Carbohydrate Research, 204 (1990) 233–239
Elsevier Science Publishers B.V., Amsterdam

Note

Epimerization and isomerization of various monosaccharides using metal–diamine systems

Tomoe Yamauchi, Kazuyoshi Fukushima, Ryoji Yanagihara, Shuichi Osanai, and Sadao Yoshikawa

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi Kohhoku-ku, Yokohama-shi 223 (Japan)

(Received July 1st, 1989; accepted for publication in revised form March 27th, 1990)

Aldoses react with Ni–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tetmen) or Ca–tetmen complex in methanolic solution to give the corresponding 2-epimer and ketose. In the Ca (II)–tetmen–aldose system, D-glucose underwent appreciable conversion into its 2-epimer and the ketose, whereas D-mannose was unreactive toward epimerization and isomerization. D-Glucose is an aldose having the 2,3-hydroxyl groups *trans*-disposed, whereas these groups are *cis*-disposed in D-mannose. The results suggest that certain configurations favor the formation of complexes that suppress epimerization.

We present a reasonable reaction mechanism for forming the corresponding ketohexose from the aldohexose without C-1–C-2 interconversion, which is distinct from the 1,2-enediol rearrangement.

Epimerization in the xylose–lyxose and ribose–arabinose systems were performed with various molar ratios of metal complex to sugar in order to clarify the effect of this molar ratio on the epimerization and isomerization.

The influence of the stereospecificity of the hydroxy group was estimated by using various kinds of monosaccharide. All data obtained were in fair agreement with the proposed mechanism for epimerization and ketose formation.

INTRODUCTION

We have recently reported the epimerization and isomerization of aldoses using various kinds of nickel(II) and calcium(II) complexes of diamine derivatives[1]. In these studies, the effects of such structural features as the *N*-alkyl chain-length and the degree of *N*-substitution of these diamine ligands were examined. Some of the other factors that influence the epimerization were also discussed.

The mechanism of this novel, regiospecific rearrangement of such epimers as glucose and mannose, was clarified[2] by ^{13}C-n.m.r. spectroscopy, but the influence of the position of hydroxyl groups in aldoses upon epimerization remained unresolved. Because of the variety of possible configurations in aldoses, the stability of the complex-

0008-6215/90/$ 03.50

es should vary according to their configurations. In order to understand the effects of configuration on the epimerization of aldoses, a variety of aldohexoses, aldopentoses, and 6-deoxyaldohexose have been studied, along with two ketoses, D-fructose and D-tagatose. We determined the epimerization efficiency of the systems by measuring the amount of epimers as a percentage of the total amount of aldose. The results obtained revealed a great diversity in the ratio of epimers formed from the various sugars.

EXPERIMENTAL

Materials. — Commercial sugars of the highest quality available were used. D-Glucose, D-mannose, D-galactose, D-talose, D-quinovose, D-rhamnose, D-ribose, D-arabinose, D-xylose, D-lyxose, L-arabinose, and L-xylose were examined. All other reagents were of the highest commercial grade and were used without further purification. *N,N,N',N'*-Tetramethylethylenediamine (tetmen) was chosen as the diamine ligand.

General epimerization reaction. — Aldose (1 equiv.) was added to a methanolic solution of $NiCl_2 \cdot 6H_2O$ (1 equiv.) and tetmen (2 equiv.). This solution was incubated for 5 min at 65° with stirring. The mixture was then kept at pH 6.5 with M HCl for 0.5 h at room temperature. Samples of the mixture were made neutral and deionized by successive use of a cation-exchange resin (Dowex 5W X8, H^+ form) and an anion-exchange resin (Dowex 2 X8, HCO_3^- form). After eluting 500 mL of water through the resin columns, the aqueous solutions were concentrated to exactly 250 mL.

Analytical procedures. — The concentration of each sugar was determined by h.p.l.c., g.l.c., and colorimetry. The foregoing aq.solution was directly assayed by h.p.l.c. (Jasco DIP-1, column: Wako PAK WB-T-131, 60°, eluate flow rate: 0.4 mL/min, mM NaOH, detector: Shodex RI SE-51). The absolute concentrations and the recoveries of each sugar were determined from calibration curves prepared from known sugar concentrations. The samples were also analyzed by g.l.c. after trimethylsilylation (stainless-steel column, 1 m × 3 mm, filled with 5% silicone gum SE-30 on Chromosorb WAW, 80–100 mesh at 180° isothermally, flame-ionization detector, f.i.d, 250°, carried gas: N_2). Total aldose and ketose were determined colorimetrically u.v.-visible spectrophotometer: Shimazu UV-160). Aldoses were determined by the *o*-aminobiphenyl–AcOH method; for ketoses, the resorsinol–hydrochloric acid method was adopted. The absorbances were determined at 380 or 500 nm, respectively.

RESULTS AND DISCUSSION

Nickel(II) complex system. — Table I summarizes the results of aldose epimerizations conducted in the nickel(II)–tetmen complex system.

Haworth projection formulas of the pyranoses under consideration are shown in Fig. 1. Losses of original sugar through the reaction process were small and $>85\%$ recovery was readily available in every instance. Table I shows that the resultant compositions of 2-epimers are almost equal, irrespective of which sugar is epimerized. This tendency was

TABLE I

Analytical results for epimerization using the Ni(II) complex

Run	*Substrate*	*Composition of products (%)*			*Recovery (%)*	*Color of soln.*
		Glc	*Man*	*Fru*		
1–1	D-Glucose	54 :	40 :	6	92	Green
1–2	D-Mannose	52 :	42 :	6	91	Green
		Gal	*Tal*	*Tag*		
1–3	D-Galactose	29 :	51 :	20	90	Green
1–4	D-Talose	27 :	55 :	18	93	Green
		Qui	*Rha*	*Ketose*		
1–5	D-Quinobose	66 :	33 :	1	90	Green
1–6	L-Rhamnose	65 :	34 :	1	88	Green
		Ara	*Rib*	*Ribu*[a]		
1–7	D-Arabinose	38 :	61 :	1	94	Green → bluegreen
1–8	D-Ribose	39 :	60 :	1	100	Green → bluegreen
1–9	L-Arabinose	63 :	36 :	1	100	Green → bluegreen
		Xyl	*Lyx*	*Xylu*[b]		
1–10	D-Xylose	41 :	58 :	1	85	Green[c]
1–11	D-Lyxose	43 :	56 :	1	86	Green[c]
1–12	L-Xylose	43 :	56 :	1	90	Green[c]
1–13	L-Lyxose	43 :	56 :	1	89	Green[c]

[a] D-*erythro*-Pentulose. [b] D-*threo*-Pentulose. [c] A white precipitate was noted a few min later.

observed with all the sugars studied: such aldohexose pairs as glucose–mannose, galactose–talose, and with aldopentoses (ribose–arabinose, xylose–lyxose) and 6-deoxyaldohexoses (D-quinovose, L-rhamnose). These results indicate that the nickel(II) complexes of tetmen promote C-2 epimerization of aldoses to provide a near-equilibrium mixture of 2-epimeric aldoses rapidly under mild conditions. For numerous sugars, the ratio between the 2-epimers reached a definite value, namely 60:40. The contrast between the two epimers may be explained in terms of the configuration of the 2-hydroxyl groups; the aldose having two hydroxyl groups attached on the same side of the sugar skelton (C-2 and C-4) is preponderant. The foregoing results show that the epimerization of aldoses is affected both by coordination and by the configuration of the two hydroxyl groups.

Calcium(II) complex system. — The analytical data for the epimerization using Ca(II) complex are shown in Table II. The equilibrium between two epimers that is obviously evident with Ni(II) complex was barely observed in the Ca(II)–tetmen epimerization conditions. The epimerization from the mannose type of sugar took place only to a small extent in comparison with that from the glucose type.

Glucose type

	R^1	R^2	R^3
Glc	CH_2OH	H	OH
Gal	CH_2OH	OH	H
Qui	CH_3	H	OH
Xyl	H	H	OH
Ara	H	OH	H

Mannose type

	R^1	R^2	R^3
Man	CH_2OH	H	OH
Tal	CH_2OH	OH	H
Rha	CH_3	H	OH
Lyx	H	H	OH
Rib	H	OH	H

Fig. 1. Haworth projection formulas of the five pairs of homomorphous pyranoses.

TABLE II

Analytical results for epimerization using the Ca(II) complex

Run	*Substrate*	*Composition of product (%)*			*Recovery (%)*
		Glc	*Man*	*Fru*	
2–1	D-Glucose	62 :	22 :	16	98
2–2	D-Mannose	5 :	94 :	1	100
2–3	D-Fructose	0 :	0 :	100	100
		Gal	*Tal*	*Tag*	
2–4	D-Galactose	52 :	0 :	48	100
2–5	D-Talose	0 :	90 :	10	97
		Qui	*Rham*	*Ketose*	
2–6	D-Quinovose	77 :	21 :	2	92
2–7	L-Rhamnose	3 :	96 :	1	100
		Ara	*Rib*	*Ribu*[a]	
2–8	D-Arabinose	87 :	2 :	11	76
2–9	D-Ribose	3 :	96 :	1	100
		Xyl	*Lyx*	*Xylu*[b]	
2–10	D-Xylose	63 :	35 :	2	80
2–11	D-Lyxose	3 :	96 :	1	92

[a] D-*erythro*-Pentulose. [b] D-*threo*-Pentulose.

Isbell *et al.*[4] recently reported similar results during the isomerization of hexoses in weak by alkaline solution. The isomerization of mannose, but not that of glucose, was greatly suppressed. They considered the inhibiting factor of isomerization of aldohexoses to be the formation of an "inert hydrogen-bonded ion or complex". Angyal *et al.*[3] concluded from his studies that sugars containing an *ax–eq–ax* sequence of three hydroxyl groups in a pyranose ring, or a *cis–cis* sequence in a five-membered ring, readily form complexes with alkaline earth metal ions.

Comparison of Tables I and II suggest the involvement of another mechanism when calcium instead of nickel ion was used.

An intermediate complex composed of calcium–tetmen–mannopyranose conclusively exists in the Ca(II) reaction system, inhibiting the sugar moiety from assuming the open-chain form suitable for epimerization.

The reason that no epimerization, or only slight epimerization, is observed for the mannose type of aldose is attributable to rigid coordination between the hydroxyl groups of the sugar and Ca(II) ion; the complex stabilizing the cyclic pyranose structure greatly suppresses epimerization. In contrast, sugars of the glucose type, which are not able to form a pyranose-ring complex with calcium(II), undergo epimerization to a considerable extent, in a manner similar to that observed in the epimerization using the Ni(II) complex.

The noteworthy formation of the corresponding ketose along with production of the 2-epimer was observed with glucose–mannose and galactose–talose. The fact that glucose and mannose could not be produced from fructose under the same epimerization conditions means that the resultant ketose is not an intermediate, but a stable product (runs 2–3).

It is well known that ketoses are produced from the corresponding aldoses *via* the 1,2-enediol intermediate in basic solution (Lobry de Bruyn rearrangement). This process could also apply in some cases with our isomerizations. However, when a 6-deoxyaldohexose, or an aldopentose was used, a pronounced decrease in yield of the corresponding ketose was observed. This result cannot be explained by the mechanism of the Lobry de Bruyn rearrangement alone. The ketose must be formed by another mechanism distinct from the Lobry de Bruyn rearrangement. These results suggest that, in the isomerization of aldohexoses, the C-6 hydroxyl group plays an important role in epimerization.

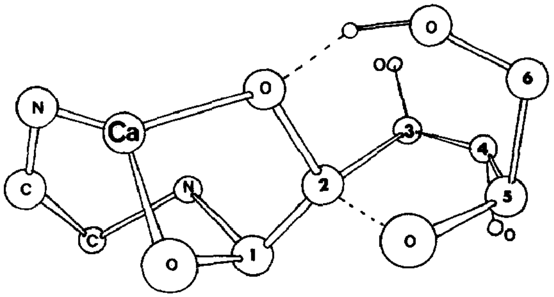

Fig. 2. The proposed intermediate for ketose formation (glucose → fructose).

In order to illustrate the formation of fructose, we present in Fig. 2 a plausible intermediate. We chose glucose as a model substrate. In this mode of coordination, HO-5 is close to C-2, which explains the favored production of a 5-membered furanose ring. The hydrogen bond through O-2–HO-6 stabilizes the fructofuranose ring-structure. This provides a plausible explanation for the indispensibility of the 6-hydroxyl group for ketose formation. In this isomerization pathway, glucose may be converted into fructose without rearrangement of the carbon skelton; this is our assumption. Similar results were also observed in the isomerization of galactose. Tagatose, the resultant ketose, is generated through the proximity of the 5-hydroxyl group to C-2. The validity of this assumption is reinforced in other epimerizations. For example, some of us showed that in the Ca(II)–Et$_3$N complex system, 1-(^{13}C)enriched glucose was epimerized into 2-(^{13}C)mannose in a manner similar to that with the Ni(II) complex[2]. Futhermore, the formation of 1-(^{13}C)fructose without rearrangement of the carbon skelton was also observed. All of these results are consistent with our proposed reaction mechanisms.

Epimerization of the xylose–lyxose system. — The epimerization behavior of the Ni(II)–tetmen–aldopentose (Xyl–Lyx, Rib–Ara) systems was studied to clarify the effect of molar ratio of sugar to metal complex. In Fig. 3(A), the D-lyxose concentration

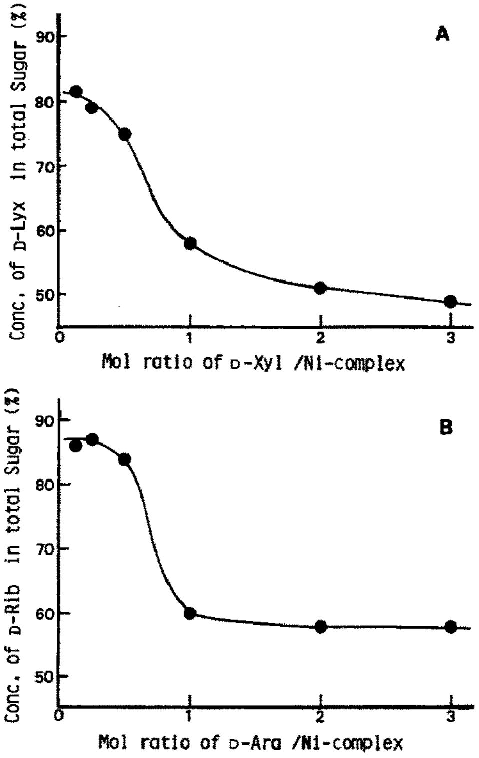

Fig. 3. Effect of mol ratio between D-pentose–nickel(II) complex on the epimerization: starting sugar (A) Xylose; (B) Arabinose.

(%) in the total sugars (equilibrium values) are plotted against the molar ratio of D-xylose–metal complex in the system. At every concentration, a white powder readily precipitated after all of the substrates had become completely dissolved, resulting in a clear green solution. When either xylose or lyxose was used as the starting sugar, the composition of the resulting epimeric mixture was always the same. It was assumed that complete equilibrium between xylose and lyxose was established at each concentration. As the epimerization of xylose proceeded through the previously considered pathway, the epimerized product, lyxose, was removed from the reaction system through the formation of precipitate. Lyxose, the epimer of the mannose type, forms a sparingly soluble complex that retains the ring structure. Consequently, in the nickel-rich solution, the concentration of lyxose was very high.

In contrast at higher molar ratios of D-Xyl–nickel–tetmen, the concentration of nickel was too low to precipitate all of the epimerized lyxose through complex formation. Therefore, as the proportion of xylose is further increased, the concentration of lyxose in the equilibrium state decreased and gradually approached the normal value (~60%) for a glucose-type monosaccharide.

The same reaction was performed for the ribose–arabinose system. Similar results were also obtained in the epimerization between arabinose and ribose, as shown in Fig. 3(B).

REFERENCES

1 K. Fukushima, M. Takahashi, H. Nagano, S. Osanai, and S. Yoshikawa, *Nippon Kagaku Kaishi*, (1988) 585–590.

2 (*a*) T. Tanase, T. Murata, S. Yano, M. Hidai, and S. Yoshikawa, *Chem. Lett.*, (1987) 1409–1412; (*b*) T. Tanase, F. Shimizu, M. Kuse, S. Yano, M. Hidai, and S. Yoshikawa, *Inorg. Chem.*, 27 (23) (1988) 4085–4094.

3 S. J. Angyal and K. P. Davies, *J.C.S. Chem. Comm.*, (1971) 500–501.

4 H. S. El Khadem, S. Ennifar, and H. S. Isbell, *Carbohydr. Res.*, 185 (1989) 51–59.