Coordination Chemistry Reviews, 92 (1988) 113–156
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

COORDINATION COMPOUNDS CONTAINING SUGARS AND THEIR DERIVATIVES

SHIGENOBU YANO *

Department of Synthetic Chemistry, Faculty of Engineering, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113 (Japan)

(Received 11 June 1987)

CONTENTS

* Present address: Department of Chemistry, Faculty of Science, Nara Women's University, Nara 630, Japan.

0010-8545/88/$15.40

ABBREVIATIONS

β-alaH	β-alanine
ampr	aminomethylpyrrolidine
en	ethylenediamine
N,N'-Me_2en	N,N'-dimethylethylenediamine
pn	propylenediamine
tn	trimethylenediamine
tmen	N,N,N'-trimethylethylenediamine
tmpn	N,N,N'-trimethylpropylenediamine
tetmen	N,N,N',N'-tetramethylethylenediamine
tren	N,N-di(2-aminoethyl)ethylenediamine
Glc	glucose
Man	mannose
Gal	galactose
Tal	talose
Fuc	fucose (6-deoxy-galactose)
Rha	rhamnose (6-deoxy-mannose)
Qui	quinobose (6-deoxy-glucose)
Ara	arabinose
Lyx	lyxose
Rib	ribose
Xyl	xylose
Fru	fructose
Sor	sorbose
Tag	tagatose
Psi	psicose
GlcN	glucosamine
GalN	galactosamine
ManN	mannosamine
GlcNN	2,3-diamino-2,3-dideoxy-glucose
ManNN	2,3-diamino-2,3-dideoxy-mannose

A. INTRODUCTION

Amino acids and sugars are important compounds in biological systems. These compounds are very interesting in coordination chemistry as ligands and in bioinorganic chemistry in connection with metal-containing enzymes. A large number of transition metal complexes containing amino acids or their derivatives have been synthesized, isolated and characterized. Nevertheless, in spite of the fact that it has been well known that sugars can form

complexes with transition metals, the field of sugars or their related compound–metal complexes is still largely unexplored.

This short review mainly describes our recent studies of the synthesis, characterizations and stereochemistry of the transition metal complexes ($M = Ni^{2+}$, Co^{3+} and Pt^{2+}) containing sugar moieties and related compounds, and novel sugar transformations promoted by nickel(II) complexes of diamines and by combinations of various metal ions (Co^{2+}, Ca^{2+}, Sr^{2+}, Pr^{3+}, Ce^{3+}) and amines. It includes those papers which were published or submitted for publication by the end of April 1987.

B. METAL COMPLEXES CONTAINING SUGAR MOIETIES

(i) Nickel(II) complexes containing an N-glycoside derived from diamines and ketoses

It is well known that cyclic sugars possessing a free reducing group are able to react with primary and secondary amines to give, under mild conditions, *N*-glycosides (glycosylamines), derivatives in which the glycosidic hydroxyl group has been replaced by an amino group. This is generally accepted as being the first step in the "Maillard reaction" or non-enzymatic browning [1].

Previously MacDermott and Busch [2,3] reported that hydroxy ketones reacted with tris(ethylenediamine)nickel(II) salts to give blue paramagnetic bis(tridentate)nickel(II) complexes in which the ligand is the Schiff's base formed from a hydroxy ketone and ethylenediamine. Because ketoses are hydroxy ketones, the above reaction strongly suggests the possible development of a method in which sugars serve as ligands to transition metal ions. Accordingly, it may be predicted that monosaccharides will react with one of the amine centers of $[Ni(diamine)_3]^{2-}$ to form the nickel(II) complexes containing *N*-glycoside(s).

When tris(diamine)nickel(II) salts in methanol are refluxed for a short time with an excess of ketoses, the resulting blue solutions were purified by chromatography on a Sephadex LH-20 gel permeation column and evaporated to give blue crystals or powder [4–6].

These blue complexes have one diamine ligand and one glycosylamine ligand (D-Fru-en, D-Fru-tn, D-Fru-pn, D-Fru-*S*-ampr, L-Sor-en, L-Sor-tn, L-Sor-pn, L-Sor-*S*-ampr etc.). Generally the yields of these complexes were relatively low. However, in the case of trimethylenediamine complexes, the reaction was found to complete more rapidly, and the desired complexes could be obtained in comparatively good yields. The complexes are fairly sensitive to moisture. In an acidic solution, all the complexes decompose

into nickel(II) complexes of the diamine and the respective monosaccharides. Similar decomposition gradually occurs also in neutral aqueous solution. These chemical properties are essentially similar to those for nickel(II) complexes derived from an aldose and a diamine as described in the next section.

The values for the effective magnetic moments of these compounds fall in the range reported for octahedral nickel(II) complexes [7].

The absorption spectra of these complexes in methanol are shown in Fig. 1. All show three peaks over the near-IR and visible regions with comparatively low intensity, agreeing with the reported pseudooctahedral *cis*-(O O)-$[NiN_4O_2]$ complexes [8]. Although some differences in peak wavenumber between absorption spectra and reflectance spectra were observed, spectra in the two states can be regarded as similar for all complexes. Accordingly, these complexes are assumed to have basically the same structure both in the solid state and in solution.

The molecular structure of $[Ni(en)(D\text{-Fru-en})]^{2+}$ [4] is the first example of an X-ray crystal structure determination of a metal complex containing an *N*-glycoside. The structures of $[Ni(en)(L\text{-Sor-en})]^{2+}$ [5] and $[Ni(S\text{-ampr})(L\text{-Sor-}S\text{-ampr})]^{2+}$ [6] were also determined by X-ray crystallography. The coordination structures of these complexes are equivalent to each other as shown in Figs. 2–4. The coordination at the central atom of the cation is essentially octahedral, with the four coordination sites being occupied by a tetradentate glycosylamine ligand; the remaining two coordination sites are occupied by a bidentate diamine. The complex cations have the *cis*-(O O)-$[NiN_4O_2]$ structure. One nitrogen atom of the diamine binds to C-2 of the sugar unit, forming the glycosylamine; this attaches to the nickel atom at four points through the 1- and 3-hydroxyl groups and the two nitrogen atoms of the diamine residue. The pyranoid ring of the D-fructosyl group is in the β-$^2C_5$ conformation, which is also adopted by β-D-fructopyranose in the free state [9] and by the calcium complexes of D-fructose [10]. The L-sorbose moiety forms the usual α-$^2C_5$ pyranose ring, which is also known to occur in crystalline L-sorbose [11]. The Ni–N distances are normal for those in octahedral nickel(II) complexes. Ni–O distances are much longer than the sum of the covalent radii, i.e. 2.05 Å (octahedral Ni(II), 1.39 Å; O, 0.66 Å) [12,13]. Thus the sugar-oxygen to nickel bond is weakened.

For the bond angles around the nickel atom, deviations from ideal octahedral geometry are observed. The deviations from 180° occur for the *trans* angles. The N Ni N bond angles appear normal for nickel(II) five-membered chelate rings. The significant deviations from the ideal angle (90°) occur for the angles contained in the N–Ni–O angles. Consequently, it is evident that some strain exists in the glycosylamine coordination system. This strain presumably comes from the elongation of the Ni–O

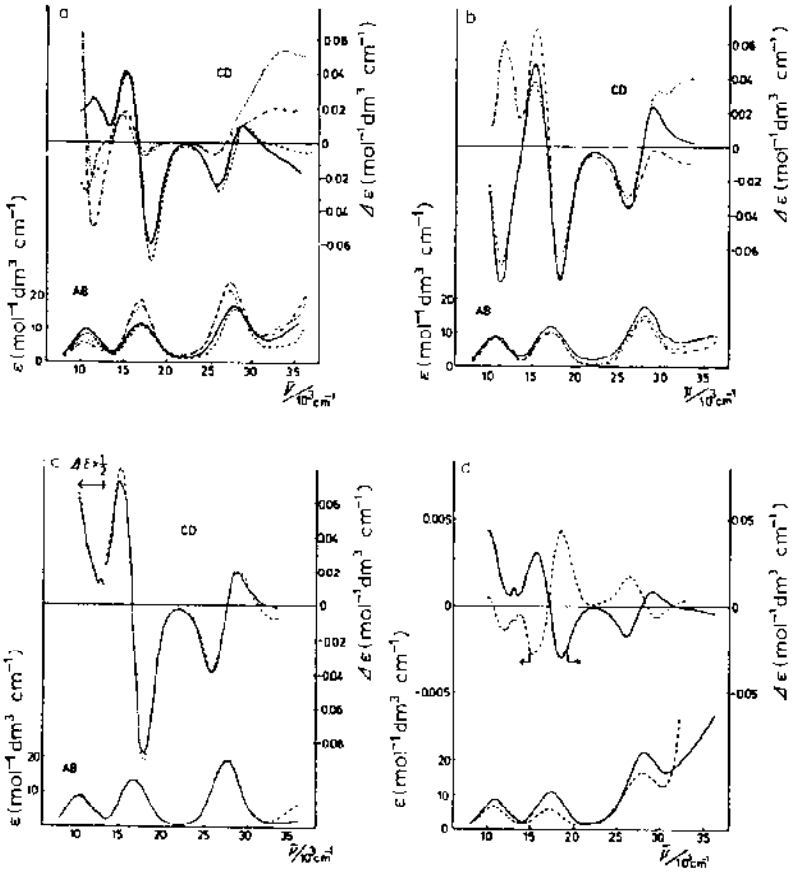


Fig. 1. Electronic absorption (AB) and circular dichroism (CD) spectra of the complexes in methanol: (a) $[Ni(en)(D\text{-}Fru\text{-}en)]^{2+}$ (———), $[Ni(en)(L\text{-}Sor\text{-}en)]^{2+}$ (- - - - - -), $[Ni(tn)(D\text{-}Fru\text{-}tn)]^{2+}$ (· · · · · ·), $[Ni(tn)(L\text{-}Sor\text{-}tn)]^{2+}$ (· - - - ·); (b) $[Ni(S\text{-}pn)(L\text{-}Sor\text{-}S\text{-}pn)]^{2+}$ (———), $[Ni(S\text{-}pn)(D\text{-}Fru\text{-}S\text{-}pn)]^{2+}$ (- - - - - -), $[Ni(R\text{-}pn)(L\text{-}Sor\text{-}R\text{-}pn)]^{2+}$ (· - - - ·); (c) $[Ni(S\text{-}ampr)(L\text{-}Sor\text{-}S\text{-}ampr)]^{2+}$ (———), $[Ni(S\text{-}ampr)(D\text{-}Fru\text{-}S\text{-}ampr)]^{2+}$ (- - - - - -); (d) $[Ni(en)(D\text{-}Tag\text{-}en)]^{2+}$ (———), $[Ni(en)(D\text{-}Psi\text{-}en)]^{2+}$ (- - - - - -).

bond distances which can be compared with the Ni–N bond distances. These crystal structures suggest the general coordination pattern of the sugar unit in the ketosylamine ligands, which binds to the metal to form the five-membered chelate ring using the glycosylated nitrogen atom and the adjacent hydroxyl groups.

The three crystal structures of the nickel(II) complexes of D-Fru-en,

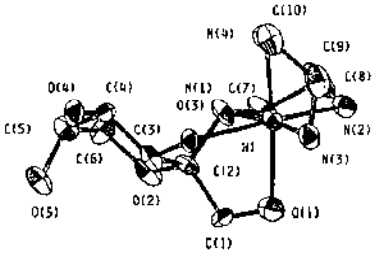


Fig. 2. Perspective drawing of the complex cation $[Ni(en)(D\text{-}Fru\text{-}en)]^{2+}$. Selected bond lengths (Å): Ni–N(1) = 2.070(8), Ni–O(1) = 2.205(7), Ni–O(3) = 2.137(6), N(1)–C(2) = 1.51(1), O(1)–C(1) = 1.42(2), C(1)–C(2) = 1.51(2), C(2)–C(3) = 1.58(1), O(3)–C(3) = 1.44(1), C(3)–C(4) = 1.50(2), O(4)–C(4) = 1.42(2), O(5)–C(5) = 1.42(2), C(5)–C(6) = 1.55(2), C(6)–O(2) = 1.44(2), O(2)–C(2) = 1.42(2). Selected bond angles (deg): N(1)–Ni–O(1) = 79.5(3), N(1)–Ni–O(3) = 79.5(3), C(2)–O(2)–C(6) = 118.9(9).

L-Sor-en and L-Sor-*S*-ampr showed that the coordination geometries are very similar; the configuration of the secondary nitrogen atom for the three complexes is *S* in the notation of Cahn et al. [14]; they have the same *S* anomeric configuration, and the Δ configuration around the nickel atom, which is defined by the two diamine chelates. From these results some important conclusions could be drawn. The conformation of the chelate ring involving the sugar pyranose ring will depend on the orientation of the hydroxyl group on the C-3 atom of the sugar residue; this will force the absolute configuration around the glycosidic nitrogen atom and the orienta-

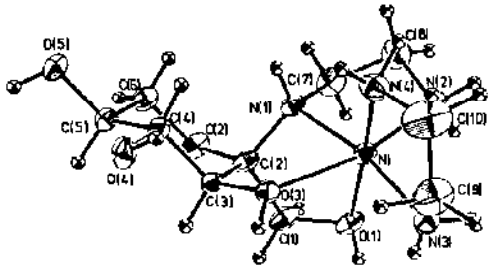


Fig. 3. Perspective drawing of the complex cation $[Ni(en)(L\text{-}Sor\text{-}en)]^{2+}$. Selected bond lengths (Å): Ni–N(1) = 2.109(3), Ni–O(1) = 2.137(3), Ni–O(3) = 2.118(2), N(1)–C(2) = 1.466(4), O(1)–C(1) = 1.441(5), C(1)–C(2) = 1.532(5), C(2)–C(3) = 1.553(4), O(3)–C(3) = 1.425(4), C(3)–C(4) = 1.513(4), O(4)–C(4) = 1.436(4), O(5)–C(5) = 1.422(5), C(5)–C(6) = 1.524(5), C(6)–O(2) = 1.438(5), O(2)–C(2) = 1.419(4). Selected bond angles (deg): N(1)–Ni–O(1) = 76.1(1), N(1)–Ni–O(3) = 78.2(1), C(2)–O(2)–C(6) = 114.8(2).

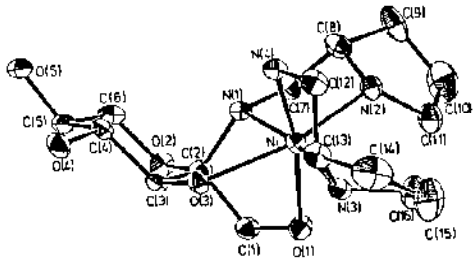


Fig. 4. Perspective drawing of the complex cation $[Ni(S\text{-ampr})(L\text{-Sor-}S\text{-ampr})]^{2+}$. Selected bond lengths (Å): Ni–N(1) = 2.085(5), Ni–O(1) = 2.133(4), Ni–O(3) = 2.159(4), N(1)–C(2) = 1.475(8), O(1)–C(1) = 1.438(8), C(1)–C(2) = 1.520(9), C(2)–C(3) = 1.537(8), O(3)–C(3) = 1.425(7), C(3)–C(4) = 1.528(9), O(4)–C(4) = 1.422(7), O(5)–C(5) = 1.427(8), C(5)–C(6) = 1.527(9), C(6)–O(2) = 1.429(8), O(2)–C(2) = 1.403(7). Selected bond angles (deg): N(1)–Ni–O(1) = 79.1(2), N(1)–Ni–O(3) = 77.6(2), C(2)–O(2)–C(6) = 114.9(5).

tion of the hydroxymethyl group on the anomeric carbon atom (this decides the overall configuration of the complexes) and will influence the chelate conformation of the diamine part of the glycosylamine derived from ketoses. Consequently, the coordination structures of the glycosylamines derived from D-Fru, L-Sor and D-Tag, which have the same *S* C-3 configuration, are expected to be similar to each other (Figs. 5(a)–5(c)), and a glycosylamine from D-Psi, which is the C-3 epimer of D-fructose, would form the enantiomeric Λ structure as shown in Fig. 5(d). These structural features are evident in the circular dichroism (CD) curves of the complexes.

The CD spectra of the ketosylamine complexes are shown in Fig. 1. In the octahedral approximation, only the lowest energy *d*–*d* transition $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ is magnetic dipole allowed for d^8 metal complexes [15]. Therefore it is ordinarily seen in the pseudooctahedral nickel(II) complexes that the CD intensity in the higher energy *d*–*d* transition region ($(15–30) \times 10^3$ cm^{-1}) is significantly weaker than that in the lowest transition region ($(10–15) \times 10^3$ cm^{-1}) [16–18]. However, in the case of the ketose–diamine complexes, where the diamine part is en, pn or tn, the CD intensity over the three *d*–*d* transition regions is comparable. Since these complexes are fairly distorted from the octahedron, as shown by X-ray crystallography, it seemed that the two higher energy transitions would be magnetic dipole allowed owing to the reduction in symmetry from O_h. (Since these complexes actually have C_1 symmetry, all electronic states belong to the "A" representation. In this condition, all transitions are magnetically allowed.) The complexes containing D-Fru, L-Sor or D-Tag moieties, in which each C-3 atom has the same *S* configuration, show different CD spectra in the first absorption region, but their CD spectra are nearly identical with each other

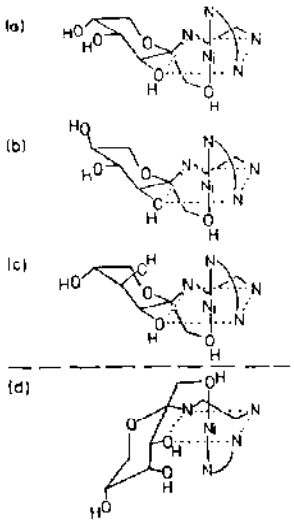


Fig. 5. Structures of ketose diamine complexes derived from (a) D-fructose, (b) L-sorbose, (c) D-tagatose, and (d) D-psicose.

over the second and third absorption regions (Fig. 1). For the complex containing a D-Psi residue, whose absolute configuration around the C-3 atom is *R*, the CD pattern in the second and third absorption region is opposite in sign to those observed for the D-Fru, L-Sor or D-Tag complexes. This reversal of sign can be attributed to the configurational effect of the glycosylamine complexes, as discussed above on the basis of the three crystal structures. Therefore the results obtained indicate that the coordination structure of the glycosylamine ligands derived from a ketose and a diamine significantly contributes to the CD signs over the second and third absorption regions.

In these ketose–diamine nickel complex systems, it was found that the overall configuration of these complexes affects the CD spectra in the second and third absorption regions. The pattern of the CD curves in the first absorption region is swayed by the seemingly small chiral effects except in the overall configurational effect.

(ii) N-*Glycoside complexes derived from aldoses*

(a) Nickel(II) complexes of N-*glycosides derived from diamines and aldoses [18]*

The reactions of aldoses with $[Ni(en \text{ or } tn)_3]^{2+}$ have led to the isolation of

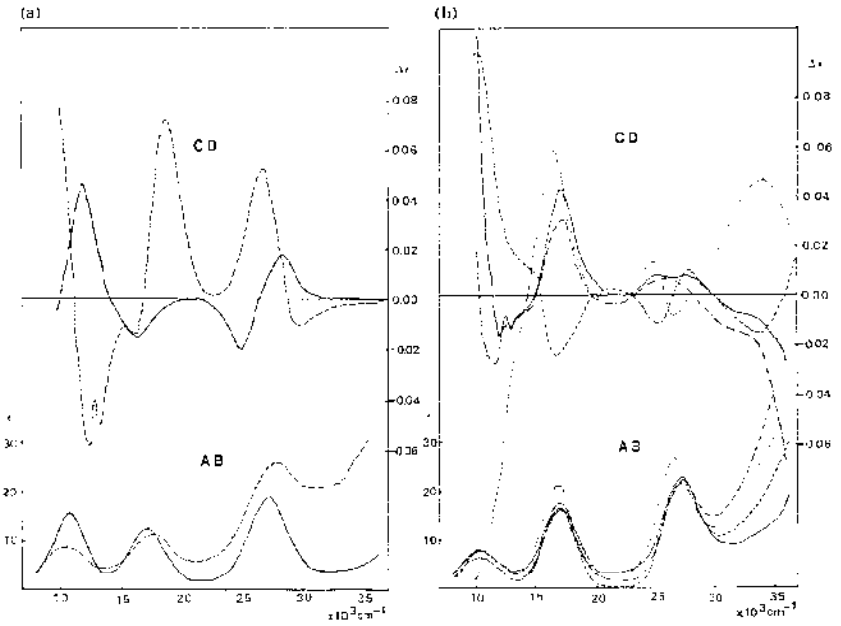


Fig. 6. Absorption and CD spectra of the nickel(II) complexes: (a) $[Ni(D\text{-Glc-en})_2]^{2+}$ (———), $[Ni(D\text{-Man-en})_2]^{2+}$ (- - - - - -); (b) $[Ni(D\text{-Glc-tn})_2]^{2+}$ (———), $[Ni(D\text{-Man-tn})_2]^{2+}$ (· - · - ·), $[Ni(D\text{-Gal-tn})_2]^{2+}$ (- - - - - -), $[Ni(L\text{-Rha-tn})_2]^{2-}$ (· · · · · ·).

the blue octahedral complexes $[Ni(N\text{-glycoside})_2]^{2+}$, which are made up from the two tridentate glycosylamine residues derived from the reaction of an aldose and a diamine. The magnetic data demonstrate that nickel ions in these complexes have two unpaired electrons, and the magnetic moments fall within the range for octahedral complexes of nickel(II) [7]. Absorption and CD spectra of the complexes are shown in Fig. 6. The absorption spectra of the complexes in the near-IR and visible regions consist of the three principal bands with comparatively low intensities characteristic of octahedral nickel(II) complexes [8].

Thus the preparation methods of these complexes, their magnetic properties and their electronic absorption spectra are essentially similar to those for nickel(II) complexes containing a ketosylamine as described in the previous section.

Figure 7 shows the X-ray crystal structure of the complex cation in $[Ni(L\text{-Rha-tn})_2]Br_2 \cdot 2H_2O \cdot CH_3OH$ (**1**), where the two *N*-glycoside molecules complete an octahedral coordination around the nickel atom in the *meridional* mode; the complex has approximately C_2 symmetry. The ab-

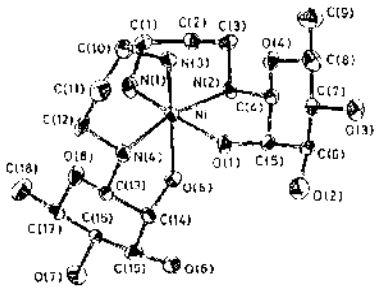
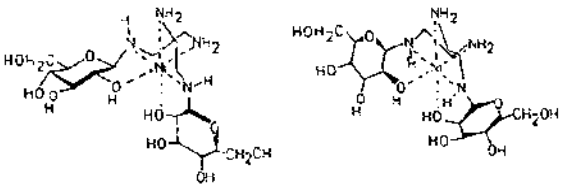


Fig. 7. ORTEP drawing and atomic numbering scheme for the $[Ni(L\text{-}Rha\text{-}tn)_2]^{2+}$ ion except for the hydrogen atoms. Selected bond distances (Å): Ni–N(1) 2.08(1), Ni–N(2) 2.11(1), Ni–O(1) 2.17(1), Ni–N(3) 2.09(1), Ni–N(4) 2.09(1), Ni–O(5) 2.18(1). Selected bond angles (deg): N(1)–Ni–N(2) 92.3(2), N(3)–Ni–N(4) 90.9(2), N(2)–Ni–O(1) 78.1(2), N(4)–Ni–O(5) 79.1(2), N(1)–Ni–O(1) 168.7(2), N(2)–Ni–N(4) 165.7(2), N(3)–Ni–O(5) 168.1(2).

solute configuration of the two coordinated chiral nitrogen atoms is *S*. Each pyranoside ring of the sugar moieties has the β-$^1C_4$ chair conformation. The hydroxyl group on C-2, which coordinates to the nickel atom, is axial with respect to the pyranose ring. Each sugar residue forms a five-membered chelate ring with the nickel atom in the λ-*gauche* conformation. The δ-*gauche* conformation occurs when D-Man is the original sugar. Each diamine residue forms a six-membered chelate ring with a chair conformation. The ring angles at the central atom for the diamine rings are about 90°. The values are significantly larger than those reported for the five-membered diamine rings in $[Ni(en)(D\text{-}Fru\text{-}en)]Cl_2 \cdot CH_3OH$ (**2**) [4]. In **1** the average angle between the terminal coordinated atoms of the *N*-glycoside ligands at the nickel atom, i.e. N(1)–Ni–O(1) and N(3)–Ni–O(5), is 168.4°. The corresponding value in $[Ni(D\text{-}GlcN\text{-}en)_2]Br_2 \cdot 4H_2O$ (**3**) (GlcN is glucosamine) [19] is 160.7°. Clearly, the *N*-glycoside ligands in **1** are almost strain free. The amelioration of such a distortion in **1** is presumably due to the strain-relieving effects of the six-membered ring relative to the five-membered ring in **3**. These structural features support the view that six-membered diamine chelates are an aid in the preparation of metal complexes with *N*-glycosides. Actually, sugars reacted with $[Ni(tn)_3]^{2+}$ to give good yields of the *N*-glycoside complexes [4,6]. This crystal structure is very important for predicting the general coordination pattern of mannose-type aldose units of the *N*-glycoside ligands.

The crystal structure of $[Ni(D\text{-}GlcN\text{-}en)_2]Br_2 \cdot 4H_2O$ [19] is also very important for predicting the general coordination pattern of glucose-type sugar units, although D-GlcN is an amino sugar. These data suggest that an *N*-glycoside from an aldose and a diamine coordinate to the nickel ion



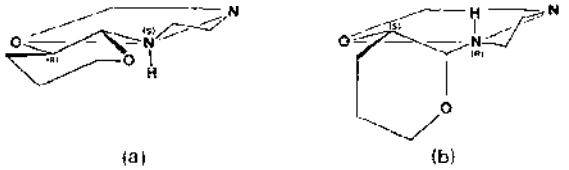
(a) (b)

Fig. 8. Structures of nickel(II) complexes containing *N*-glycosides derived from an aldose and a diamine: (a) $[Ni(D\text{-Glc-en})_2]^{2+}$ and (b) $[Ni(D\text{-Man-en})_2]^{2+}$.

through the oxygen atom of the hydroxyl group on the C-2 of the sugar moiety and through the two nitrogen atoms of the diamine and the two *N*-glycoside ligands to complete an octahedral coordination around the nickel atom in the *meridional* mode (Fig. 8). The *gauche* conformation of the chelate ring formed by the sugar moiety will depend on the absolute configuration around the C-2 carbon atom, and the chelate conformation involving a sugar residue will influence the absolute configuration around the glycosidic nitrogen atom. For example, when the pyranoid ring of the D-glucose-type sugars, whose absolute configuration around the C-2 carbon atom is *R*, has the usual β-$^4C_1$ form, the chelate ring taken by the sugar moiety adopts the λ-*gauche* form (Fig. 9(a)), and the absolute configuration of the secondary nitrogen atom will be *S*. All these environments are the inverse of those for the D-mannose-type sugars; the chelate conformation of the sugar part is δ-*gauche*, and the absolute configuration of the secondary nitrogen atoms is *R* (Fig. 9(b)). These structural features are evident in the CD curves of the D-Glc, D-Gal and D-Man complexes, where the first two complexes and the last complex are nearly mirror images (Fig. 6). Thus the results suggest that some of the coordination patterns of aldose units in their *N*-glycoside complexes are predictable by correlation of their CD spectra.

(b) A novel μ-mannofuranoside binuclear nickel(II) complex containing N-glycosides

It is well known that N-substituted diamines show somewhat different



(a) (b)

Fig. 9. Coordination structures of the *N*-glycoside ligands: (a) D-GlcN-en, (b) D-Man-en.

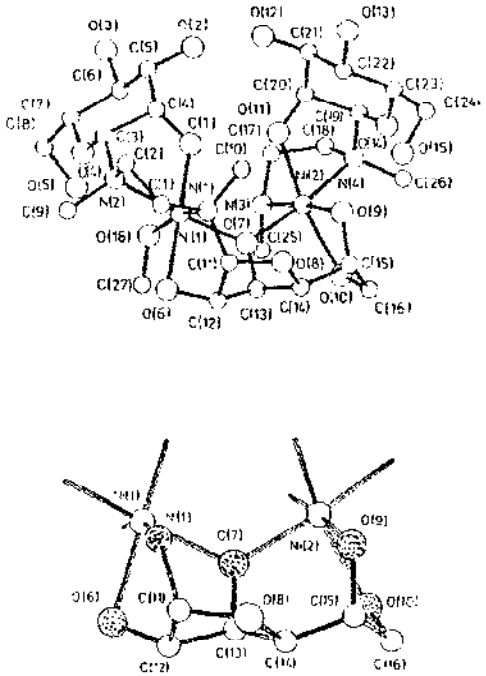


Fig. 10. Perspective drawing and atomic numbering scheme for the μ-Man-[Ni_2(MeOH)(*N*-D-Man-*N*,*N*′-Me_2en)(*N*,*N*′-D-Man_2-*N*,*N*′-Me_2en)]$^{2+}$ ion. Selected bond distances (Å): Ni(1)–Ni(2) 3.596(4), Ni(1)–O(1) 2.02(1), Ni(1)–O(6) 2.12(2), Ni(1)–O(7) 2.02(1), Ni(1)–O(16) 2.15(2), Ni(1)–N(1) 2.19(2), Ni(1)–N(2) 2.13(2), Ni(2) O(7) 2.02(1), Ni(2) O(9) 2.09(1), Ni(2)–O(10) 2.16(2), Ni(2)–O(11) 2.04(1), Ni(2)–N(3) 2.10(2), Ni(2)–N(4) 2.19(2). Selected bond angles (deg): O(1) Ni(1) 83.2(6), O(6) Ni–O(7) 82.1(5), O(6)–Ni(1)–N(1) 79.5(6), N(1)–Ni(1)–N(2) 84.0(6), O(7)–Ni(2)–O(10) 89.3(6), O(9)–Ni(2)–O(10) 77.9(6), O(11) Ni(2)–N(4) 79.7(6), N(3)–Ni(2)–N(4) 82.8(7).

characteristics owing to steric effects and inductive effects. In the work of Tanase et al. [20], *N*,*N*′-dimethylethylenediamine (*N*,*N*′-Me_2en) was used as a diamine component. D-Mannose reacted with [$Ni(H_2O)_2$(*N*,*N*′-Me_2en)$_2$]Cl_2 in methanolic solution to give the novel blue-green μ-mannofuranoside binuclear nickel(II) complex, μ-Man-[Ni_2(MeOH)(*N*-D-Man-*N*,*N*′-Me_2en)(*N*,*N*′-D-Man_2-*N*,*N*′-Me_2en)]Cl_2 · MeOH · $5H_2O$ containing three *N*-glycosides formed from *N*,*N*′-Me_2en and D-Man. A perspective drawing of the complex cation is given in Fig. 10. The metal centre of the complex is binuclear with one of the mannose residues linking the two nickel atoms. The complex cation contains three mannose residues forming *N*-glycosides with *N*,*N*′-Me_2en. Two of them adopt the β-$^4C_1$ pyranose form and

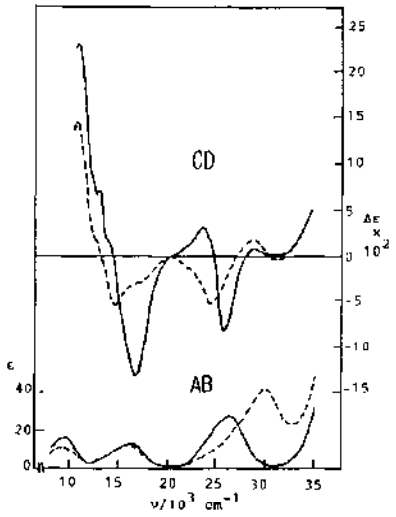


Fig. 11. Absorption (lower curve) and CD (upper curve) spectra: mannose complex (———); glucose complex (- - - - -).

coordinate to nickel through the glycosidic nitrogen atom and the oxygen atom of the C-2 hydroxyl group in a manner similar to that in [Ni(L-Rhatn)$_2$]Br$_2$ · 2H$_2$O [18 (a)]. The other mannose residue adopts the unusual furanose form and links two nickel atoms with an oxygen bridge via the C-3 hydroxyl group. Furthermore, it attaches to two nickel atoms through the glycosidic nitrogen atom and the oxygen atoms of the C-2, C-5 and C-6 hydroxyl groups. It seems to be the most suitable form for linking two nickel atoms because in the furanose form all donor atoms are pushed out of the ring plane in the same direction. It is probably for this reason that a stable binuclear complex was obtained using only D-mannose. The results of this X-ray crystal structure determination suggest the possibility of selective complexation for a mannose-type sugar via modification of the diamine in $[Ni(H_2O)_2(diamine)_2]^{2+}$ salts as will be described in the next section.

When D-glucose instead of D-mannose was used as the starting sugar, a blue–green oily compound which shows CD curves similar to those of the D-mannose complex isolated above was obtained, although its yield was very low (Fig. 11). Monosaccharides recovered from the oily compound proved to be 28% D-glucose and surprisingly 72% D-mannose, indicating that the starting D-glucose was partially epimerized during the reaction. This observation is very important in relation to transformation of sugars by metal complexes, and in fact gave us a significant clue to develop the C-2

epimerization of aldoses promoted by nickel(II)- diamine complexes as will be described in the next section.

(c) Nickel(II) complexes containing an N-*glycoside derived from* N,N-*di(2-aminoethyl)ethylenediamine and aldoses*

Figure 12 shows a perspective drawing of the complex cation in (N,N'-di(D-mannosyl-2-aminoethyl)ethylenediamine)nickel(II) dichloride methanol. [Ni(N,N'-(D-man)$_2$-tren)]$Cl_2 \cdot CH_3OH$ (**1**) which was derived from the reaction of [Ni$(H_2O)_2$(tren)]Cl_2 with D-mannose, where tren is N,N-di(2-aminoethyl)ethylenediamine [21]. The nickel atom is octahedrally coordinated with a cage-type hexadentate N-glycoside ligand (N,N-(D-Man)$_2$-tren), which contains two mannose moieties. Both sugar units adopt the stable β-$^4C_1$-pyranose form and attach to nickel through the glycosidic nitrogen atom and the oxygen atom of the C-2 hydroxyl group as observed in the case of [Ni(L-Rha-tn)$_2$]$Br_2 \cdot H_2O \cdot CH_3OH$ [18 (a)]. One of them is in the *facial* mode (N(1), N(2), O(1)) and the other in the *meridional* mode (N(1), N(3), O(6)). Further, the cage-type tetradentate tren ligand directs two

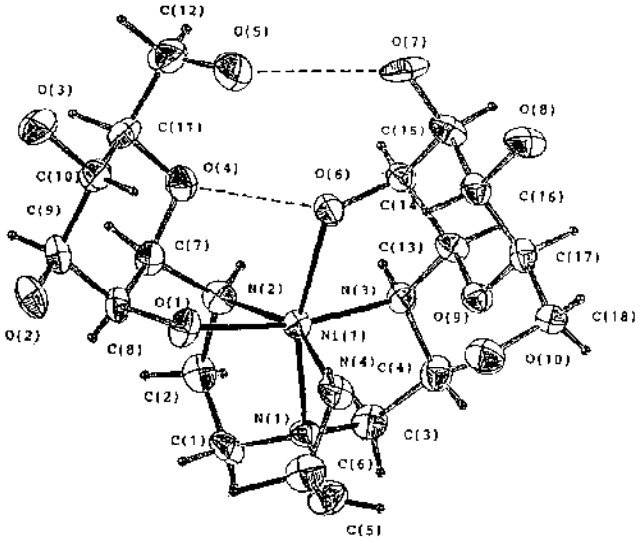


Fig. 12. ORTEP drawing of the complex cation [Ni(N,N-(D-Man)$_2$-tren)]$^{2+}$. Selected bond distances (Å): Ni(1)–O(1) 2.110(5), Ni(1)–O(6) 2.182(5), Ni(1)–N(1) 2.101(7), Ni(1)–N(2) 2.151(8), Ni(1)–N(3) 2.069(6), Ni(1)–N(4) 2.092(7). Selected bond angles (deg): O(1)–Ni(1)–N(2) 77.3, O(1)–Ni(1)–N(3) 168.6(3), O(6)–Ni(1)–N(1) 161.2(2), O(6)–Ni(1)–N(3) 78.62, N(1)–Ni(1)–N(2) 81.8(3), N(1)–Ni(1)–N(3) 83.7, N(1)–Ni(1)–N(4) 83.7, N(2)–Ni(1)–N(4) 154.3(3).

mannose units to the same side in the complex forming two blocks such as a hydrophobic polyamine part and a hydrophilic sugar part, and this brings about the unique intramolecular sugar–sugar hydrogen bonding network (O(5)...O(7), 3.030(10) Å; O(4)...O(6), 2.969(8) Å) around the metal centre; the pair of C-6 oxygen and cyclic oxygen is combined with the *cis* oxygen pair on C-2 and the C-3 hydroxyl groups. However, for glucose-type sugars which have the *trans* arrangement of C-1, C-2 and C-3 hydroxyl groups, it seems difficult to form similar cage-type complexes containing tren and glucose-type sugars. Actually, when D-glucose or D-glucosamine was used instead of D-mannose, the complexes containing only one sugar moiety, $[Ni(N\text{-(D-Glc)-tren})(H_2O)]Cl_2 \cdot 1/2H_2O$ (**2**) and $[Ni(N\text{-(D-GlcN)-tren})(H_2O)]Cl_2 \cdot H_2O$ (**3**) were obtained. The results of these studies indicate that the intramolecular hydrogen bonding around the metal centre is thought to be a significant driving force to complete the cage-type complexes involving sugar–sugar interactions. The magnetic moments and the absorption spectra indicate that all these nickel(II) complexes have essentially octahedral stereochemistry.

Many excellent studies have been made in connection with metal-containing enzymes [22], discussing the interactions between the amino acid side-chains contained in transition metal complexes but the literature concerning the structural details of sugar–sugar interactions around metal centres is sparse. Accordingly, the stereochemical features of this complex (**1**) which has a unique sugar–sugar interaction could provide useful information for the study of interactions between oligosaccharide chains in glycoproteins.

(d) Nickel(II) complexes containing N-glycosides derived from aldoses and β-alanine

Weitzel et al. reported [23] in 1957 the isolation of several metal complexes of the *N*-glycosides derived from an aldose and an amino acid. They confirmed the composition of the compounds by elemental analysis but made no comment on the spectral and stereochemical features. Tsubomura et al. [24] reinvestigated their synthetic procedures, but it was difficult to isolate analytically pure metal complexes containing a series of monosaccharides. However, blue or green compounds were obtained from the reaction between $[Ni(\beta\text{-ala})_2(H_2O)_2]$, which is unusually soluble in methanol, and bis(amino acidato)nickel(II) complexes, where β-ala is β-alaninato, and the aldoses are D-glucose, D-galactose, D-xylose, D-ribose, 4,6-*O*-benzylidene-D-glucose (4,6-Bnz-D-Glc) and 3-*O*-methyl-D-glucose (3-Me-D-Glc)). Analytical data indicated that they have two *N*-glycoside ligands, which are made from a β-alanine and an aldose, except for the 3-Me-D-Glc complex. The 3-Me-D-Glc complex has an *N*-glycoside and an aqua ligand and is solvated with methanol. All these compounds are gradually hydro-

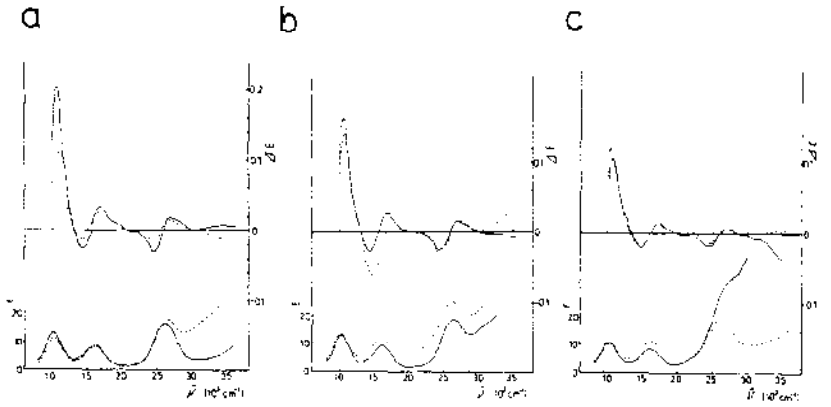


Fig. 13. Absorption spectra (lower curve) and CD spectra (upper curve): (a) [Ni(D-Glc-β-ala)$_2$]·H_2O (———), [Ni(D-Gal-β-ala)$_2$]·CH_3OH·1/2H_2O (- - - - - -); (b) [Ni(D-Xyl-β-ala)$_2$]·2H_2O (———), [Ni(D-Rib-β-ala)$_2$]·H_2O (- - - - - -); (c) [Ni(4,6-Bnz-D-Glc-β-ala)$_2$]·2H_2O (· ——), [Ni(β-ala)(H_2O) (3-Me-D-Glc-β-ala)]·CH_3OH (- - - - - -).

lyzed in water. The near-IR and visible absorption spectra and the CD spectra of these complexes are shown in Fig. 13. The magnetic moments and the absorption spectra indicate that all these nickel(II) complexes are essentially octahedral. The CD intensities of these complexes in the *d–d* transition regions are comparable to (or stronger than) those of the previously studied nickel(II) complexes containing *N*-glycosides derived from an aldose and a diamine [4,18]. Even if the hydroxyl group(s) on the C-3, C-4 or C-6 atoms were protected, *N*-glycoside complexes were obtained. However, no sugar complex was obtained using 2-deoxy-D-glucose. From all these results, it can be concluded that these *N*-glycoside ligands derived from an aldose and β-alanine are tridentate ligands with coordination through the oxygen atom of the carboxylate of the β-ala moiety, through the oxygen atom of the hydroxyl group on the C-2 atom of the aldose residue, and through the nitrogen atom of β-ala (Fig. 14).

Since the Amadori rearrangement occurs immediately after the formation of the amino acids *N*-glycoside as the second step of the Maillard reaction and forms ketose-amino acids [1,25], it is difficult to stop the the Maillard reaction at the first step and to isolate such *N*-glycosides. Therefore it is an important fact that the Maillard reaction stopped at the first step and that the *N*-glycosides derived from amino acids and sugars can be obtained very easily using the nickel β-alaninato complex.

(e) Nickel(II) complexes of N-glycosides derived from amino sugars and ethylenediamine [19]

Tris(ethylenediamine)nickel(II) ions in methanol reacted with the hydro-

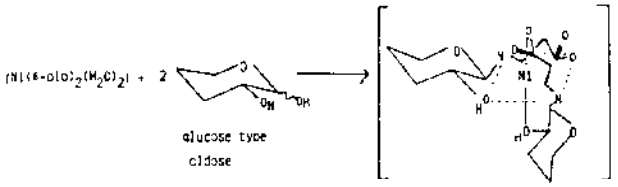


Fig. 14. Proposed structure of the glucose-type sugar–β-ala complex.

chloride salts of D-glucosamine (D-GlcN), D-galactosamine (D-GalN) or D-mannosamine (D-ManN) to give blue–violet, paramagnetic bis(tridentate) nickel(II) complexes in which the tridentate ligand is the *N*-glycoside formed from an amino sugar and a diamine. The magnetic moments of these complexes fall within the range of 2.9 3.4 μ_B reported for octahedral complexes of nickel(II) [7]. Absorption and CD spectra of the complexes are presented in Fig. 15. The solution and reflectance spectral results indicate that geometric structures are essentially equivalent in solution and in the

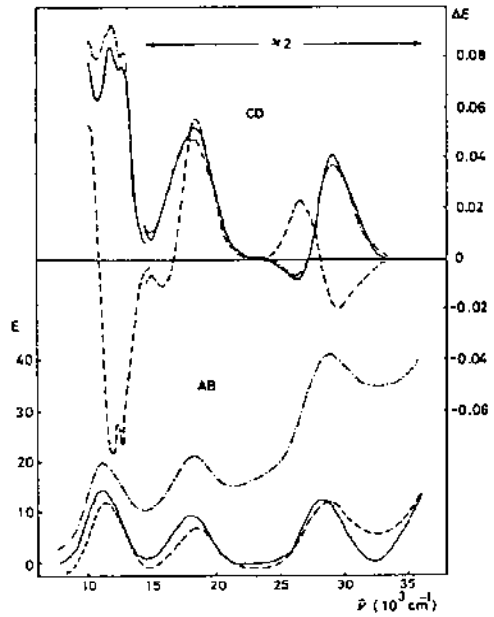


Fig. 15. Electronic absorption (lower curve) and CD (upper curve) spectra of the complexes in water: $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$ (———), $[Ni(D\text{-}GalN\text{-}en)_2]^{2+}$ (· · · · ·), $[Ni(D\text{-}ManN\text{-}en)_2]^{2+}$ (- - - - - -).

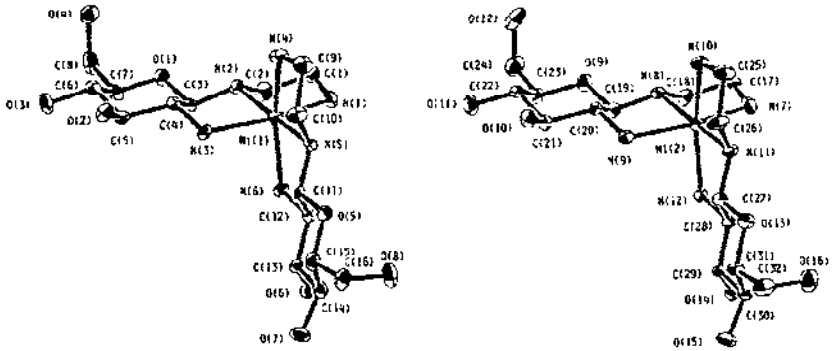


Fig. 16. ORTEP view of $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$ ions with the atomic numbering scheme except for the hydrogen atoms in an asymmetric unit. Selected bond distances (Å): Ni(1)–N(1) 2.16(1), Ni(1)–N(2) 2.10(1), Ni(1)–N(3) 2.19(1), Ni(1)–N(4) 2.15(1), Ni(1)–N(5) 2.12(1), Ni(1) N(6) 2.19(1), Ni(2)–N(7) 2.13(1), Ni(2)–N(8) 2.09(1), Ni(2)–N(9) 2.19(1), Ni(2)–N(10) 2.13(1), Ni(2) N(11) 2.09(1), Ni(2)–N(12) 2.22 (1). Selected bond angles (deg): N(1)–Ni(1)–N(2) 80.2(0.4), N(1)–Ni(1)–N(3) 159.4(0.4), N(4) Ni(1) N(5) 79.9(0.4), N(2)–Ni(1)–N(3) 80.2(0.4), N(4)–Ni–N(6) 161.7(0.4), N(5)–Ni(1)–N(6) 81.9(0.4), N(7)–Ni(2)–N(8) 80.0(0.4), N(7)–Ni(2)–N(9) 159.3(0.4), N(8)–Ni(2)–N(9) 80.1(0.4), N(10)–Ni(2)–N(11) 81.3(0.4), N(10)–Ni(2)–N(12) 162.5(0.4), N(11)–Ni(2)–N(12) 81.3(0.4).

solid state. The solution spectra of the complexes in the near-IR and visible regions consist of the principal bands ν_1, ν_2 and ν_3 with comparatively low intensities (10–20), which are characteristic of octahedral $[Ni(II)N_6]$-type complexes [8]. The complexes obtained exhibit a high degree of hydrolytic stability in contrast with the instability of the analogous complexes derived from monosaccharides [4–6]. This fact is noteworthy in connection with the medical usefulness of amino sugars.

A perspective drawing of the complex cations $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$ showing thermal motion ellipsoids is given in Fig. 16. There are two complexes in the asymmetric unit. The structures of both complex cations are nearly identical. The nickel atom is surrounded by six nitrogen atoms at apices of a distorted octahedron. One nitrogen atom of ethylenediamine binds to the C-1 carbon of the glucosamine. Two *N*-glycoside ligands coordinate to the nickel atom meridionally with the Δ configuration in the same way as the similar tridentate ligands: the complex has approximately C_2 symmetry. Each *N*-glycoside ligand coordinates to the metal at three points through the sugar amino group on C-2 and through the two nitrogen atoms of the ethylenediamine residue. The pyranose ring of the sugar moiety is in the usual β-$^4C_1$ chair conformation. The two chelate conformations involving sugar moieties are both λ. The arrangement of the group around the secondary nitrogen atom is *S*. The two nitrogen atoms on C-1 and C-2,

coordinating to the nickel atom, occupy equatorial positions with respect to the pyranose ring. There are no significant differences between analogous bond distances and bond angles in the two independent complex ions. The Ni–N distances are normal for nickel(II) complexes containing ethylenediamines [26]. The large deviations from the ideal angle (90°) occur for ring angles at the nickel atoms for the five-membered chelate rings. The average angle between the terminal coordinated atoms of the *N*-glycoside ligands at the nickel atom is 160.7°. Thus the complex cations are found to be highly distorted from ideal O_h symmetry. The bond distances and angles for each sugar moiety are similar to the reported values for *N*-acetyl-D-glucosamine [27] and the hydrochloride of D-glucosamine [28]. Thus in the glucopyranose rings, there seems to be no significant strain upon coordination.

The CD spectra of the three complexes show dominant CD bands in the vicinity of ν_1 and comparatively weak CD bands in the region of ν_2 and ν_3 as discussed above and by Gillard [15] (Fig. 15).

The crystal structure of the $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$ ion indicates that the *gauche* conformation of the chelate ring formed by the sugar moiety will depend on the orientation of the amino group on C-2 of the sugar moiety and the chelate conformation involving a sugar residue will influence the absolute configuration around the secondary glycosidic nitrogen atom. Accordingly, each amino group of D-glucosamine or D-galactosamine, which are the C_4 epimers of each other, is in the equatorial position with respect to each pyranose ring, producing a λ-*gauche* conformation involving the sugar moiety and yielding an *S* configuration for the secondary nitrogen atom. In contrast, the five-membered chelate ring involving the D-mannosamine moiety, which is the C_2 epimer of D-glucosamine, will adopt the δ-*gauche* conformation, and the configuration of the secondary nitrogen atom is expected to be *R*. Thus the coordination patterns of the other two *N*-glycosides (D-GalN-en and D-ManN-en) were predicted as shown in Fig. 17. These stereochemical features that may have influence on the conforma-

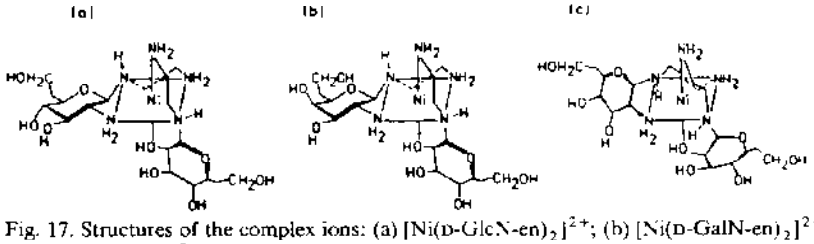


Fig. 17. Structures of the complex ions: (a) $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$; (b) $[Ni(D\text{-}GalN\text{-}en)_2]^{2+}$; (c) $[Ni(D\text{-}ManN\text{-}en)_2]^{2+}$.

tional and vicinal effects are in the same sense for the D-GlcN-en and D-GalN-en complexes, and these are in the opposite sense for the D-ManN-en complex. In fact, the CD curves of $[Ni(D\text{-}GlcN\text{-}en)_2]^{2+}$ and $[Ni(D\text{-}GalN\text{-}en)_2]^{2+}$ are quite similar to each other, and that of $[Ni(D\text{-}ManN\text{-}en)_2]^{2+}$ has the opposite sign in the first absorption region where the first two complexes and the last complex are nearly mirror images (Fig. 15). Thus the CD pattern of the first *d–d* transition offers a potentially useful tool in assigning the coordination geometry of amino sugars.

(f) Cobalt(III) complexes containing an N*-glycoside derived from ethylenediamine and aldoses*

Metal complexes are divided into two classes, substitution inert and substitution labile, on the basis of their chemical properties. Therefore it is interesting to examine these two types of complexes in order to elucidate the interaction of sugars with metals.

A monosaccharide (D-Man, L-Rha or D-Rib) reacted with $[(en)_2Co(O_2)(OH)Co(en)_2]^{3+}$ ions to give substitution-inert diamagnetic cobalt(III) complexes containing an ethylenediamine and an *N*-glycoside ligand derived from ethylenediamine and an aldose [29]. The electronic absorption spectra of these complexes closely resemble each other, and they have two main peaks in the *d d* transition region (Fig. 18). Each lowest energy peak shows a symmetrical curve without any shoulder in the first absorption region, which is characteristic for the *cis*(O–O)-$[CoN_4O_2]$ type [30]. The CD curves of $[Co(L\text{-}Rha\text{-}en)(en)]^+$ (**2**) and $[Co(D\text{-}Rib\text{-}en)(en)]^+$ (**3**) closely resemble each other and are nearly mirror images of that of $[Co(D\text{-}Man\text{-}en)(en)]^+$ (**1**)

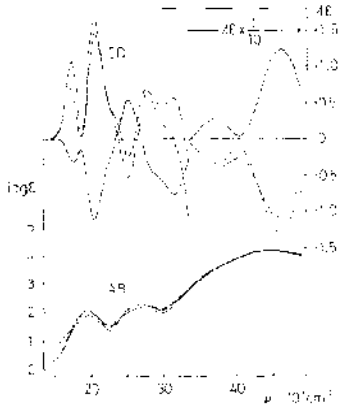


Fig. 18. Absorption and CD spectra of the cobalt(III) complexes in water: $[Co(D\text{-}Man\text{-}en)(en)]^+$ (**1**) (———), $[Co(L\text{-}Rha\text{-}en)(en)]^+$ (**2**) (– · – · –), $[Co(D\text{-}Rib\text{-}en)(en)]^+$ (**3**) (- - - - -).

TABLE 1

Observed H–H vicinal coupling constant values [a] (^3J) in the sugar rings (Hz)

Complex	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$
1	4.3	3.5	2.1	7.8	3.4, 5.8
2	4.3	3.5	2.1	6.1	6.7
3	4.0	4.0	0.0	4.0, 5.3	–

[a] Not simulated values.

in the first absorption region (Fig. 18). From the empirical rule on the CD signs in this region and from comparison with the CD signs of optically active *cis*(O,O)-[$Co(O)_2(en)_2$]-type complexes in this region [31], **1** could be assigned the Δ configuration and **2** and **3** the Λ configuration.

The conformations of the sugar rings were analyzed by the observed $^3J_{H,H}$ coupling constant values (Table 1) on the basis of the Karplus relationship [32]. These considerations led to the conclusion that each sugar ring in **1** and **2** is not in the usual chair conformation but adopts the β-$^3S_5$ skew-boat conformation, and that in **3** takes the five-membered α-$^2T_3$ twist conformation.

Recently, Reuben [33] demonstrated that the isotopic multiplets observed in the ^{13}C NMR spectra of amides, carbohydrates or amines with partially deuterated exchangeable protons (NH, NH_2, OH) are very useful in spectral assignments and molecular structure determinations. These multiplets are due to upfield deuterium isotopic effects on the ^{13}C chemical shifts and can be observed in the slow exchange conditions. Previously, Yashiro et al. [34(a)] demonstrated the first application of the isotopic multiplets to the ^{13}C NMR spectra of the coordination compounds, which could provide interesting examples of dihedral angular dependence of the three-bond effects. Ishida et al. [34(b)] applied this method to reveal the existence of the C–N bond formation between the C-1 of a sugar unit and the N atom of en such as C-1(sugar)–$NHCH_2CH_2NH_2$. Generally, it can be predicted that partial deuteration of the coordinated NH_2 group and that of the coordinated NH group would cause the neighbouring ^{13}C resonances to result in quartets or in triplets corresponding to three isotopomers (C–NH_2, C–NDH, C–ND_2) and those to result in doublets corresponding to two isotopomers (C–NH, C–ND) respectively. The ^{13}C signal of C-1 of the sugar unit of $[Co(D\text{-Rib-en})(en)]^+$ in an H_2O–D_2O mixture showed a doublet, and one of the ^{13}C signals of en gave a doublet as shown in Fig. 19, where all the ^{13}C NMR signals were assigned completely by the ^{13}C–^1H shift correlation two-dimensional (2-D)NMR spectroscopy. These results correspond to the existence of the two isotopomers: C-1(sugar)–NH(en) and C-1(sugar)–ND(en). Thus the real existence of the C–N bond in the *N*-glyco-

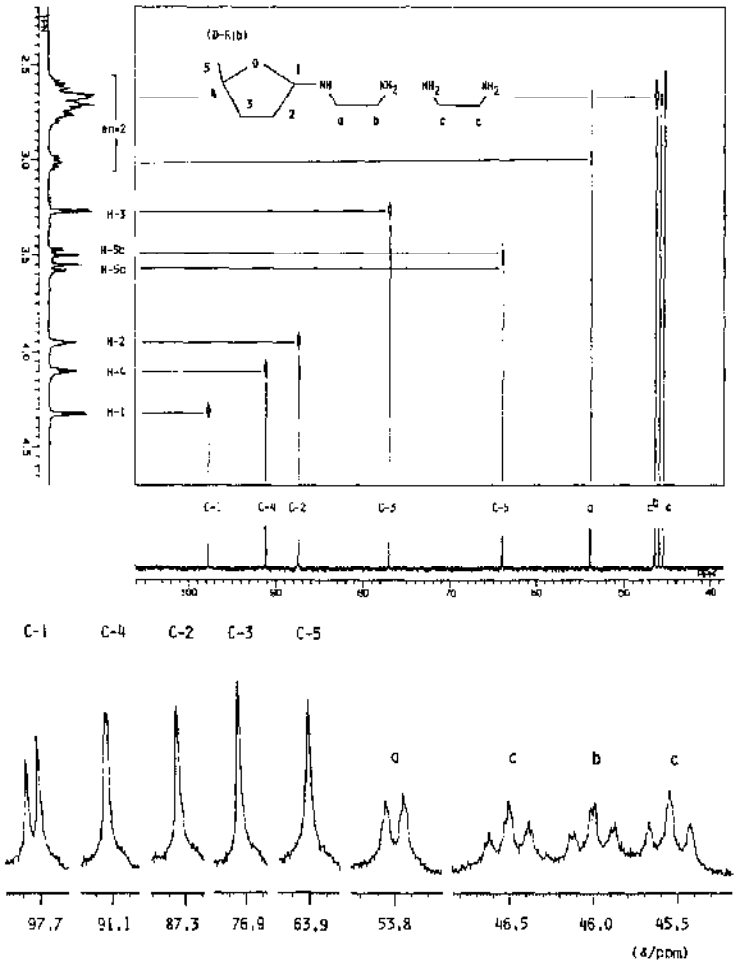


Fig. 19. NMR spectra of $[Co(D\text{-}Rib\text{-}en)(en)]^{+}$: ^{13}C–^{1}H shift correlation 2-D NMR spectrum (upper diagram) and ^{13}C NMR spectrum in an H_2O D_2O (lower diagram) mixture.

side could be unambigiously proven by the application of the isotopic multiplets in the ^{13}C NMR spectra.

From all these results, coupled with the inspection of the scale model, it was concluded that the sugar unit of each tetradentate *N*-glycoside ligand facially coordinates to the cobalt atom through the N atom on C-1 and through the two O atoms on C-2 and C-3 (Fig. 20).

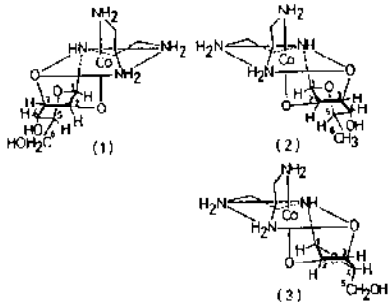
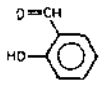


Fig. 20. Proposed structures of Δ-[Co(D-Man-en)(en)]$^+$, Λ-[Co(L-Rha-en)(en)]$^+$ and Λ-[Co(D-Rib-en)(en)]$^+$.

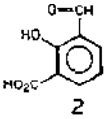
It is very interesting that three-point metal bindings induce the conformational changes from the chair conformation that the free sugars usually take [35]. This coordination geometry would be generally possible for sugars containing the *cis* arrangement between two hydroxyl groups on C-2 and C-3 such as D-mannose, L-rhamnose and D-ribose. However, it seems to be impossible for sugars containing the *trans* arrangement between C-2 and C-3 hydroxyl groups such as D-glucose and D-galactose. The results of this work suggest the novel aspect of selective complexation for aldoses.

(iii) Schiff's base complexes derived from amino sugars

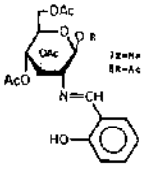
Adam and Hall [36] demonstrated that sugar–salicylaldimine–metal complexes are readily prepared by reaction, in alcoholic solution, of a salicylaldimine with a metal ion (usually metal acetate). The salicylaldimine ligands are 2-deoxy-D-glucopyranosyl-2-salicylaldimine (**4**), methyl-3,4-6-tri-O-acetyl-2-deoxy-2-salicylaldimino-D-glucopyranoside (**7**), 1,3,4,6-tetra-O-acetyl-2-deoxy-2-salicylaldimine-D-glucopyranoside (**8**), and methyl-3.4,6-tri-O-acetyl-2-deoxy-2-(3-carboxylsalicylaldimino)-D-glucopyranoside (**9**). These have been derived from 2-amino-2-deoxy-D-glucose and some its derivatives with salicylaldehyde. Copper(II), zinc(II) and cobalt(II) complexes were formed from ligand **7**, whereas only copper(II) would form a complex with ligand **8**. The sugar ligand **4** forms a water-soluble complex with copper(II), and ligand **9** forms a binuclear copper(II) complex **16** (Fig. 21). These products were studied by ^{1}H NMR, visible absorption and ESR spectroscopy, mass spectrometry, and by their magnetic moment data. When nickel(II) acetate was mixed with a methanol solution of the sugar ligand, no colour change could be seen, and both starting materials were recovered upon volume reduction. This lack of complexation may be due to the combined effects of a normally lower stability constant for nickel–salicyl-

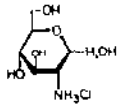


1

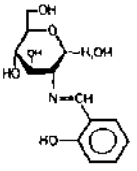


2

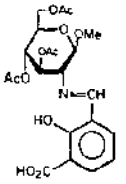




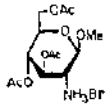
3



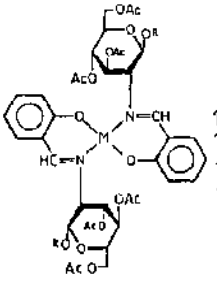
4



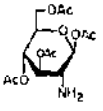
9



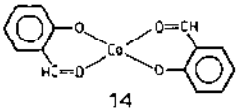
5



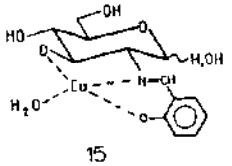
10 M=Cu, R=H
11 M=Zn, R=H
12 M=Co, R=H
13 M=Cu, R=Ac



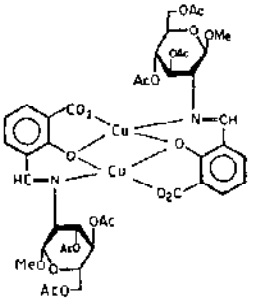
6



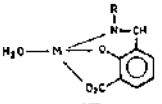
14



15



16



17

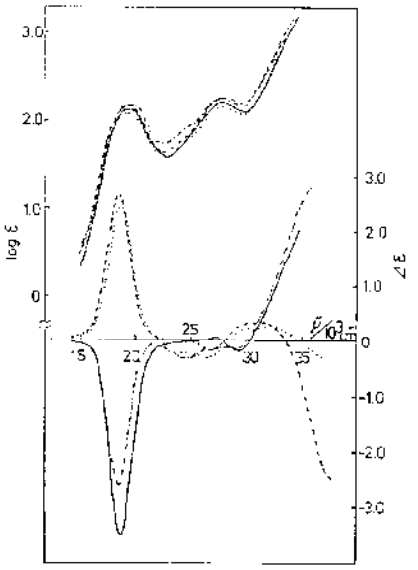


Fig. 22. Electronic absorption and CD spectra of aldonato complexes: Δ-[Co(D-gluconato)(en)$_2$]$^+$ ( ), Λ-[Co(D-gluconato)(en)$_2$]$^+$ (- - - - - -), Δ-[Co(L-mannonato)(en)$_2$]$^+$ (· – · – ·), and Λ-[Co(L-mannonato)(en)]$^-$ (· · · · · ·).

aldimine complexes compared with the analogous copper(II) complexes, and the possibility that the sugar salicylaldimines are poor ligands.

(ii) Cobalt(III) complexes of the aldonic acids [37]

Stable complexes of the type [Co(aldonato)(en)$_2$]$^+$, where aldonato is the diacid anion of D-gluconic acid or L-mannoic acid, were prepared by the reaction of aldonic acid lactones with *rac*-[Co(CO_3)(en)$_2$]$^-$. Two diastereoisomers (Δ and Λ) have been separated by ion exchange chromatography from each of the aldonato complexes. These complexes were characterized by NMR, electronic absorption and CD spectra. The absorption and CD

Fig. 21. **1**, Salicylaldehyde; **2**, 3-formyl-2-hydroxybenzoic acid; **3**, D-glucosamine HCl; **4**, 2-deoxy-D-glucopyranosyl-2-salicylaldimine; **5**, methyl-3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-glucopyranoseHBr; **6**, 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-D-glucopyranose; **7**, methyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-salicylaldimino-D-glucopyranoside; **8**, 1,3,4,6-tetra-*O*-acetyl-2-glucopyranoside; **9**, methyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-(3-carboxylsalycilaldimino)-D-glucopyranoside; **10**, [Cu(**7**)$_2$]; **11**, [Zn(**7**)$_2$]; **12**, [Co(**7**)$_2$]; **13**, [Cu(**8**)$_2$]; **14**, [Co(**1**)$_2$]; **15**, [Cu(H_2O)(**4**)]$^+$; **16**, [Cu_2(**9**)$_2$].

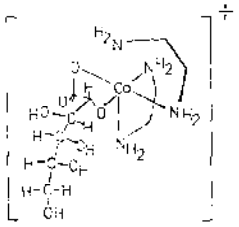


Fig. 23. Proposed structure of Λ-[Co(D-gluconato)(en)$_2$]$^+$.

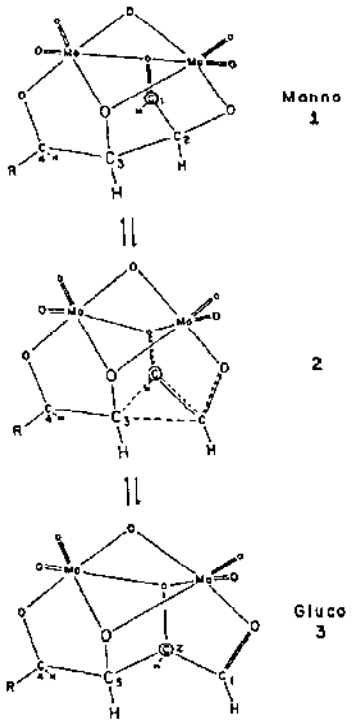
spectra for the series of complexes are shown in Fig. 22. The band positions and the intensities of the absorption spectra for these complexes are nearly identical, and their spectral patterns in the first absorption region are characteristic for *cis*-(O,O)-[CoN_4O_2] complexes. Their absolute configurations were determined from the CD signs in the first absorption region. On the basis of the NMR spectral data, two-point coordination of an aldonato ligand through the carboxylate group and the deprotonated hydroxyl group on C-2 was established, generating the five-membered chelate ring. In Fig. 23 a proposed structure of the Λ-D-gluconato complex is illustrated.

C. ALDOSE TRANSFORMATION AND MOLECULAR RECOGNITION BY METAL COMPLEXES

It is interesting to develop the methods whereby metals promote transformation of sugars in bioinorganic chemistry and in industry. In this section we introduce our new observations on the novel C-2 epimerization of aldoses promoted by combinations of metals and amines involving a novel rearrangement of the carbon skeleton and the similar reaction promoted by molybdate [38,39]. Although it is well known that a number of enzymes catalyse transformation of sugars and their derivatives, there is no report of a specific enzyme which catalyses C-2 epimerization of aldoses.

(i) Epimerization by molybdate

Bilik and his coworkers [38] have shown that in mildly acidic molybdate solutions, aldoses epimerize at C-2 with the formation of a thermodynamic equilibrium mixture of the two epimers. Generally, the reaction proceeds without the production of ketoses, and only minor amounts of secondary products are formed. On the basis of experiments with D-[1-^{3}H]glucose that gave D-[2-^{3}H]mannose as the major product (along with starting hexoses), they proposed that the reaction occurs by hydrogen exchange between C-1



Scheme 1.

and C-2 of the cyclic sugar with inversion of configuration at both carbon atoms.

Recently, Hayes et al. [39] investigated the above molybdate-catalysed C-2 epimerization of aldoses by using ^{13}C- and ^{2}H-enriched aldoses and ^{13}C NMR spectroscopy. The epimerization product of D-[1-^{13}C]mannose was exclusively D-[2-^{13}C]glucose, demonstrating that the reaction involves a 1,2-shift of the carbon skeleton, resulting in inversion of configuration at C-2. All the aldoses examined reacted similarly, producing equilibrium mixtures of the starting [1-^{13}C]aldose and the 2-epimeric 2-^{13}C product.

They proposed the reaction mechanism that the aldehyde aldose forms anionic complexes with dimolybdate involving the carbonyl oxygen and the hydroxylic oxygen atoms at C-2, C-3 and C-4 (1) as shown in Scheme 1. In this complex, rearrangement (epimerization) can occur through a transition state (2) in which C-1 and C-2 are enantiomeric. Bond formation between C-2 and C-3 regenerates the starting aldose while bond formation between C-1 and C-3 produces the C-2 epimer (3). Besides catalysing bond breaking

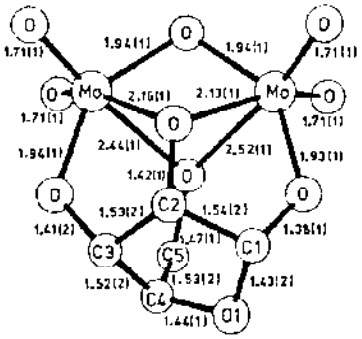


Fig. 24. Perspective drawing of molybdenum(VI) complex of D-lyxose.

and formation, the molybdate complex assures the stereospecificity of the rearrangement. In the complex, only the C-2 epimeric aldoses can form through the inversion of the C-1–C-2 fragment. The configuration at C-3 is maintained since bond breaking and bond formation occur on the same face of this carbon. Formation of a strong complex with molybdate induces rehybridization so that in the transition state, C-1 and C-2 have the same hybridization and form a transitory tricentric bond with C-3.

This mechanism is consistent with all the experimental observations: (a) only aldoses react, (b) OH-2 and OH-3 are essential, (c) OH-4 is not essential but is an important determinant of rate, (d) H-1, H-2 and H-3 are retained in the reaction, and, most importantly, (e) epimerization at C-2 is accompanied by a 1,2-shift in the carbon skeleton.

Taylor and Waters [40] reported interesting work on the molybdate-catalysed C-2 epimerization of pentoses and stereoselective complexation of one of the C-2 epimeric pentoses. They obtained a complex composed of two molybdates and one sugar moiety derived from the reaction between ammonium molybdate and D-xylose and determined its crystal structure by X-ray crystallography. The molecule is illustrated in Fig. 24 together with relevant distances. The metal centre is binuclear with a triple-oxygen bridge linking the two molybdenum atoms. All Mo–O distances are normal. The monosaccharide in the complex is in fact D-lyxose in an unusual furanose form. This observation indicated that molybdenum(VI) catalyzed the C-2 epimerization of the starting D-xylose and established an equilibrium with its C-2 epimer, D-lyxose, and this sugar preferentially complexed with the metal centre.

(ii) Epimerization and stereoselective uptake of aldoses by nickel(II) complexes

Previously, when we used *N*,*N*′-dimethylethylenediamine as the diamine component, of the many natural aldoses, only D-mannose gave a binuclear

nickel(II) complex containing *N*-glycosides, and we determined its crystal structure by X-ray crystallography [19] as described in the earlier section. In addition when we used D-glucose as a starting sugar, a nickel(II) complex containing D-mannose was surprisingly obtained, although its yield was very low and it could not be obtained as a solid compound. In the light of these results, we investigated the reactions of natural aldoses and nickel(II) complexes of diamines in order to develop a suitable complex for metal-assisted epimerization of monosaccharides and to establish the stereoselective complexation of various aldoses. Firstly, we simplified the reaction between aldoses and diamines in the hope of emphasizing the bridging ability of the *N*-mannofuranoside residue, as observed in the previous case [19]. Secondly, we chose *N*,*N*,*N*′-trimethylethylenediamine (tmen) as the diamine component, which has only one reactive proton (secondary amino group) in the molecule.

(a) Epimerization of aldoses by nickel(II) complexes of N-alkyl group substituted diamines

Aldoses are rapidly epimerized at C-2 in the presence of $[Ni(H_2O)_2(tmen)_2]Cl_2$ in methanolic solution (Table 2), and of the two C-2 epimers, only the mannose-type epimers having the *cis* arrangement of the C-2 and C-3 hydroxyl groups (D-mannose, D-lyxose, and D- or L-rhamnose) form complexes stereoselectively with nickel(II) (Scheme 2) [41]. When D-Gal, D-Tal, D-Ara and D-Rib were used as the starting sugar, they were epimerized but gave two kinds of complexes and the stereoselective complexation was not realized, as shown in Scheme 2. However, when *N*,*N*,*N*′-trimethylpropylenediamine was used as the amine component, all the aldoses used were epimerized, and the mannose-type epimers were incorporated into nickel(II) complexes stereospecifically (Scheme 2). Sugars are easily recovered from the complexes by treatment of slightly acidic aqueous solutions. It was also revealed that these nickel(II) complexes promote C-2 epimerization of aldoses to provide rapidly a near-equilibrium mixture of C-2 epimeric aldoses without forming any detectable side-reaction products including ketoses (Table 2).

Bilik and coworkers [38] and Haynes et al. [39] reported the closely related reactions described in the previous section, in which, in mildly acidic solutions of molybdate, aldoses epimerize at C-2 over a long reaction time (90 °C, 2–13 h) with the formation of a thermodynamic equilibrium mixture of the two epimers. Contrary to this, the present reaction is very fast (60 °C, 3–5 min) in mild basic conditions and involves the stereoselective uptake of the mannose-type C-2 epimers. The new aldose transformation system is depicted in Scheme 3. This cyclic system involves the process of C-2 epimerization of sugars and the stereospecific coordination of one of the C-2

TABLE 2

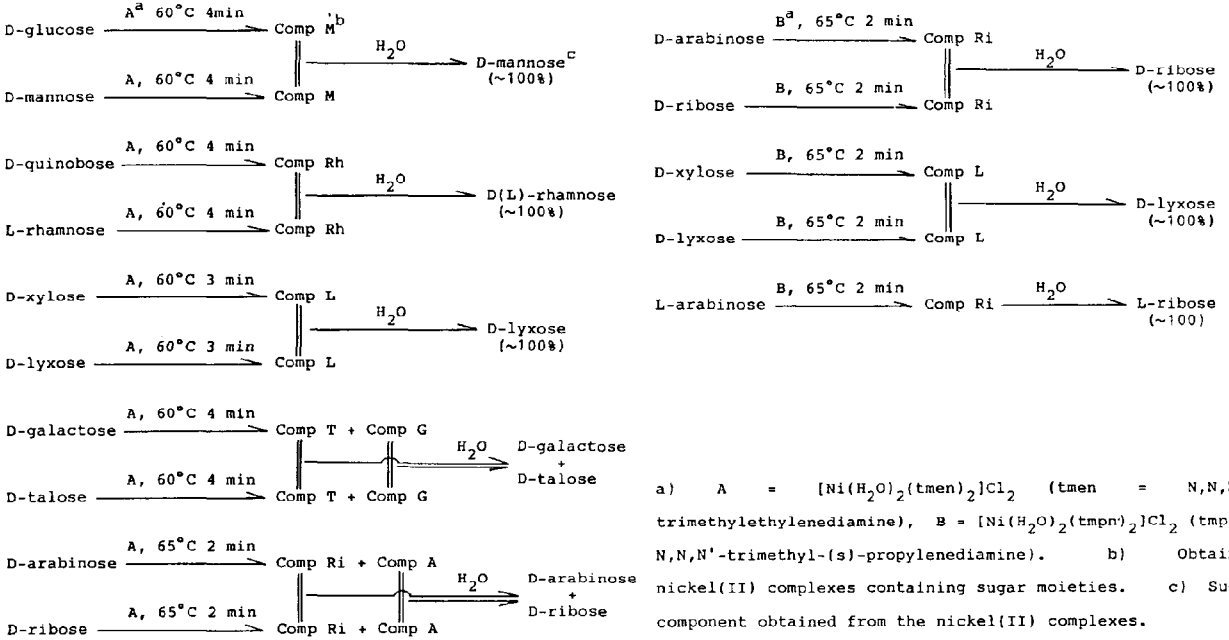
Ratios of C-2 epimeric aldoses obtained from the reaction promoted by nickel(II)–diamine complexes

No.	Substrate	[Ni]/[sugar] [a]	Diamine [b]	Condition	Ratio of C-2 epimers [c]	Yield of total aldoses (%) [d]
					Glc : Man	
1	D-glucose	1	tmen	60 °C, 4 min	45 : 55	94
2	D-glucose	0.1	tmen	60 °C, 30 min	69 : 31	82
3	D-mannose	1	tmen	60 °C, 4 min	34 : 66	93
						Qui : Rha
4	D-quinobose	1	tmen	60 °C, 4 min	55 : 45	85
5	L-rhamnose	1	tmen	60 °C, 4 min	55 : 45	91
						Xyl : Lyx
6	D-xylose	1	tmen	60 °C, 3 min	49 : 51	79
7	D-xylose	1	tmpn	65 °C, 2 min	41 : 59	71
8	D-lyxose	1	tmen	60 °C, 3 min	50 : 50	72
9	D-lyxose	1	tmpn	65 °C, 2 min	39 : 61	67
						Ara : Rib
10	D-ribose	1	tmen	65 °C, 2 min	31 : 69	85
11	D-ribose	1	tmpn	65 °C, 2 min	17 : 83	69
12	D-arabinose	1	tmen	65 °C, 2 min	54 : 46	67
13	D-arabinose	1	tmpn	65 °C, 2 min	36 : 64	64

[a] $[Ni(H_2O)_2(diamine)_2]Cl_2$ and the starting aldose (substrate) with the stated ratio of [Ni]/[sugar] were incubated at 60–65 °C in methanol. [b] tmen = *N,N,N′*-trimethylethylenediamine; tmpn = *N,N,N′*-trimethyl-(*S*)-propylenediamine. [c] Ratios of C-2 epimeric aldoses based on the obtained aldoses. [d] Yields (%) of total aldoses based on the starting sugars.

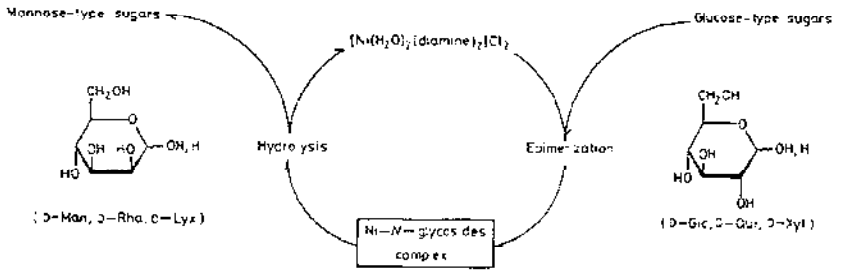
epimeric aldoses from which the mannose-type sugars are recovered by hydrolysis. Therefore this reaction has much potential for the synthesis of expensive and naturally rare aldoses, including acid-unstable oligosaccharides from their C-2 epimers, as well as being of theoretical importance.

D-[1-^{13}C]Glucose was used as a starting sugar to clarify the mechanism of this C-2 epimerization [42], the results of which demonstrated that the present reaction involves a novel exchange of C-1 and C-2 atoms by inversion of the C-1–C-2 fragment and proceeds without any C–H proton exchange in a deuterium-labelled solvent. Several blank tests suggest that a certain complex of Ni^{2+}, tmen and aldose is the reactive species in this epimerization. When *N,N,N′,N′*-tetramethylethylenediamine (tetmen), *N,N,N′,N′*-tetramethyltrimethylenediamine (tetmtn) and triethylamine were used as the amine component, the starting aldose was epimerized at C-2 with the combination of tetmen and Ni^{2+} ions and almost no epimerization occurred with Ni^{2+}–tetmtn and Ni^{2+}–triethylamine systems. These



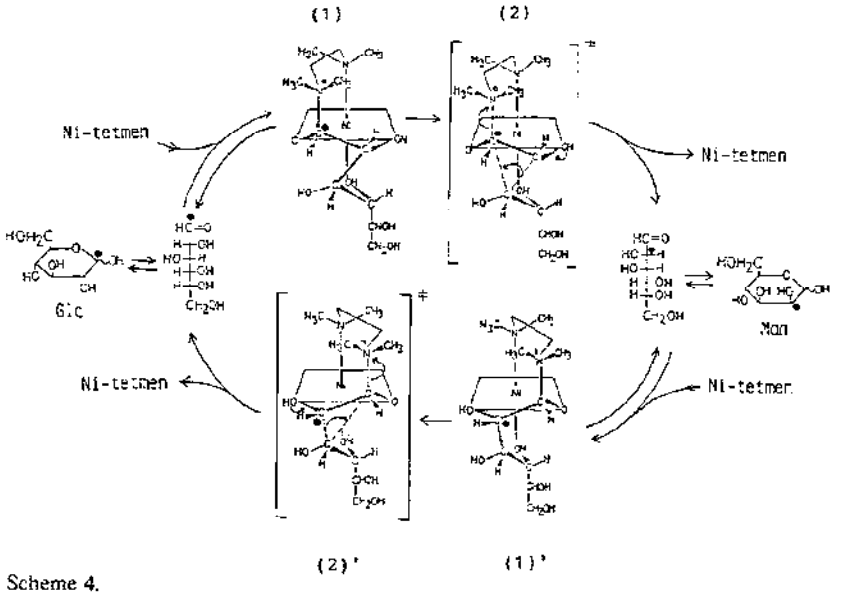
Scheme 2.

a) A = $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = N,N,N'-trimethylethylenediamine), B = $[Ni(H_2O)_2(tmpn)_2]Cl_2$ (tmpn = N,N,N'-trimethyl-(s)-propylenediamine). b) Obtained nickel(II) complexes containing sugar moieties. c) Sugar component obtained from the nickel(II) complexes.



Scheme 3.

results indicated that the length of the methylene carbon chain of the diamine is extremely important and the formation of *N*-glycosides is not essential for this epimerization since aldoses do not form *N*-glycosides with the tertiary amines. In the light of these results, coupled with inspection of the above ^{13}C NMR study, we proposed a possible mechanism for epimerization in the Ni^{2+}-diamine–D-glucose system in Scheme 4, i.e. D-glucose (substrate) reacts with the diamine to give the carbinol-ammonium-like adduct (not *N*-glycoside) which forms the reactive complex **1** with Ni^{2+}. In this complex, C-2 epimerization can occur through a transition state (**2**), in



Scheme 4.

which C-2 C-3 bond breaking and C-1–C-3 bond formation take place simultaneously, accompanied by elimination of the diamine residue. The product, D-mannose, is then disconnected from the reactive complex. Although this novel rearrangement was observed in the C-2 epimerization by molybdate [39], the present reactions provide the first example of its occurrence using metals and nucleophilic diamines under mild basic conditions: this method might be developed to provide a general 1,2-carbon shift reaction of carbohydrates with metal complexes.

Oligosaccharides have widespread occurrence in nature: in glycoproteins, glycolipids, proteoglycanes, and anti-tumors as well as in cell walls of plants, starch, and glycogen in animal cells. Hetero-oligosaccharides in glycoproteins and glycolipids on the surfaces of animal cell membranes have especially attracted much attention because they play important roles in cell–cell recognition and adhesion, tissue typing and hormone receptor sites. Therefore it has been desirable to develop the simple and effective synthetic procedures of naturally rare oligosaccharides in the field of biochemistry.

The newly discovered sugar transformation reaction using $[Ni(H_2O)_2(tmen)_2]^{2+}$ was applied to the synthesis of the (1–6)-linked disaccharides having the mannose reducing terminal from their C-2 reducing terminal epimers which are abundant in nature and are very difficult to synthesize by organic procedures (Table 3) [43]. The detailed structures of these disaccharides were determined by 2-D NMR spectroscopy (H–H shift relationship, proton *J*-resolution) as shown in Fig. 25. (1–4)-Linked disaccharides (D-lactose (4) and D-cellobiose (5)) were not epimerized in this reaction. Although conspicuous epimerization did not occur with D-maltose (6), the results of the complete hydrolysis of the reaction mixture (Glc : Man) indicate that slight C-2 epimerization had occurred. With respect to the effective synthesis of mannose-reducing terminal disaccharides, using naturally abundant polysaccharides as starting sugars, Bilik et al. reported the C-2 epimerization of D-melibiose by molybdate [37 (g)], in which the yield of D-Gal-(1–6)-D-man is comparatively low (25%) because of its thermodynamic instability, and both substrate and product are likely to be hydrolysed under such acidic conditions. Therefore the present reaction might be superior to the epimerization by molybdate. In addition, this reaction has the substrate selectivity that distinguishes between (1–6) and (1–4) O-glycosidic linkages. These features could be very important in relation to the enzymatic reactions as well as mechanisms of the C-2 epimerization.

(b) Stereoselective uptake of one of the epimeric aldoses by nickel(II) complexes

Both C-2 epimeric pairs of aldoses such as D-Glc : D-Man, D-Qui : L-Rha, D-Gal : D-Tal, D-Ara : D-Rib and D-Xyl : D-Lyx reacted with $[Ni(H_2O)_2$(tmen

TABLE 3

Results of C-2 epimerization of disaccharides

No.	Substrate	Diamine	C-2 epimerization products		Recovered substrate (%) [a]
			Formula	Yield (%) [a]	
1	melibiose (1)	tmen [b]	α,D-Gal-(1–6)-D-Man (8)	48	41
2	melibiose (1)	tetmen [c]	α,D-Gal-(1–6)-D-Man (8)	39	52
3	isomaltose (2)	tmen	α,D-Glc-(1 6)-D-Man (9)	54	44
4	isomaltose (2)	tetmen	α,D-Glc-(1–6)-D-Man (9)	48	45
5	gentiobiose (3)	tmen	β,D-Glc-(1–6)-D-Man (10)	41	55
6	gentiobiose (3)	tetmen	β,D-Glc-(1–6)-D-Man (10)	32	56
7	lactose (4)	tmen	—	0	93
8	cellobiose (5)	tmen	—	0	99
9	maltose (6)	tmen	α,D-Glc-(1–4)-D-Man (11) [d]	11 [d]	81
10	laminaribiose (7)	tmen	α,D-Glc-(1–3)-D-Man (12) [d]	9 [d]	88

[a] High performance liquid chromatography yield based on the starting disaccharides. [b] Substrates were treated with $[Ni(H_2O)_2(tmen)_2]Cl_2$ for 10 min at 60 °C in methanol. tmen = *N,N,N′*-trimethylethylenediamine. [c] Substrates were treated with $NiCl_2$ (1 equivalent) and tetmen (2 equivalents) for 10 min at 60 °C in methanol. tetmen = *N,N,N′,N′*-tetramethylethylenediamine. [d] The yield and the structure were determined from the result of complete hydrolysis of the reaction mixture.

TABLE 4

Best-fit values of some of the structural parameters of the samples and of the reference materials determined from EXAFS data

No.	Complex	EXAFS						X-ray	
		Neighbour	atom	r (Å)	σ (Å)	N	R [a]	r (Å)	N
1	Nickel foil	1st	Ni–Ni	2.46	0.063	12.0 [b]	0.066	2.49	12
2	Complex **1** ($[Ni(L\text{-Rha-tn})_2]^{2+}$)	1st	Ni–O,N [c]	2.12	0.084	6.0 [b]	0.265	2.12	6
3	Complex **2**	1st	Ni–O,N [c]	2.14	0.077	5.0	0.250	2.10	6
		2nd	Ni–Ni	3.59	0.045	0.9	0.034	3.60	1
($[Ni_3(MeOH)(N\text{-D-Man-}N,N'\text{-Me}_2\text{en})(N,N'\text{-D-Man}_2\text{-}N,N'\text{-Me}_2\text{en})]^{2+}$)									
4	Complex **3**	1st	Ni–O,N [c]	2.21	0.122	6.8	0.206	–	–
		2nd	Ni–Ni	3.28	0.096	2.3	0.061	–	–

[a] Reliability factor, which indicates the quality of curve fitting, defined by $R = \{\Sigma[(k^3x)_{obs} - (k^3x)_{calc}]^2/\Sigma[(k^3x)_{obs}]^2\}^{1/2}$.

[b] The number (N) of neighbour atoms references to nickel foil and complex **1**, $[Ni(L\text{-Rha-tn})_2]^{2+}$.

[c] All back-scattering atoms in the first sphere are calculated as oxygen atoms.

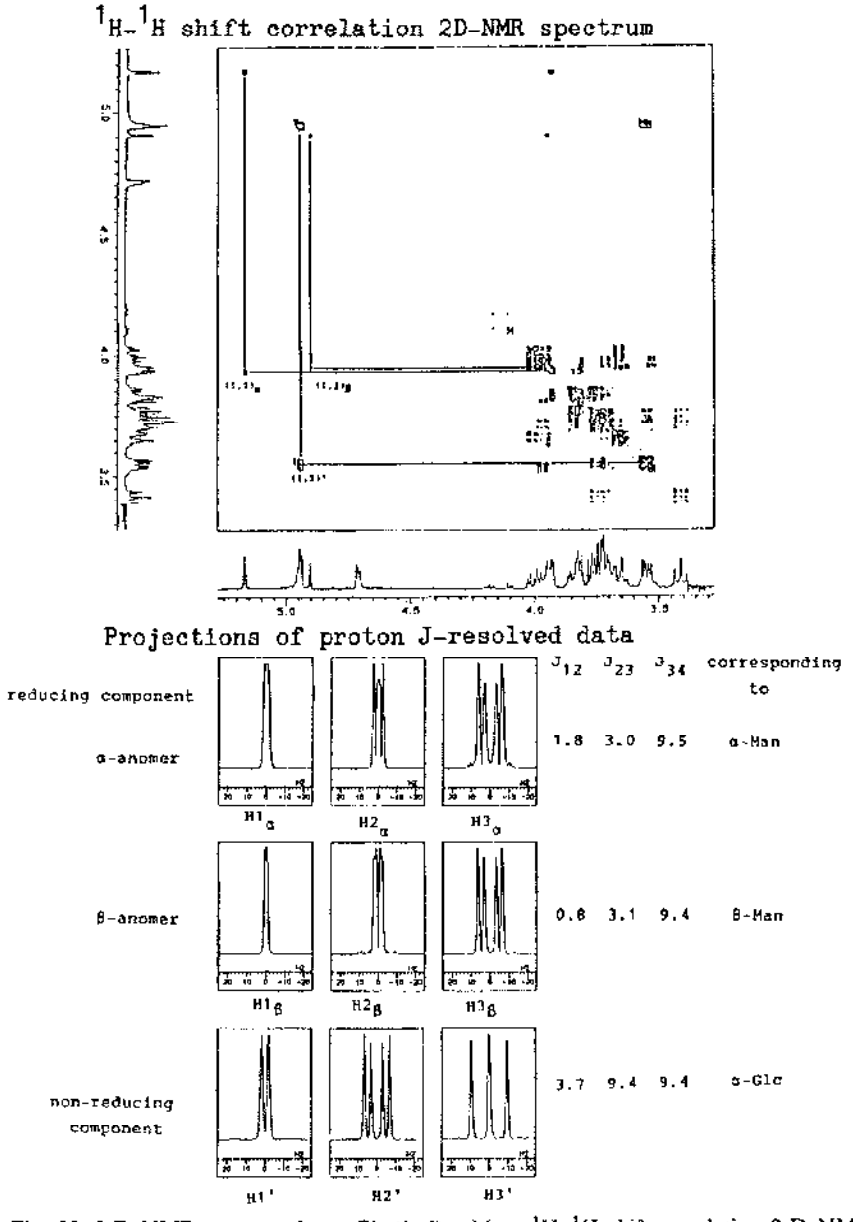


Fig. 25. 2-D NMR spectra of α,D-Glc-(1–6)-D-Man: ^{1}H–^{1}H shift correlation 2-D NMR spectrum (upper diagram) and projections of proton *J*-resolved data (lower diagram).

or tmpn)$_2$]$^{2+}$ to give the identical green complexes containing only mannose-type sugars such as Man, Qui, Tal, Rib and Lyx (Scheme 2). These green complexes are too hygroscopic to be isolated as powders suitable for the usual characterizations.

In order to elucidate the factor that caused the stereoselective uptake of one of the C-2 epimeric aldoses, the nickel(II) complexes containing *N*-glycoside complexes were investigated by extended X-ray absorption fine structure (EXAFS) spectroscopy [44].

Figure 26 presents the results of Fourier transforms of the EXAFS data. The results of the curve fitting analysis are presented in Table 4. One Ni–Ni distance (3.59 Å) was refinable, consistent with the crystallographic data on complex **2**, μ-Man-[Ni$_2$(MeOH)(*N*-D-Man-*N*,*N*′-Me$_2$en)(*N*,*N*′-D-Man$_2$-*N*,*N*′-Me$_2$en)]Cl$_2$ · MeOH · 5H$_2$O [19] in which the mannofuranoside

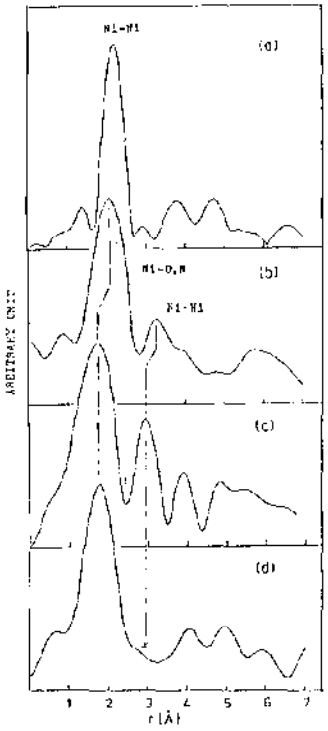


Fig. 26. Fourier transform of $k^3x(k)$: (a) Nickel foil; (b) μ-Man-[Ni$_2$(MeOH)(*N*-D-Man-*N*,*N*′-Me$_2$en)(*N*,*N*′-D-Man$_2$-*N*,*N*′-Me$_2$en)]Cl$_2$·MeOH·5H$_2$O; (c) nickel(II)–tmen–mannose complex; (d) [Ni(L-Rha-tn)$_2$]Br$_2$·2H$_2$O·CH$_3$OH.

residue links the two nickel atoms. Similarly, the best fit was obtained for a mean Ni Ni distance of 3.28 Å for the unknown nickel(II)–tmen–mannose complex **3**. The results of the present EXAFS study show that the complex **3** has a nickel polynuclear structure involving the *N*-mannofuranoside bridging. Our recent EXAFS studies [44 (b)] also suggested that D-Rib and D-Lyx complexes form similar polynuclear structures involving *N*-furanoside bridging as observed in the case of D-Man. All these results of EXAFS studies suggest that the key to the stereoselective complexation of mannose-type aldoses having some donor groups lies in the bridging part of the mannofuranoside residue which seems to have a strong affinity for nickel(II) ions.

(iii) Epimerization by combinations of various metal ions (Ca^{2+}, Co^{2+}, Sr^{2+}, Pr^{3+}, Ce^{3+}) and amines [45]

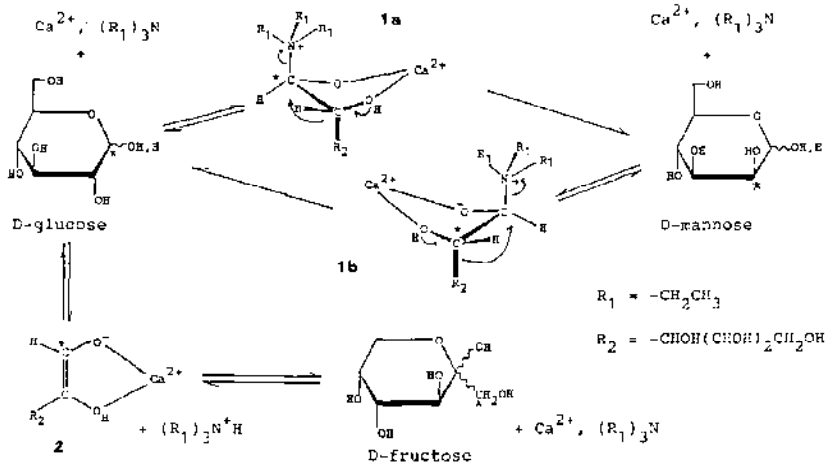
The C-2 epimerization of aldoses (D-Glc and D-Man) was examined, in methanol, by combinations of diamines, monoamines or aminoalcohols with some transition metal, alkaline earth metal and rare earth metal ions which have affinity for carbohydrates [46]. Among the metal ions used, only Ca^{2+}, Co^{2+}, Sr^{2+}, Pr^{3+} and Ce^{3+} proved to be effective, as listed in Table 5. The Ca^{2+}–Et_3N (triethylamine) system in particular has many advantages for

TABLE 5

Results of C-2 epimerization of aldoses promoted by metal ions and nucleophilic reagents

No.	Metal ions [a]	Nucleophilic reagent [a]	D-Glucose (substrate) [a]		D-Mannose (substrate) [a]	
			D-Man (%) [b]	D-Glc (%) [c]	D-Glc (%) [b]	D-Man (%) [c]
1	Ni^{2+}	$(CH_3)_2NCH_2CH_2N(CH_3)_2$	55	43	41	53
2	Ni^{2+}	Et_3N	Trace	99	0	100
3	Co^{2+}	$(CH_3)_2NCH_2CH_2N(CH_3)_2$	17	67	7	88
4	Ca^{2+}	$(CH_3)_2NCH_2CH_2N(CH_3)_2$	17	74	2	93
5	Ca^{2+}	Et_3N	38	32	10	74
6	Ca^{2+}	Et_3NH	38	25	17	66
7	Ca^{2+}	$(iPr)_2NH$	37	33	17	62
8	Ca^{2+}	$(CH_3)_2NCH_2CH_2OH$	18	66	Trace	86
9	Ca^{2+}	$NH_2CH_2CH_2OH$	14	63	6	78
10	Sr^{2+}	$(CH_3)_2NCH_2CH_2N(CH_3)_2$	3	86	2	97
11	Sr^{2+}	Et_3N	15	65	12	71
12	Pr^{3+}	Et_3N	7	70	2	78
13	Ce^{3+}	Et_3N	5	74	2	74

[a] Starting aldoses were treated with metal ions (1 equivalent) and nucleophilic reagents (2 equivalents) in methanol at 60 °C for 5 min. [b] Yields of C-2 epimers based on the starting aldoses. D-Man = D-mannose; D-Glc = D-glucose. [c] Yields of recovered starting aldoses.



Scheme 5.

practical use, although some defects were observed; low yields of C-2 epimeric aldoses compared with those in the Ni(II)–diamine systems and ketose (D-fructose) formation as byproducts.

^{13}C NMR studies using [1-^{13}C]D-glucose of the Ca^{2+}–Et_3N system revealed that a novel C-2 epimerization of aldoses involving the exchange of C-1 and C-2 atoms by inversion of the C-1–C-2 aldose fragment, as observed in the case of nickel(II)–diamine complexes [41] and molybdate [39], and ketose formation without rearrangement of the carbon skeleton occurred. On the basis of these results, we proposed a plausible mechanism for the C-2 epimerization and the aldose–ketose isomerization (Scheme 5). Aldoses are epimerized through intermediate complexes (**1a, 1b**) in which starting aldoses might attach to Ca^{2+} ions in an open-chain form and and in a conformation suitable for stereospecific rearrangement. As for ketose formation (byproduct), this proceeds via an ene-diol intermediate forming a chelate with Ca^{2+}-**2**, promoted by the monoamine which acts as a base catalyst [47].

Analogous C-2 epimerization might occur in biological systems, since Ca^{2+} ions and simple amine residues are often observed in such systems. Thus this work could suggest a significant new important role of Ca^{2+} ions in biological systems.

D. PLATINUM(II) COMPLEXES CONTAINING AMINO SUGARS HAVING ANTI-TUMOUR ACTIVITY

A great number of platinum complexes have been examined since the anti-tumour activity of cisplatin was shown by Rosenberg et al. [48]. Much

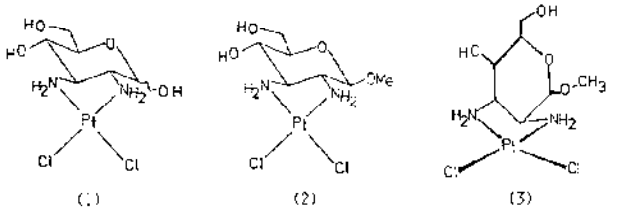


Fig. 27. Structures of complexes: $[PtCl_2$(D-GlcNN)] (**1**); $[PtCl_2$(D-Me-GlcNN)] (**2**); $[PtCl_2$(D-Me-ManNN)] (**3**).

work has been devoted to decreasing their toxicity and increasing their solubility. Many complexes, including various anionic leaving groups instead of chloride ions have been prepared, but in almost all cases ammine or simple alkylamines, which are toxic themselves, have been used as the neutral ligands [49].

Recently, many anti-cancer reagents that have sugar residue(s), e.g. bleomycin, adriamycin and many antibiotics, have been widely used clinically. Therefore it is of interest to examine the action of platinum compounds having sugar residues in vivo. In addition, metal complexes containing sugar residues are expected to exhibit fairly good solubility since sugars contain hydroxyl groups.

Tsubomura et al. [50] have synthesized and fully characterized cisplatin-type complexes of amino sugars, $[PtCl_2$(amino sugar)], for the first time. In this study, methyl-2,3-diamino-2,3-dideoxy-α-D-mannopyranoside (D-Me-ManNN), methyl-2,3-diamino-2,3-dideoxy-β-D-glucopyranoside (D-Me-GlcNN) and 2,3-diamino-2,3-dideoxy-D-glucose (D-GlcNN) were used. The structural assignments of the newly prepared complexes $[PtCl_2$(D-GlcNN)] (**1**), $[PtCl_2$(D-Me-GlcNN)] (**2**) and $[PtCl_2$(D-Me-ManNN)] (**3**) were made by absorption, CD and NMR spectroscopy (Fig. 27). The chelate conformations of the three diamino sugars are δ, δ and λ in the D-GlcNN, D-Me-GlcNN and D-Me-ManNN complexes respectively. These stereochemical features that may have influence on the conformational effect in their CD spectra are in the same sense for the D-GlcNN and D-Me-GlcNN complexes, and in the opposite sense for the D-Me-ManNN complexes. These structural features are evident in the CD curves; the CD curves of **1** and **2** are quite similar to each other and that of **3** has the opposite sign; the first two complexes and the last complexes are nearly mirror images (Fig. 28). These complexes, especially complex **1**, are reasonably soluble in water. The crystal structure of compound **3** was confirmed by X-ray crystallography (Fig. 29). Two chloride ions and a bidentate D-Me-ManNN ligand complete square-planar coordination around platinum through N(1) and

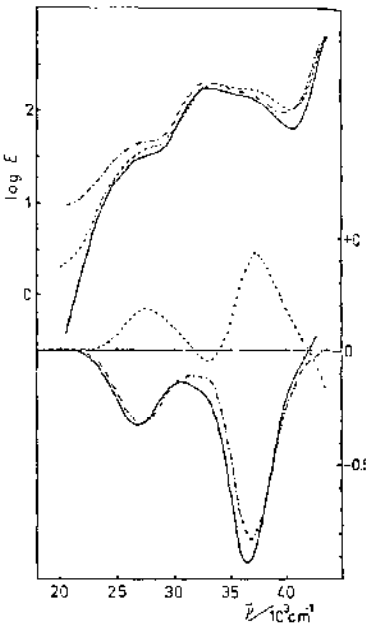


Fig. 28. Absorption (upper) and CD (lower) spectra of the platinum(II) complexes: $[PtCl_2$(D-GlcNN)] (———), $[PtCl_2$(D-Me-GlcNN)] (– · – · –), $[PtCl_2$(D-Me-ManNN)] (– – – – –).

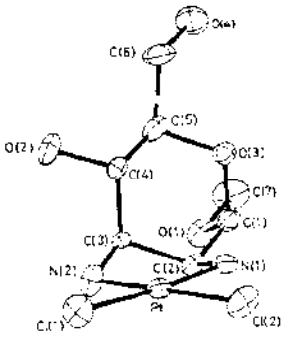


Fig. 29. ORTEP drawing of $[PtCl_2$(D-Me-ManNN)] H_2O. Selected bond distances (Å): Pt–Cl(1) 2.305(4), Pt- Cl(2) 2.310(4), Pt–N(1) 2.02(1), Pt–N(2) 2.03(1), N(1)–C(2) 1.49(2), N(2)–C(3) 1.51(1); Selected bond angles (deg): Cl(1)–Pt–Cl(2) 92.8(1), N(1) Pt N(2) 83.8(5), Cl(1)–Pt–N(1) 174.8(3), Cl(2)–Pt–N(2) 174.7(3).

TABLE 6

Anti-tumour screening results of platinum(II) complexes (T/C%), tested against sarcoma S180 and leukemia L1210 [a]

	S180				L1210			
$[PtCl_2$(D-GlcNN)$]\cdot H_2O$		220 (10)		411 (50)	106 (8)		127 (32)	
$[PtCl_2$(D-Me-GlcNN)$]\cdot 3/2H_2O$					116 (8)	145 (16)	122 (32)	
$[PtCl_2$(D-ManNN)$]$ [b]	129 (5)	269 (10)	326 (20)	237 (50)			127 (32)	118 (64)
$[PtCl_2$(D-Me-ManNN)$]\cdot H_2O$		139 (10)		229 (50)	108 (8)		127 (32)	
$[PtCl_2(NH_3)_2]$ (cisplatin)			237 (8)			150–200 (7)		

[a] Dose (mg kg^{-1}) is given in parentheses. [b] T. Suami, personal communication, 1986.

N(2). The pyranose ring of the D-Me-ManNN unit has the α-$^4C_1$ chair conformation. The amino groups on C-2 and C-3 are axial and equatorial respectively with respect to the pyranose ring. The Pt–N(1)–C(2)–C(3)–N(2) chelate adopts the λ-*gauche* conformation. Although intermolecular hydrogen bonds are found between solvated water molecules, chloride ions, hydroxyl groups and amino groups, no intermolecular interactions between platinum atoms is observed.

These complexes, especially complex **1**, show good anti-tumour activity in vivo against sarcoma S180 in mice: T/C 411% (ICR/CRJ mice, 10^6 cells (Table 6). Schedule day 1: dose 50 mg kg^{-1}, i.p.). The T/C value for cisplatin is 237% (dose, 8 mg kg^{-1}; other conditions are the same). These newly obtained complexes are reasonably soluble in water (solubility is greater than 20 mg ml^{-1} for complex **1**, and greater than 2 mg ml^{-1} for complex **3** at 35°C).

This study thus confirms that platinum complexes containing sugar residues may easily be prepared, and promises that a number of novel anti-cancer complexes containing amino sugars could be prepared since many amino sugars have widespread occurrence in nature.

ACKNOWLEDGEMENTS

I gratefully acknowledge assistance from Dr. T. Tsubomura, Mr. T. Takahashi, Mr. T. Tanase and Mr. K. Ishida during the writing of this review. Especially, I thank Professor S. Yamada for encouraging me to write this review. I would like to express my especial thanks to Professor S.

Yoshikawa for his encouragement and helpful suggestions. I thank Dr. Y. Mizobe for reading the final edition before submission.

REFERENCES

1 L.C. Maillard, Hebd. Seances Acad. Sci., 154 (1912) 66.
2 T.E. MacDermott and D.H. Busch, J. Am. Chem. Soc., 89 (1967) 5780.
3 T.E. MacDermott, B.E. Sewall and D.H. Busch, J. Am. Chem. Soc., 89 (1967) 5784.
4 (a) S. Takizawa, H. Sugita, S. Yano and S. Yoshikawa, J. Am. Chem. Soc., 102 (1980) 7969.
(b) S. Yano, S. Takizawa, H. Sugita, H. Shioi, T. Takahashi, T. Tsubomura and S. Yoshikawa, Carbohydr. Res., 142 (1985) 1795.
5 (a) T. Tsubomura, S. Yano, S. Yoshikawa, K. Toriumi and T. Ito, Polyhedron, 2 (1983) 123.
(b) T. Tsubomura, S. Yano, S. Yoshikawa, K. Toriumi and T. Ito, Bull. Chem. Soc. Jpn., 57 (1984) 1833.
6 T. Tsubomura, S. Yano, K. Toriumi, T. Ito and S. Yoshikawa, Inorg. Chem., 24 (1985) 3218.
7 F. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, 2nd edn., Interscience, New York, 1966, p. 882.
8 (a) L. Sacconi, Transition Met. Chem. Ser. Adv., 4 (1968) 210.
(b) J.W. Martin and N.F. Curtis, J. Chem. Soc., Dalton Trans., (1975) 87.
9 J.A. Kanters, G. Roelofsen, B.P. Alblas and K. Meinders, Acta Crystallogr., Sect. B, 33 (1977) 665.
10 (a) D.C. Craig, N.C. Stephenson and J.D. Stevens, Cryst. Struct. Commun., 3 (1974) 195, 277.
(b) W.J. Cook and C.E. Bugg, Acta Crystallogr., Sect. B, 32 (1976) 656.
11 S.H. Kim and R.D. Rosenstein, Acta Crystallogr., 22 (1967) 648.
12 D.L. Johnston and W.D. Horrocks, Jr., Inorg. Chem., 10 (1971) 687.
13 L. Pauling, The Nature of the Chemical Bond, 3rd edn., Cornell University Press, Ithaca, NY, 1960, Tables 7-5, 7-13 and 7-15.
14 R.S. Cahn, C.K. Ingold and V. Prelog, Experientia, 12 (1956) 81.
15 R.D. Gillard, in H.A.O. Hill and P. Day (Eds.) Physical Methods in Advanced Inorganic Chemistry, Interscience, New York, 1968, Chapt. 5.
16 S. Kitagawa, T. Murakami and M. Hatano, Inorg. Chem., 14 (1975) 2347.
17 M.J. Harding, S.F. Mason and B.J. Peart, J. Chem. Soc., Dalton Trans., (1973) 955.
18 (a) H. Shioi, S. Yano, K. Toriumi, T. Ito and S. Yoshikawa, J. Chem. Soc., Chem. Commun., (1983) 201.
(b) S. Yano, H. Shioi, T. Tsubomura, K. Toriumi, T. Ito, T. Takahashi and S. Yoshikawa, unpublished result, 1984.
19 S. Yano, Y. Sakai, K. Toriumi, T. Ito, H. Ito and S. Yoshikawa, Inorg. Chem., 24 (1985) 498.
20 T. Tanase, K. Kurihara, S. Yano, K. Kobayashi, T. Sakurai and S. Yoshikawa, J. Chem. Soc., Chem. Commun., (1985) 1562.
21 T. Takahashi, Y. Sato, T. Tanase, K. Kobayashi, T. Sakurai, S. Yano and M. Hidai, Chem. Lett., (1987) 2153.
22 (a) H. Sigel, in H. Sigel (Ed.), Metal Ions in Biological Systems, Vol. 2, Dekker, New York, 1973, p. 63.
(b) O. Yamauchi, K. Tsujide and A. Odani, J. Am. Chem. Soc., 107 (1985) 5938.

23 G. Weitzel, H.-U. Geyer and A.-M. Fretzdorff, Chem. Ber. 90 (1957) 1153.
24 T. Tsubomura, S. Yano and S. Yoshikawa, Inorg. Chem., 25 (1986) 392.
25 W. Pigmen and D. Horton (Eds.), The Carbohydrates. Chemistry and Biochemistry. Vol. 1B, Academic Press, New York, 1980, p. 883.
26 (a) L.N. Swink and M. Atoji, Acta Crystallogr., 13 (1960) 639.
(b) Y.I. Smolin, J. Chem. Soc. D, (1969) 395.
(c) M. ul-Haque, C.N. Caughlan and K. Emerson, Inorg. Chem., 9 (1970) 2421.
27 (a) S.S.C. Chu and G.A. Jeffrey, Proc. R. Soc. London. Ser. A, 285 (1965) 470.
(b) R. Chandrasekharan and M. Mallikarjunan, Z. Kristallogr., 129 (1969) 29.
28 (a) L.N. Johnson, Acta Crystallogr., 21 (1966) 885.
(b) F. Mo and L.H. Jensen, Acta Crystallogr., Sect. B, 31 (1975) 2867.
29 (a) K. Ishida, S. Yano and S. Yoshikawa, Inorg. Chem., 25 (1986) 3552.
(b) S. Yano, K. Ishida and S. Yoshikawa, unpublished results, 1987.
30 (a) H. Yamatera, Bull. Chem. Soc. Jpn., 31 (1958) 95.
(b) N. Matsuoka, J. Hidaka and Y. Shimura, Bull. Chem. Soc. Jpn., 40 (1967) 1868.
31 A.J. MaCaffery, S.F. Maison and B.J. Norman, J. Chem. Soc., (1965) 5094.
32 (a) M. Karplus, J. Chem. Phys., 30 (1959) 11.
(b) M.J. Karplus, J. Am. Chem. Soc., 85 (1963) 2870.
33 J. Reuben, J. Am. Chem. Soc., 106 (1984) 6180.
34 (a) M. Yashiro, S. Yano and S. Yoshikawa, J. Am. Chem. Soc., 108 (1986) 1096.
(b) K. Ishida, M. Yashiro, S. Yano, M. Hidai and S. Yoshikawa, J. Am. Chem. Soc., 110 (1988) 2015.
35 (a) M. Rudrum and D.F. Shaw, J. Chem. Soc., (1965) 52.
(b) R.U. Lemieux and J.D. Stevens, Can. J. Chem., 44 (1966) 249.
36 (a) M.J. Adam and L.D. Hall, J. Chem. Soc., Chem. Commun., (1979) 234.
(b) M. Adam and L.D. Hall, Can. J. Chem., 60 (1982) 2229.
37 T. Tsubomura, S. Yano and S. Yoshikawa, Bull. Chem. Soc. Jpn., submitted for publication.
38 (a) V. Bilik and L. Stancovik, Chem. Zvesti, 27 (1973) 544.
(b) V. Bilik and J. Caplovic, J. Chem. Zvesti, 27 (1973) 547.
(c) V. Bilik, L. Petrus and V. Frakas, Collect. Czech. Chem. Commun., 43 (1978) 1163.
(d) V. Bilik, L. Petrus and V. Farkas, Chem. Zvesti, 29 (1975) 690.
(e) V. Bilik, L. Petrus and J. Zemek, J. Chem. Zvesti, 32 (1978) 242.
(f) V. Bilik, L. Petrus, I. Stancovic and K. Linck, Chem. Zvesti, 32 (1978) 372.
(g) V. Bilik, E. Jurcova and V. Sutoris, Listy Cukrov., 94 (1978) 88.
39 M.L. Hayes, N.J. Pennings, A.S. Serianni and R. Barker, J. Am. Chem. Soc., 104 (1982) 6764.
40 G.E. Taylor and J.M. Waters, Tetrahedron Lett., 22 (1981) 1277.
41 T. Tanase, F. Shimizu, S. Yano and S. Yoshikawa, J. Chem. Soc., Chem. Commun., (1986) 1001.
42 T. Tanase, F. Shimizu, M. Kuse, S. Yano, S. Yoshikawa and M. Hidai, J. Chem. Soc., Chem. Commun., (1987) 659.
43 T. Tanase, K. Ishida, T. Watanabe, M. Komiyama, K. Koumoto, S. Yano, M. Hidai and S. Yoshikawa, Chem. Lett., (1988) 327.
44 (a) T. Tanase, F. Shimizu, S. Yano, M. Hidai, S. Yoshikawa and K. Asakura, Nippon Kagaku Kaishi, 3 (1987) 322.
(b) S. Yano, T. Tanase, F. Shimizu and M. Hidai, unpublished results, 1987.
45 T. Tanase, T. Murata, S. Yano, M. Hidai and S. Yoshikawa, Chem. Lett., (1987) 1409.
46 S.J. Angyal, Chem. Soc. Rev., 9 (1980) 415.

47 (a) J.C. Speck, J. Adv. Carbohydr. Chem., 13 (1958) 63.
(b) R.W. Gracy and E.A. Noltmann, J. Biol. Chem., 243 (1968) 5410.
(c) A.S. Mildvan, Enzyme, 2 (1970) 511.
48 B. Rosenberg, L. VanCamp, J.E. Trosko and V.H. Mansour, Nature (London), 222 (1969) 385.
49 S.J. Lippard (Ed.), Platinum, Gold, and Other Metal Chemotherapeutic Agents, American Chemical Society, Washington D.C., ACS Symp. Ser. 209, 1983; M.P. Hacker, E.B. Douple and I. H. Krakoff (Eds.), Platinum Coordination Complexes in Cancer Chemotherapy, Martinus Nijhoff, Boston, 1984; L.S. Hollis, A.R. Amundsen and E.W. Stern, J. Am. Chem. Soc., 107 (1985) 274.
50 (a) T. Tsubomura, S. Yano, K. Kobayashi, T. Sakurai and S. Yoshikawa, J. Chem. Soc., Chem. Commun., (1986) 459.
(b) S. Yano, T. Tsubomura and S. Yoshikawa, unpublished results.