fragments are joined by a common $\mu_2,\eta^1,\mu_2,\eta^1$-$Te_2^{2-}$ ligand and two Te_3^{2-} chains. The tetramolybdenum anion has virtual C_{2h} symmetry with a crystallographically imposed inversion center. The Te–Te distances of 2.74–2.84 Å are typical for single bonds [Te–Te distances in Te_4^{2-}·2MeOH are 2.76 (1) and 2.72 (1) Å;[11] elemental Te has a Te–Te contacts of 2.84 Å[17]] with the Te(2)–Te(2′) distance being the longest, 2.841 (2) Å. The Mo–Te bond distances range between 2.693 (2) and 2.796 (3) Å with the shortest being the Mo–Te(2) contacts.

The Mo–Mo distance in **1** is surprisingly short when compared with those in other face-sharing bioctahedral Mo_2^{III} species. Several studies[18] of $Mo_2Cl_9^{3-}$ salts with different cations have shown that the Mo–Mo distance is quite variable, ranging from 2.52 to 2.82 Å in 10 different compounds. Nonetheless, all of these are longer than the value found here. In five $Mo_2Br_9^{3-}$ compounds[18b] the Mo–Mo distance ranged from 2.57 to 3.12 Å, and in $Cs_3Mo_2I_9$ it is 3.07 Å. Since the telluride ions forming the bridges in these cases are more similar in size to I^- than to Cl^- or Br^-, the occurrence of such a short Mo–Mo distance is of even greater interest. However, the comparison of halide-bridged and chalcogen-bridged species may be misleading, if we note that in the $(Me_2S)Cl_2Mo(\mu\text{-}Cl)_2(\mu\text{-}Me_2S)MoCl_2(Me_2S)$ molecule the Mo–Mo distance, 2.462 (2) Å, is nearly 0.3 Å shorter than it is in the $[(Me_2S)Cl_2Mo(\mu\text{-}Cl)_3MoCl_2(Me_2S)]^-$ ion, 2.746 (9) Å.[19]

It is interesting to note that **1** is composed of Te_2^{2-} and Te_3^{2-} fragments when the polytelluride source was an extract of a melt of nominal composition K_2Te_4. Kolis and co-workers have shown that $M(Te_4)(CO)_4^{2-}$ [where M = Cr, Mo, W] could be synthesized from various polytelluride sources [Te_x^{2-} where x = 2, 3, or 4] under identical reaction conditions.[3] Presumably, a complex equilibrium of Te_x^{n-} species is established in solution[20] thus allowing the substrate to "choose" a telluride ion of a desired chain length. This phenomenon has been observed in the polysulfide and polyselenide systems[21] and is likely to be a recurring theme in polytelluride solution chemistry.

Acknowledgment. The support of the National Science Foundation for the work at Texas A&M University is gratefully acknowledged.

Supplementary Material Available: Tables of crystal data, positional parameters, general displacement parameters, bond distances, and bond angles and an ORTEP drawing of the $[K(crypt)]^+$ ion (11 pages); a table of structure factors (14 pages). Ordering information is given on any current masthead page.

(17) Cherin, P.; Unger, P. *Acta Crystallogr.* **1967**, *23*, 670.
(18) (a) Subbotin, M. Y.; Aslanov, L. A. *Zh. Neorg. Khim.* **1986**, *31*, 393. (b) Stranger, R.; Grey, I. E.; Madsen, I. C.; Smith, P. W. *J. Solid State Chem.* **1987**, *69*, 162.
(19) Boorman, P. M.; Moynihan, K. J.; Oakley, R. T. *J. Chem. Soc., Chem. Commun.* **1982**, 899.
(20) A recent report of isolated telluride ions in liquid ammonia involved very different experimental conditions as noted by the authors: Schultz, L. D.; Kochler, W. H. *Inorg. Chem.* **1987**, *26*, 1989.
(21) Draganjac, M.; Rauchfuss, T. B. *Angew. Chem., Int. Ed. Engl.* **1985** *24*, 742.

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Received July 22, 1988

Articles

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Novel C-2 Epimerization of Aldoses Promoted by Nickel(II) Diamine Complexes, Involving a Stereospecific Pinacol-Type 1,2-Carbon Shift

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Received December 10, 1987

The newly discovered C-2 epimerization of aldoses promoted by nickel(II) diamine complexes has been investigated in detail by using ^{13}C-enriched D-glucose, ^{13}C NMR spectroscopy, and EXAFS (extended X-ray absorption fine structure) analysis. Aldoses treated with nickel(II) diamine complexes (diamine = *N,N,N′*-trimethylethylenediamine (*N,N,N′*-Me_3en), *N,N,N′,N′*-tetramethylethylenediamine (*N,N,N′,N′*-Me_4en), etc.) in methanolic solutions were rapidly (60 °C, 3–5 min) epimerized at C-2 to give equilibrium mixtures where the ratio of C-2 epimers shifts to the side of the naturally rare mannose-type aldoses (having the cis arrangement of C-2 and C-3 hydroxyl groups) compared with those in the thermodynamic equilibrium states. The epimerization product of D-[1-^{13}C]glucose was exclusively D-[2-^{13}C]mannose, demonstrating that the reaction involves a stereospecific 1,2-shift of the carbon skeleton resulting in inversion of configuration at C-2. Furthermore, the absorption and circular dichroism spectra of the reaction solutions indicated the presence of an intermediate nickel(II) complex containing both diamine and sugar components, which was directly revealed by EXAFS analysis to be a mononuclear nickel(II) complex having octahedral coordination geometry. All these observations strongly suggest that the C-2 epimerization proceeds through an intermediate mononuclear nickel(II) complex, where the carbinolamine-like adduct of aldose with diamine in an open-chain form is epimerized at C-2 by a stereospecific rearrangement of the carbon skeleton or a pinacol-type rearrangement involving a cyclic transition state.

Introduction

Effective synthetic procedures for naturally rare carbohydrates are highly desirable in the fields of biochemistry and medicinal chemistry, and it is important to develop methods whereby metals promote transformation of sugars in bioinorganic chemistry. In a series of reports, 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.[2-8]

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(2) Bilik, V.; Stancovik, L. *Chem. Zvesti* **1973**, *27*, 544.
(3) Bilik, V. *Chem. Zvesti* **1972**, *26*, 183.
(4) Bilik, V.; Caplovic, J. *Chem. Zvesti* **1973**, *27*, 547.

0020-1669/88/1327-4085$01.50/0

Later, by the use of ^{13}C-enriched carbohydrates, Baker et al. demonstrated that the epimerization by molybdate involves a novel rearrangement of the carbon skeleton, or 1,2-carbon shift.[9] These were significant advancements in the preparation of rare sugars. However, the reaction proceeds slowly under strict conditions (90 °C, 2–13 h, pH 4.5), and yields of the mannose-type C-2 epimers having the cis arrangement of C-2 and C-3 hydroxyl groups are comparatively low because of their thermodynamic instabilities. Furthermore, detailed mechanisms involving the stereochemistry required for the rearrangement of the carbon skeleton are still not fully understood.

In order to elucidate the carbohydrate–transition-metal interactions, we have studied the synthesis and characterization of transition-metal complexes containing *N*-glycosides derived from the reaction of sugars and diamines.[10-17] During our investigations, we obtained and characterized a novel binuclear nickel(II) complex formed from D-mannose and *N,N'*-dimethylethylenediamine (*N,N'*-Me_2en).[17] Furthermore, when D-glucose was used as a starting sugar instead of D-mannose, a nickel(II) complex containing D-mannose was unexpectedly obtained in a very low yield. Prompted by this knowledge, we have investigated the reactions of natural aldoses and nickel(II) complexes of diamines in order to develop suitable complexes for metal-assisted epimerization of monosaccharides. We recently found that aldoses are epimerized at C-2 in a very short time (60 °C, 3–4 min) by a nickel(II) *N,N,N'*-Me_3en complex, $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ (*N,N,N'*-Me_3en = 1-(dimethylamino)-2-(methylamino)ethane), which was accompanied by a stereoselective complexation of some mannose-type epimers (mannose, lyxose, and rhamnose).[18] This reaction has much potential for the synthesis of naturally rare aldoses as well as theoretical importance.[19] We now present a more detailed study of the C-2 epimerization promoted by nickel(II) diamine complexes, and both the reaction characteristics and its mechanistic aspects are substantiated by experimental results. In particular, a ^{13}C NMR study using ^{13}C-enriched D-glucose and EXAFS (extended X-ray absorption fine structure) analysis surprisingly revealed that the reaction proceeds through an intermediate mononuclear nickel(II) complex, where a stereospecific rearrangement of the carbon skeleton takes place with considerable rapidity.

Experimental Section

Materials. All reagents were of the best commercial grade and were used without further purification. D-[1-^{13}C]-Glucose was purchased from Aldrich Co., Ltd., and D-talose and D-quinovose were obtained from Sigma Co., Ltd. $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ was prepared as follows. *N,N,N'*-Me_3en (2 equiv) was added to a methanol–water solution of $NiCl_2\cdot 6H_2O$ (1 equiv) at room temperature. The blue-green solution was evaporated to dryness to give a blue powder of $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ quantitatively, which was collected, washed with ethanol followed by ether, and dried in vacuo. Good elemental analysis was obtained for C, H, N, and Cl. $[Ni(en)_3](NO_3)_2$,[20,21] $[Ni_2Cl_2(en)_4]Cl_2$,[22,23] and $Ni(N,N,N',N'\text{-}Me_4en)Cl_2$[24] were prepared by known methods. $[Ni(N\text{-(L-Rha)tn})_2]Br_2\cdot CH_3OH\cdot 2H_2O$ and $(\mu\text{-D-Man})[Ni_2(CH_3OH)(N\text{-(D-Man)-}N,N'\text{-}Me_2en)(N,N'\text{-(D-Man)}_2\text{-}Me_2en)]Cl_2\cdot CH_3OH\cdot 5H_2O$ were prepared as described previously.[14,17]

The following abbreviations are used: *N,N,N'*-Me_3en, 1-(dimethylamino)-2-(methylamino)ethane; *N,N,N',N'*-Me_4en, 1,2-bis(dimethylamino)ethane; *N,N*-Me_2en, 1-(dimethylamino)-2-aminoethane; *N,N'*-Me_2en, 1,2-bis(methylamino)ethane; *N,N'*-Ph_2en, 1,2-bis(phenylamino)ethane; en, 1,2-diaminoethane; *N,N,N',N'*-Me_4tn, 1,3-bis(dimethylamino)propane; *N,N*-Me_2-*N'*-Eten, 1-(dimethylamino)-2-(ethylamino)ethane; *N,N*-Me_2eta, 2-(dimethylamino)ethanol; *N,N*-Me_2GlyMeamide, *N,N*-dimethylglycine *N*-methylamide, Et_3N, triethylamine; D-Glc, D-glucose; D-Man, D-mannose; D-Gal, D-galactose; D-Tal, D-talose; L-Rha, L-rhamnose (6-deoxy-L-mannose); D-Qui, D-quinovose (6-deoxy-D-glucose); D-Xyl, D-xylose; D-Lyx, D-lyxose; D-Rib, D-ribose; D-Ara, D-arabinose; *N*-(L-Rha)tn, 1-(L-rhamnosylamino)-3-aminopropane; *N*-(D-Man)-*N,N'*-Me_2en, 1-(D-mannosylmethylamino)-2-(methylamino)ethane; *N,N'*-(D-Man)$_2$-*N,N'*-Me_2en, 1,2-bis(D-mannosylmethylamino)ethane.

General Epimerization Reaction. (1) Promoted by $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$. To a methanolic solution of $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ (1.1 mmol) was added the aldose (1.1 mmol), and the mixture was incubated at 60 °C for 3–4 min with stirring. The reaction mixture was then dissolved in 50 mL of water and was kept at pH 6.5 with 0.5 M H_2SO_4 for 1 h at room temperature. Subsequently, the solution was treated with an excess of Dowex 50W-X8 (H^+) and Dowex 1-X2 (HCO_3^-) prior to HPLC or ^{13}C NMR analysis.

(2) Promoted by Nickel(II) and Other Diamines. The aldose (1.1 mmol) was treated with $NiCl_2\cdot 6H_2O$ (1.1 mmol) and the diamine (2.2 mmol) in methanol at 60 °C for 5 min without isolating the starting nickel complex. The reaction mixture was then dissolved in 50 mL of water and purified as described above.

Measurements. ^{13}C NMR spectra were obtained at 100 MHz with a JEOL GX-400 superconducting FT spectrometer at 35 °C with the spectrometer locked to the resonance of ^2H_2O in the sample. Chemical shifts are given relative to internal TMS by setting spectral parameters to give the anomeric resonance of β-D-[1-^{13}C] glucose at 97.4 ppm.[25]

HPLC analyses were performed with a TSK HLC-803D chromatographic system using a column of anion-exchange resin (TSK SA60) maintained at 65 °C. Sugar components were eluted with 0.5 M borate buffer adjusted to pH 8.5 at a flow rate of 0.5 mL/min and fluorimetrically detected by the reaction with 2-cyanoacetamide at 95 °C for 5 min.[26] For the separation of D-Gal and D-Tal, 0.5 M borate buffer adjusted to pH 7.0 was used as eluant with a flow rate of 0.4 mL/min. Ketoses were electrochemically detected by the reaction with the copper(II) *o*-phenanthroline complex.[27]

Visible and near-infrared absorption spectra were measured with a Hitachi Model 340 recording spectrophotometer. Circular dichroism spectra were recorded on a Jasco J-500 recording spectropolarimeter.

X-ray Measurements. Beam line 10B at the Photon Factory of the National Laboratory for High Energy Physics[28] (2.5 GeV, 90–150 mA) was used with a Si(311) channel-cut monochromator. The experiments were done in the transmission mode on boron nitride pellets and methanolic solutions. The monochromated X-ray beam (1 × 10 mm) passed through the first ionization chamber (17 cm; detecting gas N_2), which measured the incident beam intensity I_0, then through the sample, and finally through another ionization chamber (31 cm; detecting gas 85% N_2 + 15% Ar), which measured the transmitted intensity I.[29] The

(5) Bilik, V.; Petrus, L.; Farkas, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1163.
(6) Bilik, V.; Petrus, L.; Farkas, V. *Chem. Zvesti* **1975**, *29*, 690.
(7) Bilik, V.; Petrus, L.; Zemek, J. *Chem. Zvesti* **1978**, *32*, 242.
(8) Bilik, V.; Petrus, L.; Stancovic, L.; Linek, K. *Chem. Zvesti* **1978**, *32*, 372.
(9) Hayes, M. L.; Pennigs, N. J.; Serianni, A. S.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 6764.
(10) Takizawa, S.; Sugita, H.; Yano, S.; Yoshikawa, S. *J. Am. Chem. Soc.* **1980**, *102*, 7969.
(11) Yano, S.; Takizawa, S.; Sugita, H.; Takahashi, T.; Tsubomura, T.; Shioi, H.; Yoshikawa, S. *Carbohydr. Res.* **1985**, *142*, 179.
(12) Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1833.
(13) Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Inorg. Chem.* **1985**, *24*, 3218.
(14) Shioi, H.; Yano, S.; Yoshikawa, S.; Toriumi, K.; Ito, T. *J. Chem. Soc., Chem. Commun.* **1983**, 201.
(15) Yano, S.; Sakai, Y.; Toriumi, K.; Ito, T.; Ito, H.; Yoshikawa, S. *Inorg. Chem.* **1985**, *24*, 498.
(16) Ishida, K.; Yano, S.; Yoshikawa, S. *Inorg. Chem.* **1986**, *25*, 3552.
(17) (a) Tanase, T.; Kurihara, K.; Yano, S.; Kobayashi, K.; Sakurai, T.; Yoshikawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1562. (b) Tanase, T.; Kurihara, K.; Yano, S.; Kobayashi, K.; Sakurai, T.; Yoshikawa, S.; Hidai, M. *Inorg. Chem.* **1987**, *26*, 3134.
(18) Tanase, T.; Shimizu, F.; Yano, S.; Yoshikawa, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1001.
(19) Tanase, T.; Shimizu, F.; Kuse, M.; Yano, S.; Hidai, M.; Yoshikawa, S. *J. Chem. Soc., Chem. Commun.* **1987**, 659.
(20) Watanabe, T.; Atoji, M. *Kagaku (Tokyo)* **1951**, *21*, 301.
(21) Swink, L. N.; Atoji, M. *Acta Crystallogr.* **1960**, *13*, 639.
(22) Ginsberg, A. P.; Martin, R. L.; Brookes, R. W.; Sherwood, R. C. *Inorg. Chem.* **1972**, *11*, 2884.
(23) Joung, K. O.; O'Connor, C. J.; Sinn, E.; Carline, R. L. *Inorg. Chem.* **1979**, *18*, 804.
(24) Sacconi, L.; Bertini, I.; Mani, F. *Inorg. Chem.* **1967**, *6*, 262.
(25) Walker, T. E.; London, R. E.; Whaley, T. W.; Barker, R.; Matwiyoff, N. A. *J. Am. Chem. Soc.* **1976**, *98*, 5807.
(26) Honda, S.; Matsuda, Y.; Takahashi, M.; Kakehi, K. *Anal. Chem.* **1980**, *52*, 1079.
(27) Watanabe, N.; Toda, G.; Ikeda, Y. *Bunseki Kagaku* **1984**, *33*, E241.
(28) *Photon Factory Activity Report*; National Laboratory for High Energy Physics: Ibaraki, Japan, 1986; No. 3.
(29) In order to avoid higher harmonics contamination, we measured X-ray absorption spectra keeping the maximum absorbance by the system less than 4. Under such conditions, the amount of higher harmonics X-rays detected by SSD is less than 0.2% of that of the fundamental X-rays. Nomura, M. *KEK Reports*; National Laboratory for High Energy Physics: Ibaraki, Japan, 1985; No. 85-7.

Table I. Results of C-2 Epimerization of Aldoses Promoted by $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$

no.	starting aldose[a]	conditions[a]	ratio of C-2 epimers[b]	total aldoses[c]
1	D-Glc	60 °C, 4 min	45:55[d]	94
2	D-Man	60 °C, 4 min	34:66[d]	93
3	D-Qui	60 °C, 4 min	55:45[e]	85
4	L-Rha	60 °C, 4 min	55:45[e]	91
5	D-Xyl	60 °C, 3 min	49:51[f]	79
6	D-Lyx	60 °C, 3 min	50:50[f]	72
7	D-Ara	65 °C, 2 min	54:46[g]	67
8	D-Rib	65 °C, 2 min	31:69[g]	85
9	D-Gal	60 °C, 4 min	80:20[h]	60

[a] Starting aldoses (1 equiv) were treated with $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ (1 equiv) in methanol under the listed conditions. [b] Ratios of C-2 epimers based on the aldoses obtained from the reaction mixtures. [c] Yields of aldoses based on the starting aldoses (percent). All values were determined by HPLC. [d] Glc:Man. [e] Qui:Rha. [f] Xyl:Lyx. [g] Ara:Rib. [h] Gal:Tal.

absorption spectra, $\mu x = \ln (I_0/I)$, where x is the sample thickness and μ is the total absorption, were recorded as a function of the X-ray photon energy E, with an integration time of 1–2 s/point (constant I_0 accumulation) at room temperature and 500 steps covering the K edge for Ni (7650–9800 eV). Samples measured were $[Ni(en)_3](NO_3)_2$ (powder), $[Ni_2Cl_2(en)_4]Cl_2$ (powder), $[Ni(N\text{-(L-Rha)tn})_2]Br_2\cdot CH_3OH\cdot 2H_2O$ (powder), $(\mu\text{-D-Man})[Ni_2(CH_3OH)(N\text{-(D-Man)-}N,N'\text{-}Me_2en)(N,N'\text{-(D-Man)}_2\text{-}N,N'\text{-}Me_2en)]Cl_2\cdot CH_3OH\cdot 5H_2O$ (powder), $Ni(N,N,N',N'\text{-}Me_4en)Cl_2$ (powder), a methanolic solution of $NiCl_2\cdot 6H_2O$ (0.1 M) and $N,N,N',N'\text{-}Me_4en$ (0.2 M) (25 °C), and a methanolic solution of $NiCl_2\cdot 6H_2O$ (0.1 M), $N,N,N',N'\text{-}Me_4en$ (0.2 M), and D-glucose (0.1 M) (an equilibrium state was obtained about 40–60 min after the initiation of the reaction; 25 °C).

EXAFS Analysis. The extended X-ray absorption spectrum is derived from the absorption spectrum above the Ni K edge; $E_0 = 8332$ eV. $\mu(\mathbf{k})$ is the absorption coefficient as a function of $\mathbf{k}$, the photoelectron wave vector defined as

$$\mathbf{k} = [(2m/\hbar^2)(E - E_0)]^{1/2}$$

After conversion of E into photoelectron wave vector $\mathbf{k}$, the data were multiplied by $\mathbf{k}^3$ and the modulation of the absorption coefficient, $\chi(\mathbf{k}) = (\mu - \mu_0)/\mu_0$, was obtained by removing a cubic spline background fit to the data with four sections each of $\Delta\mathbf{k} = 4.0$ Å^{-1}, normalized with the edge jump, and corrected for the μ_0 dropoff via Victoreen's true absorption. The theoretical expression of the obtained $\mathbf{k}^3[\chi(\mathbf{k})]$ for the case of single scattering is[30]

$$\mathbf{k}^3[\chi(\mathbf{k})] = \sum_i (\mathbf{k}^2 N_i/r_i^2) S_i[F_i(\mathbf{k})] \exp(-2\sigma_i^2\mathbf{k}^2) \sin(2\mathbf{k}r_i + \Phi_i(\mathbf{k}))$$

where r_i, N_i, S_i, $F_i(\mathbf{k})$, $\Phi_i(\mathbf{k})$, and σ_i represent the interatomic distance, the coordination number, the reducing factor, the backscattering amplitude, the phase shift, and the Debye–Waller factor, respectively. The backscattering amplitude $F_i(\mathbf{k})$ and the phase shift $\Phi_i(\mathbf{k})$ functions employed were the theoretical curves tabulated by Teo and Lee[31,32] as

$$F_i(\mathbf{k}) = A_i/(1 + B_i^2(\mathbf{k} - C_i)^2)$$

$$\Phi_i(\mathbf{k}) = P_{0i} + P_{1i}\mathbf{k} + P_{2i}\mathbf{k}^2 + P_{3i}/\mathbf{k}^3$$

Four parameters, N_i, r_i, E_{0i}, and σ_i, were varied in the nonlinear least-squares refined curve fitting, and the fixed reducing factors S_i obtained from the analysis of model compounds were used. All calculations were performed on a HITAC M-682H computer at the Computer Center of the University of Tokyo with the systematic programs EXAFS1.[33] Plots of background-substracted raw EXAFS data ($\mathbf{k}^3[\chi(\mathbf{k})]$) and the results of curve fitting (observed vs calculated EXAFS oscillations) are available as supplementary material.

Table II. Results of C-2 Epimerization of D-Glucose or D-Mannose Using Various Diamines and Their Derivatives with Nickel(II) Ions

		D-Glc (substrate)[a]		D-Man (substrate)[a]	
no.	diamine or deriv[a]	ratio of C-2 epimers[b,d]	yield of aldoses[c]	ratio of C-2 epimers[b,e]	yield of aldoses[c]
1	en	0:100	98	0:100	99
2	$N,N\text{-}Me_2en$	11:89	86	trace:100	95
3	$N,N'\text{-}Me_2en$	2:98	95	7:93	85
4	$N,N'\text{-}Ph_2en$	0:100	96	0:100	93
5	$N,N,N'\text{-}Me_3en$	38:62	91	42:58	86
6	$N,N\text{-}Me_2\text{-}N'\text{-Eten}$	51:49	91	47:53	82
7	$N,N,N',N'\text{-}Me_4en$	56:44	98	44:56	94
8	$N,N,N',N'\text{-}Me_4tn$	2:98	82	0:100	82
9	Et_3N	trace:100	99	0:100	99
10	$N,N\text{-}Me_2eta$	trace:100	99	trace:100	99
11	$N,N\text{-}Me_2$GlyMeamide	0:100	96	0:100	100

[a] Substrate (D-Glc or D-Man) was treated with $NiCl_2\cdot 6H_2O$ (1 equiv) and the listed diamine or its derivative (2 equiv) in methanol at 60 °C for 5 min. [b] Ratios of C-2 epimers based on the aldoses obtained from the reaction mixture. Values were determined by HPLC. [c] Yields of aldoses (D-Glc + D-Man) based on the substrate (percent). Values were determined by HPLC. [d] Man:Glc. [e] Glc:Man.

Results and Discussion

C-2 Epimerization of Aldoses Promoted by Nickel(II) Diamine Complexes. Aldoses treated with $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ (60 °C, 3–4 min) were rapidly epimerized at C-2 to give mixtures of C-2 epimers (Table I). Ratios of C-2 epimeric aldoses varied according to the starting aldoses used; D-Xyl, D-Lyx, L-Rha, and D-Qui gave ca. 1:1 mixtures of C-2 epimers, which were regarded as an equilibrium states, whereas D-Glc, D-Man, D-Gal, D-Tal, D-Ara, and D-Rib did not reach equilibrium. In addition, when D-Glc, D-Man, D-Xyl, D-Lyx, L-Rha, or D-Qui was used as a starting sugar, a stereoselective complexation of the mannose-type aldoses having a cis arrangement of C-2 and C-3 hydroxyl groups was observed; that is, of the two C-2 epimers in the reaction mixture, nickel(II) ions form complexes only with D-Man, D-Lyx, or D/L-Rha with the formation of N-glycoside bonds between sugars and diamines.[18,34] Although this stereoselective complex formation is very useful for the preparation and isolation of the mannose-type aldoses from their C-2 epimers, the characteristics of the present epimerization were complicated by the presence of N-glycoside bond formation. With extended reaction time, the color of the reaction mixtures changed from blue-green to green (3–4 min), and to brown (about 30 min), indicating the occurrence of complicated side reactions probably involving N-glycoside formations and subsequent degradations or browning reactions[35] as well as ketose formations.

Thus, we explored more simple and effective C-2 epimerization systems using other N-substituted diamines and their derivatives with nickel ions (Table II). It was surprisingly observed that $N,N,N',N'\text{-}Me_4en$, which cannot form N-glycosides with aldoses, is very effective for the epimerization with nickel(II) ions. These observations importantly indicated that the C-2 epimerization did not proceed through the formation of N-glycoside. Furthermore, the fact that both Et_3N and $N,N,N',N'\text{-}Me_4tn$ promote almost no epimerization interestingly showed that the length of the methylene carbon chain in the diamines is very important in this reaction.

Since the reaction promoted by the tertiary symmetrical diamine $N,N,N',N'\text{-}Me_4en$ and the nickel(II) system was very simple, without any browning reaction via N-glycoside formation, we chose $N,N,N',N'\text{-}Me_4en$ as a diamine for subsequent, more detailed studies of C-2 epimerization of aldoses. First of all, the optimum reaction conditions were determined by varying the ratio of sugar:nickel:diamine, reaction temperature, and reaction time. In the D-Glc ⇌ D-Man transformation system, the reaction rate increases with increasing concentrations of Ni^{2+} and diamine, and

(30) Sayers, D. E.; Stern, E. A.; Lytle, F. W. *Phys. Rev. Lett.* **1971**, *27*, 1204.
(31) Teo, B. K.; Lee, P. A.; Simons, A. L.; Eisenberger, P.; Kincaid, B. M. *J. Am. Chem. Soc.* **1977**, *99*, 3854.
(32) Teo, B. K.; Lee, P. A. *J. Am. Chem. Soc.* **1979**, *101*, 2815.
(33) Kosugi, N.; Kuroda, H. Program EXAFS1; Research Center for Spectrochemistry, University of Tokyo: Tokyo, Japan, 1985.
(34) Further detailed studies concerning the stereoselective complexation of the mannose-type aldoses with be dealt with elsewhere.
(35) Paulsen, H.; Pflughaupt, K. W. *Carbohydrates: Chemistry and Biochemistry*; Academic: New York, 1980; Vol. IB, p 881.

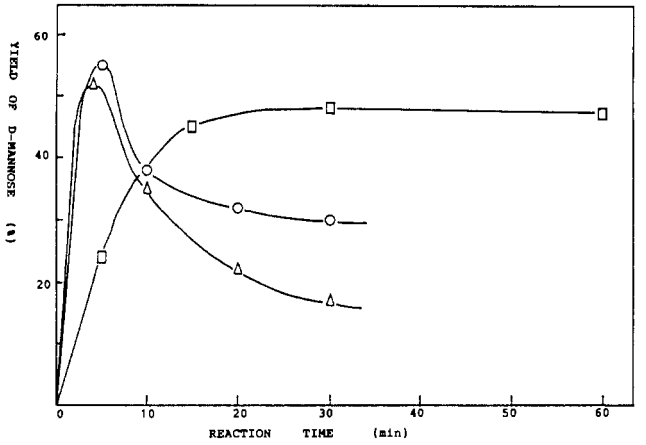


Figure 1. Plots showing the yield of D-mannose (C-2 epimer) vs reaction time. D-Glucose (substrate) was treated with (○) $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N′,N′*-Me_4en (2 equiv) at 60 °C, (□) $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N′,N′*-Me_4en (2 equiv) at 25 °C, and (△) $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)_2]Cl_2$ (1 equiv) at 60 °C, all in methanol.

Table III. Results of C-2 Epimerization of Aldoses Promoted by the Nickel(II)–*N,N,N′,N′*-Me_4en Complex Compared with the Ratios of C-2 Epimers in the Thermodynamic Equilibrium States

no.	starting aldose[a]	conditions[a]	ratio of C-2 epimers[b]	total aldoses[c]	ratios of C-2 epimers in thermodynamic equil[d]
1	D-Glc	60 °C, 5 min	44:56[e]	98	70:30[e]
2	D-Glc	25 °C, 30 min	52:48[e]	99	
3	D-Man	60 °C, 5 min	44:56[e]	94	
4	D-Man	25 °C, 30 min	43:57[e]	99	
5	D-Gal	60 °C, 5 min	36:64[f]	80	86:14[f]
6	D-Tal	60 °C, 5 min	31:69[f]	80	
7	D-Qui	60 °C, 5 min	55:45[g]	82	
8	L-Rha	60 °C, 5 min	56:44[g]	80	
11	D-Xyl	60 °C, 5 min	29:71[h]	100	67:33[h]
12	D-Xyl	25 °C, 30 min	33:67[h]	100	
13	D-Lyx	60 °C, 5 min	30:70[h]	100	
14	D-Lyx	25 °C, 30 min	34:66[h]	100	
15	D-Ara	60 °C, 5 min	31:69[i]	88	69:31[i]
16	D-Rib	60 °C, 5 min	31:69[i]	98	

[a] Starting aldoses (1 equiv) were treated with $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N′,N′*-Me_4en (2 equiv) in methanol under the listed conditions. [b] Ratios of C-2 epimers based on the aldoses obtained from the reaction mixtures. Values were determined by HPLC. [c] Yields of aldoses based on the starting aldoses (percent). Values were determined by HPLC. [d] Ratios of C-2 epimers in thermodynamic equilibria calculated from $G°'$ values given by Angyal.[37] [e] Glc:Man. [f] Gal:Tal. [g] Qui:Rha. [h] Xyl:Lyx. [i] Ara:Rib.

the best yield of the C-2 epimer was obtained with a ratio of sugar:nickel:diamine of 1:1:2.[36] Further additions of Ni^{2+} and diamine could not improve the reaction. When the reaction was carried out at 60 °C with the ratio mentioned above, it reached an equilibrium within 5 min where any significant side reactions including the ketose formation were not observed, but extended reaction times decreased the yield of the C-2 epimer due to ketose formation promoted by diamines, which act as simple bases (Figure 1). Even under milder reaction conditions at 25 °C, the C-2 epimerization proceeded smoothly and reached equilibrium after 40–60 min.

Several aldoses were treated with $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N′,N′*-Me_4en (2 equiv) in methanol at 60 °C for 5 min, and the results are listed in Table III. Unlike the case with $[Ni(H_2O)_2(N,N,N'\text{-}Me_3en)]Cl_2$, all aldoses used were rapidly epimerized at C-2 to give equilibrium mixtures of C-2 epimers. The ratios of C-2 epimers in the equilibria greatly shift to the side of the mannose-type aldoses compared with those in the thermodynamic equilibrium states[37] (Table III). Because of the remarkably fast reaction rate and the high yields, the present epimerization could be very useful for the synthesis of naturally rare mannose-type aldoses from their C-2 epimers.

(36) Although the present reaction proceeds with a catalytic amount of nickel(II) diamine complexes, the nickel catalysts become inactivated within several turnovers. We are now investigating the catalytic reaction, including kinetic studies as well as inhibition mechanisms.

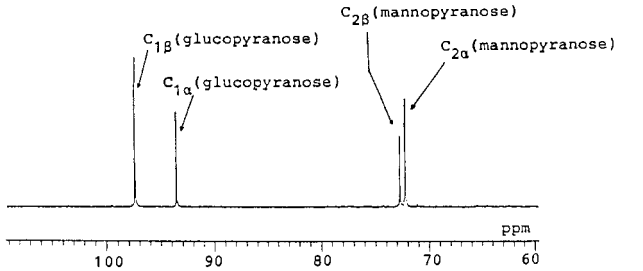
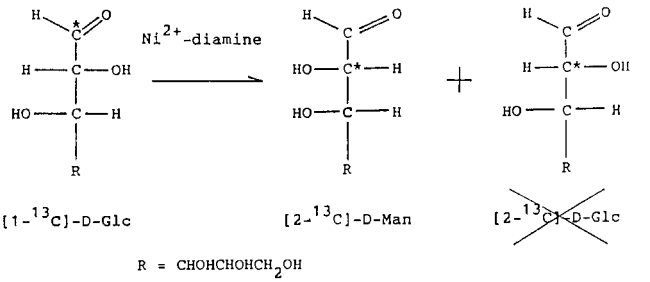


Figure 2. ^{13}C NMR spectrum of the product mixture obtained from the reaction of D-[1-^{13}C]glucose with Ni^{2+} and *N,N,N′,N′*-Me_4en.

Scheme I



The results of several blank tests showed that both nickel ions and diamines are indispensable to the epimerization and neither can be replaced by other normal acids and bases.[38] In addition, several analogues of D-glucose were tested. Methyl glycosides (methyl α-D-glucopyranoside, methyl α-D-mannopyranoside) and 4-O-substituted disaccharides (D-lactose, D-cellobiose) did not epimerize, but in contrast, 3-*O*-methyl-D-glucose did epimerize. These results demonstrate that the free C-1 carbonyl group and the C-4 hydroxyl group are essential, and the C-3 hydroxyl group is not essential to the epimerization. These experimental results suggest that a complex of Ni^{2+}, diamine, and aldose is the reactive species in this C-2 epimerization.

C-2 Epimerization of D-[1-^{13}C]Glucose. D-[1-^{13}C]Glucose was used as a starting sugar to clarify the mechanism of this C-2 epimerization. It was treated with $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N′,N′*-Me_4en (2 equiv) at 60 °C for 5 min in methanol, and the sugar mixture in the reaction solution was purified as described in the Experimental Section. The ^{13}C NMR spectrum of the product mixture is given in Figure 2. Besides the peaks at 97.4 and 93.6 ppm for C-1 of β- and α-D-glucopyranose (substrate), two new resonances appeared at 72.7 and 72.2 ppm, which were surprisingly assigned to those for C-2 of β- and α-D-mannopyranose, respectively.[25] The expanded spectrum showed the unenriched carbon resonances, in which C-1 of β- and α-D-mannopyranose (95.5, 95.2 ppm) exhibited large one-bond C–C coupling constants (42.7 and 46.4 Hz, respectively) as expected for a 2-^{13}C-enriched aldose. This observation demonstrates that the reaction involves a novel exchange of C-1 and C-2 atoms by inversion of the C-1–C-2 fragment. In general, the exchange of C-1 and C-2 atoms produces a new chiral center on the C-1 atom, resulting in the production of two epimeric isomers, D-[2-^{13}C]-mannose and D-[2-^{13}C]glucose (Scheme I). However, the product from D-[1-^{13}C]glucose was exclusively D-[2-^{13}C]mannose, indi-

(37) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157.

(38) Several blank tests were run as follows. Aldoses were treated with (a) Ni^{2+} (1 equiv), (b) *N,N,N′*-Me_3en or *N,N,N′,N′*-Me_4en (2 equiv), (c) NaOH (2 equiv), (d) Ni^{2+} (1 equiv) + NaOH (2 equiv), and (e) H_2SO_4 (1 equiv) + *N,N,N′*-Me_3en or *N,N,N′,N′*-Me_4en (2 equiv) under the standard reaction conditions described in the Experimental Section. In no cases were the starting aldoses epimerized.

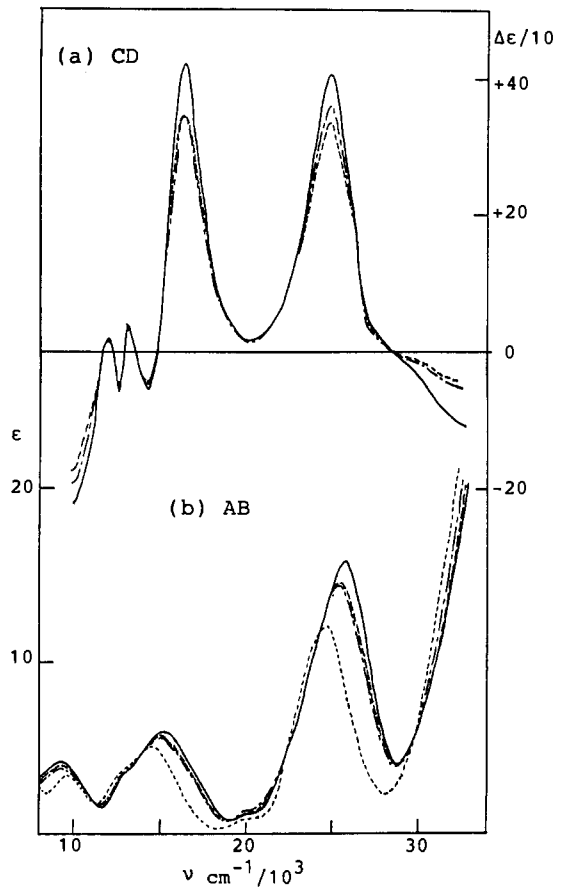


Figure 3. CD (a) and AB (b) spectra of the reaction solutions: (—) $NiCl_2 \cdot 6H_2O$ (1 equiv) + *N,N,N',N'*-Me_4en (2 equiv) + D-Glc (1 equiv), at 25 °C after 60 min (containing D-Man and D-Glc in the ratio 49:51); (- - -) $NiCl_2 \cdot 6H_2O$ (1 equiv) + *N,N,N',N'*-Me_4en (2 equiv) + D-Glc (1 equiv), at 25 °C after 5 min (containing D-Man and D-Glc in the ratio 24:76); (—) $NiCl_2 \cdot 6H_2O$ (1 equiv) + *N,N,N',N'*-Me_4en (2 equiv) + D-Man, at 25 °C after 5 min (containing D-Man and D-Glc in the ratio 82:18); (- - -) $NiCl_2 \cdot 6H_2O$ (1 equiv) + *N,N,N',N'*-Me_4en (2 equiv) (the starting solution).

cating that the rearrangement proceeds with complete stereospecificity. In addition, when this reaction was carried out in CH_3OD with $NiCl_2$ + *N,N,N',N'*-Me_4en or $[Ni(D_2O)_2(N,N,N',N'\text{-}Me_4en)_2]Cl_2$, no carbon-bound proton was exchanged. This completely ruled out the possibility that the present epimerization proceeds via an ene–diol intermediate catalyzed by base.[39]

Absorption and CD Spectra of the Reaction Solutions. The methanolic solution of $NiCl_2 \cdot 6H_2O$ and D-Glc (or D-Man) showed no Cotton effect in the d–d transition region for Ni(II) complexes, demonstrating that, without diamines, starting aldoses are away from the coordination sphere of nickel, resulting in no significant interaction between sugars and metal ions. In contrast, in the presence of *N,N,N',N'*-Me_4en, the reaction solutions immediately exhibited Cotton effects in the d–d transition region with moderate intensities (Figure 3a), and these spectra were quite different in intensity and in spectral patterns from those observed in the mild alkaline solutions (methanolic NaOH, etc.) of nickel ions and aldoses. The latter show very weak CD spectra, probably reflecting the weak interactions between sugars and metal ions as reported by Angyal.[40] Furthermore, the solutions of $NiCl_2 \cdot 6H_2O$ and methyl glycosides (methyl α-D-glucopyranoside or methyl α-D-mannopyranoside), which do not have free carbonyl groups, gave no moderate CD spectra in spite of the addition of diamines. These observations strongly suggested the presence of a comparatively stable intermediate nickel(II) complex containing both sugars and diamines, and considering the failure of methyl glycosides, the formation of carbinolamine-like adducts of sugars with diamines is thought to be a rational initial step in this C-2 epimerization.

Furthermore, CD spectra showed almost identical patterns during the reaction independent of the ratios of C-2 epimers (Glc/Man) contained in the solution (Figure 3a). These results indicate that the dominant stable intermediate complexes have almost identical structures in the first coordination sphere around the nickel no matter which epimer is used as a substrate. In addition, these CD spectra are very similar to that of the solution containing Ni^{2+}, *N,N,N',N'*-Me_4en, and 2-deoxy-D-glucose. This implies that no rigid chelation of sugar parts, especially the coordination of C-2 hydroxyl groups,[10,11,15] is included in the complexes.

Absorption (AB) spectra of the reaction solutions also support these conclusions. The AB spectrum of the starting methanolic solution of $NiCl_2 \cdot 6H_2O$ and *N,N,N',N'*-Me_4en (Figure 3b), which is similar to that reported for dimeric Ni(*N,N,N',N'*-Me_4en)Cl_2[24] (**5**), changed with the addition of aldoses to those characteristic of mononuclear octahedral complexes such as Ni(*N,N,N',N'*-Me_4en)$(NO_2)_2$.[24] The energy of the first absorption band maximum (9.33×10^3 cm^{-1}) indicates that the intermediate complex contains one diamine unit.

These observations suggested that the stable intermediate nickel(II) complexes, regarded as one species concerning the local structure around the metal center, were predominant in the reaction mixture, and possible minor nickel species were not detected in AB and CD spectra. Thus, with an aim to obtain direct structural information around nickel, we have tried an EXAFS analysis of the reaction solutions described in the next section.

EXAFS Analysis for the Intermediate Nickel(II) Complex. In order to further develop discussion as to the reaction mechanism, it is necessary to obtain an understanding of the structural details around the metal center. EXAFS is best suited for the purpose because it can pursue local structure changes around a selected atomic species at every step during the reaction.

First, the EXAFS spectra of $[Ni(en)_3](NO_3)_2$ (**1**), $[Ni_2Cl_2(en)_4]Cl_2$ (**2**), $[Ni(N\text{-}(L\text{-}Rha)tn)_2]^{2+}$ (**3**), and (μ-D-Man)$[Ni_2(CH_3OH)(N\text{-}(D\text{-}Man)\text{-}N,N'\text{-}Me_2en)(N,N'\text{-}(D\text{-}Man)_2\text{-}N,N'\text{-}Me_2en)]^{2+}$ (**4**) were measured as reference compounds to examine the reliability of our EXAFS analysis for nickel(II) complexes containing diamines and sugars. In this study, we used alternative Fourier-filtering techniques to avoid trivial errors from strong parameter correlations in multiterm curve fittings. The fourier transforms of the raw data are presented in Figure 4, and the results of the curve-fitting analysis are listed in Table IV. The Fourier transforms of monomeric **1** and **3** show two intense peaks at about 1.6 and 2.7 Å (before phase-shift correction), which were back-Fourier-transformed by the use of proper windows to produce abstracted EXAFS oscillations subjected to the curve-fitting analysis (Figure 4a,c). The first large peaks are attributable to the nitrogen and oxygen atoms directly coordinating to the nickel, and the second peaks were ascribed to the contribution of carbon atoms in the chelation rings. The Fourier transform of **4** (Figure 4d) exhibits a small peak around 3.3 Å together with two intense peaks as observed in those of **1** and **3**, and it is assigned to the Ni–Ni interaction with a distance of 3.56 Å. In the Fourier transform of **2** (Figure 4b), four significant peaks are observed at about 1.6, 2.1, 2.6, and 3.3 Å (before phase-shift correction), which are assigned to the nitrogen atoms coordinating to the nickel (r = 2.05 Å), the bridging chlorine atoms (r = 2.50 Å), the carbon atoms included in the five-membered chelate rings (r = 2.96 Å), and the nickel atoms in the outer shell (r = 3.70 Å), respectively, from the one-term curve-fitting analysis. All these results derived from EXAFS analysis are in good agreement with those from X-ray crystallography and demonstrate that the Ni–Ni interactions within the distance of ca. 3.8 Å are clearly observable in the EXAFS spectroscopy using the SOR ring radiation.

The Fourier transform of the methanolic solution of $NiCl_2 \cdot 6H_2O$ (1 equiv) and *N,N,N',N'*-Me_4en (2 equiv) is shown in Figure 5b, and is very similar to that of Ni(*N,N,N',N'*-Me_4en)Cl_2 (**5**) (Figure 5a), the latter being reported to have a dimeric structure of nickel with the four-coordinated tetrahedral configuration from the results of elemental analysis and magnetic susceptibility.[24]

(39) Sowden, J. C.; Schaffer, R. *J. Am. Chem. Soc.* **1952**, *74*, 505.
(40) Angyal, S. J. *Chem. Soc. Rev.* **1980**, *9*, 415.

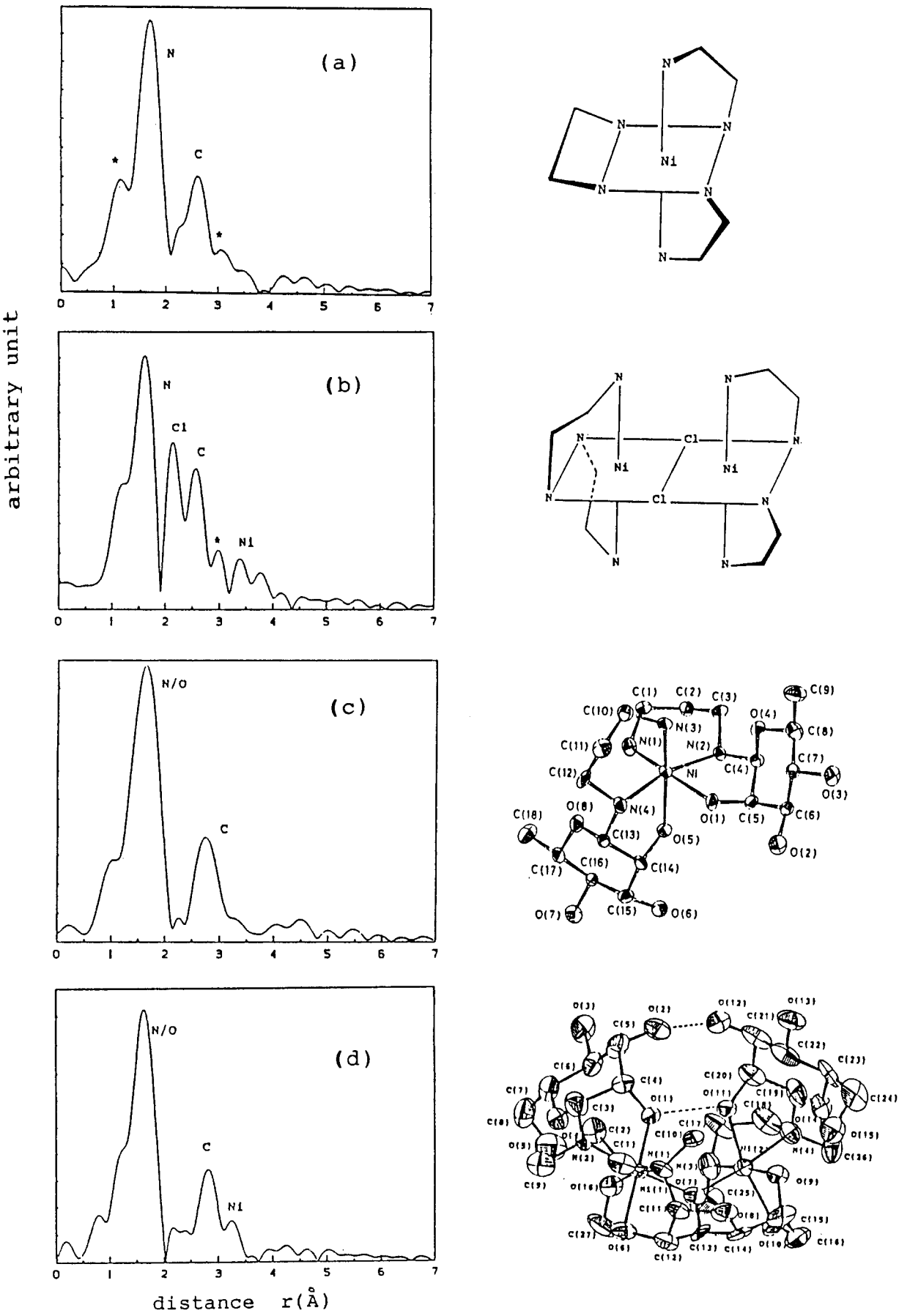


Figure 4. EXAFS Fourier transforms with structural views of the complexes: (a) $[Ni(en)_3](NO_3)_2$ (**1**); (b) $[Ni_2(en)_4Cl_2]Cl_2$ (**2**); (c) $[Ni(N\text{-(L-Rha)tn})_2]^{2+}$ (**3**); (d) (μ-D-Man)$[Ni_2(CH_3OH)(N\text{-(D-Man)-}N,N'\text{-}Me_2en)(N,N'\text{-(D-Man)}_2\text{-}N,N'\text{-}Me_2en)]^{2+}$ (**4**). The peaks marked with asterisks were not assigned to any reasonable backscattering atoms.

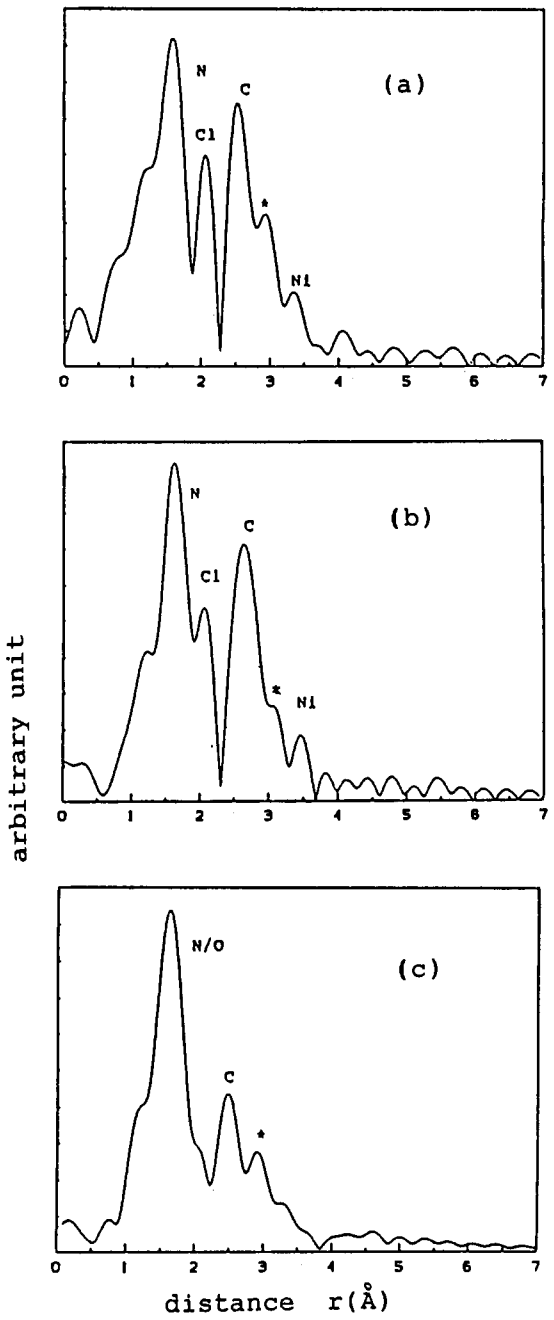


Figure 5. EXAFS Fourier transforms: (a) Ni(*N,N,N',N'*-Me_4en)Cl_2 (**5**); (b) $NiCl_2 \cdot 6H_2O$ + 2 *N,N,N',N'*-Me_4en (in methanol) (**6**); (c) $NiCl_2 \cdot 6H_2O$ + 2 *N,N,N',N'*-Me_4en + D-Glc (in methanol, an equilibrium state at 25 °C) (**7a**, **8a**). The peaks marked with asterisks were not assigned to any reasonable backscattering atoms.

Four peaks around 1.6, 2.1, 2.6–2.7, and 3.4 Å (before phase-shift correction) are observed in both cases and are assigned to the nitrogen (or oxygen) atoms in the first shell, the bridging chlorine atoms, the carbon atoms binding to the coordinating nitrogen atoms, and the nickel atoms in the outer shell, respectively, just as in the analysis of dimeric complex **2** (Table IV). However, the coordination numbers of N (or O), Cl, C, and Ni of the starting complex in the solution systematically differ from those of **5**, suggesting that dimeric structure of nickel has the six-coordinated octahedral geometry as in **2** (Table IV). The estimated structure **6** is shown in Scheme II.

In contrast, the Fourier transform of the methanolic solution of $NiCl_2 \cdot 6H_2O$ (1 equiv), *N,N,N',N'*-Me_4en (2 equiv), and D-glucose (1 equiv) (an equilibrium state at 25 °C) dramatically changes from that of the starting solution (Figure 5c); the Ni–Cl and Ni–Ni peaks disappear and the remaining two peaks at about 1.6 and 2.5 Å are attributable to the nitrogen and/or oxygen atoms in the first coordination sphere (N = 5.8) and the carbon atoms in the outer shell. These directly indicate that the stable intermediate complex proposed in the preceding section is a mononuclear nickel(II) complex having the six-coordinated octahedral structure. Furthermore, considering the AB and CD spectral data, the mononuclear intermediate nickel(II) complex can be thought to contain one diamine residue and one sugar unit.

Thus, useful information was obtained from the EXAFS study with regard to the dynamic structural changes around the nickel center during the reaction; the mononuclear intermediate nickel(II) complex was produced with the addition of substrate aldose to the nickel–*N,N,N',N'*-Me_4en solution in which the binuclear nickel(II) complex with the chlorine bridge predominantly existed as a precursor.

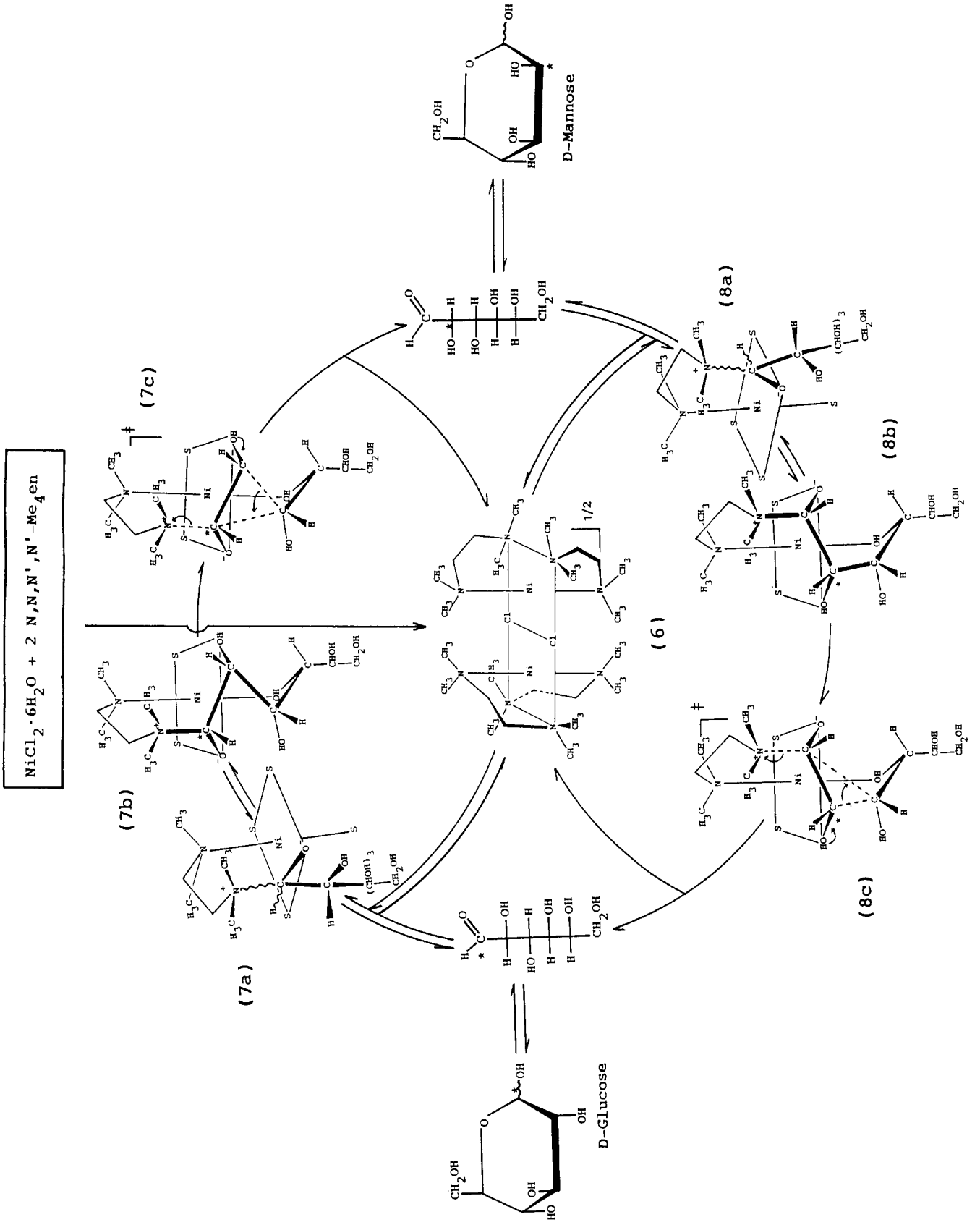
Proposed Reaction Mechanism. In light of the results of NMR and EXAFS studies as well as AB and CD spectral data, we propose a possible mechanism for the epimerization of Glc to Man with the nickel(II)–*N,N,N',N'*-Me_4en complex (Scheme II).

The initial step is probably the reaction of the dimeric starting nickel(II) complex **6** and D-glucose in the aldehyde form with the formation of a carbinolamine-like adduct, to give the comparatively stable intermediate complex with a mononuclear octahedral structure **7a**. The direct addition of diamine to form the carinolamine intermediate is a more reasonable initial step than the hydration of aldoses as proposed by London,[41] because aldoses easily react with amino groups to yield glycosylamines through the carbinolamine intermediates in methanolic solution.[35] This is also supported by our previous studies on the formation of *N*-glycoside–nickel(II) complexes[10-17] as well as the results of blank tests.[38] In **7a**, the terminal amino group plays an important role in anchoring the sugar unit to the nickel, because aldoses have very weak affinities for nickel(II) ions. Moreover, it is expected that two diastereomeric carbinolamines, 1*S*,2*S*-**9** and 1*R*,2*S*-**9**, are involved in complex **7a** (Scheme III). Of the two diastereomeric carbinolamines, only 1*R*,2*S*-**9** can take the rigid conformation suitable for the pinacol-type rearrangement of the carbon skeleton around the metal center of **7b**, where the C-1 ammonium group and C-2 hydroxyalkyl group have the anti conformation. In **7b**, the valence electrons on the C-1 carbon are withdrawn by the metal via the coordination of the C-1 hydroxyl group and by the C-1 ammonium group, producing an electron-poor carbon 1, and consequently, C-2 epimerization can occur through the transition state **7c**, in which C-2–C-3 bond breaking and C-1-C-3 bond forming take place simultaneously accompanied by elimination of the diamine residue. Then, D-mannose (product) is disconnected from the complex. In contrast to this, the other carbinolamine, 1*S*,2*S*-**9**, which will be transformed into D-glucose if possible, cannot take the conformation suitable for this rearrangement, resulting in the failure to transform. On the basis of this mechanism, it can be said that the stereospecificity of this reaction might be determined at the step forming the complex **7b** and retained with the cyclic transition state **7c**.

D-Mannose in the reaction solution also transformed into D-glucose through the similar intermediate complexes **8a** and **8b**. In the cycle as depicted in Scheme II, **7a** and **8a** are thought to be the predominant species in the reaction, which were characterized by AB and CD spectra and EXAFS analysis. As regards the ratio of C-2 epimeric aldoses in the equilibrium state, it must be basically determined by these predominant species to be ca. 1:1, but it is also expected that the probable weak interactions between aldoses and nickel ions, including the complexation of cyclic sugars with axial–equatorial–axial arrangement of hydroxyl groups as shown by Angyal,[40] shift it further to the side of the mannose-type epimers.

This proposed mechanism of the rearrangement can be accommodated within the context of a pinacol-type rearrangement and is consistent with all experimental observations. Although a few asymmetric syntheses using pinacol-type rearrangements with organoaluminum complexes have been reported recently,[42-44]

(41) London, R. E. *J. Chem. Soc., Chem. Commun.* **1987**, 661.
(42) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1983**, *24*, 4997.


NiCl2·6H2O + 2 N,N,N',N'-Me4en
D-Mannose
D-Glucose
(6)
(7a)
(7b)
(7c)
(8a)
(8b)
(8c)
1/2

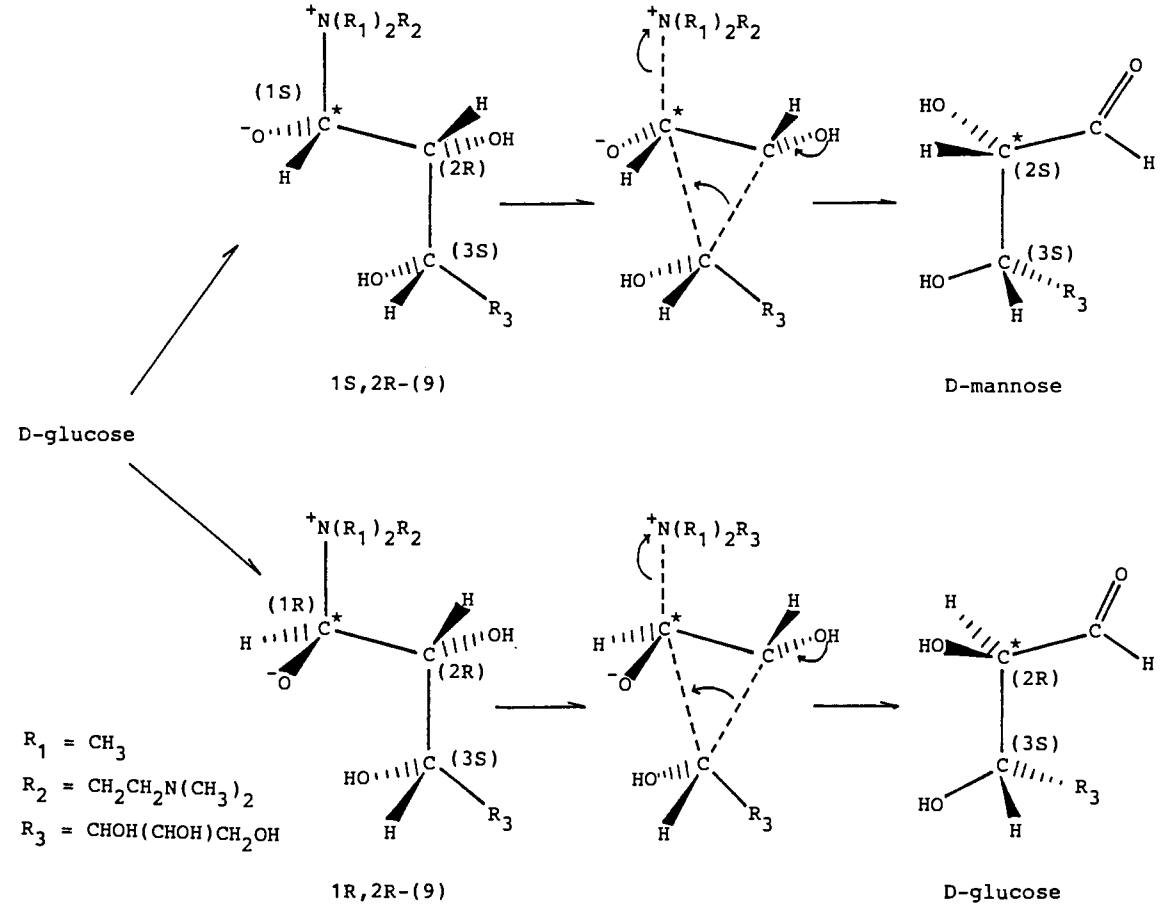
Scheme II

Table IV. Atomic Parameters Determined by Curve-Fitting Analysis

		EXAFS				X-ray crystallogr	
no.	complex	A–B[a]	r, Å[b]	N	σ	r, Å	N
1	$[Ni(en)_3](NO_3)_2$ (powder) (**1**)	Ni–N	2.10	6.0[c]	0.036	2.12 (1)	6
		Ni–C	2.99	6.0[c]	0.077		
2	$[Ni_2(en)_4Cl_2]Cl_2$ (powder) (**2**)	Ni–N	2.05	3.9	0.043	2.10 (1)	4
		Ni–Cl	2.50	2.0[d]	0.051	2.51 (5)	2
		Ni–C	2.96	2.6	0.030		
		Ni–Ni	3.70	1.0[d]	0.094	3.756 (1)	1
3	$[Ni(N$-(L-Rha)tn$)_2]^{2+}$ (powder) (**3**)	Ni–N/O[e]	2.08	6.9	0.052	2.12 (4)	6
		Ni–C	3.11	5.1	0.057		
4	(μ-D-Man)$[Ni_2(CH_3OH)(N$-(D-Man)-N,N'-Me_2en)-(N,N'-(D-Man)$_2$-N,N'-Me_2en)$]^{2+}$ (powder) (**4**)	Ni–N/O[e]	2.06	6.8	0.039	2.10 (6)	6
		Ni–C	3.13	3.8	0.029		
		Ni–Ni	3.56	1.4	0.096	3.596 (4)	1
5	Ni(N,N,N',N'-Me_4en)Cl_2 (powder) (**5**)	Ni–N	2.05	2.8	0.032	unknown	
		Ni–Cl	2.45	1.6	0.050		
		Ni–C	2.94	4.6	0.037		
		Ni–Ni	3.64	1.0	0.095		
6	$NiCl_2 \cdot 6H_2O$ + 2 N,N,N',N'-Me_4en (in methanol) (**6**)	Ni–N	2.07	3.5	0.038	unknown	
		Ni–Cl	2.45	2.0	0.054		
		Ni–C	3.02	8.2	0.049		
		Ni–Ni	3.73	0.8	0.084		
7	$NiCl_2 \cdot 6H_2O$ + 2 N,N,N',N'-Me_4en + D-Glc (in methanol) (**7a**, **8a**)	Ni–N/O[e]	2.08	5.8	0.049	unknown	
		Ni–C	2.89	3.5	0.040		

[a] A is the absorber (Ni) and B is the backscattering atom. [b] Estimated errors are ±0.03 Å for inner shell and ±0.04 Å for outer shell. [c] The numbers of neighbor atoms (Ni–N/O, Ni–C) referenced to complex **1**. [d] The numbers of neighbor atoms (Ni–Cl, Ni–Ni) referenced to complex **2**. [e] All backscattering atoms in the first sphere are calculated as nitrogen.

Scheme III



the present stereospecific pinacol-like rearrangement promoted by nickel(II) complexes is the first finding in the field of carbohydrate chemistry as well as coordination chemistry.

In summary, aldoses treated with nickel(II) diamine complexes are rapidly epimerized at C-2 to give equilibrium mixtures of C-2 epimers. The mechanism of this epimerization involves the formation of monomeric nickel(II) intermediate complexes, where the carbinolamine-like adducts from aldoses and diamines undergo stereospecific rearrangement of the carbon skeleton or a pinacol-type 1,2-carbon shift. In other words, this novel epimerization is a new type of 1,2-carbon skeletal rearrangement using metal complexes and could lead to some new synthetic procedures in organic chemistry. Furthermore, the remarkable aspect is the

(43) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 1817.
(44) Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* **1984**, *25*, 4253.

extremely mild set of conditions required for this rearrangement, suggesting that analogous processes might occur in biological systems.

Acknowledgment. We wish to thank Dr. Koshiro Toriumi of the Institute for Molecular Science and Dr. Kiyotaka Asakura of the Faculty of Science, University of Tokyo, for their technical assistance and helpful suggestions during the course of EXAFS measurements and analysis and Dr. Nobuyuki Watanabe for detecting ketoses in HPLC analysis. This work was partially supported by Grants-in-Aid for Scientific Research from the Ministry of Education of Japan (63107002, 63470035, 63612002), and by a grant-in-aid from the Mitsubishi Foundation.

Supplementary Material Available: Plots of background-subtracted raw EXAFS data ($\mathbf{k}^3[\chi(\mathbf{k})]$) and the results of curve fitting (observed vs calculated EXAFS oscillations) (4 pages). Ordering information is given on any current masthead page.

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Structural and Conformational Study of the Aluminum-Thymulin Complex Using 1-D and 2-D NMR Techniques

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Received December 15, 1987

The interaction between aluminum and thymulin, a linear nonapeptide of thymic origin isolated from serum, was investigated by means of one- and two-dimensional NMR experiments. These experiments were performed in dimethyl-d_6 sulfoxide solution at different metal:peptide ratios. The results lead the following conclusions: (i) the Al(III) complexation corresponds to a fast exchange on the NMR time scale; (ii) the evolution of ^1H and ^{13}C NMR chemical shifts indicates the existence of one type of complex with a 1:2 stoichiometry, associating two peptide molecules and one Al(III) ion; (iii) analysis of the spectra suggests that Al(III) has a specific binding site involving the Asn^9COO^- terminal group and the hydroxyl group of the Ser^4 residue; (iv) from the NOESY data a conformation has been proposed and compared to the biologically active Zn(II)-thymulin complex.

Introduction

Thymulin, formerly called FTS (for facteur thymique sérique), is a thymic hormone isolated from serum,[1,2] which has been characterized by its capacity to induce T-cell markers and functions on immature cells.[3] Its amino acid sequence was determined to be <Glu^1-Ala^2-Lys^3-Ser^4-Gln^5-Gly^6-Gly^7-Ser^8-Asn^9, and the synthetic hormone proved to be biologically active.[2]

The biological activity of this peptide was shown to be zinc-dependent, and the binding of this metal to thymulin was demonstrated by using labeled molecules ($Kd = (5 \pm 2) \times 10^{-7}$ M).[4] More recently, 1-D and 2-D NMR determinations carried out in DMSO-d_6 led to the conclusion that zinc forms two complexes with the nonapeptide, associating one Zn^{2+} with one (1:1 complex) or two (1:2 complex) peptide molecules. The association constants ($K_1 = 3540$ M^{-1} and $K_2 = 5.0 \times 10^6$ M^{-2} for the 1:1 and 1:2 complexes respectively) are not indicative of a strong interaction and the $Ser^4O\gamma H$, $Ser^8O\gamma H$ and $Asn^9CO_2^-$ sites are coordinated to the metal ion in the 1:1 complex, while in the 1:2 complex the $Ser^8O\gamma H$ site probably no longer interacts with the metal ion.[5]

The importance of metal ions (other than Zn^{2+}) in the biological activity of thymulin has recently been demonstrated.[6]

Among the series of 16 metals investigated in this study,[6] only aluminum and gallium proved to be as active as zinc. However, monoclonal antibodies have been shown to recognize the nonapeptide molecule specifically when complexed with zinc, but neither the free molecule nor the complexes it forms with other metals, notably aluminum.[7]

NMR data indicate the existence on the thymulin molecule of two zinc-specific conformations with a unique structure; it will be of great interest to compare these conformations with those obtained with other metals, and more specifically with aluminum. Such a comparison will be considered very important for the structure-activity relationship, since the thymic hormone is virtually devoid of biological activity.

To this end, we have attempted to obtain information on the conformational states of the nonapeptide-aluminum complex in dimethyl sulfoxide solution by means of the ^1H, ^{13}C, ^{27}Al one- and two-dimensional (^1H, ^1H NOESY) NMR spectroscopy.

From analyses of the spectral data, it is concluded that Al^{3+} interacts with free thymulin to give one kind of complex where the $Ser^4O\gamma H$ and $Asn^9CO_2^-$ sites are bonded in a 1:2 (metal:peptide) complex.

Experimental Section

Materials. Synthetic serum thymic factor was provided by Institut Choay, Paris.[8] $Al(NO_3)_3 \cdot 9H_2O$ was purchased from Sigma. Dimethyl-d_6 sulfoxide (99.95% D) from the Commissariat à l'Energie Atomique (Gif-sur-Yvette, France) was used as solvent.

One-Dimensional NMR Instrumentation. ^1H NMR spectra at 250 MHz and ^{13}C NMR spectra at 62.8 MHz were recorded on a Bruker WM 250 spectrometer equipped with an Aspect 3000 computer system. Field stabilization was provided by an internal deuterium lock-signal. Samples were examined at 33 ± 1 °C. The usual ^1H spectrometer conditions were 2800-Hz sweep width, 16K data points and 250 scans. ^{13}C NMR spectra were recorded with quadrature detection and broad-band proton decoupling. Spectra were obtained by accumulating 60 000-90 000 transients for a $1.5-10 \times 10^{-2}$ M solution of nonapeptide with 16K data points. A radio-frequency pulse of 90° was used, with a spectral width of 15 000 Hz without repetition time. Both ^1H and ^{13}C

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(1) Dardenne, M.; Pléau, J.-M.; Man, N. K.; Bach, J.-F. *J. Biol. Chem.* **1977**, *252*, 8040-8044.
(2) Bach, J.-F.; Dardenne, M.; Pléau, J.-M.; Rosa, J. *Nature (London)* **1977**, *266*, 55-57.
(3) Bach, J.-F. *Clinics in Immunology and Allergy*; Saunders: Philadelphia, PA, 1983; Vol. 3, pp 133-156.
(4) Gastinel, L. N.; Dardenne, M.; Pléau, J.-M.; Bach, J.-F. *Biochim. Biophys. Acta* **1984**, *797*, 147-155.
(5) Cung, M.-T.; Marraud, M.; Laussac, J.-P.; Pasdeloup, M.; Haran, R.; Lefrancier, P.; Dardenne, M.; Bach, J.-F. In *Peptides*; Theodoropoulos, D., Ed.; Walter de Gruyter: Berlin, 1987, pp 295-298.
(6) Dardenne, M.; Pléau, J.-M.; Nabarra, B.; Lefrancier, P.; Derrien, M.: Choay, J.; Bach, J.-F. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 5370-5373.
(7) Dardenne, M.; Savino, W.; Berrih, S.; Bach, J.-F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7035-7038.
(8) Lefrancier, P.; Derrien, M.; Amiot, J.-L.; Choay, J. In *Peptides*; Ragnarman, E., Ed.; Almquist and Wicksell: Stockholm, 1984; pp 251-254.

0020-1669/88/1327-4094$01.50/0