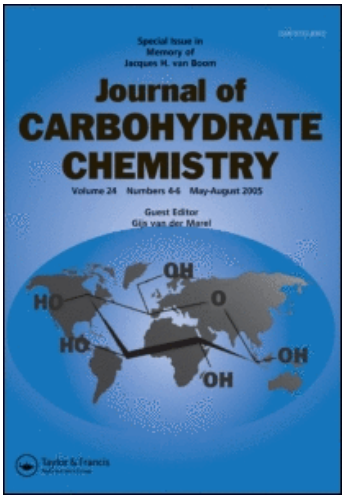

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FACTORS CONTROLLING STEREOSELECTIVITY IN THE KOENIGS-KNORR TYPE D-MANNOPYRANOSYLATION

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ABSTRACT

The factors controlling stereoselectivity in the formation of cyclohexyl α- and β-D-mannopyranosides with D-mannosyl chloride, cyclohexanol and silver triflate (AgOTf), were examined. For the syntheses of β-D-mannopyranosides, dichloromethane (CH_2Cl_2) as solvent could be used only at low temperature, while the use of tetrahydrofuran (THF) as solvent proved to be effective at room temperature. Diallyl ether (All_2O) was effectively used in CH_2Cl_2 as an olefinic additive. Stereoselectivities in these reactions were changed by use of THF as an oxonium ion source and All_2O as an inhibitor to prevent complex formation of the silver ion with the allyloxy group of the glycosyl donor.

INTRODUCTION

Many efforts[2] have been carried out to reveal the mechanism of Koenigs-Knorr type glycosylation reactions. The proposed mechanistic pathways in the case of mannosyl halide and soluble silver salts are shown in Fig 1. One route to glycosylation can be explained via C-X bond-cleavage of (I) by silver salts (step a) followed by the attack of acceptor (step b) (SN1) to give α-glycoside (II) or solvent molecule to form oxonium[3,4] or nitrilium ion[5] products (step g). In some cases stable pyridinium,[6] ammonium[7] and phosphonium[7] salts have been isolated and used as starting materials in further

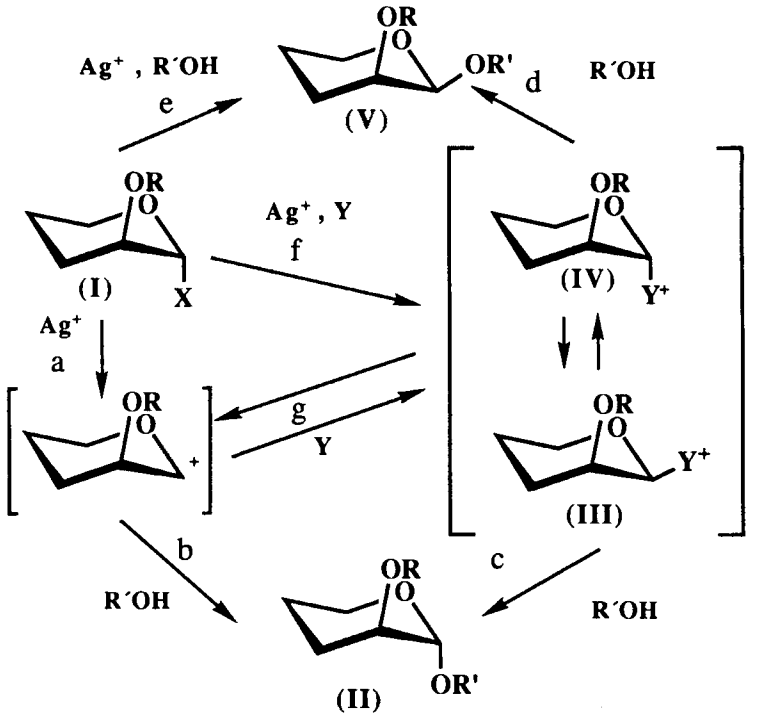


Fig.1
Glycosylation of R'OH with mannopyranosyl halide in the presence of Ag^+.
Y is a solvent molecule glycosylated on its hetero atom.

glycosylation reactions. These β- and α-oxonium and nitrilium cations (**III** and **IV**) can lead to the formation of α- and β-glycosides (**II** and **V**), respectively (steps c and d). However, when the acceptor or the solvent is a strong nucleophile and the electrophilicity of silver ion is comparatively low, β-glycoside (**V**) is formed (SN2) (step e) or directly enters into the equilibrium (step f). In a mannosylation reaction, α-glycoside is produced in an SN1 type reaction due to steric factors and thermodynamic stabilities or via step c in the presence of a suitable solvent Y. Therefore β-D-mannopyranoside is obtained mainly in an SN2 type reaction (step e) or a solvent mediated pathway (step d).

We have used CH_2Cl_2 and THF as two different types of solvents during our studies. When CH_2Cl_2 and AgOTf were used as solvent and as promotor respectively, the glycosylation pathway can be described only by steps a and b as in Fig. 1. But there is also possibility to obtain β-D-mannopyranoside in CH_2Cl_2 by using a less electrophilic silver salt, by means of using complexes formed by AgOTf with some ligands *in situ*,

compatible with the nucleophilicity of the acceptor (step e). On the other hand, THF is available to form an oxonium cation.[3] The glycosylation pathway in THF could be described as shown in Fig. 1 without steps b and e.

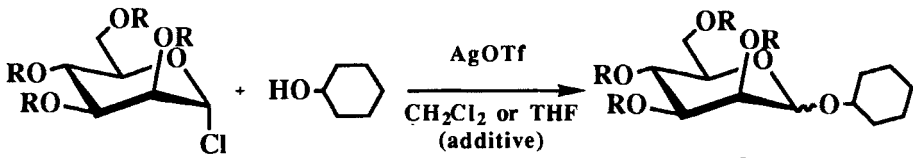
As is well known, α- and β-D-mannopyranosides exist in many structures of bioactive molecules. They prompted us to study in detail the α- and β-D-mannopyranosylation reaction with regard to an effective synthesis of these products. In a previous paper[8] we have reported the effect of complexation of silver ions with an olefin and an acceptor. They proved to play an important part in β-D-mannopyranosylation. But in this case, it was difficult to find out plausible mechanisms.

In order to explain the plausible pathway of glycosylation and to find some conditions to obtain synthetically difficult β-D-mannopyranosides with high stereoselectivity, we chose D-mannopyranosyl chloride derivatives (**1**) and (**2**) as glycosyl donors and cyclohexanol as acceptor. The glycosylations were performed in the presence of AgOTf, as promotor, according to the previous paper.[8]

RESULTS AND DISCUSSION

The D-mannopyranosylation was elaborated concerning reaction time, temperature, solvent and the molar proportion of AgOTf and **1** in CH_2Cl_2. The results are summarized in Table I. A small excess (1.5 equiv) of AgOTf gave better yields than large amounts (4 equiv) of AgOTf independent of the temperature. The reason for these results seems to be decomposition of the donor after the formation of the carbonium ion (step a) by a lot of AgOTf. These glycosylations were complete within 0.5 h at 0 °C (entries 3, 4 and 5) but were not complete within the same time at −78 °C in THF (entries 15 and 16). Therefore we performed the reactions at 0 °C and −40 °C during 0.5 hour and 5 hours at −78 °C, respectively.

Though at 0 °C in CH_2Cl_2 only α-glycoside was formed (entries 1, 2 and 3), at low temperature β-glycoside was also produced (entries 6 ~ 11), probably because of the lower reactivity of AgOTf at low temperature. In contrast to the case of CH_2Cl_2, in THF even at



(1) R=All (-$CH_2CH=CH_2$)
(2) R=Pr (-$CH_2CH_2CH_3$)

(3α, 3β) R=All
(4α, 4β) R=Pr

Table I
Glycosylation of cyclohexanol with **1**

Entry	Solvent	AgOTf (v.s. **1**, equiv)	Temp (°C)	Time (h)	Yields and Ratios 3α (%)	3β (%)	3α+3β (%)	α : β
1	CH_2Cl_2	1	0	0.5	55	0	55	100 : 0
2		1.5	0	0.5	65	0	65	100 : 0
3		4	0	0.5	56	0	56	100 : 0
4		4	0	2.5	46	0	46	100 : 0
5		4	0	5.0	45	0	45	100 : 0
6		1.5	-40	0.5	32	23	55	58 : 42
7		4	-40	0.5	21	8	29	72 : 28
8		1.5	-78	0.5	23	18	41	56 : 44
9		1.5	-78	5.0	28	21	49	57 : 43
10		4	-78	0.5	26	9	35	74 : 26
11		4	-78	5.0	26	6	32	81 : 19
12	THF	1.5	0	0.5	44	24	68	65 : 35
13		4	0	0.5	31	20	51	61 : 39
14		1.5	-40	0.5	49	14	63	78 : 22
15		1.5	-78	0.5	0	0	0	
16		1.5	-78	5.0	15	5	20	75 : 25
17		4	-78	5.0	21	9	30	70 : 30

Table II
Glycosylation of cyclohexanol with **2**

Entry	Solvent	AgOTf (v.s. **2**, equiv)	Temp (°C)	Time (h)	Yields and Ratios 4α (%)	4β (%)	4α+4β (%)	α : β
1	CH_2Cl_2	1.5	0	0.5	65	0	65	100 : 0
2		4	0	0.5	53	0	53	100 : 0
3		1.5	-40	0.5	28	24	52	54 : 46
4		1.5	-78	5.0	19	21	40	47 : 53
5	THF	1.5	0	0.5	44	21	65	68 : 32
6		4	0	0.5	42	20	62	68 : 32
7		1.5	-40	0.5	41	19	60	68 : 32
8		1.5	-78	5.0	37	9	46	80 : 20

0 °C β-glycoside is formed (entries 12 and 13) and the amount of β-glycoside decreases at low temperatures (entries 12 ~ 14, 16 and 17). AgOTf is sparingly soluble in CH_2Cl_2 but dissolves completely in THF. As we mentioned in a previous paper,[8] this matter of fact shows the complex formation between the silver ion and THF, and we have proposed that β-glycoside formation was made possible by the low electrophilicity of the *in situ* generated silver complex. Regarding these changes of stereoselectivity, it should be possible to explain these results by the shift of equilibrium between α- and β-oxonium ions (Fig. 1, **IV** and **III**). The earlier reports,[3,4] using glucosyl halide in THF and diethylether, claim that α-glycosides are obtained almost exclusively. On account of the reverse anomeric effect,[9] β-oxonium ion is more stable than the α-anomer. But in the case of D-mannopyranose derivatives having axial allyloxy at *C*–2, steric stability of the onium ion must be decreased, which means high temperatures should result mainly in the formation of α-oxonium ions and therefore lead to β-glycoside. These tendencies are also present in the case of donor **2** (Table II).

Allyl benzyl ether having both olefinic and aromatic properties was used effectively as an inhibitor to avoid complex formation.[8] We have decided to use All_2O, which is inert under glycosylation conditions, as a ligand to reduce the electrophilicity of the silver ion. The results are summarized in Table III and IV. Addition of All_2O increased the β-selectivities in the case of donor **1** (compare entries 3, 7 and 11, Table I with entries 4, 6 and 10, Table III), but this was not the case with donor **2** (compare also entries 1 ~ 4, Table II with entries 1, 3, 4, 6 ~ 9, Table IV) and with both donors in THF as solvent (compare entry 13, Table I with entry 5, Table III and entries 5 and 6, Table II with entries 2 and 5, Table IV). On account of the above mentioned results, the addition of All_2O obviously inhibits allyloxy groups of **1** to form a complex with Ag^+, and the coordination of All_2O to Ag^+ has no effect on glycosylation. Generally, allyl groups change into electron withdrawing groups by complex formation to Ag^+. This should result in a predominant SN2-type mechanism of the following glycosylation reaction. However, in contrast to this, we obtained β-glycoside when a greater amount of All_2O was used. When an intermolecular complex with Ag^+ is formed only at the less crowded 6-*O*-All group, **5** should be a possible result. The through-bond effect,[10] which leads to an increase of β-selectivity in proprotion to the electron donating capacity of the protecting group at *O*–6 in a hexapyranose ring, may be a possible explanation for these results. But we can also expect intramolecular complexes in **1** with 2,6- or 4,6-di-allyloxy as ligands for example, so that the explanation is not completely satisfying. As shown in Table V, proportions of the anomers in the glycosylation of **1** in CH_2Cl_2 vary independently with the ratio (All_2O : AgOTf) and the amount of AgOTf. It is very interesting that the results depend dramatically upon the ratio of All_2O : **1** = 4 (entries 4 and 5).

Table III
Glycosylation of cyclohexanol with **1** in CH_2Cl_2 with All_2O

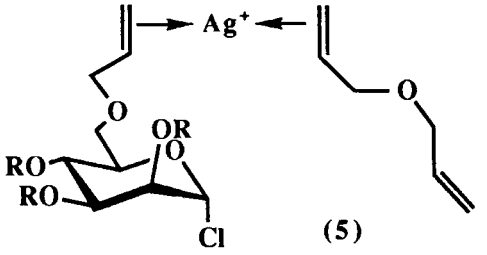
Entry	AgOTf (v.s. **1**, equiv)	All_2O (v.s. **1**, equiv)	Temp (°C)	Time (h)	Yields and Ratios 3α (%)	3β (%)	3α+3β (%)	α : β
1	1.5	3	0	0.5	66	0	66	100 : 0
2	1.5	4	0	0.5	35	17	52	67 : 33
3	1.5	5	0	0.5	33	19	52	63 : 37
4	4	8	0	0.5	30	17	47	64 : 36
5[a]	4	8	0	0.5	33	19	52	63 : 37
6	4	8	-40	0.5	28	23	51	55 : 45
7	1.5	3	-78	0.5	24	19	43	56 : 44
8	1.5	3	-78	5.0	26	18	44	59 : 41
9	4	8	-78	0.5	25	18	43	58 : 42
10	4	8	-78	5.0	28	20	48	58 : 42

a. In THF

Table IV
Glycosylation of cyclohexanol with **1** in CH_2Cl_2 with All_2O

Entry	AgOTf (v.s. **2**, equiv)	All_2O (v.s. **2**, equiv)	Temp (°C)	Time (h)	Yields and Ratios 4α (%)	4β (%)	4α+4β (%)	α : β
1	1.5	3	0	0.5	74	2	76	97 : 3
2[a]	1.5	3	0	0.5	39	18	57	68 : 32
3	1.5	8	0	0.5	64	2	66	97 : 3
4	4	8	0	0.5	57	4	61	94 : 6
5[a]	4	8	0	0.5	42	19	59	71 : 29
6	1.5	3	-40	0.5	33	31	64	52 : 48
7	1.5	8	-40	0.5	33	30	63	53 : 47
8	1.5	3	-78	5.0	27	24	51	53 : 47
9	1.5	8	-78	5.0	29	22	51	57 : 43

a. In THF



(5)

Table V
The effect of All_2O in the glycosylation[a] with **1**

Entry	Table-Entry	AgOTf (v.s. **1**, equiv)	All_2O (v.s. **1**, equiv)	All_2O / AgOTf	α : β
1	---	1	8	8.0	67 : 33
2	III-4	4	8	2.0	64 : 36
3	III-3	1.5	5	3.3	63 : 37
4	III-2	1.5	4	2.7	67 : 33
5	---	2.5	4	1.6	84 : 16
6	III-1	1.5	3	2.0	100 : 0
7	I-1	4	0	0	100 : 0

a. All the reactions were performed at 0 °C, 0.5 h.

Table VI
Glycosylation[a] of cyclohexanol with **1** in CH_2Cl_2 with other additives

Entry	Additives	Ratio (v.s. **1**, equiv)	Yields and Ratios 3α (%)	3β (%)	3α+3β (%)	α : β
1	Collidine	8	0	0	0	
2	Collidine	4.4	13	10	23	57 : 43
3	$MeNCH_2CH_2NMe$	8	0	0	0	
4[b]	$MeNCH_2CH_2NMe$	2	15	15	30	50 : 50

a. Reaction time was 2.5 h, trace amount of glycosides were produced at 0.5 h.
b. All the reactions were performed with 4 equivalent of AgOTf for 0.5 h at 0 °C.

We also examined other additives, for example collidine, which is used as an acid scavenger, and *N,N'*-dimethylethylenediamine (Table VI). These amines were effective to obtain β-D-mannopyranoside (entries 2 and 4). It is reasonable to suppose that these amines act as a ligand for AgOTf like All_2O. They lower the nucleophilicitiy of AgOTf, and in greater amounts, of course, they act as bases, since the results were strongly dependent on the amount of these amines, meaning an exess of them gave no glycosyl products (entries 1 and 3) and the donors remained.

In summary, the application of THF as a solvent in Koenigs-Knorr type mannopyranosylation was found to be effective to obtain β-selectivity, and the steric instability of β-oxonium ions played an important role in the stereoselectivity. The use of All_2O as a ligand to AgOTf was effective to increase the yield when excess amount of AgOTf was used. There is a change in stereoselectivity when the complex formation is inhibited by addition of All_2O, so the amount of β-product is increased. We think that the use of complex type promotor has yet possibilities for improvement by changing the nucleophilicities of protecting groups or additives and this will be an improved glycosylation method.

EXPERIMENTAL

General Methods. Solutions were evaporated under diminished pressure below 50 °C (bath). Optical rotations were measured with a Jasco DIP-4 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded with JEOL PS-100 and FX-90Q spectrometer in $CDCl_3$, respectively. Flash chromatography was performed on Kiesel gel 60 (Merck). Preparative TLC was on Kiesel gel 60HF (Merck).

Standard procedure for glycosylation of cyclohexanol with 1. - To a solution of freshly distilled cyclohexanol (124 mg, 1.23 mmol, 1.5 equiv) in dry THF or CH_2Cl_2 (10 mL) was added, in the dark, dry AgOTf (848 mg, 3.30 mmol, 4.0 equiv) and additives, if needed. Then to the solution kept at the specified temperature was added dropwise a solution of **1** (296 mg, 0.82 mmol) in dry THF or CH_2Cl_2 (4 mL) during 5 min. After 0.5 h or 5 h, the mixture was poured into an ice-cold 1:1 mixture of saturated aq solution of $NaHCO_3$ and NaCl, filterd, and extracted with $CHCl_3$. The residue obtained by usual processing of extract was purified by flash chromatography (hexane-ethyl acetate) to give anomeric mixture (**3α** and **3β**). These mixtures were once separated by preparative TLC and pyhsical constants measured. In the other experiments the ratios of the anomers were caliculated by optical rotations. **4α** and **4β** were obtained from **2** following the same method. **3α**, **3β**, **4α** and **4β** were obtained as syrups.

Cyclohexyl 2,3,4,6-Tetra-*O*-allyl-α-D-mannopyranoside (3α). $[\alpha]_D$ +59.2 ° (*c* 0.99, $CHCl_3$); ^1H NMR δ 6.10~5.69 (m, 4H, 4=CH), 5.40~5.02 (m, 8H, $4=CH_2$), 4.94 (d, 1H, H-1, $J_{1,2}$ = 1.5 Hz), 4.46~3.97, 3.8~3.45 {m, 15H, H-2, 3, 4, 5, 6a, 6b, OCH(cyclohexyl), $4CH_2$}, 2.00~1.06 (m, 10H, cyclohexyl); ^{13}C NMR δ 95.95 (C-1, $J_{C\text{-}1,\ H\text{-}1}$ = 171.4 Hz).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.20; H, 9.08. Found: C, 68.10; H, 9.30.

Cyclohexyl 2,3,4,6-Tetra-*O*-allyl-β-D-mannopyranoside (3β). $[\alpha]_D$ − 44.4 ° (*c* 1.05, $CHCl_3$); ^1H NMR δ 6.10~5.68 (m, 4H, 4=CH), 5.40~5.00 (m, 8H, $4=CH_2$), 4.44 (s, 1H, H-1), 4.42~3.12 {m, 15H, H-2, 3, 4, 5, 6a, 6b, OCH(cyclohexyl), $4CH_2$}, 2.08~1.08 (m, 10H, cyclohexyl); ^{13}C NMR δ 99.07 (C-1, $J_{C\text{-}1,\ H\text{-}1}$ = 154.9 Hz).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.20; H, 9.08. Found: C, 67.93; H, 9.40.

Cyclohexyl 2,3,4,6-Tetra-*O*-propyl-α-D-mannopyranoside (4α). $[\alpha]_D$ +57.1 ° (*c* 1.15, $CHCl_3$); ^1H NMR δ 4.98 (d, 1H, H-1, $J_{1,\ 2}$ = 1.5 Hz), 3.83~3.35 {m, 15H, H-2, 3, 4, 5, 6a, 6b, OCH (cyclohexyl), $4OCH_2$}, 1.95~1.12 (m, 18H, cyclohexyl, $4CH_2$), 0.98~0.87 (m, 12H, $4CH_3$); ^{13}C NMR δ 95.82 (C-1, $J_{C\text{-}1,\ H\text{-}1}$ = 167.7 Hz).

Anal. Calcd for $C_{24}H_{40}O_6$: C, 66.92; H, 10.79. Found: C, 66.64; H, 10.60.

Cyclohexyl 2,3,4,6-Tetra-*O*-propyl-β-D-mannopyranoside (4β). $[\alpha]_D$ − 48.4 ° (*c* 1.15, $CHCl_3$); ^1H NMR δ 4.45 (s, 1H, H-1), 3.81~3.25 {m, 15H, H-2, 3, 4, 5, 6a, 6b, OCH (cyclohexyl), $4OCH_2$}, 2.08~1.23 (m, 18H, cyclohexyl, $4CH_2$), 0.98~0.87 (m, 12H, $4CH_3$); ^{13}C NMR δ 98.89 (C-1, $J_{C\text{-}1,\ H\text{-}1}$ = 152.6 Hz).

Anal. Calcd for $C_{24}H_{40}O_6$: C, 66.92; H, 10.79. Found: C, 66.73; H, 10.74.

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