# SOME CONSEQUENCES OF LONE PAIR INTERACTIONS IN THE CHEMISTRY OF MONOSACCHARIDES

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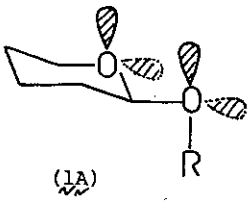
Abstract - The lone pair repulsions implicated in the anomeric effect are suggested to increase the nucleophilicities of the participating atoms (β-effect). An analogous longer-range effect (the γ-effect) is also proposed, and the roles of these effects demonstrated in mechanistic proposals for the oxidation of acetals and some reductions of the glycosuloses.

The roles played by the lone pairs of electrons of hetero-atoms which are either involved in chemical reactions, or are adjacent to the site of chemical changes, have been highlighted recently by Deslongchamps[1] and Box[2] among others. The recognition of these stereo-electronic effects due to lone pair bearing atoms have allowed some seemingly puzzling reactions to be rationalised and will enable synthetic chemists to prepare novel compounds which have interesting reactivities. Some lone pair interactions have been described in the context of the stereochemistry of some organic molecules, in particular the oxygen heterocycles. The anomeric effect, the reverse anomeric effect and their consequences on the relative stabilities of the C-1 epimers of carbohydrates have been detailed and elegantly rationalised by Lemieux[3] and others[4].

The anomeric effect arises, in part, from the unfavourable interaction (repulsion) of the lone pair orbitals of O-5 and O-1 in β- glycosides (1), and is substantially relieved in α-glycosides (2). The most favourable conformation of β-glycosides is (1B), in which the group R is in its sterically favoured position and moreover there exists only one pair of eclipsed lone pairs. The most favourable conformation of α-glycosides is (2A) when R is in its sterically favoured position and there are no eclipsed lone pairs.

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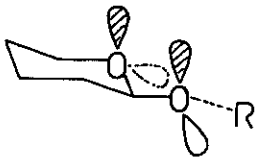
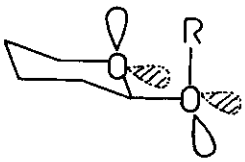
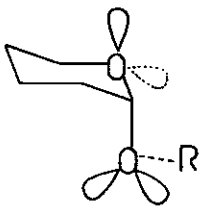


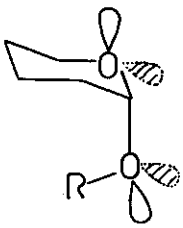

(1B)



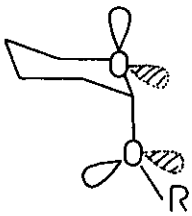

(1C)




(2A)




(2B)

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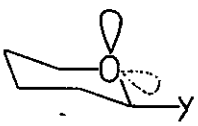
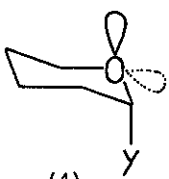



(3)

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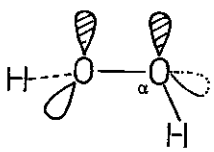


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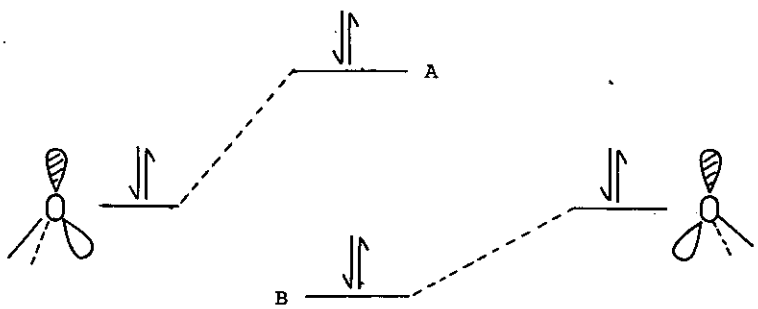



(6)

The reverse anomeric effect, is observed in molecules like (3) and (4), where Y is a more electropositive atom (group) than carbon, for example $-NR_3^+$. The epimer (3) is more stable than the epimer (4) partly because of the greater electrostatic stabilisation available to Y in (3) than in (4), by virtue of the orientation of the lone pairs on O-5.

These lone pair interactions are greatly minimised in protic solvents which can hydrogen bond to the lone pairs and so reduce their electron densities. Thus the anomeric effects are most pronounced in the non-polar, aprotic solvents.

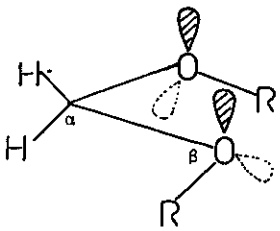
While these effects have been demonstrated by comparing the relative stabilities of the C-1 epimers in the pyranoses and pyranosides, attention has not been forcefully called to the consequences of these lone pair interactions in the reactions of the glycosides and other acetals.

The hydrogen peroxide molecule can take up one of many conformations in which there are eclipsed lone pairs, as shown in (5). These lone pairs are close enough to interact, and the result of the interaction can be shown in a qualitative manner by the molecular orbital diagram (6). The orbitals will interact in both a bonding (attractive) and an anti-bonding (repulsive) manner and so produce two 'new' orbitals as shown. Each 'new' orbital will be filled and so the overall interaction will be repulsive, net anti-bonding. These atoms cannot move apart and so the orbital interaction will exist as long as the parent n-orbitals are properly oriented.

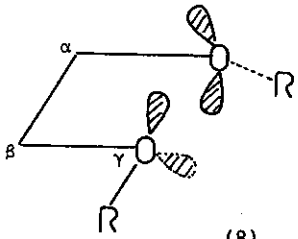
The dramatic chemical consequence of this redistribution of orbitals is that the 'new' orbital (A) now has a much increased nucleophilicity as compared to each of the parent orbitals since it is at a higher energy level. This significantly increased nucleophilicity, due to the generation of a 'new' highest occupied molecular orbital (HOMO) because of an interaction of the lone pair orbitals, is known as the α-effect[5].

This concept, when extended to embrace the simple acetal (7), gives qualitatively the same result, but because the lone pair orbitals are now farther apart, the extent of elevation of the new HOMO, will be less than that found in the α-effect. However, one oxygen would have become a better nucleophile than the other, as long as the interaction lasted. This is the ß-effect.

Similarly, one of the oxygen atoms of the glycol (8) will show an enhanced nucleophilicity, as long as the lone pair orbitals are properly oriented to cause interaction. The distance between the oxygen atoms in the glycol (8) is larger than




(7)

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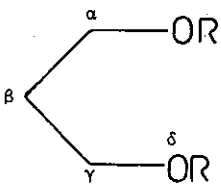


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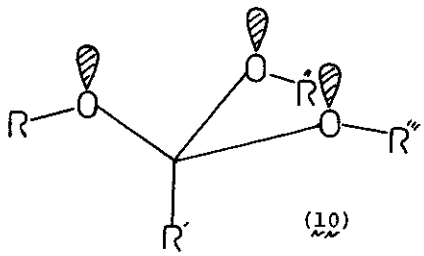


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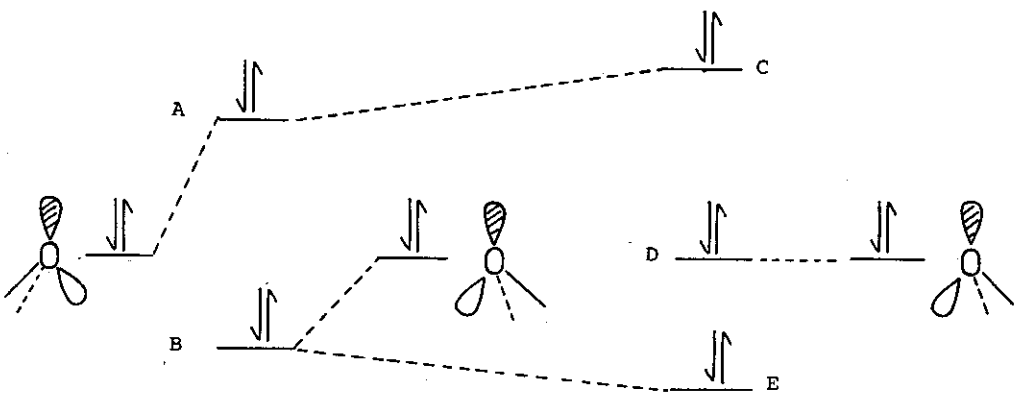
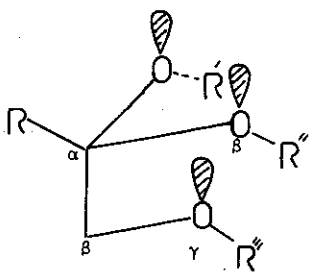



(6A)

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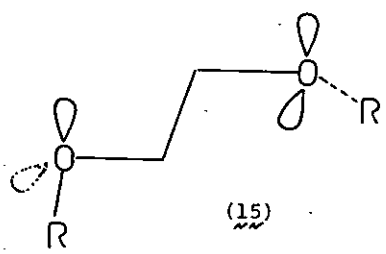



(15)

that in the acetal (7), thus the new HOMO generated in the interaction of the lone pairs of the glycol (8) will not be as elevated in energy as that formed by the similar interactions in the acetal (7). The γ-effect will therefore be smaller than the β-effect. It must be recognised that with the increasing distance between the oxygen atoms and the increasing conformational variety available to homologous molecules, the frequency and longevity of the interactions of the lone pairs will decrease in the sequence (5) > (7) > (8) > (9) etc...

An acyclic orthoester will exist with an appreciable population of conformational states such as shown in (10), when three lone pairs are interacting. The molecular orbital diagram (6A) indicates that the new HOMO (C) will be even higher in energy than the orbital (A), and so will be more nucleophilic than (A), or any of the parent orbitals.

By extending this concept by way of an analogous process, it should be apparent that the conformational isomer (11) will show an enhanced nucleophilicity at the O-β, which will be greater than the nucleophilicity shown by O-β of the acetal (7). This additional effect of O-γ can be described as a buttressing γ-effect. These lone pair interactions will be affected directly by the negative inductive effects of the neighbouring, participating atoms. These inductive effects will serve not only to reduce the spatial requirements of the lone pair by influencing the electron density to lie closer to the nuclei, but will also reduce the nucleophilicity of the atoms involved because of the reduced availability of the electron densities. However, for a given system, like (8), interacting atoms will be more nucleophilic than non-interacting atoms. The orthoesters, like (10), will probably be just as nucleophilic as the acetals (7) because of the additional negative inductive effect of the third oxygen atom. In the case of the acetals, electron donating groups on the α-carbon will offset the negative inductive effects of the oxygen atoms and so this system will show an increased nucleophilicity as compared to the simple acetal (7). A quantitative treatment of the effect of the inductive effect on the energy level and spatial distribution of n-orbitals will be very valuable in the future development of these concepts.

The lone pair interactions of O-5 and O-1 are more severe in β-glycosides (1) than in α-glycosides (2)[3], and so it should be expected that any enhancement of the nucleophilicity of either O-5 or O-1 will be greater in β-glycosides than in α-glycosides.

That this is indeed the situation is demonstrated by the enhanced reactivity of

O-1 of β-aldopyranoses over that of α-aldopyranoses towards acylating agents[6], and by two well known reactions of sugars, the ozonolytic oxidation of the C-1 of glycosides to produce esters[7], and the oxidations of aldoses to lactones by bromine/water[8,9].

The mechanism proposed[7] for the ozonolyses of acetals is shown in scheme 1, and requires a hydride shift to occur from C-1 to the electrophilic oxygen of ozone. The intimate ion pair formed, would then collapse, with retention of configuration to the hydrotrioxide, thence to the products observed.

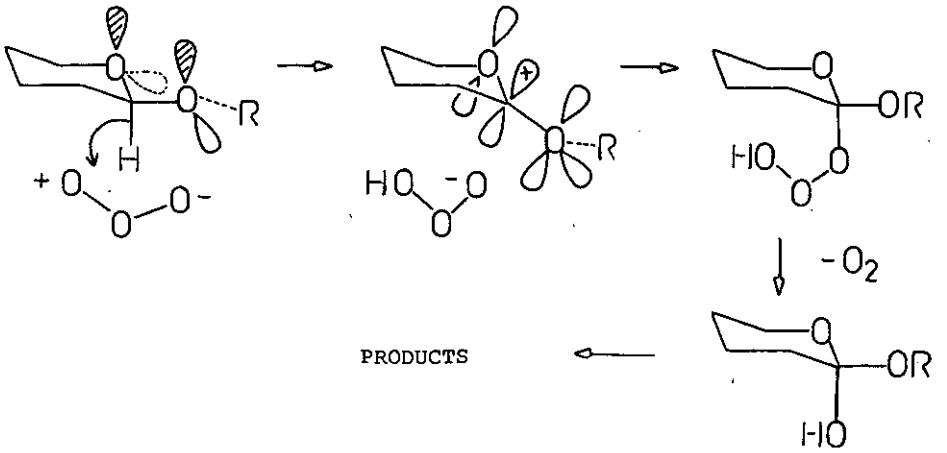
This mechanism may be modified to recognise the β-effect, and be as shown in schemes 2 and 3.

The bonding of the electrophilic ozone to O-1 (which has an enhanced nucleophilicity) would convert the unfavourable anomeric effect to the favourable reverse anomeric effect and so this process would be energetically favourable. The intermediate could then collapse as shown, through a six-membered transition state, to the chiral intimate ion pair encountered in scheme 1,and thence to the products observed.

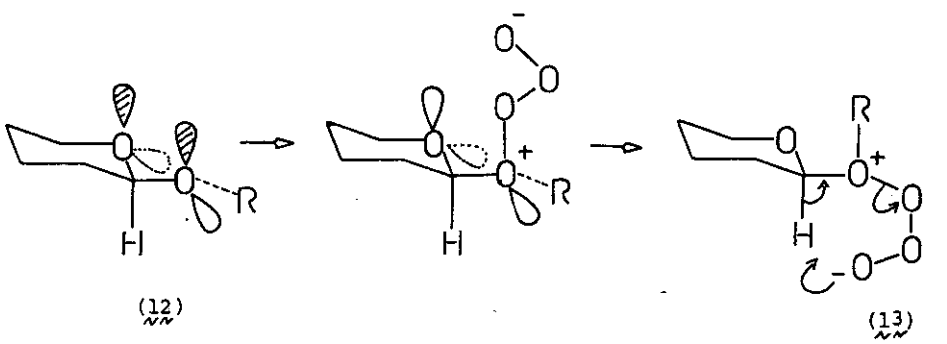
Because the β-effect is more pronounced in β-glycosides than in α-glycosides, the nucleophilicity of O-1 in the α-glycoside would be smaller and so the process less likely to occur. The bonding of ozone to the axial O-1 of an α-glycosides would not only be sterically retarded, but would also convert the favoured anomeric situation into the less favoured reverse anomeric situation and hence this bonding would be energetically unfavourable. The α-glycosides would therefore be expected to react very slowly, if at all, relative to β-glycosides, as is observed[7].

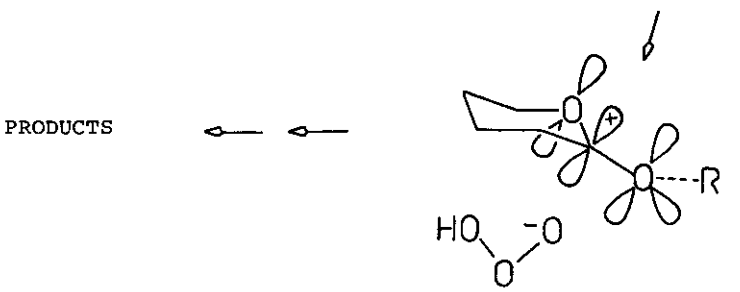
The data gathered by Deslongchamps et al favour the mechanism outlined in scheme 2, rather than scheme 1, particularly in two respects.

Firstly they observed that cyclic acetals reacted faster than acyclic acetals, and in addition, 1,3-dioxolanes reacted faster than 1,3-dioxanes. These facts are easily accommodated as shown in scheme 3. Cyclic acetals experience a more significant (continuous) β-effect than acyclic acetals, because the acyclic acetals can ameliorate the situation by conformational changes. Cyclic acetals are therefore more nucleophilic. In a 1,3-dioxolane, the intermediate (14) will have the O-1—O-O and the C-2—H bonds coplanar, or nearly so, thus effecting rapid elimination, whereas for a 1,3-dioxane this coplanarity would have to be achieved by significant conformational change. Thus the 1,3-dioxolane reacts

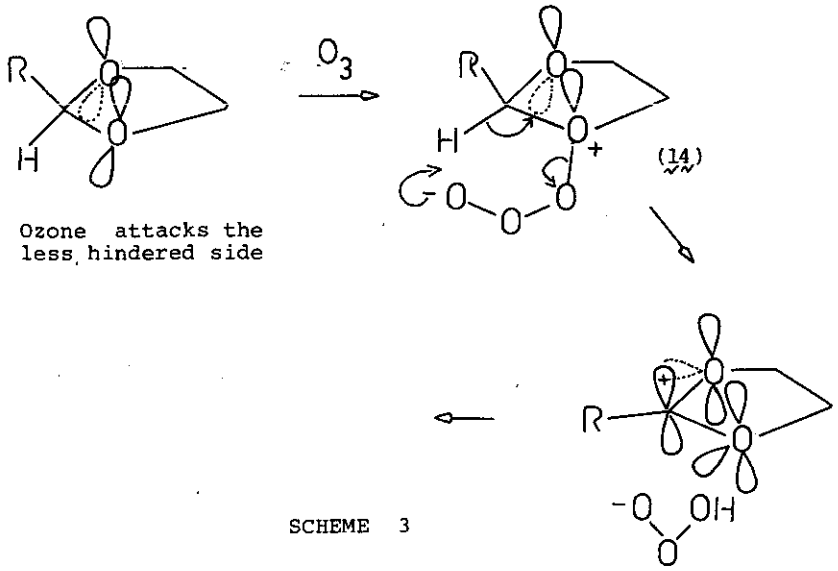



SCHEME 1



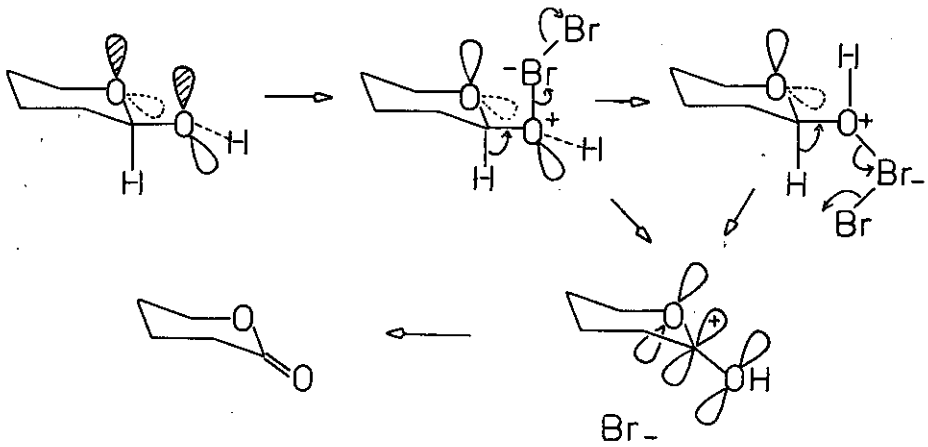




SCHEME 2

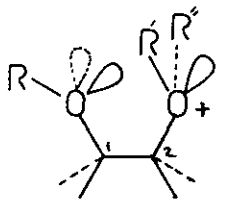



Ozone attacks the less hindered side

SCHEME 3




SCHEME 4



(16)

more rapidly than the 1,3-dioxane.

Secondly, the rates of ozonolyses of the tetrahydropyranyl ethers (12), scheme 2, were in the order R = isopropyl, R = $CH_3$ > R = t-butyl. The steric effect suggested is accommodated by the intermediate (13) rather than by the hydride transfer process.

The mechanisms proposed by Bentley for the oxidation of aldoses to lactones[9], could be modified to that shown in scheme 4, in order to recognise the role of the the β-effect. Again, the more significant β-effect encountered in the β-aldopyranoses would demand a faster rate of oxidation of β-aldopyranoses than α-aldopyranoses. In these mechanisms shown in schemes 2 and 4, the site of electrophilic attack proposed, O-1, was chosen as it satisfied the requirement of being sterically less hindered than O-5. The electrophile is proposed to bond via the lone pair on O-1 which was engaged in an interaction with the axial lone pair on O-5. This seemed to be the logical orbital, as this lone pair - lone pair interaction is present in the most stable conformation of the acetal and so must be the site of greatest electron density in the molecule, hence the obvious site for electrophilic attack. The steric requirement would then bias attack onto O-1 rather than O-5, or it might be assumed that the electrophile could be transferred from O-5 to O-1.

Other examples of the enhancement of the nucleophilicity of an oxygen atom, which is β- or 1,3 to another oxygen atom, and of the differential enhancement of nucleophilicity, abound in the ozonolytic cleavages of 4,6-O-benzylidene-α-D-hexopyranosides[7], and the reactions of these sugars with N-bromosuccinimide[10].

The γ-effect would be manifested as an increase in the nucleophilicity of an oxygen atom, 4 atoms away from another lone pair bearing atom, when their disposition is gauche or cisoid, so that a lone pair - lone pair interaction can be achieved. All the implications for the nucleophilicity and stability of (8) relative to (15) should be appreciated readily from the foregone discussion. The situation shown in the diagram (16) should result in a decreased nucleophilicity for the O-1. This should arise from: (a) the increased negative inductive effect of O-2; (b) the stabilisation of the positive charge on O-2 by an electrostatic interaction with the lone pairs on O-1, this in turn, resulting in a stabilisation (lowered energy) of the n-orbitals of O-1, and (c) the unfavourable repulsions which would arise if O-1 was to become positively charged by bonding to an electrophile. This reduced nucleophilicity of O-1 of the system (16) will be refer-

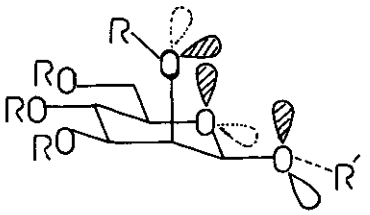
red to as a consequence of an inverse γ-effect. The system (16) will be more stable than the system (8).

The relative stabilities of the α- and β-anomers of the peracetylated mannosides has long been known to favour the α-mannoside (17) greatly over the β-mannoside (18), and further, the difference in stabilities of the mannosides is known to be more pronounced than found between the peracetylated glucosides (19) and (20). The situation was analysed as being due to the additional non-bonded interactions between O-1 and the lone pairs of O-2 in the compound (18), which were not present in the compound (17); while the lone pairs of O-2 of the glucoside are similarly disposed to those of O-1 in both compounds (19) and (20) and so do not greatly accentuate the relative stabilities of these[11].

In other words, the β-mannoside (18) experiences the anomeric effect and two γ-repulsions, O-2—O-1 and O-2—O-5; while the α-mannoside (17) only experiences the γ-repulsion O-2—O-5. On the other hand the β-glucoside (19) experiences the anomeric effect and one γ-repulsions O-2—O-1, while the α-glucoside (20) does not experience the anomeric effect but still experiences a γ-repulsion.

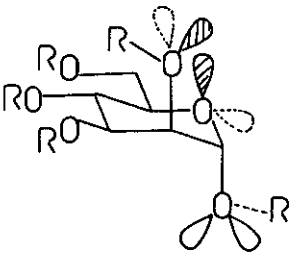
The acetals (21) and (22) have been shown to possess different stabilities, with the compound (22) being more stable than the compound (21), and this was rationalized as due to the interactions of the lone pairs of the ring oxygens with those of the substituent oxygen (two γ-repulsions)[12]. Of great significance also was the result that the alcohol (23) was more stable than its epimer at C-5, and that the ester (24) was almost as stable as its epimer at C-5. Hydrogen bonding was suggested to account for the stability of the alcohol (23), while the very reduced electron density at O-5 of the ester (24) diminished the interaction between O-5 and O-1 or O-3, hence the stability of the ester (24). As in the case of the anomeric effect, a polar, protic solvent hydrogen bonds to the interacting lone pairs and reduces the repulsions, or stabilisations. Non-polar, aprotic solvents allow the effects to be most pronounced[12]. Again, although the roles of the lone pairs of O-2 in the systems (17), (18), (19), and (20), and of O-5 in the systems (21), (22), (23), and (24), have been recognised in the stereochemical context, the role of these lone pairs in the chemistry of these and related molecules has not been highlighted.

Let us consider the ozonolyses of the β-glycosides (25) and (26). In the more stable conformations of the mannoside (25), the lone pair of O-1 which experiences the β- and the γ-effects, is the lone pair thought to be the preferred

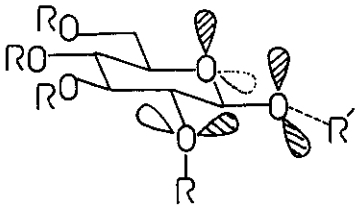


(18) R = R' = Ac

(25) R = Ac, R' = $CH_3$

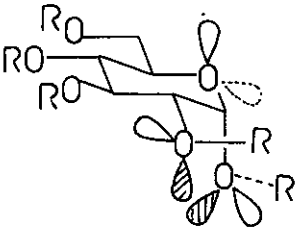


(17) R = Ac

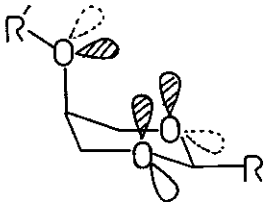


(19) R = R' = Ac

(26) R = Ac, R' = $CH_3$

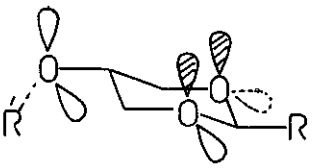


(20) R = Ac

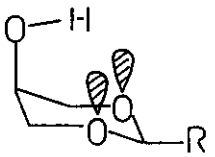


(21) R = Ph, R' = $CH_3$

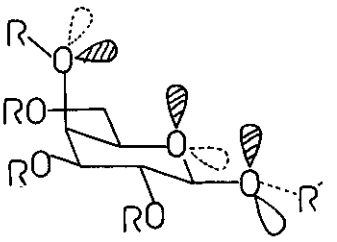
(24) R = Ph, R' = Ac



(22) R = Ph, R' = $CH_3$



(23)



(27) R = Ac, R' = $CH_3$

site of electrophilic attack. However, in the more stable conformations of the glucoside (26), the two lone pairs of O-1 are each affected by only one interaction: one lone pair experiences the β-effect while the other lone pair experiences the γ-effect in a transoid situation. The transoid γ-effect will be less significant than the cisoid γ-effect, as any small change of the chair conformation of the molecules will move the transoid oxygens apart, while bringing the cisoid oxygens closer together. The O-1 of the glucoside (26) will therefore experience one large and one small effect which will not be concentrated on one lone pair, as is the case in the mannoside (25), but spread out onto two lone pairs. Thus the O-1 of the mannoside (25) should be more nucleophilic than the O-1 of the glucoside (26). Based on the mechanism proposed in scheme 2, the mannoside (25) should be oxidised by ozone more rapidly than the glucoside (26). This is in fact observed[7]. The molecule (27) will experience a γ-effect between O-4 and O-5. This effect will enhance the β-effect present, and so should enhance the rate of ozonolysis of the galactoside (27) relative to the glucoside (26). This too was found to occur[7]. The stabilisation achieved on the formation of the respective intermediates like (13), scheme 2, from the compounds (25) and (26) will arise from the reverse anomeric effect and the inverse γ-effect. The γ-effect shown by the galactoside (27) which enhanced the nucleophilicity of O-1, via the β-effect, would be an example of the 'buttressing γ-effects'.

These results and rationalisations allow the prediction to be made that the rates of ozonolytic cleavages of the compounds (21)-(24) will be in the order (21) > (24) > (22) > (23). Further, the 4,6-O-benzylidene-α-D-galactopyranosides will undergo ozonolytic cleavages of the 1,3-dioxane ring much faster than the corresponding α-glucopyranosides. The additional γ-effect experienced by the 1,3-dioxane oxygens of the galactoside should make them even more nucleophilic than those of the glucoside and hence the greater predicted reactivity.

Because of the variety in the relative dispositions of the hydroxyl groups of a simple glycoside, one would predict that these hydroxyl groups will experience different β- and γ-effects and so show varying nucleophilicities. This clearly has implications for the selective functionalisation of the hydroxyl groups of glycosides. The situation here is not as stark as that discussed above, because of the roles of the solvents, the electrophilic reagents and the other reaction conditions on the path of these reactions.

The roles of the β- and γ-effects in the selective esterification and alkylation of the monosaccharides, and the selective removal of protecting groups from functionalised monosaccharides is a topic deserving of consideration and discussion. However, this discussion can only be meaningful if the mechanisms of the reactions involved are properly understood.

Any extension of the ideas related above to describe the interactions of the lone pairs of dissimilar heteroatoms, for example the interactions found in a deoxyaminosugar, will require a close examination of the relative energy levels of the interacting orbitals. The molecular orbital diagram (6A) suggests that when two interacting lone pairs have different energies, then the lower energied orbital will experience a reduction in energy (become more stable and less nucleophilic), while the higher energied orbital will be increased in energy and become more nucleophilic.

The lone pairs of electrons, borne by the oxygen atoms of the 4,6-O-benzylidene-hexopyranosides and hexopyranosiduloses have now been shown to influence the mechanisms of (a) their elimination and enolisation reactions[2] and (b) some oxidation reactions of their acetal groups. As was suggested above, there are several other reactions of the monosaccharides which involve the nucleophilic attack by their oxygen atoms on various electrophiles. The selectivity shown by these reactions will no doubt be subject to rationalisation, in part, by the application of the β- and γ-effects. All of these reactions have in common the feature of the monosaccharide being the nucleophilic agent. It will be valuable to examine and discuss the role of stereo-electronic interactions in reactions where the monosaccharide is the electrophilic agent.

The concepts discussed above, namely the β-effect and the γ-effect, can be extended logically, and can describe other similar stereo-electronic interactions, which will enable the electrophilic reactions of monosaccharide to be rationalised. The rest of this review will focus on some of the addition reactions of the carbonyl groups of the 4,6-O-benzylidene-hexopyranosiduloses, as these reactions easily provide an opportunity to define and develop the other stereo-electronic interactions referred to above.

The lone pair interactions which increase the nucleophilicity of one of the participating atoms, are all net-repulsive, destabilising interactions, because all the orbitals are completely filled. If, however, a lone pair orbital interacted

with a partially full, or empty, orbital, a net attractive, or stabilising overall effect would be the result. The energy level of the partially full orbital would be elevated as shown in the molecular orbital diagrams (28) and (29), corresponding to the carbon radicals (30) or (31), and (32), (33) or (34).

In a qualitative manner, these molecular orbital diagrams would also apply to the corresponding carbonium ions. The empty orbital might be a p-orbital, or a $sp^n$-orbital which would interact more efficiently with the $sp^3$ hybridised n-orbital of the oxygen atom. Whether the empty orbital remained a p-orbital or became some kind of $sp^n$ hybridised orbital would clearly depend on the gain in stability to be achieved on undergoing the hybridisation process in order to achieve a more efficient interaction and hence greater stabilization.

The stability of the carbonium ion systems should be greater than those of the radical systems, as the highest energied orbital will be vacant in all the cases involving the carbonium ions.

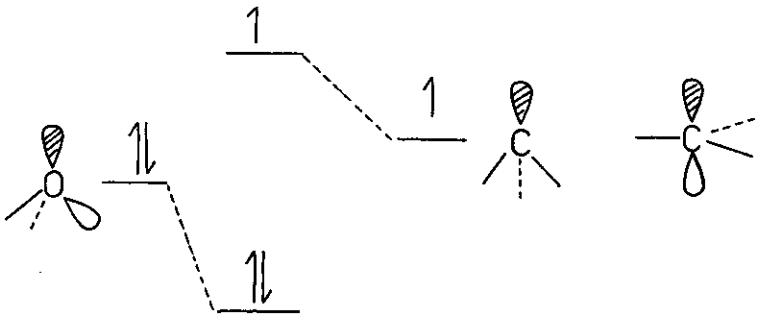
These situations represent cases of the inverse β- and γ-effects. The molecular orbital diagram (29) shows that the vacant or partially full orbital is further elevated in energy by each additional interaction.

An examination of the structures of the 4,6-O-benzylidene-hexopyranosiduloses (35), (36), (37) and (38) reveals several interesting features, similar to those described in the structures (30), (31) and (33), if the 'p-orbital' of the carbonyl carbon is made the centre of attention.

Models reveal that the carbonyl carbon of a 3-ulose, (35) and (36), experiences β-interactions from O-4 and O-2, in addition to a γ-interaction from an axial O-1. The 'p-orbital' of the carbonyl carbon of a 2-ulose, (37) and (38), experiences β-interactions from O-5, O-3 and O-1.

Axial and equatorial oxygens interact differently with the neighbouring carbonyl group. Whereas the equatorial O-2 is close to both C-3 and O-3, and so interacts with both centres, the axial O-2 will be quite close to the 'p-orbital' of C-3 but remote from the 'p-orbital' of the O-3. This arrangement will facilitate the polarisation of the carbonyl group, so making the π bond weaker.

The interaction of an equatorial oxygen atom's n-orbital with the carbonyl group's π and π* orbitals can be represented, qualitatively, by the molecular orbital diagram (39). The parent orbitals are seen to interact so as to elevate the π* orbital and lower the π orbital in energy. This increased separation of these energy levels of the carbonyl group might account for the bathochromic shift of



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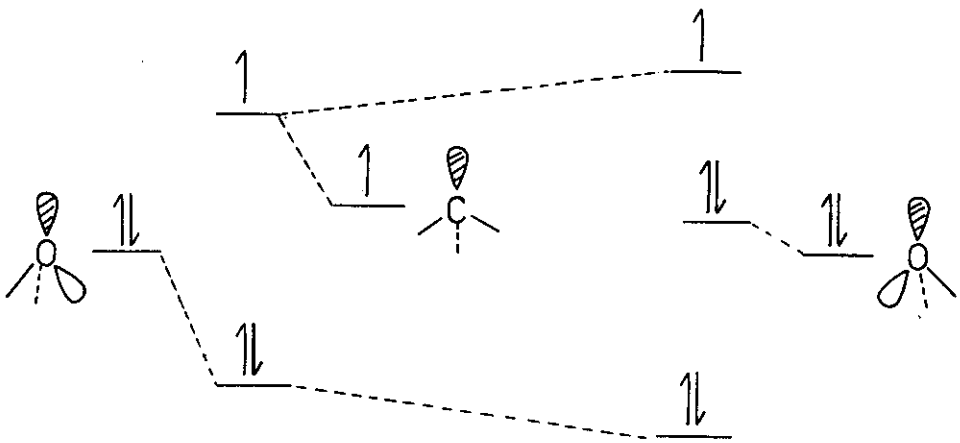

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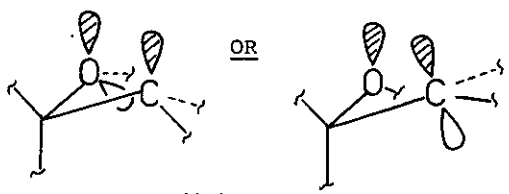

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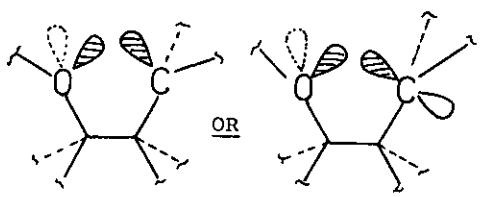

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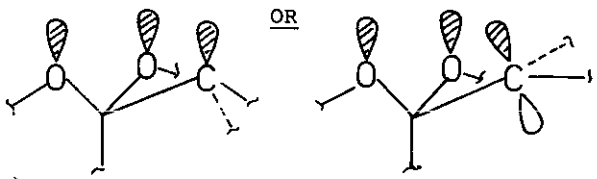


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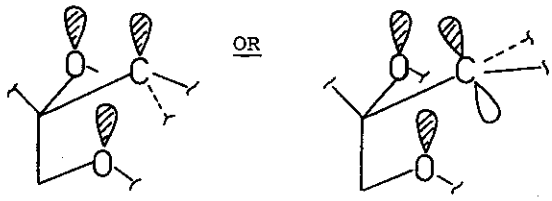


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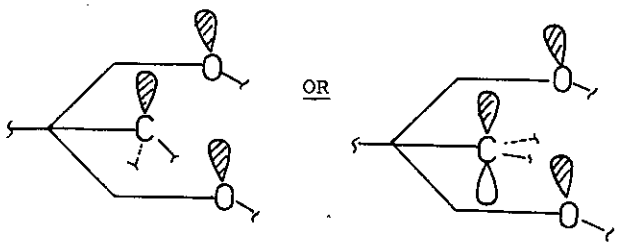


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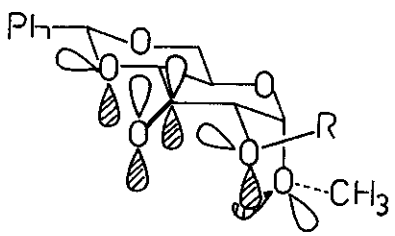


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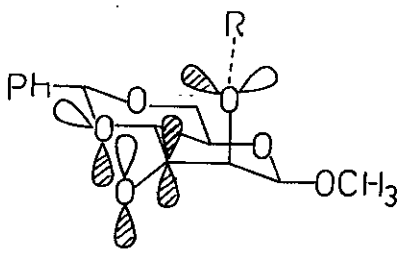


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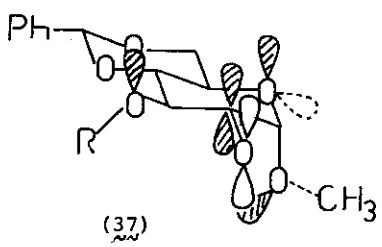


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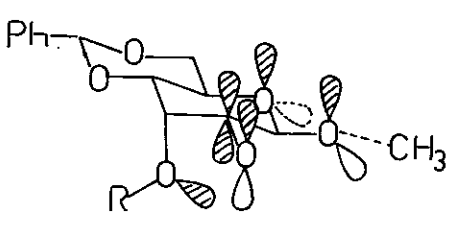


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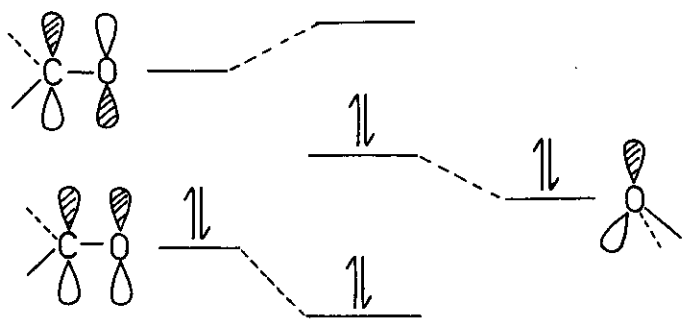

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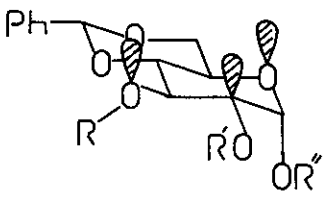
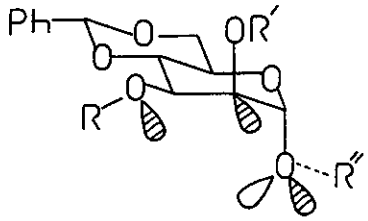


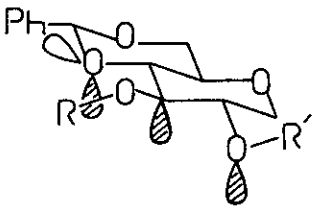
(40)

(54) R' = MgX,



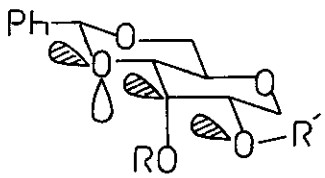
(41)

(55) R' = MgX,



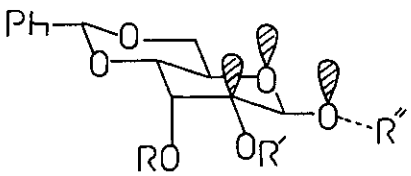
(42) R = H

(50) R = MgX,



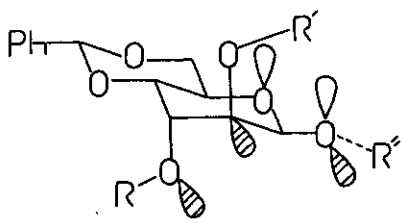
(43) R = H

(51) R = MgX,



(44) R' = H

(58) R' = MgX,



(45) R' = H

(59) R' = MgX,

the $\pi$-$\pi^*$ transition in the ultraviolet spectra of these compounds[13].

The interaction of the axial, lone pair bearing atom with the carbonyl group described above, and the resulting enhanced polarisation of the carbonyl group might account for the hypsochromic shift of the $\pi$-$\pi^*$ transition in the ultraviolet spectra of these compounds[13].

These interactions in (35), (36), (37) and (38) are seen to involve one 'lobe' of the 'p-orbital' of the carbonyl carbon to a greater extent than the other, because of the 'shape' of the $sp^3$ hybridised n-orbitals. This should create the awareness that changing the 'p-orbital' of the carbonyl carbon to a $sp^3$ hybrid orbital will result in this type of orbital being more highly stabilised in some orientations than others. This situation at C-2 is shown in diagrams (40) and (41), while the situation at C-3 is shown in (42) and (43).

Addition reactions to carbonyl groups will fall into two discrete classes. There will be additions in which the $\pi$ bond is broken when the nucleophile injects its electron density into the $\pi^*$ (LUMO) orbital and bonding to the carbonyl carbon is occurring. The carbonyl oxygen may or may not be coordinated to a Lewis acid entity at the time of nucleophilic attack on the $\pi^*$ orbital, at the carbonyl carbon. There will be additions in which the $\pi$ bond has been modified before the approach of the group or atom to be attached to the carbonyl carbon. This will be the situation when there is an initial reduction of the carbonyl group to a radical anion in a single-electron-transfer process[14].

The occurrence of a single-electron-transfer process between an anionic entity and an electrophile will depend on the stabilities of the radicals generated from the anion and the electrophile. On transferring one of its electrons to an electrophile the anionic entity will become a more stable radical, while the electrophile will become a less stable (higher energied) radical. The stability of the radical generated from the electrophile will depend on the structure of the molecule.

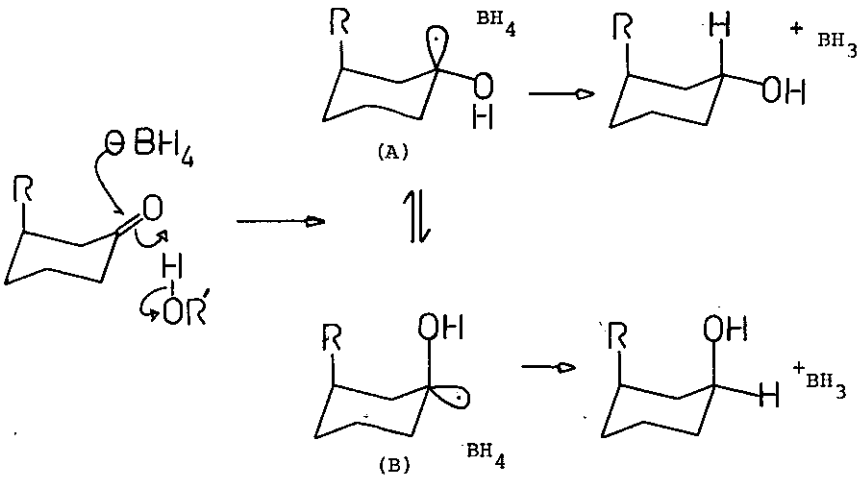
The ketyl (radical anion) generated by donating an electron to a carbonyl group might be quite unstable if it is free and the molecule has the features of a carbonyl group with an additional electron in its $\pi^*$ orbital. If the oxygen atom is complexed, or sigma bonded, to a Lewis acid, the reduced species will have the features of a tetrahedral[15] (or nearly so) carbon radical which is partially stabilised by the electron density of the n-orbitals of the oxygen atom through an $\alpha$-interaction. This radical will certainly be more stable than the ketyl men-

tioned above. Additional features of the carbonyl compound might further stabilise the carbon radical and so make the single-electron-transfer process an overall favoured one. Further, the movement of the energies of the HOMO of the electron donor (high to lower) and the acceptor (low to higher) will bring these orbitals together, in a favoured case, and facilitate the interaction of the radicals.

The 2-uloses and the 3-uloses which are the subjects of this paper would most certainly give rise to fairly stable tetrahedral carbon radicals, on accepting an electron from a donor, because of the extensive stabilisation arising from the β-interactions shown in (40), (41), (42), and (43). The α-interaction of the lone pairs of the erstwhile carbonyl oxygen would thereby be tremendously reinforced. There is now little doubt that the reactions of some Grignard reagents[14] and lithium aluminium hydride[16] with suitable electrophiles do proceed via single-electron-transfer processes, as overwhelming evidence has been generated to support this mechanistic feature of these reactions. The alkyllithiums are also the subjects of intense investigations to determine the limits of the extent to which the single-electron-transfer process directs their modes of reaction[17].

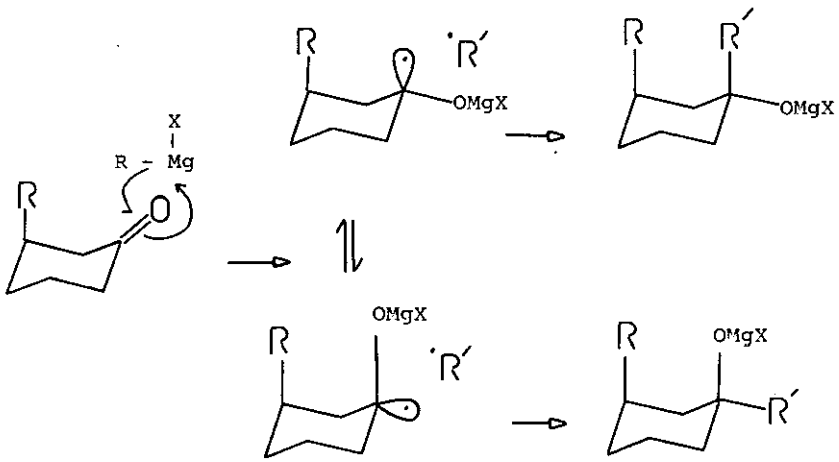
Sodium borohydride has been the subject of thorough investigations by many researchers, and recently Wigfield et al[18] have revealed several interesting features of the reductions performed by this reagent. They did not think it necessary to examine the possibility of an electron-transfer process occurring in these reductions by sodium borohydride. However, the similarity in the abilities of lithium aluminium hydride and sodium borohydride to reduce alkyl halides[19], highlighted by the very facile, but puzzling, reduction of carbon tetrachloride by sodium borohydride[20], suggest that, like lithium aluminium hydride, sodium borohydride can react via an electron-transfer process with suitable electrophiles. By extending Wigfield's mechanism for the reactions of sodium borohydride with cyclic ketones, to embrace the single-electron-transfer process, one can arrive at a mechanism which satisfies all the known features of these reactions. This mechanism is shown in Scheme 5.

The stereochemistry of the produced alcohol will be determined by the bulk of the group R-, because the $BH_4$ radical must approach the carbon radical closely in order to transfer the hydrogen atom. The $BH_4$ radical will be hindered in its approach to the radical (A) by R-, if the group R- is large, and will more easily approach the radical (B). The radical (A) will be more stable than the radical

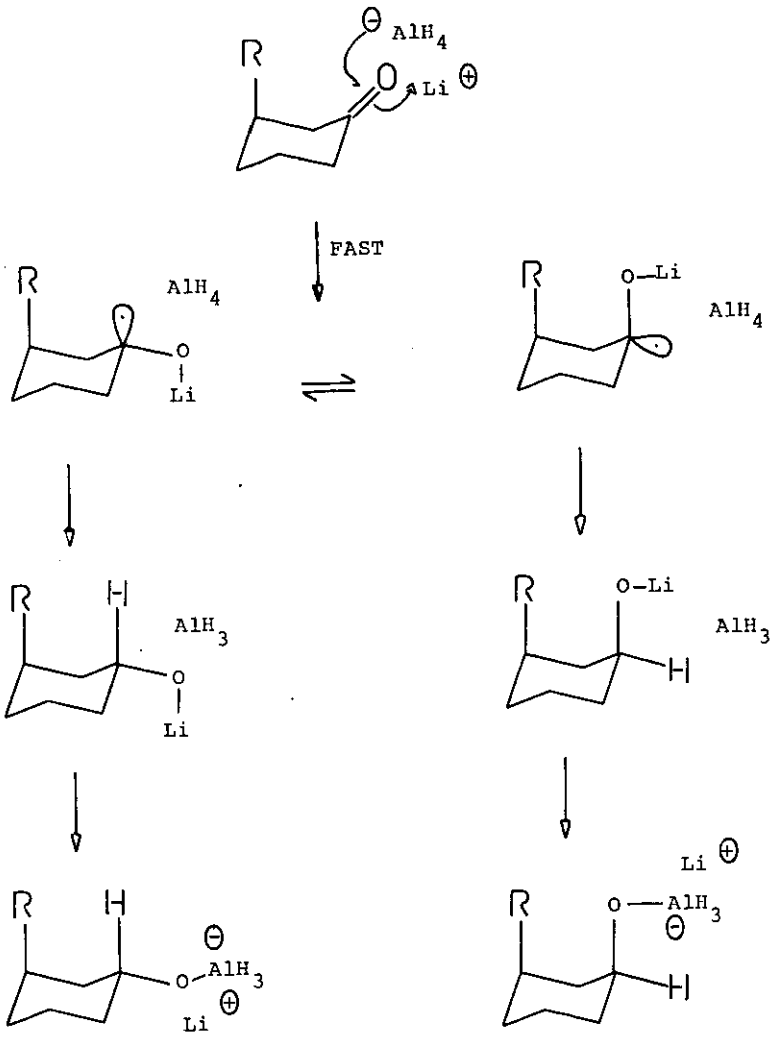



$BH_3 + R'-O^{\ominus} \rightarrow R'-O-BH_3 \xrightarrow{\text{Ketone}}$ similar reductions

SCHEME 5




SCHEME 7




$R'\text{-}O\text{-}AlH_3^{\ominus}$ —Ketone→ similar reductions

SCHEME 6

(B) because the hydroxyl group is equatorial in (A) but axial in (B). Further, if R- is small, not only will the approach to (A) be unhindered, but also the process of transferring the hydrogen atom to (A) will not be restricted by torsional interactions[18]. The approach to the radical (B) will also be unhindered but the process of transferring the hydrogen atom will be restricted by torsional strain.

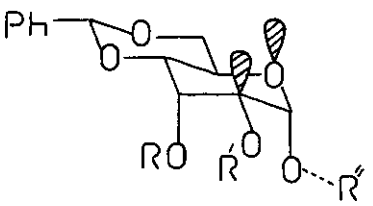
This dynamic situation allows for the inclusion of other structural features of the ketone which can contribute to the stability of the axial radical, like (A) or the equatorial radical, like (B). The more stable radical will then yield the major product, if there are no inhibiting steric factors, while such steric factors that do exist will control the approach of the $BH_4$ radical.

The mechanism of the reduction of a cyclic ketone by lithium aluminium hydride can be represented as in Scheme 6 . The role of the cation is made obvious in Scheme 6 and the difference in the reactivities of sodium and lithium aluminium hydrides[19] can now be easily appreciated.

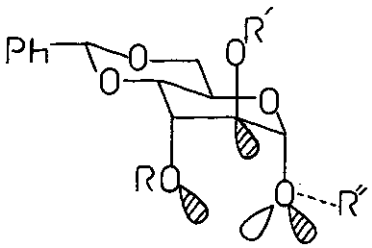
By using the mechanism proposed in Scheme 5, the reductions of the 2-uloses and the 3-uloses by sodium borohydride can be rationalised.

The anomers of 4,6-O-benzylidene-D-ribo-hexopyranosid-2-ulose will accept electrons to produce radical intermediates like (44), (45), (46) and (47). The axial -OR group at C-3 will not stabilise the radicals (44) or (46). The radical (44) will therefore be stabilised by the fixed β-interaction from O-5 and a variable (due to free rotation) β-interaction from O-1. On the other hand, the radical (45) will be stabilised by two variable β-interactions, from O-1 and O-3, and by the very strong hydrogen bonding[12] of the OH-2 to O-5 and O-1 . The fixed interactions will be more significant than the transient variable interactions, but the radical (44) will be less stable than the radical (45) because of the unusually strong hydrogen bonding in radical (45). Thus the 4,6-O-benzylidene-β-D-ribo-hexopyranosid-2-uloses will be reduced preferentially to altro-compounds by sodium borohydride[21].

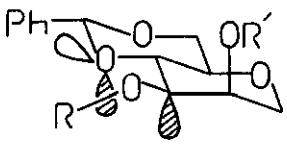
The radical (46) will not be stabilised by the axial O-1, but will be stabilised by the fixed β-interaction from O-5. The radical (47) will be stabilised by the two variable β-interactions from O-1 and O-3. Hydrogen bonding of OH-2 to O-5 in the radical (47) will not be favourable enough to offset the energetic disadvantages of the OH-2 being axial. The radical (46) will therefore be more stable than the radical (47) and an allo-compound will be the major product from the



(46) R' = H,

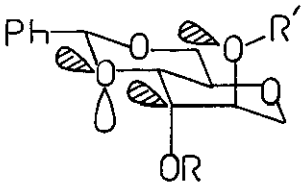


(47) R' = H



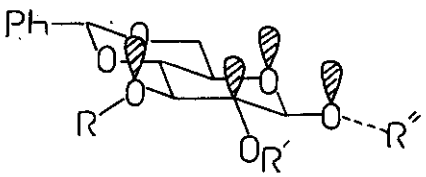
(48) R = H

(52) R = MgX

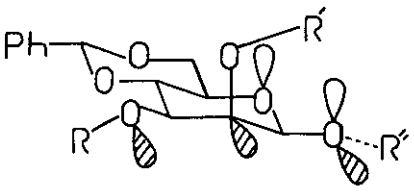


(49) R = H

(53) R = MgX



(56) R' = MgX



(57) R' = MgX

reduction of an α-D-ribo-hexopyranosid-2-ulose[21].

The O-5 has effectively controlled the paths of the reductions of these 2-uloses. It should be noted that the β-interactions from O-1 and O-3 will be stronger if the groups R- and R"- are alkyl rather than acyl, as the availability of the lone pair is important to the strength of the β-interaction.

An analogous analysis will reveal that the α-D-arabino-hexopyranosid-2-uloses will be reduced to the gluco-compounds preferentially[21], while the β-D-arabino-hexopyranosid-2-uloses will be reduced to the manno-compounds preferentially[21].

The 4,6-O-benzylidene-ribo-hexopyranosid-3-uloses and the arabino-hexopyranosid-3-uloses present the interesting situations of the O-1 and O-5 not contributing to the stabilisation of the intermediate radicals formed during their reductions. The O-2, and particularly the O-4, will be important centres of stabilisation in these reductions.

The arabino-hexopyranosid-3-uloses will produce radicals like (48) and (49) during their reductions. Hydrogen bonding between the OH-3 and O-4 will be stronger in the cisoid (49), than in the transoid (48). Further, the radical (49) is stabilised by one fixed and one variable β-interactions, while the radical (48) is stabilised by only one fixed β-interaction. The arabino-hexopyranosid-3-uloses will therefore be reduced preferentially to altro-compounds by sodium borohydride[22].

The ribo-hexopyranosid-3-uloses will produce radical intermediates like (42) and (43) during their reductions. Here both radicals are nearly equally stabilised by β-interactions, but hydrogen bonding favours the radical (43) and this radical is transformed into the major product of the reactions, the allo-compound[22].

The reductions of the 2- and 3-uloses by sodium borohydride usually yield products of similar configurations, in similar distributions, to those products obtained from the reactions of these uloses with the Grignard reagents[21, 22]. This would suggest that both reactions are subject to similar restraining or stabilising factors, particularly when the unencumbered Grignard reagents are considered.

Ashby and his co-workers[14] have demonstrated that the single-electron-transfer process was involved in the reaction of Grignard reagents with some benzophenones, by various trapping experiments and by the isolation and characterisation of addition products other than the expected 1,2-addition products. This was made possible by the stability and longevity of the extensively delocalised radicals generated from the benzophenones. However, less stable and localised radicals

will have much shorter lifetimes and will be difficult to detect or trap becaue of the rapidity with which they will react with their solvent-caged partners. The inability to detect or trap these radicals will not be evidence that these radicals are not generated in these reactions. There is also evidence that methylmagnesium bromide does participate in an electron-transfer mediated addition to enones[14].

Ashby et al[14] have shown that a methylmagnesium halide reacted much faster with acetone than with benzophenone, while a tert-butylmagnesium halide reacted much faster with benzophenone that with acetone. This dichotomy was rationalised by the suggestion that the tert.-butylmagnesium halide reacted with the benzophenone by a fast electron-transfer process, but with acetone by a slow ionic (polar) process. However, the methylmagnesium halide was thought to react with acetone by a fast polar process, but with the benzophenone by a slow electron-transfer process. It might well be that all the reactions go via electron-transfer processes, but that the rate determining step of electron transfer is very fast in both the reaction of methylmagnesium halide with acetone and tert.-butylmagnesium halide with benzophenone, but very slow in both the reaction of methylmagnesium halide with benzophenone and tert.-butylmagnesium halide with acetone. This could be appreciated by considering the separation of the HOMO of the 'anion' and the LUMO of the ketone. If the HOMO of the bonded 'methyl anion' is closer to the LUMO of acetone than to the LUMO of benzophenone, and the HOMO of the bonded 'tert.-butyl anion' is closer to the LUMO of benzophenone than to the LUMO acetone, then the observed rates of electron transfer and hence the overall rates will be due to the orbital separations and not to a duality of mechanisms.

The mechanism of the Grignard reaction, via an electron-transfer process, is shown in Scheme 7, and is derived from the mechanism proposed by Ashby et al[14]. If R'- is a small group, like methyl, then the stereochemistry of the products will depend on the size of the group R-, as was discussed for the metal hydride reductions.

Hydrogen bonding was shown to be an important factor affecting the stabilities of the radicals generated in the metal hydride reductions, and so too, the chelation of the magnesium ion in the intermediate radicals generated in the Grignard reactions will be important. Magnesium is significantly larger than hydrogen and its accommodation in the radical intermediates, in similar positions to the hydroxyl hydrogen of the previously discussed radicals, will be more subject to steric

factors. Other factors such as the strength of the Mg-O- linkages and the possibility of multiple coordination of the magnesium ion, will also help to determine the stereoselectivity of the reaction. Yoshimura's work[21,22] indicates that the Grignard reactions are not as stereoselective as the borohydride reductions. These instances of reduced stereoselectivity in the Grignard reactions will be due to the generation of radicals of comparable stabilities because of the above-mentioned additional factors.

The pair of radicals generated during the Grignard reactions of the ribo-hexopyranosid-3-uloses, (50) and (51), will both experience the same number of β-interactions, but chelation in the cisoid (51) will be more favourable than in the transoid (50). The radical (51) will be more stable than the radical (50) and will be transformed into the major product, an allo-compound[22].

The arabino-hexopyranosid-3-uloses will produce radicals (52) and (53). The chelation of the magnesium atom by O-3 and O-4 in (53) will be stronger than the chelation by O-3 and O-2 in (52), because O-4 is a better electron donor than O-2, having been 'activated' by the β-effect from O-6. The O-2 is only activated by a small γ-effect from O-5 (and when possible, from an equatorial O-1). Thus radical (53) is more stable than the radical (52) and will be transformed into the major product, an altro-compound[22].

The α-arabino-hexopyranosid-2-uloses will produce the radicals (54) and (55) in the Grignard reactions. The radical (54) will be favoured both by the stabilisation by the β-interactions from O-5 and O-3, and from the chelation possible with the cisoid O-1. The two variable β-interactions, from O-1 and O-3 in (55), combined with the unfavourable axial orientation of the alkoxymagnesium group ( the chelation with O-5 alone should not be unusually strong) do not make radical (55) quite as stable as the radical (54). The major product of the Grignard reaction will be derived from the radical (54) and will be a gluco-compound[21].

The pair of radicals generated during the Grignard reactions of the β-arabino-hexopyranosid-2-uloses, (56) and (57) are interesting because while the radical (56) will experience the larger number of β-interactions, chelation of the magnesium atom will be poor as O-1 and O-3 are transoid to O-2. On the other hand, the axial alkoxymagnesium group will be strongly chelated in the radical (57) by O-5 and O-1, while the radical bearing orbital will be stabilised by two variable β-interactions. The very favourable chelation in the radical (57) makes this radical more stable than the radical (56) and hence the major product of the

Grignard reaction will be the manno-compound[21].

The situation described for the pair of radicals (56) and (57) will be exaggerated in the pair of radicals (58) and (59), as the axial -OR group in (58) does not assist in stabilising the radical orbital. The radical (59) will be more stable than the radical (58) and the major product from the Grignard reactions of the β-ribo-hexopyranosid-2-uloses will be the altro-compounds[21].

The mechanistic proposals presented have not only enabled the reactions discussed to be rationalised, but they also have predictive value. The fact of being able to rationalise the outcomes of the clearly similar sodium borohydride reductions and the Grignard reactions of the uloses by a single, uncomplicated but dynamic proposal might well be the strongest evidence for the correctness of the gross features of the proposed mechanisms.

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