CHEMISTRY LETTERS, pp. 2273-2276, 1990.

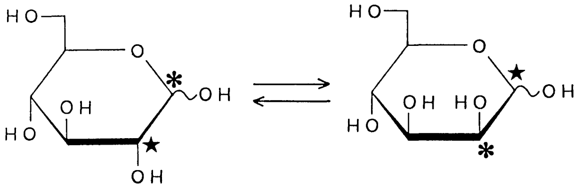
C-1,C-2 Stereospecific Rearrangements of Aldohexoses by Calcium Ion in Basic Solution

Ryoji YANAGIHARA,* Shuichi OSANAI,* and Sadao YOSHIKAWA
Department of Applied Chemistry, Faculty of Science
and Technology, Keio University, Yokohama 223

In aqueous or methanolic solution containing Ca^{2+} and hydroxide ion, aldoses are rapidly epimerized at C-2. This reaction involves C-1,C-2 stereospecific rearrangement. [2-^{13}C]-D-Mannose is formed from [1-^{13}C]-D-glucose by this reaction.

Aldoses were epimerized at C-2 in methanol by Ni^{2+}-diamine[1)] or Ca^{2+}-amine[2)] catalyst. [1-^{13}C]-D-Glucose(1*-Glc) was converted into [2-^{13}C]-D-mannose(2*-Man) via the stereospecific rearrangement of carbon skeleton. It rapidly proceeded under mild condition. Among many ligands used in the Ni^{2+} system, diamine was effective for the epimerization but monoamine was not. This result implied that the chelating agent which connected metal ion and aldose was neccessary for the epimerization. In the Ca^{2+} system, however, monoamine was also effective. Prompted by these results, we have investigated the epimerizations of aldohexoses using Ca^{2+} and the most fundamental and simplest base like OH^-. We thought that the base OH^-, as well as the monoamine, would be effective in the Ca^{2+} system.

The reactions were carried out in a similar manner as described in the previous paper.[3)] Aldoses which possesed isotopic ^{13}C anomeric carbon were used as substrates to clarify the mechanism of this reaction. Aldose (D-glucose or D-mannose) was added to aqueous or methanolic solution of calcium chloride dihydrate and/or base (cf. Table 2 and 3), and kept at 65 °C for 5 min with stirring. The reaction mixture was then cooled in an ice bath, followed by pH adjustment at 6.5, and deionized by ion-exchange resin (Dowex H^+ , HCO_3^- form). Resulting sugars were monitored through ^{13}C NMR spectra and their compositions were qualitatively



Scheme 1. Stereospecific Rearrangements of Carbon Skeleton of Aldoses by Ca^{2+}-Base System

and quantitatively analyzed by gas-liquid chromatography of trimethylsilylated products.$^{4)}$ Gas chromatograph equipped with a glass capillary column (OV-1 BONDED ; 0.25mm I.D. X 25m) was used and operated isothermally at 185 °C.

The ^{13}C NMR spectra of products were shown in Fig. 1 and 2. They were measured with a JEOL FX90A spectrometer in D_2O with dioxane as an internal standard (67.4 ppm), and assigned by reference to the authentic data shown in Table 1. The yields and ^{13}C positions of the products under various conditions were summarized in Table 2 and 3. The results showed that 1*-Glc was converted into 2*-Man and [1-^{13}C]-D-fructose(1*-Fru) under

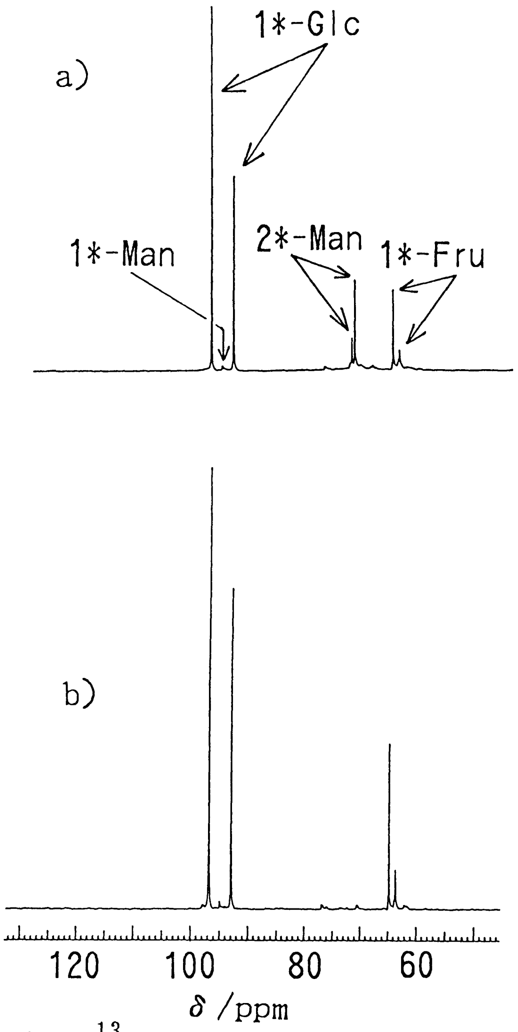


Fig.1. ^{13}C NMR Spectra of Products Derived from 1*-Glc
a) By $Ca(OH)_2$ in H_2O (Run 1)
b) By NaOH in H_2O (Run 4)

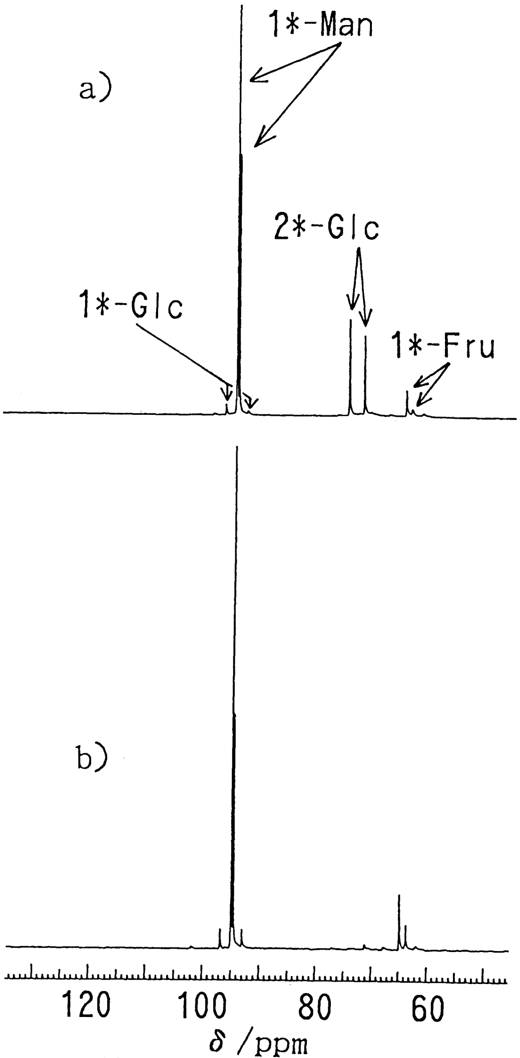


Fig.2. ^{13}C NMR Spectra of Products Derived from 1*-Man
a) By $Ca(OH)_2$ in H_2O (Run 10)
b) By NaOH in H_2O (Run 11)

Table 1. ^{13}C Chemical Shifts of Hexoses (δ/ppm)

Hexose[a]		C-1	C-2
Glc	β-Pyra[6]	96.7	75.1
	α-Pyra[7]	92.2	71.7
Man	α-Pyra[8]	95.2	71.9
	β-Pyra[8]	94.9	72.4
Fru	β-Pyra[6]	64.9	98.9
	β-Fura[6]	63.7	102.3

a) Pyra : pyranose, Fura : furanose.

coexistence of Ca^{2+} and base. 1*-Man was also converted into 2*-Glc and 1*-Fru under the same condition (Fig. 2). No conversion was observed in $CaCl_2$ solution. In NaOH or $NaOCH_3$ solution, 1*-Glc was converted into 1*-Man and 1*-Fru without rearrangement of carbon skeleton. The results were due to the reversible enolation which has been well-known as the "Lobry-Alberda (L-A) rearrangement". In this reaction, the yield of C-2 epimer was smaller than that of ketose. But in the reaction containing Ca^{2+}, the yield of D-mannose was larger than that of D-fructose in contrast to the case of Na^+. In the presence of Ca^{2+}, the epimerization of aldose in basic solution was quite different from L-A rearrangement.

D-Fructose was formed without the rearrangement of carbon skeleton. Therefore, the mechanism of forming ketose in Ca^{2+} system was similar to L-A rearrangement. In some cases, in which 2*-Man was obtained in relatively high yield, a small quantity of 2*-Fru was formed from 1*-Glc. It was formed by L-A rearrangement from 2*-Man which had been previously prepared as a main product.

Whether the substrate was D-glucose or D-mannose, the amount of D-

Table 2. Reaction of [1-^{13}C]-D-glucose

Run	Reagents Base	Reagents A:C:B[a]	Solvent[b]	^{13}C Position[c] Man	^{13}C Position[c] Fru	Composition of products/%[d] Glc	Man	Fru	Recov.[e] %
1	$Ca(OH)_2$	1:0:1	W	1<2	1	75	17	8	94
2	$Ca(OH)_2$	1:4:1	W	1<2	1	68	24	8	88
3	——	1:1:0	W	none	none	100	0	0	99
4	NaOH	1:0:1	W	1	1	74	3	23	98
5	$Ni(OH)_2$	1:0:1	W	none	none	100	0	0	99
6	NaOH	1:1:1	M	1<2	1>2	23	42	35	91
7	NaOH	1:4:1	M	2	1>2	15	62	23	93
8	NaOH	1:0:1	M	1	1	70	2	28	96
9	$NaOCH_3$	1:0:1	M	1	1	69	4	27	93

a) Molar ratio of (aldose):(calcium chloride dihydrate):(base).

b) W : water , M : methanol.

c) "1<2" means that [1-^{13}C] is the minor component of the product and [2-^{13}C] is the major one; "1" means that [1-^{13}C] is the only product.

d) Analyzed by gas-liquid chromatography of trimethylsilylated derivatives.

e) Recovery of all sugars in weight%.

Table 3. Reaction of D-Mannose

Run	Reagents		Solvent	Composition of products/%			Recov.
	Base	A:C:B		Glc	Man	Fru	%
10	$Ca(OH)_2$	1:0:1	W	38	54	8	87
11	NaOH	1:0:1	W	4	87	9	99
12	NaOH	1:1:1	M	17	61	22	91
13	NaOH	1:4:1	M	13	75	12	95

mannose in the product was increased with increasing the concentration of Ca^{2+} (Run 6,7,12, 13). In the Ca^{2+}-amine reaction system, the aldose which was obtained in high yield had strong affinity to Ca^{2+} because of its axial-equatorial-axial sequence of three hydroxy groups in a pyranose ring.8) Since D-mannose had such sequence,9) the addition of Ca^{2+} moved the equilibrium between epimers to the side of D-mannose.

This conversion was also observed in aqueous solution though it could not be promoted by Ni^{2+} complexes. Probably Ca^{2+} was able to form the active intermediate complex without assistance of chelation of diamine because of the strong affinity of Ca^{2+} to sugars.

This specific transformation was promoted by very simple catalyst in not only methanolic solution but also aqueous solution, so it might occur in biological system in fact. This stereospecific rearrangement of carbon skeleton might be involved in formose reaction processes since $Ca(OH)_2$ was used as a catalyst for them. This reaction became more important in biofunctional chemistry.

References

1) T.Tanase, F.Shimizu, M.Kuse, S.Yano, M.Hidai, and S.Yoshikawa, Inorg. Chem., 27, 4085(1988).
2) T.Tanase, T.Murata, S.Yano, M.Hidai, and S.Yoshikawa, Chem. Lett., 1987, 1409.
3) K.Fukushima, M.Takahashi, H.Nagano, S.Osanai and S.Yoshikawa, Nippon Kagaku Kaishi, 1988, 585.
4) C.C.Sweeley, R.Bentley, M.Makita, and W.W.Wells, J. Am. Chem. Soc., 85, 2947(1963).
5) P.E.Pfeffer, K.M.Valentine, and F.W.Parrish, J. Am. Chem. Soc., 101, 1265(1979).
6) A.S.Perlin, B.Casu, and H.J.Koch, Can. J. Chem., 48, 2596(1970).
7) W.Voelter and E.Breitmaier, Org. Magn. Reson., 5, 311(1973).
8) T.Yamauchi, K.Fukushima, R.Yanagihara, S.Osanai, and S.Yoshikawa, Carbohydr. Res., in press.
9) S.J.Angyal and J.A.Mills, Aust. J. Chem., 32, 1993(1979).

(Received September 13, 1990)