

Chemistry of Oxo-Sugars. IV. Isomerization of 4-Oxoglycosides in a Pyridine Solution¹⁾

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4-Oxoglycosides of xylo-configuration (1a, 1b) rearranged in pyridine-*d*₅ to give exclusively 3-oxoglycosides of ribo-configuration through enediol intermediates. On the other hand, 4-oxoglycosides of lyxo- and arabino-configuration (5, 6) gave an epimeric mixture of both isomers. The reason for this difference was discussed on the basis of AM1 calculations.

Key words 4-oxoglycoside; isomerization; AM1 calculation; enolization; pyridine; ¹³C-NMR

In a preceding paper,¹⁾ we showed that methyl 2-oxoglycosides rearrange, in pyridine-*d*₅, into 3-oxoglycosides through a hydride shift. The products, on further standing in the same solvent, gradually change into dioxo derivatives with liberation of methanol. This elimination reaction was particularly evident for the compounds which carried a 4-axial-OH group. It was also observed that enolization between positions 2 and 3 was reversible, but enolization of the 3-oxo group toward C-4 was not observed.

In this paper, we describe the transformation of 4-oxoglycosides in pyridine-*d*₅, to see whether or not the hydride shift occurs for 4-oxo derivatives.

Results and Discussion

Changes of Me α - and β -D-xylo-4-OG³⁾ (1a, 1b) Me α -D-xylo-4-OG (1a), on standing in pyridine-*d*₅ at 27 °C, gradually changed into Me α -D-ribo-3-OG (2a), which became the major component in the mixture after 2 weeks. The β -anomer, Me β -D-xylo-4-OG (1b), changed more rapidly to give Me β -D-ribo-3-OG (2b) similarly.

During these processes, the formation of 4a and 4b, which are expected to be generated by hydride shift, or

any product therefrom, was not observed. Compounds 4a and 4b, if produced, are known to give different kinds of products in pyridine-*d*₅.¹⁾

Thus, we conclude that the above changes proceeded through the 3,4-enediol intermediates (3a, 3b, respectively). This implies that enolization of the 4-carbonyl group occurred toward the 3-position and that protonation of the intermediary 3,4-enediol (3a, 3b) occurred preferentially at the C-4 position.

In order to clarify why the protonation at C-4 is preferred, the electron densities at C-3 and C-4 in the enediols (3a, 3b) were calculated by AM1⁴⁾ for the most stable conformations obtained by MM2 calculations. The results showed that the 4-position was more electron-rich than the 3-position for both the α - and β -anomers, indicating that C-4 should be preferably protonated over C-3. AM1 calculations also showed that the heats of formation for the 3-oxo derivatives were larger than those for the corresponding 4-oxo isomers, both for α - and β -anomers, supporting the view that the 3-oxo derivatives (2a, 2b) were thermodynamically more stable than the corresponding 4-oxo isomers (1a, 1b). These results explain why the 4-oxo derivatives (1a, 1b) isomerized into the

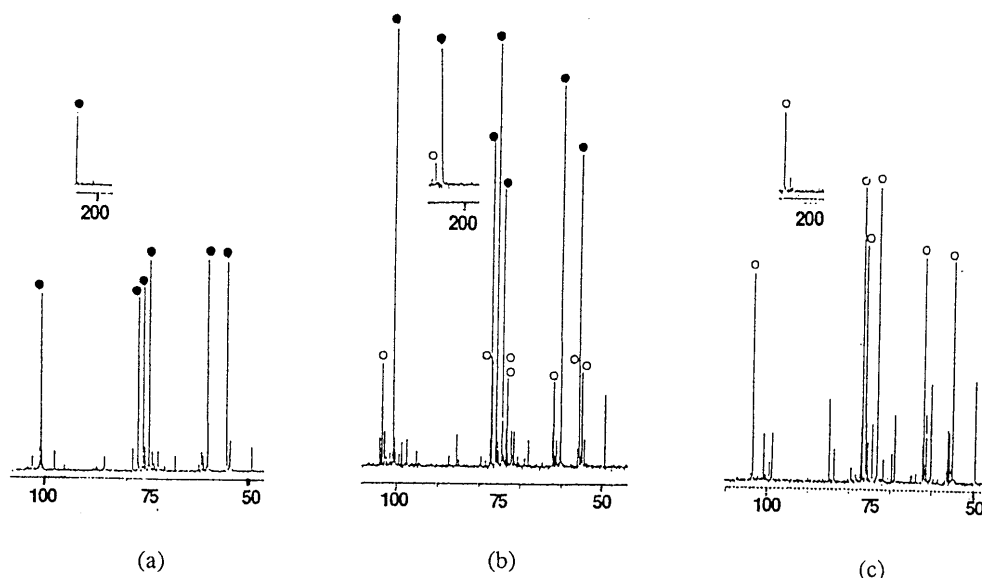


Fig. 1. ¹³C-NMR Changes of Me α -D-xylo-4-OG (1a) in Pyridine-*d*₅

(a): after 1 h, (b): after 2 d, (c): after 2 weeks. ●, Me α -D-xylo-4-OG (1a); ○, Me α -D-ribo-3-OG (2a).

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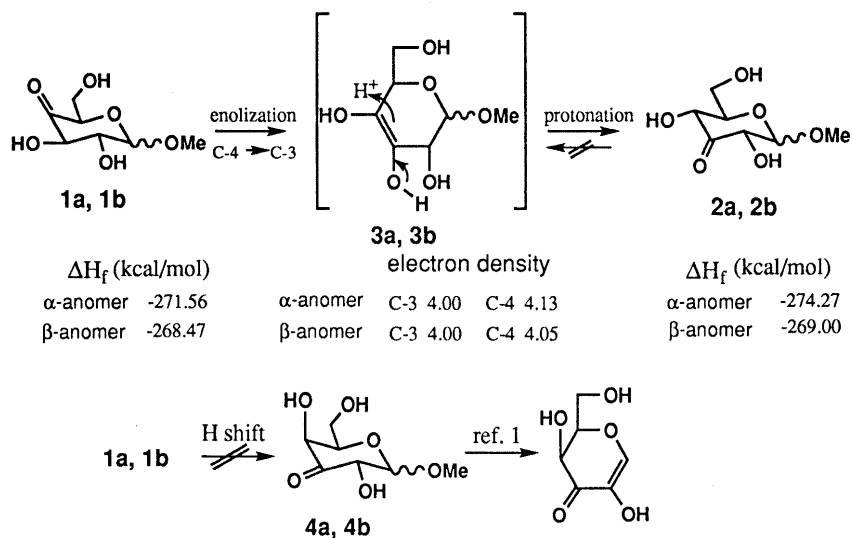


Chart 1

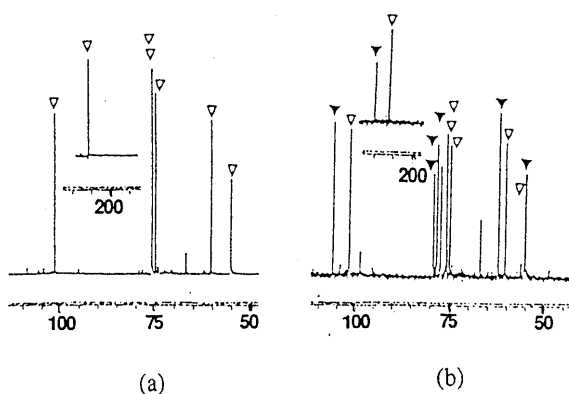


Fig. 2. ^{13}C -NMR Changes of Me α -D-lyxo-4-OG (5) in Pyridine- d_5 (a): after 1 h, (b): after 3 d. ∇ , Me α -D-lyxo-4-OG (5); \blacktriangledown , Me α -D-arabino-4-OG (6).

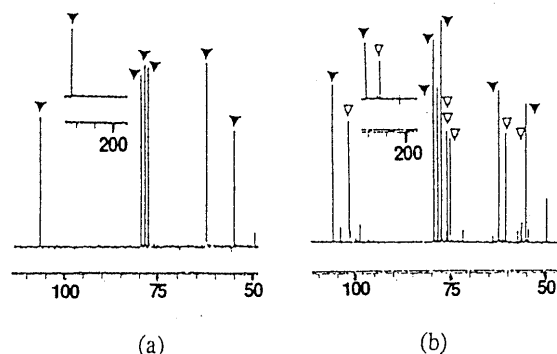


Fig. 3. ^{13}C -NMR Changes of Me α -D-arabino-4-OG (6) in Pyridine- d_5 (a): after 1 h, (b): after 3 d. ∇ , Me α -D-lyxo-4-OG (5); \blacktriangledown , Me α -D-arabino-4-OG (6).

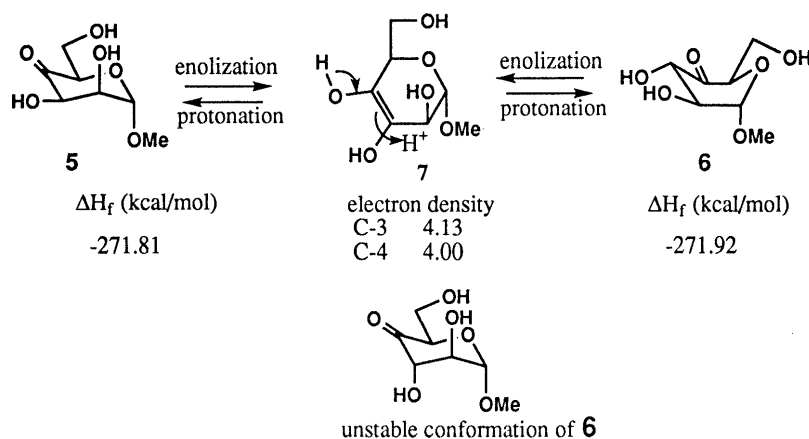


Chart 2

3-oxo derivatives (2a, 2b) through 3,4-enediol intermediates (3a, 3b).

Isomerization of Me α -D-lyxo-4-OG (5) and Me α -D-arabino-4-OG (6) The compounds which bear 2-axial OH showed different features of transformation. These compounds exist only in oxo forms, when dissolved in pyridine- d_5 (while most of the other oxoglycosides are mixtures of oxo and hydrate forms).³⁾ On standing for 3 d,

each compound gave almost the same mixture, which was proved to be a *ca.* 1:1 mixture of 5 and 6. On further standing for a week, the mixture did not change further, suggesting that 5 and 6 are in equilibrium.

Epimerization at C-3 in these compounds indicates that they are produced through the 3,4-enediol (7). In order to explain why the 4-carbonyl group did not migrate to the 3-position but gave only an epimeric mixture at C-3, MM2

and AM1 calculations were again carried out for **5**, **6**, and the 3,4-enediol (**7**).

The results showed that, for the 3,4-enediol with 2-axial OH (**7**), the electron density at C-3 was larger than that at C-4, indicating that, in contrast to the 3,4-enediol with 2-equatorial OH (**3a**), the protonation at C-3 was preferable. Calculations also showed that the most stable conformations of **5** and **6** are 4C_1 and ${}^3B^0$, respectively. The difference in the heats of formation between them was negligible, suggesting that they are equally thermodynamically stable. In addition, the calculations showed that the 3,4-enediol with 2-axial OH (**7**) is more stable than that with 2-equatorial OH (**3a**) by *ca.* 2 kcal/mol.

The above transformations of 4-oxoglycosides in pyridine can be summarized as follows. (1) 4-Oxoglycosides isomerize to 3-oxoglycosides or epimerize at C-3. These changes are explicable by an enolization mechanism, which always occurs toward C-3. The enolization of C-3 carbonyl toward C-4 was not observed (the 3-carbonyl group enolized toward C-2).¹⁾ (2) Protonation of the intermediary 3,4-enediol is favored at the C-4 position when 2-OH is equatorial and at the C-3 position when

2-OH is axial.

Experimental

Reaction of 4-Oxoglycosides in Pyridine- d_5 Oxoglycosides (15–40 mg) were dissolved in pyridine- d_5 (0.6 ml) and the mixture was kept standing at 27°C, during which time the ${}^{13}\text{C}$ -NMR spectra (500 MHz; internal standard, tetramethylsilane) were measured periodically. Identification of the compounds in the solution was made by comparisons of the spectra with those of authentic specimens in the same solvent.³⁾ The ratio of the components was roughly determined from the intensity ratio of anomeric carbons, which is roughly proportional to the component ratio.

References and Notes

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- 2) Present address: Department of Chemistry, Zhengzhou University, Zhengzhou 450052, P. R. China.
- 3) All oxoglycosides in this paper were reported in a previous paper [Liu H.-L., Sato Y., Tsuda Y., *Chem. Pharm. Bull.*, **41**, 491–501 (1993)]. Abbreviations: Me = methyl, OG = hexopyranosidulose.
- 4) MOPAC Ver. 5.00 (QCPE No. 445), Stewart J. J. P., *QCPE Bull.*, 1989. 9. 10; Hirano T., *JCPE Newsletter*, **1**, 36 (1989); Revised as Ver. 5.01 by Toyoda J., for Apple Macintosh.