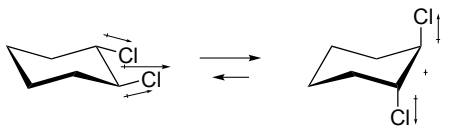
Chapter 1
General Introduction

1.1 Introduction

Electronic effects of functional groups within a molecule control both the 3-dimensional structure and reactivity of the molecule. These electronic effects are dependent on the nature, positioning and configuration of the groups within the molecule, and are therefore called stereoelectronic effects.[1]

A basic example of the influence of stereoelectronic effects of substituents in a molecule on its structure can be found with 1,2-*trans* dichlorocyclohexane. When only steric factors are taken into account, this molecule is expected to prefer a chair conformation having both substituents in an equatorial position to minimize unfavorable 1,3-diaxial interactions (Figure 1.1, **1**). However, this molecule also readily adopts the opposite chair conformation placing both chloride substituents in axial position (**2**).[2-4] The conformational preference is dependent on the solvent and shifts to the side of the chair with axial substituent positioning in more apolar solvents. The preference can be explained by the interaction of the dipoles associated with the C-Cl bonds.[5-6] In the di-equatorial constellation these dipoles are parallel where they oppose each other in the di-axial situation, which is more favorable.[7] The reduction of the overall dipole of the molecule is beneficial, especially in apolar solvents, as can be seen in Figure 1.1. In tetrachloromethane the di-axial conformer is favored where the molecule preferentially adopts a di-equatorial conformation in the polar dimethyl sulfoxide.[2]



1 **2**

Solvent	Equatorial : Axial (%)
CCl_4	35 : 65
$CHCl_3$	52 : 48
DMSO	80 : 20

Figure 1.1 Conformational equilibrium of 1,2-*trans* dichlorocyclohexane.

Stereoelectronic effects also play a decisive role in stabilizing charge in a molecule. For example, the through-space electron donation of substituents with free electron pairs (lone pairs) with proximal positive or partial positive charges can be a strong stabilizing effect.[1,8-9] This is reflected in the conformational preference of 4-methoxycyclohexanone (Figure 1.2, **3**-**4**), which prefers to place the methoxy substituent in an axial position (**4**, $^4C_1$).[10-12] Only in the axial position the methoxy group oxygen can donate electron density into the partial positive charge present on the carbonyl carbon.[13-16] The axial conformer is in equilibrium with the chair that places the methoxy group in an equatorial position (**3**, $^1C_4$) which is beneficial for steric reasons.[7] The stabilizing effect of the electron donation becomes stronger with increasing strength of the positive charge present in the molecule and also depends on the electron density available on the heteroatom substituent.[15,17] Thus, when a positively charged oxocarbenium ion instead of a polarized carbonyl group is present in the molecule (**5**-**6**), the equilibrium between the equatorial and the axial

conformers shifts over to the side of the latter as determined using reactions involving this oxocarbenium ion.[13] The conformer with the axial methoxy substituent benefits from a stronger through-space stabilization thereby overruling the unfavorable steric interactions.

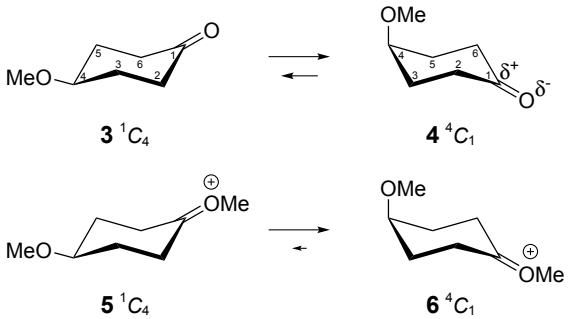


Figure 1.2 Conformational equilibrium of 4-methoxycyclohexanones.

Hyperconjugative effects are stabilizing interactions based on the delocalization of electrons from a filled (bonding) molecular orbital (donor) into an empty or antibonding molecular orbital (acceptor). It is required that the two bonds are properly aligned to allow for overlap between the donating and accepting orbitals.[1,7] In a saturated system, the two substituents have to take up an antiperiplanar orientation so that the bonding donor orbital is parallel to the antibonding acceptor orbital (Figure 1.3). The strength of the stabilizing effect depends on the degree of overlap and on the type of orbitals involved. σ-Bonds of electron donating substituents (C-H, C-C and especially C-Si) are good donors, the π* and σ* orbitals of electron withdrawing substituents (carbonyls, halogens, heteroatoms, etc.) generally form good acceptors and carbocations (empty p-orbitals) are excellent acceptors.[1,6]

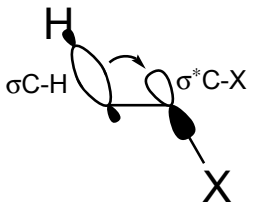
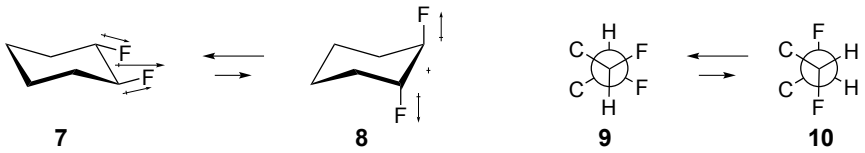


Figure 1.3 Hyperconjugation in saturated systems delocalizes electron density from the σ-bond donor to the σ* antibonding acceptor orbital. Optimal overlap of the two orbitals occurs when both substituents are placed antiperiplanar to each other.

1,2-*Trans* difluorocyclohexane (**7**-**8**, Figure 1.4) displays a different conformational behavior than its dichloro counterpart **1**-**2**. Fluorides are significantly smaller and more

electron withdrawing than chlorides, and based on the dipole interactions outlined above in combination with the smaller steric penalty it could be expected that difluorohexane preferentially takes up a di-axial conformation. However, it is found to favor the diequatorial configuration instead (**7**).[2] An explanation for this behavior can be found in the hyperconjugative stabilization that is possible in the diequatorial situation.[1] When both substituents are in an equatorial position, a carbon-carbon σ-bond can delocalize its electrons into the C-F σ* (**9**) stabilizing this conformer.[1] This effect is also referred to as the "gauche effect".



7 **8** **9** **10**

Solvent	Equatorial : Axial (%)
CCl_4	75 : 25

Figure 1.4 Hyperconjugation causes the small fluorides in 1,2-t*rans* difluorocyclohexane to take up a di-axial conformation.

The anomeric effect is defined as the preference of an electron withdrawing substituent at C1 of a carbohydrate pyranoside (the anomeric center) to adopt an axial orientation (See Figure 1.5 and 1.6).[1,7,9,18] This preference can be explained by a hyperconjugative stabilization arising from the donation of electron density from the lone pair of the ring oxygen into the σ* (C1-X) antibonding orbital of the aglycon (Figure 1.5 and **13**-**14**).

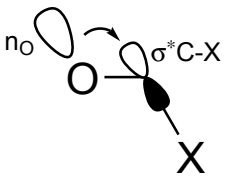
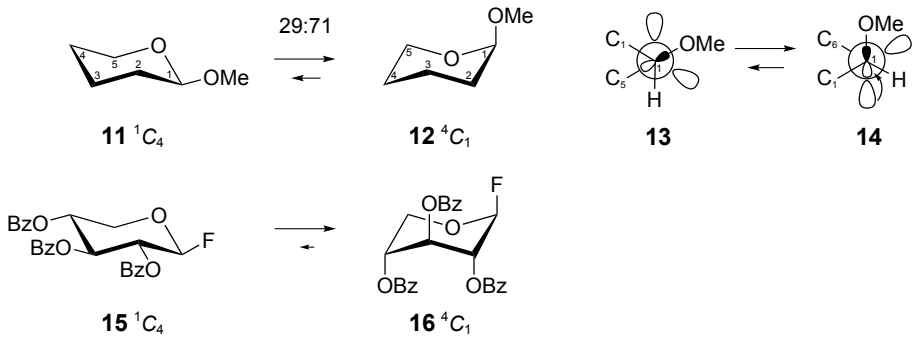


Figure 1.5 Orbital overlap in the stabilizing anomeric effect.

The results of the anomeric effect become clearly visible in a mono-substituted tetrahydropyran. In solution two chair conformers of 2-methoxy tetrahydropyran (Figure 1.6, **11**-**12**) are in equilibrium, with the chair conformer having the methoxy group positioned axially (**12**) predominating.[18] In case of tri-*O*-benzoyl-1-fluoro-β-D-xylopyranose (**15**-**16**), the anomeric effect is so strong that it completely shifts the equilibrium between the $^4C_1$ (**15**) and $^1C_4$ (**16**) chairs to the sterically highly disfavored all-axial $^1C_4$ conformation (**16**).[18]



11 $^1C_4$ **12** $^4C_1$ **13** **14**

15 $^1C_4$ **16** $^4C_1$

Figure 1.6 The anomeric effect causes 2-methoxy tetrahydropyran to take up a conformation with the methoxy group predominantly positioned axially. 1-Fluoro-β-D-xylopyranose preferentially takes up a $^1C_4$ chair conformation as a result of the anomeric effect.

1.2 Furanoses

Furanoses are five membered ring carbohydrates, and their chemistry is determined to a large extent by stereoelectronic effects exerted by the ring substituents. This influence becomes clear in reactions taking place at the anomeric center, for example during glycosylation reactions. During a glycosylation, an anomeric leaving group is expelled leading to the development of positive charge at the anomeric center. Because five membered rings can readily adopt a flattened (envelope) structure[19-20] this positive charge can be relatively easily accommodated leading to the formation of an oxocarbenium ion, or oxocarbenium ion like species. To account for the stereoselectivity (or lack thereof) it is often hypothesized that glycosylations proceed *via* these intermediates. Woerpel and co-workers have devised a model that takes into account the different conformations of the intermediate oxocarbenium ions to explain the stereochemical outcome of *C*-furanosylations.[14,21-26] They proposed a "two conformer" model in which the equilibrium of two oxocarbenium ion conformers, the ^3E (**17**) and E_3 (**18**) envelopes, is decisive for the product stereochemistry (Figure 1.7).[21-23] In case of the ^3E envelope, the C3 carbon atom is positioned above the plane formed by the C4-O4-C1-C2, while in the E_3 envelope C3 is below the plane. Attack of a nucleophile on these envelopes can occur from the top or bottom face. When the oxocarbenium ion is approached from the *endo* face, that is on the side of the envelope where the outlying C3 is positioned, it is referred to as "inside attack", while attack on the other side is termed "outside" (Figure 1.7). The outside attack pathway suffers from an eclipsing interaction of the incoming nucleophile with the axial substituent at C2 in the transition state. It also leads to a product having unfavorable eclipsing C1-C2 interactions. Since an inside attack is devoid of the eclipsing interaction in the transition-state and leads to a product featuring a staggered C1-C2 conformation, this mode of attack is favored. Thus, a reaction on the ^3E envelope (**17**) takes place from the

top of the molecule (leading to **19**) and reaction on the E_3 envelope (**18**) takes place on the bottom (to lead to **20**). The equilibrium between the two envelope conformers is defined by stabilizing and destabilizing steric and stereoelectronic effects in the oxocarbenium ions and therefore the stereochemical course of reactions proceeding through these oxocarbenium ions is shaped by the nature of the substituents. It should be noted however that because of their high reactivity and limited lifetime glycosyl oxocarbenium ions have never been spectroscopically detected.

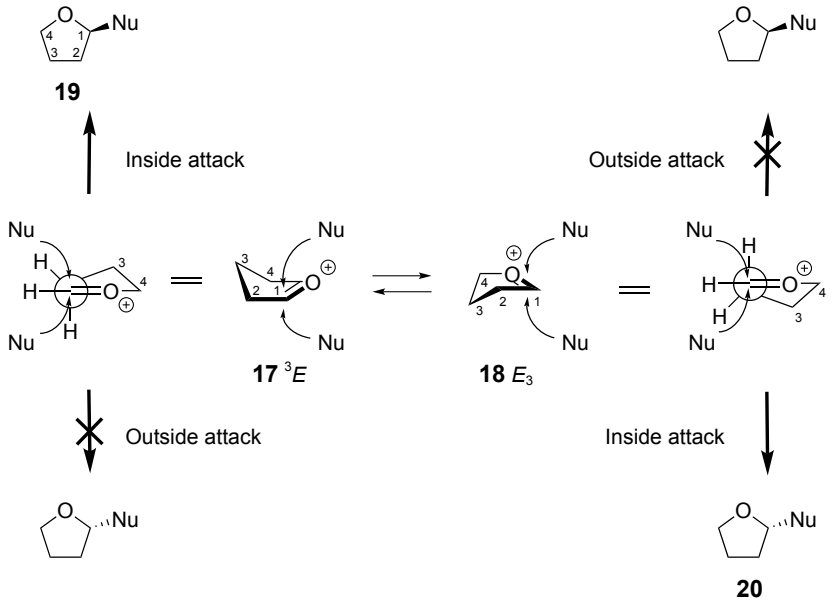


Figure 1.7 The two-conformer model proposed by Woerpel and co-workers. The two furanosyl ^3E (**17**) and E_3 (**18**) envelope oxocarbenium ions are preferentially attacked by the incoming nucleophile following an inside trajectory to provide different epimeric products (**19** and **20** respectively).

Pentofuranoses have three (protected) electron withdrawing groups mounted on the ring, being a hydroxyl group at C2 and C3 and a hydroxymethyl at C4. Woerpel and co-workers have determined the effect of each of the individual substituents in reactions using mono-substituted tetrahydrofurans. In the reaction of (*S*)-3-benzyloxy tetrahydrofuranyl acetate (**21**) with allyltrimethylsilane as nucleophile and $SnBr_4$ as Lewis acidic promoter, the 1,3-*cis* product is obtained with high stereoselectivity (Figure 1.8). This was explained using the equilibrium of the two oxocarbenium ion envelopes **23** and **24** and the inside attack model. If attack on both ions takes place at a comparable rate, the product ratio mirrors the relative stability of the two conformers, and the *cis*-product arises from **24**, where the *trans*-product is formed from **23**. It was reasoned that E_3 oxocarbenium ion **24** is more stable than its E_3 counterpart **23** because of the through-space stabilization of the

pseudoaxial C3-alkoxy lone pair that can donate electron density into the oxocarbenium ion.[21,24] If the substituent is positioned in a pseudoequatorial position this generates an unfavorable dipole-charge interaction by having the negative terminus directed away from the positive anomeric center.

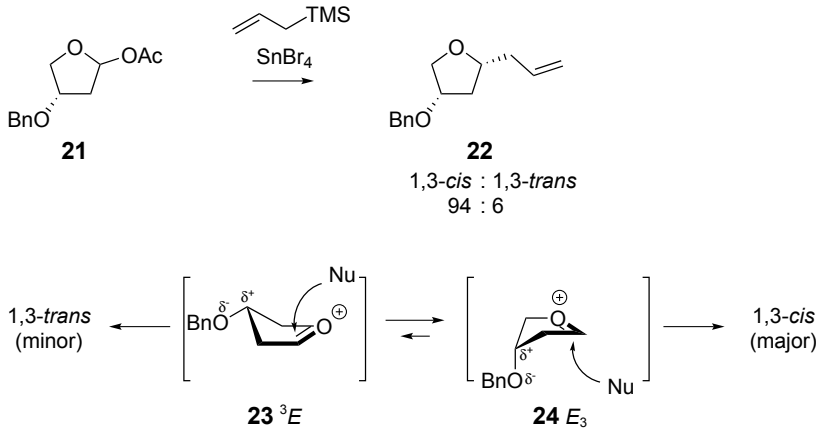


Figure 1.8 The C3 alkoxy substituent can provide through-space stabilization in a pseudoaxial position.

(*R*)-2-benzyloxy tetrahydrofuran acetate (**25**) reacts with allyltrimethylsilane to primarily give 1,2-*cis*-product **26**, originating from the E_3 envelope (Figure 1.9, **28**).[24] This envelope is favored over the alternative ^3E envelope **27**, because hyperconjugative stabilization of the oxocarbenium ion by the axial C2-H2 bond can only take place in the E_3 envelope. A C2-alkoxy group therefore preferentially takes up a pseudoequatorial position in an oxocarbenium ion for stereoelectronic reasons. This position is also favorable from a steric point of view, minimizing 1,3-diaxial interactions with the ring substituent at C4.

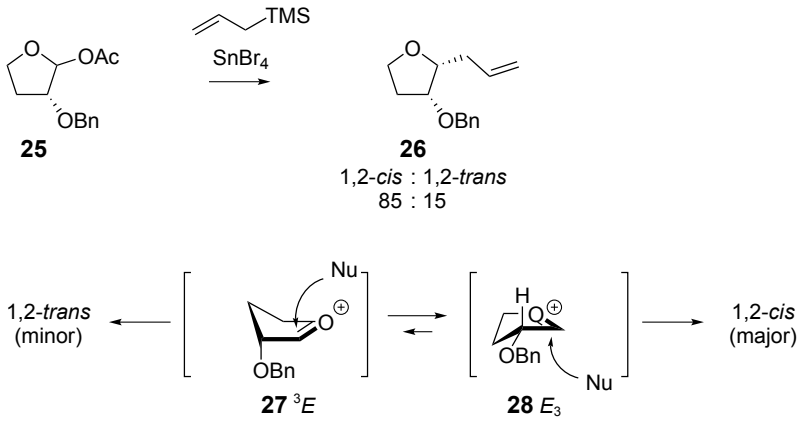


Figure 1.9 The C2 alkoxy substituent is preferentially positioned pseudoequatorially to allow hyperconjugative stabilization of the oxocarbenium ion from the C2-H2 bond.

The (*S*)-4-benzyloxymethyl tetrahydrofuran acetate (**29**) does not have an electron withdrawing substituent directly attached to the furanose ring but has a methylene group in-between the electronegative oxygen and the C4 ring atom. When **29** reacted with allyltrimethylsilane, a mixture of anomers resulted with minimal preference for the 1,4-*trans* product (Figure 1.10).[24,27] The major product originates from the E_3 envelope (**32**), where the C4 alkoxymethyl group is in a pseudoaxial position. In this position, the C5-oxygen can donate electron density through-space into the electron depleted oxocarbenium ion thereby stabilizing the E_3 conformer. In the ^3E envelope (**31**) the C4 substituent takes up a sterically more favorable pseudoequatorial position. The contrasting effects of the through-space interaction and steric preferences makes both envelopes similar in stability, explaining the observed mixture of anomers (**30**).

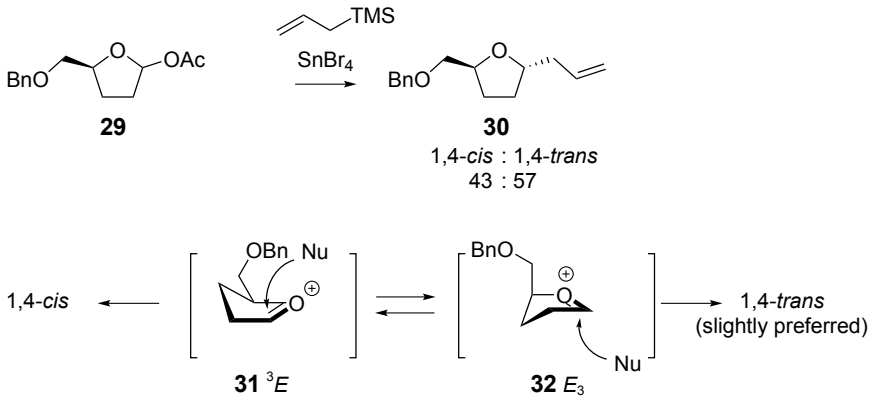


Figure 1.10 The combined effect of stabilizing through-space and destabilizing steric interactions from the C4 alkoxymethyl substituent makes that both envelopes are similar in stability.

When the C2-alkoxy and C3-alkoxy substituents are combined, as in acetates **33** and **37**, the experimental results corroborate the preferences of the individual substituents (Figure 1.11). In 2,3-*cis* dibenzyloxy acetate **33**, both substituents are able to take up their preferred position in the E_3 oxocarbenium ion (**36**). In this conformer the pseudoequatorial C2 substituent has a pseudoaxial C-H bond that is positioned for optimal hyperconjugative stabilization and the pseudoaxial C3 oxygen allows for the most effective through-space stabilization. The product (**34**) ratio reflects the E_3 conformer preference, with the reaction being highly stereoselective for the product originating from this envelope: the 1,2-*cis* product.[24] When the two substituent preferences are conflicting, erosion of stereoselectivity is observed. In 2,3-*trans* dibenzyloxy acetate **37**, only one of the two substituents is able to adopt an optimal position for stabilization in either envelope. In the ^3E conformer (**39**), the C2 substituent allows for optimal stabilization by placing the C-H in pseudoaxial position. The C3 substituent is in a pseudoequatorial position in this envelope and does not provide any through-space stabilization. In the E_3 envelope (**40**), the pseudoaxial C3 substituent can donate electron density from the C3-oxygen lone pairs into the oxocarbenium ion, but the pseudoequatorial position of H2 does not allow for hyperconjugative stabilization. The reaction of 2,3-*trans* dibenzyloxy acetate with allyltrimethylsilane gives a mixture of products, with a slight preference for the 1,2-*trans* product.[24]

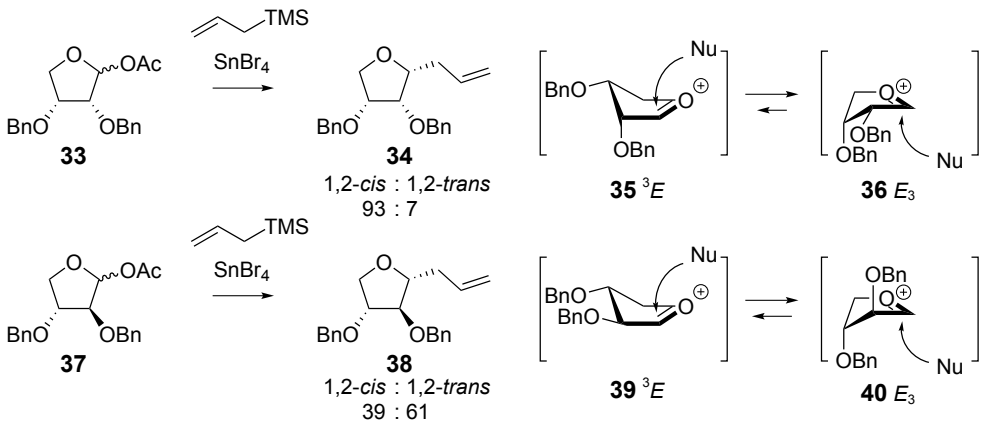


Figure 1.11 The combined effect of both C2 and C3 substituents determine the product ratio.

The situation becomes more complex when a third substituent is present on the furanosyl ring, as in fully functionalized pentofuranoses. Allylation of ribofuranose **41**, the (*S*)-4-benzyloxymethyl analogue of 2,3-*cis*-dibenzyloxy furanose **33**, leads to the 1,2-*cis* product (Figure 1.12).[24,28-30] This outcome can be explained by invoking the E_3 envelope (**44**) as product forming intermediate. In this envelope the pseudoequatorial C2 alkoxy is

positioned favorably, and the pseudoaxial C3 alkoxy and C4 alkoxymethyl groups allow for optimal stabilization by through-space interactions with the oxocarbenium ion. The E_3 (**43**) places none of the substituents in a favorable position, and is therefore significantly less stable. Performing the nucleophilic substitution with arabinofuranose **45**, the C2 epimer of ribose **41**, lead to a product mixture with a preference for the 1,2-*cis* product.[31-32] This indicates that the major product originates from the ^3E conformer (**47**). In this envelope, the only favorably positioned substituent is the pseudoequatorial C2 alkoxy group. The alternative E_3 conformer (**48**) places both the C3 alkoxy and C4 methyleneoxy groups in stabilizing positions. However, in this envelope there is a significant 1,3-diaxial steric clash between the C2 and C4 substituents. The overall energy of this conformer is probably higher than its ^3E counterpart shifting the equilibrium to the side of the latter conformer. In all, conformer preferences of furanosyl oxocarbenium ions are a result from the combination of individual substituent stereoelectronic effects and in fully functionalized systems it can be difficult to predict the overall effect.

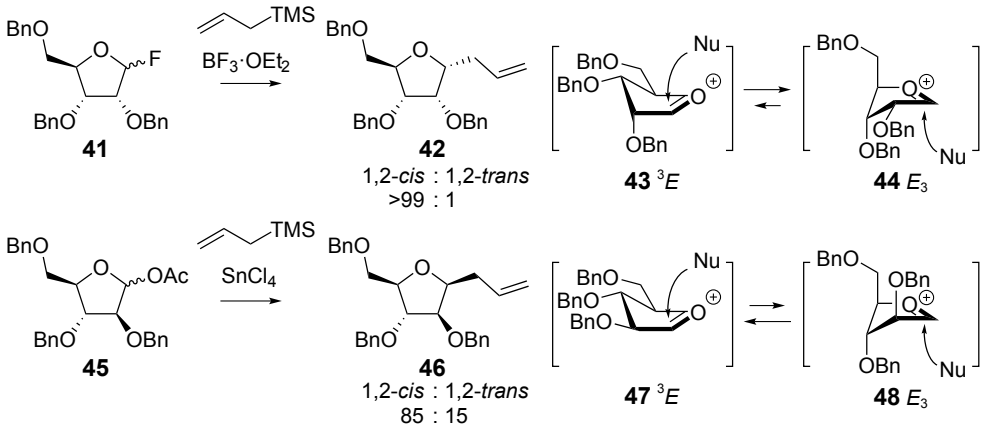


Figure 1.12 *C*-allylation of D-ribo and D-arabinofuranoses.

In contrast to the above described furanosylations using *C*-nucleophiles a similar systematic study for *O*-glycosylations is lacking. A few striking examples are reported that agree with the two conformer model established with *C*-glycosylations. For example, Mukaiyama and Suda reported that when perbenzylated ribose **49** was activated with tributylphosphine oxide and trifluoromethanesulfonic anhydride and then reacted with cyclohexanol, the 1,2-*cis* linked product was preferentially formed (Figure 1.13).[33] A possible explanation for this stereochemical result can be found in the preference of the intermediate oxocarbenium ion to adopt an E_3 conformation.

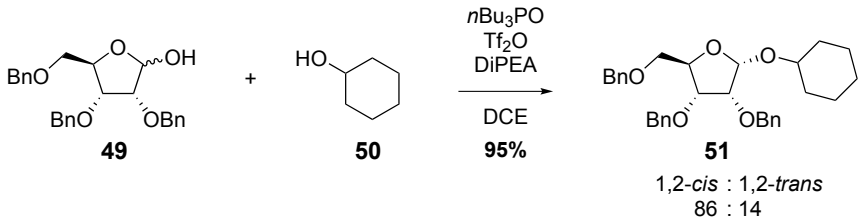


Figure 1.13 An example of a *cis* selective ribofuranosylation.

O-Glycosylation reactions of arabinofuranosyl donors 2'-carboxybenzyl D-arabinofuranoside **52** and thio-L-arabinofuranoside **55** predominantly gave the 1,2-*cis* product isomer **54** and **57**, respectively (Figure 1.14).[34-38] The stereoselectivities found in these arabinosylation reactions are in line with the selectivity seen for the reaction of a *C*-nucleophile with arabinose acetate **45**. These results can be accounted for by assuming that nucleophilic attack of glycosyl acceptor **53** and **56** primarily occurs on the ^{3}E envelope oxocarbenium ion intermediates to give the 1,2-*cis* linked products. It should be noted however, that *O*-nucleophiles are generally more reactive than *C*-nucleophiles (such as allyltrimethylsilane) and competing reaction pathways, for example involving the direct S_N2-displacement of anomeric triflates, can lead to different stereochemical results.[39-40]

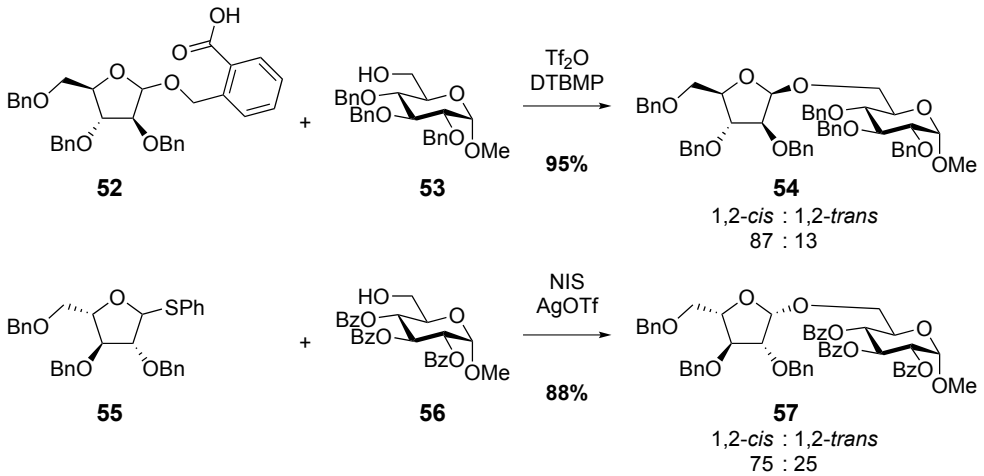


Figure 1.14 Examples of stereoselective arabinofuranosylations.

1.3 Pyranoses

The stereoelectronic substituent effects that play a role in the allylation of pyranoses, six membered ring carbohydrates, have been investigated in detail as well. A two-conformer model similar to the furanosyl system has been proposed to account for the stereoselectivity observed with pyranosides, where the intermediate oxocarbenium ion adopts either a $^{3}H_{4}$ (**58**) or a $^{4}H_{3}$ (**59**) half-chair conformation (Figure 1.15).[14,41-45] When a nucleophile adds to the half-chairs following an outside attack pathway this leads to an unfavorable skew-boat transition state and product (**62** and **63**). Nucleophilic attack from the inside leads to a chair like transition state and product and is therefore generally more favorable (**60** and **61**).[9,41-42,46] Therefore, when the oxocarbenium ion adopts a $^{3}H_{4}$ half-chair, inside attack will take place on the top of the molecule while attack on the $^{4}H_{3}$ half-chair proceeds from the bottom face.

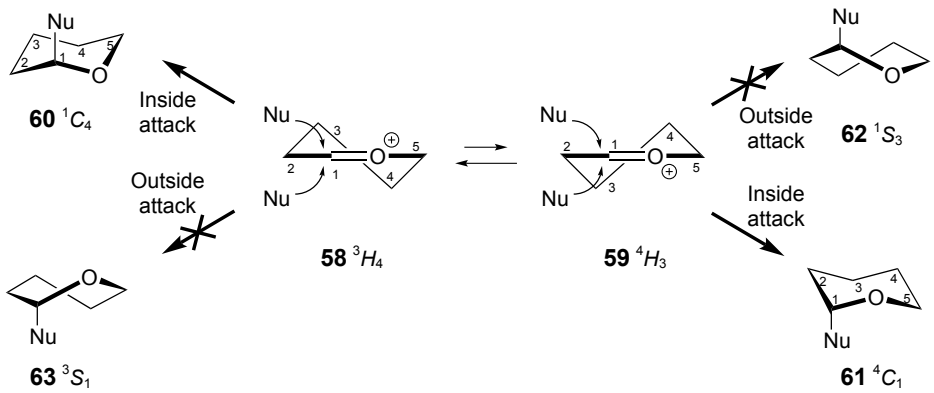


Figure 1.15 The two-conformer model for pyranoses. A nucleophile adds to an oxocarbenium ion half-chair following an inside attack trajectory to lead to the favorable chair product.

To determine the individual substituent preferences in pyranosides, Woerpel and co-workers reacted mono-substituted tetrahydropyranyl acetates with allyltrimethylsilane under the agency of borontrifluoride etherate and determined their product ratios.[14,41-42,45,47-49] From these results the half-chair preferences were assessed (Figure 1.16). The C2 benzyloxy substituent prefers to be in an equatorial position, placing the C2-H2 bond optimally for hyperconjugative stabilization (Figure 1.16a).[42] The C3 and C4 benzyloxy substituents both prefer to be positioned axial, to allow for stabilization of the oxocarbenium ion by through-space electron density donation (Figure 1.16b and c).[42] The C5 benzyloxymethyl group prefers to be in equatorial position, for steric reasons (Figure 1.16d).[42,49] The preference of the C2-, C3- and C4- alkoxy substituents is in line with those found in the furanosyl oxocarbenium ions. The results of the methyleneoxy functionalized pyranoside and furanoside seem to indicate that that there is a difference in the

preference for the C5-pyranosyl and C4-furanosyl methyleneoxy group. In a furanosyl oxocarbenium ion this substituent has a small preference for an axial position, where it prefers an equatorial position in a pyranosyl oxocarbenium ion. It can be reasoned that the axially oriented C5 substituent in the pyranose system leads to an unfavorable steric interactions with the incoming nucleophile,[45,49] where in the furanosyl system this interaction does not play a role given the inside attack trajectory (see Figure 1.7).

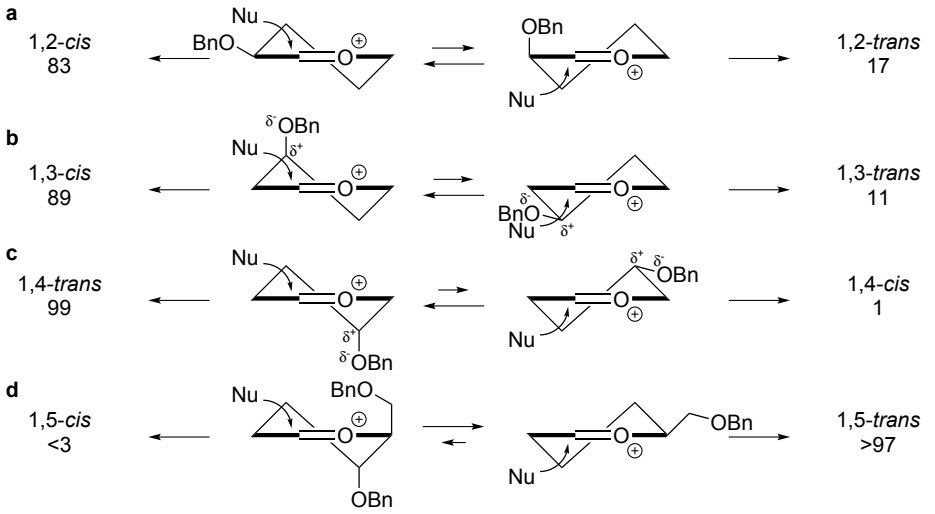


Figure 1.16 Individual substituent preferences in pyranosyl oxocarbenium ions.

In tetrahydropyran systems featuring multiple substituents the substituent preferences can be in line with or opposing each other. If all substituents are configured such that they can all adopt an optimal stabilizing position, this reinforces the half-chair preference (Figure 1.17). For example, the reaction of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl lyxopyranoside **64** with allyltrimethylsilane gives the 1,2-*cis* isomer as major product.[45] It can be reasoned that the $^{3}H_{4}$ half-chair (**66**) that places the C2, C3 and C4 alkoxides in positions for optimal stabilization, is at the basis of this observed selectivity. The alternative $^{4}H_{3}$ half-chair (**67**) does not benefit from any of the substituent stabilizing interactions.

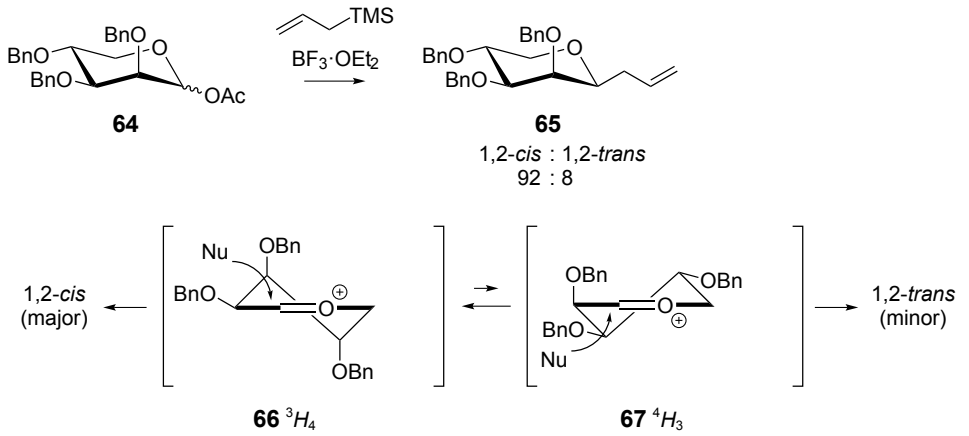


Figure 1.17 Substituent effects on *C*-allylation of lyxopyranose.

When a C5 alkoxymethyl group is added to the system, as in mannose **68**, the stereochemical course of the reaction alters dramatically. From the reaction shown in Figure 1.18 only the 1,2-*trans* product is isolated and formation of this product can originate from the $^4H_3$ half-chair oxocarbenium ion intermediate **71**. However when the pair of mannosyl half chair oxocarbenium ions **70** and **71** is analyzed, it becomes apparent that the $^3H_4$ half-chair **70** should be energetically more favorable because it places three out of four substituents in optimal positions.[45,50-51] Nucleophilic addition to this oxocarbenium ion should lead to the 1,2-*cis* product. To account for the 1,2-*trans* selectivity observed, Woerpel and co-workers suggested that the developing diaxial interactions between C3, C5 and the incoming nucleophile make this mode of attack too sterically congested. Therefore the nucleophile preferably reacts with the higher energy $^4H_3$ half-chair oxocarbenium ion, following a Curtin-Hammett kinetic scenario.[45]

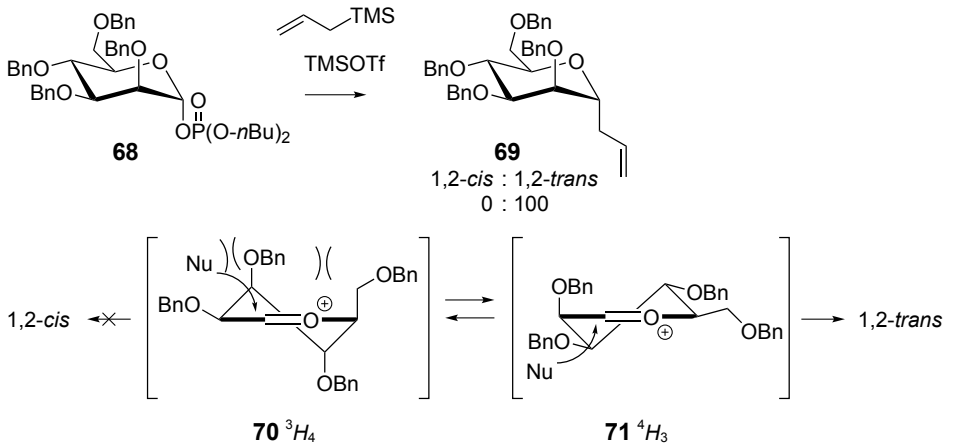


Figure 1.18 Mannopyranosyl *C*-allylation.

The orientation of the C6 oxygen substituent in hexopyranoses also contributes to the stability of pyranosyl oxocarbenium ion conformers. Rotation around the C6-O6 bond is possible and the interaction of this C6 oxygen substituent with the (partial) positive charge at the anomeric center depends on the orientation of this group, being *trans-gauche*, *gauche-trans* and *gauche-gauche* (See Figure 1.19).[52-53] Bols and co-workers investigated the influence of the different C5-C6 rotamers on the rate of hydrolysis of dinitrophenyl glycosides (**72**-**75**). They employed fused bicyclic ring systems to lock the C5-C6 rotamers and found that hydrolysis of the *gg*-rotamer **74** proceeded fastest and the *tg*-rotamer **72** slowest in the series.[52] The deactivating effect of the conformational lock, imposed on the system by the C4-C6 ring, is reflected by significantly increased hydrolysis rate of unconstrained **75**. The differences in reactivity between the three locked rotamers **72**, **73** and **74** was explained by Bols and co-workers to arise from the different dipole-charge interactions that are developed upon expulsion of the aglycon, with the C6-O6 dipole in **74** emerging as the least destabilizing. The conformational preference of the C5 alkoxymethyl to adopt a *gauche-gauche* configuration has also been observed in dioxocarbenium ions by the group of Woerpel.[49]

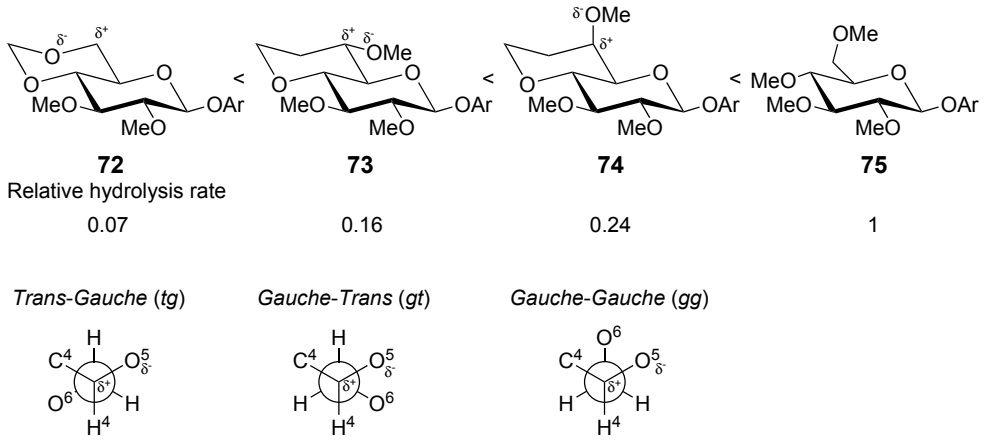


Figure 1.19 Deactivating effect of the conformationally restrained C6 oxygen on the hydrolysis (phosphate buffer in 1,4-dioxane, pH 6.5) of dinitrophenyl glycosides.

The influence of the carbohydrate substitution pattern on the acidic hydrolysis of different α-methyl sugars has long been known.[54] As displayed in Figure 1.20, the rate of the hydrolysis correlates with the amount of axial substituents, with gulose **78** hydrolyzing more rapidly than galactose **77**, which in turn hydrolyzes more rapidly than glucose **76**.[14,55-56] The differences in hydrolysis rate can in part be explained with differences in stability of the starting compounds. Considering oxocarbenium ions as intermediates it becomes apparent that the oxocarbenium ion derived from the most reactive epimer,

gulose **78**, can adopt the $^4H_3$ half chair **79** in which all ring substituents contribute favorably.

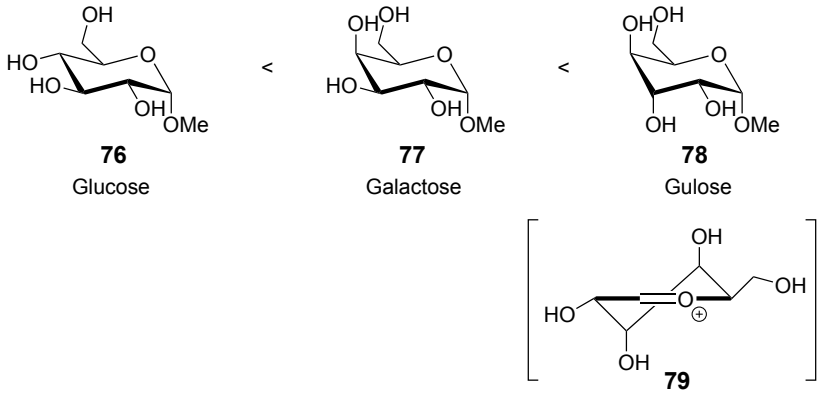


Figure 1.20 The rate of glycoside hydrolysis correlates with the amount of axial substituents.

The relative stability of this oxocarbenium ion has also been used to explain the unusual high 1,2-*cis* selectivity observed in *O*-glycosylations with gulosyl donors. For example, it was shown that gulose donor **80** reacts with glycosyl acceptor **53** in a pre-activation protocol to form 1,2-*cis* as the major product (Figure 1.21).[57] The *cis* product can originate from the $^4H_3$ half-chair (**83**) that benefits from optimal substituent stabilization. When this result is compared to the result of the *C*-allylation of mannose donor **69**, described above, it becomes clear that the orientation of the substituent at C5 is of decisive influence.

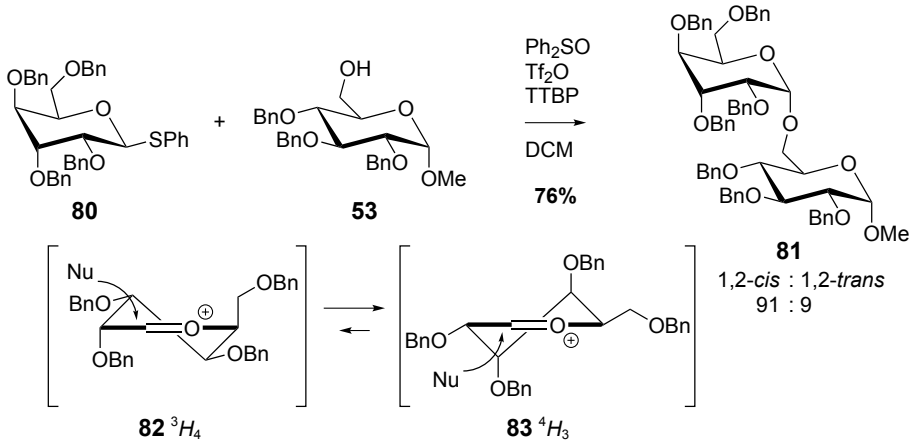


Figure 1.21 Gulose donors react in a pre-activation protocol to form 1,2-*cis* products.

Glycuronic acids are carbohydrates in which the terminal primary alcohol is oxidized to a carboxylic acid. The C5-carboxylic acid ester substituent can have a strong influence on the

reactivity of a pyranoside and generally glycuronic acid esters are less reactive their "non-oxidized" counterparts in glycosylation reaction, because the electron withdrawing C5 carboxylic acid ester impedes the development of positive charge at the anomeric center during a glycosylation reaction.[58-59] Oxidation of mannose however gives a donor with a reactivity that is significantly higher than expected.[60-62] Another striking feature of these donors is the fact that they afford primarily the 1,2-*cis* (β) products in glycosylation reactions (Figure 1.22),[58,60-61,63-65] in contrast to conformationally unbiased mannose donors that give predominantly 1,2-*trans* (α) products as in the case of the *C*-allylation of benzylated mannose acetate **68** described above (see Figure 1.18). The strong 1,2-*cis* selectivity and high reactivity of mannuronic ester donors can be related to the stability of the $^{3}H_{4}$ conformer of the oxocarbenium ion (**84**).[66] This conformer is stereoelectronically most favored by the positive contribution of the C2, C3 and C4 substituents and the crucial influence of the pseudoaxial C5 carboxylate function. This substituent is less sterically demanding than the alkoxymethyl substituent in mannose and more importantly, the pseudoaxial C5 carboxylate in the $^{3}H_{4}$ conformation allows through-space stabilization of the positive charge at the anomeric center.[57,62,64] This feature also becomes apparent in the conformation adopted by mannuronic ester anomeric α-triflates. These species are found in a conformational mixture, in which the $^{1}C_{4}$ chair conformation **87** having the anomeric triflate in an equatorial position predominates over the expected $^{4}C_{1}$ chair conformation **86** (**86**:**87** = 1:1.4).[63] It is also of interest to note that the anomeric triflate **86**-**87** is relatively unstable and decomposes at a relatively low temperature (-40 °C).[61] The increased reactivity of mannuronic ester donors, as also confirmed in a series of competition experiments, corresponds to the relative stability of the oxocarbenium ion.[61] For example, mannuronic acid donor **89** appeared to be more reactive than benzylidene donor **88** and as reactive as perbenzylated mannose donor **90**, one of the most reactive mannosyl donors known to date.[67]

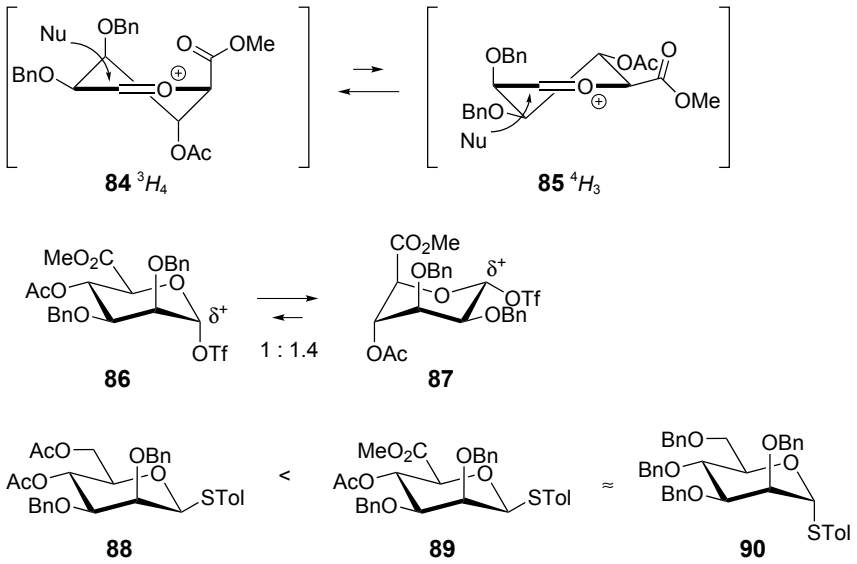


Figure 1.22 Mannuronic acid donors are highly reactive and in contrast to their non-oxidized analogs are highly 1,2-*cis* selective.

The favorable interactions of axially positioned alkoxy substituents on the stability of oxocarbenium ions also becomes apparent in positively charged iminosugars, carbohydrates of which the ring oxygen is replaced by a nitrogen atom. Bols and co-workers determined the pK_a values of a broad range of polyhydroxylated piperidines.[56,68-71] In the series comprising the iminosugar equivalents of glucose, mannose and galactose (Figure 1.23), it becomes clear that the basicity of the all-equatorial glucose (**91**) is less than that of the iminosugars bearing one axial hydroxyl group. Both mannose (**92**) and galactose (**93**) have a beta hydroxyl substituent configured in axial position and this causes an increase in basicity of 0.8 pK_a units. The difference between an equatorial and axial gamma hydroxyl is smaller as judged from the pK_a difference between **95** and **94** (0.4 pK_a units). Removal of a hydroxyl group leads to an increase of 1.4 pK_a units (compare **91** and **94**). The differences in pK_a indicate that an equatorial hydroxyl is more electron withdrawing than an axial hydroxyl and that the distance of the substituent to the positively charged center also plays a role. To account for the differences between the equatorial and axial epimers, Bols and co-workers reasoned that a ring substituent in equatorial position generates a more unfavorable dipole-charge interaction than the same group in axial position (see Figure 1.24).[69] In addition, the axial hydroxyl is also positioned properly to allow for through-space stabilization of the cation.

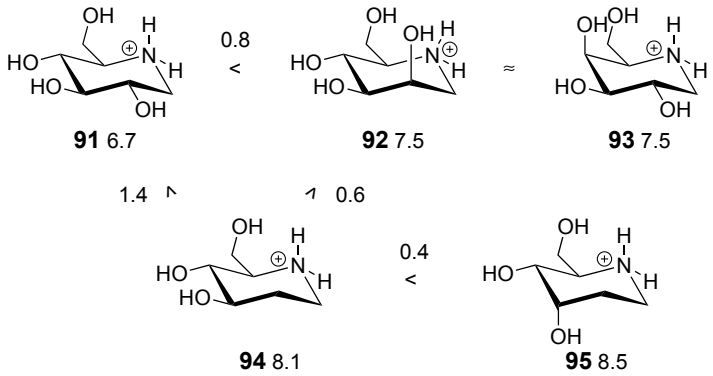


Figure 1.23 The pK_a of ammonium ions **91**-**95** depends on the configuration of the beta and gamma hydroxyls.

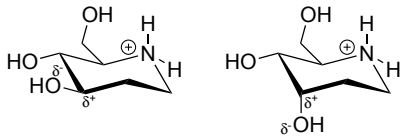


Figure 1.24 Dipole-charge interactions in protonated iminosugars with axially and equatorially oriented hydroxyl groups.

Bols and co-workers also noted that some of the iminosugars change their conformation upon protonation to adopt a more axial-rich conformation.[69] This behavior can be explained by the more favorable stereoelectronic effects of the axially oriented hydroxyl substituents on the ammonium cation. These are more stabilizing by virtue of through space electron donation and less destabilizing by virtue of the more favorable dipole-charge interaction than their equatorial counterparts. For example, mono-substituted piperidines change their conformational preference under acidic conditions (Figure 1.25).[72] In a non-protonated state the equilibrium between the $^4C_1$ and $^1C_4$ conformers of 3-hydroxypiperidine **96**-**97** lies to the side of the equatorial conformer. Protonation shifts the equilibrium to the side of the axial isomer (**99** *vs* **98**). This effect is less pronounced for the gamma hydroxyl analogue (Figure 1.25b), in line with the diminished effect of this substituent on the pK_a value. 4-Hydroxypiperidine (**100**-**103**) prefers the $^4C_1$ conformer under both basic and acidic conditions (**100** and **102**), but this preference is less pronounced under acidic conditions.

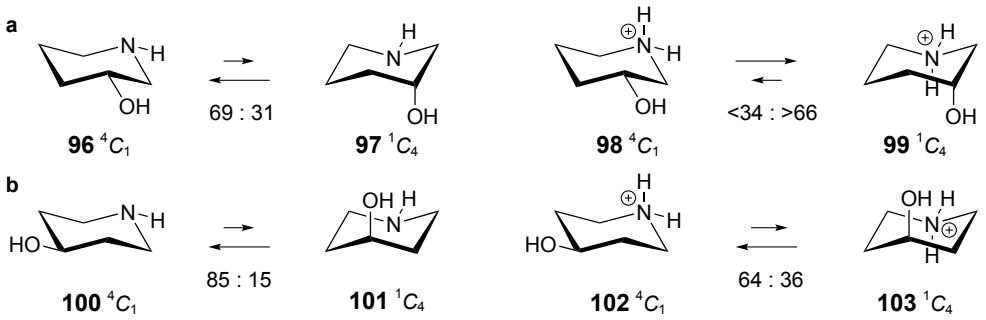


Figure 1.25 Changes in conformational equilibria induced by the protonation of the nitrogen atom.

1.4 Summary and thesis outline

Stereoelectronic effects are decisive in determining the structure and reactivity of molecules. In systems, in which (partial) positive charge is present or develops, the intrinsic destabilizing effects of electron withdrawing substituents, such as alkoxy groups in carbohydrates, can be minimized or even be made stabilizing by correct spatial positioning. This thesis investigates how stereoelectronic effects in carbohydrate based oxocarbenium ions, iminium ions and ammonium ions influences their shape and reactivity, by a combination of computational and experimental methods. **Chapter 2** focuses on detailing the steric and stereoelectronic effects that become apparent in furanosyl oxocarbenium ions of multiply substituted pentoses. Substitution reactions on these oxocarbenium ions all take place to give the 1,2-*cis* addition products with large selectivity, an outcome that can be explained using the conformations of the oxocarbenium ions involved. **Chapter 3** expands the work described in Chapter 2 to furanosyl oxocarbenium ions derived from ketosides featuring different anomeric substituents. **Chapter 4** describes an investigation into the Ugi multi component reaction of iminium ions, derived from the four possible D-pentofuranoses. The stereochemical outcome of this multi component reaction is set in the addition step in which the isocyanide reacts with the iminium ion. Where it is often assumed that Ugi reactions take place under thermodynamic control these results indicate that they in fact are under kinetic control. In **Chapter 5** the construction of a furanose iminosugar library is described from all possible pentofuranosyl iminosugars. **Chapter 6** details how the conformation of mannuronic acid derived iminosugars depends on the pH. Different C5 functionalities (the free acid, the methyl ester and amide) are probed and it is shown that the ester and free acid can flip their conformation, depending on protonation of the endocyclic amine. The last Chapter, **Chapter 7**, summarizes the research described in this Thesis and suggests future research objectives.

References and Notes

[1] Kirby, A. J., *Oxford Chemistry Primers, Stereoelectronic Effects*, Oxford University Press Inc., **1996**.

[2] Freitas, M. P.; Rittner, R.; Tormena, C. F.; Abraham, R. J. *Spectrochim. Acta Mol. Biomol. Spectros.* **2005**, *61*, 1771-1776, 10.1016/j.saa.2004.07.007.

[3] Reeves, L. W.; Stromme, K. O. *Trans. Faraday Soc.* **1961**, *57*, 390-398, 10.1039/tf9615700390.

[4] Kwestroo, W.; Meijer, F. A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 717-736, 10.1002/recl.19540730904.

[5] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry*, Oxford University Press, **2000**.

[6] Smith, M. B.; March, J., *March's Advanced Organic Chemistry*, John Wiley & Sons, Inc., **2007**.

[7] Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, Kluwer Academic/Plenum Publishers, **2000**.

[8] Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917-1920, 10.1016/s0040-4039(98)00047-1.

[9] Deslongchamps, P., *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, **1983**.

[10] Stolow, R. D.; Giants, T. W. *J. Chem. Soc., Chem. Commun.* **1971**, 528-529, 10.1039/c29710000528.

[11] Baldry, K. W.; Gordon, M. H.; Hafter, R.; Robinson, M. J. T. *Tetrahedron* **1976**, *32*, 2589-2594, 10.1016/0040-4020(76)88032-5.

[12] Dibble, D. J.; Ziller, J. W.; Woerpel, K. A. *J. Org. Chem.* **2011**, *76*, 7706-7719, 10.1021/jo200950s.

[13] Baghdasarian, G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 6851-6858, 10.1021/jo060968z.

[14] Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201, 10.1039/b600056h.

[15] Nagao, Y.; Goto, M. *Heterocycles* **1995**, *41*, 883-888, 10.3987/COM-95-7026.

[16] Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4174-4182, 10.1021/jo00222a001.

[17] Collins, L. J. *Tetrahedron Lett.* **1970**, 1547-1550, 10.1016/S0040-4039(01)98018-9.

[18] Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019-5087, 10.1016/s0040-4020(01)90118-8.

[19] Taha, H. A.; Richards, M. R.; Lowary, T. L. *Chem. Rev.* **2013**, *113*, 1851-1876, 10.1021/cr300249c.

[20] Fuchs, B., *Topics in Stereochemistry* **1978**, *10*, 1-94.

[21] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209, 10.1021/ja993349z.

[22] Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152, 10.1021/ja0375176.

[23] Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063-2066, 10.1021/ol0492647.

[24] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879-10884, 10.1021/ja0524043.

[25] Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609-6621, 10.1021/jo400945j.

[26] Lavinda, O.; Tran, V. T.; Woerpel, K. A. *Org. Biomol. Chem.* **2014**, *12*, 7083-7091, 10.1039/c4ob01251h.

[27] Finch, O. C.; Furkert, D. P.; Brimble, M. A. *Tetrahedron* **2014**, *70*, 590-596, 10.1016/j.tet.2013.12.012.

[28] Araki, Y.; Kobayashi, N.; Ishido, Y.; Nagasawa, J. *Carbohydr. Res.* **1987**, *171*, 125-139, 10.1016/s0008-6215(00)90883-8.

[29] Tian, Y.; Wu, S. H.; Wei, Z. *Carbohydr. Res.* **2005**, *340*, 235-244, 10.1016/j.carres.2004.11.014.

[30] Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145-148, 10.1246/cl.1989.145.

[31] van Delft, P., **2013**, *Synthetic Studies Towards Oligonucleotide Derivatives and Conjugates*, Ph.D Thesis, Leiden University.

[32] Doboszewski, B. *Nucleos. Nucleot. Nucl.* **2009**, *28*, 875-901, 10.1080/15257770903306518.

[33] Mukaiyama, T.; Suda, S. *Chem. Lett.* **1990**, 1143-1146, 10.1246/cl.1990.1143.

[34] Zhu, X. M.; Kawatkar, S.; Rao, Y.; Boons, G. J. *J. Am. Chem. Soc.* **2006**, *128*, 11948-11957, 10.1021/ja0629817.

[35] Lee, Y. J.; Lee, K.; Jung, E. H.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2005**, *7*, 3263-3266, 10.1021/ol0510668.

[36] Kaeothip, S.; Boons, G. J. *Org. Biomol. Chem.* **2013**, *11*, 5136-5146, 10.1039/c3ob40958a.

[37] Lee, Y. J.; Lee, B. Y.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2006**, *8*, 3971-3974, 10.1021/ol061444o.

[38] Baek, J. Y.; Joo, Y. J.; Kim, K. S. *Tetrahedron Lett.* **2008**, *49*, 4734-4737, 10.1016/j.tetlet.2008.05.118.

[39] Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118, 10.1021/jo902222a.

[40] Moume-Pymbock, M.; Crich, D. *J. Org. Chem.* **2012**, *77*, 8905-8912, 10.1021/jo3011655.

[41] Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169, 10.1021/ja993366o.

[42] Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528, 10.1021/ja037935a.

[43] Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322-5323, 10.1021/ja050830i.

[44] Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157-1160, 10.1021/ol0500620.

[45] Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641-2647, 10.1021/jo0522963.

[46] Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032-7035, 10.1021/ja00517a042.

[47] Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907-4910, 10.1021/ol8019956.

[48] Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039-8050, 10.1021/jo901639b.

[49] Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545-553, 10.1021/jo8017846.

[50] The mannosyl $^{3}H_{4}$ half-chair was calculated to be 3-4 kcal mol^{-1} lower in energy than the corresponding $^{4}H_{3}$ half-chair, see ref 45 and 51.

[51] Amat, L.; Carbo-Dorca, R. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1188-1198, 10.1021/ci0000272.

[52] Jensen, H. H.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205-9213, 10.1021/ja047578j.

[53] Moume-Pymbock, M.; Furukawa, T.; Mondal, S.; Crich, D. *J. Am. Chem. Soc.* **2013**, *135*, 14249-14255, 10.1021/ja405588x.

[54] Overend, W. G.; Sequeira, J. S.; Rees, C. W. *J. Chem. Soc.* **1962**, 3429-3439, 10.1039/jr9620003429.

[55] Bols, M.; Liang, X. F.; Jensen, H. H. *J. Org. Chem.* **2002**, *67*, 8970-8974, 10.1021/jo0205356.

[56] McDonnell, C.; Lopez, O.; Murphy, P.; Bolanos, J. G. F.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374-12385, 10.1021/ja04746t.

[57] Dinkelaar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982-4991, 10.1021/jo900662v.

[58] van den Bos, L. J.; Codée, J. D. C.; Litjens, R. E. J. N.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 3963-3976, 10.1002/ejoc.200700101.

[59] Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; Van der Marel, G. A., *Top. Curr. Chem.* **2011**, *301*, 253-289, 10.1007/128_2010_111.

[60] Codée, J. D. C.; Walvoort, M. T. C.; de Jong, A. R.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Carbohydr. Chem.* **2011**, *30*, 438-457, 10.1080/07328303.2011.624284.

[61] Walvoort, M. T. C.; de Witte, W.; van Dijk, J.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Org. Lett.* **2011**, *13*, 4360-4363, 10.1021/ol2016862.

[62] Codée, J. D. C.; van den Bos, L. J.; de Jong, A. R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38-47, 10.1021/jo8020192.

[63] Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 12080-12081, 10.1021/ja905008p.

[64] Walvoort, M. T. C.; Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carbohydr. Res.* **2010**, *345*, 1252-1263, 10.1016/j.carres.2010.02.027.

[65] Walvoort, M. T. C.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2010**, *75*, 7990-8002, 10.1021/jo101779v.

[66] DFT calculations at B3LYP/6-311G** level indicate that the $^{3}H_{4}$ conformer is favored by 5 kcal mol^{-1} over its $^{4}H_{3}$ counterpart (unpublished results).

[67] Koeller, K. M.; Wong, C. H. *Chem. Rev.* **2000**, *100*, 4465-4493, 10.1021/cr990297n.

[68] Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3447-3449, 10.1002/1521-3773(20010917)40:18<3447::aid-anie3447>3.0.co;2-8.

[69] Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218-1226, 10.1002/1521-3765(20020301)8:5<1218::aid-chem1218>3.0.co;2-x.

[70] Pedersen, C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 115-122, 10.1016/j.tet.2004.10.039.

[71] Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259-265, 10.1021/ar050189p.

[72] Terui, Y.; Tori, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 127-133, 10.1039/p29750000127.