Reactivity and selectivity in glycosylation reactions

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Chapter 2

Acceptor reactivity in glycosylations

Introduction

The chemical glycosylation reaction involving the union of two species to form a new glycosidic bond is dependent on a large set of variables.[1–3] The previous chapter introduced the basic concepts of reactivity and selectivity in glycosylation reactions, primarily from the perspective of the glycosyl donor. As amply illustrated by the vast amount of chemical carbohydrate literature, the donor is the reactant to which most of the attention has been directed and it is now well appreciated how the reactivity depends on the substitution pattern of the glycoside and how donor reactivity affects the outcome of a glycosylation reaction. The reactivity of the acceptor, on the other hand, is less well studied and detailed knowledge of this reaction partner may provide new mechanistic understanding and practical guidelines for glycosylation reactions. Although it was stated by Paulsen in 1982 that the nature of the acceptor is mostly *a priori* determined, differences in reactivity can influence the glycosylation outcome both in terms of stereoselectivity and isolated yield.[4] Not many studies directed at understanding and

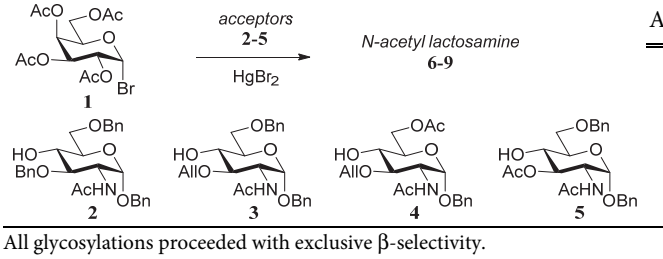
harnessing acceptor reactivity have been reported and, notwithstanding the systematic studies that have been reported and that will be described in this Chapter, the influence of the acceptor on the outcome of a glycosylation reaction is often neglected.

Numerous examples of glycosylation reactions indicate that the reactivity of the acceptor, like that of glycosyl donors, can be manipulated by changing protecting groups.[5–15] Unfortunately, most studies that report on new glycosylation methods, strategies or mechanisms, employ a rather variable set of acceptors, often chosen because of ease of availability, or used because a target oriented approach is taken. As a result the acceptors used in these studies differ greatly in steric and electronic properties, making it difficult to establish structure-reactivity relationships.[16–21] Unexpected stereoselectivities and/or poor yields, as a result of ill understood acceptor reactivity, continue to be reported,[22–26] clearly indicating the need for more systematic and deeper insight into how glycosylations are influenced by the reactivity of the glycosyl acceptor. At a time when the mechanism of glycosylation and the reactivity of the donor is understood better than ever before, the details of the mechanism and the influence of the acceptor therein will be an important pursuit to arrive at a more complete and generalized picture of glycosylation reactions.[27] This Chapter surveys the systematic approaches that have been undertaken to probe the influence of the reactivity of the acceptor on the outcome of a glycosylation reaction and describes methods to analyze and quantify acceptor reactivity.

Observations on acceptor reactivity

In two early examples by Sinaÿ in 1978[28] and Paulsen in 1981,[29] the influence of the acceptor on the glycosylation outcome was recognized. The work of Sinaÿ clearly showed how the yield of glycosylations of galactosyl bromide **1** (Table 1) varied upon changing the protecting groups on the acceptor. *N*-acetyl-glucosamine acceptors **2-5**, with an *O*-benzyl (**2**) or *O*-allyl (**3**, **4**) group at C-3 gave good yields, regardless of the nature of

Table 1. Acceptor protecting groups influencing glycosylation yield. (Sinaÿ, 1978).



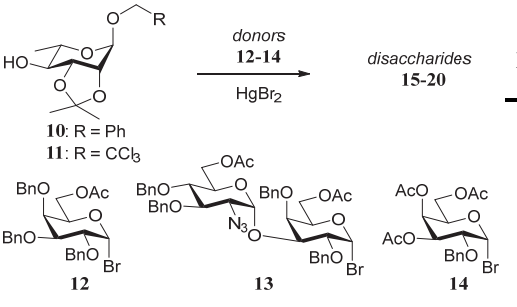
Acceptor	Product	Yield (%)
2	**6**	87
3	**7**	77
4	**8**	78
5	**9**	5

All glycosylations proceeded with exclusive β-selectivity.

the protecting group at C-6 (*O*-benzyl or *O*-acetyl). In contrast, the yield dropped to a mere 5% when the acceptor bearing an *O*-acetyl at the C-3 (**4**) was used.

Paulsen and Lockhoff examined a set of donors (**12-14**, Table 2) with two very similar rhamnosyl acceptors, differing only in the anomeric protection (*O*-benzyl in **10** *vs O*-trichloroethyl in **11**). In this set of experiments both the influence of the reactivity of the donor (**12**>**13**>**14**) and acceptor (**10**>**11**) was evident. The trichloroethyl protected rhamnosyl acceptor **11** provided relatively more of the α-linked products than the benzyl protected analogue **10**, which could be correlated to the lower reactivity of acceptor **11**. The more nucleophilic **10** can displace the α-bromide of 'armed' donor **12** to provide the β-product. Lowering the reactivity of either the donor or the acceptor hampers this direct substitution pathway and the less reactive acceptor can only substitute the more reactive β-bromide, formed by *in situ* anomerization with $HgBr_2$, giving the α-galactosyl linkage.

Table 2. Decrease in acceptor reactivity leads to increase in α-selectivity. (Paulsen and Lockhoff, 1981).

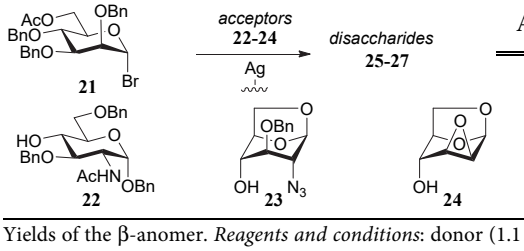


	Acceptor **10**		Acceptor **11**	
Donor	Product	α : β (yield)	Product	α : β (yield)
12	**15**	19 : 81 (75%)	**18**	81 : 19 (82%)
13	**16**	34 : 66 (66%)	**19**	100 : 0 (54%)
14	**17**	100 : 0 (81%)	**20**	100 : 0 (87%)

Yields of combined isolated anomers. *Reagents and conditions*: donor (1 eq.), acceptor (1 eq.), powdered 4Å M.S., $HgBr_2$ (0.1 eq.), DCM, room temperature (**20**), 0°C (**17**), or -20°C (**15**, **16**, **18**, **19**).

In another example by Paulsen and Lebuhn the silver-silicate promoted glycosylation of mannosyl bromide **21** with different glucose and glucosamine acceptors was investigated (Table 3). While the conformationally locked glucosamine acceptor **23**

Table 3. Conformationally restricted acceptors provide more β-product. (Paulsen and Lebuhn, 1983).



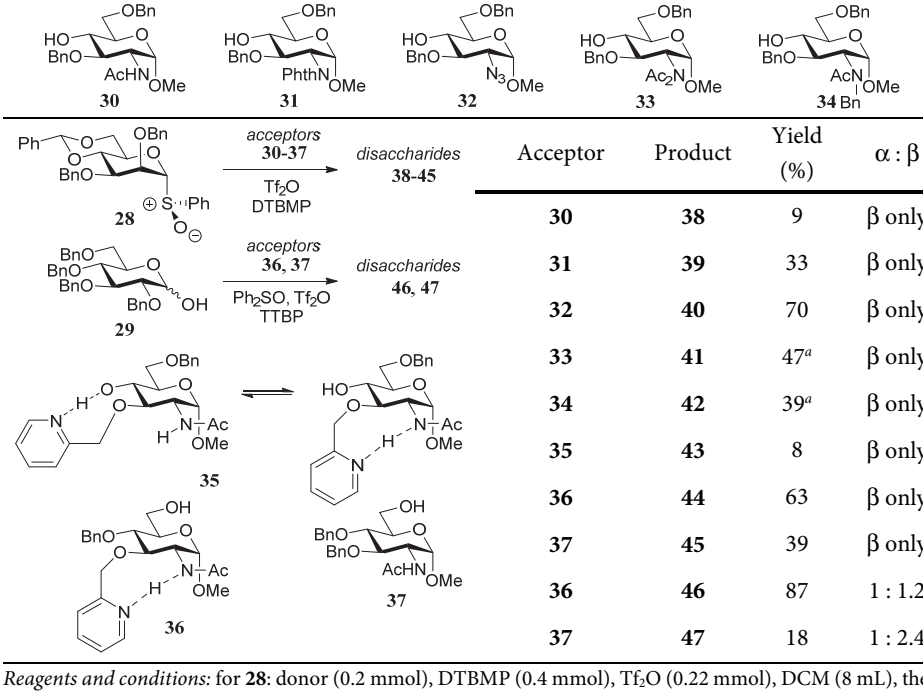
Acceptor	Product	Yield (%)	α : β
22	**25**	75	α only
23	**26**	65	1 : 6
24	**27**	63	1 : 5.5

Yields of the β-anomer. *Reagents and conditions*: donor (1.1 eq.), acceptor (1 eq.), powdered 4Å M.S., silver-silicate, DCM, room temperature (or 35°C for **25**).

and glucose acceptor **24** proved efficient acceptors for the synthesis of 1,2-*cis*-linked disaccharides **26** and **27**, likely formed through an S_N2-type displacement of the activated bromide, the use of *N*-acetyl glucosamine **22** only gave the undesired α-product.[30]

Over the years it has become clear that *N*-acetylglucosamine C-4–OH acceptors are generally very poor nucleophiles.[4] In a detailed study by Crich and co-workers, several glucosamine acceptors (**30**-**34**, Table 4) were used to investigate the underlying reasons why *N*-acetylglucosamine acceptors behave so poorly in glycosylation reactions.[31] Glucosamine acceptors bearing various *N*-protecting groups were investigated (acetyl **30**, phthalimide **31**, azide **32**, and imides **33** and **34**). Glycosylations of these acceptors with mannosyl sulfoxide **28** are reported in Table 4 and the results showed the azide to be far superior to the imides, which in turn are superior to amide **30** in terms of isolated yield. Competition experiments of **30**, **31**, and **32** by glycosylating a mixture of an equimolar amount of all three acceptors and analyzing the product mixture

Table 4. Intermolecular hydrogen-bonding is detrimental to acceptor reactivity. (Crich and Dudkin, 2001).



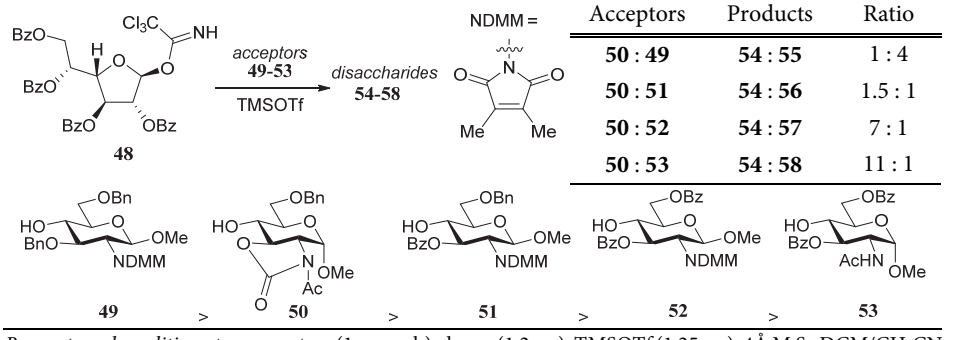
Acceptor	Product	Yield (%)	α : β
30	**38**	9	β only
31	**39**	33	β only
32	**40**	70	β only
33	**41**	47[a]	β only
34	**42**	39[a]	β only
35	**43**	8	β only
36	**44**	63	β only
37	**45**	39	β only
36	**46**	87	1 : 1.2
37	**47**	18	1 : 2.4

Reagents and conditions: for **28**: donor (0.2 mmol), DTBMP (0.4 mmol), Tf_2O (0.22 mmol), DCM (8 mL), then acceptor (0.4 mmol, 2 mL DCM), -78°C to 0°C; for **29**: donor (0.1 mmol), Ph_2SO (0.28 mmol) Tf_2O (0.15 mmol), toluene/DCM (3/1, 1 mL), -78°C to -40°C then TTBP (0.5 mmol, 0.5 mL DCM), acceptor (0.1 mmol, 1 mL DCM), -78°C to room temperature.

by HPLC, revealed a ratio of 1:3:10 (**30**:**31**:**32**) supporting the results of the individual glycosylations. An intermolecular hydrogen-bonding network from the amide (NH and C=O) was hypothesized to be at the basis of the poor reactivity of **30** and to support this, picolyl protected **35** and **36** were prepared to disrupt this network by favoring intramolecular hydrogen-bonding. Glycosylation with C-4–OH acceptor **35** was as ineffective as with benzylated acceptor **30**. To account for this result the hydrogen-bond interaction between C-4–OH and the picolyl-*N* was forwarded as destructive for the acceptor reactivity, instead of making the acceptor more reactive. The C-6–OH derivatives **36** and **37** in comparison gave the anticipated result. Intramolecular hydrogen-bonding between the picolyl and amide provided a more reactive acceptor, leading to a higher yield in the glycosylation reaction with **36**, with respect to the coupling of C-3–*O*-benzyl acceptor **37** which is incapable of forming an intramolecular hydrogen-bond. The use of glucose donor **29**, activated under dehydrative conditions, corroborated these findings, and a good yield was obtained in the condensation with acceptor **36** while the coupling of **29** and acceptor **37** proceeded with poor yield. Cyclic carbamates have also been used as a protecting group to provide appropriate glucosamine C-4–OH acceptors. The cyclic nature of the 2-*N*-3-*O*-carbamate ties back the group at C-3, rendering the C-4–OH more accessible.[32–34]

Rúveda and co-workers investigated the relative reactivities of a series of dimethylmaleimide (DMM) protected glucosamine acceptors (**49**, **51**, and **52**, Table 5) by competition experiments.[35] The reactivity of these nucleophiles was compared to that of *N*-acetyl glucosamine acceptor **53** and cyclic carbamate **50**. From these results it

Table 5. Acceptor competitions revealed the effect of protecting groups on the reaction rates. (Rúveda, 2006).



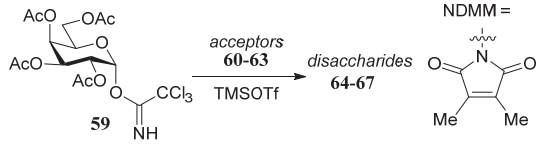
Acceptors	Products	Ratio
50 : **49**	**54** : **55**	1 : 4
50 : **51**	**54** : **56**	1.5 : 1
50 : **52**	**54** : **57**	7 : 1
50 : **53**	**54** : **58**	11 : 1

Reagents and conditions: two acceptors (1 eq. each), donor (1.2 eq.), TMSOTf (1.25 eq.), 4Å M.S., DCM/CH_3CN (29/1, 0.34 M), -30°C.

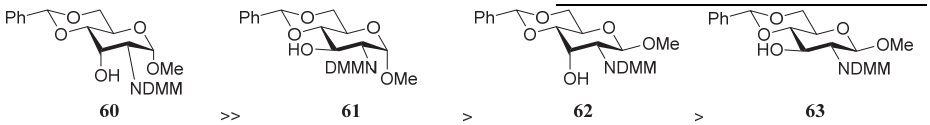
becomes clear that benzoyl groups in the acceptor have a retarding effect on the glycosylation rate, as **49** proved to be the most reactive acceptor, followed by **51** and finally **52**. Also in this study the poor reactivity of *N*-actyl glucosamine **53** is apparent.

Another set of competition experiments, comparing benzylidene allosamine and glucosamine acceptors with the DMM *N*-protecting group, was conducted by the same research group (Table 6).[36] Allosamine **60** by far outcompeted its epimeric acceptors **61** and **62**. These results show that axially orientated hydroxyl groups, as in **60** (C-3–OH), although sterically more encumbered, are not always less reactive than their equatorial counterparts.[37] In this particular series, the relative reactivity results were supported by NMR and computational studies on the possibility of hydrogen-bond formation between the C-3–OH and the maleimide C=O.

Table 6. Acceptor competitions revealed the effect of protecting groups on the reaction rates. (Rúveda, 2011).



Acceptors	Products	Ratio
60 : **61**	**64** : **65**	10 : 1
60 : **62**	**64** : **66**	13 : 1
61 : **62**	**65** : **66**	2 : 1
61 : **63**	**65** : **67**	5 : 1
62 : **63**	**66** : **67**	3 : 1

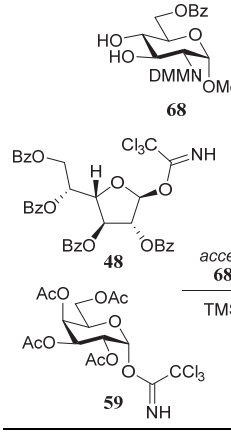


Reagents and conditions: two acceptors (1 eq. each), donor (1.1 eq.), TMSOTf (0.28 eq.), 4Å M.S., DCM, -25°C.

The influence of the C-6 protecting group on the regioselectivity of DMM protected glucosamine acceptors **68**-**70** when glycosylated with donors **48** and **57** was investigated by the group of Rúveda (Table 7).[38] The regioselectivity for the C-3-OH over the C-4–OH increased in the order of C-6–OBz > C-6–OTBDPS > C-6–OBn. The C-6–OBz in **68** makes the C-4–OH more electron poor than the C-3–OH, leading to the strong preference to glycosylate the latter alcohol (C-3/C-4, 1:0 for **48**, and 2:1 for **67**). The bulky TBDPS sterically hampers the nucleophilic attack of the C-4–OH, leading to improved C-3/C-4-regioselectivity with respect to the C-6–OBn (compare 5:1 for **70** and 3.2:1 for **69**, with donor **48**). Notably, the β-anomeric acceptors showed different regioselectivities (see also Table 16), which was again attributed to the difference in hydrogen-bonding capacity of the DMM group with the C-3-OH in the different

anomers.[39,40] The conformational change at the reducing end of an acceptor in a monosaccharide, disaccharide or oligosaccharide, has been reported to influence reactivity of the nucleophilic hydroxyl on the other side of the acceptor.[41–43]

Table 7. Stereoelectronic effects of protecting groups influence the regioselectivity of diols. (Rúveda, 2007).

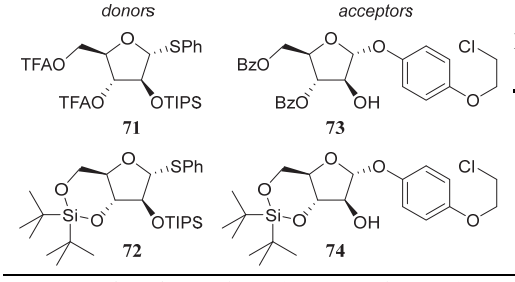


Donor	Acceptor	Yield (%)	(1→3) : (1→4)
48	**68**	68	1 : 0
48	**69**	71	3.2 : 1
48	**70**	73	5 : 1
59	**68**	91	2 : 1
59	**69**	56	1 : 1
59	**70**	50	1.6 : 1

Reagents and conditions: donor (0.11 mmol, 1.1 eq.), acceptor (0.1 mmol, 1 eq.), 4Å M.S., TMSOTf (0.21 mmol, 2.1 eq.), DCM/CH_3CN (37/1), -25°C.

The group of Konovov investigated the difference in reaction rates by observing differences in the activation temperature of the reaction (Table 8).[44] Two donors of varying reactivity (**71** and **72**) were glycosylated with acceptor **73**, bearing two electron-withdrawing benzoyl groups, and with acceptor **74** having the cyclic silylidene protecting group. The activation temperature varied from -42°C to -22°C following the order of reactivity of both the donor and acceptor.

Table 8. The impact of acceptor reactivity on the temperature of activation. (Kononov, 2014).

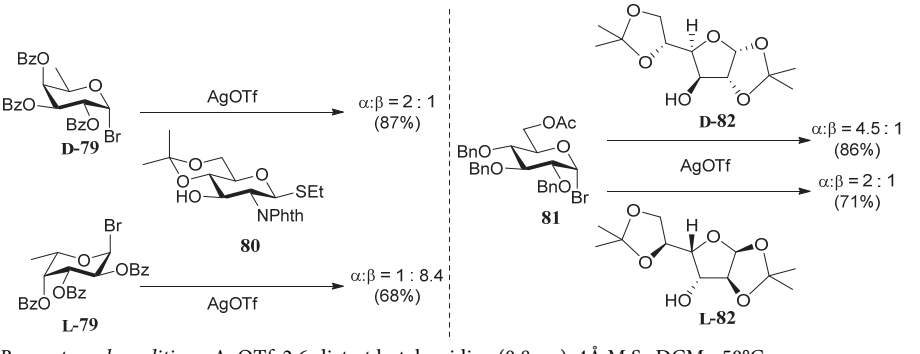


Donor	Acceptor	Product	T_{act} (°C)	Yield (%)	α : β
71	**73**	**75**	-22	66	1 : 2
71	**74**	**76**	-30	84	1 : 6.3
72	**73**	**77**	-39	92	1 : 4.5
72	**74**	**78**	-42	80	1 : 3

Reagents and conditions: donor (0.042 mmol, 1.5 eq.), acceptor (0.028 mmol, 1 eq.), powdered 4Å M.S., NIS (0.042 mmol, 1.5 eq.), AgOTf (0.003 mmol, 0.1 eq.), DCM (1 mL), -78°C to T_{act}, then to +10°C.

In the early 90's Spijker and van Boeckel were the first to introduce the concept of double stereodifferentation[45] in synthetic carbohydrate chemistry.[46] They unambiguously showed how the chirality of the coupling partners could impact the transition state of the glycosylation reaction. Carbohydrates experience different steric effects when coupled to different enantiomers of the same reaction partner. In their 1991 publication, two situations are highlighted (Scheme 1). Either two enantiomeric donors (D-fucosyl bromide **D-79** and L-fucosyl bromide **L-79**) were coupled to the same D-glucosamine acceptor **80**, or the absolute chirality of the acceptor was changed from D-diacetoneglucose **D-82** to its L-enantiomer **L-82** while keeping the donor the same (D-glucosyl bromide **81**). Remarkable results were obtained. While neighboring group participation to provide 1,2-*trans*-glycosides is generally a very powerful stereocontrolling phenomenon, the glycosylation of donor **D-79** and acceptor **80** provided an anomeric mixture (α:β, 2:1). The use of the enantiomeric donor **L-79** restored the expected *trans*-selectivtity (α:β, 1:8.4). The difference in α:β product ratio is less pronounced in the second case, in which acceptor **D-82** provides more α-product than its enantiomer **L-82**. The observed changes in stereoselectivity are clearly the result of drastically different steric interactions in the diastereoisomeric transition states.

Scheme 1. Double stereodifferentation in glycosylation reactions. (Spijker and van Boeckel, 1991).

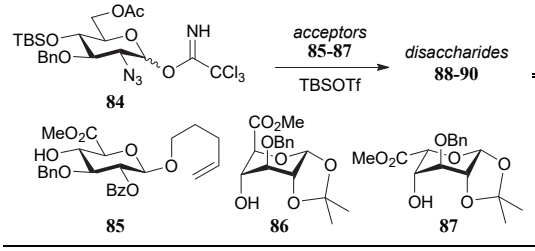


Reagents and conditions: AgOTf, 2,6-di-*tert*-butylpyridine (0.8 eq.), 4Å M.S., DCM, -50°C.

Another clear manifestation of the effect of the shape of the acceptor on the outcome of a glycosylation reaction can be observed when carbohydrate acceptors are locked in 'inverted' chair conformations. As was shown above, conformationally locking a glucose/glucosamine acceptor in a $^1C_4$ chair places the C-4–OH in a position that is well accessible leading to a better nucleophile.[30,47] It is well established in the field of heparin synthesis that glycosylations of glucosazide donors with L-idose/L-iduronic acid acceptors, generally adopting a $^1C_4$ chair conformation, proceed with excellent α-

selectivity (an important manifestation of double stereodifferentiation).[48,49] Based on this knowledge Seeberger and co-workers decided to lock D-glucuronic acid ester acceptors for heparin synthesis in a similar $^1C_4$ chair conformation (Table 9).[50,] In condensations with glucosazide donor **84** D-glucuronic acid acceptor **85** provided an anomeric mixture (**88**; α:β, 3:1) in relatively low yield. By conformationally locking the glucuronate acceptor in the inverted $^1C_4$ conformation (as in **86**), a high yield and excellent α-selectivity was obtained in the condensation with **84**. The use of L-iduronic acid acceptor **87** provided an analogous result.

Table 9. Conformational restriction leads to higher yields and α-selectivities. (Seeberger, 2002).

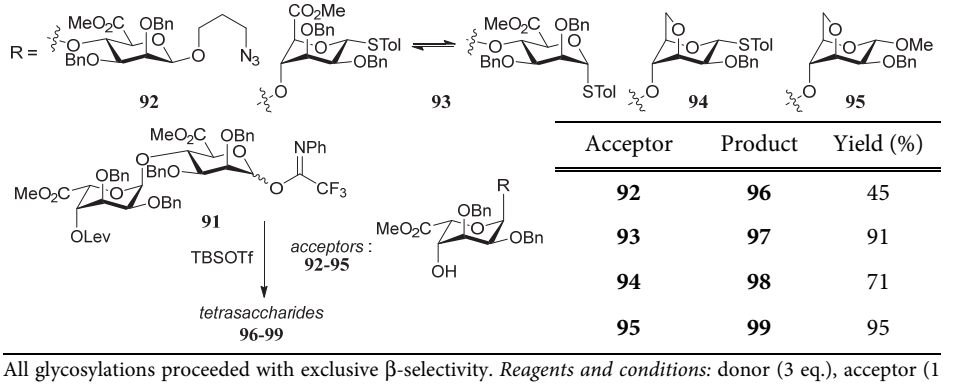


Acceptor	Product	Yield (%)	α : β
85	**88**	57	3 : 1
86	**89**	86	α only
87	**90**	91	α only

Reagents and conditions: donor (1.25 eq.), acceptor (1 eq.), TBSOTf (0.125 eq.), 4Å M.S., DCM, -78°C to room temperature, 2.5 h.

A rigid conformational lock is not always necessary to mold an acceptor in a reactive conformation, as was described by Zhang *et al.* (Table 10).[51] They showed that the conformational rigidity of disaccharide acceptor **92** hampered the glycosylation with donor **91**. Changing the reducing end of the disaccharide acceptor from a β-*O*-(azidopropyl) mannuronic acid to an α-*S*-tolyl manuronic acid (**93**), provided a more

Table 10. Conformational flexibility of acceptor **161** dramatically increased glycosylation yield. (Codée, 2015).



Acceptor	Product	Yield (%)
92	**96**	45
93	**97**	91
94	**98**	71
95	**99**	95

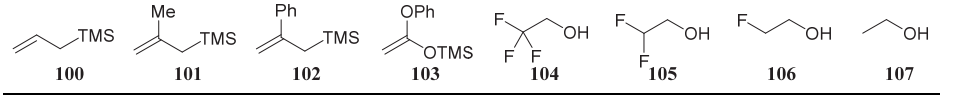
All glycosylations proceeded with exclusive β-selectivity. *Reagents and conditions:* donor (3 eq.), acceptor (1 eq.), TBSOTf (0.6 eq.), 4Å M.S., DCM, -78°C to -45°C.

flexible acceptor, as judged from the broadened resonances observed in NMR-spectroscopy. The flexible character of acceptor **93** led to greatly enhanced glycosylation productivity. The contribution of the $^1C_4$ structure in the conformational equilibrium of **93** was verified by the use of model disaccharide acceptors having a conformationally locked $^1C_4$ reducing end saccharide (either an α-*O*-methyl (**94**) or an α-*S*-tolyl (**95**)).

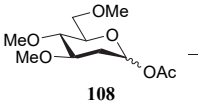
Systematic studies on acceptor reactivity

Although it is clear that the nature of the protecting groups has an influence on the glycosylation outcome it is often difficult to dissect electronic, steric and conformational effects.[52] Woerpel and co-workers have reported a systematic study relating the effect of the nucleophilicity of the acceptor on the outcome of a glycosylation reaction, using both *C*- and *O*-model nucleophiles.[53–57] Table 11 reports the results of both sets of nucleophiles, with 2-deoxyglucosyl acetate or ethanethiolate donors **108** and **109**. The trend that becomes apparent from these results is that poorer nucleophiles provide more α-product. To account for these results, it was reasoned that the poorest *C*- and *O*-nucleophiles **100** and **104**, as assessed by Mayr's nucleophilicity parameter *N*,[58–63] or the field inductive parameter *F*,[64] react with the glucosyl oxocarbenium ion that

Table 11. Model *C*- and *O*-nucleophilic acceptors in glycosylations correlating nucleophilicity to stereoselectivity. (Woerpel, 2008-2010).



100 **101** **102** **103** **104** **105** **106** **107**

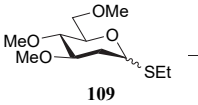


108

acceptors **93-96** → *products* **110-113**

$BF_3{\cdot}OEt_2$

Acceptor	N^a	Product	Yield (%)	α : β
100	1.8	**110**	80	89 : 11
101	4.4	**111**	79	43 : 57
102	6.2	**112**	83	61 : 39
103	8.2	**113**	83	45 : 55

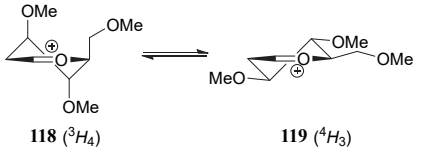


109

acceptors **97-100** → *products* **114-117**

NIS

Acceptor	F^b	Product	Yield (%)	α : β
104	0.38	**114**	80	83 : 17
105	0.29	**115**	78	67 : 33
106	0.15	**116**	69	56 : 44
107	0.0	**117**	82	51 : 49



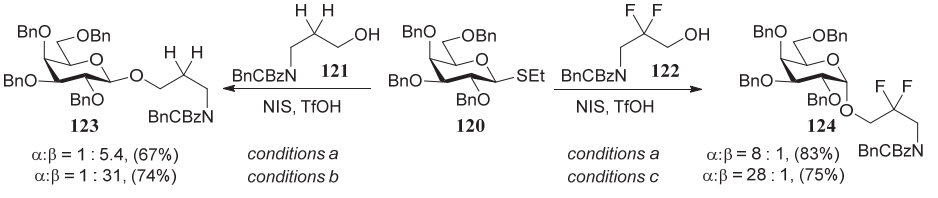
118 ($^3H_4$) **119** ($^4H_3$)

[a]Mayr's nucleophilicity parameter. [b]Field inductive parameter.[61] *Reagents and conditions for acetyl donors*: donor (1 eq.), acceptor (4 eq.), BF_3OEt_2 (1.5 eq.), DCM, -42°C to 0°C. *Reagents and conditions for thiodonors*: donor (1 eq.), acceptor (4 eq.), NIS (2 eq.), CH_3CN, 0°C.

preferentially takes up a $^4H_3$ conformation (**119**), in a stereoselective manner from the α-face. The selectivity is reduced when the nucleophilicity is increased. This erosion of stereoselectivity (from **110** to **113**, and from **114** to **117**) is caused by alternative reaction pathways becoming accessible for the stronger nucleophiles: either a non-selective S_N1 reaction in which both sides of oxocarbenium ion **119** are attacked, or an S_N2-type substitution.

In line with the results of Woerpel, a glycosylation study of linkers **121** and **122** with donor **120** by the group of Seeberger, found the more nucleophilic **121** to give high β-selectivity whereas the weaker nucleophile **122** gave mainly the α-product (Scheme 2).[65] These results can be explained by an S_N2-type substitution of the reactive primary alcohol on the intermediately formed anomeric α-triflate, where attack of the weaker difluoro acceptor requires a more reactive electrophile, either an intermediate oxocarbenium ion or the corresponding β-triflate. By tweaking the reaction temperature and solvent, nearly complete α-stereoselectivity could be obtained. A variety of different donors provided a similar reactivity-stereoselectivity trend.

Scheme 2. Linkers of varying nucleophilicity gave opposite glycosylation stereoselectivity. (Seeberger, 2016).

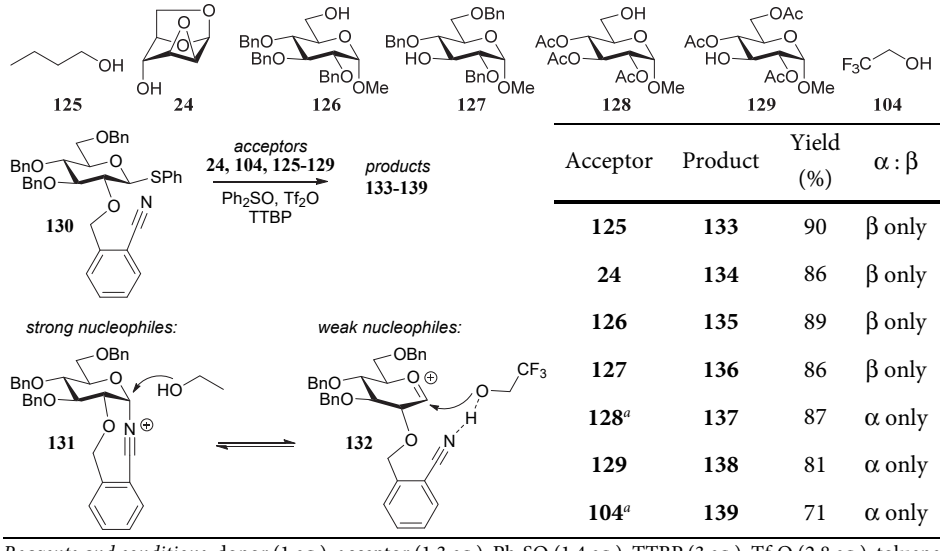


Reagents and conditions: donor (1.5 eq.), acceptor (1 eq.), NIS (1.5 eq.), TfOH (0.2 eq.); a) DCM, -20°C; b) CH_3CN -40°C; c) toluene/dioxane (3/1), room temperature.

Le Mai Hoang and Liu introduced donors equipped with a 2-cyanobenzyl group at the C-2-OH and they investigated these donors, using a preactivation glycosylation scheme, with a panel of acceptors (Table 12).[66] Next to the model acceptors *n*-butanol **125** and trifluoroethanol **104**, this study also included carbohydrate acceptors with benzyl and acetyl protection groups. It was observed that the stronger nucleophiles stereoselectively provided the β-linked product, while the use of weaker nucleophiles led to the generation of the α-linked products in a fully stereoselective manner.[67] The stronger nucleophiles **24**, **125-127** can partake in an S_N2-like substitution of the anomeric α-triflate, a closely related contact ion pair, or as suggested by the authors by a substitution of the intermediate α-nitrilium ion **131**, to provide selectively the β-product. The weaker, acetyl bearing acceptors **128** and **129** and trifluoroethanol **104** can be

directed by hydrogen-bonding with the cyano functionality on the C-2–*O*-protecting group to the α-face of the donor (as in **132**), as poorer nucleophiles are generally also stronger acids, forming hydrogen-bonds more readily. Alternatively, the weaker acceptors may also attack the oxocarbenium ion selectively on the α-diastereotopic face without coordination by the 2-cyanobenzyl group.

Table 12. Reactive acceptors give pure β-selectivity, weak acceptors pure α-selectivity. (Le Mai Hoang, 2014).

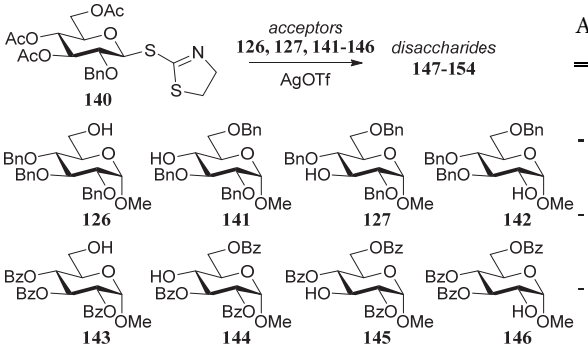


Acceptor	Product	Yield (%)	α : β
125	**133**	90	β only
24	**134**	86	β only
126	**135**	89	β only
127	**136**	86	β only
128[a]	**137**	87	α only
129	**138**	81	α only
104[a]	**139**	71	α only

Reagents and conditions: donor (1 eq.), acceptor (1.3 eq.), Ph_2SO (1.4 eq.), TTBP (3 eq.), Tf_2O (2.8 eq.), toluene -60°C. [a]Et_2O was used as solvent.

A systematic study by Demchenko revealed the effect of acyl *vs* alkyl protecting groups and the position of the free alcohol on the carbohydrate acceptors on the stereochemistry of glycosylations with STaz donor **140** (Table 13).[68] The acceptors studied, varied from tri-*O*-benzyl protected acceptors **126**, **127**, **141**, and **142** to tri-*O*-benzoyl protected acceptors **143**-**146**. While the yields of the silver triflate mediated reactions proved independent of acceptor reactivity, the stereoselectivity of the glycosylations involving the *O*-benzyl protected acceptors is generally lower than the selectivity for the same acceptors bearing *O*-benzoyl groups. The latter group consistently give higher α-selectivities. It was observed that the *O*-benzyl protected acceptors were converted faster to their respective products than their *O*-benzoyl protected counterparts.

Table 13. Differentially substituted glucose acceptors provide a trend in reaction times and stereoselectivity. (Demchenko, 2010).

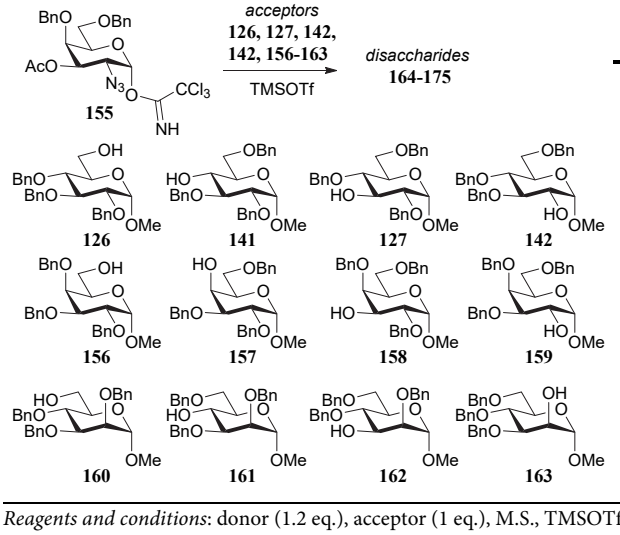


Acceptor	Product	Time (h)	Yield (%)	α : β
126	**147**	1.5	81	2.7 : 1
143	**148**	2	89	7.4 : 1
141	**149**	14	90	6.8 : 1
144	**150**	16	89	11.7 : 1
127	**151**	8	85	6.5 : 1
145	**152**	12	87	12.1 : 1
142	**153**	6	87	9.3 : 1
146	**154**	12	72	12.0 : 1

Reagents and conditions: donor (0.11 mmol, 1.1 eq.), acceptor (0.10 mmol, 1 eq.), 3Å M.S., AgOTf (0.22 mmol, 2 eq.), 1,2-dichloroethane (2 mL), room temperature.

In an extension of the work of Demchenko, Kalikanda and Li investigated the effect of different configurations of the glycosyl acceptors. In one of the few systematic studies devoted to acceptor reactivity, they studied twelve tri-*O*-benzylated acceptors, having either a *gluco*-, *galacto*-, or *manno*-configuration in glycosylations with galactosazide donor **155** (Table 14).[69] Again, it becomes clear that the most reactive alcohols react in a β-selective manner, while the least reactive nucleophiles provide α-linked products. Although the exact mechanism of these glycosylations are not clear, the

Table 14. Systematic study of the impact of configuration of the acceptor reactivity. (Kalikanda and Li, 2011).



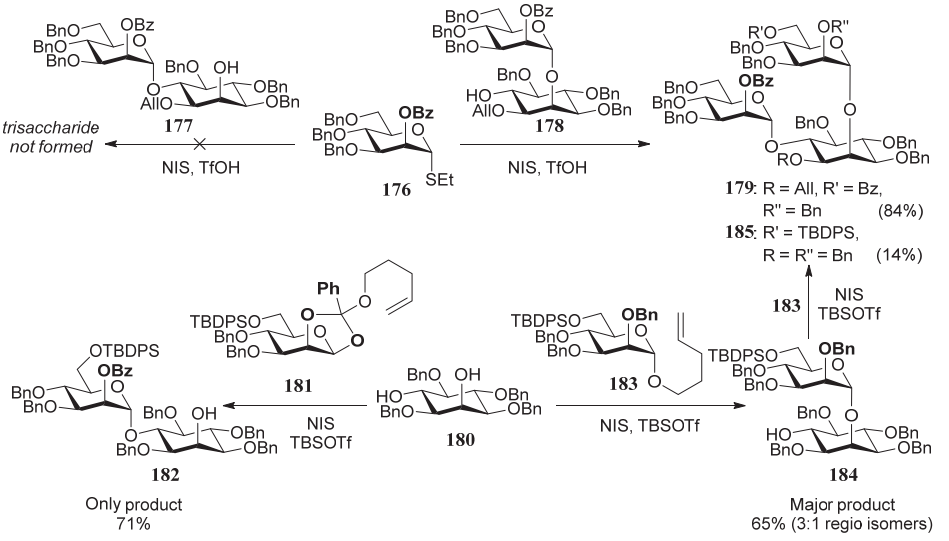
Acceptor	Product	Yield (%)	α : β
126	**164**	98	β only
141	**165**	56	1.8 : 1
127	**166**	53	1 : 3.4
142	**167**	68	α only
156	**168**	75	1 : 4
157	**169**	63	α only
158	**170**	65	3 : 1
159	**171**	90	1.3 : 1
160	**172**	90	1 : 10
161	**173**	81	1.2 : 1
162	**174**	82	1 : 4.7
163	**175**	93	α only

Reagents and conditions: donor (1.2 eq.), acceptor (1 eq.), M.S., TMSOTf (0.15 eq.), DCM (0.2 M), -78°C.

result show that in general, the primary alcohols are the most reactive and the secondary, axially orientated hydroxyls are the least reactive. Notably, the reactivity order, as assessed from the α/β-product ratio, in the glucose series matches those established in Demchenko's study described above.[68] However, the relative order of reactivity may strongly depend on the donor used and the steric interactions between donor and acceptor in the product forming transition state.

In fact, the relative reactivity of two alcohol nucleophiles can even be reversed depending on the donor system used and it has already been suggested by Paulsen that for an optimal glycosylaton outcome the reactivity of both reaction partners should be "matched".[70–73] This becomes apparent form the following striking examples. Scheme 3 shows an attempted synthesis by van Boom and co-workers of a mycobacterial phospholipid using mannosyl donor **176** and *myo*-inositol acceptor **177**.[74] Glycosylation of the C-2–OH of this acceptor proved ineffective, but the construction of the desired pseudo-trisaccharide **179** in a different order was successful. In the event, pseudo-disaccharide **178**, in which the mannosyl substituent had already been installed at the C-2–OH, could be effectively glycosylated at the inositol C-6–OH with mannosyl donor **176** to give product **179** in 84% yield.[75] Similar results were later reported by Fraser-Reid, who noted a distinct preference of donors **181** and **183** for different alcohols on diol **180**.

Scheme 3. Donor-acceptor match and mismatch, led to the formulation of reciprocal donor-acceptor selectivity. (van Boom, 1990, 1992; Fraser-Reid, 2000).



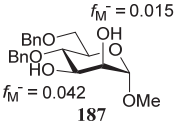
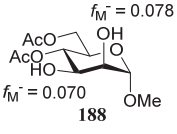
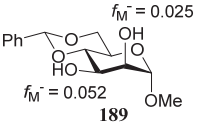
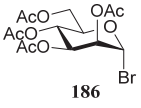
Reagents and conditions: van Boom: donor (1.1 eq.), acceptor (1 eq.), NIS (1.2 eq.), TfOH (0.24 eq.), DCE, -10°C. Fraser-Reid: donor (1.3 eq.), acceptor (1 eq.), NIS (1.3 eq.), TBSOTf (cat), DCM, room temperature.

The preference of the equatorial hydroxyl in structures **178**, **180**, and **184** to be glycosylated with a donor bearing a participating group (**176** or **181**) is evident from the results in Scheme 3. However, donor **183**, bearing a non-participating benzyl group preferentially glycosylates the axial hydroxyl.[76,77] From these observations Fraser-Reid developed the concept of reciprocal donor acceptor selectivity (RDAS), to classify reactions of diols that have different regioselective preferences towards different donors.[78–81] The RDAS concept still awaits a better mechanistic explanation but the counter-intuitive outcome of several more recent reactions have been interpreted with this phenomenon.[82–86]

Quantification of acceptor reactivity

Notwithstanding the progress that has been made in computational chemistry, only few attempts have been reported to investigate the nucleophilicity of glycosyl alcohol acceptors. The Fukui function, and its atom-condensed numerical indices provide a measure of change in electron density at the atom of interest when an electron is subtracted (or added). The Fukui indices have been reported as a measure for site selectivity of electrophilic (f^-) or nucleophilic (f^+) reactions. For the reaction of the OH-nucleophile on an electrophilic center, the index f^- can be computationally approached. Kalikanda and Li have computed Fukui f^--indices for a series of mannosyl diol acceptors (Table 15).[87] The higher value of the two computed for each diol system will indicate the regioselectivity of the reaction. Indeed, the diols **187** and **189** are completely

Table 15. Fukui values determined for mannosyl diol acceptors. (Kalikanda and Li, 2010).

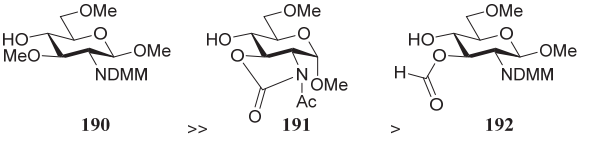
		 **187**	 **188**	 **189**
Entry	Electrophile	Ratio O3/O2	Ratio O3/O2	Ratio O3/O2
1	Ac_2O (+pyridine)	6: 1	3 : 2	1 : 0
2	 **186**	1 : 0	3 : 1	1 : 0

Thiophenyl and trichloroimidate donors also gave trisaccharide byproducts, the disaccharides were formed with the same selectivity regardless of the donor. Atom-condensed Fukui values f_m^- were based on Mulliken charges and were obtained by DFT (Q-CHEM 3.2, B3LYP/6-31+G*). *Reagents and conditions*: donor (1 eq.), acceptor (1 eq.), 3Å M.S., AgOTf (1 eq.), DCM, -30°C.

stereoselective in experimental glycosylations with donor **186** and with acetic anhydride. When the Fukui values are close to each other a loss in stereoselectivity is observed (as for **188**), the preference then found can be a result of the different steric requirements and hydrogen-bonding capabilities.[88]

The group of Rúveda and Stortz also employed Fukui functions, and discussed the chemical hardness/softness and atomic charges as indicators for the relative reactivity of a series of acceptors (**190**-**192**, Figure 1). They reached the conclusion that carbohydrate acceptors and donors are neither well described by hard-hard (atomic charges) interactions nor by soft-soft (Fukui functions) interactions.[35,39] The chemical softness (*s*) in these examples provided the best correlation with experimental results (see Table 5), with the lowest $s_{O\text{-}4}$ value in **190** corresponding to the most reactive acceptor (**49**).

Figure 1. Computation evaluation of relative acceptor reactivities. (Rúveda, 2006).

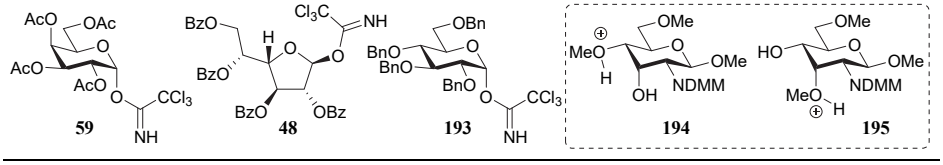


Atomic charge *q*, atom condensed Fukui value *f* and local chemical softness *s* are determined by multiple approaches, see the original publication for details.

In a different approach by the same group, the reactivity of the acceptors was assessed by calculation of the methylated regioisomeric acceptors (see examples **194** and **195**).[89] The charged structures served to mimic the glycosylation transition state and allow for the investigation of the influence of intramolecular hydrogen-bonding on the stability and geometry on the acceptor part.[90,91] Table 16 reports the experimental and computational results of a variety of diol acceptors (see also Table 7 above). Galactopyranose and -furanose donors **59** and **48** were glycosylated with glucosamine acceptors **68**, **69**, **198**, and **199**, and allosamine acceptors **196** and **197**. Experimentally, acceptors **196** and **197** gave exclusive condensation with donor **59** at the axial C-3 position rather than the equatorial C-4 position. The calculated energy difference between the isomeric cationic structures **194** and **195** and their respective α-anomers provided evidence in support of the regioselectivities observed. Applying the same technique to glucosamine acceptors **68**, **69**, **198**, and **199**, the calculated energy

differences again correlated well with the experimentally observed regioselectivity ratios, bar the glycosylation pair **59** and **198**. The computational gas-phase approach may be a shortcoming in this case, and the steric hindrance in the transition state with a carbohydrate donor will be significantly different. In benzylidene allose diols **200** and **201** the C-3-OH also proved to be the most reactive nucleophile, both experimentally and computationally. Questioning whether the computational method would allow the comparison of the reactivity of individual acceptors with a single free hydroxyl group, the authors compared the energies of formation (from the neutral hydroxyl acceptor and methyl cation) of structures **202** and **203**. The energy difference ΔΔE of 7.9 kcal·mol^{-1} between the two systems is in agreement with the observed reactivity difference (Table 6; **61**/**63**, 5:1). It appears that this relatively simple method is a promising way to estimate relative acceptor reactivities qualitatively when a higher level of theory, a larger set of acceptors, and an experimentally well-understood donor/activator system is used.

Table 16. Regioselectivity approach by glycosylations and computations. (Stortz, 2011).



Acceptor	O-3/O-4 Donor **59**	O-3/O-4 Donor **48**	O-3/O-4 Donor **193**	$E_{3\text{-O-Me}}-E_{4\text{-O-Me}}$ (kcal·mol^{-1})
196	1 : 0			-8.64
197	1 : 0			-6.93
68	2 : 1	1 : 0		-4.60
69	1 : 1	3.2 : 1		-1.85
198	1 : 13	1 : 1		-0.03
199	0 : 1	1 : 2.9		+2.15
200			2.6 : 1	-4.39
201			1.2 : 1	-2.25

Energies obtained by DFT (Jaguar 6.0, B3LYP/6-31+G**). *Reagents and conditions*: donor (1.1 eq.), acceptor (1 eq.), TMSOTf (2.1 eq.), 4Å M.S., DCM/CH_3CN (29/1, 0.34 M), -25°C.

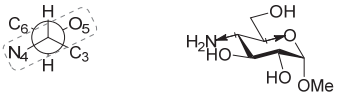
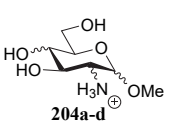


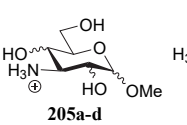
Figure 2. Anti-periplanar relationship between the ring oxygen and the C-4 substituent in methyl glucoside.

Bols and Inouye have taken a rather different approach to estimate the reactivity of different carbohydrate alcohols. They evaluated model systems in which specific hydroxyl groups were changed to amine functions.[92,93] The pK_as of their ammonium salts were determined by titration and the results are displayed in Table 17. The pK_a values indicate the 6-NH_2 group to be the most nucleophilic (towards H_3O^+). The order of reactivity in glucose found with aminoglycosides **204-207a/b**, C-6–NH_3^+ > C-3–NH_3^+ > C-2–NH_3^+ > C-4–NH_3^+, roughly corresponds with the nucleophilicity on the parent hexoses.[94–96] Using the pK_a data in Table 17, the authors established correlations between the effects of the neighboring substituent and the pK_a values of the ammonium group. It was pointed out that an anti-periplanar arrangement of the C-4–N and the C-5–O in **206a/b/d** (Figure 2), but also of C-2–N and C-1–O in **204a/b/d** led to a less basic NH_2 group.[97]

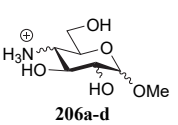
Table 17. pK_a values of aminosugars. (Inouye, 1968; Bols, 2011).



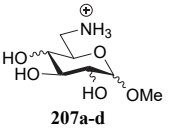
204a-d



205a-d



206a-d



207a-d

a = α-Glc
b = β-Glc
c = α-Gal
d = α-Man

Position	α-Glc	pK_a	β-Glc	pK_a	α-Gal	pK_a	α-Man	pK_a
2-NH_3^+	**204a**	7.5	**204b**	7.2	**204c**	7.9	**204d**	7.2
3-NH_3^+	**205a**	7.8	**205b**	7.6	**205c**	8.0	**205d**	8.1
4-NH_3^+	**206a**	6.8	**206b**	6.7	**206c**	7.3	**206d**	7.2
6-NH_3^+	**207a**	8.9	**207b**	8.6	**207c**	8.9	**207d**	9.0

Conclusions

The reactivity of a glycosyl acceptor is of fundamental importance to the outcome of a glycosylation reaction. The nucleophilicity of a carbohydrate alcohol is influenced by electronic aspects, through inductive effects and hydrogen-bonding, and by steric and conformational effects. The protecting groups on the acceptor play a pivotal role in shaping the acceptor reactivity. In contrast to the reactivity of glycosyl donors, for which Relative Reactivity Values have been established[98,99] to provide a numerical means to

compare their reactivity, the relative reactivity of glycosyl acceptors remains relatively poorly understood and no numerical scales are available to assess acceptor reactivity. The insightful competition experiments performed by Rúveda did provide relative acceptor reactivities based on kinetics but to be more generally useful should be significantly expanded.[38] It would also be of interest to see how relative acceptor values change with different donors. A systematic evaluation of different well established donor systems with the same set of acceptors may provide an accurate structure-reactivity-stereoselectivity map. Another approach would be to establish Kinetic Isotope Effects for donor-acceptor combinations or to perform cation-clock kinetics. Both methods have been used by the group of Crich, but only on the relatively nucleophilic and minimally intrusive *iso*-propanol.[100–104] An extention of these methods spanning a wider range of acceptors, such as the model acceptors introduced by Woerpel and the set used in Chapter 3 of this Thesis, will provide the much needed insight how the reactivity of the acceptors determines the position of the operational reaction mechanisms along the S_N2-S_N1-continuum.

Footnotes and references

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