Reactivity and selectivity in glycosylation reactions

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Chapter 1

General introduction

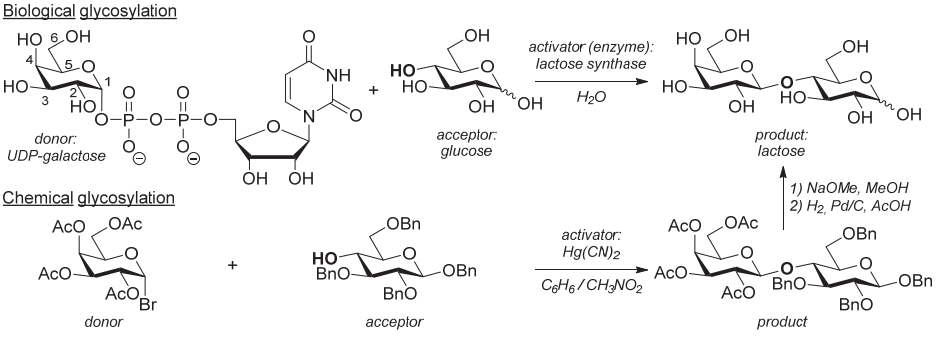
Introduction

Carbohydrates are the most diverse and abundant class of biomolecules on earth, and play important roles in all facets of life, amongst others in cell-cell recognition and activation of the immune system.[1,2] Extracting carbohydrates from natural sources, if available at all, is a tedious and expensive process owing to the complex mixture of similar compounds present. Synthetic chemistry is one of the most important suppliers of well-defined carbohydrates and glycoconjugates, in sufficient quantities and free from contaminants that may interfere with or are detrimental to the activity. However, the assembly of complex oligosaccharides remains a complex task and gaining full control over the stereoselectivity in the crucial glycosylation reaction still is a major challenge in synthetic carbohydrate chemistry. This Thesis investigates the mechanisms of the glycosylation reaction by establishing structure-reactivity-selectivity relationships.

In a glycosylation reaction, a carbohydrate donor is activated to provide an electrophilic species to react with a nucleophilic acceptor molecule (see Scheme 1), which

can be as simple and small as water, or as structurally complex and large as a protein.[3–8] In a chemical glycosylation, the glycosyl donor has protecting groups to temporarily inactivate the reactive carbohydrate alcohol groups and avoid side reactions, and a leaving group at the anomeric (C-1) position.[9,10] This leaving group can be activated by a promotor to make it sufficiently reactive to be substituted by the nucleophilic acceptor, which also bears protecting groups to mask positions where reactions must be avoided. The additional synthetic steps to construct protected building blocks and exchange or remove them can in itself be a monumental undertaking, but one that is often unavoidable due to inherent similarities between the carbohydrate alcohols.[11–15]

Scheme 1. Depiction of a glycosylation reaction: synthesis of lactose through enzymatic and chemical methods.[a]



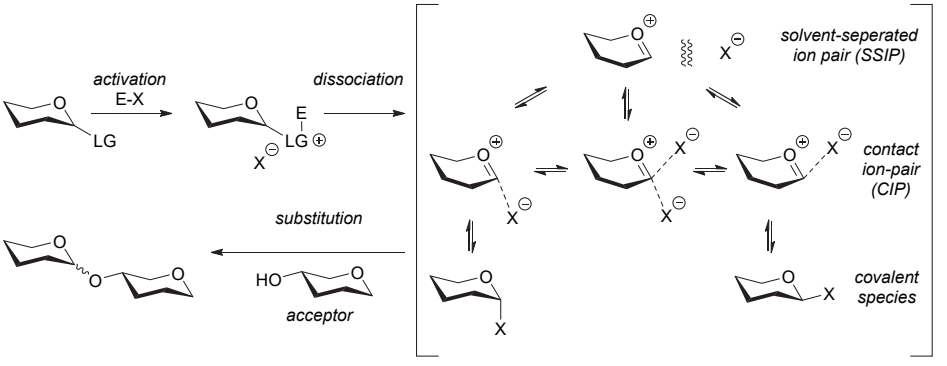
[a]UDP = uridine diphosphate. Numbers indicate the conventional labelling of glycosides. The biosynthetic pathway,[16] and conditions for enzymatic biosynthesis[17] and chemical synthesis[18] are reported in cited references.

The glycosylation reaction mechanism

There is no single general reaction mechanism to describe every chemical glycosylation reaction. For over a century, and especially the past 50 years,[19,20] many new glycosylation protocols have been developed and each of these requires different reagents and reaction conditions. The current mechanistic understanding, which was already formulated and proposed in the 1960s and 1970s,[21–24] centers on the equilibrium between a covalent glycosylating species, in which the anomeric leaving group is attached to the glycosyl donor, and the related ion pairs, in which the leaving group is dissociated from the donor (see Scheme 2). Substitution may take place on any of the intermediate states, with partially dissociated bonds, or in a geometry not generally depicted in a reaction scheme.[25] Although donors may look similar, their behavior in glycosylation reactions

may be very different. Whether a reaction is feasible is determined by many factors, not the least of which are the potential of ionization at the anomeric center, the geometry of the donor when it undergoes glycosylation, and the nucleophilicity of the acceptor.

Scheme 2. General glycosylation mechanism.[a]



[a]LG = leaving group. E-X = electrophilic activator. Donor and acceptor substituents are left out for clarification. The fate of the acceptor proton, donor leaving group and activator is ignored.

Earlier work on chemical glycosylations evolved around (modified) Koenings-Knorr reactions featuring glycosyl halides as glycosyl donors.[20,26,27] When activated and sufficiently reactive, the covalently linked leaving group can be substituted in an S_N2 substitution reaction, or isomerized to the opposite anomer followed by an S_N2 substitution. The intermediacy of the oxocarbenium ion (solvent-separated ion pair, SSIP, Scheme 2) in a glycosylation reaction was largely ignored as it was argued that the lifetime of an oxonium-type ion in water is too short even for solvent equilibration, and for the typical low polarity glycosylation solvents the ion pairs would not separate sufficiently to allow the free oxocarbenium ion to play a role as an intermediate.[28,29] Instead, exploded transition states with elongated bonds or tightly packed contact ion pairs (CIP) were deemed responsible for the interconversion of anomeric halides and some glycosylations.

Donor reactivity: electronic and conformational aspects

A large variety of anomeric leaving groups exists to date, each with its own reactivity and activation scheme.[9,19] Using them in tandem enables orthogonal glycosylation strategies.[30] Chemically similar groups may be distinguished by their reactivity, resulting in chemoselective glycosylations. The difference in reactivity is a result of the cumulative electronic properties, the position and orientation of the ring substituents.[31]

The nature of the anomeric leaving group has a large impact on the outcome of a glycosylation reaction. In general, a better leaving group, for example a glycosyl bromide *versus* a glycosyl chloride, gives a more reactive donor.[20] The higher reactivity can lead to a faster S_N2 substitution, but also a faster anomerisation reaction to provide the opposite anomer. Generally, an equatorially oriented β-anomer, lacking the stabilizing anomeric effect, is more reactive than its α-anomer, which is often the most prevalent species present. The role of the more reactive β-anomer becomes more important when poor acceptors are to be glycosylated.[22,32,33] When better leaving groups such as triflates are employed,[34] the potency to depart is high enough to cause a large degree of S_N2 substitution but also establish a fast equilibrium between various ionic species.

The reactivity of the donor is largely determined by the different protecting and functional groups present, a fact already known for over half a century.[35–37] Inductive effects from electronegative atoms and electron-withdrawing groups destabilize the developing positive charge at the anomeric center upon departure of the leaving group. Ether-type protecting groups (benzyl, methyl, etc.) are less electron-withdrawing than esters (acetyl, benzoyl, etc.) and these are consequently termed "arming" and "disarming", respectively (Figure 1D).[38–40] Removing an oxygen substituent from the carbohydrate ring (e.g. in the common deoxysugars rhamnose and fucose) increases the reactivity of the donor.[41] The configuration of the donor is important as well, with a pattern of hydrolysis reactivity following the order: α-galactose > α-mannose > α-glucose. This trend is in part related to the eclipsing interactions that develop between neighboring substituents, upon the formation of an oxocarbenium ion-type intermediate.[42] More severe torsional strain may be imposed on the system by ring-fusing the carbohydrate ring with another five- or six-membered ring, which makes the system more rigid. The isopropylidene, benzylidene and butane diacetal (BDA) are examples of such torsionally restrained systems (Figure 1A).[43,44] Trans-fused six-membered ring systems such as the benzylidene in **2** are unable to ring flip from their di-equatorial setting to a di-axial constellation: the atoms end up too far apart. Additional eclipsing interactions are developed in the secondary ring, which must now deviate from its preferred chair conformation to conform to the changing geometry associated with the transition to the oxocarbenium ion in the primary ring. These attributes come at the cost of an energy penalty and these fused-ring systems are therefore torsionally disarming. The cyclic protecting groups also severely limit the conformational space of the

oxocarbenium ion (Figure 1C), which is of critical importance to the stereoselectivity of the reaction (*vide infra*).

Besides torsionally disarming the system, cyclic diol protecting groups can also impose electronic effects. The 4,6-*O*-benzylidene system is interesting in this respect, since it fixes the C-6–O-6 dipole such that it is directed away from the anomeric center. This results in the most disarming orientation of the O-6 group: the *tg* rotamer (Figure 1B).[45–47] The relative reactivity of different donors has been investigated by the groups of Fraser-Reid, Ley, and Bols complemented by an extensive study by the group of Wong, and by now a large set of relative reactivity values (RRV) exists (Figure 1D).[38–40,48–59]

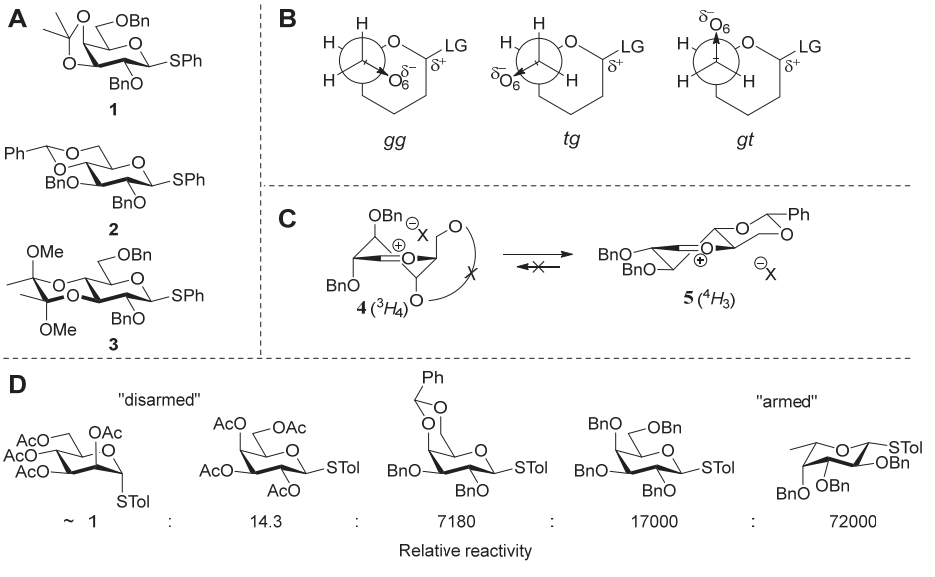


Figure 1. (A) Example structures of isopropylidene, benzylidene, and BDA cyclic protecting groups. (B) Top-view Newman projection of the C-6–C-5 bond, with *gg*-, *tg*-, *gt*-rotamers, the C-6–O-6 dipole is indicated by the small arrow, and partial charges are displayed. (C) Both oxocarbenium ion conformations available for a donor without torsional strain, only the $^4H_3$ conformation is available for benzylidene and BDA structures **2** and **3**. (D) Armed-disarmed principle with relative reactivity values obtained by the laboratory of Wong, relative to tolyl tetraacetyl-1-thio-α-D-mannopyranoside.

Glycosylation stereoselectivity

There are numerous strategies that enable the stereoselective formation of glycosylation linkages, but unfortunately these are often not generally applicable and each new glycosylation presents another challenge. Two types of products can be formed in a glycosylation reaction: 1,2-*trans*- and 1,2-*cis*-linked glycosidic bonds. For the former

type, anchimeric assistance of an acyl-type protecting group on C-2 is usually sufficient to direct stereoselectivity (Figure 2). This form of neighboring group participation is reliable, but its efficiency does depend on the other groups on the carbohydrate ring.[60–64] Double stereodifferentiation (see also next chapter) or severe steric hindrance (as is the case with 4,6-silylidene protected galactopyranosides) may thwart effective neighboring group participation.[65–67]

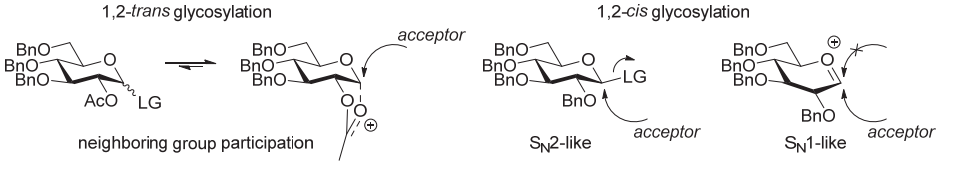


Figure 2. 1,2-*trans* and 1,2-*cis* glycosylation strategies.

1,2-*Cis*-glycosidic linkages are much more difficult to construct and can generally only be affected using a non-participating group at C-2. Several different approaches have been reported to date to install specific 1,2-*cis*-linkages, which for example make use of remote participation,[68–70] site selective delivery of the acceptor, [71,72] steric screening from one of the ring faces by a bulky group[66,67,73], or exploiting the anomeric effect during or after the glycosylation,[74–80] among others.[81–83] From a mechanistic point of view, two pathways may be followed: inverting a 1,2-*trans*-leaving group in an S_N2 reaction, or exploiting the stereoselective addition on oxocarbenium ion-type intermediates in an S_N1 reaction.

Several examples have been reported using the S_N2 directed inversion of a leaving group. For example glycosyl halides can be used. Here, α-halides are generated and an equilibrium is set up with the more reactive β-halide.[22] Substitution of the latter halide then provides the α-product. The same idea applies for other anomeric leaving groups and *in situ* formed anomeric functionalities, such as those formed in the presence of participating solvents, such as DMF, acetonitrile or diethyl ether.[84–86] Inversion reactions also happen when the nucleophile is part of a chimeric activator, as was demonstrated for carboxylic acid and phosphate acceptors on the activation and inversion of trichloroimidates.[87,88]

On the S_N1 side of the reaction continuum, oxocarbenium ions and their associated ion pairs can provide 1,2-*cis*-stereoselective glycosylations. Simple carbocations or oxocarbenium ions have long been regarded as "flat" and unselective but the recent appreciation of the effect of the rich stereochemical environment of (cyclic)

carbohydrate oxocarbenium ions has changed that perspective. The generation of an oxocarbenium ion is preceded by efficient orbital overlap of the ring oxygen's lone pair electrons and the antibonding σ*-orbital of the leaving group. For an axial leaving group the orbitals readily overlap as they have an *anti*-periplanar orientation leading directly to an oxocarbenium ion in a half-chair conformation. The opposite anomer with equatorial orientation must change its conformation first to accommodate efficient orbital overlap (which may occur with *syn*-periplanar arrangement), and will provide a skew-boat conformation.[89–92] These initially formed oxocarbenium ion conformations can be attacked immediately, with or without steric screening from its counter ion. In the absence of an acceptor, or in reactions with poor nucleophiles, the oxocarbenium ion may change to its most stable conformation, which then dictates the stereochemical outcome.

A model system to account for the stereoselectivity of cyclic oxocarbenium ions was devised by Woerpel and co-workers, which was termed the two-conformer model.[93–96] This model assumes that the most stable oxocarbenium ions will have a C-1–O-4/5 double bond and therefore a flat constellation of four atoms (C-2–C-1–O-5–C-5 in six-membered ring pyranoses and C-2–C-1–O-4–C-4 in five-membered ring furanoses). This gives rise to two low energy conformations of a five-membered ring (^3E and E_3) and eight of a six-membered ring ($^3H_4$, $^4H_3$, $^{2,5}B$, $B_{2,5}$, ^3E, E_3, ^4E, E_4) excluding the completely flat geometry. For six-membered rings the $^3H_4$ and $^4H_3$ half-chair conformations are generally energetically most favorable as these have less steric (eclipsing and 1,3-diaxial) interactions than their relatives in the boat and envelope conformations, resulting in two conformations relevant for the stereoselectivity in this model. Central to this model are two possible approaches for the nucleophile: from the top or bottom side, arbitrarily defined for the D-glycosides in the representations in Figure 3. Since furanoses have only a single out-of-plane ring atom, the type of nucleophilic attack is also referred to as inside or outside attack, relating to the concave or convex face of C-3 respectively.[97] Without considering the type of substituents on the furanose ring, two things become readily apparent. Firstly, the incoming nucleophile has eclipsing interactions with the axially orientated substituent on C-2 when performing an outside attack, and 1,3-(*pseudo*)diaxial interactions with the axially orientated substituent of C-3 for the inside attack.

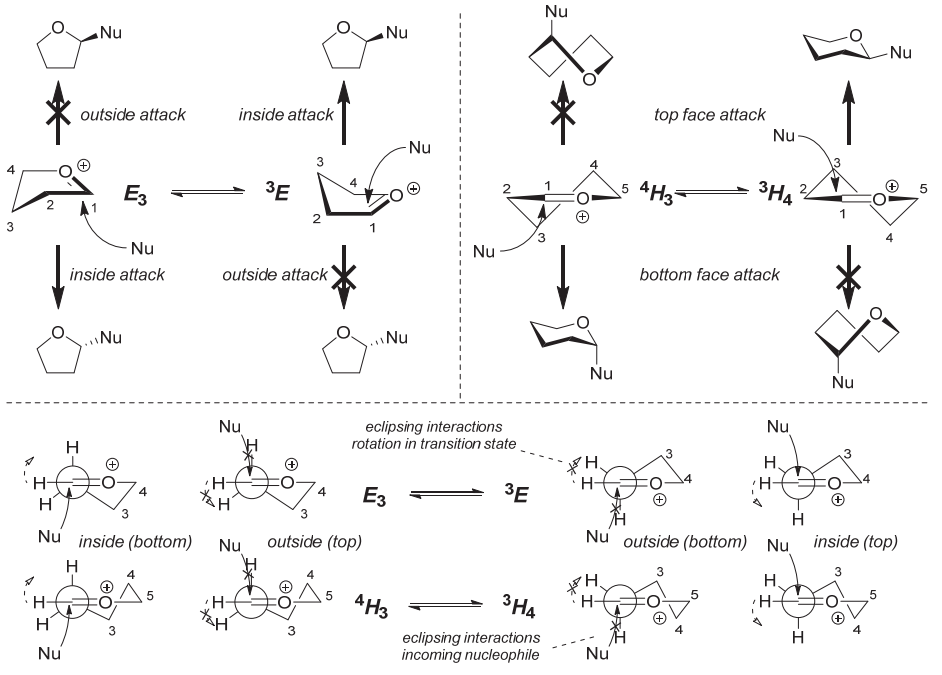


Figure 3. (top) The two-conformer model for furanoses and pyranoses. (bottom) Newman projections along the C-1–C-2 bond visualizing the movement of the nucleophile and equatorial substituents at C-1 and C-2, and consequently the eclipsing interactions that occur, indicted by crossed arrows.

Secondly, rehybridisation of the anomeric center will lead to an eclipsed C-1–C-2 situation upon outside attack, while inside attack will provide a staggered constellation. In the pyranose case, attack on the top face of the $^4H_3$ conformer will change the half-chair conformation to a skew-boat conformation with increasing eclipsing interactions between the *pseudo*-equatorial substituents on C-1 and C-2 in the transition state.[98] Attack from the top face of the alternative $^3H_4$ half chair, or bottom face of the $^4H_3$ however, will lead to a favorable chair conformation, free of eclipsing interactions, and has therefore a lower transition state energy. These arguments dictate the general rules for facial selectivity: in furanosides inside attack will be favorable where pyranosyl oxocarbenium ions will be preferentially attacked on the face that leads to a chair-like, lowest energy transition state.

Having established the face-selective preferences of oxocarbenium ions in the two-conformer model, the next goal was to qualitatively and ultimately quantitatively predict *which* conformation is preferentially formed and attacked. The group of Woerpel has made predictions based on experimental evidence and rationalization of relative (de)stabilization properties of the ring substituents. The individual substituent effects

were gauged by glycosylating allyltrimethylsilane with a series of (partially) substituted furanosides and pyranosides ("stripped-down carbohydrates").[93,94,99–102] In summary, the substituents prefer to occupy a *pseudo*-equatorial orientation to minimize steric interactions with its neighbors when the substituent is an electropositive/neutral group, such as carbon-substituent. When a substituent has an electronegative element bound to the cyclic oxocarbenium ion, which is the case for all carbohydrates, the preference for the orientation of the substituents at C-3 (for furanosides) and C-3 and C-4 (for pyranosides) changes dramatically. By placing them in a *pseudo*-axial orientation the oxygen (or another electronegative element) is brought closer in space to the oxocarbenium ion. In effect, this constellation has a more favorable dipole direction of the C–O bond and electrostatic stabilization from the lone electron pairs on oxygen towards the anomeric center. The preference for a *pseudo*-equatorial orientation of C-2 is enhanced by an electronegative substituent. The decisive effect at play here is the hyperconjugative stabilisation of the *pseudo*-axially orientated C–H or C–C bond, overlapping its σ-orbital with the p- or π^*-orbital of the oxocarbenium ion (a σ-bond of a carbon and an electronegative element is generally a very poor hyperconjugative σ-bond donor). For the C-4 position in furanosides and C-5 in pyranosides, steric and electronic effects strongly oppose each other and the rotation around the C-4–C-5 or C-5–C-6 bond also plays an important role. In general, most stabilization can be effected in the geometry that places the lone pairs on O-6 closest to the oxocarbenium ion anomeric carbon atom (*i.e.* the *gg*-rotamer, see Figure 1B).

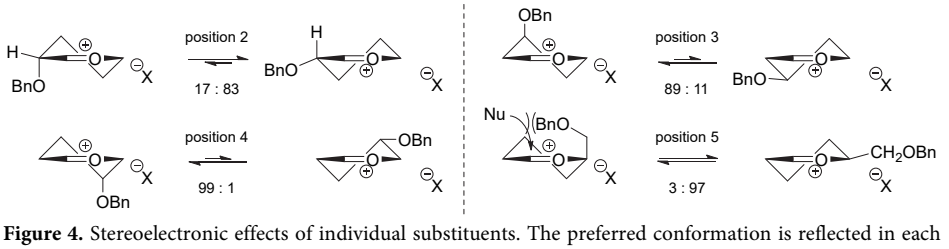


Figure 4. Stereoelectronic effects of individual substituents. The preferred conformation is reflected in each case by the isolated product ratios (given below the equilibrium arrows) of glycosylation with allyltrimethylsilane, based on the inside-attack model.

With this set of preferences Woerpel and co-workers have formulated qualitative selectivity rules, and substantial experimental evidence has corroborated these (Figure 4). In some cases, an axial-rich half-chair conformation may have interfering 1,3-diaxial interactions with the incoming nucleophile, especially with the C-5 position (See Figure 4) and when C-3 has a methyl substituent.[93,100,103] The validity of the two-conformer

model can be called into question when other conformations start to become relevant, including skew-boat and twist structures. A quantitative approach based on Density Functional Theory, predicts the favorable geometries of an oxocarbenium ion based on their relative energies, and their thermodynamic distribution can dictate the stereoselectivity behind the reaction.[104–106] The contribution of unusual conformations and their selectivity are difficult to estimate and quantum mechanical calculations from these structures have yet to give a decisive answer. Ultimately, the energy difference of the transition states leading to the different products and their pre-equilibria in a Curtin-Hammett type scenario are the deciding factors in the reaction outcome.[22,107]

Conclusions

The glycosylation reaction is not just a simple substitution reaction proceeding with either an S_N2 or S_N1 reaction profile. The buildup of positive charge at the anomeric center, a secondary carbon atom, can be sustained by the lone pairs of the ring oxygen atom, but is inductively destabilized by the oxygen ring-substituents. Overall, the intricate balance of stabilizing and destabilizing stereoelectronic effects in the system determines how well the positive charge can be accommodated during a glycosylation reaction. Depending on the nucleophilicity of the acceptor, stronger or weaker electrophilic species may be required for an effective glycosylation. Currently it is impossible to predict, up front, where on the S_N2-S_N1 reaction continuum a glycosylation will take place and deeper insight into the factors that decide this position (reactivity of the activated donor, reactivity of the acceptor, role of the solvent) are dearly needed.

Outline of this thesis

In this thesis several approaches have been undertaken to systematically investigate the glycosylation mechanism. The main focus of the content described here is the origin of the stereoselectivity observed in glycosylation reactions and the constructions of models with a qualitative predictive value. Both reaction partners, the donor and acceptor, are systematically studied. **Chapter 2** provides an overview of the current ideas and findings regarding the reactivity of the acceptor nucleophile. Although many isolated cases have been reported on the influence of the acceptor on the outcome of a glycosylation reaction, a focused study on how to exploit acceptor reactivity has not before been reported. **Chapter 3** introduces a set of fluorinated ethanol-based nucleophiles to serve as model acceptor of gradually decreasing reactivity in a set of well-established model

glycosylation reactions. With the use of this model set it is shown how the selectivity of glycosylations of three types of glycosyl donors changes upon changing acceptor nucleophilicity, as a consequence of a change in reaction mechanism. **Chapter 4** expands on Chapter 3 with a focus on how the stereoselectivitiy of glucosazide-based donors changes depending on acceptor nucleophilicity. Both the reactivity of the donor and of the acceptor have impact on the outcome of the glycosylation reaction selectivity. Whereas the donors in Chapter 4 all had a 4,6-tethering group, in **Chapter 5** a glucosazide with a 3,4-tethering group (a butane diacetal, BDA) is investigated. Although the conformational restraint imposed by the 3,4- and 4,6-tethering protecting groups is similar, it is shown that the different torsional and electronic effects of the groups have a major effect on the glycosylation results. **Chapter 6** provides a systematic approach to establish a first set of relative reactivities for carbohydrate acceptors. Two donors from Chapters 3 and 4 are used as model donors because the stereoselectivity of glycosylations of these donors was shown to strongly correlate with the reactivity of the acceptor nucleophiles. A broad and systematic set of C-4–OH acceptors, varying in benzyl and benzoyl protecting groups, as well as the nature of the C-6 functionality are examined and structure-reactivity-stereoselectivity relationships are established. **Chapter 7** describes the syntheses, of the complete set of diastereoisomeric *ribo*-, *arabino*-, *xylo*- and *lyxo*furanoside donors, modified at the C-2 and C-5 position. These are used in **Chapter 8**, to establish the effect the substituents (C-2–N_3, C-2–F, C-5–CO_2Me) have on the stereochemical outcome of the glycosylations of these donors. The putative oxocarbenium ion intermediates are studied by DFT calculations. **Chapter 9** provides a concise summary of the results of this thesis, as well as an outlook for extended investigations and new paths to take to unravel the details of the glycosylation mechanism.

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