1, Hiyoshi Kohhoku-ku, Yokohama-shi 223 (Japan)

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ABSTRACT

Several *N*-substituted ethylenediamine (en) Ni(II) derivatives containing ether linkages were prepared in order to study the effect of ligand structure on C-2 epimerization of aldohexoses. The reagent consisted of a Ni(II)-alkylenediamine derivative in methanol. The presence of ether linkages in the ligand increased the solubility of the complexes, and resulted in an increase in the rate of epimerization. Epimerization occured rapidly under mild conditions, and the same equilibrium point was reached regardless of whether the reaction was started from glucose or mannose. Among the ligands studied, *N,N'*-dialkylethylenediamine was the most active in C-2 epimerization.

INTRODUCTION

We reported recently a novel C-2 epimerization of aldopentoses and aldohexoses catalyzed by nickel(II) or calcium(II) complexes containing various mono-, di- or poly-amine ligands[1,2], and a mechanism for this rearrangement was proposed based on ^{13}C-n.m.r.[3,4] and EXAFS[3] studies. However, the influence of ligand structure on the reaction remained to be examined.

In this study, we have prepared a wide variety of diamines containing ether linkages and have compared these ligands in terms of their solubility and coordinating ability to the corresponding methylene group or amino group. In a previous paper, we found that the epimerization reaction proceeded more rapidly when *N,N'*-disubstituted ethylendiamines containing hydrophobic *N*-alkyl substituents were used as ligands, and the extent of epimerization depended on the solubility of the diamines in the solvent, methanol. Use of the ether-containing diamine ligands in the present study eliminated problems of insolubility frequently encountered with the conventional lipophilic ligands.

The effects of ligand structure, such as the number of ether linkages, *N*-alkoxylated or alkylated chain length, and the degree of *N*-substitution, on the kinetics and thermodynamics of the reaction have been studied, as well as other factors.

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EXPERIMENTAL

Materials. — D-Glucose, D-mannose, and D-fructose (Tokyo Kasei Chemicals Co.), and nickel chloride hexahydrate (Wako Chemicals Co.) were used without further purification. The *n*-alcohols (**1**), 2-ethoxyethanol, 2-hexyloxyethanol, and such amines as 2-ethoxyethylamine (**6**) and 2,2′-diethoxydiethylamine (**8**) were purchased from Tokyo Kasei Chemical Co., Tokyo.

Ligands. — Several ethylenediamine ligands containing ether linkages were prepared as outlined in Scheme 1. The structures of these compounds were confirmed by ^{1}H- and ^{13}C-n.m.r. spectroscopy and i.r. spectroscopy (Table I), and their purities were demonstrated by t.l.c.[5] The non-oxygenated ligands, **L**, **M**, **N**, **O**, and **P** were prepared as described in the previous paper[1].

$$\mathrm{R(OC_2H_4)_nOH}\ (\mathbf{1}) \xrightarrow{\mathrm{CH_2{=}CHCN}} \mathrm{R(OC_2H_4)_nOC_2H_4CN}\ (\mathbf{2})$$

$$\xrightarrow{\mathrm{H_2/Ni\ (Raney)}} \mathrm{R(OC_2H_4)_nOC_3H_6NH_2}\ (\mathbf{3}) \xrightarrow{\mathrm{(\text{-}CO_2CH_3)_2}}$$

$$\mathrm{[R(OC_2H_4)_nC_3H_6NHCO\text{-}]_2}\ (\mathbf{4}) \xrightarrow{\mathrm{LiAlH_4,THF}} \mathrm{[R(OC_2H_4)_nC_3H_6NHCH_2\text{-}]_2}\ (\mathbf{5})$$

Ligand: A,B,C,D,E,F,G,

$$\mathrm{C_2H_5OC_2H_4\text{-}NH_2}\ (\mathbf{6}) + \mathrm{BrC_2H_4Br} \rightarrow \mathrm{(C_2H_5OC_2H_4\text{-}NHCH_2\text{-})_2}\ (\mathbf{7})$$

Ligand: H

$$\mathrm{(C_2H_5OC_2H_4)_2\text{-}NH}\ (\mathbf{8}) + \mathrm{BrC_2H_4Br} \rightarrow \mathrm{[(C_2H_5OC_2H_4)_2\text{-}NCH_2\text{-}]_2}\ (\mathbf{9})$$

Ligand: I

Scheme 1. Preparation of the ethylenediamine derivatives containing ether linkages.

Epimerization and product analysis. — An aldose (1 equiv.) was added batchwise to a methanolic solution containing $NiCl_2.6H_2O$ (1 equiv.) and diamine (2 equiv.), and the mixture was incubated for 5 min at 60° with stirring. The mixture was treated as described previously[1] prior to the following analysis.

The epimerization efficiency of the reaction system was assessed by quantification of the corresponding epimers. The samples were analyzed after trimethylsilylation by gas–liquid chromatography (g.l.c.), on a Hitachi Model 663-50 gas chromatograph using a 1 m × 3 mm stainless-steel column packed with 5% Silicon gum SE-30 on Chromosorb W (80–100 mesh) operated isothermally at 180°; detector: FID, 250°, with N_2 as the carrier gas. Aldoses and ketoses were quantified colorimetrically. The absorbance was measured with a Shimazu UV-160 u.v.–visual spectrophotometer. The 2-aminobiphenyl–AcOH method was used for aldose quantification, and for the ketoses, resorsinol–HCl method was used. The absorbances were determined at 380 and 500 nm, respectively.

TABLE I

Boiling points and R_F values of the *N*-substituted ethylenediamines

	N-*Substituted ethylenediamines*[a]	*B.p.* *(°/mmHg)*	R_F[b]
Abbr.	A: (12-3)(12-3)'en		0.16
Structure	$(C_{12}H_{25}\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	B: (8-3)(8-3)'en		0.25
Structure	$(C_8H_{17}\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	C: (4-3)(4-3)'en	140–143/0.25	0.37
Structure	$(C_4H_9\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	D: (2-3)(2-3)'en	118–119/0.35	
Structure	$(C_2H_5\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	E: (2-2-3)(2-2-3)'en	156–158/0.05	0.16
Structure	$(C_2H_5\text{-O-}C_2H_4\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	F: (6-2-3)(6-2-3)'en		0.12
Structure	$(C_6H_{13}\text{-O-}C_2H_4\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	G: (2-2-2-3)(2-2-2-3)'en	195–200/0.08	0.05
Structure	$(C_2H_5\text{-O-}C_2H_4\text{-O-}C_2H_4\text{-O-}C_3H_6\text{-NH-}CH_2\text{-})_2$		
Abbr.	H: (2-2)(2-2)'en	83–85/0.10	0.11
Structure	$(C_2H_5\text{-O-}C_2H_4\text{-NH-}CH_2\text{-})_2$		
Abbr.	I: (2-2)(2-2)(2-2)'(2-2)'en	140–143/0.20	0.74
Structure	$((C_2H_5\text{-O-}C_2H_4)_2\text{-N-}CH_2\text{-})_2$		
Abbr.	J: (0-2)(0-2)'en	Commercial origin	
Structure	$(HO\text{-}C_2H_4\text{-NH-}CH_2\text{-})_2$		
Abbr.	P: L,L'-323	55.5–57.0[c]	0.22[d]
Structure	$(C_{12}H_{25}NHC_3H_6NHCH_2\text{-})_2$		

[a] The characteristics of other non-oxygenated diamines are shown in ref. 1. [b] Developing solvent 90:8:1 (v/v) $CHCl_3$–MeOH–conc. aq NH_4OH. [c] Melting point (°), recrystalised from acetone. [d] Developing solvent 70:30:5 (v/v) $CHCl_3$–MeOH–conc. aq. NH_4OH.

RESULTS AND DISCUSSION

The complex composed of Ni(II) and *N*-alkylated ethylenediamine ligands is expected to catalyze the conversion of an aldohexose into its corresponding 2-epimer with a high degree of specificity.

Analytical results are summarized in Table II. The yield of the epimer as a function of the ethylenediamine derivative used in the formulation are shown. Absolute recoveries of the epimerized and converted sugar varied between 85 and 100% of the starting sugar. As shown in Table II, final solution compositions are almost identical when either D-glucose or D-mannose was used as the starting sugar, except for runs 9, 10, 11, 15 and 16. The solubility of the intermediate complex in methanol is an important factor influencing the epimerization reaction. The introduction of ether oxygen atoms enhanced the solubility of the *N*-alkylated ethylenediamine, and consequently of the resulting complex. Ligands **A** and **B** may be regarded as homologues of *N*,*N*'-didodecylethylenediamine M(L,L'en ; L and en denote the dodecyl and ethylendiamine groups, respectively). Ligand **A** possesses the trimethyleneoxy group, which is inserted between the dodecyl group and the nitrogen of *N*,*N*'-didodecylethylenediamine M(L,L'en). In

TABLE II

Analytical results of epimerization using (Ni(II)-diamine complexes

Run	*Ligand*[a]	*Starting sugar*	*Composition of products (%)*				*Recovery (%)*	*Color of soln.*
			Glc	*Man*	*Fru*	*Other*		
1	**A**:(12-3)(12-3)′en	D-Glucose	62	: 36	: 2	: 0	97	Yellowish green
		D-Mannose	53	: 38	: 1	: 8	91	Green
2	**B**:(8-3)(8-3)′en	D-Glucose	58	: 36	: 4	: 2	90	Green
		D-Mannose	54	: 37	: 5	: 4	91	Green
3	**C**:(4-3)(4-3)′en	D-Glucose	59	: 35	: 5	: 1	92	Green
		D-Mannose	53	: 37	: 6	: 4	93	Green
4	**D**:(2-3)(2-3)′en	D-Glucose	56	: 34	: 7	: 3	92	Blue green
		D-Mannose	53	: 38	: 7	: 2	93	Green
5	**E**:(2-2-3)(2-2-3)′en	D-Glucose	55	: 37	: 8	: 0	85	Green
		D-Mannose	52	: 36	: 9	: 3	87	Blue green
6	**F**:(6-2-3)(6-2-3)′en	D-Glucose	53	: 34	: 3	:10	90	Green
		D-Mannose	53	: 38	: 4	: 5	90	Green
7	**G**:(2-2-2-3)(2-2-2-3)′en	D-Glucose	53	: 37	: 8	: 2	86	Green
		D-Mannose	51	: 37	: 9	: 3	87	Green
8	**H**:(2-2)(2-2)′en	D-Glucose	63	: 27	:10	: 0	92	Green
		D-Mannose	58	: 29	:12	: 1	92	Green
9	**I**:(2-2)(2-2)(2-2)′(2-2)′en	D-Glucose	94	: 0	: 5	: 1	93	Yellowish green
		D-Mannose	0	:100	: 0	: 0	83	Yellowish green
10	**J**:(0-2)(0-2)′en	D-Glucose	98	: 0	: 1	: 1	88	Blue purple
		D-Mannose	0	:100	: 0	: 0	94	Blue purple

11	K:Ethylenediamine (en)	D-Glucose	100	: 0	: 0	: 0	97	Blue
		D-Mannose	0	:100	: 0	: 0	88	Blue
12	L:O,O′en	D-Glucose	63	: 37	: 0	: 0	100	Green
		D-Mannose	61	: 39	: 0	: 0	100	Green
13	M:L,L′en	D-Glucose	67	: 33	: 0	: 0	100	Green
		D-Mannose	66	: 34	: 0	: 0	100	Green
14	N:M,M′en	D-Glucose	64	: 36	: 0	: 0	98	Green
		D-Mannose	64	: 36	: 0	: 0	98	Green
15	O:S,S′en	D-Glucose	86	: 14	: 0	: 0	97	Green
		D-Mannose	3	: 97	: 0	: 0	96	Green
16	P:L,L′-323	D-Glucose	100	: 0	: 0	: 0	100	Yellowish green
		D-Mannose	0	:100	: 0	: 0	100	Yellowish green

[a] The structures of the ligands (A–J and P) are given in Table I. O: Octyl, L: Dodecyl (Lauryl), M: Tetradecyl (Myristyl), S: Octadecyl (Stearyl), O means *N*-octyl substituted, and O′ means *N*′-octyl substituted derivative.

the ligand **B**, an ether oxygen atom is substituted for C-4 of the dodecyl group, dividing the dodecyl group into C_8 and C_3 alkoxyl groups. Low epimerization of glucose:mannose resulted when *N,N'*-dioctadecylamine **O**(S,S'en) was used as a ligand (run 15). On the other hand, the epimerization proceeded readily if ligands **A**, **B**, or other ether diamines were used. Both the increase in epimerization and solubility of the complex appear to be due to introduction of the ether linkage in the long hydrophobic alkyl group.

There was little difference among the ligands **B**, **F**, and **G** with regard to the epimerization. These three diamines could be considered as polyoxygenated analogues of didodecyl ethylenediamine. This result indicates that, once the ligand imparts a degree of solubility, the influence of the number of ether linkages of the ligand on the epimerization is small.

When **P**(L,L'-323), was used as a ligand (run 16), its epimerization activity was negligible. The ligand **P**(L,L'-323) is analogous to **A**(12-3)(12-3)'en if the oxygen atom of the ether group had been replaced by nitrogen. Epimerization occurs through substitution of the aldohexose into the Ni(II) ethylenediamine complex. Complex formation between sugar and Ni(II) is indispensable for the epimerization. **P**(L,L'-323) is known to complex strongly with Ni(II), coordinating its four amino groups. This complex is not so labile and will not accept substitution of the aldohexose. Similar results were observed in runs 10 and 11, in which **J**(0-2)(0-2)'en or ethylenediamine (en) **K** were tested as ligands. In run 11, the ligand, which has only primary amino groups, forms a stable complex, and cannot accept the introduction of the aldose. A similar state would occur for the ligand **J**(0-2)(0-2)'en (Fig. 1).

From these results, it may be concluded that epimerization depends upon the ability of the aldose molecule to insert into the intermediate complex. Those complexes, which can loosely coordinate the amine ligand and incorporate aldose into the complex, showed high levels of epimerization. In such a reaction system, the epimerization progresses rapidly to an equilibrium mixture of 2-epimers, regardless of whether the reaction is started from glucose or mannose. In such a case, the sum of the percentage of each epimerized aldose totaled 100%.

This reaction system has the further advantage of permitting a simple washing to regenerate the ion-exchange resin used for the deionization. When ligands containing long alkyl chains are used, the resin may have been poisoned by the inability to remove the adhesive and viscous alkylethylenediamine by simple washing. In contrast, the ether diamines were readily removed from the used resin by elution with methanol. Equally good results for the epimerization were achieved by using the cleaned, regenerated resin.

Fig. 1. Postulated structures of the tetradentate ligand complexes.

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