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C-2 Epimerization of Disaccharides by Nickel(II)-Diamine Complex. A New Synthesis of (1→6)-Linked Disaccharides Having Mannose as a Reducing Unit

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(1→6)-Linked disaccharides having mannose as a reducing unit were synthesized from their naturally abundant C-2 epimers by the novel C-2 epimerization promoted by nickel(II)-diamine complex, $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = N,N,N'-trimethylethylenediamine).

Oligosaccharides are of wide spread occurrence in nature; in glycoproteins, glycolipids, proteoglycans, and antibiotics as well as in starch and cell walls of plants, and in glycogen in animal cells. Especially, hetero-oligosaccharides in glycoproteins and glycolipids on the surfaces of animal cell membranes have attracted much attention, because they play important roles in cell-cell recognition and adhesion, tissue typing, and hormone receptor sites. So, it has been desired to develop a simple and effective synthetic procedure for naturally rare oligosaccharides.

We have previously reported the novel C-2 epimerization of monosaccharides in which aldoses are epimerized by treatment of $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = N,N,N'-trimethylethylenediamine) in a very short time (60 °C, 3-5 min) to give the almost 1:1 mixtures of two C-2 epimeric aldoses.[1,2] An examination using [1-^{13}C]-D-glucose as a starting sugar showed that the epimerization involves a novel stereospecific rearrangement of carbon skeleton or 1,2-carbon shift.[2,3] In the present study, we applied this reaction to the preparation of disaccharides having mannose as a reducing unit from their C-2 epimers which are abundant in nature.

To a methanolic solution (30 mL) of $[Ni(H_2O)_2(tmen)_2]Cl_2$[1] (1.1 mmol) was added a (1→6)-linked disaccharide (melibiose 1, isomaltose 2, or gentiobiose 3[4]) (1.1 mmol), and the solution was incubated at 60 °C for 10 min with stirring, and the disaccharides contained in the solution were analyzed by HPLC.[1] In every case, two peaks were observed; the later peak was assigned to the starting disaccharide (1, 2, or 3) and faster band was fractionated and purified[5] prior to assignments (7, 8, or 9).

The complete hydrolysis[6] of 7, 8, and 9 gave ca. 1:1 mixture of D-Gal and D-Man, D-Glc and D-Man, and D-Glc and D-Man, respectively. 100 MHz ^{13}C NMR spectra of 7, 8, and 9 in D_2O are given in Fig. 1. In these spectra, three peaks were observed in the anomeric carbon region of 90-105 ppm; two anomeric peaks in 95-97 ppm are corresponding to those of α- and β-D-mannopyranose,[7,8] and lower side peaks at 100.4 (7), 100.0 (8), and 104.9 ppm (9) were assigned to the nonreducing anomeric carbons of α-D-galactopyranose, α-D-glucopyranose, and β-D-glucopyranose, respectively.[8] This indicated that D-mannose residues constitute the reducing unit and D-galactose and D-glucose residues the nonreducing components. In the hydroxymethyl carbon region of 60-66 ppm, only one peak was observed in every case, which suggested that the two monosaccharides were linked by (1→6) O-glycosidic bondings, the peak of hydroxymethyl carbon (C-6) of the reducing unit being shifted to lower field. The other peaks were assigned from the chemical shift data of related compounds,[8] but it should be noted that these assignments might involve a degree of uncertainty. So we made two dimensional NMR studies for the representative product 8 to perform a complete structural analysis.[7] The ^1H-^1H shift correlated spectrum showed three spin networks corresponding to α- and β-reducing unit and nonreducing unit (Fig. 2), and in combination with the ^{13}C-^1H shift correlated spectrum, the assignment of ^{13}C peaks mentioned above were unambiguously confirmed. Further the coupling constants (J_{12}, J_{23}, J_{34}) in each unit derived from the 2D J-resolved NMR spectrum (Table 1) clearly indicate that 8 is O-α-D-glucopyranosyl-(1→6)-D-mannopyranose. Consequently, it was revealed that, in this reaction, (1→6)-linked

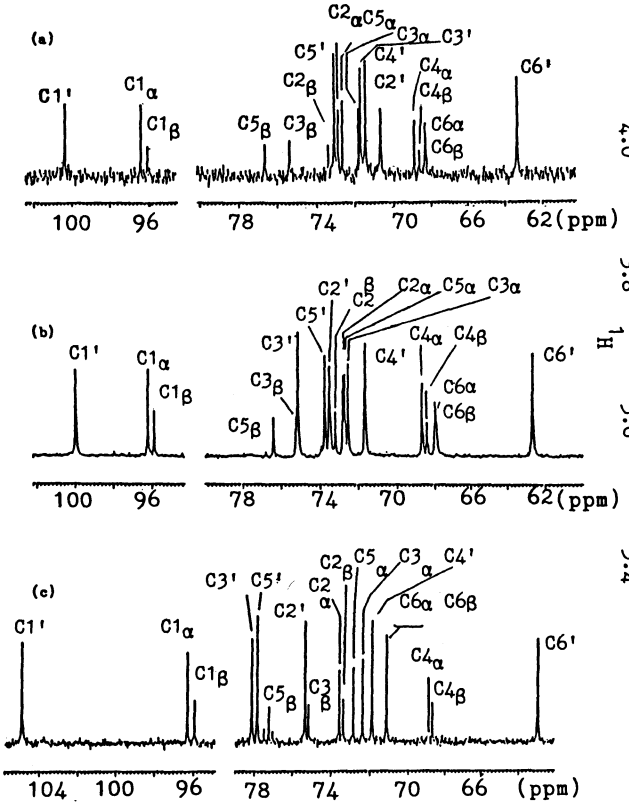


Fig.1. ^{13}C NMR spectra of 7 (a), 8 (b), and 9 (c).

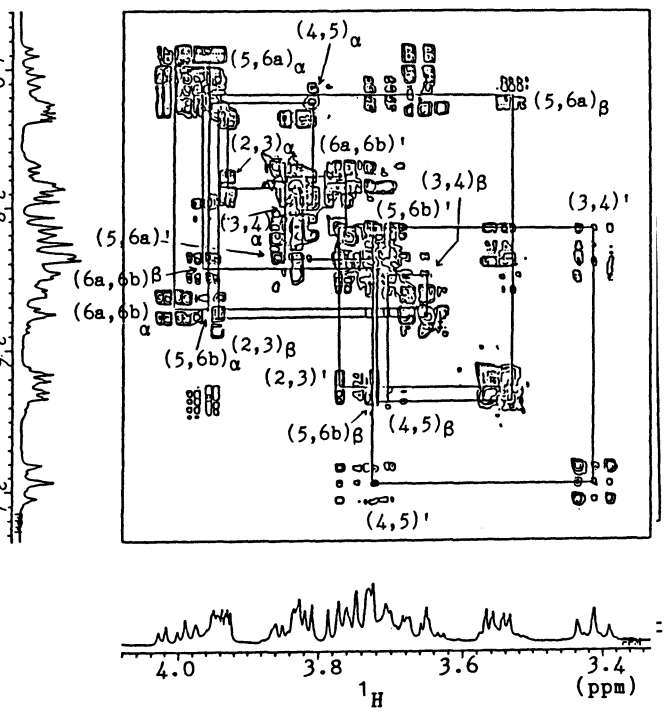


Fig.2. ^1H-^1H shift correlated spectrum of 8 in the non-amomeric region.

Table 1. The Coupling Constants Derived from Two-dimensional J-Resolved Spectrum of 8

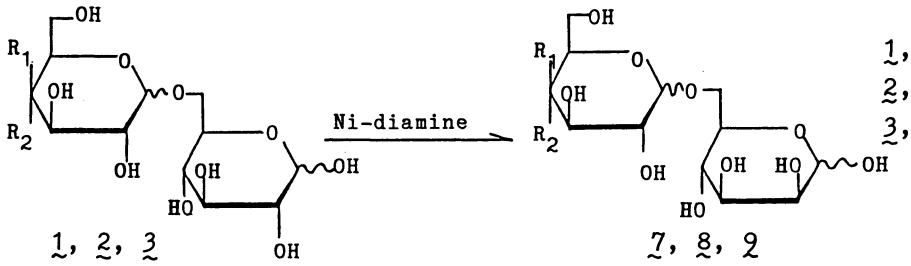
Unit	J_{12}	J_{23}	J_{34}	Corresponding to[a]
α reducing unit	1.8	3.0	9.5	α-D-mannopyranose
β reducing unit	0.8	3.1	9.4	β-D-mannopyranose
nonreducing unit	3.7	9.4	9.4	α-D-glucopyranose

a) Ref. 9.

Table 2. Results of C-2 Epimerization of Disaccharides

No.	Substrate[a]	Yields of C-2 epimers R-Glc[b]	R-Man[b]	(R-Glc:R-Man)[c]	C-2 Epimerization products
1	melibiose (1)	41	48	(46 : 54)	α-D-Gal-(1→6)-D-Man (7)
2	isomaltose (2)	44	54	(45 : 55)	α-D-Glc-(1→6)-D-Man (8)
3	gentiobiose (3)	55	41	(57 : 43)	β-D-Glc-(1→6)-D-Man (9)
4	lactose (4)	93	0	(100 : 0)	-
5	cellobiose (5)	99	0	(100 : 0)	-
6	maltose (6)	81	11[d]	(88 : 12)[d]	(α-D-Glc-(1→4)-D-Man (10))[d]

a) The starting disaccharides were treated with $[Ni(H_2O)_2(tmen)_2]Cl_2$ (1 equiv.). b) Yields of C-2 epimeric disaccharides based on the substrate (%). (R = O-glycopyranosyl residue) c) Ratios of C-2 epimers obtained from the reaction mixture. d) The values were determined from the result of complete hydrolysis of the reaction mixture (Glc:Man = 94:6), which might indicate that the C-2 epimerization product is α-D-Glc-(1→4)-D-Man in a yield of at most 11%.



1, 2, 3 → 7, 8, 9

1, 7 R_1=OH, R_2=H, α(1→6)
2, 8 R_1=H, R_2=OH, α(1→6)
3, 9 R_1=H, R_2=OH, β(1→6)

Scheme 1.

disaccharides having mannose as a reducing unit were easily obtained in comparatively high yields and no appreciable by-product including free monosaccharide was detected (Table 2 and Scheme 1). In contrast, (1→4)-linked disaccharides (lactose 4, cellobiose 5, and maltose[10] 6) were not epimerized.[3b]

With respect to the effective synthesis of disaccharides having mannose as a reducing unit, Bilik et al. reported the C-2 epimerization of melibiose by molybdate,[11] in which the yield of α-D-Gal-(1→6)-D-Man is comparatively low (25%) because of its thermodynamic instability and both substrate and product are likely to be hydrolyzed in such an acidic condition. Compared with this epimerization catalyzed by molybdate, the present reaction appears to be more effective to the synthesis of oligosaccharides having mannose as a reducing unit because of high yields and mild alkaline conditions. In addition, this reaction has the substrate selectivity that distinguishes between (1→6)- and (1→4)-linkages. These features could provide important information in relation to detailed mechanism of this reaction.[2,3b,11]

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4) The fully systematic names are as follows; melibiose, O-α-D-galactopyranosyl-(1→6)-D-glucose (α-D-Gal-(1→6)-D-Glc); isomaltose, O-α-D-glucopyranosyl-(1→6)-D-glucose (α-D-Glc-(1→6)-D-Glc); gentiobiose, O-β-D-glucopyranosyl-(1→6)-D-glucose (β-D-Glc-(1→6)-D-Glc); lactose, O-β-D-galactopyranosyl-(1→4)-D-glucose (β-D-Gal-(1→4)-D-Glc); cellobiose, O-β-D-glucopyranosyl-(1→4)-D-glucose (β-D-Glc-(1→4)-D-Glc); maltose, O-α-D-glucopyranosyl-(1→4)-D-glucose (α-D-Glc-(1→4)-D-Glc).

5) Fractionations were carried out on the same HPLC system (column; anion exchange resin (TSK) 10 mm x 300 mm) as that used for sugar analysis and fractions were collected before the reaction with 2-cyanoacetamide and were adjusted pH 4.5 with 1 M H_2SO_4 prior to deionization (Dowex 50WX8 (H^+) and 1-X2 (HCO_3^-)). Then methanol was added and evaporated (repeated 4-5 times) to remove the remaining boric acid as trimethylborate. The remaining oily disaccharide was recrystallized from n-butanol-methanol mixed solvent.

6) Disaccharides were completely hydrolyzed by 1 M H_2SO_4 solution (100 °C, 8 h) and were neutralized with $CaCO_3$. Then, monosaccharides contained in the solution were analyzed by HPLC.

7) ^{13}C NMR spectra were obtained at 100 MHz with a JEOL GX-400 superconducting FT spectrometer and chemical shifts are given in ppm downfield from external TMS. Two-dimensional NMR experiments were carried out with the same instrument by means of JEOL PLEXUS (version 1.5) program.

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10) When maltose was used as a substrate, conspicuous C-2 epimerization did not occur, but the result of complete hydrolysis of the reaction mixture (Glc:Man=94:6) might indicate that slight C-2 epimerization occurred and the product was α-D-Glc-(1→4)-D-Man in a yield of at most 11%.

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