THE ROLE OF LONE PAIR INTERACTIONS IN THE CHEMISTRY OF THE ANOMERIC CENTRE OF MONOSACCHARIDES

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Abstract - The interactions of the lone pair orbitals of O-5 with the lone pair orbitals, or empty orbitals, of substituents on the anomeric carbon (C-1) are reviewed and these interactions are shown to be of great importance in the anomeric effect, the reverse anomeric effect and the reactions at the anomeric centre of monosaccharides.

INTRODUCTION

In previously published papers describing the roles of lone pairs in the chemistry of the monosaccharides[1,2,3,4] attention has largely been focused on the chemistry of O-1, C-2, O-2, C-3 and O-3.

There are several reactions which result in substitution at the anomeric centre whose mechanisms deserve attention and clarification, particularly in the areas of the difference in the reactivities of anomers, and the natures of the intervening processes in situations where these reactivities seem to be reversed.

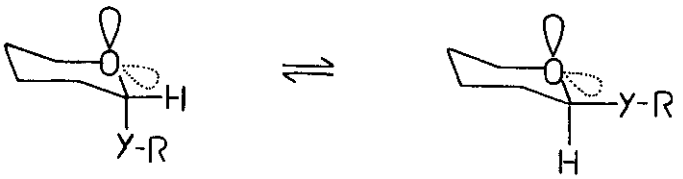
In the papers referred to above, the chemistry of C-1 was discussed only in connection with the enolisation of the glycos-2-uloses and the E1-like-E2 reactions of β-mannopyranosides[4]. Here an attempt will be made to discuss other aspects of the chemistry of C-1.

The large number of reactions at C-1 and O-1 whose results have been rationalised by way of the anomeric effect or the reverse anomeric effect require that a discussion of these anomeric effects precede all the other discussion.

DISCUSSION

The Anomeric Effect, The Exo-anomeric Effect and The Reverse Anomeric Effect.

The anomeric effects [5,6] refer to the distribution at equilibrium of, and hence the differences in stabilities of, the two stereoisomers at the anomeric centre, shown by the structures (1) and (2), where the atom Y can bear one or more, or no



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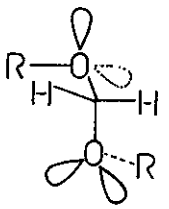
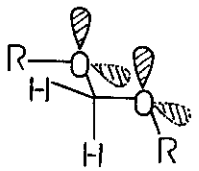


(3)

(5) R : CH_3



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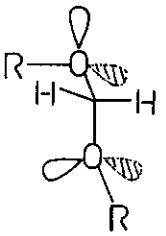
(7) R : CH_3



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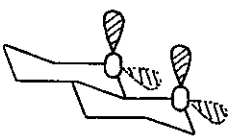

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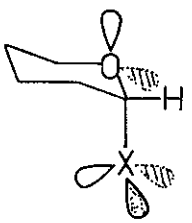

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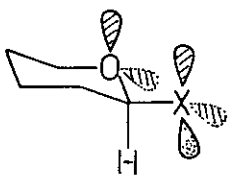

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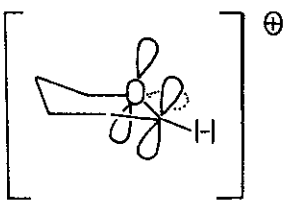

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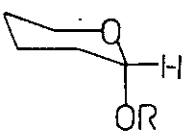

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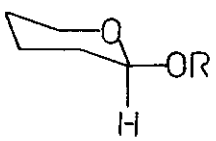


(13)

lone pairs of electrons. A consideration of the steric factor alone would suggest the greater stability and equilibrium concentration of the anomer (2), but the electronic factors often lead to the greater stability and equilibrium concentration of the anomer (1). This unusual stereochemical feature of some oxygen heterocycles is the anomeric effect. The situation in which the steric and electronic factors lead to the greater equilibrium concentration and stability of the anomer (2) is described as that due to the reverse anomeric effect.

Attention has been drawn to the roles of both the n-σ^* interactions[5] and the destabilising lone pair orbital interactions[5,6] in these anomeric effects, but the n-σ^* interactions have yielded more easily to theoretical manipulation than the lone pair repulsions.[5] Thus Wolfe et al. stated that a consideration of n-σ^* interactions reproduced not only the rotational behaviour of a given molecule but also the trends from molecule to molecule, and that the conformational behaviour of the XCH_2YH molecules, and the trends in the polyfluoromethanes, might also be discussed quantitatively in terms of destabilising lone pair orbital interactions, but that this was more difficult to convey in a simple way.[5] Nevertheless, reference has often been made to the n-σ^* interactions as the origins of the anomeric effect, while apparently ignoring the co-existing lone pair orbital interactions, which must be recognised in order to rationalise many reactions of the monosaccharides.[1]

Recently, F. Jorgensen et al. demonstrated, by photoelectron spectroscopy and non-empirical PRDDO molecular orbital calculations, that gauche,gauche acetals (3) were more stable than anti,anti acetals (4), particularly as indicated by the relative energies of the lone pair bearing orbitals.[7] Thus the HOMO and H-1 of gauche, gauche dimethoxymethane (5) are almost degenerate (separated by 0.02 eV), the similar orbitals of gauche,anti dimethoxymethane (6) are separated by about 0.24 eV, and those of anti,anti dimethoxymethane (7) are separated by 0.69 eV. The conformer (5) has no eclipsed lone pairs, the conformer (6) has one pair of eclipsed lone pairs and the conformer (7) has two pairs of eclipsed lone pairs. The calculated separation of the HOMO and H-1 of the lone pair bearing orbitals of anti,anti acetals was supported by the separation of these orbitals of the rigid anti,anti acetal model compound (8) of 0.85 eV, as measured by photoelectron spectroscopy. This very strong interaction of the lone pair orbitals of the anti, anti acetal (ΔE : 19.6 kcal/mol) and the smaller though significant interaction of the lone pairs of the gauche,anti acetal (ΔE : 5.5 kcal/mol) indicate the

importance of the lone pair interaction phenomenon.

These orbital splittings, which are mediated by both through-space[8,9] and through-bond[8,9] mechanisms, have resulted in the formation of a 'new', very energetic HOMO from the interaction of the less energetic lone pair orbitals. This 'new' HOMO must be more reactive than any of the 'parent' orbitals, and it is this formation of a molecular orbital of enhanced energy, and enhanced reactivity, that had been defined as the β-effect.[1]

Photoelectron spectroscopic and molecular orbital theoretical calculations[8,9] have also provided evidence for the through-space and through-bond mediated lone pair orbital interactions previously defined as the γ-effect[1]

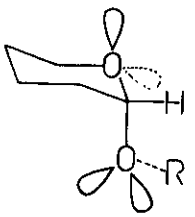
A full, though qualitative, discussion of the anomeric and related effects must include both the roles of the n-σ^* interactions and the lone pair orbital interactions. Only a few generalised examples will be used to draw attention to the roles of these important stereo-electronic factors in the anomeric, exo-anomeric and reverse anomeric effects, and it will be seen that these stereo-electronic effects sometimes support each other and sometimes oppose each other. An appreciation of the interplay of these effects will facilitate the discussion of the chemistry at the anomeric centre.

The Anomeric Effect.

The anomeric effect is best exemplified by the glycosyl halides, as generally represented by the simple molecules (9) and (10). The anomer (9) is known to be more stable than the anomer (10) (references 5 and 6). There can only be one pair of eclipsed lone pair orbitals in the anomer (9), but there are always two pairs of eclipsed lone pair orbitals in the anomer (10). The anomer (10) therefore experiences far more destabilisation by the lone pair orbital interactions than the anomer (9). Both the anomers (9) and (10) possess a n-σ^*(X, C-O) interaction between the shaded lone pair orbital of the halogen atom X and the anti-coplanar C-O bond. There is a n-σ^*(O-5, C-X) interaction present in the anomer (9) which is not present in the anomer (10). This last-mentioned n-σ^* interaction present in the anomer (9) is a stabilising interaction and combines with the lone pair orbital effects stated above in making the anomer (9) a more stable molecule than the anomer (10).

The Exo-anomeric Effect.[10,5]

The exo-anomeric effect can be illustrated by a consideration of the stereo-electronic factors which influence the generalised conformations of the α- and β-glyco-



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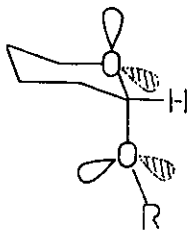

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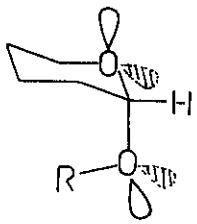

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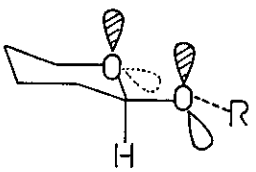

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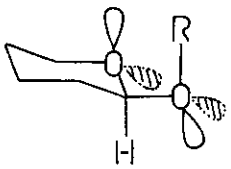

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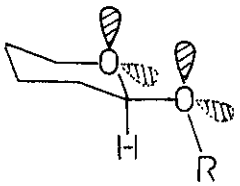

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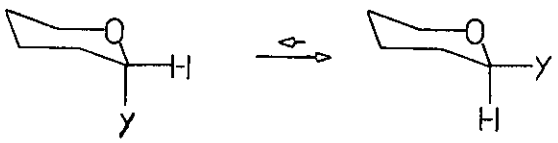
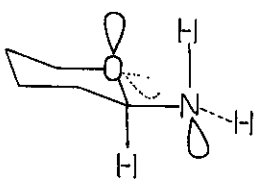


(15) Y : NH_2

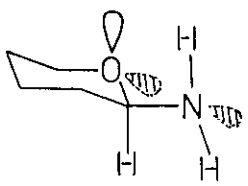
(17) Y : pyridinium

(14) Y : NH_2

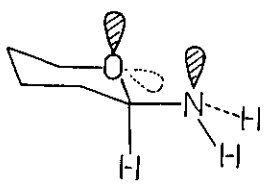
(16) Y : pyridinium



(14A)



(14B)



(14C)

sides (12) and (13), which can be equilibrated via the carboxonium ion (11). The conformations (13A) and (13B) each possess one pair of eclipsed lone pair orbitals and one n-σ^*(O-1, C-O-5) interaction. The conformation (13C) possesses two pairs of eclipsed lone pair orbitals and no stabilising n-σ^* interaction, thus being the least stable conformation of the three shown. The conformations (12B) and (12C) are each destabilised by one pair of eclipsed lone pair orbitals. The conformation (12C) possesses a stabilising n-σ^*(O-1, C-O-5) interaction, but also the destabilising 1,3 steric interactions between the group R and the carbons C-3 and C-5. The conformation (12A), like the other conformations of the α-glycoside, possesses a stabilising n-σ^*(O-5, C-O-1) interaction, in addition it possesses a n-σ^*(O-1, C-O-5) interaction, and further, it has the group R in the least sterically hindered position (gauche to the O-5, rather than gauche to the C-2). The conformation (12A) will therefore be the most stable conformation of the α-glycoside. Since all the conformations of the α-glycoside possess a larger number of stabilising interactions and a smaller number of destabilising interactions than the conformations of the β-glycoside, the α-glycoside will be more stable than the β-glycoside. Under equilibrating conditions, the most favoured structure of the glycoside will be that shown by the conformation (12A), in which the aglycone is exo- to the surface containing the atoms O-1, C-1, O-5, C-2, C-3 and C-5.

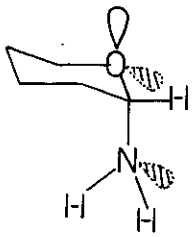
The Reverse Anomeric Effect.[10,5]

There are two situations which will lead to the reverse anomeric effect, these are:

i) when the atom attached to C-1 bears a lone pair of electrons in a n-orbital of comparable energy to those orbitals on O-5, and two substituents, particularly when one of these substituents can assist in the stabilisation of a near by lone pair orbital on O-5. This will be illustrated by a consideration of the equilibrium between the generalised glycosylamines (14) and (15).

ii) when the atom attached to C-1 bears an empty, or half full, orbital. This will be illustrated by a consideration of the equilibrium between the generalised glycosyl pyridinium salts (16) and (17).

An examination of the conformations of the molecule (14) shows that the conformations (14B) and (14C) possess the similar features of one eclipsed pair of lone pair orbitals, and one N-H bond eclipsed with a lone pair on O-5. While the eclipsed lone pair orbitals result in a destabilising effect, the (n-σ^*) interaction of the other lone pair of O-5 with the low lying N-H σ^* orbital will lower the energy level of the lone pair orbital and hence will result in a partial stabilisation of



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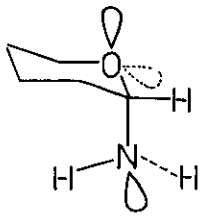

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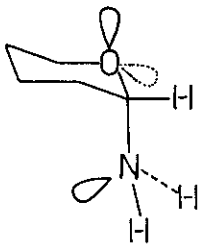

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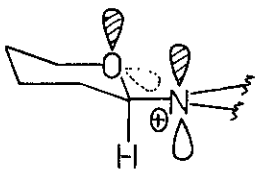

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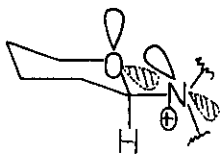

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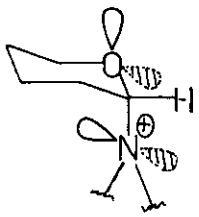

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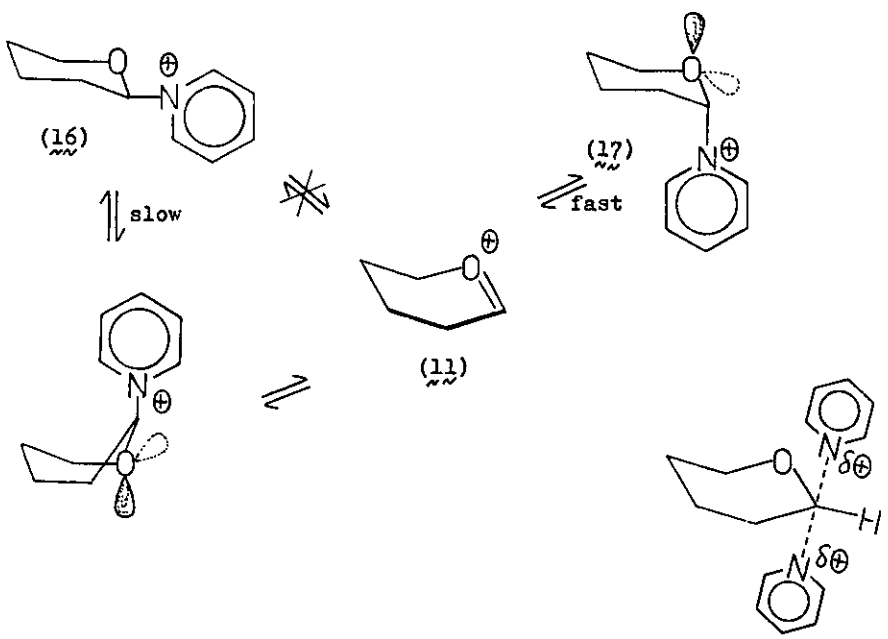


SCHEME 1.

these conformations.

The conformation (14A) possesses two n-σ^*(O-5, N-H) interactions similar to those described above and no lone pair interactions. The n-σ^*(O-5, N-H) interactions will not only stabilise the two O-5 lone pair orbitals, but will also lower the energy level of the O-5,C-1 bond by inducing a small positive charge on O-5,and will raise the energy level of the lone pair on the nitrogen atom by inducing a small negative charge on the nitrogen atom. The lone pair on the nitrogen atom is ideally disposed to participate in a n-σ^*(N, C-O-5) interaction with the anti-coplanar C-1,O-5 σ^* orbital. This n-σ^* interaction will be a particularly strong interaction because of the effects described above which should bring the lone pair orbital of the nitrogen atom closer to the σ^*(C-O-5) orbital. The conformation (14A) will therefore be a very stable conformation.

Each of the conformations of (15) possesses a n-σ^*(O-5, C-N) interaction and the conformations (15B) and (15C) each possess a n-σ^*(O-5, N-H) interaction. The conformation (15A) possesses an eclipsed pair of lone pair orbitals. Only the conformation (15B) possesses a n-σ^*(N, C-O-5) interaction, and this conformation will be the most stable conformation of the compound (15).

The steric factor and the above-described electronic factors will favour the greater stability of the molecule (14).

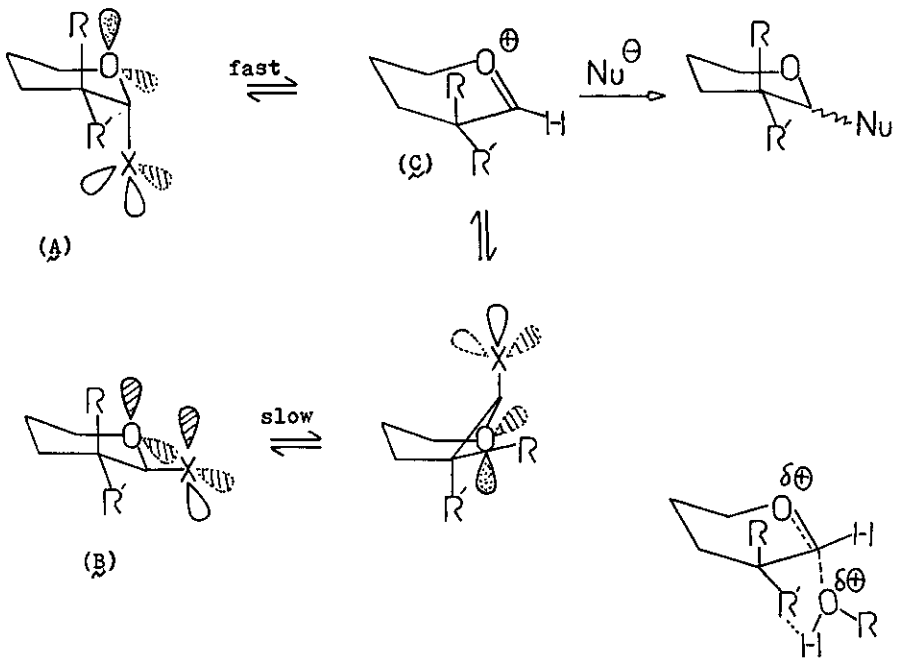
The relative stabilities of some monosaccharide analogues of the molecules (16) and (17) have been reported[11] and the anomers (16) were shown to be more stable than the anomers (17). The two conformations (16A) and (16B) each possess a highly stabilising β-interaction between a lone pair orbital of O-5 and the p-orbital of the positively charged nitrogen atom. Only the conformation (17A) will be stabilised by this strong β-interaction. All the conformations of the molecule (17) will be stabilised by n-σ^*(O-5, C-N) interactions.

The establishment of an equilibrium between the anomers (16) and (17) by way of a carboxonium ion, as is shown in the scheme 1, should favour the larger concentration of the anomer (16) because of the very different Sn1 reactivities of the two anomers. The n-σ^*(O-5, C-N) interaction present in the anomer (17) will ensure the easy cleavage of the axial C—N bond,because as the pyridine departs, this n-σ^* interaction will be linearly transformed into the π-bond of the carboxonium ion intermediate (11). The anomer (16) does not possess a similar n-σ^* interaction in the conformation shown, and would have to undergo the energetically unfavourable conformational change to the boat conformation shown, in order to participate in

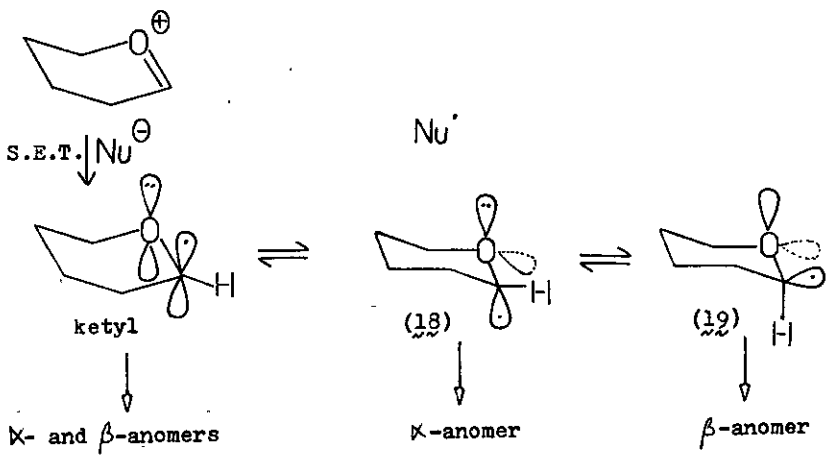
a reasonably facile Sn1 process. The Sn2 attack by the pyridine on either of the anomers would produce the transition state shown as an inset in scheme 1, and this transition state must fragment more easily to the anomer (16) rather than to the anomer (17) because of the greater electronic stability of the anomer (16).
The steric and electronic factors do favour the greater stability of the β-anomer (16) and moreover indicate that the β-interaction ($n-\pi^*$) must be more important than the $n-\sigma^*$ interaction in these molecules.
The influence of substituents at C-2 and C-4 on the anomeric effect of the pyranosides has been discussed[1] and those considerations can easily be extended to a discussion of their influence on the reverse anomeric effect.

The Relative Reactivities of The Anomers In Sn1 and Sn2 Processes.

When the atom attached to C-1 bears two or more lone pairs of electrons, we have seen that the anomeric effect results in the greater stability of the anomer in which the atom is axial (or psuedo-axial). This is the situation which exists for the very reactive glycosyl halides and glycosyl perchlorates.[12,13]
The C-X bond of the glycosyl halides, which have the halogen atom in the axial orientation, have been shown to be appreciably longer than the corresponding C-X bond of the simple alkyl halides. This lengthening of the C-X bond indicates the greater importance of the $n-\sigma^*$(O-5, C-X) interaction over the $n-\sigma^*$(X, C-O-5) interaction which is also present in these molecules.[5]
This dominant $n-\sigma^*$(O-5, C-X) interaction and its manifestation as a lengthening of the C-X bond indicate the greater Sn1 reactivity of the α-anomers, as it is this $n-\sigma^*$ interaction which is progressively transformed into the π-bond of the intermediate carboxonium ion during the departure of the halogen atom in the fragmentation of the anomer (9). Since a similar $n-\sigma^*$ interaction does not exist in the shown conformation of the anomer (10), a similarly facile fragmentation of this anomer is not possible. If the anomer (10) undergoes the energetically unfavourable conformational change to the boat (or alternate chair) conformation , which will place the atom X in a psuedo-axial (or axial) orientation, the desired $n-\sigma^*$ interaction will be established and would lead to a relatively easy fragmentation of this intermediate conformation. The ease of attaining the required conformation will therefore become the important factor in the Sn1 reaction of the β-anomer (10), and this factor will result in the lower Sn1 reactivity of β-anomers than the corresponding α-anomers.
In general, reactive sugar derivatives like the glycosyl halides and perchlorates



SCHEME 2.



SCHEME 3.

will undergo substitution by a Sn1 process as is shown in the scheme 2. The α-attack by the nucleophile on the carboxonium ion will proceed through a chair-like transition state and will be sterically favoured, while the β-attack must proceed through a boat-like transition state and hence will be sterically less favoured. Substituents on the pyran ring will influence the stabilities of the transition states realised during both the fragmentation and the addition processes.

If, for example, the group R of the anomer (A) is a halogen atom (or an alkoxyl group), the β-effect between the halogen's lone pair and the axial lone pair of O-5 will enhance the strength of the $n\text{-}\sigma^{\bullet}$(O-5, C-X) interaction and cause an easier fragmentation of this anomer to the carboxonium ion intermediate. The β-attack by the nucleophile on this carboxonium ion will be discouraged by the repelling electron density of the halogen atom, which would be cis with the nucleophile in the boat-like transition state leading to a β-anomer. The α-attack by the nucleophile on the carboxonium ion would not be affected by the transoid halogen atom, and the chair-like transition state would lead to the formation of an α-anomer.

If the group R' of the anomer (A) is a halogen atom, it would not influence the axial lone pair of O-5, nor hence the strength of the $n\text{-}\sigma^{*}$(O-5, C-X) interaction. On the other hand, the halogen atom would assist in the fragmentation process because of the repulsion between the lone pairs of the halogen atom and those of the leaving group X. The α-attack by the nucleophile on the carboxonium ion would be discouraged by the cisoid halogen atom's electron density during the formation of the chair-like transition state leading to an α-anomer. The β-attack by the nucleophile on the carboxonium ion would not be affected by the halogen atom in the boat-like transition state leading to the β-anomer.

The corresponding reactions of the β-anomer (B), via the boat-like conformation shown, are interesting because this conformation permits the now psuedo-axial halogen atom to influence the ease of the fragmentation process by its β-effect with the psuedo-axial lone pair of O-5. On the other hand, the reorientation of the halogen atom from an equatorial to a psuedo-axial position further reduces the ease of attaining the boat-like conformation.

This mechanism shown in scheme 2 cannot be applied to all Sn1 reactions of sugars as the nature of the leaving group X, and the charge at the nucleophilic centre are of great importance in determining the details of the course of the reaction. The fragmentation of the anomer (A) is facilitated by the $n\text{-}\sigma^{\bullet}$(O-5, C-X) interaction, and also the lone pair - lone pair repulsions of the eclipsed orbitals.

As the C-X bond lengthens, so this lone pair - lone pair repulsion will decrease, while the n-σ^* interaction develops into a π-interaction. If the group X had no lone pairs, then the only driving force for the fragmentation would be the transformation of the n-σ^* interaction into the π-bond of the carboxonium ion. If the group X was $(NH_2R)^+$, the departure of this group would still be assisted by the n-σ^*(O-5, C-$\overset{+}{N}H_2R$) interaction, but now would also be retarded by the n-σ^*(O-5, $\overset{+}{N}$-H) interaction.

While a negatively charged nucleophile would be repelled by the electron density of an electron rich substituent R', in its α-attack on the carboxonium ion (C), a neutral alcohol could become hydrogen bonded to the substituent R' and in this way have its α-attack on the carboxonium ion facilitated, as is shown by the inset in scheme 2.

Thus each monosaccharide derivative/nucleophile combination should be examined individually in order to appreciate the detailed mechanistic events occurring during the Sn1 process.

The reported Sn1 reactions of the glycosyl halides and perchlorates are always accompanied by some Sn2 reaction, in part because of the low polarities of some of the solvents used. The mechanistic features of the Sn2 reactions of these very reactive derivatives are quite different from the mechanistic features of their Sn1 reactions, and lead to a far greater reactivity of the β-glycosyl halides in comparison to the corresponding α-glycosyl halides.[6,13] Often, the 'Sn1' reactions of the α-glycosyl halides seem to be only as fast as the 'Sn1' reactions of the β-glycosyl halides, because some of the β-glycosyl halide is in fact reacting very rapidly by a Sn2 pathway.

The n-σ^*(O-5, C-X) interaction present in the α-glycosyl halide very effectively reduces the availability of the σ^* orbital to an external attacking nucleophile. In addition, the attacking nucleophilic orbital will be repelled by the axial lone pair on O-5, which is close and parallel to the favoured trajectory of approach of the nucleophilic orbital in its attack on the required lobe of the σ^* orbital (which lies along the projection of the C-X bond, at the backside of C-1). Thus O-5 very effectively reduces the Sn2 reactivity of the α-glycosyl halides.

There is one pair of eclipsed lone pair orbitals in the α-glycosyl halides, and the displacement of the halide atom in a Sn2 reaction will result in the loss of this destabilising factor. There are however two pairs of eclipsed lone pair orbitals in the β-glycosyl halide, and the displacement of the halide atom in an

Sn2 reaction will result in a much greater gain in stability than that to be expected in the Sn1 reaction of the α-glycosyl halide.

The β-glycosyl halide does not possess a n-σ^*(O-5, C-X) interaction and so the very important σ^*(C-X) orbital will be very available to an approaching nucleophile, quite unlike the situation of the α-glycosyl halide.

Thus, β-glycosyl halides will be dramatically more reactive in Sn2 reactions than α-glycosyl halides.

The solvolyses of the glycosides has been reviewed,[14] and it is clear that the mechanisms of these processes are influenced by several factors, including the nature of the substituents which are close to the anomeric centre. Unlike the very clearcut situation of the glycosyl halide, which has a well defined leaving group and bonds of different strengths at the reacting anomeric centre, the glycosides can have two C-O bonds attached to the anomeric centre of nearly equal strengths. The factors which influence the cleavage of one of these C-O bonds rather than the other will be several and often quite subtle, and a discussion of these reactions will be done elsewhere.

Any discussion of a substitution reaction at C-1 which proceeds via a carboxonium ion like (11) must address the possibility of the process of the attack by the nucleophile on the carboxonium ion taking place by a single electron transfer process.[15]

One possible mechanism of such a single electron transfer mediated addition reaction is shown in the scheme 3. The transfer of the electron from the donor to the carboxonium ion should result in the initial formation of a planar ketyl, which could then pyramidalise to either of the radicals (18) or (19). These three radical intermediates will be interconvertible if the 'counter-radical' is stable enough to allow the equilibrium to be established. The relative abundance of these intermediates would then depend on their relative stabilities.

The coplanarity of the axial radical orbital of (18) with the axial lone pair of O-5 ensures the efficient stabilisation of this radical by an α-interaction. The radical orbital of intermediate (19) is not coplanar with either lone pair of O-5, and so this radical will not be as stable as either the ketyl or the radical (18). Molecular orbital theoretical calculations[16,17] indicate that the transoid arrangement of the interacting orbitals, found in the intermediate (18), leads to the most efficient interaction and hence to the most efficient stabilisation of a radical orbital. The cisoid arrangement of the interacting orbitals, found in the

ketyl, will result in a less efficient interaction of the orbitals, and so the ketyl will be less stable than the radical (18). The radical (19) will be the least stable radical formed.

It therefore seems clear that any process which produces a radical orbital at C-1 under conditions which will allow an equilibration of the possible radical intermediates, will result in the greatest abundance of the radical like (18) and so produce an α-anomer as the major product. It also follows that an attack on the ketyl will be greatly favoured if the transition state bears a resemblance to the radical (18), barring the fact that this transition state would be chair-like and hence sterically very favoured.

If the 'counter radical' is very reactive and unstable, a relatively low stereoselectivity of addition would result, but the α-anomer would still be the major product of addition to C-1.

It should follow from the above discussion that the homolyses of suitable glycosyl derivatives which have an axial substituent at C-1, so producing directly an axial radical orbital and an intermediate resembling radical (18), will proceed more rapidly than the homolyses of the corresponding glycosyl derivatives which have an equatorial substituent. Electronic factors[1] which will stabilise one or more of the possible radical intermediates will clearly influence the homolytic process. Some examples of photochemical reactions which result in the formation of free radicals at the anomeric centres of monosaccharides, have been reviewed,[18] and the reactions of these radicals are consistent with the thesis developed above.

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