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Significant solvent effect in anomerization reaction of pyranosides with 2,3-*trans* carbamate and carbonate

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ABSTRACT

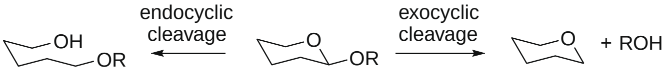
A pronounced solvent effect was observed in the anomerization reaction of pyranosides carrying 2,3-*trans* carbamate or carbonate. While significant anomerization from the β- to α-direction was observed in CH_3CN, none was observed in ether.

The elucidation of hydrolytic cleavage patterns of glycosides is important in carbohydrate chemistry, biochemistry, and technology.[1,2] Since carbohydrates are asymmetrical acetals, there are two possible patterns for glycoside cleavage. The first is exocyclic cleavage, where the bond between the anomeric carbon and exocyclic oxygen breaks to form the cyclic oxocarbenium ion (Scheme 1), and the other is endocyclic cleavage, where the bond between the anomeric carbon and the pyranose ring oxygen breaks. Although the exocyclic cleavage of pyranosides is well established in carbohydrate chemistry, the latter cleavage is not common in pyranosides, despite being reported as early as 1941.[1a] Since Post and Karplus hypothesized the existence of the endocyclic cleavage mechanism in the hydrolysis of *N*-acetylglucoside in lysozyme,[3] several attempts to capture the endo-cleaved cation generated have been reported.[4]

Two groups, ours and Crich's, independently found that pyranosides with 2,3-*trans* oxazolidinone are anomerized from the β- to α-direction relatively easily by weak Lewis acids than pyranosides without an oxazolidinone ring.[5] Oscarson also reported the anomerization of a disaccharide carrying a 2,3-*trans* oxazolidinone and suggested the possibility of endocyclic cleavage.[6] Recently, we showed evidence for endocyclic cleavage of pyranosides carrying 2,3-*trans* carbamate and carbonate by the capture of the endocyclic cleaved cation by intra- and inter-molecular Friedel–Crafts reaction, Cl addition, and reduction using Et_3SiH.[7] Quantum mechanical calculations for the endocyclic cleavage-induced anomerization revealed that pyranosides carrying 2,3-*trans* oxazolidinone groups show a lower transition state energy than typical pyranosides.[8]

Here we report a significant solvent effect for the anomerization of pyranosides carrying 2,3-*trans* carbamate and carbonate. Although the solvent effect involving exocyclic cleavage is well known,[9] this report is the first example of a solvent effect involving the endocyclic cleavage reaction.

As shown in Table 1, the 2,3-*trans* oxazolidinone carrying β-pyranoside **1** was anomerized in CH_2Cl_2 with 2 equiv of $BF_3{\cdot}OEt_2$ at −30 °C for 12 h (entry 3). The anomerized α-pyranoside **2** was obtained in 63% yield together with 16% of the starting material **1**. In CH_3CN, a higher yield (89%) of α-pyranoside **2** was obtained under the same conditions (entry 1). After prolonged reaction time (70 h), the yield of β-anomer was the same as entry 1 (entry 2), although the reason of α-anomer decrease is not clear. On the other hand, anomerization was not observed in ether (entry 5). This tendency was again observed when the 2,3-*trans* carbamate carrying galactosamine derivative **3** was used as a substrate. In CH_3CN, the anomerized product **4** was obtained in 80% yield (entry 6). In ether, the starting material



Scheme 1. Exocyclic cleavage and endocyclic cleavage.

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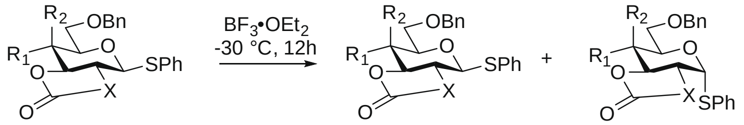
Table 1

Anomerization reaction of phenylthioglycosides with 2,3-*trans* carbamate and 2,3-*trans* carbonate in various solvents



1 R_1 = OAc, R_2 = H, X = NBn
3 R_1 = H, R_2 = OAc, X = NBn
5 R_1 = OBn, R_2 = H, X = NBn
7 R_1 = OAc, R_2 = H, X = O

1, **3**, **5**, **7**

2 R_1 = OAc, R_2 = H, X = NBn
4 R_1 = H, R_2 = OAc, X = NBn
6 R_1 = OBn, R_2 = H, X = NBn
8 R_1 = OAc, R_2 = H, X = O

Entry		R_1, R_2	X	Solvent	Products	Yields (%)
1	**1**	R_1 = OAc, R_2 = H	NBn	CH_3CN	**1** **2**	10 89
2[a]	**1**	R_1 = OAc, R_2 = H	NBn	CH_3CN	**1** **2**	10 50
3	**1**	R_1 = OAc, R_2 = H	NBn	CH_2Cl_2	**1** **2**	16 63
4	**1**	R_1 = OAc, R_2 = H	NBn	Toluene	**1** **2**	45 27
5	**1**	R_1 = OAc, R_2 = H	NBn	Et_2O	**1** **2**	90 0
6	**3**	R_1 = H R_2 = OAc	NBn	CH_3CN	**3** **4**	8 80
7	**3**	R_1 = H R_2 = OAc	NBn	CH_2Cl_2	**3** **4**	13 73
8	**3**	R_1 = H R_2 = OAc	NBn	Toluene	**3** **4**	29 55
9	**3**	R_1 = H R_2 = OAc	NBn	Et_2O	**3** **4**	94 0
10[b]	**5**	R_1 = OBn, R_2 = H	NBn	CH_3CN	**5** **6**	5 87
11[b]	**5**	R_1 = OBn, R_2 = H	NBn	CH_2Cl_2	**5** **6**	79 10
12	**5**	R_1 = OBn, R_2 = H	NBn	Et_2O	**5** **6**	94 0
13	**7**	R_1 = OAc, R_2 = H	O	CH_3CN	**7** **8**	62 10
14	**7**	R_1 = OAc, R_2 = H	O	CH_2Cl_2	**7** **8**	46 14
15	**7**	R_1 = OAc, R_2 = H	O	Et_2O	**7** **8**	99 0
16[c]	**7**	R_1 = OAc, R_2 = H	O	CH_3CN	**7** **8**	33 42
17[d]	**7**	R_1 = OAc, R_2 = H	O	CH_3CN	**7** **8**	45 25

[a] The reaction period is 70 h.

[b] The products **5** and **6** were not separated. The yields were determined by integration of ^{1}H NMR spectra.

[c] The reaction was carried out at 0 °C for 3 h.

[d] The reaction was carried out at −30 °C for 36 h.

3 was recovered without anomerization (entry 9). In the case of pyranoside **5** benzyl protected at the 4-position, a more pronounced solvent effect was observed. Thus, the anomerized **6** was obtained in 94% yield in CH_3CN (entry 10), but anomerization was not as effective as in CH_2Cl_2 (entry 11). In the case of 2,3-*trans* carbonate carrying glucose **7**, the anomerization ratios were small than those in the case of pyranosides carrying 2,3-*trans* carbamates **1**, **3**, and **5**, but anomerization was observed in CH_3CN and CH_2Cl_2 (entries 13–15). More α-product was obtained after 3 h at 0 °C or after a prolonged reaction period (entries 16 and 17).

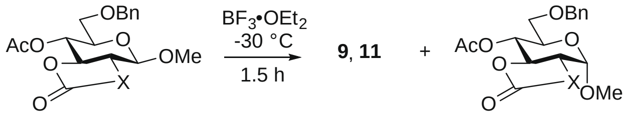
Furthermore, the solvent effect in the anomerization reaction of O-pyranosides was also observed (Table 2). A significant anomerization was observed in CH_3CN (entry 1), whereas no anomerization occurred in Et_2O (entry 4). In the case of *trans*-carbonate carrying pyranoside **11**, the complete anomerization from the β- to α-direction was observed in CH_3CN and toluene after 12 h (entries 9 and 10).

As shown in Table 3, the disaccharide **13** was also anomerized in CH_3CN, and α-product **14** was obtained in 65% yield (entry 1).

The observed rapid anomerization rate in CH_3CN is probably due to the high polarity of the solvent, which stabilizes the zwitterionic cationic intermediate.

In conclusion, we report a pronounced solvent effect in the anomerization of pyranosides with 2,3-*trans* carbamate and 2,3-*trans* carbonate, which are substrates that are easily anomerized.[9]More detailed results concerning the endocyclic cleavage will be reported in due course.

Table 2
Anomerization reaction of O-pyranosides with 2,3-*trans* carbamate and 2,3-*trans* carbonate in various solvents



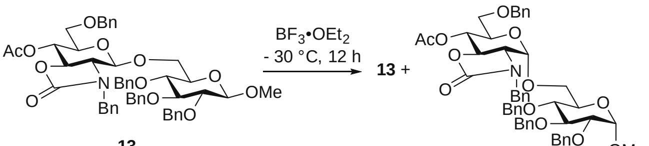
9 X = NBn
11 X = O

10 X = NBn
12 X = O

Entry		X	Solvent	Products	Yields (%)
1	**9**	NBn	CH_3CN	**9**	17
				10	80
2	**9**	NBn	CH_2Cl_2	**9**	64
				10	29
3	**9**	NBn	Toluene	**9**	35
				10	43
4	**9**	NBn	Et_2O	**9**	89
				10	0
5	**11**	O	CH_3CN	**11**	5
				12	71
6	**11**	O	CH_2Cl_2	**11**	47
				12	33
7	**11**	O	Toluene	**11**	7
				12	69
8	**11**	O	Et_2O	**11**	82
				12	0
9[a]	**11**	O	CH_3CN	**11**	0
				12	86
10[a]	**11**	O	Toluene	**11**	0
				12	88

[a] The reaction period is 12 h.

Table 3
Anomerization reaction of disaccharide **13** in various solvents



13

14

Entry		Solvent	Products	Yields (%)
1	**13**	CH_3CN	**13**	31
			14	65
2	**13**	CH_2Cl_2	**13**	90
			14	5
3	**13**	Et_2O	**13**	95
			14	0

Acknowledgments

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9. To a solution of β-thioglycoside **1** (78.0 mg, 0.150 mmol) in CH_3CN (1.9 mL), $BF_3 \cdot OEt_2$ (37 μL, 0.30 mmol) was added at −30 °C. After stirring the mixture at −30 °C for 12 h, satd $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc. The combined layers were washed with brine. After drying the organic layers, the solvent was evaporated. The residue was purified by preparative TLC (hexane/EtOAc 7:3). The β-thioglycoside **1** (7.8 mg, 10%) and α-thioglycoside **2** (69.0 mg, 89%) were obtained.