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The Effect of Protecting Groups in the Glycosyl Acceptor on the Stereoselectivity of the Trityl–Cyanoethylidene Condensation: A New Mechanism of 1,2-*cis*-Glycoside Formation

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Based on the effect of protecting groups in the glycosyl acceptor on the stereoselectivity of the trityl–cyanoethylidene condensation a new mechanism of 1,2-*cis*-glycoside formation is proposed.

The effects of protecting groups in a molecule of glycosyl *donor* (particularly of those at C-2) on the stereochemical outcome of glycosylation reactions have been studied in detail.[1] General features of the influence of protecting groups neighbouring the hydroxy group to be glycosylated in a glycosyl *acceptor* on the stereoselectivity of 1,2-*trans*-glycosylation are rather well known as well. Ether groups (usually benzyl) around the hydroxy function promote a high stereoselectivity (and efficiency) of 1,2-*trans*-glycosidic bond formation, that causes their wide application in oligosaccharide synthesis, whereas acyl protections usually decrease the stereoselectivity (for example, *cf.* refs. 2 and 3). This is explained by an increase or decrease of the nucleophilicity of the oxygen atom due to positive or, respectively, negative inductive effects of the protecting groups.[4] However, a direct comparison of various protecting groups has been accomplished only in a few publications[4,5] and systematic investigations of the protecting group influence in a glycosyl acceptor on the stereoselectivity of 1,2-*trans*-glycosylation have not been described so far.

In this communication we report on the effect of protecting groups in a glycosyl acceptor on the stereochemistry of the trityl–cyanoethylidene condensation[6] (Scheme 1).

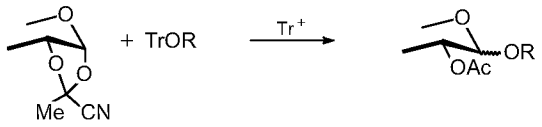
The galactose derivative **1**[7] was used as a glycosyl donor and a series of 3-*O*-trityl ethers of methyl D-glucopyranoside **2**–**4** served as glycosyl acceptors. We also studied glycosylation of the trityl ether **5** with an inverted $^1C_4$ conformation. For the reaction of **1** and **2** we observed recently[8] preferential formation of the α-linked disaccharide **7**.

The trityl ethers **3**, $[\alpha]_D$ +20.3° (*c* 0.4, chloroform), and **4**, $[\alpha]_D$ −9.9° (*c* 0.6, chloroform), were obtained from the known compound **2**[9] by deacetylation and subsequent *p*-nitrobenzoylation or benzylation, respectively. Tritylation of 1,6-anhydro-2,4-di-*O*-benzoyl-D-glucopyranose[10] with triphenylmethylium perchlorate in the presence of *symm*-collidine followed by conventional debenzoylation and acetylation afforded **5**, m.p. 201–202 °C, $[\alpha]_D$ −20.5° (*c* 0.7, chloroform).

Glycosylation reactions were performed in dichloromethane, the ratio **1**:trityl ether:$TrClO_4$ being 1:1.05:0.12. The ratio of β- and α-disaccharides **6**[8] and **7**[8] (in the case of the trityl ethers **3** and **4** the reaction mixtures were analysed after deacylation or debenzylation and subsequent acetylation) or **8**, $[\alpha]_D$ −46.7° (*c* 0.6, chloroform), and **9**, $[\alpha]_D$ +116.5° (*c* 0.5, chloroform), was measured quantitatively by GLC ('Hewlett-Packard 5890' instrument equipped with a flame-ionisation detector and 'Ultra-1' column). The stereochemical results are given in Table 1.

Table 1 Stereochemical results of glycosylation of the trityl ethers **2**–**5**.

Entry	Trityl ether	Disaccharides	α:β ratio
1	**2**	**6** and **7**	1:0.71
2	**3**	**6** and **7**	1:1.8
3	**4**	**6** and **7**	only β
4	**5**	**8** and **9**	1:5



Scheme 1

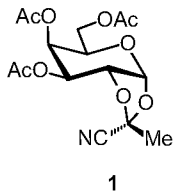
A marked increase of β-stereoselectivity on replacement of acetyl groups by more electron-withdrawing *p*-nitrobenzoyl ones (entry 2) should be noted. Still more pronounced β-selectivity was observed for the bicyclic trityl ether **5** (entry 4). These results cannot be explained, obviously, only in terms of the inductive effect of the protecting groups.

For an explanation of the results obtained we propose a new mechanism of 1,2-*cis*-glycoside formation, which includes the intermolecular dioxacarbenium ion **11** as a key intermediate. The mechanism of the trityl–cyanoethylidene condensation can be outlined as follows. Abstraction of the cyano group by tritylium cation in the first stage leads to the 1,3-dioxolenium ion **10.** Reaction of the latter with the oxygen atom of the trityloxy group affords the normal glycosylation product, 1,2-*trans*-glycoside, Scheme 2, pathway (*a*).

Competitive interaction of **10** with the carbonyl oxygen of the acyl group vicinal to the trityloxy group results in the formation of dioxacarbenium ion **11**, Scheme 2, pathway (*b*). Subsequent intramolecular glycosylation of **11** affords 1,2-*cis*-glycoside. Transfer of the acetoxy group onto the molecule of 1,2-cyanoethylidene derivative with the formation of 1-glycosylacetates was observed as a side reaction in some cases of the trityl–cyanoethylidene condensation.[11] This evidences the possibility of intermolecular nucleophilic participation of acyl groups.

The proposed mechanism allows us to explain the effect of protecting groups on the stereochemistry of glycosylation. For example, replacement of acetyl groups by less prone to participation *p*-nitrobenzoates should suppress the formation of the intermolecular ion **11**. This should cause, in turn, a decrease in the proportion of 1,2-*cis*-glycoside. Indeed, the β-selectivity for **3** was almost 3 times as high as that for the acetylated analogue **2**. The lack of participating protecting groups in **4** completely excludes the pathway (*b*), thus providing stereospecific β-glycosylation.

The conformation of the glycosyl acceptor can also play an important role in the realization of the mechanism discussed. Analysis of molecular models has shown that the formation



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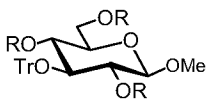
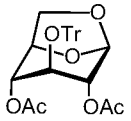


2 R = Ac
3 R = *p*-$O_2NC_6H_4CO$
4 R = $PhCH_2$



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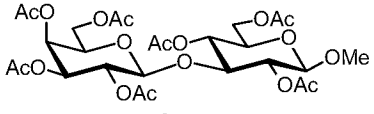

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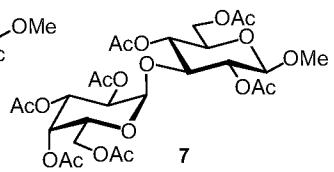

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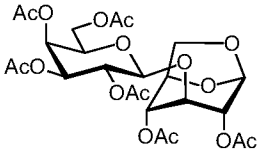

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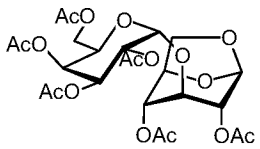

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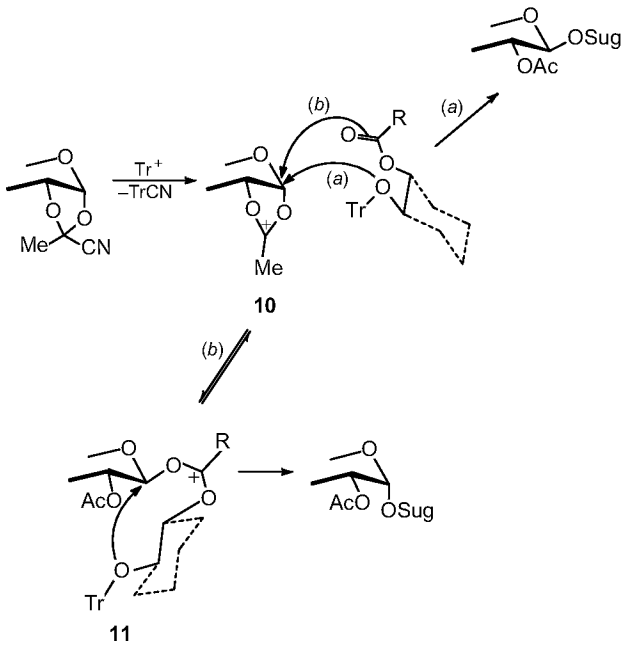

Scheme 2

of the unstrained seven-membered transition state enabling intermolecular glycosylation within the ion **11** is only possible if the dihedral angle between acyloxy and trityloxy functions is *ca.* 60°, *i.e.* on their *trans*-diequatorial or *cis*-orientation. In the case of *trans*-diaxial orientation, as in the trityl ether **5**, the formation of the unstrained transition state is impossible thus preventing the intermolecular glycosylation of **11**. As a result, the β-selectivity of glycosylation of **5** is significantly higher in comparison with the conformational free **2**.

We believe the proposed mechanism can affect, along with other factors such as polar and sterical effects of protecting groups and double stereodifferentiation,[12] the stereochemistry not only of the trityl–cyanoethylidene condensation but of the other methods of 1,2-*trans*-glycosylation as well.

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