ACCOUNTS
of chemical research

Mechanism of a Chemical Glycosylation Reaction

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RECEIVED ON MARCH 1, 2010

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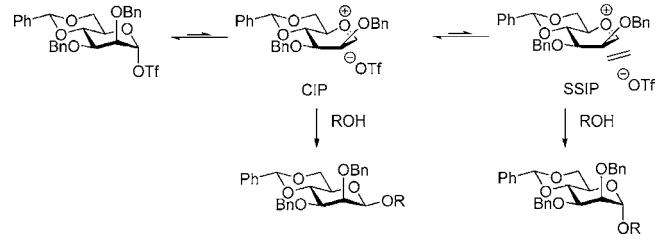


Glycosylation is arguably the most important reaction in the field of glycochemistry, yet it involves one of the most empirically interpreted mechanisms in the science of organic chemistry. The β-mannopyranosides, long considered one of the more difficult classes of glycosidic bond to prepare, were no exception to this rule. A number of logical but circuitous routes for their preparation were described in the literature, but they were accompanied by an even greater number of mostly ineffective recipes with which to access them directly.

This situation changed in 1996 with the discovery of the 4,6-*O*-benzylidene acetal as a control element permitting direct entry into the β-mannopyranosides, typically with high yield and selectivity. The unexpected nature of this phenomenon demanded study of the mechanism, leading first to the demonstration of the α-mannopyranosyl triflates as reaction intermediates and then to the development of α-deuterium kinetic isotope effect methods to probe their transformation into the product glycosides. In this Account, we assemble our observations into a comprehensive assessment consistent with a single mechanistic scheme.

The realization that in the glucopyranose series the 4,6-*O*-benzylidene acetal is α- rather than β-directing led to further investigations of substituent effects on the stereoselectivity of these glycosylation reactions, culminating in their explanation in terms of the covalent α-glycosyl triflates acting as a reservoir for a series of transient contact and solvent-separated ion pairs. The function of the benzylidene acetal, as explained by Bols and co-workers, is to lock the C6−O6 bond antiperiplanar to the C5−O5 bond, thereby maximizing its electron-withdrawing effect, destabilizing the glycosyl oxocarbenium ion, and shifting the equilibria as far as possible toward the covalent triflate. β-Selective reactions result from attack of the nucleophile on the transient contact ion pair in which the α-face of the oxocarbenium ion is shielded by the triflate counterion. The α-products arise from attack either on the solvent-separated ion pair or on a free oxocarbenium ion, according to the dictates of the anomeric effect. Changes in selectivity from varying stereochemistry (glucose versus mannose) or from using different protecting groups can be explained by the shifting position of the key equilibria and, in particular, by the energy differences between the covalent triflate and the ion pairs. Of particular note is the importance of substitutents at the 3-position of the donor; an explanation is proposed that invokes their evolving torsional interaction with the substituent at C2 as the chair form of the covalent triflate moves toward the half-chair of the oxocarbenium ion.

Introduction

The study of the role of carbohydrates and their conjugates in biology is an area of considerable importance and rapid current expansion[1] that is underpinned by the discipline of carbohydrate chemistry.[2,3] The development of improved methods for carbohydrate chemistry and particularly glycosidic bond formation is therefore critical.[4] Ideally such methods are developed rationally; unfortunately, while our understanding of the mechanisms of glycosidic bond hydrolysis, chemical or enzymatic, has reached a high level of sophistication,[5,6] that of chemical glycosidic bond formation[7] leaves much to be desired.[8−11] The kinetics of displacement of anomeric halides by simple amines, alcohols, and thiolates were studied in 1950s and 1960s, when they were shown to be either uni- or bimolecular depending on the

Published on the Web 05/24/2010 www.pubs.acs.org/acr
10.1021/ar100035r

nucleophile and the substrate,[12,13] but very few studies have been conducted with the inclusion of an actual promoter.[14−16] Indeed, according to Green and Ley "much of the evidence used to substantiate proposed interglycosyl coupling mechanisms is anecdotal or circumstantial".[10] Most contemporary thinking revolves around the concept of a series of covalently bound glycosyl donors, which are considered to be in equilibrium with the corresponding contact and solvent-separated ion pairs (CIPs and SSIPs).[17] This concept was first applied by Rhind-Tutt and Vernon to methanolysis reactions of glycosyl halides,[12] was taken up by Lucas and Schuerch,[18] and was extended in the seminal contribution of Lemieux et al.[19]

One reason for the paucity of mechanistic work in the area is the obvious complexity of most glycosylation systems, which require interaction of a donor with an acceptor in the presence of an often insoluble activator or promoter. Our 1997 demonstration[20] that the recently discovered 4,6-*O*-benzylidene directed β-mannosylation reaction,[21,22] employing glycosyl sulfoxide[23,24] donors in conjunction with trifluoromethanesulfonic anhydride, proceeded via the intermediacy of covalent glycosyl triflates provided us with a relatively simple system to study and the opportunity to begin to fill some of the gaps in this important area. In this Account, we summarize our observations on factors affecting the stereochemical outcome of our β-mannopyranosylation reaction and assemble them into an harmonious data set consistent with a single mechanistic scheme invoking covalent glycosyl triflates, contact and solvent-separated ion pairs, and the equilibria relating them.

The β-Mannosylation Reaction

When a 4,6-*O*-benzylidene-protected mannosyl sulfoxide[25] carrying ether-type blocking groups on O2 and O3 is activated with trifluoromethanesulfonic anhydride (Tf_2O) at −78 °C in dichloromethane, followed by the addition of an alcohol, β-mannosides are formed with high yield and selectivity.[21,22,26] In contrast, when the sulfoxide is activated in the presence of the acceptor α-selective reactions are typically observed. While the benzylidene acetal may be replaced by comparable structures, such as boronate esters,[27,28] suitably modified oxathianes in the 6-deoxy-6-thia-series,[29] and, no doubt, silylene acetals, the inclusion of O4 and O6 of the donor in a six-membered ring is critical to the achievement of high β-selectivity: both the absence of such a ring and its expansion by a single carbon atom[30] result in a loss of selectivity (Figure 1).

Subsequently, it was demonstrated that the sulfoxide donors may be replaced by simple thioglycosides[26] of either

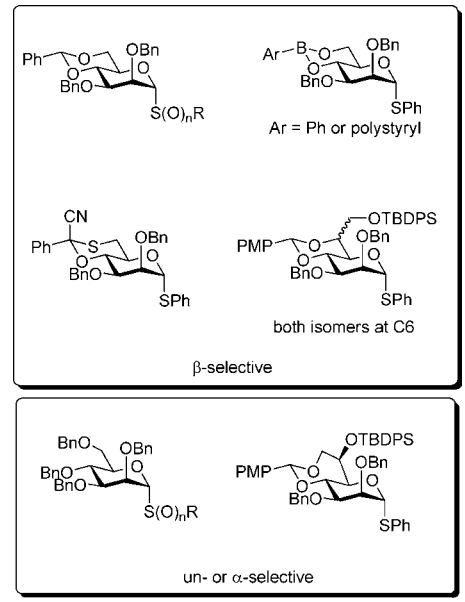
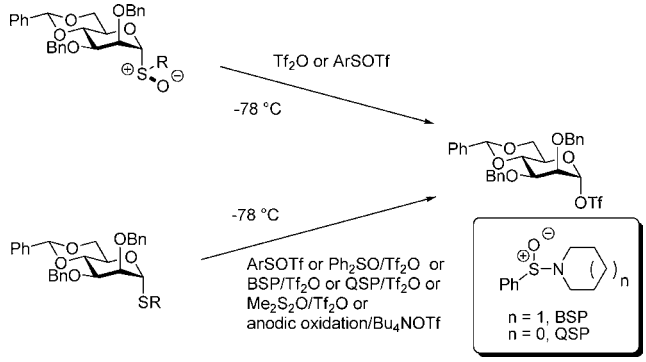


FIGURE 1. Importance of the second ring on β-mannosylation.

anomeric configuration, provided that activation prior to the addition of the acceptor is achieved with Tf_2O in conjunction with a donor, such as the convenient crystalline 1-benzenesulfinyl piperidine (BSP),[31] its more soluble counterpart, preferred for NMR experiments, 1-benzenesulfinyl pyrrolidine,[32] by diphenyl sulfoxide[33] or dimethyl disulfide,[34] or by a combination of *N*-iodosuccinimide and triflic acid.[35] Thioglycosides may also be activated for this chemistry with arenesulfenyl triflates, as we first demonstrated with benzenesulfenyl triflate[26] but for which we now prefer 4-nitrobenzenesulfenyl triflate[36] owing to the commercial availability of the corresponding chloride. The 4,6-*O*-benzylidene-directed β-mannosylation method has been extended to other rapid glycosylation systems including trichloroacetimidates,[37] glycosyl phosphates,[38] and, in conjunction with Tf_2O, 2-carboxybenzyl glycosides and the like,[39,40] to anomeric hemiacetals when activated with a suitable triflate-based system,[33] to pentenyl glycosides when used in conjunction with a selenenyl triflate,[41] and to various other systems.[42,43]

Low-temperature NMR experiments in CD_2Cl_2 led us to propose that activation of the sulfoxide by Tf_2O results in the rapid formation of covalent α-mannosyl triflates[20] and that, on subsequent addition of the acceptor, these are displaced in an S_N2-like manner to give the β-mannosides selectively. Similar NMR experiments demonstrated the formation of the same glycosyl triflates from thioglycosides on activation with benzenesulfenyl triflate,[26] or with the sulfinamides and triflic anhydride.[31] Activation of thioglycosides with 1 equiv of diphenyl sulfoxide and triflic anhydride also affords the glycosyl triflates,[44] but the use of excess diphenyl sulfoxide leads

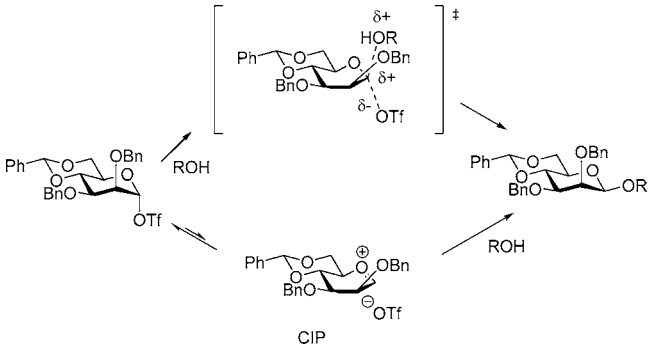
SCHEME 1. Formation of Glycosyl Triflates from Glycosyl Sulfoxides and Thioglycosides



to the more stable *O*-glycosyl diphenylsulfonium salts.[23,45] It has also been shown by NMR spectroscopy that glycosyl triflates may be generated electrochemically from thioglycosides with tetraalkylammonium triflates as supporting electrolyte (Scheme 1).[46]

Adapting Singleton's method[47] for the determination of kinetic isotope effects by NMR, we prepared a donor labeled to the extent of approximately 50% with deuterium at the anomeric position and to a similar extent, as an internal standard, at the benzylidene acetal position; the enrichment being necessary to achieve the signal-to-noise ratios required for precise integration of the spectra. Working with methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside as acceptor, we determined the α-deuterium kinetic isotope effect (KIE) for formation of the β-mannoside at −78 °C in CD_2Cl_2 to be 1.20, which converts to an anticipated value of 1.13 at 25 °C and argues against the intervention of an S_N2 mechanism.[48] We concluded that β-mannoside formation in the system studied proceeds in a dissociative manner or at best through what has been termed an exploded transition state.[5] In such a scenario, the β-selectivity arises from β-face attack on a contact ion pair, which is in dynamic equilibrium with the α-covalent triflate and in which the triflate counterion shields the α-face with which it is closely associated (Scheme 2).

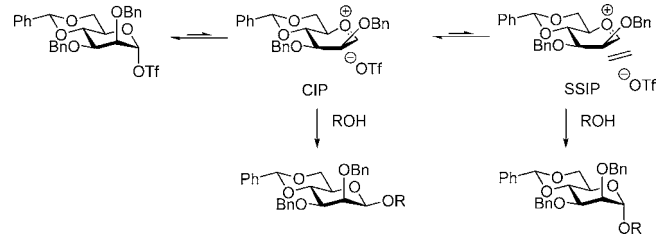
SCHEME 2. Mechanism of the β-Mannosylation Reaction as Determined by KIE Measurements



Origin of the Benzylidene Acetal Effect

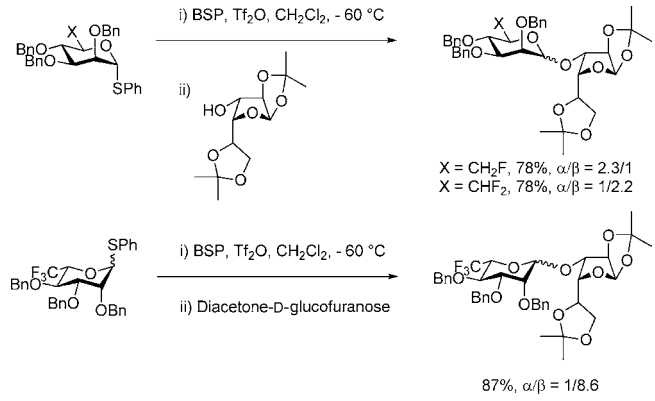
As noted, the benzylidene acetal, or a related six-membered ring, is crucial for the observation of high selectivity; the fully benzyl-protected donors are converted to covalent glycosyl triflates under comparable conditions but give negligible selectivity on subsequent introduction of the acceptor alcohol.[26] Rare exceptions to this rule have been observed and have been attributed to a high degree of stereochemical matching between the donor and acceptor.[49] Fraser-Reid and co-workers had earlier observed that 4,6-*O*-benzylidene acetals had a disarming effect on the hydrolysis of pentenyl glycosides in the glucopyranose series. On the basis of computational studies, they attributed this effect to increased torsional strain in the fused bicyclic system as the chair−chair glycosyl donor collapses to the intermediate chair−sofa oxocarbenium ion, although the exact torsional interaction in question was never specified.[50] Later, Bols and co-workers, still working in the glucose series, identified the major component of the benzylidene effect as being due to the cyclic protecting group locking the C5−C6 bond in the *trans*−*gauche* (*tg*) conformation in which the C6−O6 bond is held antiperiplanar to the C5−O5 bond, thereby maximizing its electron-withdrawing effect on the oxocarbenium ions.[51] In the β-mannosylation reaction, the working hypothesis is therefore that the benzylidene acetal serves to shift an entire series of equilibria toward the covalent triflate, effectively removing the α-selective solvent-separated ion pair (SSIP) from consideration (Scheme 3). In the case of the perbenzyl system, the C5−C6 bond is freely rotating and so O6 exerts less of an electron-withdrawing effect. Accordingly, the oxocarbenium ions are less-destabilized, and there is a subtle shift in the position of the covalent triflate−CIP−SSIP equilibria in favor of the latter, resulting in the observed loss of selectivity.

SCHEME 3. Working Hypothesis for β-Mannosylation



This hypothesis led us to investigate the 6-deoxy-6-mono-, 6,6-difluoro, and 6,6,6-trifluoro systems with the anticipation that increased fluorine content would lead to increased β-selectivity as was indeed found to be the case (Scheme 4).[52] In a similar manner, the use of electron-withdrawing but nonparticipating protecting groups for O2 in a series of 3,4-di-*O*-

SCHEME 4. Effect of Fluorination at the 6-Position on Mannosylation Stereoselectivity

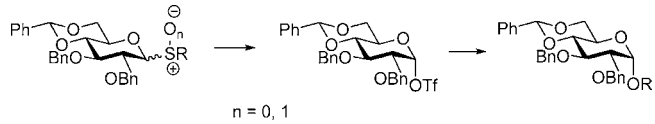


benzyl rhamnopyranosyl and 3,4,6-tri-*O*-benzyl mannopyranosyl donors increases β-selectivity over that seen with the corresponding 2-*O*-benzyl ethers.[53]

The Glucose/Mannose Paradox

The simplicity of our working hypothesis for β-mannosylation, which hews closely to the general Vernon–Lemieux glycosylation mechanism, was upset by the observation that the 4,6-*O*-benzylidene-protected glucopyranosyl donors, while proceeding via the α-glucosyl triflates, were α- rather than β-selective (Scheme 5).[54,55]

SCHEME 5. α-Selective Glucopyranosylation Reactions



To probe this paradox, we studied the 2- and 3-deoxy systems and found a loss of β-selectivity in the mannose series and of α-selectivity in the glucose series (Figure 2).[56] While we choose not to overemphasize these results on the basis of the more highly armed nature of the donors, particularly for the 2-deoxy series, they did suggest a role for the C3–O3 bond

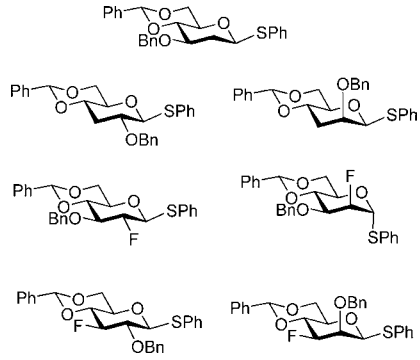
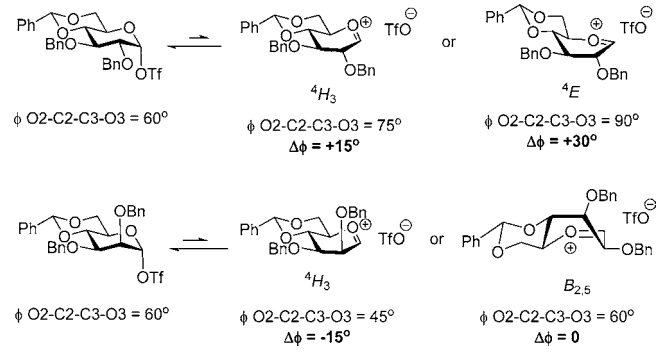


FIGURE 2. Deoxy and deoxy-fluoro donors exhibiting reduced selectivity.

as well as for the more obvious C2–O2 bond in these reactions. To escape from the more armed nature of the deoxy systems, we undertook the synthesis of four deoxy-fluoro donors and were surprised to find a continued loss of selectivity in both the gluco and manno series (Figure 2).[57]

Clearly, in both the typical β-mannosylation and α-glucosylation processes the role of O2 and O3 is more than one of a simple electron-withdrawing group, although this aspect certainly cannot be ignored. We conclude that the dominant interaction is a torsional one between the O2 and O3 groups. Thus, in the benzylidene-protected mannopyranose series, as the α-covalent triflate collapses to the oxocarbenium ion, the O2–C2–C3–O3 torsion angle is compressed from 60° to 45° if the $^4H_3$ conformation of the oxocarbenium ion is adopted or remains unchanged at 60° if the alternative $B_{2,5}$ conformation predominates (Scheme 6). On the other hand, in the glucose series, as the covalent triflate fragments to the oxocarbenium ion and the chair conformation of the pyranose ring is transformed to either the envelope or the sofa, the O2–C2–C3–O3 torsion angle opens up (Scheme 6).[57] It has to be noted that in the oxocarbenium ion, the O5–C1–C2–O2 torsion angle is the same in the glucose and the mannose series, albeit opposite in sign, at least for the most likely half-chair conformer, indicating that the main effect is not one of differing interactions of the C2–O2 dipole with the oxocarbenium ion.

SCHEME 6. Evolution of the O2–C2–C3–O3 Torsion Angle on Formation of the Oxocarbenium Ion in Glucose and Mannose



We conclude that in the mannose series the oxocarbenium is destabilized compared with the glucose series (Figure 3) resulting in the covalent triflate–CIP–SSIP equilibria favoring the covalent triflate to a greater extent in mannose. This has the effect of diminishing the concentration of the CIP and so of the SSIP in the mannose series resulting in high β-selectivity. In glucose, there is a small shift in the equilibria away from the covalent triflate, resulting in a sufficient concentration of the SSIP for it to dominate the chemistry and for the reaction to be α-selective.

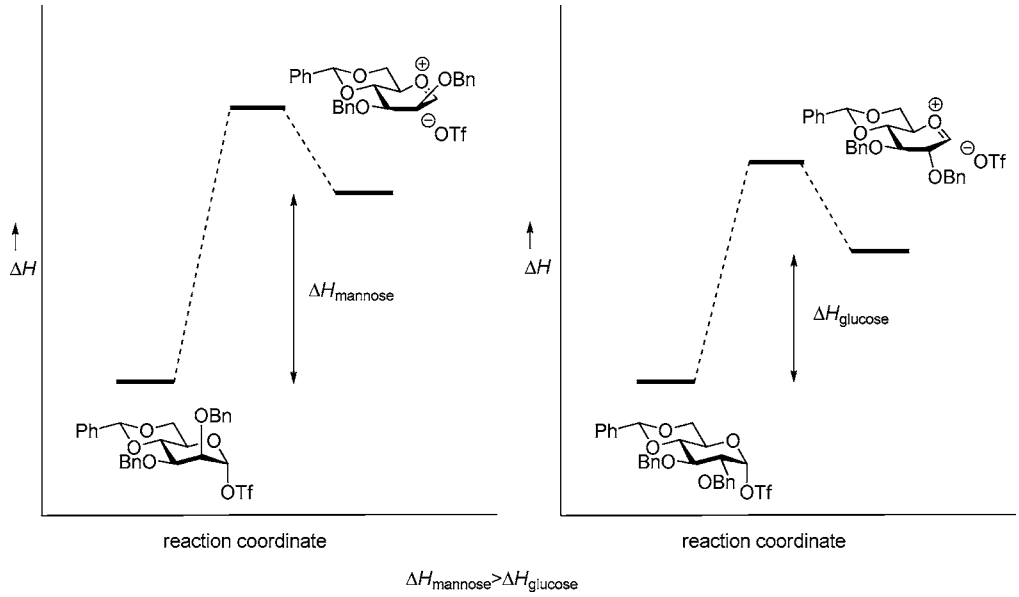
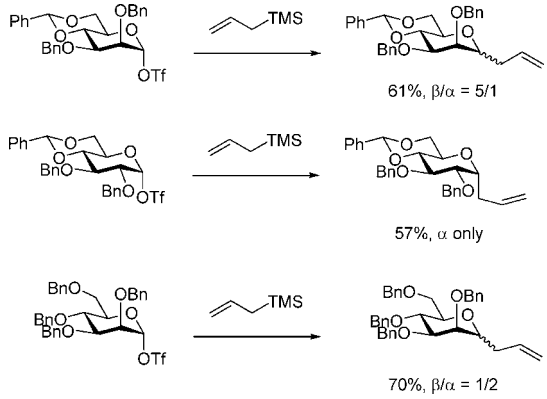


FIGURE 3. Reaction coordinates for oxocarbenium ion formation in mannose and glucose.

C-Glycosides

Carbon-based nucleophiles, allyl silanes and stannanes, and silyl enol ethers behave in the same manner as alcohols in their reactivity toward 4,6-*O*-benzylidene-protected mannopyranosyl and glucopyranosyl triflates. Thus, these nucleophiles are predominantly β-selective with the benzylidene-protected mannosyl donors, and predominantly α-selective with the corresponding glucopyranosyl donors.[58] Not surprisingly therefore, with a tetra-*O*-benzyl mannopyranosyl triflate the same carbon nucleophiles give anomeric mixtures of *C*-glycosides (Scheme 7). The close parallels between the *O*- and *C*-glycoside series, point to a commonality of mechanism in the two cases and strongly argues against any mechanism involving donor−acceptor hydrogen bonding[11] in the formation of the *O*-glycosides.

SCHEME 7. Stereoselectivity of *C*-Glycoside Formation Mirrors That of *O*-Glycoside Formation



2,3- and 3,4-*O*-Carbonates

In keeping with the mechanistic hypothesis the use of electron-withdrawing protecting groups likely to destabilize any anomeric oxocarbenium ions should be expected, absent neighboring group participation, to lead to enhanced β-selectivity. The 2,3-*O*-carbonates were attractive in this respect; moreover, they had been previously described as promoting β-selective mannosyl and rhamnosylations for reactions conducted with glycosyl bromide donors by the insoluble silver salt method.[59,60] However, working in the rhamnopyranosyl and 4,6-*O*-benzylidene-protected mannopyranosyl series, thioglycoside-derived glycosyl triflates were found to be extremely α-selective.[61,62] The same thioglycosides activated with insoluble silver salts were β-selective, while the corresponding mannosyl bromides were α-selective when activated in dichloromethane with the soluble silver triflate. Therefore, the origin of the β-selectivity previously reported with 2,3-*O*-carbonate-protected α-manno and rhamnopyranosyl bromides is clearly the heterogeneous nature of the reactions.[62] The α-selective glycosylations observed with the same donors in the solution phase is best interpreted as a destabilization of the intermediate glycosyl triflates or bromides with respect to oxocarbenium ion owing to the approximate half-chair conformer imposed on the covalent triflates and bromides by the *cis*-fused carbonate. In effect, the presence of the cyclic carbonate reduces the O2−C2−C3−O3 torsion angle, as observed crystallographically in the thioglycosides,[63,64] and thereby reduces the energy penalty that has to be paid to access the oxocarbenium ion (Figure 4).

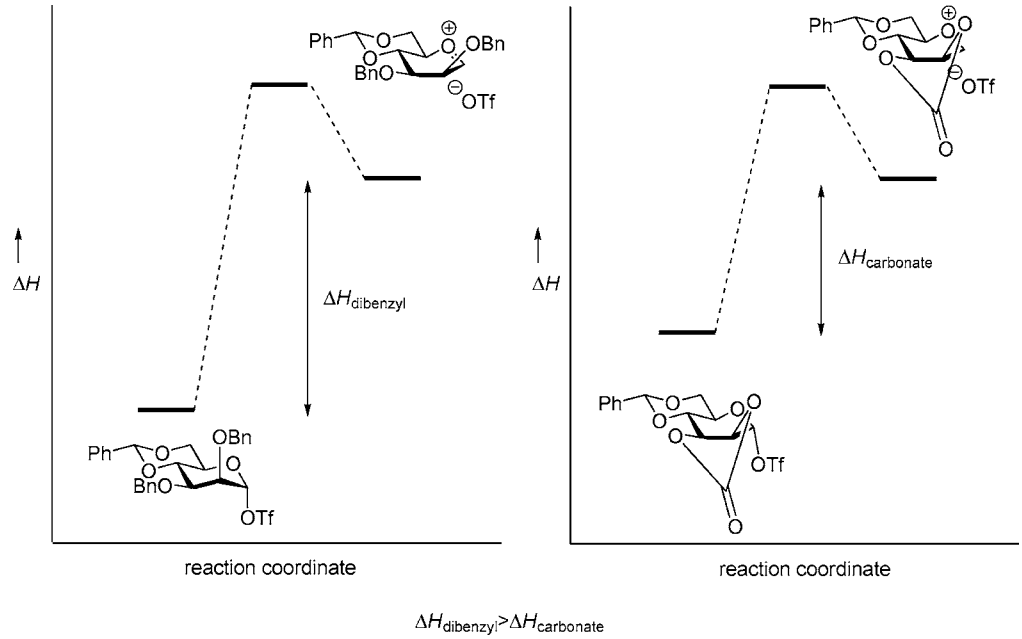


FIGURE 4. Energetic consequences of a 2,3-*O*-carbonate on oxocarbenium ion formation in the mannose series; a case of ground-state destabilization.

In the glucopyranosyl series, the 2,3-*O*-carbonate group is *trans*-fused and opposes the formation of the oxocarbenium ion, and its use results in β-selective glucosylations.[65] The 3,4-*O*-carbonates are *trans*-fused in both the gluco- and mannopyranose systems and in both cases provoke moderate β-selectivity (Figure 5).[62,65] This is due to the combination of their moderate electron-withdrawing effect and the conformational rigidity that they impose on the system, both of which act to increase the energetic barrier between the observable covalent glycosyl triflates and the oxocarbenium ion. Not surprisingly in view of the greater proximity of the electron-withdrawing functionality to the anomeric center in the glucose series, the 2,3-*O*-carbonate generally exhibited greater β-selectivity than its 3,4-regioisomer.

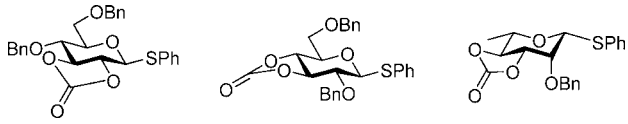


FIGURE 5. β-Selective carbonate-protected donors.

3,4-Bisacetals

In view of the strongly β-directing effect of the 4,6-*O*-benzylidene acetal in the mannopyranose series, it was naturally of interest to examine a second series of *trans*-fused bicyclic donors, namely those provided by the application of the bisacetal protecting groups. In this event, a 3,4-bisacetal and a simplified version lacking the two methoxyl groups were found to be highly α-selective (Figure 6).[61] With hindsight, this result is perhaps not surprising because the 3,4-*O*-bridged system does nothing to control the conformation of the all-important C5−C6 bond and does not offer the same degree of electron-withdrawing character as the moderately β-selective 3,4-*O*-carbonate. This result agrees with the earlier computational evidence of Fraser-Reid and co-workers, albeit in the glucose series, to the effect that six-membered rings *trans*-fused onto the 3- and 4-positions of pyranosyl donors do not destabilize oxocarbenium ions to the same extent as six-membered rings fused across the 4- and 6-positions.[50]

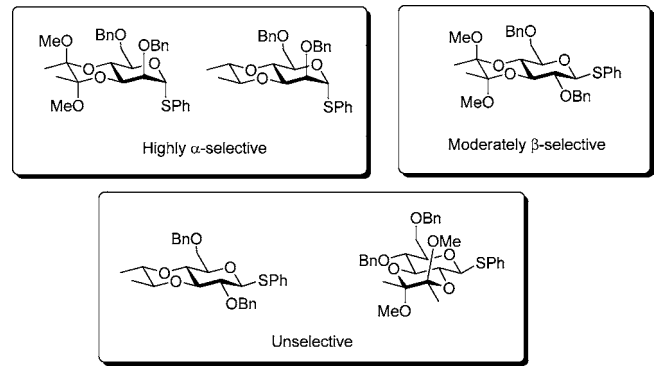


FIGURE 6. Bisacetal-protected donors.

Continuing the mannose−-glucose paradox, application of the same 3,4-bisacetal protecting group in the glucose series gave a series of moderate to highly β-selective coupling reactions (Figure 6).[66] Moreover, and in stark contrast to the mannosyl series, cyanoborohydride reduction to give a des(bismethoxy) system resulted in somewhat diminished selectivity.[66] A 2,3-*O*-bisacetal-protected glucopyranosyl donor

did not show appreciable selectivity.[66] The contrasting behavior between the glucosyl and mannosyl donors carrying the 3,4-*O*-bisacetal-type protecting groups still awaits satisfactory explanation.

Influence of the C3 substituent

The C3 substituent has been revealed to be of critical importance in the 4,6-*O*-benzylidene-protected mannopyranosylation reaction. For practical reasons, the early work employed *O*-benzyl ethers and resulted in highly β-selective reactions. As the complexity of the synthetic targets advanced differential protection of the O2 and O3 positions became necessary and a variety of groups were introduced as protecting groups at O3, often to the detriment of selectivity. Thus, both silyl ethers and glycosidic bonds on O3 of 2-*O*-benzyl-4,6-*O*-benzylidene-protected mannopyanosyl donors were very significantly less β-selective than their 3-*O*-benzyl counterparts (Figure 7).[67] Most strikingly, a 2-*O*-benzyl-3-*O*-TBDMS-protected system was considerably less selective than its regioisomeric 2-*O*-TBDMS-3-*O*-benzyl congenor.[68] The detrimental effect of a bulky group at O3 could be palliated by the use of a less bulky propargyl group on O2 in place of the typical benzyl ether, but a 2,3-di-*O*-propargyl system was again unselective. The importance of the O2−C2−C3−O3 interaction is brought out once again by these results as is its very subtle nature. Parallel results were obtained with a series of 3-amino-2-*O*-benzyl-3-deoxy donors in which the amino group was protected in a variety of different ways.[69] Thus, donors carrying the relatively small 3-azido and bulky 3-nitro groups were unselective despite their somewhat electron-withdrawing nature, while the best results in terms of β-selectivity were obtained when the amine was protected as a Schiff's base, that is, when it resembled sterically the 3-*O*-benzyl ether. We hypothesize that bulky groups at the 3-position buttress the O2-protecting group and thereby lead to a greater shielding of the β-face of the system and correspondingly diminished β-selectivity;[68] an effect that can be overcome to some extent by the use of a sterically minimal protecting group at O2 based on the propargyl ether function.[70] The use of propargyl-protecting groups at both O2 and O3 presumably diminishes the O2−C2−C3−O3 torsional interaction, whose compression is a critical factor in the prototypical reaction and thereby reduces selectivity.[70] The best compromise is found in the use of protecting groups having the approximate steric bulk of benzyl ethers on both O2 and O3 of the mannopyranosyl donors. For these reasons, we have developed a series of orthogonal arylpropargyl[71,72] and benzyl ethers removal under a variety of conditions to be used in conjunction with the standard benzyl, naphthylmethyl, and *p*-methoxybenzyl ethers for the selective protection of O2 and O3.

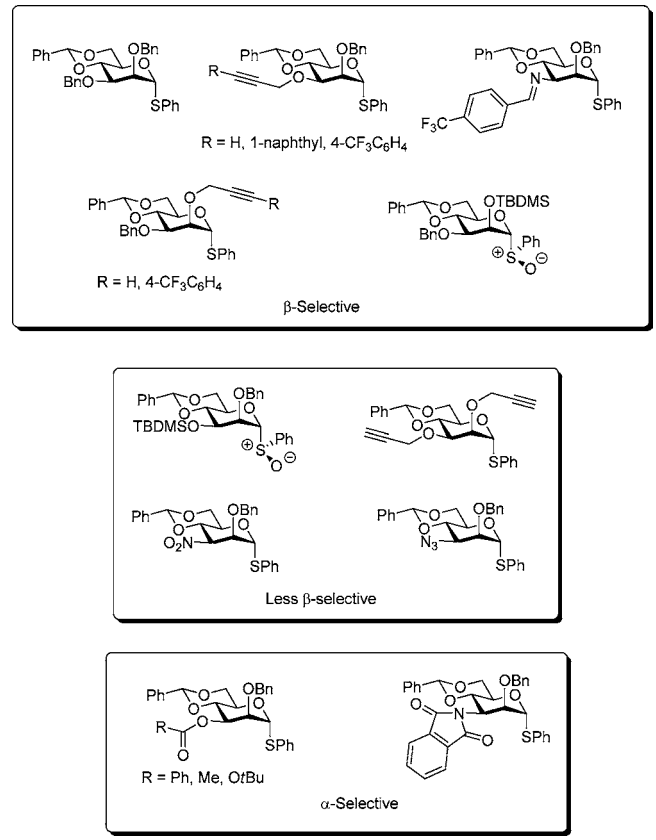


FIGURE 7. Influence of the C2 and C3 substitutents on selectivity.

When an ester is employed as a protecting group of a 4,6-*O*-benzylidene-protected mannopyranosyl donor highly α-selective glycosylation reactions are observed (Figure 7).[61] This effect, which has been employed in the synthesis of complex oligosaccharides[73,74] and which does not appear to be the result of participation by the ester,[75,76] has yet to be satisfactorily explained. The phenomenon extends to the 3-deoxy-3-phthalimido series of mannosyl donors (Figure 7).[69]

Overkill

In view of the ability of both the 4,6-*O*-benzylidene acetal and 2-*O*-sulfonyl groups[53] to support β-mannosylation or rhamnosylation individually, a logical next step was the combination of these two effects in a single donor. Unfortunately, although it proved possible to activate this type of donor with the BSP/Tf_2O combination, we were unable to induce it into productive glycosylation reactions. Variable-temperature NMR studies revealed the derived glycosyl triflate to be stable in CD_2Cl_2 solution until 20 °C, a decomposition temperature some 30 °C above that for the corresponding 2,3-di-*O*-benzyl system, and led to the conclusion that the combination of the two disarming protecting groups destabilizes the oxocar-

benium ion too much for facile reaction (Figure 8).[53] A more severe example of overkill was seen in the glucopyranosyl series when the combination of a 4,6-*O*-benzylidene acetal and a 2,3-*O*-carbonate groups resulted in a thioglycoside that was unreactive toward the usual activation conditions below room temperature (Figure 8).[65]

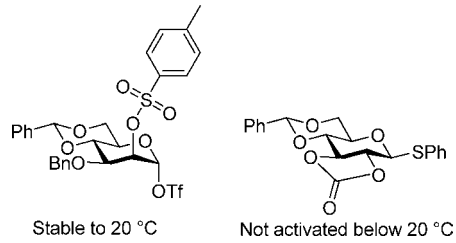


FIGURE 8. Unreactive donors combining the acetal function with electron-withdrawing groups.

Conclusion and Parallels with Nature

Our studies over the 14 years since discovery of the scope and limitations of the 4,6-*O*-benzylidene-directed β-mannosylation reaction have enabled us to piece together a fairly comprehensive picture of the mechanism of this important glycosylation reaction and of the factors that affect it. The concept of a series of equilibria between an observable covalent α-glycosyl triflate, formed in situ, and a set of transient contact and solvent-separated ion pairs and the effect of the various substituents on the position of these equilibria are sufficient to rationalize the enormous bulk of the experimental facts. High β-selectivity is generally attained for substituents that destabilize the oxocarbenium ion of the ion pairs and thereby limit the concentration of the α-selective solvent-separated ion pair. On the other hand, substituents that reduce the energy barrier to oxocarbenium ion formation lead to loss of β-selectivity and even α-selective reactions. The remaining question concerns the highly α-directing effect of esters at the 3-position. One of the less foreseen conclusions to emerge from our investigations has been the significant role played by substituents at the 3-position of the donor, which are mostly rationalized by their differing interactions with the substituent at the 2-position on passing from the glycosyl triflate to the oxocarbenium ion in the various ion pairs. Importantly, it is the difference in the interactions of the 2- and 3-substituents that is responsible for the differing selectivities between the glucose and mannose series. In this respect, the parallel with the interplay between the substrate 2- and 3-OH's in the enzymatic hydrolysis of various mannopyranosides is noteworthy. Thus, Davies and collaborators determined through X-ray crystallographic means that retaining β-glucosidase and β-mannosidase enzymes transfer the discrimination between their gluco- and manno-configured substrates from the 2- to the 3-position as the transition state for formation of the bound intermediate is approached.[77] Furthermore, in recent work[78] and in analogy to our explanation of the 2,3-*O*-carbonate effect, it was suggested that the function of the metal ion in a series of calcium-dependent α-mannosidases is to coordinate to both O2 and O3 and to distort the ground state toward a half-chair conformation that facilitates oxocarbenium ion formation.

I am most grateful to my numerous co-workers for their many invaluable contributions to this project.

BIOGRAPHICAL INFORMATION

David Crich studied for his doctoral degree with D. H. R. Barton at the ICSN and remained there for his postdoctoral studies with D. H. R. Barton and P. Potier. After periods on the faculties at University College London, the University of Illinois at Chicago, and Wayne State University, he returned to the ICSN in 2009.

FOOTNOTES

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