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Editor's Choice

First Detection of Unprotected 1,2-Anhydro Aldopyranoses

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The unprotected 1,2-anhydro aldopyranoses have been detected for the first time using low-temperature NMR spectroscopy. The formation of these unstable chemical species was successfully achieved through an intramolecular dehydration of saccharides in aqueous media under extremely mild and essentially neutral conditions.

Keywords: Unprotected 1,2-anhydro sugar | Aldopyranose | Low-temperature NMR spectroscopy

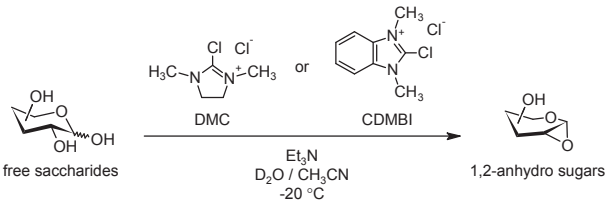
The 1,2-anhydro sugars possess a bicyclic structure where a six-membered pyranose ring and a three-membered oxirane ring are fused sharing the anomeric carbon and C2 carbon. The 1,2-anhydro derivatives, whose hydroxy groups are appropriately protected, have been known to be stable and have been extensively employed as glycosyl donors for the synthesis of various glycosides. For example, acetylated 1,2-anhydro glucose (Brigl's anhydride)[1] was used as donor substrate for synthesis of maltose and sucrose.[2] Danishefsky et al. reported the synthesis of β-linked oligosaccharides using suitably protected 1,2-anhydro sugars that can be prepared from the corresponding glucals by dimethyldioxirane oxidation.[3]

In contrast to those protected sugar derivatives, there has been no proof for the actuality of *unprotected* 1,2-anhydro sugars; even their existence has been wrapped in mystery for nearly a hundred years. In 1920, Pictet et al. claimed the synthesis of an unprotected 1,2-anhydro sugar.[4] Their results, however, were disputed by Brigl in 1929.[5] Since then, unprotected 1,2-anhydro sugars have only been recognized as undetectable intermediates in the alkaline hydrolysis of phenyl β-glucoside[6] or alcolysis of β-glucosyl fluoride under severe conditions.[7]

A theoretical study for levoglucosan formation from phenyl β-glucoside has rationalized the existence of unprotected 1,2-anhydro sugars.[8] Bennet et al. reported computational analysis of formation of unprotected 1,2-anhdyro sugars from *p*-nitrophenyl glycosides.[9] Quite recently, the participation of a partially protected 1,2-anhydrofuranose was confirmed in a nucleoside synthesis.[10] However, in spite of the fact that unprotected 1,2-anhydro sugars possess potential utilities as a new donor substrate in the synthetic field of glycoscience, the direct experimental observation of totally unprotected 1,2-anhydro sugars has not been achieved yet.

One of the main reasons for the lack of basic information is that there are no efficient methods for constructing the fused bicyclic structure of 1,2-anhydro sugars under neutral and mild reaction conditions without using protecting groups. To accomplish the formation and detection of unprotected 1,2-anhydro moieties, it is necessary to completely develop a new dehydration methodology that takes place under extremely mild and essentially neutral conditions. Recently, the concept of "*direct anomeric activation*" using formamidinium-type dehydrating agents has been proposed, and a series of glycosidic compounds such as glycosyl azides and thioglycosides were prepared by the reaction of unprotected saccharides and sodium azide or thiocompounds, respectively.[11] All of these dehydration reactions proceeded under extremely mild conditions in aqueous media. The mildness of those dehydration reactions as well as the fact that there is no need to protect the sugar hydroxy groups prompted us to venture into an investigation for the first direct spectroscopic observation of unprotected 1,2-anhydro sugars.[12]

This paper shows the first clear-cut evidence for proving the existence of unprotected 1,2-anhydro sugars in a test tube, which has not been realized for nearly a hundred years in spite of the eagerness of synthetic chemists to know more about the properties of *unprotected* 1,2-anhydro sugars. The intramolecular dehydration between the anomeric hydroxy group and 2-hydroxy group of unprotected saccharides has been achieved in aqueous media using 2-chlorodimethylimidazolinium chloride (DMC) or 2-chlorodimethylbenzimidazolium chloride (CDMBI) in the presence of a base (Scheme 1). Representative procedure for synthesis of 1,2-anhydro glucose is as follows. Precooled triethylamine (0.105 mL, 0.750 mmol) was added to a solution (D_2O/CH_3CN (1/1 (v/v), 0.5 mL)) of D-glucose (22.5 mg, 0.125 mmol) and DMC (42.3 mg, 0.250 mmol) in ice/NaCl bath



Scheme 1. Synthesis of unprotected 1,2-anhydro sugars using formamidinium type dehydrating agents.

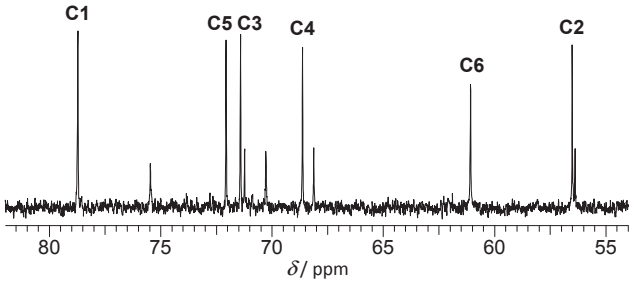


Figure 1. ^{13}C NMR spectrum of the reaction mixture of glucose and DMC in D_2O/CH_3CN at −10 °C. The small peaks at 78.7 (eclipsed), 75.5, 71.2, 70.3, 68.1 and 56.4 ppm are due to 1,2-anhydro glucose derivative whose 6-OH is substituted by an imidazoliniumoxy group.

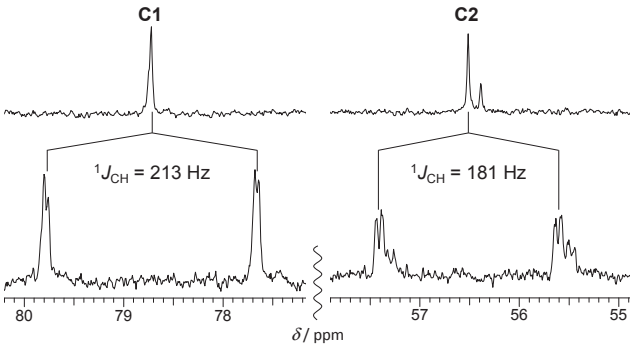


Figure 2. $^1J_{CH}$ constants of C1 and C2 in the reaction product. Upper: ^{1}H-decoupled ^{13}C NMR spectrum. Lower: ^{1}H-coupled ^{13}C NMR spectrum.

(−20 °C). After 10 min from the addition of triethylamine, NMR spectra were recorded at −10 °C.

The ^{13}C NMR of the reaction mixture showed signals at 78.7 and 56.5 ppm assignable to C1 and C2, respectively, the correctness of which was confirmed by a HSQC (Heteronuclear Single Quantum Coherence) experiment (Figure 1). Interestingly, these signals were observed in ca. 15 ppm higher magnetic fields compared with those of α-aldopyranose (92.9 (C1) and 72.5 (C2), respectively).[13] These results strongly support the existence of an epoxide ring in the product, because epoxide carbons are detected generally at higher magnetic fields than those of other cyclic ethers due to the ring strain.[14] We also measured ^{13}C NMR without composite pulse decoupling. The signals derived from the C1 and C2 had large $^1J_{CH}$ values of 213 and 181 Hz, respectively (Figure 2). In general, the $^1J_{CH}$ values of the C1 and C2 in glucose that adopt the ideal chair conformation are around 180 and 150 Hz, respectively.[15] The observed large differences can be explained by the higher s-character of the ring carbon hybrid orbitals, supporting the formation of an epoxide ring.[14b]

The ^{1}H NMR showed a doublet peak ascribable to the anomeric proton at 5.1 ppm with a small coupling constant of 2.0 Hz (Figure 3). The dihedral angle H1–C1–C2–H2 calculated with the Karplus equation was approximately 90°. In the H–H COSY spectrum, long-range spin–spin coupling between H-1 and H-3 was observed (red circle in Figure 4). The 4-bond coupling across saturated carbons is frequently seen in compounds having W-arrangement of the connecting bonds, in which H_a–C_a–C_b and C_b–C_c–H_c fragments are close to coplanar.[16] These ^{1}H NMR data were also consistent with the existence of a bicyclic structure including an epoxide ring.

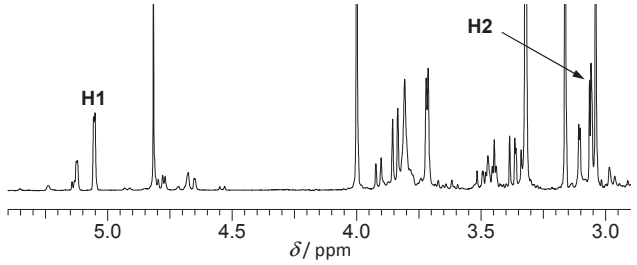


Figure 3. ^{1}H NMR spectrum of the reaction mixture of glucose and DMC in D_2O/CH_3CN at −10 °C.

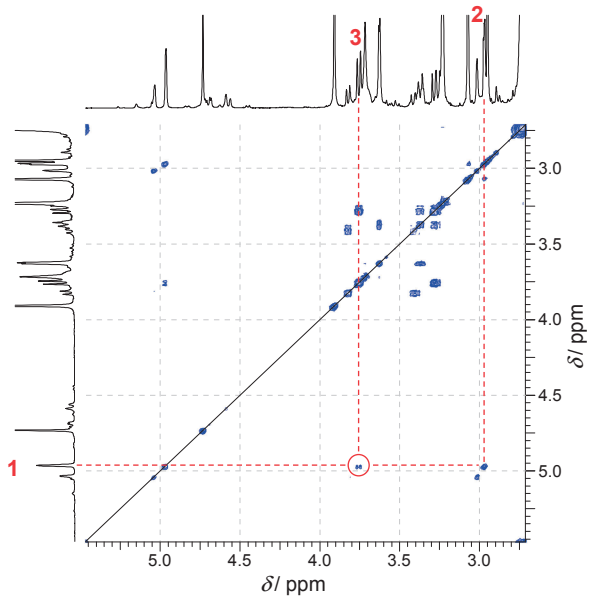


Figure 4. H–H COSY spectrum of the reaction mixture of glucose and DMC in D_2O/CH_3CN at −10 °C.

All these NMR observations clearly indicated that an intramolecular dehydration took place between the hemiacetal and 2-hydroxy group using DMC as a dehydrating agent, giving rise to 1,2-anhydro glucose. The yield of 1,2-anhydro glucose after 10 min was 63%, which was determined by ^{1}H NMR.

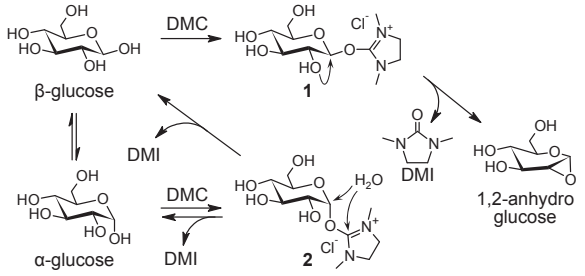
We investigated the effect of the dehydrating agents and bases on the yield of 1,2-anhydro glucose. When CDMBI was employed instead of DMC as the dehydrating agent, 1,2-anhydro glucose was obtained in comparable yields. We screened different bases and found that Et_3N gave the best results. This reaction also proceeded smoothly using tertiary amines like *N*,*N*-dimethylethylamine having the same degree of basicity as Et_3N. Other bases, *N*-methylmorpholine, pyridine, and 2,6-lutidine afforded no 1,2-anhydro glucose, because their basicities are too low to enhance the nucleophilicity of the hemiacetal and/or 2-hydroxy group.

Various unprotected monosaccharides (Entries 1–6, Table 1), disaccharides (Entries 7–11) and a trisaccharide (Entry 12) were treated with DMC or CDMBI as dehydrating

Table 1. Synthesis of 1,2-anhydro aldopyronoses from various unprotected sugars by using dehydrating agents[a]

Entry	Substrate (mM)	Dehydrating agent (equiv)	Et_3N /equiv	Yield /%[b]
1	Glucose (250)	DMC (2)	6	63
2	Mannose (250)	DMC (3)	9	50
3	Allose (250)	DMC (3)	9	65
4	Galactose (250)	DMC (2)	6	27
5	Xylose (250)	DMC (3)	9	73
6	Rhamnose (250)	CDMBI (3)	9	66
7	Cellobiose (125)	DMC (3)	9	61
8	Lactose (125)	DMC (3)	9	64
9	Xylobiose (125)	CDMBI (3)	9	52
10	Maltose (125)	DMC (3)	9	43
11	Melibiose (125)	CDMBI (3)	9	64
12	Isomaltotriose (125)	CDMBI (3)	9	51

[a]Reactions were carried out in 1:1 D_2O/CH_3CN at −20 °C. ^1H NMR was measured after 10 min from the start of the reaction. [b]Determined by ^1H NMR.



Scheme 2. Plausible reaction mechanism of 1,2-anhydro sugar formation.

agent at −20 °C in the presence of triethylamine (Table 1). All the solutions contained the 1,2-anhdyro sugars, which clearly gave signals derived from 1,2-anhydro aldopyranoses.

The formation of 1,2-anhydro moieties can be explained by a preferential nucleophilic attack of the β-hemiacetal of unprotected sugars than other hydroxy groups to the 2-position of the formamidinium agents in the presence of Et_3N as a general base, giving rise to an reactive intermediate **1** with β-configuration (Scheme 2). Then, an intramolecular attack of 2-hydroxy group to the anomeric carbon occurs, affording 1,2-anhydro glucose and 1,3-dimethylimidazolidin-2-one (DMI) as the side-product. Another possible intermediate **2** with α-configuration, which is formed by the nucleophilic attack of α-hemiacetal, cannot be converted into 1,2-anhdyro sugars due to the disadvantageous position of the imidazolinium group in **2** and is transformed into the starting hemiacetal by the attack of water.

In conclusion, we succeeded in detecting unprotected 1,2-anhydro sugars for the first time using formamidinium-type dehydrating agents in aqueous media under essentially neutral and extremely mild reaction conditions, which gave clear-cut evidence of unprotected 1,2-anhydro sugars whose existence has long been under controversy in organic chemistry. The success is greatly indebted to the mildness of the reaction condition of the intramolecular dehydration reaction in aqueous media due to the use of formamidinium-type agents. Since the resulting unprotected 1,2-anhydro sugars possess potential utilities as an efficient glycosyl donor for enzymatic glycosylations at low temperature, the optimization of the reaction conditions is now under extensive investigation.

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