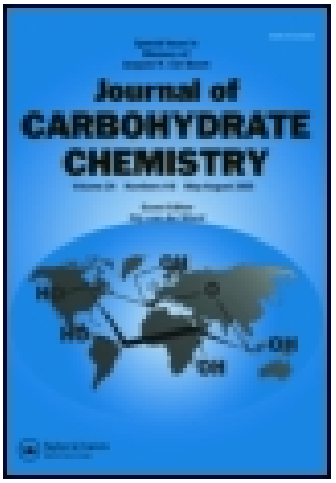

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Nickel(II)-CATALYSED TRANSFORMATIONS OF 5-AZIDO-5-DEOXY-D-GLUCOFURANOSE AND OF 5-AZIDO-5-DEOXY-L-IDOFURANOSE

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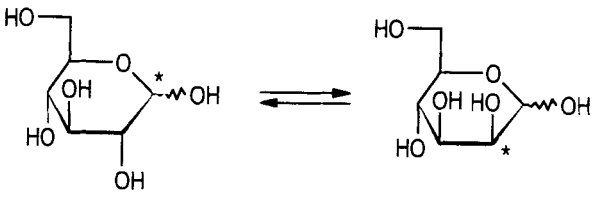
ABSTRACT

Nickel(II) catalysed isomerisation reactions of C-5 modified derivatives of D-glucose as well as L-idose were investigated. 5-Azido-5-deoxy-D-glucofuranose was successfully isomerised into the corresponding D-*manno* epimer in good yields. Contrasting this result, in the case of the 5-modified L-idofuranose probed, no evidence for successful epimerisation at C-2 could be found. However, this sugar was quantitatively rearranged into the corresponding L-sorbopyranose. Upon extended reaction periods, the latter underwent degradation to give the coresponding 4-modified methyl L-xylonate.

INTRODUCTION

Nickel(II) ions give complexes with *N*-substituted derivatives of 1,2-diaminoethane and 1,3-diaminopropane in protic solvents such as methanol. These complexes have recently been discovered to be capable of isomerising aldoses into their corresponding epimers at C-2.[1] For example, D-glucose is converted into D-mannose and the equilibrium product ratio is strongly dependent on the nature of the diamine ligand employed (Scheme 1). Remarkably, in the course of the rearrangement reaction, C-1 and C-2, as well as the substituents attached, quantitatively interchange their positions[2] as



Scheme 1

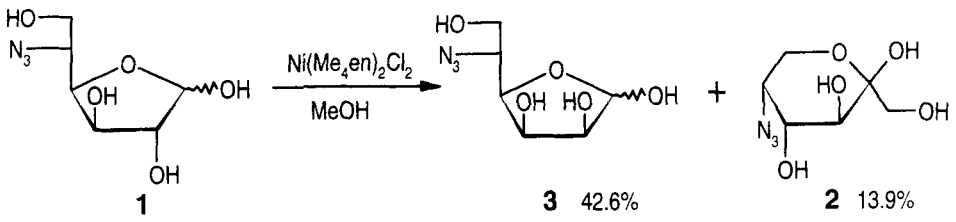
was demonstrated with the aid of aldoses regioselectively substituted with stable isotopes such as ^{2}H and ^{13}C.

Such a carbon framework rearrangement had previously been unique to the molybdate ion catalysed isomerisation reactions of aldoses discovered by Bilik[3] and closely investigated by Barker and his group[4] as well as in Serianni's laboratory.[5]

In the course of a project involved in the synthesis of sugar-shaped glycosidase inhibitors with basic nitrogen instead of oxygen in the sugar ring, we became interested in this method of isomerisation of free sugars as a possible means to prepare various ^{13}C-substituted derivatives[6] of 1-deoxynojirimycin and its D-*manno* epimer. Such compounds might prove useful for the investigation of the binding properties and interaction patterns at the active sites in glycosidases with the aid of NMR methods.

RESULTS AND DISCUSSION

In our initial approach, readily available 5-azido-5-deoxy-D-glucofuranose (**1**)[7] was exposed to the reported reaction conditions employing the Ni(II) complex with *N,N,N′,N′*-tetramethylethylenediamine as the catalyst. At 60 °C the equilibrium was reached within 5 min. The main product isolated was the thermodynamically preferred 5-azido-5-deoxy-D-fructopyranose (**2**)[8] resulting from concomitant Lobry de Bruyn-Alberda van Ekenstein rearrangement[9] under the basic reaction conditions. At ambient temperature, a reaction time of 30 to 40 min was required but the yields of the desired D-mannose derivative **3** ranged around 40%. Approximately 40% of starting material **1** could be recovered and only 15% of undesired fructose derivative **2** was formed under these conditions (Scheme 2).



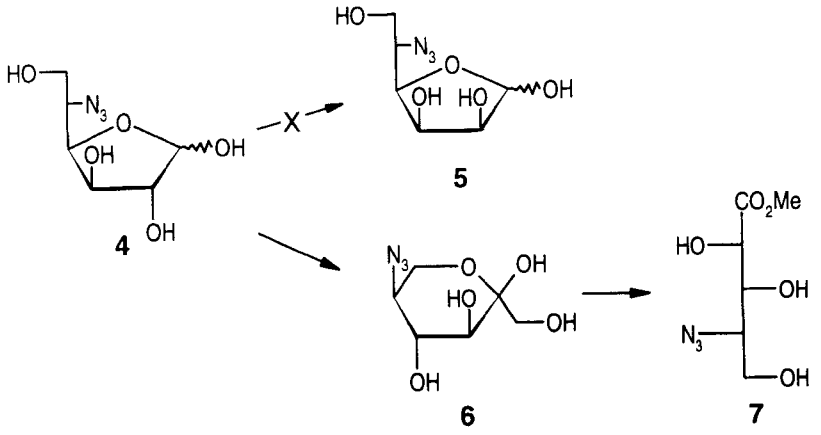
Scheme 2

Conversely, when 5-azido-5-deoxy-L-idofuranose (**4**)[8] was subjected to the same reaction conditions, no successful epimerisation at C-2 to give desired 5-azido-5-deoxy-L-gulofuranose (**5**) could be observed. Instead, slow conversion into 5-azido-5-deoxy-L-sorbopyranose (**6**),[8] the product of simple base-catalysed isomerisation following the Lobry de Bruyn - Alberda van Ekenstein pathway occurred. This material turned out to be unstable under the reaction conditions and was transformed into a faster moving product identified as methyl 4-azido-4-deoxy-L-xylonate (**7**) (Scheme 3) which could be isolated in yields around 40%.

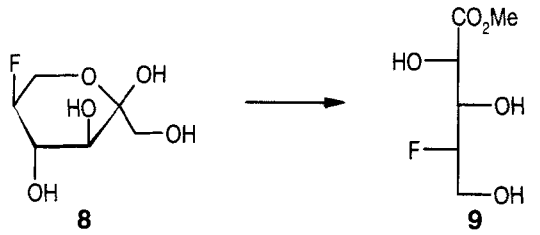
As similar reactions of ketoses are known[10] to occur in the presence of oxygen, the experiment was repeatedly conducted under an atmosphere of argon. However, this had no apparent effect on its outcome. With the aid of control experiments it could be established that the presence of nickel(II) in the reaction mixture was essential for the oxidative degradation reaction. Under otherwise identical conditions, in the absence of the transition metal ion, the starting material remained unaffected for days.

Other 5-modified ketopyranoses such as 5-deoxy-5-fluoro-L-sorbopyranose (**8**),[8] which was converted into methyl 4-deoxy-4-fluoro-L-xylonate (**9**) in 20% yield, gave comparable results (Scheme 4). Clearly, further investigations into the nature of the mechanism have to be performed.

In conclusion, it is not apparent from the published reaction mechanism of the Ni(II)-ethylenediamine complex catalysed epimerisation of aldoses at C-2, why the C-5 epimer of the successfully transformed D-glucofuranose should not be converted into the corresponding L-gulofuranose **5**, as neither C-5 and C-6 nor their substituents play a role in the proposed catalytic cycle. In order to determine if an *erythro* relationship between



Scheme 3



Scheme 4

the substituent at C-5 and O-4, which is coordinated by the nickel, is necessary for productive binding, further experiments need to be carried out. The same is true as to the nature of the unexpected oxidative degradation reaction of L-sorbopyranoses leading to the corresponding one carbon shorter methyl aldonates.

EXPERIMENTAL

General Methods. Melting points were determined on a Tottoli apparatus (Büchi 530) and are uncorrected. Optical rotations were measured with a Perkin Elmer 341 Polarimeter at 589 nm at ambient temp. NMR spectra were recorded at 300.13 or 200 MHz (^{1}H) as well as 75.47 or 50.29 MHz (^{13}C). Residual non-deuterated solvent was

used as internal standard for determination of chemical shifts. TLC was performed on precoated aluminum plates (Merck 5554) employing 5% vanillin/sulfuric acid as well as ceric ammonium molybdate as staining agents. For column chromatography, silica gel 60, 230-400 mesh (Merck 9385), was used. Nickel(II) chloride hexahydrate, *N,N,N',N'*-tetramethylethylenediamine and *N,N'*-diethylethylenediamine were purchased from Merck and were used without further purification.

General Procedure for isomerisation reactions. To a 10% solution of nickel(II) chloride hexahydrate (1 equiv) and *N,N,N',N'*-tetramethylethylenediamine or *N,N'*-diethylethylenediamine (2 equiv) in dry methanol, a 20% solution of the respective starting material (1 equiv) was added and the mixture was stirred at ambient temp for 40 min after which period of time the solution was diluted with distilled water (1:1, v/v) followed by adjustment of the pH of the mixture to 7 with 0.5 M sulfuric acid. After having been stirred for one additional h, the mixture was treated with acidic ion exchange resin Amberlite IR 120 and weakly basic Amberlite IRA 68. The resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel or on Dowex 50 W X 2, 100-200 mesh (Ca^{2+}). For TLC, ethyl acetate/MeOH 4:1 was employed. Chromatography on silica gel was performed with ethyl acetate as the mobile phase.

5-Azido-5-deoxy-D-mannofuranose (3). Applying the general procedure to 5-azido-5-deoxy-D-glucofuranose (**1**, 1010 mg, 4.92 mmol)[7] gave 5-azido-5-deoxy-D-mannofuranose (430 mg, 42.6%, 75.6% by recovery of starting material) as a colourless oil: $[\alpha]_D^{20}$ +0.5° (*c* 1.1, MeOH); ^{1}H NMR (MeOH-d_4) δ 5.23 (d, 1 H, $J_{1,2}$ 5.4 Hz, H–1α), 5.22 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1β; α:β 2:1); ^{13}C NMR δ 101.9, 96.6 (C-1/α,β), 78.8, 78.6, 78.3, 72.3 (2 C), 70.9 (C-2, C-3, C-4/α,β), 63.0, 62.3 (2 C), 61.7 (C-5, C-6/α,β).

Anal. Calcd for $C_6H_{11}N_3O_5$ (205.17): C, 35.73; H, 5.40. Found: C, 36.00; H, 5.66.

As the side product, known[8] 5-azido-5-deoxy-D-fructopyranose (**2**) was obtained (140 mg, 13.9%). In addition, unreacted starting material **1** (441 mg, 43.6%) was collected.

Reaction of 5-azido-5-deoxy-L-idofuranose (4) - Formation of methyl 4-azido-4-deoxy-L-xylonate (7). Following the general procedure, reaction of idofuranose **4**[8] (106 mg, 0.57 mmol) with the catalyst gave a mixture of L-sorbopyranose **6**[8] and a

concomitantly formed faster moving product. After 24 h, all starting material as well as compound **6** had been consumed. Following work-up, the faster moving product could be isolated (40 mg, 37.7%) by chromatography and was identified as methyl 4-azido-4-deoxy-L-xylonate **7**: $[\alpha]_D^{20}$ -8.1° (*c* 0.8, MeOH); ^{1}H NMR (MeOH-d_4) 4.28 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-2), 3.97 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-3), 3.82-3.54 (m, 3 H, H-4, H-5, H-5'), 3.78 (s, 3 H, CO_2Me); ^{13}C NMR δ 174.5 (C-1), 73.4, 72.9 (C-2, C-3), 67.3 (C-4), 62.8 (C-5), 52.7 (OMe).

Anal. Calcd for $C_6H_{11}N_3O_5$ (205.17): C, 35.73; H, 5.40. Found: C, 35.32; H, 5.79.

Methyl 4-deoxy-4-fluoro-L-xylonate (9). Applying the general procedure to 5-deoxy-5-fluoro-L-sorbose[8] (**8**, 240 mg, 1.32 mmol) gave product **9** (48 mg, 20%) as a slightly yellow oil: $[\alpha]_D^{20}$ +4.7° (*c* 1.7, MeOH); ^{1}H NMR (MeOH-d_4) δ 4.57 (m, 1 H, $J_{4,F}$ 48.5 Hz, H-4), 4.33 (d, 1 H, $J_{2,3}$ 2.8 Hz, H-2), 4.13 (ddd, 1 H, $J_{3,4}$ 6.4 Hz, $J_{3,F}$ 15.5 Hz, H-3), 3.77 (s, 3 H, CO_2Me), 3.65 (m, 2 H, $J_{5,F}$ 13 Hz, H-5, H-5'); ^{13}C NMR δ 174.4 (C-1), 95.8 (d, $J_{4,F}$ 173 Hz, C-4), 72.5 (d, $J_{3,F}$ 21.2 Hz, C-3); 72.5 (d, $J_{2,F}$ 6.9 Hz, C-2), 62.2 (d, $J_{5,F}$ 21.9 Hz, C-5), 52.7 (OMe).

Anal. Calcd for $C_6H_{11}FO_5$ (182.14): C, 39.57; H, 6.09. Found: C, 39.39; H, 6.22.

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