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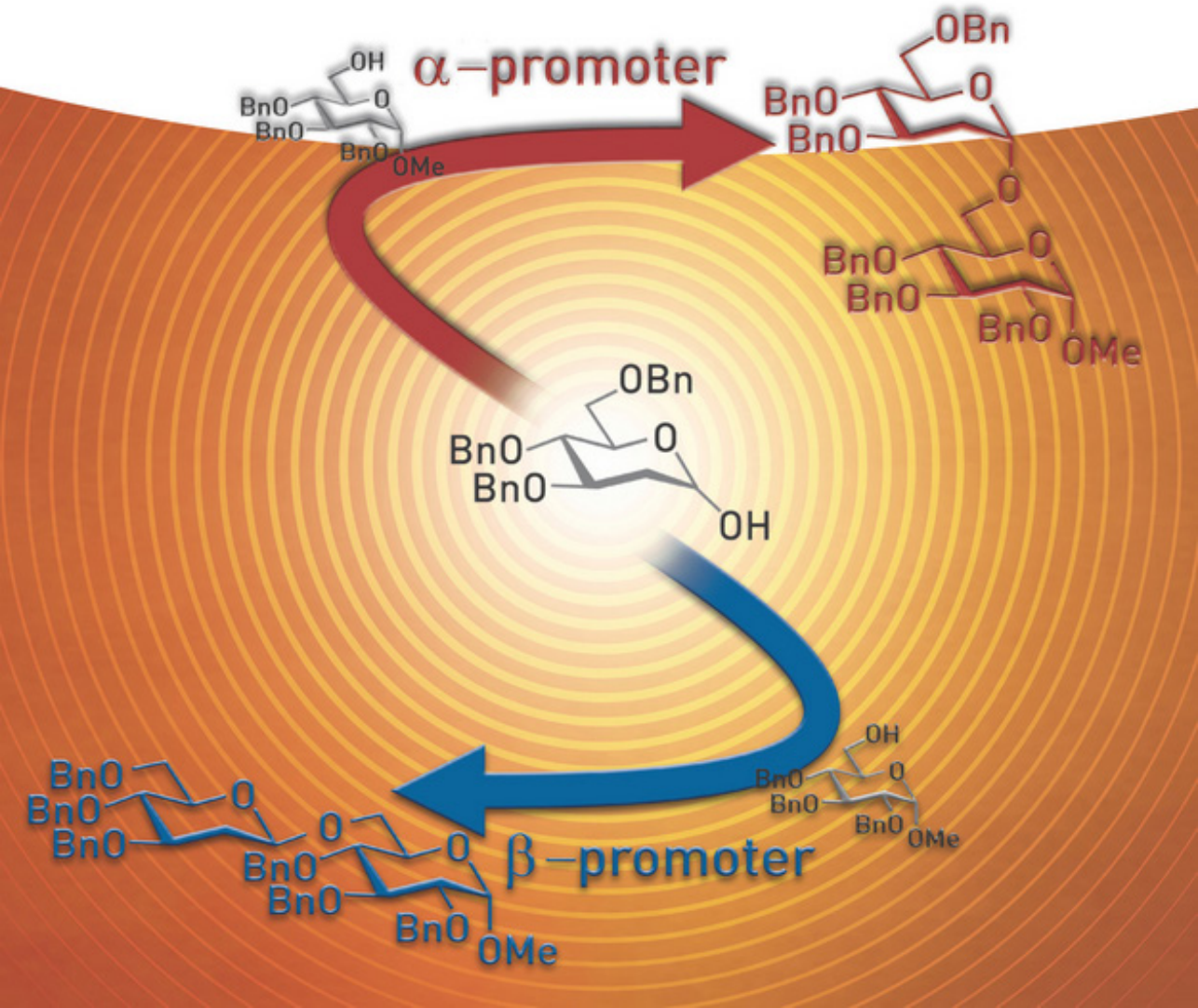
Selective Glycosylations

Synthetic Methods and Catalysts



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WILEY-VCH
Verlag GmbH & Co. KGaA

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Cover

The cover image was kindly provided by the Editor

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

Print ISBN: 978-3-527-33987-7
ePDF ISBN: 978-3-527-69622-2
ePub ISBN: 978-3-527-69624-6
Mobi ISBN: 978-3-527-69625-3
oBook ISBN: 978-3-527-69623-9

Cover Design Schulz Grafik-Design, Fußgönheim, Germany
Typesetting SPi Global, Chennai, India

Printed on acid-free paper

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Preface

The past decade has seen increased recognition of the important roles oligosaccharides play in an array of biological process including (but not limited to) protein folding, pathogen invasion, cell adhesion, and immune response. As a consequence, the field of glycoscience is undergoing rapid growth, with an ever-increasing number of investigators turning their attention to it. Despite all of this, the field is still in its infancy, especially compared to other areas of biology such as genomics and proteomics. There are several reasons for this; chief among them is the fact that glycoscientists do not enjoy ready access to homogeneous material for study, an advantage that was critical for the advances in other areas of biomedical research. This is because, unlike the other major classes of biopolymers, cells produce carbohydrates as heterogeneous mixtures, which are often intractable. As a consequence, organic synthesis (including chemoenzymatic synthesis) remains the only avenue for the production of pure oligosaccharides for biomedical evaluation. The synthesis of most oligosaccharides is a nontrivial undertaking, however, owing to issues of regiochemistry and stereochemistry. Thus, while chemical glycosylation has been known for over a century, the construction of a new oligosaccharide can still be a research project in and of itself.

Among the challenges facing the chemist who wishes to synthesize oligosaccharides, one of the most significant is controlling selectivity in the glycosylation reaction. Typical glycosylation reactions proceed through a mechanism somewhere along the S_N1–S_N2 continuum, which renders controlling selectivity in the reaction immensely difficult. While several elegant solutions to this problem have been devised, a general approach to controlling selectivity in glycosylation reactions with a broad range of substrates remains to be developed. This has prompted calls for the development of new approaches to glycosylation from numerous sectors. Before embarking on developing a new approach to glycosylation, however, it is first necessary to understand the advances that currently constitute the state of the art. The purpose of this volume is to describe the principles of chemical glycosylation. Rather than break down the text into chapters focusing on activating different classes of leaving groups, the focus is instead largely on mechanistic aspects that are responsible for selectivity. Furthermore, technologies for automated and one-pot synthesis have been extensively reviewed elsewhere and will only be covered when relevant.

This volume is organized into five parts. The first part deals with an introduction to the basic principles or carbohydrate synthesis. In Chapter 1, Codeé *et al.* outline the factors responsible for controlling additions to oxocarbenium cations. Next, Demchenko

and coworkers describe the roles protecting groups play in both attenuating glycan reactivity and controlling stereoselectivity in glycosylations in Chapter 2. This part concludes with Chapter 3 from Mong, Nokami, and coworkers, which details the roles solvents play in controlling the stereochemical outcome of glycosylation.

Part II describes ways in which electrophilic glycosyl donors can be modified to undergo selective reactions. In Chapter 4, Ishiwata and Ito provide a detailed introduction to the use of Intramolecular Aglycone Delivery (IAD) for the stereoselective synthesis of *cis*-1,2-glycans. This is followed by a discussion of the use of chiral auxiliaries in oligosaccharide synthesis by Brabham and Fascione in Chapter 5. Finally, Bohé and Crich describe how glycosyl sulfonates permit the construction of the so-called difficult linkages through S_N2-like glycosylations in Chapter 6.

The development of methods for catalytic activation of glycosyl donors is the focus of Part III. This part begins with a description of methods for the construction *C*-glycans, often through transition-metal-mediated processes, by Liu *et al.* in Chapter 7. This is followed by a comprehensive overview of recent approaches for catalytic activation of donors for O-glycosylation by Benito-Alfonso and Galan in Chapter 8. In Chapter 9, Nguyen and coworkers provide a case study in catalytic activation, focusing on their Ni-catalyzed 1,2-*cis*-glycoside synthesis. This part concludes with an introduction to the increasingly popular field of photochemical glycosylation by Ragains in Chapter 10.

In addition to the challenges in controlling the stereochemical outcome of glycosylation reactions, regioselectivity is a problem the synthetic chemist must attend to when dealing with glycosides. Current state-of-the-art approaches to addressing this issue are outlined in Part IV of the volume. In Chapter 11, Taylor provides us with a discussion of methods for regioselectively glycosylating unprotected glycosyl acceptors. This is followed by a discussion of methods for one-pot protection and functionalization of unprotected glycans by Kulkarni in Chapter 12.

The final part of the volume provides the reader with examples of classes of glycans where standard approaches to glycosylation do not always apply. This begins with an overview of recent advances in 2-deoxy-sugar synthesis by Bennett in Chapter 13. Gallo-Rodriguez and Kashiwagi follow this up with an introduction to the challenging issue of controlling selectivity in glycosylations with furanoside donors (Chapter 14). Next, Shi and O'Doherty provide us with a description of how the *de novo* synthesis can permit the construction of a number of carbohydrate natural products in Chapter 15. Finally, Lih and Wu provide an overview of the state of the art in the synthesis of sialic acids in Chapter 16.

The goal of this volume is to try to provide a holistic view of chemical glycosylation. Our target audience is not limited to individuals who are currently engaged in carbohydrate chemistry but extends to the larger synthetic community, many of whom may be new to the field. Our hope is that this volume will inspire investigators to make new, and ideally unforeseen, contributions to the field. We do this because we believe that it will be necessary to engage as many investigators as possible if we are to achieve the long-term goal of developing technologies that will permit the routine and rapid construction of oligosaccharide libraries that are desperately needed for the study of glycobiology.

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Part I

Introduction

1

Stereoselective Glycosylations – Additions to Oxocarbenium Ions

Bas Hagen, Stefan van der Vorm, Thomas Hansen, Gijs A. van der Marel, and Jeroen D.C. Codée

1.1 Introduction

Tremendous progress has been made in the construction of oligosaccharides, and many impressive examples of large and complex oligosaccharide total syntheses have appeared over the years [1]. At the same time, the exact mechanism underlying the union of two carbohydrate building blocks often remains obscure, and optimization of a glycosylation reaction can be a time- and labor-intensive process [2, 3]. This can be explained by the many variables that affect the outcome of a glycosylation reaction: the nature of both the donor and acceptor building blocks, solvent, activator and activation protocol, temperature, concentration, and even the presence and the type of molecular sieves. The large structural variety of carbohydrates leads to building blocks that differ significantly in reactivity, with respect to both the nucleophilicity of the acceptor molecule and the reactivity of the donor species. The reactivity of a donor is generally related to the capacity of the donor to accommodate developing positive charge at the anomeric center, upon expulsion of the anomeric leaving group. This also determines the amount of carbocation character in the transition state leading to the products. Most glycosylation reactions will feature characteristics of both S_N1- and S_N2-type pathways in the transition states leading to the products. It is now commonly accepted that the exact mechanism through which a glycosidic linkage is formed can be found somewhere in the continuum of reaction mechanisms that spans from a completely dissociative S_N1 mechanism on one side to an associative S_N2 pathway on the other side (Figure 1.1) [4–6]. On the S_N1-side of the spectrum, glycosyl oxocarbenium ions are found as product-forming intermediates. On this outer limit of the reaction pathway continuum, the oxocarbenium ions will be separated from their counterions by solvent molecules (solvent-separated ion pairs, SSIPs), and there will be no influence of the counterion on the selectivity of the reaction. Moving toward the S_N2 side of the spectrum contact (or close) ion pairs (CIPs) are encountered, and in reactions of these species, the counterion will have a role to play. Because glycosylation reactions generally occur in apolar solvents (dichloromethane is by far the most used one), ionic intermediates have very limited lifetimes, and activated donor species will primarily be present as a pool of

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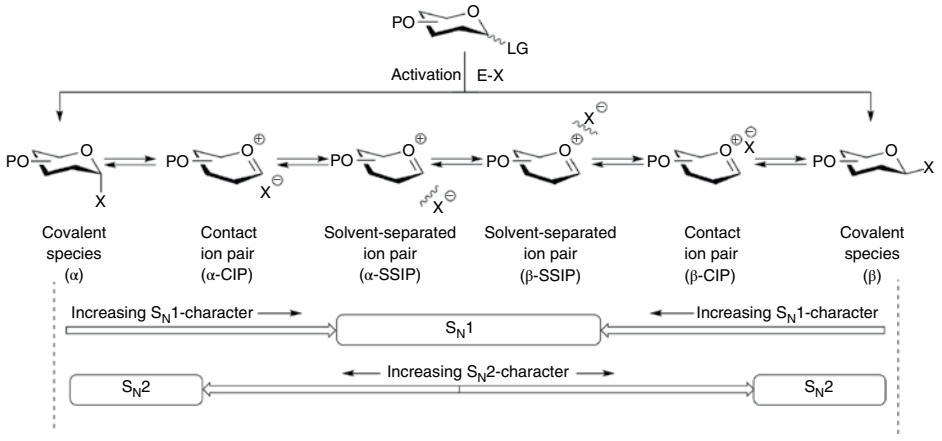
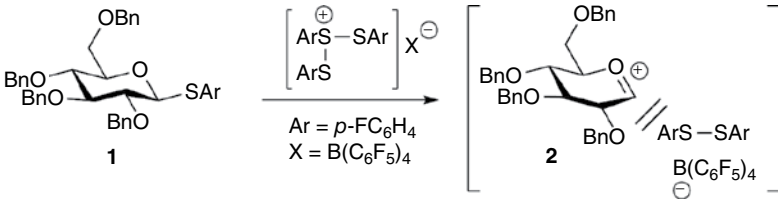


Figure 1.1 Continuum of mechanisms to explain the stereochemical course of glycosylation reactions.

covalent intermediates. The stability, lifetime, and reactivity of an oxocarbenium ion depend – besides the nature of the counterion – on the nature and orientation of the functional groups present on the carbohydrate ring. This chapter explores the role of oxocarbenium ions (and CIPs, featuring a glycosyl cation) in chemical glycosylation reactions. While it was previously often assumed that glycosylations, proceeding via an oxocarbenium ion intermediate, show poor stereoselectivity, it is now clear that oxocarbenium ions can be at the basis of stereoselective glycosylation events. The first part of this chapter deals with the stability, reactivity, and conformational behavior of glycosyl oxocarbenium ions, whereas the second part describes their intermediacy in the assembly of (complex) oligosaccharides.

1.2 Stability, Reactivity, and Conformational Behavior of Glycosyl Oxocarbenium Ions

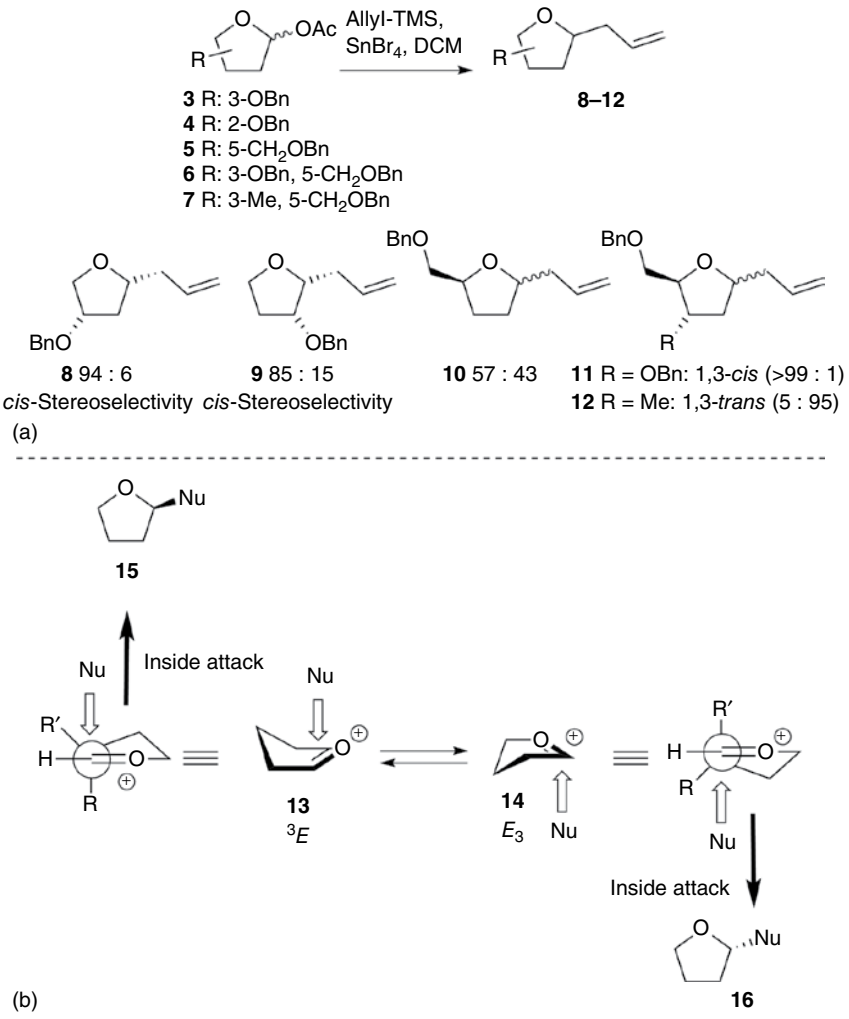
Amyes and Jencks have argued that glycosyl oxocarbenium ions have a short but significant lifetime in aqueous solution [7]. They further argued that in the presence of properly positioned counterions (such as those derived of expulsion of an aglycon), CIPs will rapidly collapse back to provide the covalent species and that the "first stable intermediate for a significant fraction of the reaction" should be the solvent-separated oxocarbenium ion. By extrapolation of these observations to apolar organic solvents, Sinnott reached the conclusion that intimate ion pairs have no real existence in an apolar environment, such as used for glycosylation reactions [8]. Hosoya *et al.* have studied CIPs by quantum mechanical calculations in dichloromethane as a solvent [9]. In these calculations, they have included four solvent molecules to accurately mimic the real-life situation. In many of the studied cases, CIPs turned out to be less stable than the corresponding solvent-separated ions, as will be described next [10]. Yoshida and coworkers have described that activation of thioglucoside **1** with a sulfonium salt activator, featuring the bulky nonnucleophilic tetrakis(pentafluorophenyl) borate counterion, in a continuous-flow microreactor, provides a reactive species (**2**) that has a lifetime on the



Scheme 1.1 Generation of glucosyl oxocarbenium ions in a continuous-flow microreactor.

order of a second (Scheme 1.1) [11]. They argued that this species was a glucosyl oxocarbenium ion, "somewhat stabilized" by the disulfide generated from the donor aglycon and the activator.

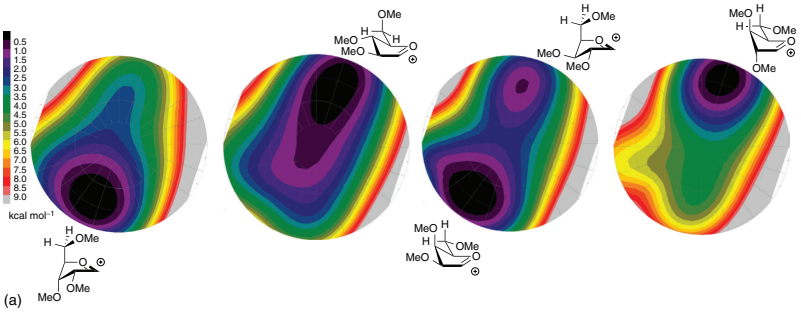
The stability of a glycosyl oxocarbenium ion is largely influenced by the substituents on the carbohydrate ring. The electronegative substituents (primarily oxygen, but also nitrogen-based) have an overall destabilizing effect on the carbocation, and the destabilizing effect can be further enhanced by the presence of electron-withdrawing protecting groups, such as acyl functions. The exact position of the substituent on the ring and its orientation influence the stability of the anomeric cation. The combined influence of all substituents on the ring determines the reactivity of a glycosyl donor, and the extensive relative reactivity value (RRV) charts, drawn up by the Ley and Wong groups for a large panel of thioglycosides, clearly illustrate these functional group effects [12–14]. From these RRV tables, it is clear that the donor reactivity spectrum spans at least eight orders of magnitude. To investigate the influence of the carbohydrate ring substituents on the stereochemical outcome of a glycosylation reaction, Woerpel and coworkers have systematically studied C-glycosylation reactions of a set of furanosides and pyranosides, featuring a limited amount of ring substituents [15–20]. Their studies in the furanose series are summarized in Scheme 1.2a [15, 17]. As can be seen, the alkoxy groups at C2 and C3 have a strong influence on the stereochemical outcome of the reaction, where the alkoxy group at C5 appears to have less effect on the reaction. The presence of an alkoxy or alkyl group at C3 leads to the formation of the allylglycosides **11** and **12** with opposite stereoselectivity. Woerpel and coworkers have devised a model to account for these stereodirecting substituent effects that takes into account the equilibrium between two possible envelope oxocarbenium ion conformers (**13** and **14**, Scheme 1.2b) [17]. Attack on these oxocarbenium ion conformers by the nucleophile occurs from the "inside" of the envelopes, because this trajectory avoids unfavorable eclipsing interactions with the substituent at C2, and it leads, upon rehybridization of the anomeric carbon, to a fully staggered product (**15** and **16**), where attack on the "outside" would provide the furanose ring with an eclipsed C1—C2 constellation. The spatial orientation of the alkoxy groups influences the stability of the oxocarbenium ions. An alkoxy group at C3 can provide some stabilization of the carbocation when it takes up a *pseudo*-axial position. Stabilization of the oxocarbenium ion featuring a C2-alkoxy group is best achieved by placing the electronegative substituent in a *pseudo*-equatorial position to allow for the hyperconjugative stabilization by the properly oriented C2—H2 bond. Alkyl substituents at C3 prefer to adopt a *pseudo*-equatorial position because of steric reasons. With these spatial substituent preferences, the stereochemical outcome of the C-allylation reactions in Scheme 1.2 can be explained. Activation of the C3-benzyloxyfuranosyl acetate with $SnBr_4$ can provide an

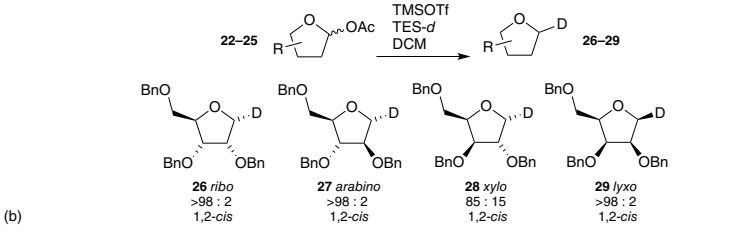


Scheme 1.2 (a) Diastereoselective C-allylations of furanosyl acetates. (b) "Inside" attack model.

oxocarbenium ion intermediate that preferentially adopts an E_3 conformation, as in **14**. Nucleophilic attack on this conformer takes place from the diastereotopic face that leads to the 1,3-*cis* product. In a similar vein, inside nucleophilic attack on the C2-benzyloxy furanosyl oxocarbenium ion E_3 conformer, derived from furanosyl acetate **4**, accounts for the stereochemical outcome of the C-allylation leading to product **9**.

To accurately gauge the combined effect of multiple substituents on a furanosyl ring, van Rijssel *et al.* [21, 22] used a quantum mechanical calculation method, originally developed by Rhoad and coworkers [23], to map the energy of furanosyl oxocarbenium ions related to the complete conformational space they can occupy. Energy maps for all four possible diastereoisomeric, fully decorated furanosyl oxocarbenium ions were generated revealing the lowest energy conformers for the ribo-, arabino-, xylo-, and lyxo-configured furanosyl oxocarbenium ions **17–21** (Scheme 1.3). It became apparent that the orientation of the C5-substituent, having a *gg*, *gt*, or *tg* relation to the substituents at



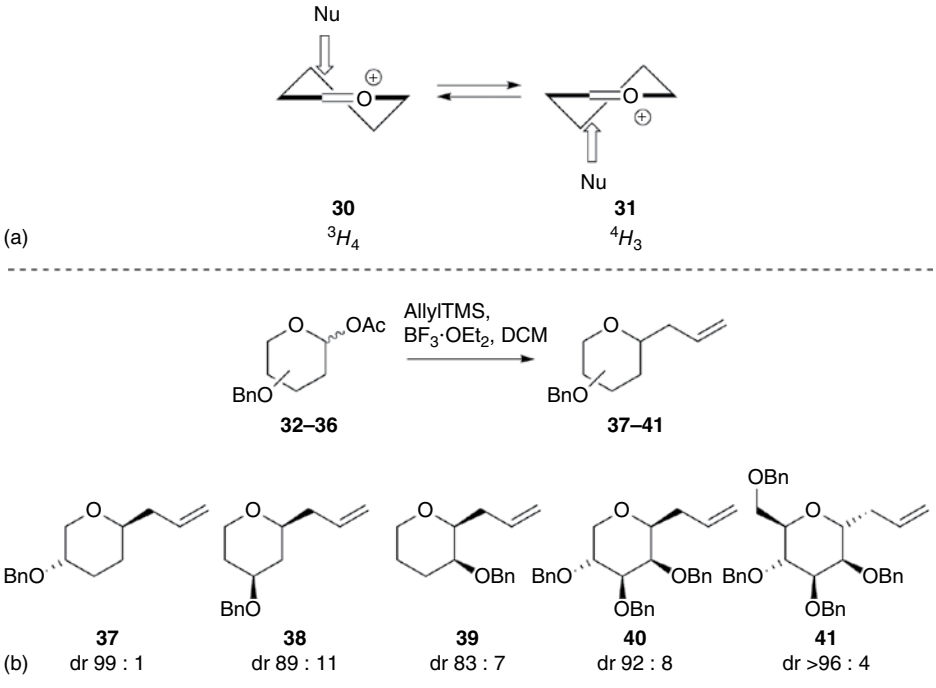


Scheme 1.3 Free energy surface maps of fully decorated furanosyl oxocarbenium ions and diastereoselective reductions of furanosyl acetates.

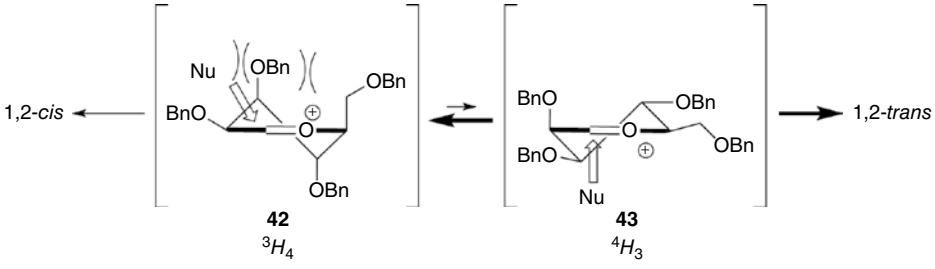
C4, was of profound influence on the stability of the oxocarbenium ions, and differences up to 4 kcal mol^{-1} were observed for structures only differing in their C4—C5 rotation. These stereoelectronic effects have also been described in the pyranose series, where a C4—C6 acetal can restrict the C6-oxygen in a *tg* position, for *manno-* and *gluco*-configured systems, or in a *gg* position for *galacto*-configured constellations [24–26]. The *tg* orientation represents the most destabilizing orientation because in this situation, the O6 atom is farthest away from the electron-depleted anomeric center, not allowing for any electron density donation for stabilization. With the lowest energy furanosyl oxocarbenium ion conformers found by the free energy surface (FES) mapping method, the stereochemical outcome of reduction reactions at the anomeric center of the four diastereoisomeric furanosyl acetates **22–25** could be explained (Scheme 1.3). Interestingly, all four furanosides reacted in a 1,2-*cis* selective manner with the incoming nucleophile (tri-ethylsilane-*d*). Only xylofuranosyl acetate **24** provided some of the 1,2-*trans* addition products, which could be related to the stability of the ^{3}E *gt* oxocarbenium ion intermediate **20**.

The stereoelectronic substituent effects found in the furanose series are paralleled in the pyranose system, where the following substituent effects have been delineated: the stability of pyranosyl oxocarbenium ions benefits from an equatorial orientation of the C2-alkoxy groups (allowing for hyperconjugative stabilization by the σ_{C2-H2} bond) and an axial orientation of the C3 and C4 alkoxy groups [20]. The C5-alkoxymethylene group has a slight preference for an equatorial position because of steric reasons [18]. These substituent preferences have been used to explain the stereochemical outcome of a series of C-allylations, using a two-conformer model. Woerpel and coworkers reasoned that six-membered oxocarbenium ions preferentially adopt a half-chair structure to accommodate the flat [C1=O5]$^{+}$ oxocarbenium ion moiety (Scheme 1.4a) [20]. These half-chair intermediates are attacked by incoming nucleophiles following a trajectory that leads to a chair-like transition state. Thus, attack of a $^{3}H_{4}$ half chair **30** preferentially occurs form the β-face (in the case of a D-pyranoside), where attack on the opposite half chair **31** (the $^{4}H_{3}$) leads to the α-product. With the described spatial substituent preferences and mode of nucleophilic attack, the stereoselectivities in the C-allylation reactions shown in Scheme 1.4b can be accounted for: the C4—OBn is trans-directing, where the C3 and C2—O—Bn promote the formation of the cis-product. In the lyxopyranosyl oxocarbenium ion, these three substituent preferences can be united, and the allylation of 2,3,4-tri-*O*-benzyl lyxopyranosyl acetate **35** proceeds in a highly stereoselective manner to provide the 1,2-*cis* product **40**.

When a C5 benzyloxymethyl group is added to this system, as in a mannosyl cation, it can be reasoned that the $^{3}H_{4}$ oxocarbenium ion is more stable than its $^{4}H_{3}$ counterpart (see Scheme 1.5): the C2, C3, and C4 groups are all positioned properly to provide maximal stabilization of the electron-depleted anomeric center, and only the C5 substituent, in itself not a powerful stereodirecting group, is not positioned favorably [18]. However, the axial orientation of this group does lead to a significant 1,3-diaxial interaction with the axially positioned C3-alkoxy group. The allylation of mannose proceeds with α-selectivity, indicating that nucleophilic attack on the β-face of the $^{3}H_{4}$ oxocarbenium is not a favorable reaction pathway. To account for this stereochemical outcome, Woerpel and coworkers have suggested a Curtin–Hammett kinetic scenario, in which the two half chairs **42** and **43** are in rapid equilibrium. Attack on the $^{3}H_{4}$ conformer suffers from unfavorable steric interactions between the incoming nucleophile and the



Scheme 1.4 (a) Two-conformer model to explain the stereoselectivity in pyranosyl *C*-allylations. (b) Observed diastereoselectivity in reactions of (partially) substituted pyranosyl acetates (major products are shown).



Scheme 1.5 The $^3H_4$ and $^4H_3$ mannosyl oxocarbenium ions and the trajectories of incoming nucleophiles.

substituents at C3 and C5, in addition to the destabilizing C3—C5 interaction, already present in the system. Attack on the α-face of the $^4H_3$ oxocarbenium ion, on the other hand, is devoid of these unfavorable steric interactions, making this transition state overall more favorable.

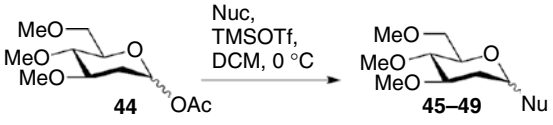
With strong nucleophiles, the two-conformer oxocarbenium ion model falls short, and S_N2-type pathways come into play [27, 28]. In a continuation of their efforts to understand the stereoselectivities of C-glycosylation reactions of (partially) substituted pyranosyl donors, the Woerpel laboratory studied the addition reactions of a series of *C*-nucleophiles, ranging from weak nucleophiles (such as allyl trimethylsilane)

to relatively strong nucleophiles (such as silyl ketene acetals) [27, 28]. Table 1.1 summarizes the stereochemical outcome of the reactions of 2-deoxy glucopyranosyl acetate donor **44** with these nucleophiles under the agency of TMSOTf as a Lewis acid catalyst [28], together with their relative nucleophilicity, as established by Mayr and coworkers [29]. The α-selectivity in the reaction with allyl trimethylsilane can be accounted for by invoking the $^4H_3$ oxocarbenium ion (**55**, Scheme 1.6a) as most likely product-forming intermediate. Nucleophilic attack on the alternative $^3H_4$ half chair **54** again suffers from prohibitively large steric interactions to be a reasonable pathway. With reactive nucleophiles, such as silyl ketene acetals **52** and **53** (Table 1.1, entries 4 and 5), the most likely product-forming pathway proceeds with significant S_N2-character taking place on the α-triflate intermediate **56** (Scheme 1.6b) [28]. Of note, no attempts were undertaken to characterize this triflate[30].

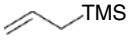
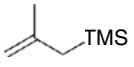
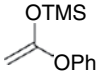
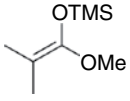
1.3 Computational Studies

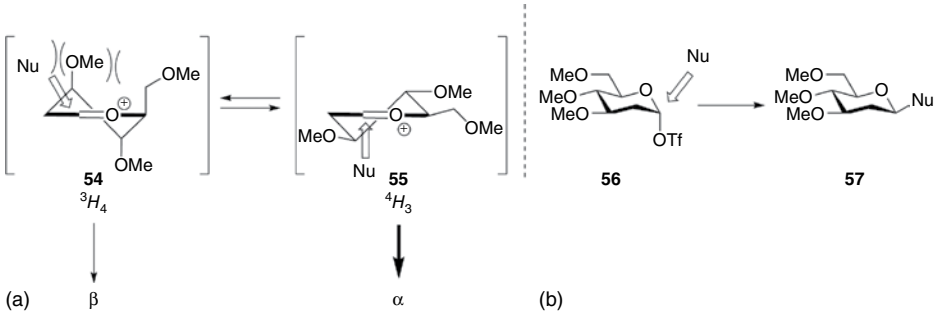
To better understand the conformational behavior, reactivity, and stability of glycosyl oxocarbenium ions, several quantum mechanical studies have been undertaken (see Table 1.2) [9, 10, 31–35]. Whitfield and coworkers have reported many computational

Table 1.1 Changing diastereoselectivity in the addition of *C*-nucleophiles of increasing reactivity.



44 **45–49**

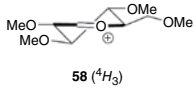
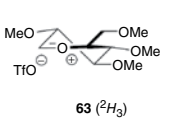
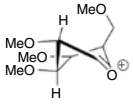
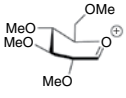
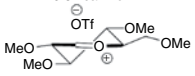
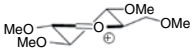
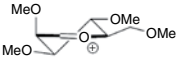
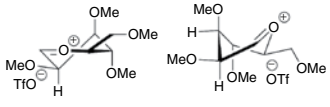
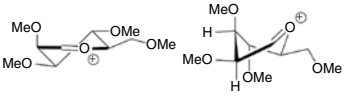
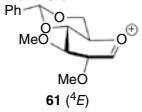
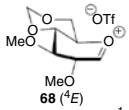
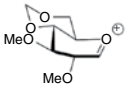
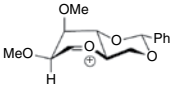
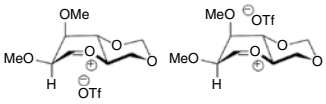
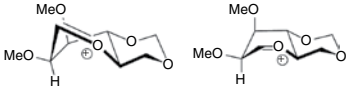
Entry	Nucleophile	N^{α}	product	α/β (yield)
1		1.8	**45**	89:11 (57%)
2	 **50**	4.4	**46**	50:50 (73%)
3	 **51**	6.2	**47**	68:32 (94%)
4	 **52**	8.2	**48**	27:73 (78%)
5	 **53**	9.0	**49**	19:81 (68%)



Scheme 1.6 Reactive intermediates in S_N1-type (a) and S_N2-type (b) pathways.

studies in which they investigated the conformational behavior of, among others, tetra-*O*-methyl gluco- and mannopyranosyl triflates as well as their 4,6-*O*-benzylidene congeners upon ionization (i.e., expulsion of the triflate leaving group) and the conformational behavior of the resulting oxocarbenium ions [32]. To prevent collapse of the initially formed ion pair, they used lithium cations to stabilize the departing anionic leaving

Table 1.2 A selection of oxocarbenium ions and their calculated energies (determined by DFT calculations).

Whitfield	Hosoya **CIPs**	Hosoya **SSIP**
tetra-*O*-Me Glc		
 **58** ($^4H_3$)	 **63** ($^2H_3$) **64** (E_3) +9.5 kcal mol^{-1}	 **71** (^2S_O) +8.5 kcal mol^{-1}
 **59** (^4E)	 **65** ($^4H_3$) +10.6 kcal mol^{-1}	 **72** ($^4H_3$) +10.6 kcal mol^{-1}
tetra-*O*-Me Man		
 **60** ($^4H_3$)	 **66** ($^3H_2$) **67** ($^OS_2$) +7.3 kcal mol^{-1}	 **73** ($^4H_3$) +10.9 kcal mol^{-1} **74** ($^OS_2$) +11.1 kcal mol^{-1}
Benzylidene-Glc	**Formylidene-Glc**	
 **61** (^4E)	 **68** (^4E) + 13.2 kcal mol^{-1}	 **75** (^4E) + 10.9 kcal mol^{-1}
Benzylidene-Man	**Formylidene-Man**	
 **62** ($B_{2,5}$)	 **69** ($B_{2,5}$) +11.7 kcal mol^{-1} **70** ($B_{2,5}$) +14.3 kcal mol^{-1}	 **76** ($^1S_5$) **77** ($B_{2,5}$) +9.8 kcal mol^{-1}

group. These calculations revealed that ionization of the tetra-*O*-methyl gluco- and mannopyranosyl α-triflates initially provides $^4H_3$ (**58** and **60**, respectively) or closely related ^4E-like oxocarbenium ions **59** (see Stoddart's hemisphere representation [36] for *pseudo*-rotational itineraries shown in Figure 1.2a). Expulsion of the anomeric triflate from the β-isomers requires a conformational change, where the glucose and mannose pyranosyl rings distort to an $^1S_3$-like structure [32]. In this constellation, the anomeric leaving group can be expelled by assistance of one of the ring oxygen lone pairs leading to an ^4E (for the glucose) or $^4H_3$ half-chair (for the mannose) oxocarbenium ion. The stability of these ions is primarily governed by sterics, since they lack the electronic stabilization described earlier. Interestingly, similar itineraries have been established to be operational in glycosyl hydrolases. Rovira and coworkers have determined that the hydrolysis of β-glucosides by retaining glucosyl hydrolases, belonging to the GH5, GH7, and GH16 families, proceeds via a trajectory, in which the substrate is first placed in a conformation that allows expulsion of the aglycon (Figure 1.2b) [37, 38]. Then passing through $^4H_3$ transition state **80**, which is close in conformational space to the starting $^1S_3$ geometry **79**, the $^4C_1$ product **81** (the covalent enzyme–glucose adduct) is obtained. This catalytic itinerary was visualized using a combination of X-ray crystallography, free-energy landscape mapping (to determine the intrinsically favorable ground-state conformations), and quantum mechanics/molecular mechanics reaction simulations. Further calculations of the Whitfield group showed that the 4,6-*O*-benzylidene glucose

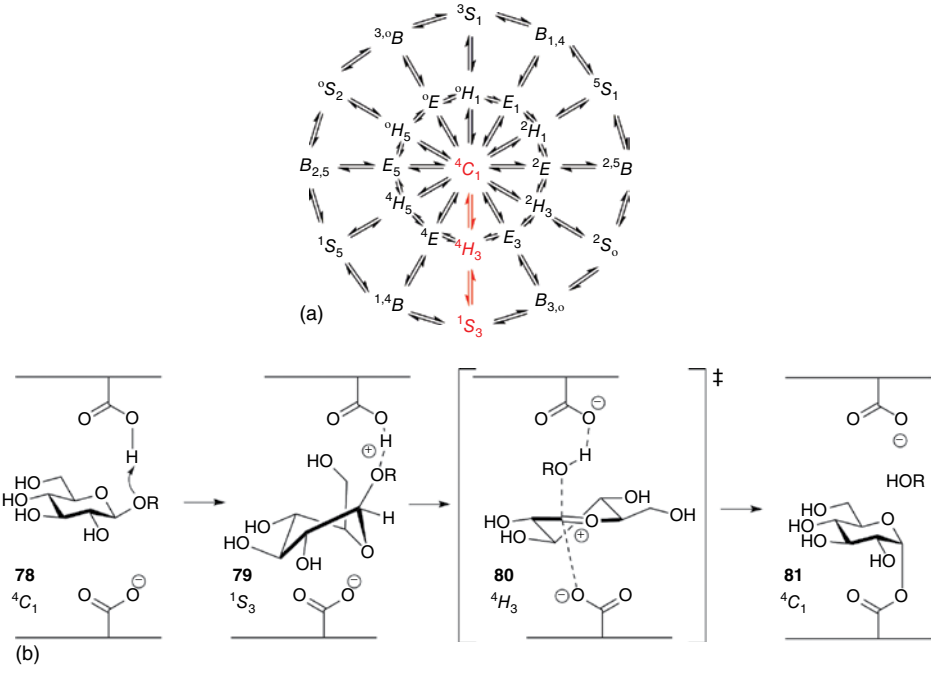


Figure 1.2 (a) Stoddart's hemisphere representation for conformational interconversions (only the Northern hemisphere is shown). (b) Conformational itinerary of the substrate as used by various β-glucosidases. The trajectory has been highlighted in the Stoddart diagram in (a) and was also calculated to be the lowest energy pathway of the ionization of a β-glycosyl triflate.