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Substituent effects in endocyclic cleavage–recyclization anomerization reaction of pyranosides

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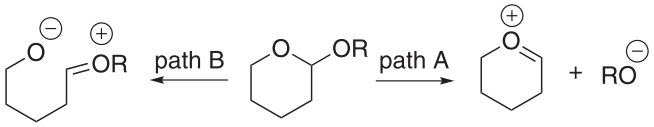
ABSTRACT

Pyranosides with 2,3-*trans* carbamate or 2,3-*trans* carbonate groups are anomerized under mild acidic conditions via endocyclic cleavage reaction. In order to understand the nature of the anomerization reaction via the endocyclic cleavage–recyclization process, the substituent effects at various positions were investigated.

1. Introduction

The reaction mechanism of acetal hydrolysis with its stereoelectronic aspects has received much attention as a fundamental issue in organic chemistry.[1] Since glycosides are acetals existing in living systems, the issue on glycosidic cleavage is also important in carbohydrate chemistry, biochemistry, and biotechnology. Since pyranosides are asymmetric acetals, there are two possibilities for their mode of C–O bond cleavage.[2] One is exocyclic cleavage, where the bond between the anomeric carbon and the exocyclic oxygen breaks giving a cyclic oxocarbenium ion (Scheme 1, path A). The cyclic oxocarbenium ion is assumed to be an important intermediate in glycosylation reactions, and a key species in carbohydrate science.[3] The other cleavage pattern is endocyclic cleavage, where the bond between the ring oxygen and the anomeric carbon is cleaved giving a linear cation (Scheme 1, path B). The endocyclic cleavage is less common in carbohydrate chemistry compared to the exocyclic cleavage. The mechanistic details of regioselectivity on the cleavage site of pyranosides are discussed extensively in the context of the stereoelectronic theory.[4] According to this theory, it is explained that, for glucosides in a $^4C_1$ chair form, the α-anomers preferentially proceed via an exocyclic pathway, whereas exocyclic cleavage in the β-anomers is energetically unfavorable unless a conformational change of the pyranoside ring is possible.[1d,5] For the β-pyranosides in a $^4C_1$ chair form, the exocyclic leaving group cannot depart easily because of lack of overlap with the electron orbital of the ring oxygen. It is also discussed that the β-pyranosides has to adopt twist boat or flattened chair conformations to be cleaved in an endocyclic manner. Thus, investigations into the cleavage patterns of pyranosides will be interesting not only to carbohydrate chemists but also to theoretical chemists studying stereoelectronic issues.



Scheme 1. Endocyclic cleavage versus exocyclic cleavage reactions.

Haworth reported as early as 1941 that 3,6-anhydro-methyl glucosides were hydrolyzed in the endocyclic cleavage mode.[6] Post and Karplus suggested the possibility of endocyclic cleavage in the hydrolysis of an oligosaccharide in lysozyme with molecular dynamics simulations.[7] These calculations were performed based on the X-ray crystallographic studies of lysozyme with an oligosaccharide substrate, wherein the conformation of *N*-acetylglucopyranoside was restricted to a $^4C_1$ chair form in the enzyme.[8] Inspired by the Post and Karplus hypothesis, several groups reported experimental evidence of conformationally locked sugar mimic

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compounds by capturing the cation generated in an endocyclic cleavage mode. For example, Franck succeeded in capturing the cation generated via endocyclic cleavage by an intramolecular aza-Diels–Alder reaction during alkyl β-acetal methanolysis.[9] Fraser-Reid demonstrated the presence of linear acetylium ions in acetic acid during acetolysis in the presence of ferric chloride.[10] Anslyn used a pseudosymmetric deuterium scrambling test to show that only a β-alkyl acetal locked in a *cis*-decalin type conformation underwent endocyclic cleavage in MeOH, with a 30% maximum ratio.[11] Deslongchamps and Dory investigated reaction pathways of the enzyme-catalyzed hydrolysis of glycosides based on quantum-mechanical calculations as well as experimental studies, showing endocyclic cleavage reactions.[12] Recently, systematic analyses on endocleavage of 6,1-anhydroglucopyranuronic acid were reported by Murphy.[13]

During the development of a glycosyl donor for the 1,2-*cis* glycosylation of 2-amino-2-deoxy sugar,[14,15] we found that pyranosides with a 2,3-*trans* carbamate group were quite easily anomerized under mild Lewis acidic conditions.[16,17] Crich and Oscarson also reported the same anomerization with 2,3-*trans* carbamate-carrying pyranosides.[18] We presented evidence that the anomerization was caused by an endocyclic cleavage reaction and subsequent recyclization of the pyranoside ring.[19] The generated linear cation was captured by intra- and inter-molecular Friedel–Crafts reactions, chloride addition, and reduction using Et_3SiH (Scheme 2). The anomerization reaction of pyranosides with 2,3-*trans* carbamate occurs at lower temperatures and milder conditions compared to other reported examples. Even the α-anomers are anomerized to the β-anomers, although higher (0 °C) temperature is required. Complete anomerization from the β- to the α-direction was observed in some cases.

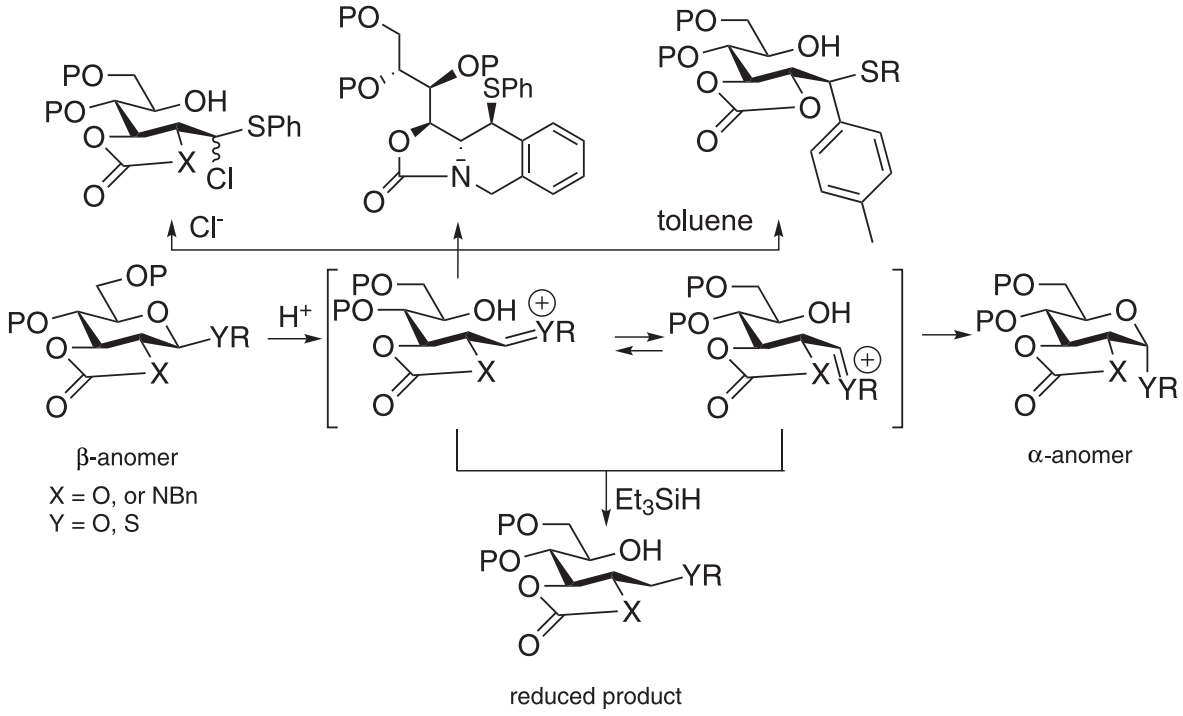
with 2,3-*trans* cyclic protecting group, inner strain caused by the fused rings distorting one ring by the force from the other is the primary factor enhancing the endocleavage reaction.[20b] The effect of the cyclic protecting group in restricting the pyranoside ring to a $^4C_1$ conformation is estimated to be a secondary factor.

In order to obtain further information aimed at the development of this endocyclic cleavage reaction for synthetic utility, we investigated substituent effects at the anomeric center, the 5-position, and the 2-position in the anomerization reaction.

2. Results and discussion

Reductive cleavage reaction of the benzylidene acetal group of a pyranoside with a 2,3-*trans* carbamate group **1a** was first carried out. When the reaction was performed at 0 °C for 30 min, anomerized α-thioglycoside **2a** and β-thioglycoside **3a** were obtained in 14% and 72% yields, respectively (entry 1, Table 1). No pyranose ring-opened diol **4a** was observed. After 6 h, β-glycoside **3a** was not obtained. Instead, α-glycoside **2a** (53%) and pyranoside-opened alcohol **4a** (11%) were obtained (entry 2). At room temperature, both α- and β-glycosides were obtained within 30 min (entry 3).

When the *N*-substituent was replaced with an electron-withdrawing *o*-nitrobenzyl group, the anomerization from the β-anomer to the α-anomer was suppressed. The β-thioglycoside **3b** was obtained in 87% yield and only a trace amount of α-glycoside **2b** was obtained at 0 °C after 30 min (entry 4). Even when the amount of $BF_3\cdot OEt_2$ was increased to 4 equiv, the α-glycoside was increased only up to 3% yield (entry 5). Similar to the *N*-benzylated substrate **1a**, the yield of α-glycoside **2b** was increased when the reaction was carried out at room temperature (entries 6 and 7). The



Scheme 2. Experimental evidence of endocyclic cleavage reaction.

The endocyclic cleavage in this series of compounds was investigated by density functional theory (DFT) calculations.[20] Transition state (TS) search calculations demonstrated that pyranosides carrying the cyclic protecting groups undergo endocyclic cleavage-induced anomerization reaction more easily than typical pyranosides.[20a] Further investigation concluded that, for glycosides electron-rich benzyl type NAP group[21] enhanced the reduction product. In the case of NAP-protected substrate **1c**, only the ring opened product **4c** was obtained even at 0 °C with 4 equiv of $BF_3\cdot OEt_2$ (entry 9) or at room temperature after 30 min (entry 10). The non-substituted substrate **1d**[17a] was submitted to the same standard reaction conditions as entry 1, but only the β-anomer