Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2503

www.rsc.org/obc

PERSPECTIVE

On a so-called "kinetic anomeric effect" in chemical glycosylation

Ian Cumpstey†

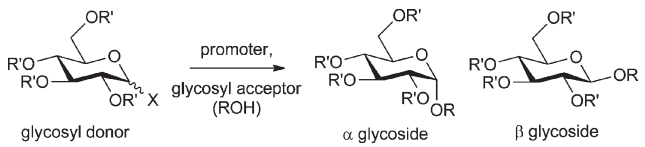
Received 6th October 2011, Accepted 6th January 2012
DOI: 10.1039/c2ob06696c

Commentary on diastereoselectivity in chemical glycosylation reactions, and dismissal of the influence of stereoelectronic effects analogous to the anomeric effect in kinetically controlled reactions.

Introduction

In a chemical glycosylation reaction, a glycosyl donor bearing an anomeric leaving group reacts with an alcohol nucleophile, the glycosyl acceptor, to form a glycosidic bond. A new stereogenic centre is created at the anomeric position (C1) of the carbohydrate (Scheme 1).

Generalised efficient universal oligosaccharide synthesising machines,[1–3] equivalent to the technologies available for oligopeptides and oligonucleotides, do not yet appear to be available, and this is one factor that holds back progress in glycobiology. Problems with automation of glycosylation will include control of the stereochemistry of the newly created glycosidic bond, as well as purification of the oligosaccharide product from undesired diastereomeric by-products, this second issue being a direct result of the failure to adequately solve the first. For progress to be made, it is helpful to have a good mechanistic understanding of the chemistry involved, and with this in mind, I address the current state of understanding of some aspects of anomeric selectivity in glycosylation reactions.



Scheme 1 General view of a chemical glycosylation reaction, showing the two possible diastereomeric glycoside products.

Experimental evidence for intrinsic diastereoselectivity in glycosylation

The question as to whether intrinsic α/β selectivities exist at all should possibly be straightforward to answer, given the massive amount of published experimental data on the results of glycosylation reactions. However, there are several problems with this. In the main, the data remains widely dispersed and its comprehensive collation into an interpretable form would be extremely tedious. An exception is Hindsgaul's catalogue of the glycosylation reactions of 1994,[4] and this dataset may be used as a model. A second problem is that diastereoselectivities are not always reported. For example, where the object of a reaction is the synthesis of a particular diastereomer that is then to be taken further in a synthetic sequence, the exact amount of the undesired diastereomer may be deemed uninteresting. Thirdly, multiple examples to examine the scope of "interesting" (which may be synonymous with "unusual") diastereoselectivities may result in their being overrepresented in the literature. Fourthly, the effect of solvents[5] on glycosylation diastereoselectivity, and the influence of protecting groups – the possible participation of C2 esters is well documented, but remote protecting groups[6–8] may also play a role – result in a very complex picture.

A brief statistical analysis of the 1994 data[4] was carried out for glucose, galactose and mannose donors with non-participating protection of C2, and excluding (*vide infra*) imidate donors or bromide donors activated by tetrabutylammonium bromide. No account was taken of the glycosylation solvent, and neither were reactions that may have been run under thermodynamic control (a matter that is not obvious from the presented data – and as mentioned below, not always obvious from the original papers either) excluded from the analysis. These results are shown in Table 1.

From these data, galactose and mannose appear to have some general overall preference for α glycoside formation, while glucose shows little general overall preference. The variation in diastereoselectivity, though, is high, and the sample sizes are small.

Thermodynamic control – the anomeric effect

The anomeric effect is a term used to refer to the phenomenon whereby electronegative axial substituents on carbons adjacent to the ring-oxygen in tetrahydropyran derivatives are stabilised relative to what might be expected from a consideration of A-values (*i.e.* steric factors: 1,3-diaxial interactions) alone.[9,10] Often – or usually – the size of the effect is sufficient that the stability of the axial anomer exceeds that of the equatorial anomer, resulting in a preponderance of the axial configuration at equilibrium. It is helpful to distinguish the effect from its

† *E-mail: ian.cumpstey@sjc.oxon.org*

Table 1 Diastereoselectivity data for pyranoside formation by glycosylation reactions with non-participatory (ether) C2 protection from Hindsgaul's 1994 data[4] summary. Mean values with standard deviations and sample sizes (*n*)

Donor configuration	% α-Configured product	*n*
Galacto	84 ± 31	16
Gluco	53 ± 32	57
Manno	71 ± 27	12

cause. A number of explanations have been advanced to explain the effect, including a dipole argument and an orbital argument relying on n → σ* overlap (Fig. 1).[11] The anomeric effect is a stereoelectronic effect, which means that it is conformationally sensitive. The fact that it is manifested as a difference in stability of configurational isomers (diastereomers) of carbohydrates is a result of the existence of essentially only one low-energy ring conformer (*i.e.* $^4C_1$ in the D series) for the common pyranoses. Similarly, the *exo*-anomeric effect refers to the higher occupancy (which is the same as the greater stability) of certain conformations of the glycosidic bond in which the aglycon is orientated such that the C1–O5 bond and the O1 lone pair have a 180° relationship;[12] it has been proposed that this effect may be explained by analogous models to those used to explain the (*endo*)-anomeric effect.

It is not uncommon for authors to attribute α-selectivity in chemical glycosylation reactions to the "anomeric effect". The majority of glycosylation reactions for glycoside formation in the chemical laboratory are run under kinetic control, that is to say that the two possible anomeric products do not interconvert under the reaction conditions; or, equally, that the less stable of the two products does not irreversibly convert into the more stable under the reaction conditions (or under quasi-thermodynamic conditions in which some product interconversion has taken place but equilibrium has not been reached by the time the reaction is quenched). This is possibly a wild assertion, as such interconversion is often not tested. However, it seems likely that it is often true as:

i) the promoters used are specifically chosen to suit the leaving group. They are hence often thiophilic (for thioglycosides), halophilic (for halides) *etc.* and often not particularly acidic or oxophilic, and not acidic enough to promote anomerisation. Exceptions could be the Lewis acids (even Brønsted acids) used as promoters for glycosyl fluorides, or possibly trichloroacetimidates (or acetates, whose use as glycosyl donors is less common), or the case when stoichiometric strong acid HX is produced as a by-product of the glycosylation reaction, which is actually a common scenario when the reaction is run in the absence of base or basic molecular sieves.[13]

ii) during glycosylation reactions, the formation of anomeric mixtures at C1 of monosaccharide constituents of oligosaccharides other than the one at which the new glycosidic bond is formed tends not to be reported, which implies not observed.

iii) in those cases where it has been tested, the glycosylation has often been found to run under kinetic control (but not always).

That said, a number of ancient and modern reactions do exist in which thermodynamic control of the anomeric selectivity is achieved. For example: i) The classical Fischer glycosylation[14] in which a reducing sugar is heated in an alcoholic solvent in the presence of acid can be and is usually run under thermodynamic control to form the equilibrium mixture of glycosides by endocyclic C–O bond-cleavage and reclosure. Usually (for aldohexoses) this will consist of a mixture of pyranosides (at the expense of first-formed furanosides), with the α anomer often predominating to a greater or lesser extent, in accordance with the anomeric effect.[15] Total anomeric stereocontrol is rarely achieved. ii) A 2,3-carbamate protecting group on *N*-acetyl glucosamine β-glycosides facilitates anomerisation to give the α-glycosides under Lewis acid catalysis by endocyclic C–O bond-cleavage and reclosure.[16] iii) Glucuronic acid β-glycosides are anomerised to the α-glycosides under Lewis acid catalysis by endocyclic C–O bond-cleavage and reclosure.[17] iv) β-Mannosides are anomerised particularly easily using a particular Lewis acid catalyst, by endocyclic C–O bond-cleavage and reclosure.[18] Of course, in all of these cases, the anomeric effect is important in determining the reaction outcome.

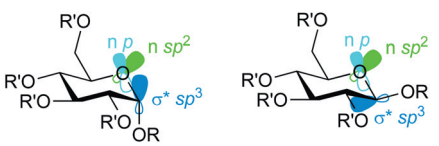


Fig. 1 Ground-state situation, illustrated for glucose. Orbital overlap to explain the anomeric effect; a p lone pair on oxygen has significant stabilising overlap with a σ* antibonding C1–O1 orbital in the α configuration and $^4C_1$ conformation (although these orbitals are not completely antiperiplanar), whereas in the β configuration, the p lone pair is almost orthogonal to the C1–O1 bond in the $^4C_1$ conformation.

Kinetic control – introduction

When the glycosylation reaction is run under kinetic control, clearly the anomeric effect (influencing the relative stability of the two anomeric products) can have no bearing on the diastereoselectivity of the reaction, which would be governed rather by the relative stability of the lowest energy transition states leading to each of the two diastereomeric products. A so-called "kinetic anomeric effect"[19,20] has been invoked as an explanation for a high degree of α selectivity in glycosylation reactions.

A high degree of diastereoselectivity might *in itself* be termed a kinetic anomeric effect; the "effect" being the formation of, say, more α product due to the lower energy transition state leading to its formation than that leading to the formation of the rival β anomer. But that explanations analogous to those that have been invoked to explain the anomeric effect (such as orbital overlap or dipole interaction) may be used to explain such a "kinetic anomeric effect" does not follow. In the ground state of the common hexopyranosides, the conformation is essentially fixed in the $^4C_1$ chair, and the required orbital interactions that explain the anomeric effect (Fig. 1) are either present (α case) or they are absent (β case).

To consider the possibility that an "anomeric effect" influences the diastereoselectivity of a glycosylation reaction, we must consider kinetic factors, specifically, the relative energies of the transition states leading to the α and β anomers. This in turn requires a consideration of the reaction mechanisms and the

orbital interactions in the different possible transition states. The question as to whether glycosylation reactions go *via* S_N1, S_N2 mechanisms, or intermediate mechanisms is pertinent, and the answer is almost certainly different for the many different chemical glycosylation reactions that have been conducted. Usually, when considering diastereoselectivity in nucleophilic substitution reactions, we are considering S_N1 reaction mechanisms, as S_N2 reactions are normally characterised by a stereospecific inversion of configuration. Hence when a kinetic anomeric effect is invoked to explain diastereoselectivity, normally this might be expected to involve an S_N1 mechanism.

Reactions *via* glycosyl cations: the S_N1 extreme

For mechanisms with oxacarbenium ion intermediates, *i.e.* S_N1 mechanisms, a discrete carbocationic intermediate is formed with an empty p orbital on the sp^2 hybridised C1. It is almost universally accepted that glycosyl cations are intermediates in glycosylation reactions.[21] The conformation of the pyranose ring is expected to change to accommodate this, adopting a conformation in which orbital interactions between the ring-oxygen lone pairs and the empty p orbital on C1 can be maximised. This covers conformations in which C5, O5, C1 and C2 are coplanar, and allowed conformations include $B_{2,5}$, $^{2,5}B$, $^{3}H_4$, $^{4}H_3$ (Fig. 2) (and also higher energy variants such as E_3, ^{3}E, ^{4}E and E_4). Woerpel's work on the glycosylation of polydeoxypyranoses has led to a model based on half-chair conformations,[22] but given: i) the conclusions from enzymatic glycosylation that some mannosidases operate with the sugar in a $B_{2,5}$ conformation;[23] ii) the well known tendancy for mannonolactone, with an sp^2 hybridised C1, to occupy a $B_{2,5}$ conformation (in contrast to say gluconolactone, which occupies a half-chair);[24] iii) recent suggestions that even ground state β-mannose has conformations close to $B_{2,5}$ as the lowest energy conformations after $^{4}C_1$;[25] ruling out the possibility of boat conformations for putative glycosyl cations in chemical glycosylation of fully functionalised sugars, and of mannose in particular could be rash.[26] However, as the possible *B* or *H* conformers are necessarily identical in the *local* environment of C1 from a stereoelectronic point of view, any arguments on the nature of a so-called kinetic anomeric effect apply equally, irrespective of whether the conformation is *B* or *H*.

Diastereoselectivity in S_N1 reactions arises from the different tendencies of the nucleophile to attack each of the two distinct diastereotopic faces of the glycosyl cation, which is quantified as the relative energies of the two possible transition states (Fig. 3). The S_N1 transition states, which are the crucial determinant of diastereoselectivity are expected (Hammond postulate) to have structures closely resembling a cationic intermediate, much more so than the ground state of the products. This means that the reaction of the glycosyl cation to form the glycoside (product) is expected to have an early transition state, and that using the glycosyl cation geometry as a model of the transition state would be reasonable. Within the broader class of oxacarbenium ions in general, glycosyl cations might be expected to have a higher reactivity – and an earlier transition state – due to the multiple electron-withdrawing groups present on the pyranosyl ring.[27] In this scenario, there will be no anticipated difference in orbital interactions between the two diastereomeric transition states (Fig. 4), and also conformationally the pyranosyl ring in the two transition states would be very similar, meaning that differences in transition state energies must be dominated by other factors, such as sterics.

In the Woerpel model (Scheme 2) the preference for attack at one or other of the two diastereotopic faces of one of two possible half-chair conformers ($^{4}H_3$ and $^{3}H_4$) of an intermediate glycosyl cation is said to be predicted by the conformation of the product developing at the transition state, which would be either a chair (favoured) or a skew-boat (*S*) (disfavoured).[22] Which of the possible half-chair conformers is chosen as being the one leading to reaction could either be the more stable or the more reactive of the two (in a Curtin–Hammett scenario with rapid conformational exchange of the cation intermediate). But the difference in the energies of these different possible transition states does not come from the presence or absence of particular orbital interactions. Even if we were to extrapolate all the way to the product in what is assumed to be its initially-formed conformation – a long way energetically, and structurally, from the transition state – the two possible conformations, skew-boat and chair, are stereoelectronically identical at C-1. Moreover, the same would also be true of the two possible product diastereomers (in their initially-formed conformations) formed from the alternative conformer of the glycosyl cation intermediate (Scheme 2). Hence, even if the transition states for α and β glycoside formation in S_N1 reaction mechanisms do not have coplanarity for C5, O5, C1 and C2, the local symmetry between α

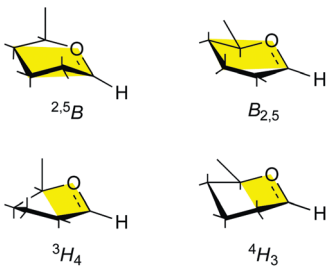


Fig. 2 Boat and half-chair conformations satisfying the requirement of coplanarity of C5–O5–C1–C2. The reference plane used to name the conformations is shaded.

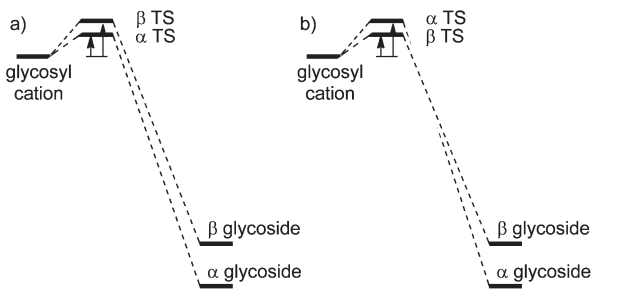


Fig. 3 Diastereoselectivity in S_N1 reactions arises from the difference in energy of the α and β transition states relative to a common intermediate glycosyl cation. One may imagine a situation (a) in which the α transition state is kinetically favoured or (b) in which the β transition state is kinetically favoured. The relative stability of the products is governed by the anomeric effect, which is conformationally dependent and does not apply at the transition states.

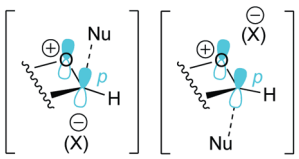


Fig. 4 Transition state situation. Illustration of generalised S_N1 transition states and the leading to α and β glycosyl bonds: the local identity of orbital interactions and geometry rules out any generalised orbital-based explanations for the so-called kinetic anomeric effect (a.k.a. α/β diastereoselectivity) that would be analogous to those used for the anomeric effect (*i.e.* based on certain interactions only being present for the α anomer). Different possible conformations of the pyranose rings (meaning the positions of C3 and C4) are deliberately not shown here as this will not influence the stereoelectronics at C1 – they are shown in Fig. 2.

and β transition states means that in the immediate vicinity of the reaction centre, *orbital interactions at the respective transition states will be the same for α and β bond-forming reactions*. Any difference in energies of the α and β transition states is therefore expected to arise from factors other than differences in orbital interactions, which may include conformational factors[28] (intramolecular steric clashes), or differences in steric crowding of the two faces.

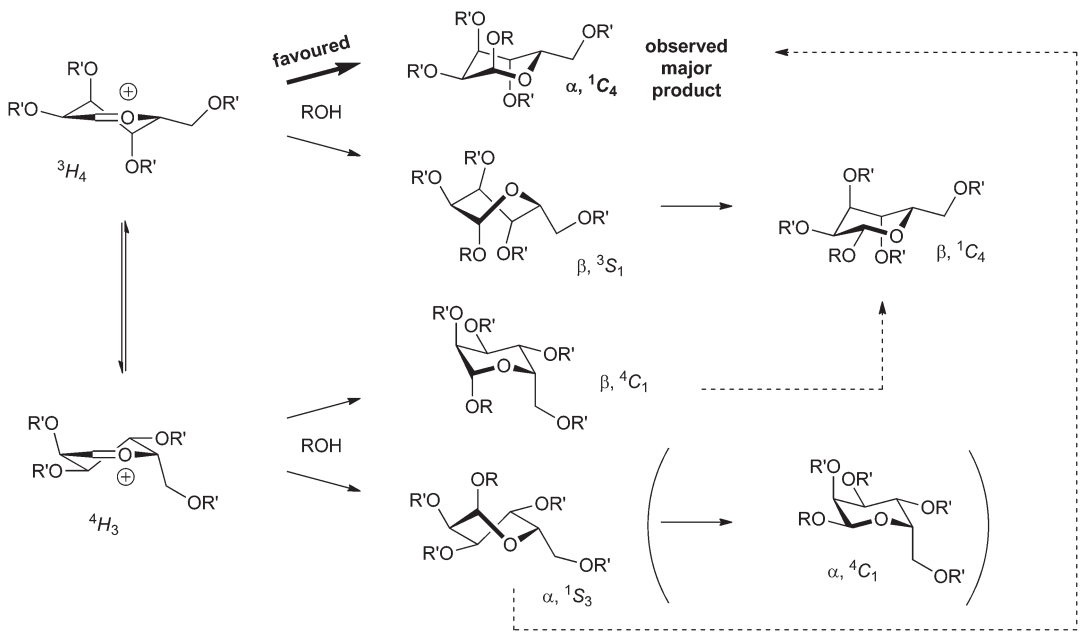
Reactions proceeding with inversion of configuration at the anomeric centre: the S_N2 situation and the S_N1–S_N2 crossover situation

S_N2 mechanisms are conspicuous by their requirement for stereospecific inversion of configuration. However, the possibility of multiple S_N2 substitutions (or at least multiple stereospecific substitutions with inversion of configuration) by potential leaving groups prior to final attack by an alcohol nucleophile to deliver the product blurs this diagnostic phenomenon. This describes the Lemieux α glucosylation[29] where the substitution of bromide by bromide equilibrates the more stable α bromide with the more reactive β bromide prior to rate-determining *O*-glycoside formation. In such a scenario, diastereo*selectivity* will operate. This may be governed by the relative energies of the two possible diastereomeric transition states as described by the Curtin–Hammett principle (Fig. 5).

Further to the Lemieux α-glucosylation, and despite the near-universal acceptance of S_N1 (like) mechanisms, a number of other examples of glycosylation reactions with S_N2 characteristics can be considered. The displacement of glycosyl chlorides by thiolate in the *gluco* series, but not the *manno*, has been shown to obey a rate-law consistent with S_N2 kinetics, and as such represents a *bona fide* S_N2 process.[30]

Inversion of configuration (of starting materials or of reactive intermediates) has been invoked to explain the stereochemical outcome of some glycosylation reactions. For example, in Schmidt's trichloroacetimidate methods (predominant inversion of configuration of the starting imidate in the *gluco* series, but not the *manno*);[31] in the Crich β mannosylation (predominant α → β inversion of an α-triflate intermediate in the *manno* series, but not the *gluco*);[32,33] and in the reactions of glycosyl sulfonium salts by Boons and others (apparent predominant β → α inversion in the *gluco* series).[34] The acetonitrile "effect", in which a preponderance of β product is seen (in the *gluco* series, but not the *manno*), has been explained by solvent participation and a proposed predominant α → β inversion.[35] Also in enzymatic glycoside hydrolysis and glycosylation,[36] reactions tend to be stereospecific with inversion or double inversion.[37] This apparent inversion of configuration that has been cited implies some characteristics of S_N2 mechanisms, without necessarily fulfilling all the criteria of an S_N2 process.

A continuum of mechanisms between S_N1 and S_N2 extremes has been proposed, with the distinction being blurred to the



Scheme 2 Woerpel model for diastereoselectivity exemplified by an L-gulosylation reaction described by the Leiden group.[22f] Note that the $^1C_4$ conformation is favoured for the L-guloside products. Orbital interactions are expected to be the same for *all four* considered transition states.

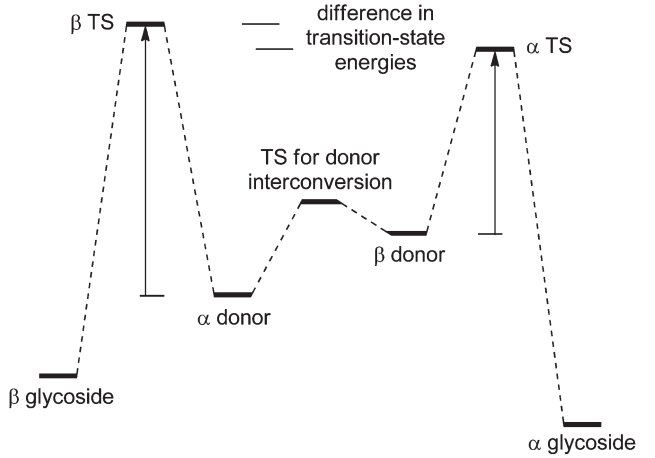


Fig. 5 Curtin–Hammett situation for glycosylation with inversion. The α and β donors are in rapid equilibrium, and the absolute difference in the energies of the two transition-state energies leading to α or β glycosides determines the diastereoselectivity (as is seen in practice for glucose in the Lemieux α-glucosylation).

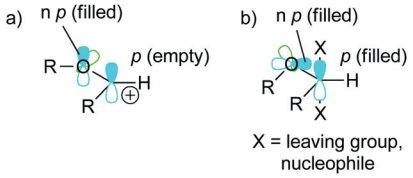


Fig. 6 Illustration of the orbital interactions and conformational consequences at an acetal carbon at (a) S_N1 (intermediate cation) and (b) S_N2 (transition state) extremes, from ref. 39.

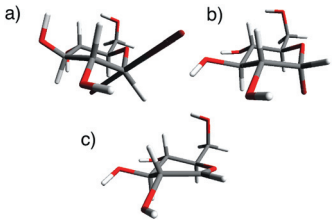


Fig. 7 (a) Naive model of an (unprotected) pyranosyl S_N2 transition state fulfilling the stereoelectronic ideal for an acyclic system,[40] and comparison with (b) chair and (c) half-chair conformations.

extent that a plateau of energies can exist.[38] In what way and to what extent a reaction described as S_N2-like is S_N2-like is not always made clear. We must imagine what this means from a structural point of view. In the S_N1 extreme, at the transition state in the bond-forming reaction, a glycosyl-cation-like C-1 is becoming associated with a nucleophile. In moving through the hypothetical mechanistic continuum towards a more S_N2-like scenario, a nucleophile and a leaving group – or a moiety previously considered as the counter-ion to the glycosyl cation – both become more associated with the reaction centre at the transition state. In an S_N2 extreme, the nucleophile and leaving group are maximally associated at the transition state. A scenario whereby the nucleophile and leaving group are *equally* associated at the transition state can only exist when the leaving group and nucleophile are identical.

The S_N1–S_N2 borderline in nucleophilic substitution reactions at acetal carbons has been examined from a molecular orbital standpoint,[39] and a significant conformational difference between these transition states has been noted in simple (acyclic) systems, which should have important consequences for a proposed mechanistic continuum in glycosylation. Just as for the S_N1 extreme with its intermediate cation, also in the S_N2 extreme, C1 becomes sp^2 hybridised at the transition state, but with the crucial difference that while the p orbital on C1 is *empty* in the S_N1 intermediate glycosyl cation, at the S_N2 transition state it is *filled*. This means that those conformations around the O5–C1 bond in which orbital interactions between the ring-oxygen lone pairs and the C-1 p orbital are maximised (*i.e.* those conformations most favoured in the S_N1 mechanism) become energy *maxima* in the S_N2 extreme, and the ideal conformation of the torsion C5–O5–C1–C2 becomes that in which the oxygen lone-pair p orbital and the C1 p orbital are orthogonal, *i.e.* 90° (Fig. 6).[39]

A molecular model[40] of such a structure reveals that this requirement is satisfied by a somewhat distorted version of the $^4C_1$ chair (Fig. 7). Clearly the two sites occupied by the nucleophile and leaving group are very different steric environments, the one under the ring being extremely crowded, and it is very likely that the constraints of the cyclic environment in the pyranose ring may cause the stereoelectronically favourable conformation (as determined in an acyclic system) to be overruled on steric grounds.[41] What should be clear, though, is that as reaction mechanisms become more S_N2-like (meaning as the nucleophile and leaving group become more associated with the reaction centre at the transition state), the stereoelectronic constraint that puts C5–O5–C1–C2 coplanar becomes weaker, although the predicted move away from coplanarity is sudden rather than gradual.[39] It may be possible to exactly define an intermediate point on the continuum between extreme S_N1 and S_N2 mechanisms, an S_N2-like extreme of the S_N1 mechanism, as being the point at which the leaving group and nucleophile are maximally associated at the transition state for which the conformation of the ring still resembles a glycosyl cation (like) conformation (*i.e.* with C5–O5–C1–C2 coplanar or close to coplanar).[41] And in those glycosylation reactions with an S_N1-like ring-conformation (coplanarity around the O5–C1 bond), even where the leaving group is still associated at the transition state, giving some S_N2-like characteristics (meaning stereospecific substitution reactions, including multiple stereospecific substitution reactions), orbital interactions – hence stereoelectronic factors – are apparently similar for the rival transition states leading to α and β products.

Conclusions

It should be clear that a statement such as "a high diastereoselectivity was achieved [in a kinetically controlled glycosylation] due to the anomeric effect" is always wrong. To say "a high diastereoselectivity was achieved [in a kinetically controlled glycosylation] due to the kinetic anomeric effect" is meaningless and misleading, and at best is a pleonasm. At least molecular orbital arguments cannot account for diastereoselectivities in glycosylation reactions. I hope that an increased clarity in explanation of

the results of glycosylation reactions will help facilitate discussion and explanations of the reaction mechanism of chemical glycosylation, and thus ultimately facilitate progress towards the goal of efficient and automated glycosylation.

Notes and references

1 O. J. Plante, E. R. Palmacci and P. H. Seeberger, *Science*, 2001, **291**, 1523–1527.
2 F. A. Jaipuri and N. L. Pohl, *Org. Biomol. Chem.*, 2008, **6**, 2686–2691.
3 Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov and C.-H. Wong, *J. Am. Chem. Soc.*, 1999, **121**, 734–753.
4 F. Barresi and O. Hindsgaul, *J. Carbohydr. Chem.*, 1995, **14**, 1043–1087.
5 H. Satoh, H. S. Hansen, S. Manabe, W. F. van Gunsteren and P. H. Hünenberger, *J. Chem. Theory Comput.*, 2010, **6**, 1783–1797.
6 K. S. Kim and D.-H. Suk, *Trends Glycosci. Glycotechnol.*, 2011, **23**, 53–66.
7 D. Crich and I. Sharma, *J. Org. Chem.*, 2010, **75**, 8383–8391.
8 M. Bols and H. Hansen, *Chem. Lett.*, 1994, 1049–1052.
9 (*a*) J. T. Edward, *Chem. Ind. (London)*, 1955, 1102; (*b*) R. U. Lemieux and P. Chu, Abstracts of papers. In: 133rd National Meeting of the American Chemical Society, American Chemical Society, Washington, DC, 1958, p. 31N San Francisco. (*c*) IUPAC Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). p 2198. XML online corrected version: http://goldbook.iupac.org (2006–) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins. ISBN 0-9678550-9-8, DOI: 10.1351/goldbook.A00372. (*d*) S. Gerber-Lemaire and P. Vogel, in *Anomeric Effects in Pyranosides and Related Acetals, Carbohydrate Chemistry: Chemical and Biological Approaches*, ed. A. P. Rauter and T. K. Lindhorst, RSC, 2009, pp. 13–32.
10 1,3-Diaxial interactions are expected to be less significant on the top face of a pyranose ring than in cyclohexanes due to the absence of axial substituents on the ring oxygen and also to the slightly distorted ring pucker, which alleviates steric clashes. On the bottom face of a pyranose ring, 1,3-diaxial interactions may be expected to be slightly more significant than in cyclohexanes, due to the slightly distorted ring pucker, which here accentuates steric clashes.
11 Recent computational work against hyperconjugative (orbital) explanations for the anomeric effect: Y. Mo, *Nat. Chem.*, 2010, **2**, 666–671.
12 R. U. Lemieux and S. Koto, *Tetrahedron*, 1974, **30**, 1933–1944.
13 A. Meijer and U. Ellervik, *J. Org. Chem.*, 2004, **69**, 6249–6256.
14 B. Capon, *Chem. Rev.*, 1969, **69**, 407–498.
15 P. M. Collins and R. J. Ferrier, *Monosaccharides*, J. Wiley & Sons, Chichester, 1995, p. 63.
16 (*a*) J. D. M. Olsson, L. Eriksson, M. Lahmann and S. Oscarson, *J. Org. Chem.*, 2008, **73**, 7181–7188; (*b*) M. Boysen, E. Gemma, M. Lahmann and S. Oscarson, *Chem. Commun.*, 2005, 3044–3046; (*c*) H. Satoh, S. Manabe, Y. Ito, H. P. Lüthi, T. Laino and J. Hutter, *J. Am. Chem. Soc.*, 2011, **133**, 5610–5619; (*d*) S. Manabe, K. Ishii and Y. Ito, *J. Am. Chem. Soc.*, 2006, **128**, 10666–10667; (*e*) S. Manabe, K. Ishii, D. Hashizumi, H. Koshino and Y. Ito, *Chem.–Eur. J.*, 2009, **15**, 6894–6901.
17 (*a*) W. Pilgrim and P. V. Murphy, *J. Org. Chem.*, 2010, **75**, 6747–6755; (*b*) C. O'Brien, M. Polakova, N. Pitt, M. Tosin and P. V. Murphy, *Chem.–Eur. J.*, 2007, **13**, 902–909.
18 Y. Wang, H.-S. Cheon and Y. Kishi, *Chem.–Asian J.*, 2008, **3**, 319–326.
19 Unrelated usage: Schmidt has used the term "kinetic anomeric effect" to refer to the preferential formation of β glycosides (or trichloroacetimidates under kinetic control) under basic alkylative glycoside formation conditions, due to the higher nucleophilicity of the β alkoxide than the α alkoxide: R. R. Schmidt and J. Michel, *Tetrahedron Lett.*, 1984, **25**, 821–823; The term has been used similarly in cycloaddition reactions involving anomeric heteroatoms; R. Huber and A. Vasella, *Tetrahedron*, 1990, **46**, 33–58.
20 Sinnott has used the term "kinetic anomeric effect" in the context of its non-existence for the alleged participation of antiperiplanar oxygen lone pairs in assisting the departure of leaving groups: M. L. Sinnott, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ACS Symposium Series, 1993, ch. 6, vol. 539, pp. 97–113.
21 It is important to note the absence of direct evidence for glycosyl cations in solution, see: L. Bohé and D. Crich, *C. R. Chimie*, 2011, **14**, 3–16; as well as the suggestion that the lifetime of glycosyl cations in organic solution should be too short to allow their existence, see: M. L. Sinnott, *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism*, RSC, London, 2007, pp. 120, 82–83, 67–70.
22 (*a*) J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, *J. Am. Chem. Soc.*, 2000, **122**, 168–169; (*b*) L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, *J. Am. Chem. Soc.*, 2003, **125**, 15521–15528; (*c*) S. Chamberland, J. W. Ziller and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 5322–5323; (*d*) C. G. Lucero and K. A. Woerpel, *J. Org. Chem.*, 2006, **71**, 2641–2647; (*e*) J. Dinkelaar, A. R. de Jong, R. van Meer, M. Somers, G. Lodder, H. S. Overkleeft, J. D. C. Codee and G. A. van der Marel, *J. Org. Chem.*, 2009, **74**, 4982–4991; (*f*) M. T. C. Walvoort, J. Dinkelaar, L. J. van den Bos, G. Lodder, H. S. Overkleeft, J. D. C. Codée and G. A. van der Marel, *Carbohydr. Res.*, 2010, **345**, 1252–1263.
23 L. E. Tailford, W. A. Offen, N. L. Smith, C. Dumon, C. Morland, J. Gratien, M.-P. Heck, R. V. Stick, Y. Bleriot, A. Vasella, H. J. Gilbert and G. J. Davies, *Nat. Chem. Biol.*, 2008, **4**, 306–312.
24 Z. Walaszek, D. Horton and I. Ekiel, *Carbohydr. Res.*, 1982, **106**, 193–201.
25 A. Ardevol, X. Biarnes, A. Planas and C. Rovira, *J. Am. Chem. Soc.*, 2010, **132**, 16058–16065.
26 But Whitfield's calculations in the context of a two-conformer model for glycosyl cations do not support a contribution from a boat conformer for any of the structures examined (including mannose configured structures): T. Nukada, A. Bérces, L. Wang, M. Z. Zgierski and D. M. Whitfield, *Carbohydr. Res.*, 2005, **340**, 841–852.
27 *In extremis* the S_N1–S_N2 "energy plateau" (*vide infra*) refers explicitly to the negligible energy difference between the energies of the glycosyl cation and that of the subsequent transition state, with the consequence that the transition state is expected to be *very* early – of course invoking S_N2 characteristics will also require the explicit participation of an associated leaving group as well as the nucleophile.
28 One caveat would be that not all chairs are equal and certain skew-boats may be lower in energy than certain chairs. See, for example: J. Rönnols, A. Burkhardt, I. Cumpstey and G. Widmalm, *Eur. J. Org. Chem.*, 2012, 74–84.
29 R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, *J. Am. Chem. Soc.*, 1975, **97**, 4056–4062.
30 A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 1960, 4637–4644.
31 R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 212–235.
32 D. Crich, *Acc. Chem. Res.*, 2010, **43**, 1144–1153.
33 This reaction has been the subject of more rigorous mechanistic investigations,[32] and H/D secondary kinetic isotope effect experiments have been consistent more with S_N1 than S_N2 values. See: D. Crich and N. S. Chandrasekera, *Angew. Chem., Int. Ed.*, 2004, **43**, 5386–5389.
34 (*a*) J. H. Kim, H. Yang, J. Park and G. J. Boons, *J. Am. Chem. Soc.*, 2005, **127**, 12090–12097; (*b*) T. J. Boltje, J.-H. Kim, J. Park and G.-J. Boons, *Org. Lett.*, 2011, **13**, 284–287; (*c*) J. Park, S. Kawatkar, J.-H. Kim and G.-J. Boons, *Org. Lett.*, 2007, **9**, 1959–1962; (*d*) M. A. Fascione, S. J. Adshead, S. A. Stalford, C. A. Kilner, A. G. Leach and W. B. Turnbull, *Chem. Commun.*, 2009, 5841–5843.
35 R. R. Schmidt, M. Behrendt and A. Toepfer, *Synlett*, 1990, 694–696.
36 For glycosyltransferases a mechanism with retention by same-face (S_Ni) has also been proposed: W. Klein, M. J. Im and D. Palm, *Eur. J. Biochem.*, 1986, **157**, 107–114; S. S. Lee, S. Y. Hong, J. C. Errey, A. Izumi, G. J. Davies and B. G. Davis, *Nat. Chem. Biol.*, 2011, **7**, 631–638.
37 M. L. Sinnott, *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism*, RSC, London, 2007, pp. 299–477.
38 (*a*) M. L. Sinnott, *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism*, RSC, London, 2007, p. 66; (*b*) J. R. Krumper, W. A. Salamant and K. A. Woerpel, *Org. Lett.*, 2008, **10**, 4907–4910.
39 D. Kost and K. Aviram, *J. Am. Chem. Soc.*, 1986, **108**, 2006–2013.
40 The model in Fig. 7(a) was constructed (to illustrate the consequences of applying a C5–O5–C1–O2 90° torsion constraint on the approximate positions of nucleophile and leaving group in a pyranosyl substitution reaction) using Avogadro molecular modelling software: a pyranosyl ring was geometry-optimised with a torsion angle constraint. The substituents at C-1 were then added by hand in a trigonal bipyramidal geometry.
41 Some calculated transition states for reactions with some S_N2 characteristics (inversion of configuration, but with kinetic isotope effects consistent with significant glycosyl cationic character at the transition state) have been found with ring-geometry resembling the S_N1 ideal: M. H. El-Badri, D. Willenbring, D. J. Tantillo and J. Gervay-Hague, *J. Org. Chem.*, 2007, **72**, 4663–4672.

