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Note

Synthesis of 1,2-*cis*- and 1,2-*trans*-glycosides of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose by anomeric O-alkylation

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ABSTRACT

The reaction of a partially protected 1-hydroxy derivative of *N*-acetyl-D-glucosamine with benzyl bromide under conditions of anomeric O-alkylation was studied. It was found that the stereoselectivity of the reaction depended on the nature of the alkali metal cation constituent of a transient ion pair. The substitution of the Li^+ cation for K^+ or complexation with a crown ether allowed the steric outcome to be shifted from β- to α-selectivity.

The anomeric O-alkylation method[1–4] offers a successful alternative to traditional methods of glycoside synthesis, which are based on electrophilic glycosyl donors. A highly nucleophilic anomeric alkoxide anion is formed as a result of the interaction of the corresponding lactol with a base. This anion represents a nucleophilic glycosyl donor and can be alkylated in situ to produce the corresponding glycoside. The feasibility of the use of unprotected or partially protected sugar derivatives is an advantage of this method. The stereochemical results of anomeric O-alkylation were explained[3] using the concept of kinetic and thermodynamic anomeric effects. Because of the higher reactivity of an equatorial β-oxide, equatorial glycopyranosides are predominantly formed under kinetic control (kinetic anomeric effect). On the other hand, if the alkylation reaction occurs faster than the isomerization of the anomeric oxides, axial glycopyranosides are formed predominantly, as the axial oxides usually prevail in the reaction mixture because of the thermodynamic anomeric effect.[5] Furthermore, complexation also affects the stereoselectivity of the glycoside synthesis in some cases where one or another anomeric alkoxide is stabilized due to the chelate effect.[6–9] Unfortunately, chelate complexation apparently does not affect the ratio of anomeric oxides in gluco- and galactopyranose series,[10] which prevents using this effect for changing the stereochemical results of anomeric alkylation.

We have presumed that the control of anomeric alkylation stereoselectivity in the case of 2-amino-2-deoxyglucopyranose derivatives could be ensured by changes in the nature of the alkali metal cation that serves as a counterion for the anomeric alkoxide anion. It was reported[11] that the anomeric O-alkylation of the 2-deoxy sugar derivative in THF in the presence of KHMDS resulted in a highly stereoselective formation of the corresponding α-glycoside. At the same time, when NaH in DMF was used as a base, the mixture of anomeric glycosides with the ratio 1:1 was formed. It seems that such considerable change of stereoselectivity could be connected not only with changing of solvent, temperature, and nature of base, but also with replacement of alkali metal cation. As shown by Beau et al.,[12] the β-stereoselectivity of anomeric alkylation of sodium alkoxides was considerably improved when LiBr was added to the reaction mixture, which was aimed at promoting the solubility of the starting unprotected sugar derivative in DMF. Because NaBr, in contrast to LiBr, is insoluble in DMF, it is conceivable that lithium alkoxide was formed in the reaction mixture as a result of the exchange reaction, which could influence the stereoselectivity of anomeric alkylation.

To test this assumption, we synthesized benzylidene derivative **1**[13,14] (Scheme 1) by the reaction of *N*-acetyl-D-glucosamine with benzaldehyde dimethyl acetal in DMSO in the presence of a catalytic amount of pyridinium perchlorate. The solution of benzylidene acetal **1** in DMF was then treated with lithium (or sodium, or potassium) *t*-butoxide, and the alkoxides obtained were in situ 1-O-benzylated at −30 °C with benzyl bromide. The selective 1-O-alkylation of **1** is possible in these conditions because of higher acidity of the hemiacetal hydroxyl group compared to the other sugar hydroxyls that allows the selective deprotonation of the glycoside hydroxyl.[15]

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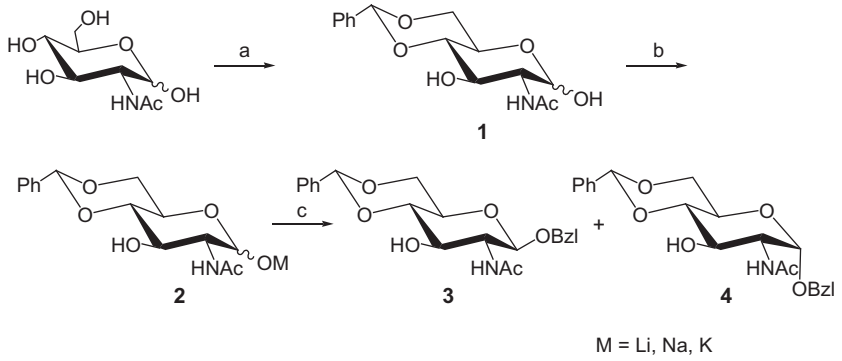

Scheme 1. Reagents: (a) $PhCH(OCH_3)_2$, $Py{\cdot}HClO_4$, DMSO; (b) $(CH_3)_3COM$, DMF; (c) BzlBr, DMF.

Table 1
Anomeric alkylation of **1** with benzyl bromide in DMF in the presence of alkali metal *t*-butoxides

Entry	Base	Volume of DMF per 100 mg of 1 (mL)	Yield[a] (%)	Anomeric ratio[b] (α/β)
1	$(CH_3)_3COLi$	2	74	1:3.3
2	$(CH_3)_3CONa$	2	69	1:2.5
3	$(CH_3)_3COK$	2	73	4.1:1
4	$(CH_3)_3COK$ + 18K6	2	70	13.0:1
5	$(CH_3)_3COLi$	1	74	1:3.0
6	$(CH_3)_3CONa$	1	72	1:3.6
7	$(CH_3)_3COK$	1	72	2.0:1
8	$(CH_3)_3COK$ + 18K6	1	75	10.0:1

[a] Isolated yield after column chromatography.
[b] Anomeric ratio is based on the isolated products.

Table 2
Optical rotation[a] of mixture of anomeric alcoholates **2** in DMF at −30 °C

Entry	Anomeric mixture[b]	Base	Volume of DMF per 100 mg of 1 (mL)	$[M]_{546}^{-30}$
1	A	$(CH_3)_3COLi$	2	−132
2	B	$(CH_3)_3COLi$	2	−132
3	A	$(CH_3)_3CONa$	2	−213
4	B	$(CH_3)_3CONa$	2	−213
5	A	$(CH_3)_3COK$	2	−147
6	B	$(CH_3)_3COK$	2	−147
7[c]	A	$(CH_3)_3COLi$	1	−132
8[c]	B	$(CH_3)_3COLi$	1	−132
9	A	$(CH_3)_3CONa$	1	−213
10	B	$(CH_3)_3CONa$	1	−213
11	A	$(CH_3)_3COK$	1	−147
12	B	$(CH_3)_3COK$	1	−147

[a] Unless otherwise indicated, the optical rotation was measured first at 10 min after reagent mixing and dissolution of base and then after 30, 90 and 240 min. In all cases the value of optical rotation did not change during the period of measurements.
[b] Two mixtures of anomers of **1** were used: mixture A with anomeric ratio 2:3 (α/β) and mixture B with anomeric ratio 3:1 (α/β) (see Section 1).
[c] Because of slow dissolution of lithium *t*-butoxide the first optical rotation was measured at 60 min after reagent mixing and then after 90 and 240 min.

It turned out that the anomeric ratios of the reaction products depended on the nature of the alkali metal (Table 1). The highest β-selectivity was observed with the lithium alkoxide for which the α/β ratio was 1:3.3 (Table 1, entry 1), whereas with potassium *t*-butoxide the stereoselectivity inverted and the benzyl α-glycoside **4** was formed predominantly (α/β = 4.1:1, Table 1, entry 3). An intermediate value of the anomeric ratio was observed in the case of sodium *t*-butoxide. Alkylation of potassium alkoxide of derivative **1** in the presence of an equivalent amount of 18-crown-6 capable of binding effectively the potassium ions resulted in a significant change in the anomeric ratio in favor of α-glycoside **4** (Table 1, cf. entries 3 and 4).

In our opinion, the results obtained can be rationalized using Hammond's postulate and the Curtin–Hammett principle, which allow predicting the ratio of the reaction products in those cases where the reactants form an equilibrium mixture. In as much as the proper application of Curtin–Hammett principle envisages an evidence of equilibrium establishing among reactants, we had been attempting to compare previously the rate of anomerisation of anomeric oxides and the rate of their alkylation. Monitoring of the reaction by TLC had been showing that the completion of the alkylation process required from 17 h (in the presence of $(CH_3)_3COK$), up to 83 h (in the presence of $(CH_3)_3COLi$) (see Section 1). For estimation of rate of glycosyl oxide anomerisation we had been measuring optical rotation of two samples of benzylidene derivative **1** with different anomeric ratios in the presence of alkali metal *t*-butoxide in DMF at −30 °C (Table 2).

As the data of Table 2 suggest, at least at 10 min after reagent mixing, the optical rotation of mixture of anomeric alcoholates of an alkali metal was constant and did not depend on the composition of initial equilibrium mixture. These data confirm significant exceeding of the rate of anomerisation over the rate of alkylation.

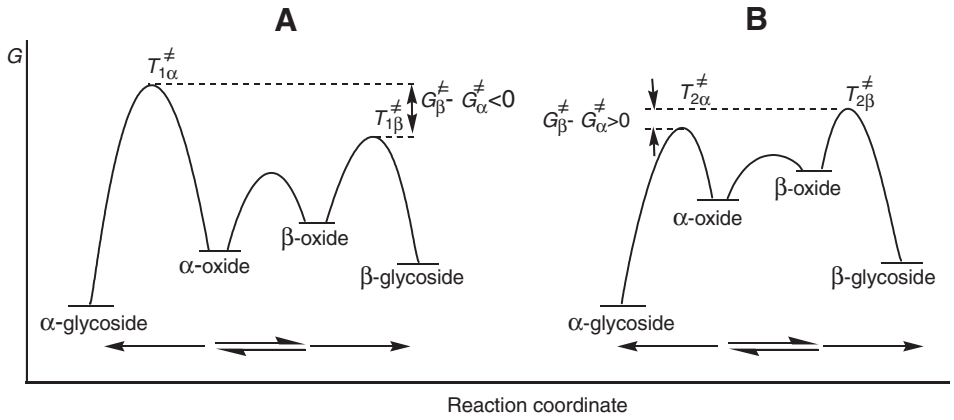

Figure 1. Possible changes in the relative energies of the transition states upon changes in the anomeric oxide reactivities. A – β-selectivity, B – α-selectivity.

Hence, there was enough time for an equilibrium to be established among the reactants; therefore, the Curtin–Hammett principle can be used in this case for forecast of products ratios.

In accordance with the Curtin–Hammett principle, the product ratio is not determined by the equilibrium constant between the reactants, but rather by the difference in the free energies of the corresponding transition states. In the cases where the equatorial (β-) glycoside prevails in the mixture of the anomeric alkylation products, the difference between the energy of the transition state in the reaction of a reactive β-oxide with an electrophile and that of a more stable axial α-oxide, $G_{\beta}^{\neq} - G_{\alpha}^{\neq}$, must be negative (Fig. 1A). On the contrary, in the case of α-selective anomeric alkylation, the energy of the transition state derived from β-oxide must be larger than that for the α-anomer, so that the difference $G_{\beta}^{\neq} - G_{\alpha}^{\neq}$ would be positive (Fig. 1B).

Such a change in the relative energy of transition states, which provides the shift from β- to α-selectivity, probably occurs with an increase in the reactivities of anomeric oxides. Indeed, the increase in the reactivity of reactant leads to the formation of an earlier transition state that is closer in energy to the reactant. This, according to Hammond's postulate, implies that the transition state and the reactant come close together in structure (early, reactant-like transition state). The difference between the energies of the transition states, which are close in structure to the corresponding anomeric oxides, should be close to the difference between the energies of these oxides.

Because in the equatorial β-oxide there is stronger repulsion of the lone electron pairs of the ring oxygen compared to axial α-oxide (two gauche interactions compared to one gauche interaction in the α-oxide), the β-oxide is destabilized and its reactivity is higher than that of the α-anomer (kinetic anomeric effect).[1,15] If the axial α-oxide is more stable than the equatorial β-oxide because of the anomeric effect, the difference between the energies of the transition states $G_{\beta}^{\neq} - G_{\alpha}^{\neq}$ must increase with approximation of the energies of the transition states and the energies of corresponding oxides and the proportion of the α-glycoside in the reaction mixture must also increase.

The change in reactivities of anomeric alkoxides can occur with the change of the alkali metal cation used as a counterion. It is well known that the complexation activity of alkali metal cations appreciably differs in as much as their size, hardness, and Lewis acidity. The greater the Lewis acidity of a cation, the more its complexation activity, and the more tightness of the ion pair that is built of an anomeric alkoxide anion and an alkali metal cation. As a rule, the lithium cation is the most powerful Lewis acid among alkali metals cations and the potassium cation is less powerful than its sodium counterpart.[16] Because a decrease of ion pair tightness corresponds to an increase of its reactivity, the change of the counterion from Li^+ to Na^+ and from Na^+ to K^+ should lead to augmentation of the alkoxide reactivity. Complexation of a cation by a crown ether should contribute to an additional increase in the alkoxide reactivity as such complexation should induce an additional decrease of ion pair tightness.

Interestingly, the stereoselectivity of 1-O-alkylation of derivative **1** depends on concentration of the reactants in the reaction mixture; increasing the concentration, as a rule, contributes to β-selectivity (Table 1, cf. entries 1–4 and 5–8). Apparently, this is related to change of dissociation degree of an ion pair with change of concentration. In more dilute solutions the dissociation degree grows and ion pair becomes less tight and more reactive. It also should be noted, that, in more concentrated solutions, alkylation in the presence of sodium *t*-butoxide was more β-selective than in the presence of lithium *t*-butoxide (Table 1, cf. entries 5 and 6). Probably, this is related to association of lithium alcoholates in more concentrated solutions,[17] which can influence both the energy of anomeric oxides and the energy of corresponding transition states and, as a result, lead to change of difference between the energies of the transition states.

In conclusion, we have shown that the change in nature of an ion pair composed of an anomeric alkoxide anion and an alkali metal cation may serve as an additional effective tool for controlling anomeric O-alkylation stereoselectivity.

1. Experimental

1.1. General methods

Reagents of reagent grade were purchased from standard vendors (Aldrich and Fluka) and used without additional purification. t-Butyl alcohol was distilled over metallic sodium. DMF was dried using azeotropic distillation with benzene with subsequent fractional vacuum distillation. Tetrahydrofuran was dried by boiling under reflux over metallic sodium. Thin-layer chromatography was performed on silica gel STH-1A-coated aluminum foil (Sorbpolimer, Russian Federation). Visualization of spots of carbohydrate derivatives was effected by exposure of TLC plates to chlorosulfonic acid vapor for 5 min at room temperature followed by heating to ~200 °C. Column chromatography was carried out on Silica Gel 60 (Fluka 220–448 mesh). ^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400.49 MHz). The chemical shifts are referred to the signal of TMS (δ_H 0.0). Optical rotation was measured with a Carl–Zeiss Polamat-S polarimeter. Melting points were determined in capillaries and were uncorrected.

1.2. General procedure for the synthesis of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (3) and benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (4) by anomeric alkylation in the presence of alkali metal *tert*-butoxides

An alkali metal (Na, K or Li, 1.68 mmol) was added to *t*-butyl alcohol (6 mL) and the mixture was heated under reflux until the metal dissolved completely. Tetrahydrofuran (3 mL) was added to the solution and the solvents were evaporated at 45 °C with a stream of dry argon to a pasty residue. Tetrahydrofuran was added to, and distilled from, the residue three times. To the synthesized alkali metal *t*-butoxide cooled to −30 °C, a solution of 400 mg (1.29 mmol) of benzylidene derivative **1**,[13,14] obtained after dissolution of **1** in hot DMF (the ratios between 1 and DMF are indicated in Table 1) followed by cooling to the room temperature, was added. The mixture was cooled to −30 °C and benzyl bromide (0.200 mL, 1.68 mmol) was added. After 5 h the reaction mixture was warmed to −20 °C and kept for completion of the reaction (approximately during 12 h in the case of potassium alkoxide and approximately during 78 h in the case of lithium one). To study the effect of crown ether on the anomeric alkylation stereochemistry, we added 18-crown-6 (440 mg, 1.68 mmol) to the reaction mixture before addition of benzyl bromide. The progress of the conversion was monitored by TLC (20:1 $CHCl_3$–EtOH). After completion of alkylation, the reaction mixture was diluted with water (50 mL) and the suspension obtained was stirred for 20 min. After 12 h the precipitate was filtered off, dried, and chromatographed on a column with silica gel using $CHCl_3$→$CHCl_3$–EtOH, 100:4 (v/v) solvent systems followed by crystallization from a dioxane–propan-2-ol mixture. For the yields of anomeric benzyl glycosides **3** and **4** and anomeric ratios, see Table 1.

1.2.1. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside 3

Mp 269–270 °C, lit.[18] 270–271 °C; $[\alpha]_{546}^{18}$ −105.0 (*c* 1.0, Py), lit.[18] $[\alpha]_{D}^{25}$ −89.0 (*c* 0.8, Py); ^{1}H NMR (DMSO-d_6): δ 7.87 (br d, 1H, $J_{NH,2}$ 8.0 Hz, NH), 7.25–7.50 (m, 10H, Ph), 5.62 (s, 1H, PhCH), 5.31 (br d, 1H, $J_{OH,3}$ 4.5 Hz, OH), 4.78 (d, 1H, PhCHb), 4.58 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1), 4.53 (d, 1H, $J_{CHa,CHb}$ 12.5 Hz, PhCHa), 4.24 (dd, 1H, $J_{6b,5}$ 5.0 Hz, H-6b), 3.77 (t, 1H, $J_{6a,6b}$ 10.0 Hz, $J_{6a,5}$ 10.0 Hz, H-6a), 3.54–3.70 (m, 2H, H-2, H-3), 3.46 (dd, 1H, $J_{4,3}$ 9.0 Hz, H-4), 3.37 (ddd, 1H, $J_{5,4}$ 9.0 Hz, H-5), 1.82 (s, 3H, CH_3CO).

1.2.2. Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside 4

Mp 263–264 °C, lit.[18] 263–264 °C; $[\alpha]_{546}^{18}$ +111.0 (*c* 1.0, Py), lit.[18] $[\alpha]_{D}^{26}$ +120.0 (*c* 1.0, Py); ^{1}H NMR (DMSO-d_6): δ 7.96 (br d, 1H, $J_{NH,2}$ 7.5 Hz, NH), 7.25–7.55 (m, 10H, Ph), 5.61 (s, 1H, PhCH), 5.16 (br d, 1H, $J_{OH,3}$ 5.0 Hz, OH), 4.80 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.70 (d, 1H, PhCHb), 4.49 (d, 1H, $J_{CHa,CHb}$ 12.5 Hz, PhCHa), 4.14 (ddd, 1H, $J_{6b,6a}$ 10.0 Hz, $J_{6b,5}$ 5.0 Hz, H-6b), 3.86 (ddd, 1H, $J_{2,3}$ 8.0 Hz, H-2), 3.72 (m, 3H, H-3, H-5, H-6a), 3.52 (ddd, 1H, $J_{4,3}$ 9.0 Hz, $J_{4,5}$ 9.0 Hz, $J_{4,6b}$ 9.0 Hz, H-4), 1.85 (s, 3H, CH_3CO).

1.3. General procedure for determination of optical rotations of mixtures of anomeric alcoholates (2) in DMF solutions at −30 °C

Two mixtures of anomers of compound **1**, different by composition, were prepared. Mixture A, with anomeric ratio 2:3 (α/β) (as determined by ^{1}H NMR in DMSO-d_6) and with optical rotation $[\alpha]_{546}^{20}$ −3 (*c* 1.4, DMF), was obtained by crystallization of **1** from a DMSO–H_2O mixture.[14] Mixture B, with anomeric ratio 3:1 (α/β) (as determined by ^{1}H NMR in DMSO-d_6) and with optical rotation $[\alpha]_{546}^{20}$ +23 (*c* 1.4, DMF) was obtained by chromatography of **1** on a column with silica gel using $CHCl_3$→$CHCl_3$–EtOH, 100:8 (v/v) solvent systems.

An alkali metal (Na, K or Li, 0.84 mmol) was added to *t*-butyl alcohol (3 mL) and the mixture was heated under reflux until the metal dissolved completely. Tetrahydrofuran (3 mL) was added to the solution and the solvents were evaporated at 45 °C with a stream of dry argon to a pasty residue. Tetrahydrofuran was added to, and distilled from the residue three times. To the synthesized alkali metal *t*-butoxide cooled to −30 °C, a solution of 200 mg (0.645 mmol) of benzylidene derivative **1**, obtained after dissolution of anomeric mixture A or B in hot DMF (the ratios between anomeric mixtures and DMF are indicated in Table 2) followed by cooling to the room temperature, was added slowly under dry argon. The mixture was shaken intensively at −30 °C until the precipitate dissolved completely. Data on optical rotation of obtained solutions at −30 °C are shown in Table 2. Unless otherwise indicated (see Table 2), the optical rotation values were measured at first time at 10 min after reagents mixing and dissolution of base and then after 30, 90, and 240 min. In all cases the value of optical rotation was not changing during all the period of measurements.

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