# THE ROLE OF LONE PAIR INTERACTIONS IN THE CHEMISTRY OF MONOSACCHARIDES THE SELECTIVE ESTERIFICATION OF 4,6-O-BENZYLIDENE-HEXOPYRANOSIDES

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Abstract - Mechanistic proposals are presented which seek to describe the course of the esterification of a 4,6-O-benzylidene-hexopyranoside by an acid chloride or an acid anhydride. These two proposals are then elaborated into a rationalisation of the selectivity observed in the esterification of the hydroxyl groups of some 4,6-O-benzylidene-hexopyranosides. Central to the rationalisations are the roles of the $\beta$- and $\gamma$-effects[1,2] which determine the relative energies of the lone pair bearing orbitals of the oxygen atoms of the reacting molecules.

## INTRODUCTION

The ability to selectively functionalise the hydroxyl groups of monosaccharides is central to the successful manipulation of these molecules. It is therefore quite important to be able to predict which one, of a number of free hydroxyl groups, will react preferentially with a given reagent, and hence to be able to decide which reagent should be employed in order to improve the chances of achieving the desired selectivity.

A number of plausible rationalisations have been offered to explain the selectivity of esterification of the hydroxyl groups of monosaccharides, but unfortunately, many of these rationalisations have limited predictive value, as they apply only to a few special systems (molecules)[3].

In a previous paper, some of the intramolecular interactions between the lone pair orbital of the oxygen atom and other orbitals on other atoms of the monosaccharide were examined[1]. The $\beta$- and $\gamma$-effects were proposed, and it was suggested that these effects determined the relative nucleophilicities of the oxygen atoms and other heteroatoms whose lone pairs were close enough to interact.

These concepts have allowed proposals to be made for the mechanisms of the phase transfer esterification and alkylation reactions of monosaccharides, as well as the tin mediated alkylations of monosaccharides by diazoalkanes[2].

## DISCUSSION

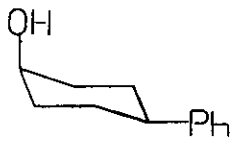
The esterification of 4,6-O-benzylidene-hexopyranosides by acid halides and acid anhydrides in pyridine, or other amine solvents, is known to proceed with marked selectivity in some cases[3].

In order to rationalise the observed selective esterification reactions, it is clearly important to first understand the modes of reaction of the esterifying agents themselves. Investigators have recognised the difference between the acid chlorides and the acid anhydrides in terms of reactivity and the nature of the reacting species in pyridine[3]. In order that these two esterifying agents are not seen as equivalent agents for the selective esterification of partially protected monosaccharides, the important mechanistic differences in the modes of reaction of alcohols with acid halides and acid anhydrides will be discussed.

Foster et al.[4] have investigated the relative rates of esterification of the alcohols (1), (2), (3) and (4). The trans cyclohexanol (2) was shown to react more readily with both an acid chloride and an acid anhydride in pyridine than the cis cyclohexanol (1). Whereas the compound (2) reacted 6.6 times faster with an acid chloride than did the compound (1), the compound (2) only reacted 3 times faster than did the compound (1) with an acid anhydride. These results indicated that both acylation processes were sensitive to the steric environment of the hydroxyl group, with the acid anhydride-pyridine reagent being much less responsive to these steric factors than the acid chloride-pyridine reagent.

It has been established that a 'proton acceptor' is an integral entity in the transition states of esterification reactions[5]. This acceptor can be sited within (on) the molecule bearing the hydroxyl group, or can be another molecule in the reaction mixture, and the acceptor plays the role as illustrated in the diagram (5). The alcohols (1) and (2) would therefore react via a trimolecular complex similar to that shown by the diagram (5), and the greater steric requirement of the acylpyridinium ion (formed from the acid chloride and pyridine) than the acid anhydride can now be seen as a consequence of the greater steric bulk of the acylpyridinium ion than the acid anhydride.

The acylpyridinium ion has been shown to be a more reactive acylating agent than



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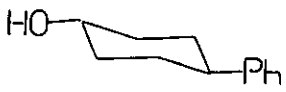

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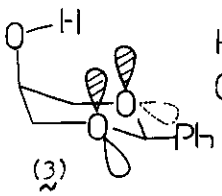

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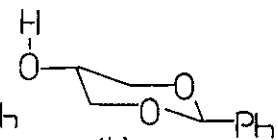

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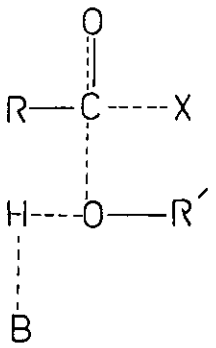
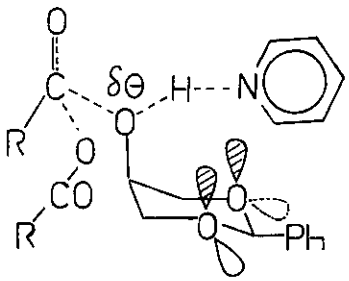


(5) X : Cl, or O.CO.R, or pyridinium.
B : proton acceptor.



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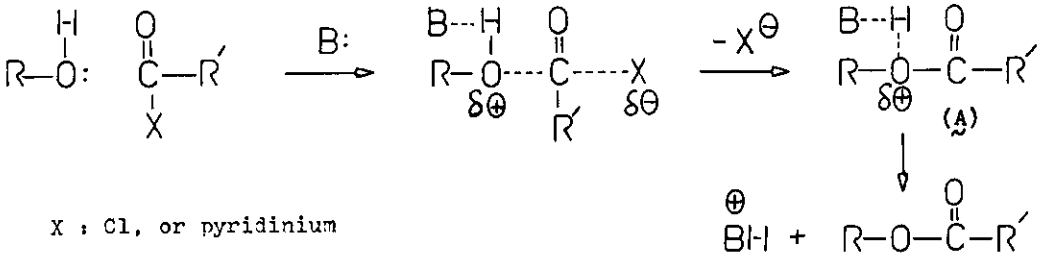
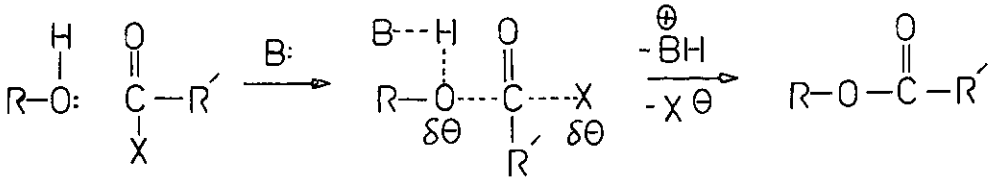


X : Cl, or pyridinium

SCHEME 1.



X : O.CO.R'

SCHEME 2.

the acid anhydride molecule[3]. This would suggest that the acylations involving the acylpyridinium ion proceed via transition states in which the -O-H bonds are still largely intact, as is shown figuratively in the scheme 1, with the consequence that a partial positive charge will be developed by the oxygen atom and a relatively weak base will be an adequate acceptor of the proton. On the other hand, acylations involving the acid anhydride molecule might proceed via transition states, figuratively shown in the scheme 2, in which the breaking of the -O-H bonds are either synchronous with, or preceed, the breaking of the R.CO-X bonds. This would require that the proton acceptor must be a basic molecule (or group), certainly more so than that required in acylpyridinium ion reactions, and probably of greater basicity than an oxygen atom of an ether or alcohol group.

The question of whether or not intermolecular hydrogen bonds formed by the reacting -OH group remain intact during the approach of the acylating agent has been examined by several investigators[3]. While this point will be difficult to resolve, it seems very likely that because of the developing steric crowding, intermolecular hydrogen bonds can be replaced by intramolecular hydrogen bonds in the transition state because of the advantageous entropic contributions and the sterically more favoured situation which would arise.

In contrast to the straightforward observations made with the alcohols (1) and (2), Foster et al. showed that the axial alcohol (3) reacted 5.6 times faster with the acid chloride-pyridine reagent than did the equatorial alcohol (4), while the alcohol (3) reacted 8 times slower with the acid anhydride-pyridine reagent than did the alcohol (4), ref. 4.

The hydroxyl group of the axial alcohol (3) is strongly hydrogen bonded intramolecularly to the oxygens O-1 and O-3, ref. 6. The hydroxyl group greatly reduces the lone pair repulsions between O-1 and O-3 by reducing the electron density in either or both of their lone pairs. Eliel has shown that the axial alcohol (3) is more stable than the equatorial alcohol (4) because of this stabilising role of the strong hydrogen bond.

This strong hydrogen bond suggests that the O-1, O-3 'site' could be a very suitable proton acceptor site in an acylation reaction, particularly with an active esterifying agent like an acylpyridinium ion. The lone pairs of the oxygen atoms O-1 and O-3 are activated by a fixed β-effect. With an intramolecular acceptor site, the steric requirements of the transition state will be vastly reduced and the attack of the acylating agent should be facilitated. As the proton is trans-

ferred from the reacting O-5 to the O-1, O-3 acceptor site, the $\beta$-effect is changed into a favourable, attractive inverse $\beta$-interaction. These features of the esterification of the axial alcohol (3) contribute to the great ease with which the reaction occurs with an acylpyridinium ion.

The esterification of the equatorial alcohol (4) will require an external proton acceptor and the entropy factor involved in the assembling of the trimolecular transition state will contribute to the slowness of the reaction as compared to that of the alcohol (3). The transition state of the esterification of the alcohol (4) is also likely to be more crowded than that of the esterification of the molecule (3) as there are three molecules in one transition state as opposed to two in the other. The transition state of the reaction of the compound (4) might thus be subject to destabilisation by steric factors, while that of the reaction of the compound (3) cannot be so affected. Thus the alcohol (3) is esterified more rapidly by an acylpyridinium ion than the alcohol (4).

The reaction of the alcohol (4) with the acid anhydride-pyridine reagent will be similar to the reaction with the acylpyridinium ion, save that the esterifying agent will be less reactive than the acylpyridinium ion, but less bulky. On the other hand, the compound (3) can react by one of two paths, either with the aid of an external proton acceptor or with the O-1, O-3 'site' acting as the proton acceptor.

If pyridine acted as the external proton acceptor, the transition state, scheme 2, would require the bonding of the hydroxyl group to the base, and the development of a small negative charge on O-5, thus leading to a transition state similar to that shown in the diagram (6). This process would significantly aggravate the lone pair repulsions between O-5, O-1 and O-3. The attainment of this transition state would therefore be retarded by the reluctance of the molecule to give up the O-5 proton, which would lead to accentuated lone pair repulsions.

If the O-1, O-3 site was the acceptor site and not pyridine, then the driving force for the removal of the hydroxyl proton would be the same for both esterification processes (with the acylpyridinium ion and the acid anhydride) , but the smaller degree of reactivity of the acid anhydride to the acylpyridinium ion would result in the acid anhydride reaction being slower than the acylpyridinium ion reaction. In fact the O-1, O-3 site might not be 'basic' enough to lead to an appreciable rate of reaction of the alcohol (3) with the acid anhydride.

The transition state shown in the diagram (6) will be quite sterically hindered as

compared to the similar transition state for the esterification of the alcohol (4) and this additional factor will result in the esterification of the alcohol (3) by the acid anhydride-pyridine reagent being slower than the corresponding esterification of the alcohol (4).

The esterification of alcohols by acid halides can be performed very efficiently in an aprotic non-polar solvent, in the absence of a soluble strong base. Iodide and chloride ions have been shown to be sufficiently active proton acceptors in acid halide-monosaccharide reactions to permit these reactions to proceed at quite reasonable rates[7]. These reactions lend support to the premise that the initial proton acceptor site in an esterification of a monosaccharide by an acid halide or an acylpyridinium ion can be within the molecule, as etheric or alcoholic oxygens are more basic than halide ions[8]. Other support for the intramolecular nature of the proton acceptor site in these reactions comes from the fact that the acylpyridinium ion reagent[9] and the acid chloride-triethylamine reagent[10] both show very similar selectivities to the acid chloride-tetrabutylammonium iodide reagent[7].

These esterifications described above demonstrate that esterifications by acid halides and acylpyridinium ions should not be compared with similar reactions done by acid anhydrides in pyridine or other simple amine solvent. Further, in order to appreciate the reactivity of an alcohol, as it has been enhanced or reduced by the environment of the hydroxyl group, the reactions of these alcohols with acid halides or acylpyridinium ions are better suited as yardsticks, as these reactions are more influenced by the environment of the hydroxyl group than by the basicities of moderately basic proton acceptors.

The effect of the polarity of the solvent in determining the selectivity of the esterification process can also be rationalised by way of the above discussion. It has been suggested that the selectivity of the esterification process increases with the decreasing polarity of the solvent used[7].

Solvents which do not form strong hydrogen bonds to the hydroxyl groups of the monosaccharide will force the molecule to be esterified via a transition state that involves an intramolecular proton acceptor site. The differential activation of the possible proton acceptor sites in the molecule by $\beta$- and $\gamma$-effects then pronouncedly influences the reaction and maximium selectivity is observed.

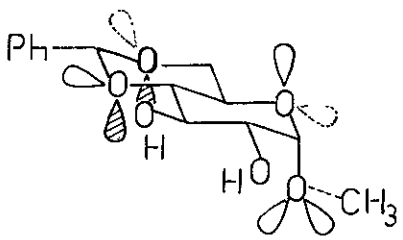
Solvents which form strong hydrogen bonds with the monosaccharide provide the opportunity for the esterification to proceed with the influence of an external proton acceptor. Since each of the externally hydrogen bonded hydroxyl groups will have

significantly polarised -O-H bonds, with significant partial negative charges on the oxygens, their reactivities will each be increased, and apart from the influence of steric factors, become similar. The polar, basic solvent will thus exert a 'levelling' effect.

The discussion above can provide the framework within which to discuss and rationalise the observed selective esterification reactions of monosaccharides and other molecules, by acid halides and acylpyridinium ions in solvents of moderate basicity and polarity. Among the important factors that must be constantly considered are: a) the association between acceptor and the proton as shown in the intermediate (A) scheme 1, will be weak and this can result in the changing of the acceptor site from one oxygen to another, depending on which has the more energetic lone pair orbital; b) the intramolecular proton acceptor will be most effective if it is cis with the hydroxyl group undergoing reaction, as slight changes in the chair conformations of the reacting molecules are likely to bring cisoid acceptor sites closer to the hydroxyl protons, while moving transoid acceptor sites away from the hydroxyl protons; and c) the intermediates like (A) scheme 1 will, by way of the positive charge on the oxygen atom, experience electrostatic stabilisations from the neighbouring oxygen atoms which are cis and 1,3 or 1,4 with respect to the this reaction site to a greater extent than from oxygen atoms which are trans and similarly located ( inverse $\beta$- and $\gamma$- interactions). These features effectively stabilise the transition state and facilitate the processes leading to the transition state.

In general it will be seen that the monosaccharide will be preferentially esterified at a particular hydroxyl group if: i) the generated intermediate like (A) scheme 1, is more favourably stabilised by inverse $\beta$- and $\gamma$-interactions and ii) the intramolecular proton acceptor is cisoid and is more activated by $\beta$- and $\gamma$-effects, than is possible for the similar intermediates derived from the reaction of the other hydroxyl groups in the molecule.

Methyl 4,6-O-benzylidene- $\alpha$-D-glucopyranoside (7) is esterified preferentially at O-2 by acid halides and acylpyridiniun ions[7, 10]. The OH-2 is cis with the O-1, which will be a suitable proton acceptor, activated by a small $\beta$-effect. The intermediate formed in the reaction of the OH-2 will result in a stabilisation of the small O-5 - O-1 electronic interaction because the strong hydrogen bond between O-2 and O-1 will reduce the electron density on O-1. The partially positively charged oxygen of the intermediate formed by the reaction of O-2 will experience an inverse



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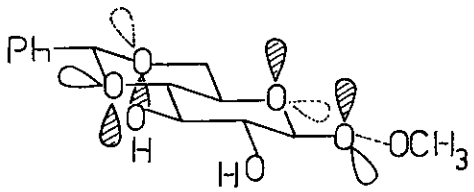

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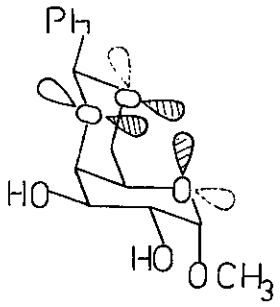

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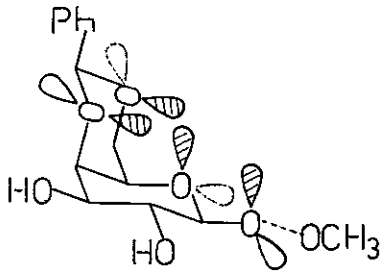

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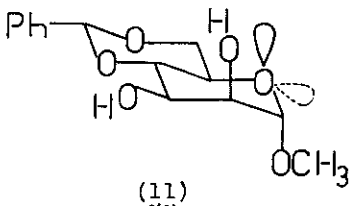

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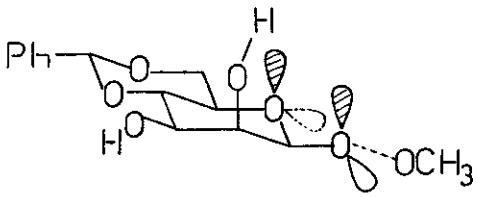

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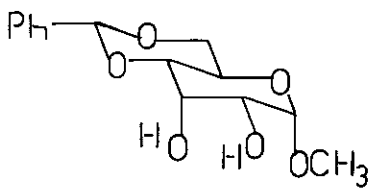

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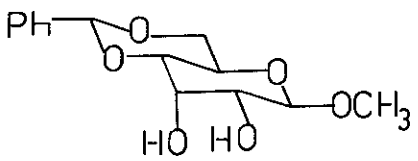

(14)

γ-interaction from the transoid O-3.

The OH-3 is trans to both O-2 and O-4 and so will not have a suitably oriented proton acceptor site for its esterification. The O-4 will be a more favourable proton acceptor than the O-2 in the esterification of the OH-3, as the weak hydrogen bonding of the reaction site with the O-4 will reduce the electron density on O-4 and hence the β-interaction between O-4 and O-6. In other words, the O-4 is activated by a strong β-interaction with O-6, while the O-2 is not similarly activated. The intermediate formed by the reaction of OH-3 will experience a small inverse γ-interaction with the transoid O-2.

The combination of these factors stated clearly make OH-2 a more favourable site of reaction than OH-3.

The β-glucopyranoside (8) is known to be less reactive than the α-glucopyranoside (7) ref. 11. The compound (8) has no cisoid proton acceptor sites available to OH-2 or to OH-3. Both hydroxyl groups show similar reactivities with acid chlorides refs. 10 and 11. Of the acceptor sites available to OH-2 and OH-3, namely O-1 and O-4 respectively, O-4 is activated by a fixed β-effect, while the O-1 can rotate about the C-1 - O-1 bond so varying the positions of the lone pairs and reducing the size of the β-effect it experiences. The O-4 will therefore be a more strongly activated proton acceptor site and this no doubt accounts for the slightly greater reactivity of the OH-3 ref. 3.

The α-galactopyranoside (9) has suitable cisoid proton acceptor sites for both the hydroxyl groups. However the O-4 is very much more activated than O-1. The conformationally mobile O-1 is activated by a small β-effect (see above), while the fixed O-4 is activated by a full β-effect and a fixed, cisoid γ-effect from O-5. The O-4 should be a far better proton acceptor site than the O-1. The intermediate formed in the reaction of the OH-2 will partially stabilise the small O-5 - O-1 electronic repulsion by hydrogen bonding, while the intermediate from the reaction of OH-3 will partially stabilise the larger electronic repulsions experienced by O-4, by hydrogen bonding. The O-3 is therefore a more suitable site of esterification than the O-2.

The β-galactopyranoside (10) possesses the same features as the anomer (9) with respect to OH-3, but it no longer has a suitable cis proton acceptor site for the intermediate formed from the reaction of OH-2. The OH-3 of the compound (10) will now be a much more favourable site for esterification than the OH-2. These reactions of the galactopyranosides have been observed[12].

The α-mannopyranoside (11) is an interesting system, as one hydroxyl group might be the preferred proton acceptor site during the esterification of the other, since these two groups are cisoid, while they are transoid to the other adjacent oxygen atoms. The axial lone pair of O-5 is suitably oriented to form a hydrogen bond between O-5 and the axial OH-2, and OH-3 can form a similar hydrogen bond to O-4, because both O-5 and O-4 are gauche with respect to O-2 and O-3 respectively. Two patterns of hydrogen bonding will be possible in this molecule, namely O-5... HO-2...HO-3 and O-4...HO-3...HO-2. It is not obvious which will be the preferred pattern of hydrogen bonding, indeed both might be equally advantageous energetically. The first pattern of hydrogen bonding should favour esterification at O-3, while the second pattern of hydrogen bonding should favour esterification at O-2. If we assume that both patterns of hydrogen bonding are equally likely to occur, then the factor which remains to distinguish between the ease of esterification of OH-2 and OH-3 will be the steric factor. In the preceeding discussion, the greater ease of esterification of an equatorial hydroxyl group over an axial hydroxyl group by an acid halide or an acylpyridinium ion was highlighted. Thus, if all other factors are equally important, the steric requirements of the reaction will bias the selectivity of the reaction towards the equatorial OH-3. This has been observed[13, 14].

The β-mannopyranoside (12) possesses the same structural features about O-5, O-2, O-3 and O-4 as is found in the diol (11), and also about O-5, O-1 and OH-2 as is found in the alcohol (3). The large β-effect present between O-5 and O-1 will now cause the OH-2 to be very strongly hydrogen bonded to the O-5, O-1 site, as in the compound (3). This very strong hydrogen bond should markedly stabilise the pattern of hydrogen bonding, namely O-5, O-1...HO-2...HO-3, and hence make O-3 the preferred site of esterification. Here, O-3 has both of its lone pairs available for the interaction with the esterifying agent, while the O-2 has only one available lone pair, and O-3 is activated as a nucleophile by the γ-interaction with O-4. Thus the OH-3 remains the site of selective esterification in the anomer (12) ref. 14.

The allopyranoside (13) is preferentially esterified[10] at the equatorial OH-2, rather than the axial OH-3. Both hydroxyl groups have suitable cis proton acceptor sites. The O-4 proton acceptor site would be expected to be a more efficient acceptor than the O-1 acceptor site, as O-4 experiences a larger β-effect activation from O-6 than O-1 does from O-5. However the steric factor compensates and biases the esterification process toward OH-2.

The β-allopyranoside (14), in which OH-2, OH-3 and O-4 are cisoid, while O-1 is trans to OH-2, would be expected to react preferentially at OH-2. In this molecule the preferred pattern of hydrogen bonding must be O-4...HO-3...HO-2, thus leaving O-2 with both lone pairs for bonding to the electrophile. The steric factor also favours the equatorial OH-2.

The discussion above leads logically to the conclusion that the selectivity of the esterification process can be varied by changing the efficiencies of the various intramolecular proton acceptor sites relative to each other. The degree of activation of the intramolecular proton acceptor clearly depends on the β- and γ-interactions it is experiencing. If the sizes of these interactions can be varied then the degree of activation of the acceptor will be changed and hence the selectivity of the esterification process. Also, any factor which varies the availability of the proton accepting lone pair will change the selectivity of the esterification process.

Factors which will decrease the energy level or availability of a lone pair will include: delocalisations (over flanking electronegative multiply bonded systems as are found in vinyl ethers, esters, aryl ethers etc.), inductive effects, and β- or γ-interactions with neighbouring empty orbitals, and these will lead to a decrease in the ability of the lone pair bearing atom to act as an acceptor. On the other hand, factors which will increase the electron density on the lone pair bearing atom, or will elevate the energy level of the lone pair orbital ( β- and γ-effects with neighbouring lone pairs) will lead to an increase in the ability of the lone pair bearing atom to act as a proton acceptor.

In 4,6-O-alkylidene(or arylidene)-hexopyranosides the efficiency of the O-1 proton acceptor site can be varied by changing the electronic nature of the aglycone, and the efficiency of the O-4 proton acceptor site can be varied by changing the electronic nature of the alkyl or aryl group. Aglycones like trifluoroethyl and 4-nitrophenyl should reduce the ability of the O-1 to act as a proton acceptor and hence reduce the selectivity of esterification at the OH-2, when compared to the effects of aglycones like the ethyl and 4-methoxyphenyl groups. In a similar manner a 4,6-O-(4-nitrobenzylidene)-hexopyranoside should show a reduced selectivity of esterification at OH-3 when compared to a 4,6-O-(4-methoxybenzylidene)-hexopyranoside. Here the effects on O-4 and O-6 will not only be inductive in nature, but will also be due to the β-interaction of the lone pairs on O-4 and O-6 with an electron-deficient "p-orbital" at C-1 of the 4-nitrophenyl group as compared to the

interactions of the same lone pairs with the electron-rich "p-orbital" at C-1 of the 4-methoxyphenyl group. The former interaction lowers the energy levels of the O-4 and O-6, while the latter interaction raises these energy levels.

Thus the natures of the aglycones and the 4,6-O-alkylidene or arylidene groups must be considered when comparing the selectivies of esterification of partially protected monosaccharides, and it should be possible to bias the selectivity of an esterification reaction to that desired by using both an aglycone and a 4,6-O-arylidene group which have the necessary electronic features.

The analysis above can be extended to the rationalisation of the selectivities of esterification of other partially protected monosaccharides. The examples given above merely illustrate the features of the analysis. Care must be taken in trying to rationalise the results of esterifications in which significant multiple esterification has occurred as then the relative yields of esters do not necessarily reflect the true selectivity of the reaction[15]. Further, reactions performed under conditions which will facilitate ester migration[3] will not necessarily reflect the true selectivities of these reactions.

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