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Low-Barrier Pathway for *endo*-Cleavage Induced Anomerization of Pyranosides with *N*-Benzyl-2,3-*trans*-oxazolidinone Groups

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Pyranosides with *N*-benzyl-2,3-*trans*-oxazolidinone undergo anomerization from the β form to the α form even in the presence of a weak Lewis acid. Experimental evidence for *endo*-cleavage, the breaking of the bond between the pyran-oxygen and anomeric carbon atoms, in the anomerization reactions was obtained. This unexpected phenomenon was investigated by quantum mechanical calculations, which found clear differences in the transition states between anomerized and non-anomerized substrates. The computations suggest that BF_3 induces *endo*-cleavage followed by rotation of the C1–C2 bond to give the α form via lower-energy transition states.

Introduction

The mechanism of acetal hydrolysis with their stereoelectronic aspects have attracted a great deal of attention in both organic chemistry and biochemistry.[1] In carbohydrate chemistry, since glycosides are asymmetric acetals, the mechanism of glycosidic cleavage is also a fundamental issue. Two possible pathways have been proposed for the cleavage mechanism (Figure 1). The first is exocyclic cleavage, where the bond between the anomeric carbon and the exocyclic oxygen atoms breaks to give the cyclic oxocarbonium ion (Figure 1, a). The oxocarbonium ion reacts with acceptors such as alcohols, phenols, and thiols to give glycosides. It is known that typical glycosylation reactions are based on this mechanism.

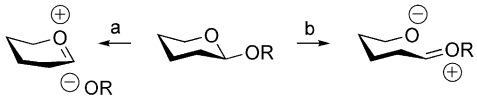

Figure 1. Exo- (a)- and endocyclic (b) cleavage of glycoside.

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The second is *endo*-cleavage, where the bond between the anomeric carbon and the pyranose ring oxygen atoms breaks (Figure 1, b). For acetals, there have been many discussions about the presence of both *exo*- and *endo*-cleavage pathways. However, in carbohydrate chemistry, the occurrence of *endo*-cleavage in pyranosides is not thought to be very common. The possibility of *endo*-cleavage taking place in pyranosides has been investigated ever since Post and Karplus proposed a hypothesis of *endo*-type hydrolysis for oligosaccharides based on molecular dynamics calculations of *N*-acetylglucopyranoside with lysozyme, where the pyran ring was fixed to a chair-form conformation.[2] Franck captured the cation generated through *endo*-cleavage by an intramolecular aza-Diels–Alder reaction in alkyl β-THP acetal methanolysis.[3]

Fraser–Reid demonstrated the existence of linear acetylium ions in acetic acid during the acetolysis of acyl-protected methyl glycosides in the presence of ferric chloride.[4] Anslyn reported that only the *cis*-decalin-type of conformationally locked β-alkyl acetals undergo endocyclic cleavage with a maximum yield of 30% in MeOH with a deuterium scrambling test.[5] It was reported that under aprotic conditions, *endo*-cleavage for typical pyranose sugars requires strong Lewis acids, such as $SnCl_4$.[6] Deslongchamps and Dory performed a detailed investigation of the reaction pathways of enzyme-catalyzed hydrolyses of α- and β-glycosides.[7] Their RHF/6-31G(d,p) calculations indicated the presence of a transition structure for the *endo*-cleavage of tetrahydropyranyl acetals under protic conditions; the transition energy relative to the β form was ca. 15 kJ mol^{-1} in vacuo.

Some other experimental studies related to *endo*-cleavage were reported by Crich and Manabe. They independently found that pyranosides with *N*-benzyl-2,3-*trans*-oxazolidi-

none groups[8] are quite easily anomerized from the β- to the α-direction, which made them the first cases of *endo*-cleavage under mild acidic conditions in aprotic media.[9] Olsson and Oscarson et al. very recently reported the anomerization of disaccharides with kinetic measurements. However, they reported that evidence of *endo*-cleavage was not obtained.[10]

We report here that we experimentally obtained evidence for the *endo*-cleavage of the anomerization of pyranosides with *N*-benzyl-2,3-*trans*-oxazolidinone groups. We detected lower-energy transition states (TS) on the pathways for the *endo*-cleavage induced anomerization under aprotic conditions with a weak Lewis acid for pyranosides with oxazolidinone groups.

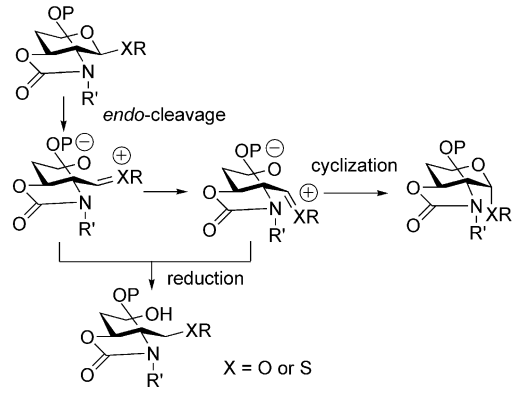
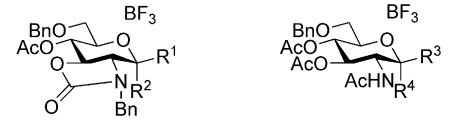


Figure 2. Proposed mechanism of anomerization of pyranosides with 2,3-*trans*-oxazolidinone groups.

Results and Discussion

To obtain evidence for the *endo*-cleavage of pyranoside **1**, a reduction reaction under acidic conditions was carried out (Scheme 1). After the reductive benzylidene cleavage reaction of compound **1** with Et_3SiH and $BF_3{\cdot}OEt_2$ at 0 °C, the α-thioglycoside **2b** was obtained as a by-product in 14% yield in addition to the β-glycoside **2a** (72%). When the reaction was carried out at room temperature, the yield of the α-product **2b** increased to 49%. Prolonged reaction times increased the yield of the α-glycoside **2b** and gave alcohol **3** in 11% yield. It is assumed that the ring-opened alcohol **3** was generated by the reduction of the ring-opened cation by Et_3SiH (Figure 2). It was previously reported that the cation generated by *endo*-cleavage was captured in an intramolecular Diels–Alder reaction in protic media.[3] However, our examples highlight a new phenomenon in that they indicate the existence of the *endo*-cleaved cation in aprotic media by simply carrying out reduction reactions. Furthermore, additional evidence for *endo*-cleavage was observed in the course of the experimental studies.[11]

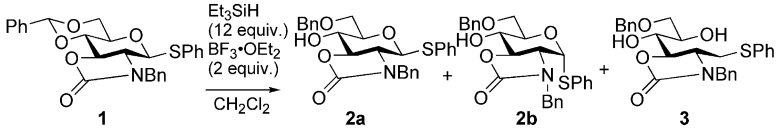
Four structures (**4a**, **5a**, **6a**, **7a**) were investigated by density functional theory with the basis set B3LYP/6-31G(d,p) by using Gaussian03.[12] BF_3 was used as the Lewis acid. Initial geometries of **4a** and **5a** were constructed on the basis of NMR and X-ray data for the related pyranosides with 2,3-*trans*-oxazolidinone groups, which indicate that the pyran ring takes a $^4C_1$ chair-form conformation.[9b,11] Geometries of **6a** and **7a** were constructed on the basis of the typical glucose $^4C_1$ chair-form conformation. Calculations were performed for two coordination modes of BF_3 to the lone pairs of the pyran oxygen atom. We describe here the results of the coordination to the axially oriented lone pair in the $^4C_1$ chair-form conformation, which showed the lowest-energy barriers of the two modes (Scheme 2).



4a R^1 = OMe, R^2 = H **6a** R^3 = OMe, R^4 = H
4b R^1 = H, R^2 = OMe **6b** R^3 = H, R^4 = OMe
5a R^1 = SPh, R^2 = H **7a** R^3 = OPh, R^4 = H
5b R^1 = H, R^2 = SPh **7b** R^3 = H, R^4 = OPh

Scheme 2. Calculated model structures.

The relevant variables to model the reaction coordinate are the rotation of the C1–C2 bond, the O5–B distance, and the C1–O5 distance. We chose the rotation of the C1–C2 bond as the first target to investigate. We explored the potential energy surface by rotating the C1–C2 bond counterclockwise from 0 to 180° in 5° steps, i.e. by decreasing the dihedral angle θ (H1–C1–C2–H2) from the β to the α direction (Figure 3) and allowing full relaxation of all other variables.



Entry	Reaction conditions	2a	2b	3
1	0 °C, 30 min	72	14	0
2	r.t., 30 min	42	49	[a]
3	0 °C, 6 h	0	53	11

[a] Compound **3** was not isolated as a pure form.

Scheme 1. Experimental investigation of the anomerization process.

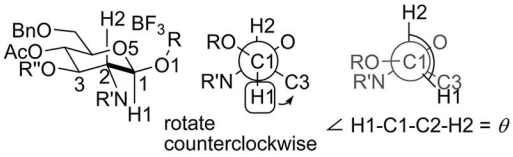


Figure 3. The dihedral angle and rotation.

The initial θ values and the C1–O5 bond lengths of the β-formed structures **4a**, **5a**, **6a**, and **7a** were 174, 175, 177, and 179°, and 0.145, 0.145, 0.144, and 0.143 nm, respectively. When the dihedral angle θ is reduced, the C1–O5 bond length increases until the bond finally breaks at θ = 105, 95, 125, and 90°, for which the energies relative to the corresponding β form were 94.2, 90.5, 123.7, and 137.8 kJ mol^{-1} for **4a**, **5a**, **6a**, and **7a**, respectively. After the bond breaks, transition states (TS) were found between θ = 28–45° for all structures. The energy relative to the corresponding β form and the values for θ of the TS for **4a**, **5a**, **6a**, and **7a** were 104.5 kJ mol^{-1} at 44.2°, 83.6 kJ mol^{-1} at 28.8°, 159.5 kJ mol^{-1} at 35.6°, and 157.1 kJ mol^{-1} at 37.3°, respectively. Figure 4 shows the TS energies relative to the β form as well as the relative energies of the α- and β forms with their structures for **4a**–**7a**. The results show that the TS energies of the structures with 2,3-*trans*-oxazolidinone groups, **4a** and **5a**, were clearly lower than the other structures without 2,3-*trans*-oxazolidinone groups, **6a** and **7a**. It is noted that the oxazolidinone groups of the TS for **4a** and **5a** obviously take a flat form rather than those of the corresponding β and α forms. The energy calculations that take the solvent CH_2Cl_2 into account with the IEF-PCM (Integral Equation Formalism for the Polarizable Continuum Model) method of the SCRF (Self-Consistent Reaction Field) theory stabilized the TS for all structures by almost the same amount, shown as dotted lines in Figure 4. These results show the same tendency as those in vacuo, which means that calculations using the vacuum condition are adequate for discussing the differences in energies between oxazolidinones (**4a** and **5a**) and the others (**6a** and **7a**).

The other relevant variables, the O5–B and the C1–O5 distances as a function of the rotation about the C1–C2 bond are plotted as shown in Figure 5. The solid and dotted lines represent the C1–O5 and O5–B distances, respectively. The plots show that these two variables have a strong dependence on the C1–C2 bond rotation. The results indicate that the O5–B distance is important for the reaction.

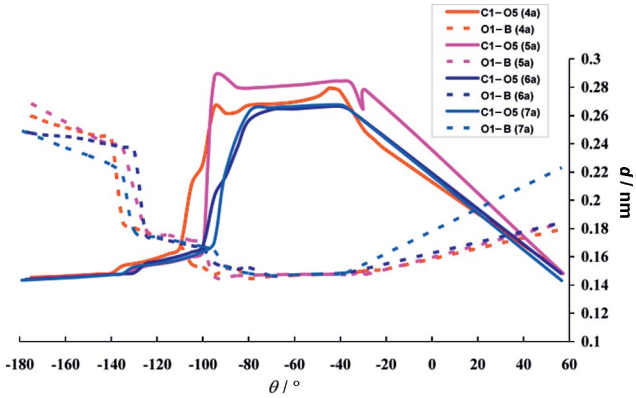


Figure 5. Changes in the O5–B and C1–O5 distances during C1–C2 rotation.

We therefore then focused on the O5–B distance and investigated the potential energy surface with BF_3 approaching the oxygen atom in the pyran ring, without a solvent. The initial O5–B and C1–O5 distances for optimized **4a**, **5a**, **6a**, and **7a** were 0.26, 0.27, 0.25, and 0.25 nm, and 0.145, 0.145, 0.144, and 0.143 nm, respectively. Starting from the equilibrium structures of **4a**, **5a**, **6a**, and **7a**, the O5–B distance was reduced from 0.22 nm in steps of 0.01 nm. The C1–O5 bond in the pyran ring became longer than 0.15 nm

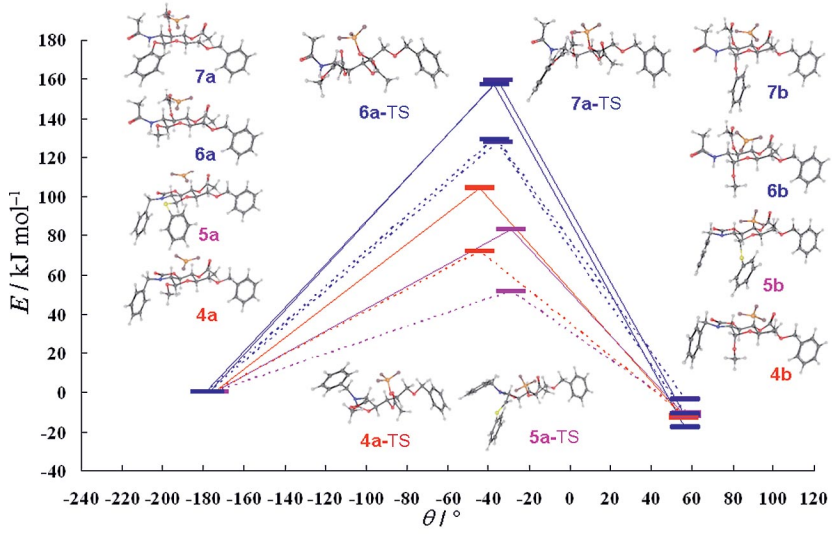


Figure 4. Relative energies for the transition state and the α- and β forms for **4**–**7**.

when the O5–B distance was 0.16, 0.16, 0.15, and 0.15 nm, for which the energies relative to the corresponding initial β form were 19.4, 20.0, 34.7, and 36.3 kJ mol^{-1} for **4a**, **5a**, **6a**, and **7a**, respectively (Figure 6). When the potential energy surface for the C1–C2 bond rotation was explored, the C1–O5 bond became longer than 0.15 nm at θ = 135, 125, 125, and 130°, for which energies relative to the corresponding β form were 35.9, 52.5, 54.1, and 47.2 kJ mol^{-1}, respectively. These values are considerably larger than those obtained in this investigation for the O5–B bond length. The results show that the effect of BF_3 is to extend the C1–O5 bond, which makes the rotation about the C1–C2 bond easier. Moreover, they indicate that pyranoses with the oxazolidinone group (**4a** and **5a**) can be *endo*-cleaved more easily than compounds without the oxazolidinone ring (**6a** and **7a**).

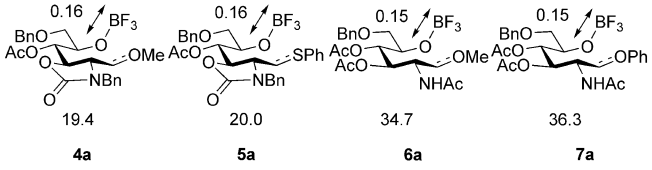
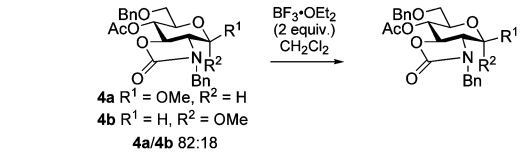


Figure 6. O5–B bond length (nm) and energy relative to the corresponding initial β form (kJ mol^{-1}) at the state where the C1–O5 bond was elongated more than 0.15 nm.

We then investigated the possibilities of *exo*-cleavage with BF_3 approaching the oxygen atom (O1) for **4a**, **6a**, and **7a** or the sulfur atoms for **5a** at the anomer site in the same manner. The initial O1–B(S–B for **5a**) and C1–O1 (C1–S for **5a**) distances for the β-formed **4a**, **5a**, **6a**, and **7a** were 0.22, 0.33, 0.23, and 0.24 nm, and 0.140, 0.183, 0.140, and 0.141 nm, respectively. The C1–O1 bond did not break even when the O1–B and S–B distances became 0.14 and 0.17 nm, respectively, whereas the C1–O5 bond broke when the O5–B distance became ca. 0.16 nm. The energies relative to the corresponding initial β form with the O1–B and S–B distances were 63.9, 121.9, 67.6, and 75.7 kJ mol^{-1}, respectively. These results indicate that BF_3-induced *endo*-cleavage is much more dominant than *exo*-cleavage for these pyranosides.

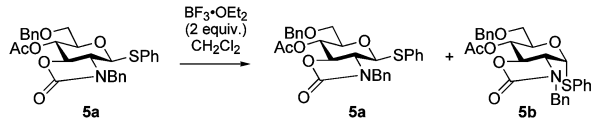
This series of computations shows that the C1–C2 bond in the pyran ring with a 2,3-*trans*-oxazolidinone group will rotate to give the α form via lower-energy transition states following *endo*-cleavage induced by BF_3. The calculations also show that pyranoses with oxazolidinones are anomerized as a result of their lower-energy barriers. The observed geometry change indicates that the oxazolidinone group prefers to take a flat form but is forced to strain in the β and α forms. As can be seen from the current calculations, this strained structure most likely makes *endo*-cleavage feasible for **4a** and **5a**.

The tendency of structures **4a**–**7a** to anomerize as proposed by the calculations was verified experimentally (Scheme 3). For the model structure **7a**, we used a *p*-methoxylphenyl group as the protecting group at the anomeric site instead of the phenoxy group (**8**), since the *p*-methoxyphenyl group can be removed under oxidative conditions and is commonly used in oligosaccharide synthesis.[13]

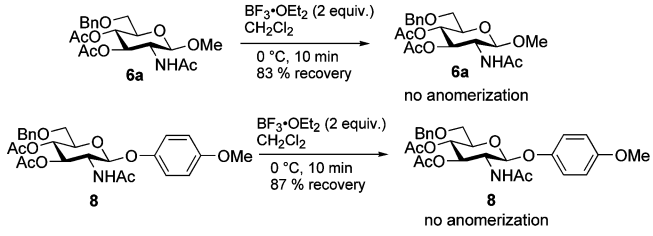


Entry	Conditions	Yield / %	4a/4b[a]
1	–30 °C, 12 h	93	36:64
2	0 °C, 30 min	80	14:86

[a] The ratio 4a/4b was determined by ^{1}H NMR spectroscopy.



Entry	Conditions	Yield(5a) / %	Yield(5b) / %
1	–30 °C, 12 h	16	63
2	0 °C, 10 min	22	59
3	0 °C, 60 min	6	76



Scheme 3. Experimental results based on the calculated model structures.

The pyranoside with *trans*-oxazolidinone **4** (α/β 18:82) was anomerized preferably in the α-direction [**4a**(β)/**4b**(α) 36:64] in the presence of 2 equiv. BF_3·OEt_2 at –30 °C after 12 h. Similarly, the thiophenyl glycoside **5** gave **5a** (β) and **5b** (α) in 16% and 63% yields, respectively, at –30 °C after 12 h. When the reaction was carried out at 0 °C, anomerization equilibrium was almost reached within 60 min. On the other hand, for the typical pyranosides **6** and **8**, the corresponding α-anomers were not observed, and the starting materials were recovered in high yields.

Conclusions

We obtained experimental evidence that *endo*-cleavage takes place for pyranosides with 2,3-*trans*-oxazolidinone groups with a weak Lewis acid by isolation of the reductive product. On the basis of these results, we explored the pathway of *endo*-cleavage induced anomerization of glycosides using quantum mechanical computations and found that transition states form as the C1–C2 bond rotates to transform the β form to the α form. Our investigation showed that pyranosides with *N*-benzyl-2,3-*trans*-oxazolidinone groups clearly possess lower energies for both the transition state and the *endo*-cleavage than pyranosides without oxazolidinone groups. The results are consistent with ex-

periments in which pyranosides with oxazolidinones were anomerized by weak Lewis acids, whereas pyranosides without oxazolidinones did not *endo*-cleave. The results from experiments performed on compounds related to the models are in good agreement with those from the computations. The calculated structural features indicate that the strained oxazolidinone groups make *endo*-cleavage more feasible. Several factors can influence the stabilization of the TS energies of pyranosides with oxazolidinone groups, such as fixing the conformation and/or electronic effects from the oxazolidinones. Our calculations suggest that there should be at least three relevant variables to model the reaction coordinates. There are still further possibilities that lower the reaction paths. Further experimental and theoretical studies to determine the characteristics and precise reaction paths of the pyranosides with oxazolidinones whilst considering these variables will reveal the detailed nature of the anomerization reactions.

Experimental Section

To a solution of compound **5a** (66.9 mg, 0.128 mmol) in CH_2Cl_2 (1.7 mL) was added $BF_3{\cdot}OEt_2$ (32 μL, 0.259 mmol) at 0 °C. After the mixture was stirred at 0 °C for 1 h, saturated $NaHCO_3$ was added. The aqueous layer was extracted with $CHCl_3$. The combined layers were washed with brine and dried with Na_2SO_4. After filtration, the solvent was removed. The residue was purified by preparative TLC ($CHCl_3$/EtOAc, 20:1) to give **5a** (50.6 mg, 76%) and **5b** (3.8 mg, 6%).

Supporting Information (see also the footnote on the first page of this article): Details of computations and experiments are provided.

Acknowledgments

Calculations were executed with Obelix of ETH Zürich, a cluster computer of the Competence Center for Computational Chemistry (C^4). The HA8000 cluster computer (t2k) at Tokyo University and the RIKEN super combined cluster (RSCC) system were also used in part. S. M. (RIKEN) thanks Ms. Akemi Takahashi (RIKEN) for her technical assistance and Ms. Kaori Otsuki and Mr. Masaya Usui at the Research Resource Center of RIKEN's Brain Science Center for performing the high-resolution MS measurements. S. M. also expresses thanks for the Grant-in-Aid for Scientific Research (C) (Grant No. 19590032) from the Japan Society for the Promotion of Science and an Incentive Research Grant from RIKEN. We thank Professor David M. Birney (Texas Tech University) for valuable discussions.

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