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Influence of the oxime and anomeric configurations on the stability of 2-deoxy-2-hydroxyimino-D-hexopyranosides

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ABSTRACT

The *Z*/*E* isomerisations of the synthesized benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroxyimino-D-hexopyranosides during the NMR measurement and during the Zemplén *O*-deacetylation were observed. In order to study stabilities and tendency of the obtained compounds to isomerise, B3LYP/6-311++G** level geometry optimisations for four stereoisomers of methyl 2-deoxy-2-hydroxyimino-D-*arabino*-hexopyranosides in both the *O*-acetylated and *O*-deacetylated forms were performed. The results of our theoretical studies are fully in agreement with the experimental data and NMR analysis. Additionally, a single-crystal X-ray diffraction data for benzyl 2-deoxy-2-hydroxyimino-α-D-*lyxo*-hexopyranoside are reported to supplement our theoretical studies.

1. Introduction

2-Deoxy-2-hydroxyiminohexopyranosides, also called oximes of hex-2-ulopyranosides, are useful intermediates in sugar synthesis, which have been applied for a long time [1–3]. Their usefulness stems from the fact that these compounds are easily transformed into different sugar derivatives. Thus, nucleophilic substitution of the allylic 3-OAc group in acetylated 2-deoxy-2-hydroxyimino glycosides with azide or hydride ions affords 3-azido-3-deoxy or 3-deoxy derivatives, respectively (pathway **A**, Scheme 1) [4,5]. In turn, reduction of the 2-hydroxyimino group is the straightforward way for the preparation of 2-amino-2-deoxy sugars (pathway **B**) [6]. The latter transformation was successfully applied to the synthesis of 2-NAc oligosaccharides [7,8] as well as aminoglycoside antibiotics [9–11]. Most importantly, reduction of the oxime is strongly stereospecific and provides mainly 1,2-*cis* 2-amino-2-deoxy glycosides [12–16].

Hydroxyimino function is also used to obtain 2-uloses by deoximination with acetaldehyde/HCl (pathway **C**) [5,17,18]. The 2-oxo group is easily reduced to the 2-hydroxyl group (pathway **D**) with a high preference for the respective β-D-mannosides when β-hex-2-ulopyranosides with D-*arabino* configuration are reduced by borohydride reagents [3]. In turn, the 3,4-elimination of acetic or benzoic acid from 2-uloses, such as *O*-protected 1,5-anhydro-D-fructoses, provides the pyranoid enolone esters (pathway **E**). A variety of synthetically useful additions are carried out with these esters with high selectivity [19].

Different methodologies have been applied to synthesise 2-deoxy-2-hydroxyimino glycosides. Lemieux introduced a very useful reaction of acetyl-protected 2-deoxy-2-nitroso-α-D-glycopyranosyl chlorides with the respective glycosyl acceptor to obtain 2-deoxy-2-hydroxyimino glycosides [1]. In turn, Lichtenthaler proposed the reaction of benzoil-protected 2-deoxy-2-hydroxyimino-α-glycopyranosyl bromides with the respective glycosyl acceptor [2]. The same goal was achieved in the reaction of respective ulosyl bromide with a glycosyl acceptor followed by oximation of the ketone group [20]. Hex-2-ulopyranoside oximes were also obtained from the previously prepared ulosides [21] and in the reaction of methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside with sodium cobaloxime followed by photolysis in the presence of nitrous oxide [12].

2-Deoxy-2-hydroxyimino glycosides are found in four

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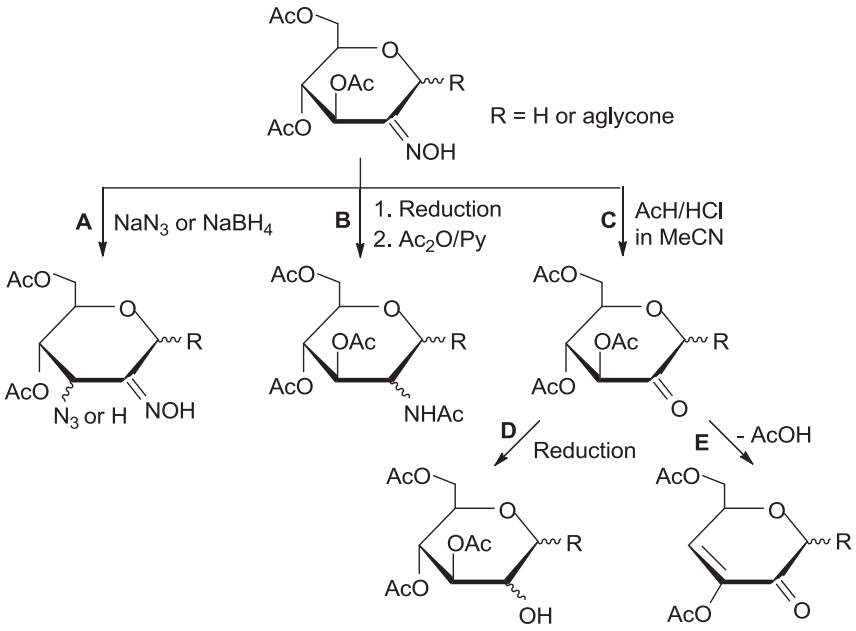

Scheme 1. Possible transformations of 3,4,6,tri-*O*-acetyl-2-deoxy-2-hydroxyimino sugars.

stereoisomeric forms. These are α or β glycosides with *Z* or *E* configurations of the oxime (Fig. 1). The ratio of stereoisomers obtained depends on the method used as well as on the stability of a particular stereoisomer.

In a search of new effective inhibitors of GlcN-6P synthase, the enzyme proposed as a target for antifungal chemotherapy [22], we paid attention to 2-deoxy-2-hydoxyimino sugars. The 2-hydroxyimino group mimics the 2-imino group present in the putative reaction intermediate proposed for the reaction catalysed by GlcN-6P synthase [23]. This prompts the assumption that the 2-deoxy-2-hydroxyimino alditols may act as GlcN-6P synthase inhibitors and consequently as antifungal agents. In order to obtain such the compounds we first synthesized benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroxyimino-D-hexopyranosides with D-*arabino* and D-*lyxo* configurations, which were next *O*-deacetylated. Undesirable changes of the 2-hydroxyimino group configuration during the experiments prompted us to study the influence of the anomeric carbon and oxime configurations on the stability of 2-deoxy-2-hydroxyimino glycosides. Oximes are known to undergo reversible *E*/*Z* isomerization due to the relatively low transition states connecting both isomers. However, some of the oxime isomers are isolable species with good stability. On the other hand, both the anomeric carbon and oxime configurations can be crucial for pharmacological properties and reactivity of the synthesized compounds [24]. Therefore, it seems to be reasoned to well understand tendency of 2-uloside oximes to isomerise. Importantly, our theoretical studies are verified with the presented experimental data. It is worthy to notice that the *E*/*Z* oxime isomerization in 2-(hydroxyimino)-2-phenylacetonitrile have been recently investigated by spectroscopic and theoretical methods [25].

Calculations were performed using DFT methods at the B3LYP/6-311++G** level for methyl 2-deoxy-2-hydroxyimino-D-*arabino*-hexopyranosides in both the *O*-acetylated and *O*-deacetylated forms. To simplify calculations, the methyl glycoside was used instead of the benzyl glycoside. We assume that this does not change a general tendency concerning the stability of 2-deoxy-2-hydroxyimino-D-hexopyranosides. Additionally, a single-crystal X-ray diffraction analysis for benzyl 2-deoxy-2-hydroxyimino-α-D-*lyxo*-hexopyranoside is reported. This improves the geometry studies presented on 2-deoxy-2-hydroxyimino glycosides.

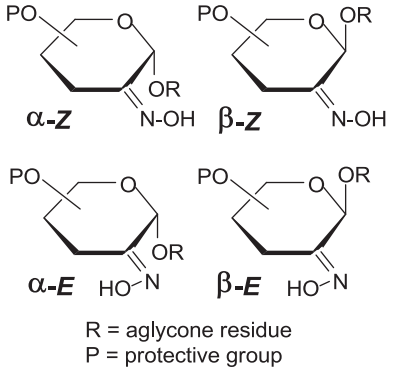

Fig. 1. Stereoisomeric forms of 2-deoxy-2-hydroxyimino glycosides.

2. Results and discussion

2.1. Synthesis and NMR investigations

Starting from 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitrosohexopyranosyl chlorides with α-D-gluco (**1**) and α-D-galacto (**2**) configurations, we synthesized benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroxyimino-D-hexopyranosides with D-*arabino* (**3**–**5**) and D-*lyxo* (**6**–**8**) configurations (Scheme 2). Both of the glycosylations provide a mixture of products, which were separated. Thus, the reaction of **1** with benzyl alcohol yields glycosides with β-*E* (**3**, 9%), α-*Z* (**4**, 46%), and β-*Z* (**5**, 8%) configurations of the anomeric carbon and oxime. Compound **5** isomerises to **3** during the NMR measurement in $CDCl_3$ to generate a mixture of **5** and **3** in a ratio of 1:2, estimated from the NMR spectrum. In turn, the reaction of **2** with benzyl alcohol yields a mixture of glycosides with β-*E* (**6**) and β-*Z* (**7**) configurations (11%) in a ratio of 1:2 estimated from the NMR spectrum, and glycoside with the α-*Z* configuration (**8**, 43%).

Geometries of the synthesized glycosides were established on the basis of NMR spectra. Thus, the H1 signals of **4** and **8** (δ 6.09 and