Computational and experimental studies of reactive intermediates in glycosylation reactions

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Chapter 1

General Introduction

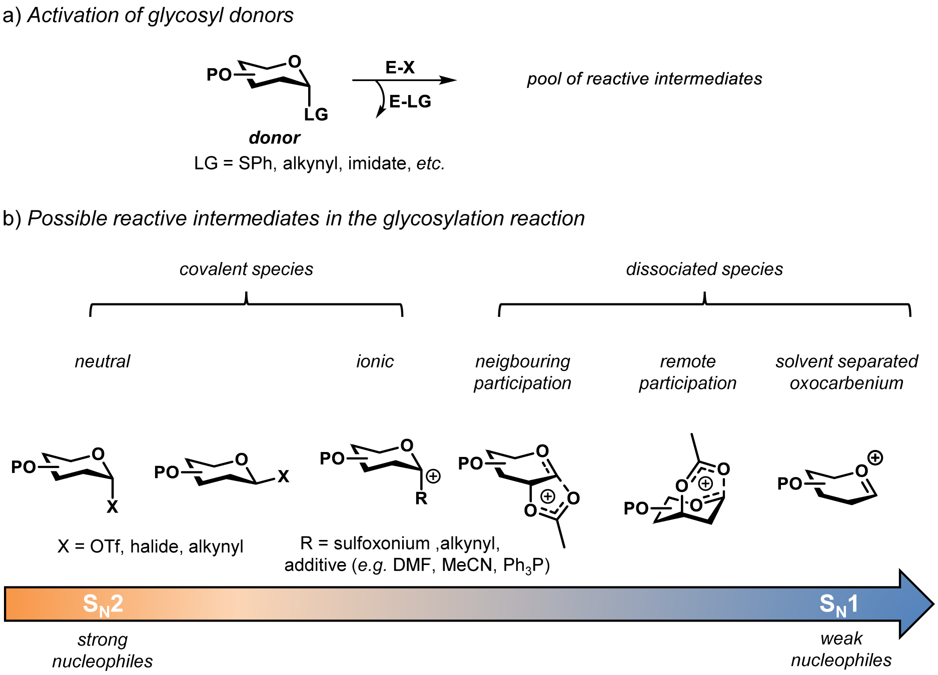
Carbohydrates, along with their derivatives known as glycoconjugates, represent the largest and most varied group of biological molecules found in nature, being present in all life forms. They serve as key structural elements, maintain energy balance, and act as vital signaling agents. Significant research has been devoted to investigate their role in biological processes, unravelling their function in encoding information (informally called the 'sugar code') to be read by enzymatic machinery and receptor proteins.[1–4] While our understanding of the 'sugar code' lags far behind our insight into the genetic code (encoded in nucleic acids), the unsurpassed diversity of carbohydrates (being variable in the configuration of the anomeric linkage, linkage position of the glycosidic bond, ring size, and branching)[5,6] makes it an important biological encoding system. Unsurprisingly, carbohydrates play a crucial role in numerous diseases, such as bacterial infections, cancer, and inflammation. This has spurred the development of carbohydrate-based therapeutics and diagnostics, including antibacterial drugs, cancer treatments, and vaccines.[7,8]

The generation of (complex) saccharides, as therapeutics or biological probes, presents a significant challenge because the isolation of specific carbohydrates in sufficient quantity and purity from complex mixtures is often difficult if not impossible.[9] Therefore, synthetic chemistry is often the method of choice to provide well-defined single molecule carbohydrates and glycoconjugates. However, the synthesis of complex carbohydrates and glycoconjugates remains a difficult endeavor, and currently no general solution exists for the stereoselective formation of all types of glycosidic linkages.[10] The majority of synthetic carbohydrate studies have been product-orientated, and thus much remains unknown regarding the exact reaction mechanisms that play a role in the formation of glycosidic linkages.

This thesis describes a combination of experimental and computational investigations into various reactive intermediates that can form during a glycosylation reaction. The structure and reactivity of possible intermediates is characterized, and the reaction paths involving these species are explored.

General concepts of the chemical glycosylation reaction

The glycosylation reaction in which two glycosyl building blocks are linked together to form more complex (oligo)saccharides is arguably the central reaction in carbohydrate chemistry. The most common approach to chemically create glycosidic bonds is a nucleophilic substitution reaction between a glycosyl donor carrying an anomeric leaving group (delivering the electrophile upon activation), and a glycosyl acceptor containing a nucleophilic alcohol. Glycosidic bonds connecting monosaccharides can either exist as α- or β-diastereomers (anomers) and the principle challenge in forming a glycosidic bonds lies in the stereoselective installation of the desired linkage.[10–13] The current view of the mechanism is described below (Figure 1a). First an anomeric leaving group of a donor glycon is activated by a (Lewis)-acidic promotor (E-X). This activation of the anomeric position leads to a mixture of reactive intermediates, consisting of covalent species, contact ion pairs, and more dissociated ionic species. The stability and reactivity of these species strongly determine which one acts as the dominant reactive intermediate, thereby dictating the reaction mechanism. Covalent reactive intermediates provide more S_N2-like reactions, while more dissociated intermediates give rise to S_N1-like reactions. Both S_N2- and S_N1-like reactions can provide the α- and β-anomers, and the stereoselectivity of the reactions is greatly determined by the nature of the reactive intermediate (Figure 1b). The formation of diastereomeric mixtures is the result of competing reaction pathways and reactive intermediates. Through careful tuning of reaction conditions, donor protecting groups and acceptor nucleophilicity, the pathways can be steered to proceed through a specific reactive species.


a) *Activation of glycosyl donors*

b) *Possible reactive intermediates in the glycosylation reaction*

Figure 1. Current view of the chemical glycosylation: a continuum of competing reaction pathways. a) Activation of glycosyl donor. b) Summary of species that have been observed to act as reactive intermediates in glycosylation reactions.

Covalent intermediates: general concepts

Covalent reactive intermediates react through an S_N2 mechanism, providing a product with inverted stereoselectivity with respect to the reactive intermediate (Figure 2). Under many glycosylation conditions, the configuration of the anomeric leaving group can equilibrate during the reaction. Due to the anomeric effect (the tendency for axial glycosides to be more stable than the corresponding equatorially linked glycosides),[14–16] the α-covalent reactive intermediate is generally the dominant species. Although the α-linked species is usually the sole observed covalent species, it is not necessarily the covalent species through which the glycosylation takes place. If substitution of the α-covalent reactive intermediate (TS-I) is relatively slow, it can isomerize to its β-counterpart, which may then act as the product-forming intermediate (TS-II in Figure 2). For a stereoselective reaction, it is required that equilibration between the α- and β-species (proceeding through TS-III) is rapid (a kinetic scenario that is often referred to as the Curtin–Hammett principle).[17,18] Notable in this regard is the work of Lemieux, who introduced this concept in the use of glycosyl halides in glycosylation reactions.[19,20]

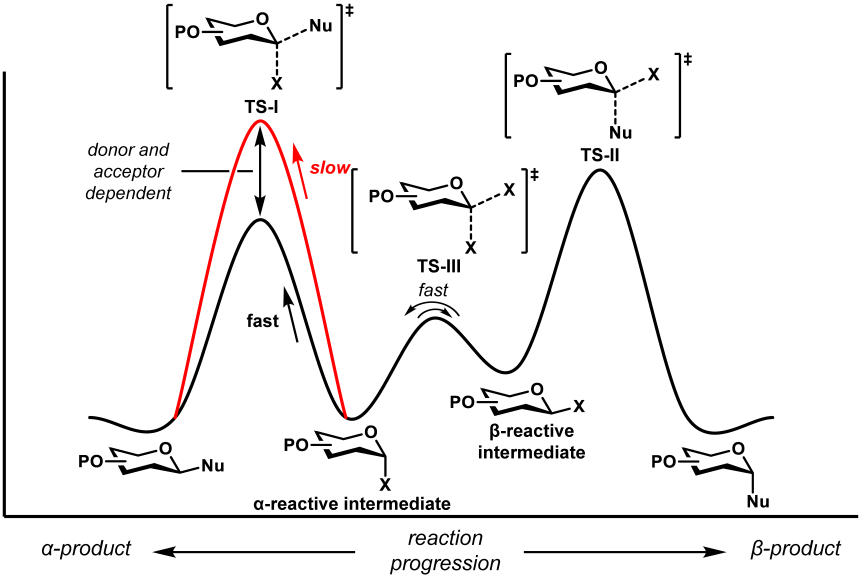


Figure 2. Schematic energy diagram of a glycosylation reaction following a Curtin-Hammett kinetic scenario.

The main requirements for a covalent species to act as a reactive intermediate are the leaving group capacity and lifetime in solution. Potent leaving groups that are commonly installed on the anomeric position include halides, triflates, and sulfonates. Furthermore, many latent leaving groups can be activated to become excellent nucleofuges, including esters, thioglycosides, imidates, alkenyls, phosphites, and hemiacetals. It must to be noted, however, that under conditions that utilize (Lewis-)acids (usually some triflate-type activator), the immediately activated glycoside (*e.g.*, the protonated ester or iodinated thioglycoside) is generally not the predominant reactive intermediate. Instead, an anomeric triflate or an oxocarbenium ion species is formed, which can act as the dominant reactive intermediate. In the sections below, common covalent intermediates are discussed.

Neutral covalent intermediates: glycosyl halides

One of the first described covalent intermediates for glycosylation reactions are the glycosyl halides.[21,22] Glycosyl chlorides and bromides can be readily formed from the anomeric acetate with HX-AcOH[23] or AcX-AcOH[24] and subsequently isolated.[25,26] These can be treated with alcohols under the control of a strong base to yield the product by direct substitution of the halide. Since these conditions are rather harsh, Lewis-acids (*e.g..* $AgCO_3$, Ag_2O, AgOTf, $Hg(CN)_2$) can be used to activate the glycosyl halide. Under these conditions, the more reactive β-halide donor can be formed *in situ*,[19] but also anomeric triflates can be generated. The harsh conditions required to synthesize and subsequently react them makes them less suitable for oligosaccharide synthesis, especially if labile protecting groups are employed.[27]

Glycosyl iodides have also been used extensively.[28] Glycosyl iodides have very limited shelf-life and are therefore generally generated *in situ*. Various conditions have been developed for the *in situ* generation of glycosyl halides (*e.g,.* treatment of glycosyl acetates with trimethylsilyliodide[29], or hexamethyldisilane and molecular iodide,[30–32] or hydrogen iodide).[33,34] The high reactivity of glycosyl iodides makes their use cumbersome, but allows for mild glycosylation conditions.

The most stable glycosyl halides are the glycosyl fluorides. Donors carrying an anomeric fluoride have been known for a long time, but this high stability precluded activation under Koenigs–Knorr conditions. In the search for methods to glycosylate with glycosyl fluorides, Mukaiyama and co-workers were the first to show glycosyl fluorides can be activated in presence of strong Lewis acids (*e.g.,* $SnCl_2$-$AgClO_4$).[35] They can be synthesized by applying a source of fluorine to anomeric acetates, other anomeric halides, hemiacetals, or thio- or seleno glycosides.[21]

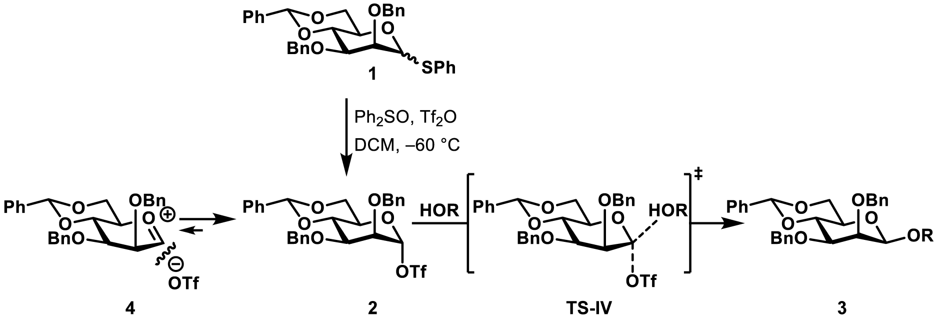
Neutral covalent intermediates: Anomeric triflates

The trifluoromethanesulfonate anion (triflate, TfO^-) is a widely used leaving group in organic chemistry, and glycosyl triflates are central covalent reactive intermediates in glycochemistry. Many popular glycosylation methods either stoichiometrically form an anomeric triflate or generate an intermediate anomeric triflate under catalytic conditions. When anomeric triflates are stoichiometrically formed in the absence of an acceptor (commonly referred to as 'pre-activation conditions') they can be studied with low-temperature NMR.[36] For example, thioglycosysides can be activated with Tf_2O and benzenesulfinyl piperidine (BSP) or Ph_2SO.[37–39] Glycosyl sulfoxides can be treated with Tf_2O and imidates can be activated with stoichiometric amounts of a (Lewis) acid featuring a triflate (*i.e.*, TfOH or TfOTMS). The advantage of these methods is that the reactive intermediate is well-defined, but catalytic *in situ* activation conditions present a more practical workflow. The latter activation mode allows for the donor and acceptor to be pre-mixed, can often be performed at higher temperatures and requires less of the harsh triflate reagent to be used. Glycosyl donors that can be activated by catalytic triflate reagents to drive the reaction include glycosyl imidates, alkynyl glycosides, glycosyl halides, and thioglycosides (which can activated by NIS in combination with a triflate based (Lewis) acid. In the glycosylation reactions employing these methods, the anomeric triflate is generally the dominant covalent intermediate, although other covalent reactive intermediates have been observed.[40–42]

Anomeric triflates have been observed to take up an axial orientation,[36] and one of the most illustrative approaches to use of axial α-triflates to selectively form the β-products is the β-Crich-mannosylation methodology.[43,44] In this glycosylation strategy a 4,6-benzylidene protecting group is installed on a mannosyl donor (as in **1**, Figure 3**)**, to promote the generation of an α-triflate (**2**) and prevent the collapse into a solvent-separated oxocarbenium ion pair. Crich and coworkers have shown these reactions to occur through a S_N2-like reaction to selectively provide β-product **3**.[45] These reactions have been shown to proceed via an 'exploded' transition state (**TS-IV**) in which significant oxocarbenium ion character develops at the anomeric center. The high β-selectivity of these reactions is the result of the 4,6-benzylidene protecting group destabilizing the oxocarbenium ion **4**,[45–47] making the substitution of the α-glycosyl triflate more favorable than formation of the oxocarbenium ion (Figure 3a).

Although the axial α-glycosyl triflate is generally much more stable than its equatorial β-counterpart, the potent leaving group ability and high reactivity of the corresponding anion[48] can allow for the rapid interconversion between the anomers, leading to Curtin–Hammett type kinetic scenarios (Figure 2). In these scenarios the nucleophilicity of the acceptor is of great importance.[49–52] In 2020, the group of Asensio reported an approach to study the β-glucosyl triflate intermediates of a 4,6-*O*-benzylidene-2,3-di-*O*-methyl-glucose donor, combining exchange NMR spectroscopy (EXSY) with kinetic and theoretical experiments. The use of ethanol as an acceptor led to reactions in which the glycosylation reaction to form products **6β** is fast enough to prevent formation of β-glycosyl triflate. They showed that the use of very weak nucleophiles (*e.g.,* hexafluoroisopropanol) enabled the interconversion of the α-glycosyl triflate **5α** and the β-glycosyl triflate **5β**, with the latter more reactive species acting as the glycosylating species, which reacts in a reaction in which significant oxocarbenium ion character builds up, to form product **7α** (Figure 3b). Low-abundant equatorial β-triflates have also been spectroscopically studied by Boltje and co-workers. Using chemical exchange saturation transfer (CEST) NMR techniques that can be used to detect species that are present in lower amounts than can be studied by EXSY experiments, they were able to detect the presence of β-glycosyl triflates of various gluco- and mannosyl donors and establish the rates of their formation.[53,54]

a) The β-Crich mannosylation



b) Summary of the results of Asensio et al.

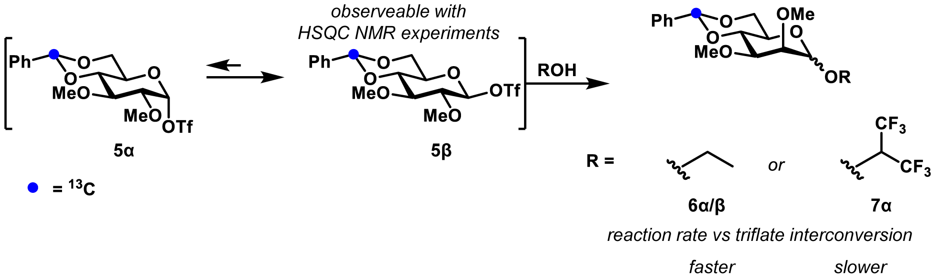


Figure 3. a) Schematic representation of the Crich β-mannosylation. b) Observation of glycosyl β-triflate **5β** and glycosylation kinetics by Asensio *et al.*[55]

Neutral covalent intermediates: other sulfonates.

Other glycosyl sulfonates have also been employed in glycosylation reaction.[56] Following initial work of Schuerch, the group of Bennet has explored the use of glycosyl tosylates. These intermediates are generated from the hemi-acetal and can be readily studied by NMR spectroscopy because of their enhanced stability in comparison to the anomeric triflates. In line with the anomeric triflates, they have been observed to take up an axial α-orientation, favoring the formation of β-products through an S_N2-like substitution reactions.[57] This greater stability requires the use of alkoxides as nucleophiles. Thus, the glycosylation reactions with glycosyl tosylates include a strong non-nucleophilic base such as potassium bis(trimethylsilyl)amide (KHMDS) in the reaction mixture. Early studies mainly focused on 2-deoxy sugars, as the high reactivity of these donors was required to use the relatively weak tosylate leaving group. To achieve stereoselective glycosylation reactions, the sulfonate leaving group must be carefully tuned to selectively form β-linkages in a S_N2-fashion. Especially, when less nucleophilic acceptors are used, the selectivity between the S_N2 and S_N1 pathways depends on both the reactivity and stability of the α-sulfonate intermediate. The group of Bennet observed that along a the series of donors **8-11**, which vary greatly in reactivity (as established by their relative reactivity value),[58,59] the selection of a suitable sulfonyl chloride (**12**-**15**) was of key importance. Disarmed donors require more reactive (electron-poor) sulfonate leaving groups, while more reactive donors require more stabilized, electron-rich sulfonate leaving groups to provide β-selective glycosylation reactions (Figure 4).[60]

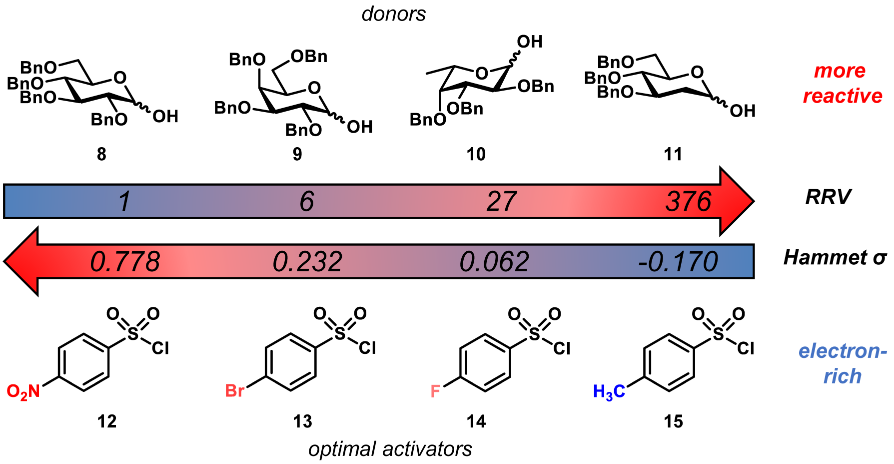


Figure 4. Glycosylation reactions with sulfonate leaving groups can be optimized by tuning the electron-withdrawing character of the leaving group, with more reactive donors requiring more electron-rich sulfonyl chloride activators and *vice versa*. RRV = relative reactivity value.[58,59] Results from Bennet *et al.*[60]

Ionic covalent intermediates: Other covalent ionic intermediates

Besides the anomeric halides and sulfonates, a plethora of other covalent intermediates has been described. For the activation of alkynyl benzoate donors, various gold(I) activators have been used featuring different non-triflate counter ions. [61] In this methodology, a glycosyl donor is equipped with an anomeric *O*-alkynyl group which is activated with a gold(I) catalyst (usually $Ph_3PAuOTf$). The gold coordinates strongly to the alkyne group, activating it and allowing an internal cyclization reaction with the anomeric ester producing a potent leaving group (Figure 5). The 1-glycosyloxyisochromenylium-4-gold(I) intermediate has been identified for a 2-azido-glucopyranosyl *ortho*-hexynylbenzoate donor by trapping the reactive intermediate with vinyl ether.[42] Furthermore, this species has been observed spectroscopically for *ortho*-hexynylbenzoate donor **16** activated with $Ph_3PAuBAr_4^F$ (BAr_4^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). This catalyst features the non-coordinating BAr_4^F anion, which does not form complexes with glycosyl cations. Instead, the glycosyloxypyrylium complex **17** was generated and characterized by 2D NMR spectroscopy.[62] However, under more typical reaction conditions, this complex was not observed. When donor **16** was activated with $Ph_3PAuOTf$ as a catalyst, anomeric triflate **2** was observed spectroscopically. Since the reactions of intermediates **2** and **17** provide similar stereoselectivity, it has been speculated that short-lived oxypyrylium complexes are also relevant reactive intermediates in many gold(I)-catalyzed glycosylation reactions using $Ph_3PAuOTf$ as a catalyst. Likely, both anomeric triflates and oxypyrylium complexes are viable glycosylating species, and which actually participates in a glycosylation reaction depends on the specific reaction conditions, donor and acceptor.

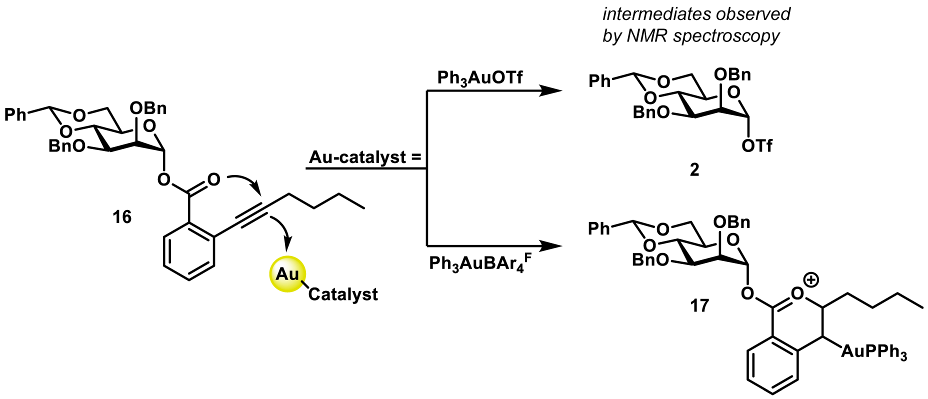


Figure 5. Activation of an *ortho*-hexynylbenzoate glycosyl donor with different Gold(I)-catalysts leads to formation of different reactive intermediates.

Ionic covalent intermediates: modulation by exogenous nucleophiles

The use of exogenous nucleophiles to form reactive intermediates that direct the stereoselectivity of glycosylation reactions, is called ‘modulated glycosylation’ or ‘reagent controlled glycosylation’.[63] This broad definition also includes the use of anionic nucleophiles that form neutral reactive intermediates, notably the halides which are discussed above. Therefore, in this paragraph, solely modulators that form ionic intermediates will be discussed. In this methodology, a donor (**18**) is activated, after which a nucleophilic additive (such as DMF, acetonitrile, or Ph_3P) reacts with the formed oxocarbenium ion or anomeric triflate (**19**) to form a pool of α- (**20**) and β- (**21**) covalent glycosyl reactive intermediates. Depending on the additive and the reactivity of the donor and acceptor at hand, the stereoselectivity of glycosylation can be steered towards the desired products (**22** and **23**) (Figure 6a).

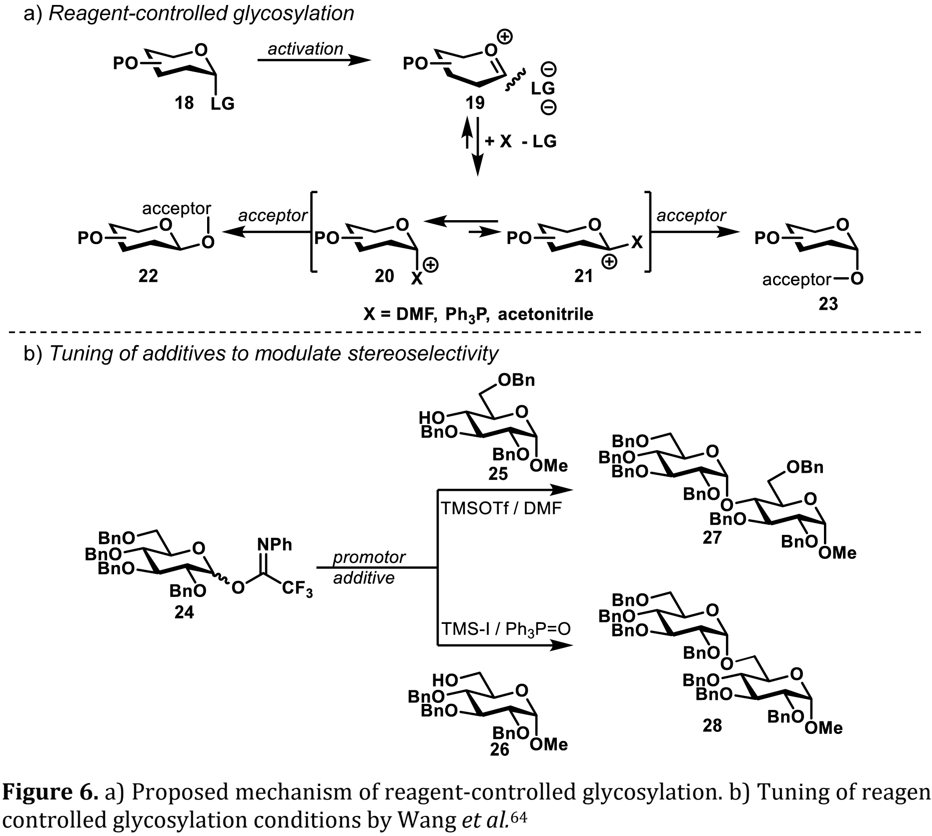


Figure 6. a) Proposed mechanism of reagent-controlled glycosylation. b) Tuning of reagent controlled glycosylation conditions by Wang *et al.*[64]

The first reagent-controlled glycosylations date back to 1973, when West and Schuerch prepared β-glucosyl sulfonium, ammonium, and phosphonium adducts to stereoselectively form α-glycosyl products.[65] However, the most common type of modulation, involves the use of a nucleophilic solvent, such as diethyl ether or acetonitrile, to influence the stereochemical outcome of the glycosylation reaction.[66–71] Notable studies into the formation of nitrilium adducts were conducted by the groups of Sinaÿ,[72,73] and Fraser-Reid.[74]

Furthermore, there has been significant interest in non-solvent modulators. Examples of these nucleophiles include dimethyl acetamide (DMA) by Koto,[75] hexamethylphosphoric triamide (HMPA) and phosphine oxides (R_3PO) by Mukaiyama and Kobashi,[76–78] aryl sulfoxides (Ar_2SO) by Crich,[79] thioethers (RSR′) by Boons[80] and Yoshida,[81] tetrabutylammonium triflate (Bu_4NOTf) by Yoshida and Nokami,[82] methyl(phenyl)formamide (MPF) by Codée,[83] and dimethylformamide (DMF)[84] and *N*-formylmorpholine (NFM) by Mong.[82] The stereoselective outcome of these reagent-controlled glycosylation reactions dependents on the modulator used. Many of these modulators such as DMF and MPF have been shown to provide α-selective glycosylations and likely these reactions adhere to Curtin–Hammett boundary conditions,[17,18] where the α-intermediate acts as a reservoir for the more reactive β-intermediate (Figure 6a).

Although these additives enhance the stereoselectivity of glycosylation reactions, other influences such as acceptor nucleophilicity remain of great importance. Careful tuning of the nucleophilic modulator to the intrinsic reactivity of the acceptor alcohol to match the reactivity of the reactive intermediate with the acceptor reactivity is thus required. An example of modulator-acceptor tuning can be found in the work of Wang *et al*. They reported an additive-dependent stereoselective glycosylation strategy using per-benzylated glucosyl imidate **24**. In this methodology activation with trimethylsilyltriflate and DMF was used to generate α-glucosyl linkages (**27** and **28**) when using secondary acceptor **25**, while for primary acceptor **28** (which in many glycosylations provide β-products[49,51,52]) these linkages were constructed by activation of the same donor with trimethylsilyl iodide in the presence of triphenylphosphine oxide.[64,85,86]

Ionic intermediates: participation

One of the cornerstones of oligosaccharide synthesis is the use of neighboring acyl protecting groups to steer the glycosylation reaction to the desired stereoisomer. Acyl groups enable the formation of bicyclic intermediates.[87] The use of C-2 acyl protecting groups results in neighboring group participation (NGP), by the formation of a bicyclic C-1,C-2 dioxolenium ion intermediate (Figure 7a), which reliably leads to 1,2-*trans* glycosidic bonds.[88,89] Observation of this intermediate by NMR-[90–93] and infrared ion spectroscopy (IRIS),[89,94–96] isolation of orthoester intermediates,[97–100] kinetic studies[101–107] and computational studies,[108–112] leave little room for doubt on the validity of NGP as the mechanism responsible for the 1,2-*trans* steering effect of C-2 acyl groups. In contrast, long-range participation (LRP) of acyl groups from distal positions (*i.e.*, C-3, C-4, and C-6), can enable the introduction of 1,2-*cis* linkages (Figure 7b). The origin and the strength of this stereodirecting effect remains poorly understood and is heavily debated.[87,113–115] Evidence for the occurrence of LRP comes from the stereoselectivity of glycosylation reactions featuring remote acyl groups on the donor glycosides[116–121] and the isolation of cyclic orthoesters.[121–126] Direct observation of bridged cations from remote esters is more sparse than those from neighboring esters, due to the inherent lower stability of the bridged cations. However, since 2019, various studies have been dedicated to detect these bridged cations in both the gas phase, by IRIS,[91,127–129] and in solution by NMR experiments.[53,54,125,130]

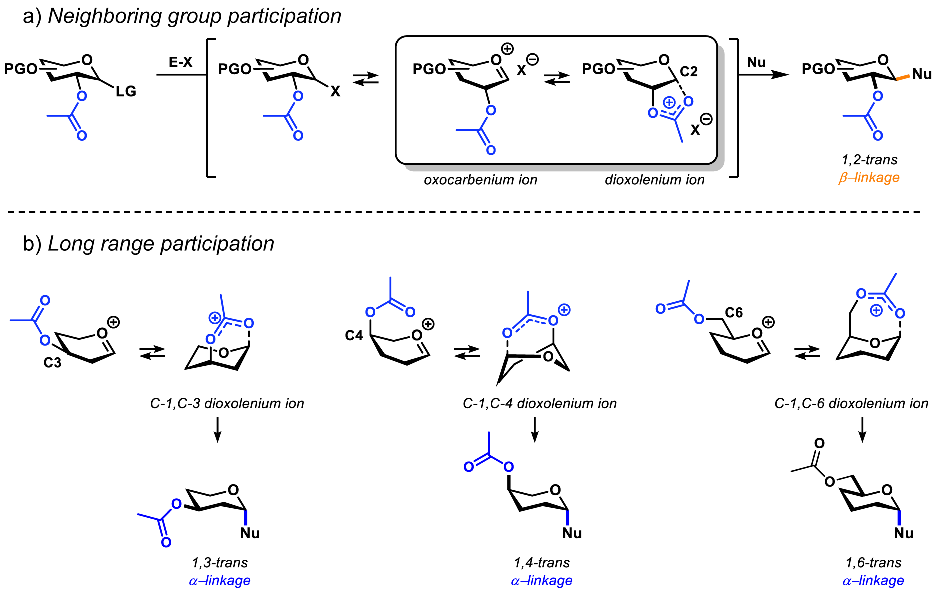


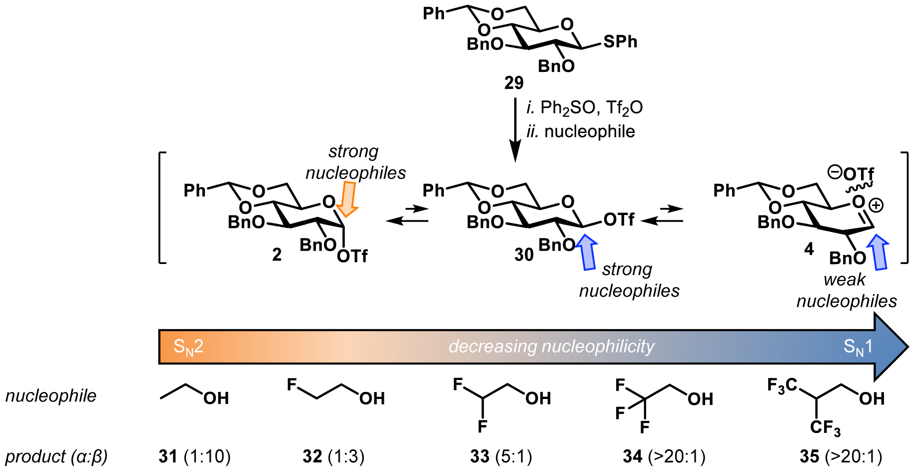
Figure 7. NGP (a) and LRP (b) in glycosylation reactions allow to control the stereoselectivity of glycosylation reactions. Schematic representation of the possible reactive intermediates in NGP and LRP. PG = protection group, E–X = promoter system, Nu = nucleophile.

Ionic intermediates: oxocarbenium ions

Oxocarbenium ions are key reactive intermediates in carbohydrate chemistry. The stability and shape of oxocarbenium ions generated from glycosyl donors is of key importance to the stereochemical outcome of glycosylation reactions.[131] The short life-time of these glycosyl cations represents a major challenge in studying these species. The fleeting nature of glycosyl oxocarbenium ions has generated much debate regarding their role in glycosylation reactions. To further understand this role, much attention has been given to directly observing glycosyl cations. These studies include investigations in the gas-phase using IRIS[94,128] and in super acid media (to stabilize the oxocarbenium) using NMR spectroscopy.[91,93,132]

Oxocarbenium ion intermediates are especially important for glycosylations employing weakly nucleophilic acceptors. Van der Vorm *et al.* have established acceptor structure-reactivity relationships for glycosylations using a series of partially fluorinated ethanol derivates and 2,3-*O*-benzyl-4,6-benzylidene-glucose donor **29**. Using a range of nucleophiles that gradually increase in nucleophilicity, they established that strong acceptors provide β-selective reactions (through intermediate **2**, which was discussed earlier) with donor **29**, while weak acceptors predominantly form α-products (**31**-**35**, Figure 8a).[49,50] Furthermore, these trends were found to be consistent among various different acceptors and for a wide range of donors.[51,52,133–135] The group of Crich, using the same 2,3-*O*-benzyl-4,6-benzylidene-glucose donor systems, has characterized the reaction mechanisms involved in the glucosylation between the strong nucleophilic acceptor isopropanol and donor **29** with kinetic isotope effect (KIE) experiments. By comparing the experimental KIE with computed KIE values, it was concluded that both stereoisomers of the product (**36α** and **36β**) were formed through a reaction mechanism at the S_N2-end of the glycosylation continuum.[45,136] The glucosyl donor was further studied by Asensio and co-workers using the weak nucleophile trifluoroethanol.[55] The KIE of glucoside α-product **28** showed that this product was formed through a dissociative pathway (S_N1-like), suggesting the involvement of discrete short-lived oxocarbenium ion intermediates (Figure 8b). Thus, changing the strong nucleophile isopropanol for the weaker nucleophile trifluoroethanol causes a shift in the reaction mechanism toward a more dissociative process (S_N1-like), as proposed by the group of Codée.[49]

a) *Results and proposed glycosylation S_N1-S_N2 continuum by van der Vorm et al.*



b) *Summary of primary ^{13}C KIE results from Crich et al. and Asensio et al.*

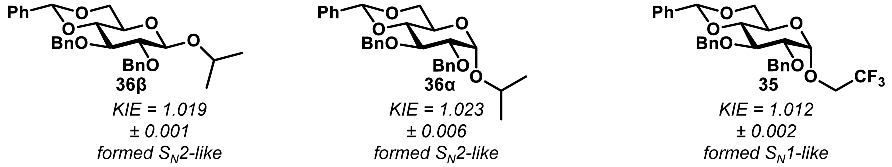


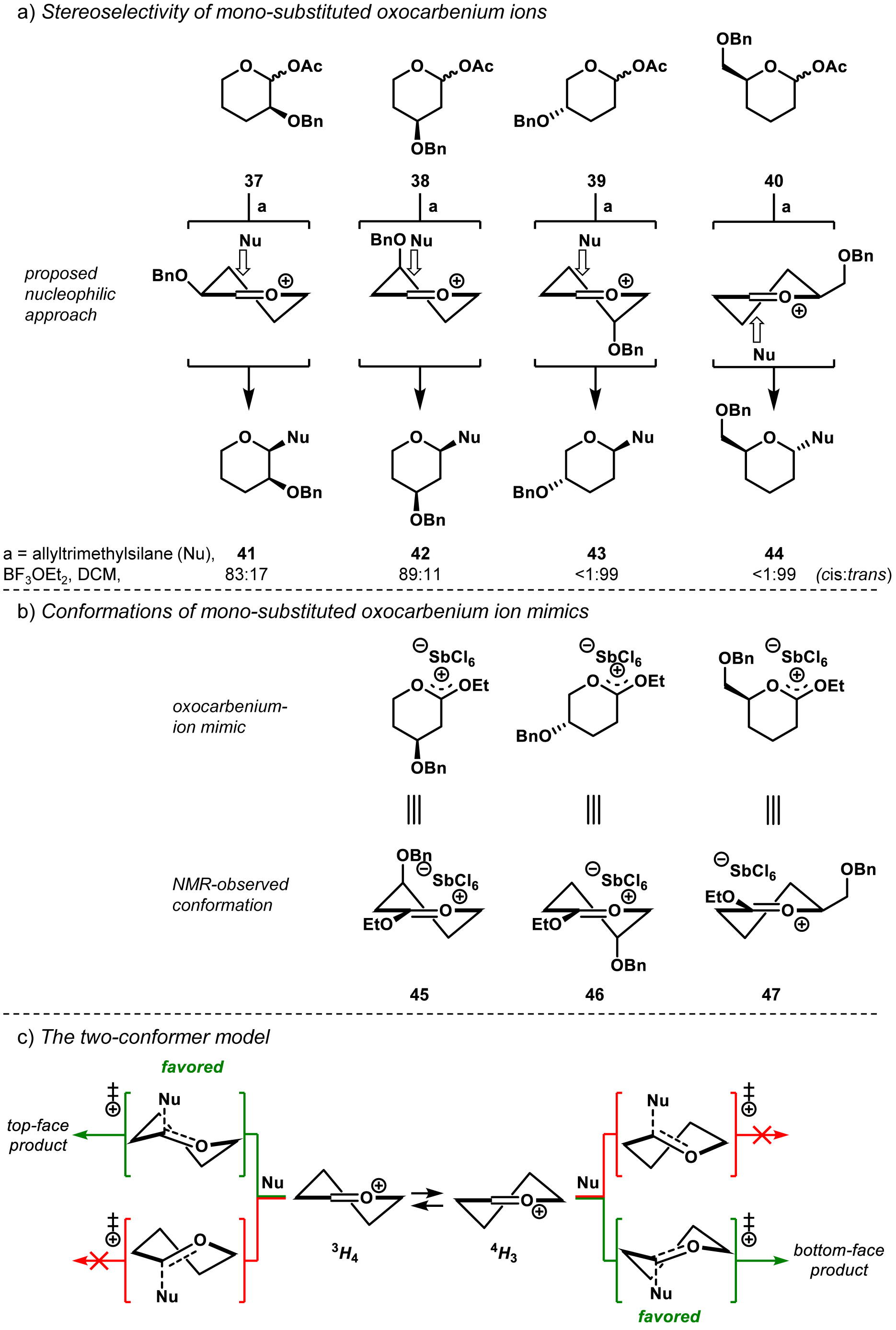
Figure 8. a) Glycosylation stereoselectivity studies of donor **29** by van der Vorm *et al.*[49] and the proposed S_N2-S_N1 reaction mechanism continuum to explain the formation of glycosylation products **31**-**35**. b) A summary of primary ^{13}C kinetic isotope effect (KIE) studies by the groups of Crich[136] and Asensio[55] to characterize the formation of glycosylation products **35**-**36.**

Although oxocarbenium ions have high reactivity, they can react with excellent stereoselectivity. The conformational preference of oxocarbenium ions, and the resulting facial selectivity, is dependent on the substituents present on the carbohydrate ring. To understand how each substituent affects the diastereomeric outcome of reactions involving oxocarbenium ions, the group of Woerpel set out to establish stereoselectivity trends. To this end, they synthesized mono-substituted tetrahydropyran acetals. The stereoselectivity of the corresponding mono-substituted oxocarbenium ions was then determined by activation of the acetals with BF_3•OEt_2 and subsequent trapping of the formed oxocarbenium ion with allyltrimethylsilane. It was observed (Figure 9a) that the C2- (**37**) and C3-OBn (**38**) mono-substituted tetrahydropyran acetals provided predominantly *cis*-products (**41** and **42**). In contrast, the C4-OBn (**39**) and C5-CH_2OBn (**40**) mono-substituted tetrahydropyran acetals formed exclusively the *trans*-products (**43** and **44**). These trends were further substantiated in extensive glycosylation studies using both *C*- and *O*-nucleophiles.[137–143]

To gain insight in the conformation of the formed oxocarbenium ions, and thus understand which species are responsible for the observed stereoselectivity, the group of

Woerpel employed a set of mono-substituted dioxocarbenium ions (**45**-**47**). These compounds, which were generated by alkylation of lactones with Meerwein salts, act as oxocarbenium ion mimics. These dioxocarbenium ion are much more stable than oxocarbenium ions, and they serve as their isolable structural homologues, with conformational preferences that are subject to similar electronic effects. Using NMR-spectroscopy, these mimics were used to gauge the individual substituent preference of oxocarbenium ions. The six-membered ring pyranosyl cations preferentially adopt a $^{3}H_{4}$ or $^{4}H_{3}$ half-chair conformation to accommodate the flat $C_1{=}O_5{}^{+}$ oxocarbenium ion moiety.[139] It was observed that the alkoxy groups on the C3- and C4-positions preferably take up an *pseudo*-axial position, likely due to electrostatic attraction between the electronegative substituent and the positive charge of the oxocarbenium.[139,144,145] In turn, the C5-alkoxymethylene group prefers an equatorial orientation for steric reasons (Figure 9b).[138] For the C2-alkoxy group, oxocarbenium ions mimics were not generated because the steric interaction between the C1 ethoxy group and the C2 substituent would lead to misleading results, since this substituent is not present in the corresponding oxocarbenium ion. However, in computational studies, it has been postulated that the stability of a cation that solely carries a C2-alkoxy group, greatly benefits from positioning it in a *pseudo*-equatorial orientation, likely as the result of hyperconjugative stabilization by the axial $\sigma_{C2\text{-}H2}$ bond.

The combination of the stereoselectivity trends, with the observations of the oxocarbenium ion conformations, led to the formulation of a model for predicting stereoselectivity. Given the observed stereoselectivity, it was reasoned (in accordance with early studies by Robert Stevens[146,147]) that the oxocarbenium ions are preferentially attacked from the same side as the C3 ring atom. Reminiscent of the Fürst–Plattner rule,[148] this addition is favored because it proceeds through a chair-like transition state, while the alternative approach results in a high energy skew-boat like transition state. Thus, the addition to a $^{3}H_{4}$ half chair occurs from the top-face, whereas addition to the $^{4}H_{3}$ half chair leads to the bottom-face product. The half chair conformations ($^{3}H_{4}$ vs $^{4}H_{3}$) adopted by the oxocarbenium ion can be predicted by an examination of the substituents, preferentially positioning C3 and C4-alkoxy groups *pseudo*-axially, while C2-alkoxy and C5-methylene groups are positioned *pseudo*-equatorially. Because the addition reactions to these half-chair intermediates by incoming nucleophiles preferentially follow a trajectory that leads to a chair-like transition state, the stereoselectivity is dependent on these substituents. This model for predicting stereoselectivity is commonly referred to as 'the two-conformer model' (Figure 9a).



a) *Stereoselectivity of mono-substituted oxocarbenium ions*

b) *Conformations of mono-substituted oxocarbenium ion mimics*

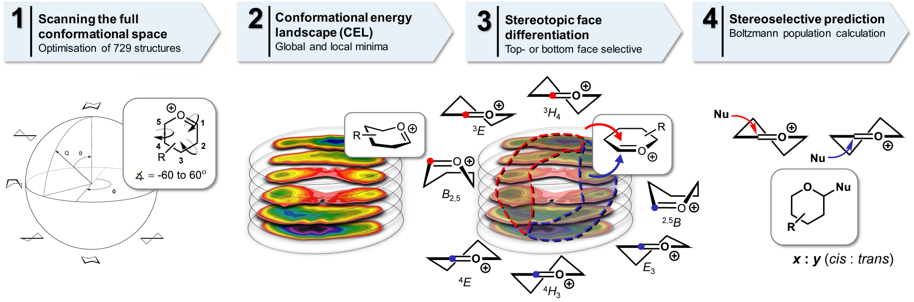
c) *The two-conformer model*

Figure 9. a) Stereoselectivity of glycosylation reactions of mono-substituted pyranosyl cations. b) The conformations of mono-substituted pyranosyl oxocarbenium ion mimics. c) The two-conformer model to predict stereoselectivity of pyranosyl cations.

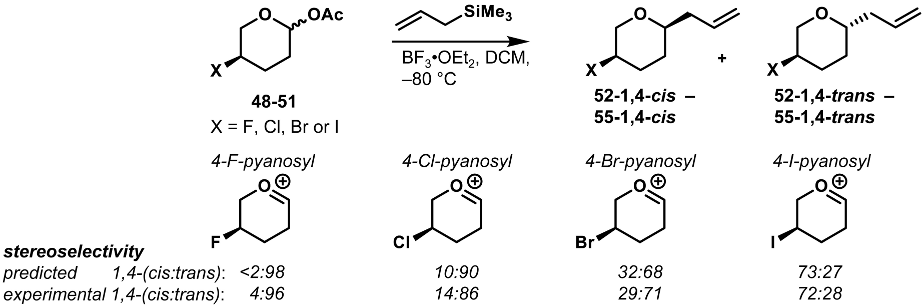
Although these substituent guidelines for oxocarbenium conformational preference can provide much insight, predicting how the combination of different substituents together influence the conformational behavior is not trivial. Therefore computational studies have been undertaken to probe the conformational behaviour.[144] A notable early example of this approach is the extensive work of Whitfield and co-workers on glucosyl, mannosyl, and galactosyl oxocarbenium ions.[46,149–151] To systematically analyze the combined effect of multiple substituents, Hansen *et al.* developed a computational method to study how the stability of pyranosyl cations is affected by the shape that they adopt.[91] This method was originally developed for furanosyl cations by Rhoad *et al.*[152] and further developed by van Rijssel and co-workers.[153–156] In this methodology, the conformational energy landscape (CEL) of the glycopyranosyl oxocarbenium ions is mapped. A CEL map is generated by plotting the energy of the possible conformations on the Cremer–Pople sphere (a spherical representation describing all possible conformations a six-membered ring can adopt). To this end, a set of conformations is generated by scanning the three ring dihedral angles (C1–C2–C3–C4, C3–C4–C5–O5, and C5–O5–C1–C2) from −60° to 60° in 15° increments, to fill the complete conformation space (Figure 10a). The geometry of all these conformers is then optimized, and the associated energies are computed using DFT. The energy landscapes are then visualized in contour plots on “slices” of the pseudo rotational sphere.

Hansen *et al.* observed that for most glycosyl cations, two families of structures are the most relevant. The continuum of (^{3}E, $^{3}H_{4}$, E_{4}, and $B_{2,5}$)-like structures is grouped on the northwest side of the spheres. These structures are likely attacked from the top-face. The “opposite” family of structures, located on the southeast side of the sphere, is composed of the range of (^{4}E, $^{4}H_{3}$, E_{3}, and $^{2,5}B$)-like conformers, which are likely approached by an incoming nucleophile from the bottom-face. The respective top and bottom-face selectivity of these two families is dictated by the preference to form chair-like transition states. The population of the top- and bottom-face selective families could be determined using the Boltzmann equation. For a wide range of glycosyl cations and nucleophiles, it was found these are a measure for the relative stereoselectivity of addition reactions to the glycosyl oxocarbenium ions. For instance, the addition reactions of allyltrimethylsilane to mono-substituted C-4 halogen-substituted oxocarbenium ions (generated from acetate donors **48-51**)[139] provided products **52-55** for which the stereoisomeric ratios were well predicted by the CEL-methodology (Figure 10b). Furthermore, this methodology also extended to fully-decorated carbohydrates. For example, the additions of triethylsilane-*d* to the oxocarbenium ions formed from glucose, galactose, and 2-deoxy-galactose (**56**-**58**) yield α-selective glycosylations. Interestingly, the same reactions on the oxocarbenium ion formed from 2-deoxy-glucose (**59**) yields a mixture of stereoisomers as products (**60**-**63**). These outcomes were predicted by the CELs (Figure 10c). In all, these studies have shown the utility of accurate predictions of the conformational space of oxocarbenium ions in rationalizing the outcome of glycosylation reactions involving oxocarbenium ions.

a) *The conformational energy landscape (CEL) methodology*



b) *Examples of CEL stereoselective predictions of allyltrimethylsilane reactions*



c) *Examples of CEL stereoselective predictions of triethylsilane-d reactions*

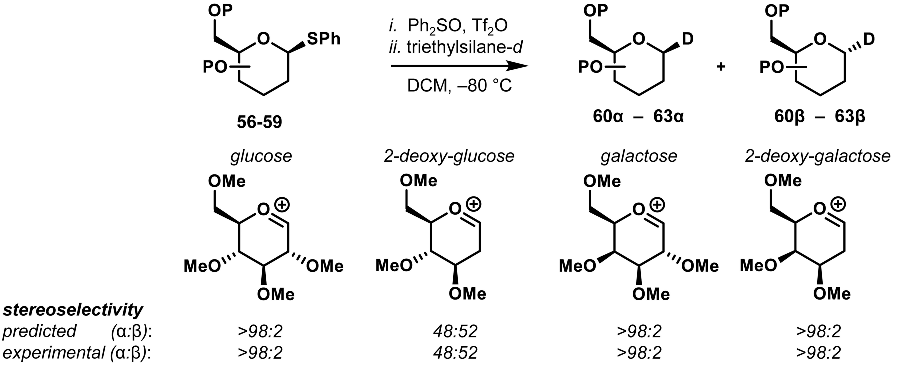


Figure 10. a) Overview of the conformational energy landscape (CEL) workflow to map the conformational and stereoselective preference of pyranosyl oxocarbenium ions. b) Examples of experimentally found stereoselectivities of additions of allyltrimethylsilane to mono-substituted 4-halogen oxocarbenium ions, *versus* CEL-predicted stereoselectivities. c) Examples of experimentally found stereoselectivities of additions of triethylsilane-*d* to glycosyl cations, *versus* CEL-predicted stereoselectivities.

Summary and thesis outline

Reactive intermediates determine the stereoselectivity of glycosylation reactions. The study of these intermediates is hindered by their short-life time, and identifying them and understanding their reactivity remains a major challenge. The research described in this thesis aims to characterize reactive intermediates that shape the stereoselective outcome in glycosylation reactions.

Chapter 2 describes a computational approach to study addition reactions of allyltrimethylsilane to mono-substituted pyranosyl oxocarbenium ions. The activation strain model is used to quantify interactions and structural features that occur in the transition states of the reactions to understand the relative energy barriers of the diastereotopic addition reactions.

Chapter 3 expands on chapter 2 by applying the methodology to oxocarbenium ions formed from glucosyl and mannosyl donors. Computational analyses are used to rationalize the experimental outcome of a pair of *C*-nucleophiles to these pyranosyl cations. It is shown that α-mannosylations occur through unusual boat-like transition states, and the physical factors responsible are elucidated.

Chapter 4 examines neighboring-group participation by C-2 acyloxy groups, through the formation of 1,2-*cis*-fused dioxolenium ions. The influence of nucleophilicity of the incoming acceptor and the electronic properties of the acyl group on the stereochemical outcome of acetal substitution reactions is experimentally and computationally probed.

Chapter 5 investigates long range participation by the 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNPA) protection group. Systematic glycosylation reactions and infrared ion spectroscopy (IRIS) are combined with isotopic labelling of the anomeric carbon to elucidate the nature of the species that are generated upon ionization.

Chapter 6 describes how uronic acid cations can be stabilized by either the C-5 carboxylic acid or a C-4 acetyl group. These glycosyl cations are studied through a combination of computational chemistry and IRIS, showing how the competition between the formation of the C-1,C-5 dioxolanium ion and the C-1,C-4 dioxepanium ion depends on the configuration of the donor glycosides.

Chapter 7 further investigates LRP by investigating the disparate behavior of glycosylation systems involving 3-*O*-benzoyl benzylidene glucosyl and mannosyl donors. This study provides an explanation for the intermediacy of 1,3-dioxanium ions in the mannosyl system and an answer as to why these do not form from analogous glucosyl donors.

Chapter 8 covers the unique reaction pathways of donors carrying a picoloyl protecting group. A set of 3-*O*-functionalized glucosyl and mannosyl donors were synthesized for systematic evaluation by reaction with a series of *O*-nucleophiles differing in hydroxyl acidity. The results provide insights into the complex interplay of acceptor acidity and glycosylation stereoselectivity mediated by the picoloyl protecting group.

Chapter 9 details quantum chemical investigation into the intrinsic competition between the backside S_N2 (S_N2-b) and frontside S_N2 (S_N2-f) pathways using a set of simple alkyl triflates as electrophile in combination with a systematic series of phenols and partially fluorinated ethanol nucleophiles. It is shown how and why the well-established mechanistic preference for the S_N2-b pathway slowly erodes and can even be overruled by the unusual S_N2-f substitution mechanism going from strong to weak alcohol nucleophiles.

Chapter 10 provides a summary of the results described in this thesis, as well as an outlook for further investigations into reactive intermediates, governing the stereoselectivity of glycosylation reactions.

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