THE ROLE OF LONE PAIR INTERACTIONS IN THE SELECTIVE FUNCTIONALISATION OF SOME 4,6-O-BENZYLIDENE-HEXOPYRANOSIDES BY BOTH THE PHASE TRANSFER ESTERIFICATION REACTIONS AND THE TIN-MEDIATED ESTERIFICATION AND ALKYLATION REACTIONS

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Abstract - The esterifications of some 4,6-O-benzylidene-hexopyranosides by the phase transfer method are reviewed and a mechanism for these reactions is proposed which takes into account the differential nucleophilicities of the oxygens, O-2 and O-3, as predicted by the β-effect and the γ-effect [1].

The similarities between the tin mediated esterification and alkylation reactions of these monosaccharides and the corresponding phase transfer reactions lead to the proposal of a mechanism for the path of the tin mediated processes.

The alkylation of diols by diazoalkanes in the presence of catalytic amounts of tin salts is reviewed and a mechanism is proposed for these reactions, which rationalises the apparently inverse reactivity of the 'hydroxyl groups'.

INTRODUCTION

The selectivity observed in the partial esterification of 4,6-O-benzylidene-hexopyranosides, and other simple monosaccharides by the phase transfer process can be rationalised or predicted if the β- and γ-effects[1] inherent in the molecules are recognised and if the mechanism of the esterification process is understood. The structures and conformations of the mono-alkoxides derived from the 4,6-O-benzylidene-hexopyranosides are shown to be crucial to the observed selective esterifications.

The reactions of the tin alkoxides of vicinal diols, found in partially protected

monosaccharides, with various esterifying and alkylating agents have provided mono-functionalised products in good yield and, in the cases of the reactions of the diols from pyranosides, with marked selectivity.
These reactions have attracted much attention, but the mechanisms of the various reactions have remained in obscurity.
Of particular interest are the alkylations of vicinal diols by diazoalkanes in the presence of tin salts, as these processes show an apparent reversal in the selectivity of functionalisation of the 'hydroxyl groups' involved, as compared to the reactions of the free diols, or the dibutylstannylene derivatives.
All of these reactions can, however, be rationalised mechanistically by examining the reactions of the 2-stanna-1,3-dioxolane intermediates, in the light of the β- and γ-effects[1] which are innate in these species.

DISCUSSION

Esterifications by the phase transfer method have been described and show interesting selectivity[3,4,5]. These conditions are very different from those encountered in the usual acid chloride-pyridine[2] or acyl chloride-tetrabutylammonium iodide-potassium carbonate-benzene[4] systems and would be expected to accomplish the observed esterifications by a different mechanistic pathway.
The esterification of an alcohol by the acid chloride-pyridine system, has been suggested to involve the attack of the acid chloride (or N-acylpyridinium chloride) on the alcohol group, with one of the other oxygens of the monosaccharide acting as an intramolecular 'base', which eventually accepts the proton liberated in the process. The base in the reaction simply recovers the proton from the acceptor site[2]. An esterification done by the phase transfer method uses an organic phase, like benzene or dichloromethane, containing the monosaccharide and the acid chloride, in contact with an aqueous phase containing a tertrabutylammonium salt and sodium or potassium hydroxide. The role of the tetrabutylammonium cation is central, as without it the reaction does not proceed at any appreciable rate[3].
It must be assumed that the sugar is converted to its alkoxide which is solubilised in the organic phase by the tetrabutylammonium ion, and then the alkoxide reacts with the esterifying agent. The alkoxide formation can occur either at the phase interface, or by tetrabutylammonium hydroxide reacting with the sugar <u>in</u> the organic layer. The formation of the alkoxide at the phase interface seems more likely as there is not a rapid loss of acid chloride from the organic layer by

reaction with hydroxide, which would be expected to occur if tetrabutylammonium hydroxide was present in appreciable concentration in this organic layer.
The central features of the mechanism of these phase transfer reactions thus become: the attack by the alkoxide on the acid chloride, and in particular, the reasons for one of the oxygens, O-2 or O-3, attacking the esterifying agent in preference to the other(s).
Of great significance, and in support of the above analysis is the fact that the esterifications by the phase transfer method are far more rapid than by the acid chloride-pyridine method, so confirming that the intermediates in the phase transfer method possess greater nucleophilicities than the simple alcohols involved in the acid chloride-pyridine or acid chloride-benzene-tetrabutylammonium iodide-potassium carbonate methods. Indeed, even the β-glucoside (1), which is known to be far less reactive than the α-glucoside (2) to the acid chloride-pyridine reagent[6], was partially esterified to a similar extent as the α-glucoside (2), in the same period of time, by the phase transfer method[3].
The methyl 4,6-O-benzylidene-D-glucopyranosides (1) and (2) and methyl 4,6-O-benzylidene-α-D-mannopyranoside (3), have been successfully selectively esterified by the phase transfer method. It is significant that the mono-alkoxides derived from these sugars can be partially stabilised by intramolecular hydrogen bonding as shown by the structures (4), (5) and (6) respectively. The proton involved in the hydrogen bond can be assumed to be closer to O-3 than to O-2 because the fractional negative charge on O-2 will be smaller than that on O-3,as it is partially dispersed by the inductive effects of O-1 and O-5. The O-3 will therefore be slightly encumbered by the proton as compared to O-2.
It must be accepted that the mutual repulsions of these partially negatively charged oxygens, O-3 and O-2, will alter the conformations of the molecules (4), (5) and (6) to some extent, so as to move these oxygens apart (if this is possible) and so reduce the electrostatic repulsion. This conformational change will be counter-balanced by the strength of the hydrogen bond, and the conformational preference of the molecule as a whole, and so might not be a very drastic conformational change.
The alkoxides (4) and (5) differ from (6) in that oxygens O-2 and O-3 are gauche and transoid, and a conformational change will move these oxygens apart. The alkoxide (6) will have difficulty in adjusting its conformation to separate the oxygens O-2 and O-3 and will possess a very strong hydrogen bond, as the oxygens

are cisoid. The hydrogen bonds in the alkoxides (4) and (5) will be weaker than that found in the alkoxide (6) for the reason above. The molecule (6) is therefore very likely to possess the same shape as the parent alcohol (3), whereas small but important differences between the shapes of (4) and (5) as compared to the molecules (1) and (2) would be expected.

A small conformational change in the alkoxide (4), intended to increase the distance between O-2 and O-3, should also increase the distance between O-1 and O-2, while having a smaller effect on that distance between O-3 and O-4. The γ-effect[1] experienced by O-2 will be decreased as O-1 moves further away, thus reducing the nucleophilicity of O-2. On the other hand, the proton bonded between O-2 and O-3 will move closer to O-3 as this hydrogen bonding becomes weaker, consequent on the increasing O-2—O-3 distance, thus making O-2 slightly more exposed or more similar to a free alkoxide oxygen.

These two effects are seen to operate in opposite directions, as regards the nucleophilicity of O-2. However, the partial negative charge on O-2 and its steric availability as compared to O-3, will be decisive. Because the O-3—O-4 distance will not be increased to the same extent as the O-2—O-1 distance, the γ-effect experienced by O-3 will nearly remain the same, and this coupled with its enhanced electron density will make O-3 of the alkoxide (4) more nucleophilic than O-3 of the alcohol (1), but still less nucleophilic than O-2 of the alkoxide (4).

A small conformational change in the alkoxide (5) will have the same effect on O-3 as it did in the molecule (4). However, this conformational change will move O-2 closer to O-1. Thus the γ-effect experienced by O-2 will be increased, resulting in an increased nucleophilicity for O-2. In addition, the aforementioned movement of the proton bonded between O-2 and O-3, closer to O-3 as these centres move apart, will also increase the relative nucleophilicity of O-2, by making O-2 more exposed.

The analysis of the nucleophilicities of O-3 and O-2 of the alkoxides (4) and (5) clearly indicates that the alkoxide (5) will be preferentially esterified at O-2, while the alkoxide (4) will be preferentially esterified at O-2, but not very markedly as compared to esterification at O-3. This is consistent with the observed esterifications of the glucosides (1) (ref. 3) and (2) (ref.3,4) by the phase transfer method.

The alkoxide (6) highlights all the effects and features described as operating in the alkoxides (4) and (5).

Although the proton bonded between O-2 and O-3 is strongly held because these centres are cisoid , it will lie closer to O-3 because, again, the fractional negative charge on O-2 is partially dispersed by the inductive effects of O-5 and O-1. O-2 will therefore be more exposed than O-3. The γ-effect between O-3 and O-4 will be similar to that between O-2 and O-5, as O-3 is gauche to O-4 and O-2 is also gauche to O-5. Thus the effects operate to make O-2 more nucleophilic than O-3. The esterification of (6) occurs overwhelmingly preferentially at O-2 when attempted by the phase transfer method[3].

The analysis when applied to methyl 4,6-O-benzylidene-β-D-mannopyranoside predicts exclusive 2-esterification, as now the nucleophilicity of O-2 will be enhanced by an additional γ-effect between O-2 and O-1. The γ-effects encountered in this molecule will also be enhanced by the β-effect, (O-5—O-1).

This method of analysis suggests that there will always be appreciable esterification at O-2, because the inductive effects of O-5 and O-1 partially stabilise the charge on O-2 and hence allow the shared proton to be more strongly bonded to O-3. The steric environment of the hydroxyl group created by the rest of the molecule seems not to be of great importance, unlike the situation in the esterifications using the acid chloride-pyridine system[2,6].

The analysis above suggests that the only 4,6-O-benzylidene-D-hexopyranosides that are likely to be esterified preferentially at O-3, by the phase transfer method, are the β-allopyranosides and the β-galactopyranosides. The talopyranosides and altropyranosides have not been considered, as the conformations of their monoalkoxides are not obvious.

The 4,6-O-benzylidene-β-D-allopyranosides will give rise to alkoxides like (7) in which O-1 and O-2 are transoid, while O-3 and O-4 are cisoid. The O-3 will therefore be activated by a larger γ-effect than O-2. This γ-effect mediated activation of O-3 might be sufficient to cause O-3 to be more nucleophilic than O-2, but at the very least, it will ensure that the proportion of esterification at O-3 will be comparable to, if not greater than, that at O-2.

The α-D-allopyranoside will produce alkoxides like (8) in which both O-2 and O-3 experience similar γ-effects. Any slight conformational changes of the ring will bring O-1 closer to O-2 than O-3 to O-4, and so increase the γ-effect at O-2 to a larger extent than that at O-3, thus increasing the nucleophilicity of O-2 over that of O-3. Thus considering all the factors affecting (8), it will be preferentially esterified at O-2.

The D-galactopyranosides will produce alkoxides like (9) and (10), which show the same features as the alkoxides (7) and (8) respectively. For these reasons, (9) would be expected to be comparably, if not preferentially, esterified at O-3, while (10) will be preferentially esterified at O-2.

Indeed, the phase transfer tosylation of methyl 4,6-O-benzylidene-α-D-allopyranoside[7] and benzoylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside[5] gave the 2-esters as the major products in 67% and 64% yields respectively. Further, methyl 4,6-O-benzylidene-β-D-galactopyranoside was converted by the phase transfer tosylation into the 3-tosylate in 61% yield[8]. These data thus lend support to the predicted reaction paths for alkoxides like (7), (8), (9) and (10).

Preferential esterifications will best be demonstrated by using tosyl chloride as the esterifying agent, as the tosyl group will not migrate under the usual conditions of the reactions[9]. Benzoates will suffer from acyl migration[4,5] and an early analysis of these reaction mixtures will be imperative if the results obtained from benzoylations are to be meaningful.

The reactions of vicinal diols with dibutyltin oxide (Bu_2SnO) have been explored, and the 2-(dibutylstanna)-1,3-dioxolanes formed in these reactions properly characterised[10].

The reactions of these 2-(dibutylstanna)-1,3-dioxolanes with esterifying[10] and alkylating[11] agents have also been investigated, and the relative reactivities (nucleophilicities) of the oxygens have corresponded to the reactivities of the hydroxyl groups of the parent diols under phase transfer conditions[3].

Thus the 2-(dibutylstanna)-1,3-dioxolanes (11), (12) and (13) were all preferentially esterified[10] at O-2, as has been found to occur with the alkoxides (5) (ref. 3), (8) and (10) (ref. 5).

The relative reactivities of the hydroxyl groups of the 4,6-O-benzylidene-hexopyranosides under phase transfer conditions have been described above and rationalised by means of the β- and γ-effects occurring in the intermediate alkoxides. In view of the similarities in the structural features common to the species shown, and hence the similarities in the various β- and γ-effects innate in these species, it was not surprising that the corresponding pairs of compounds (11) and (5), etc., all showed similar selectivities (relative nucleophilicities of O-2 and O-3) and hence yielded similar product distributions for a given reaction. The analogies can be extended by noting the similarities in the charge distributions in a 2-(dibutylstanna)-1,3-dioxolane and the mono-alkoxide derived from the

same parent diol, compounds (14) and (15). The sizes of the residual negative charges on the oxygen atoms, $\delta(-)$ and $\delta'(-)$, will no doubt be influenced by structural features in the parent diol, and the geometries of the 'rings' will no doubt be very similar, if not identical.

The one important difference between the species (14) and (15) will be due to the bulk of the dibutylstannyl group, and this will introduce a steric factor which must be taken into consideration, this steric factor being absent in the species (15). In the context of the compounds (11), (12) and (13), and regardless of the coordination pattern at tin, this steric factor will be greater at O-3, since the O-2—Sn bond will be longer than the O-3—Sn bond, as O-2 can better stabilise a negative charge (by way of the inductive effects from C-1) than O-3.

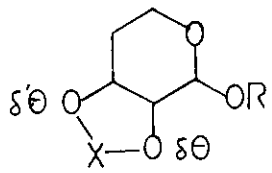
This additional steric factor might be responsible for the greater selectivity observed in the esterifications of (11), (12), and (13) than of (5), (8) and (10). The compound (9) was shown to be non-selective in its interactions with acylating agents[10], and this observed reactivity was similar to the reactivity of the alkoxide (4) (ref. 3).

In their paper[10], Munavu and Szmant had proposed that the selectivity encountered in the reactions of the α-hexopyranosides (11), (12) and (13) was due to the coordination of the tin atom by the anomeric methoxyl group. They offered in support of this coordination, the downfield shifting of the resonance of this methoxyl group in the n.m.r. spectrum of (11). However, the size of the downfield shift, 0.07 ppm, seemed too small to be significant, and further, the O-1 to tin distance seemed quite large when viewed in a model of compound (11).

Their data were best explained by the mechanistic interpretation given above, in which the β- and γ-effects were regarded as the prime factors influencing the differences in the nucleophilicities of the two oxygen atoms, O-2 and O-3.

In contrast to the selectivity observed in the reactions of the 2-(dibutylstanna)-1,3-dioxolanes, the reactions of diols with diazoalkanes in the presence of tin salts have yielded mono-functionalised products in distributions indicating an inverse selectivity[12,13].

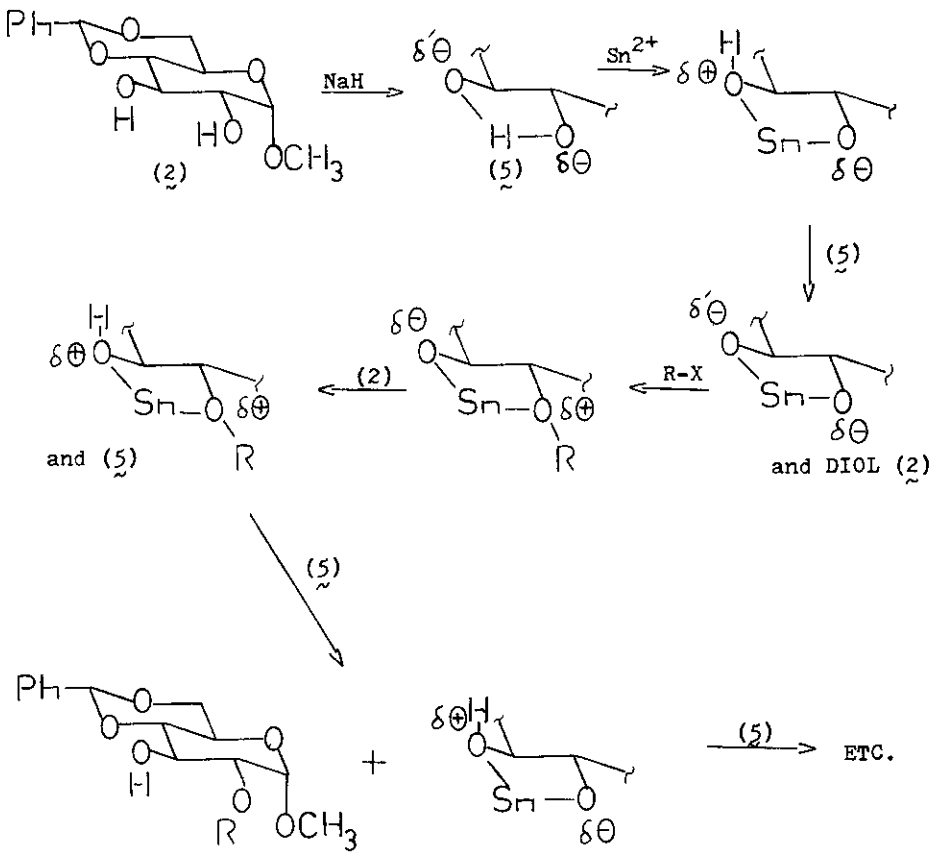
It has been suggested that these reactions occurred via the tin alkoxides, eg. (17), and Chittenden[14] showed that two hydroxyl groups were necessary for complexation with the tin atom before the reaction would proceed. More recently Shugar et al.[15] compiled additional evidence supporting the proposed role of the tin atom (its participation in the formation of a cyclic alkoxide intermediate) in the



$\delta\Theta > \delta'\Theta$

(14) X : Bu_2Sn

(15) X : H



SCHEME 1

reaction. Both Chittenden[14] and Shugar et al.[15] have pointed out that 2-stanna-1,3-dioxanes are also possible intermediates in these reactions, where the structural features of the alcohol allow, but that the 2-stanna-1,3-dioxolanes were favoured by entropy factors (greater ease of formation of the 5-membered ring). A similar preference for the 2-(dibutylstanna)-1,3-dioxolane over the 2-(dibutylstanna)-1,3-dioxane structure was noted by Munavu and Szmant[10].

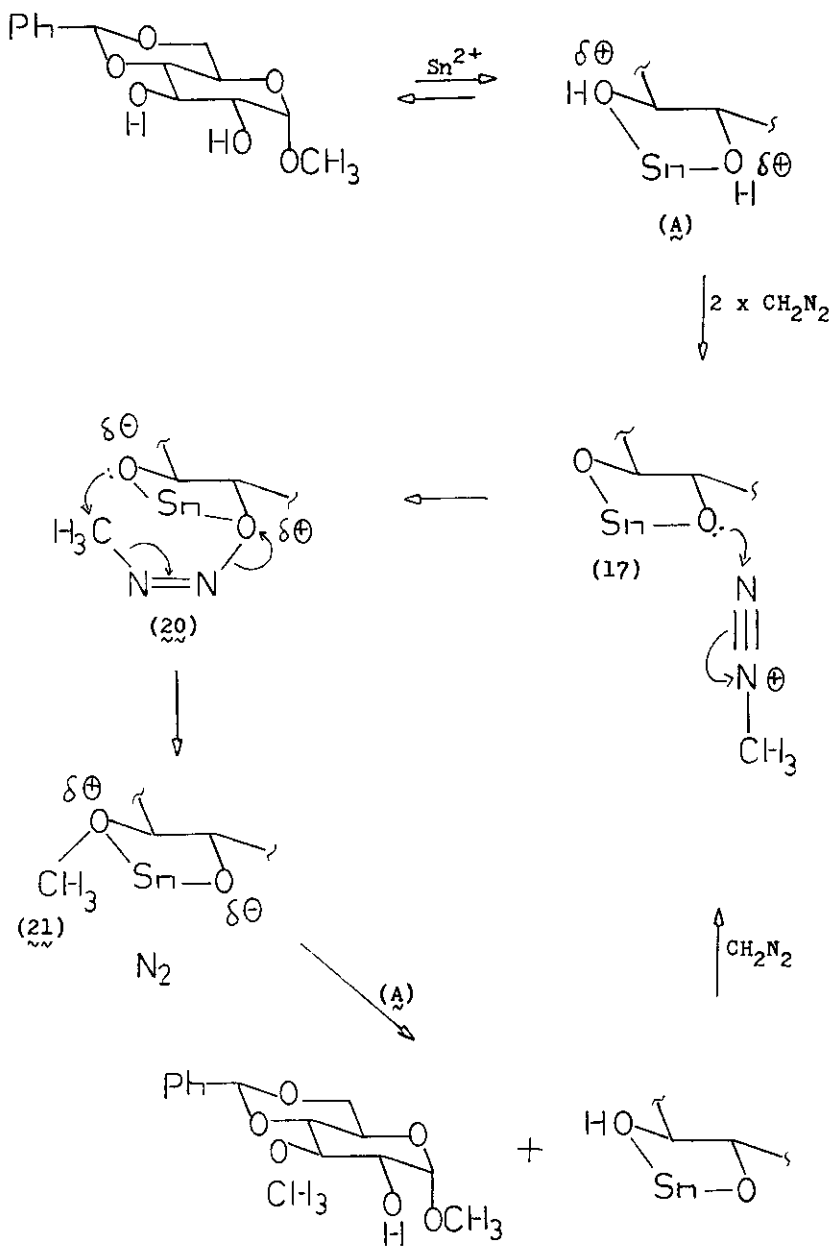
Notwithstanding the marked similarities, in structural features, between (17), (5) and (11), the intermediate (17) reacted with diazomethane to provide the 3-O-methyl ether almost exclusively, **while alkoxides (5) and (11) were preferentially alkylated at O-2 by alkyl halides, and further, the intermediate (18) produced mainly the 3-O-methyl ether** by reaction with diazomethane[13], while the alkoxide (4) was preferentially alkylated at O-2 by alkyl halides. The α-galactopyranoside derivative (19) gave exclusively the 2-O-methyl ether[12] in 91% yield, while it has been demonstrated that the alkoxide (9) was preferentially functionalised at O-3.

These results pointed to the central role of the diazoalkane in determining the outcome of each of the above reactions.

In order to confirm this thesis, methyl 4,6-O-benzylidene-α-D-glucopyranoside (5.0 mmol) was benzylated by treating its solution in dimethylformamide (25 mL) with sodium hydride (6.65 mmol), followed by $SnCl_2.0H_2O$ (0.5 mmol) and then benzyl bromide (5.0 mmol). The reaction between the benzyl bromide and the alkoxide, which was mildly exothermic and was completed in 30 minutes, gave the 2-O-benzyl ether and the 2-O,3-O-dibenzyl ether as the only products (44% and 11% yields respectively). No attempt was made to optimise the yield of the monobenzyl ether, but significantly, no 3-O-benzyl ether was detected among the reaction products. It seemed reasonable to assume that the intermediate (17) had participated in the reaction, as cyclic tin alkoxides are known to be more stable than acyclic tin alkoxides[16], and the mechanism of this model reaction was envisaged as that shown in scheme 1.

This result indicated that the intermediate (17) had reacted with a simple alkylating agent in a manner congruent with the similar reactions of intermediates (11) and (5), and thus the role of the diazoalkane was indeed central to the observed inversion of selectivity of alkylation of (17) by the diazoalkane.

The reactions of diols with diazoalkanes were performed by simply adding an excess


Ph
HO
OCH3
Sn2+
δ⊕
HO
Sn—O δ⊕
H
(A)
2 x CH2N2
δ⊕
Sn
H3C
N=N
δ⊕
(20)
Sn—O.
(17)
N
N⊕
CH3
δ⊕
CH3
Sn—O
δ⊕
(21)
N2
CH2N2
(A)
Ph
CH3
OCH3
+
HO
Sn—O

SCHEME 2

of the diazoalkane to a methanolic solution of the diol containing a catalytic amount of the $SnCl_2$ species. The diazoalkane was clearly acting both as the base (in the formation of the tin alkoxide, the 2-stanna-1,3-dioxolane system) and the source of the electrophilic agent.

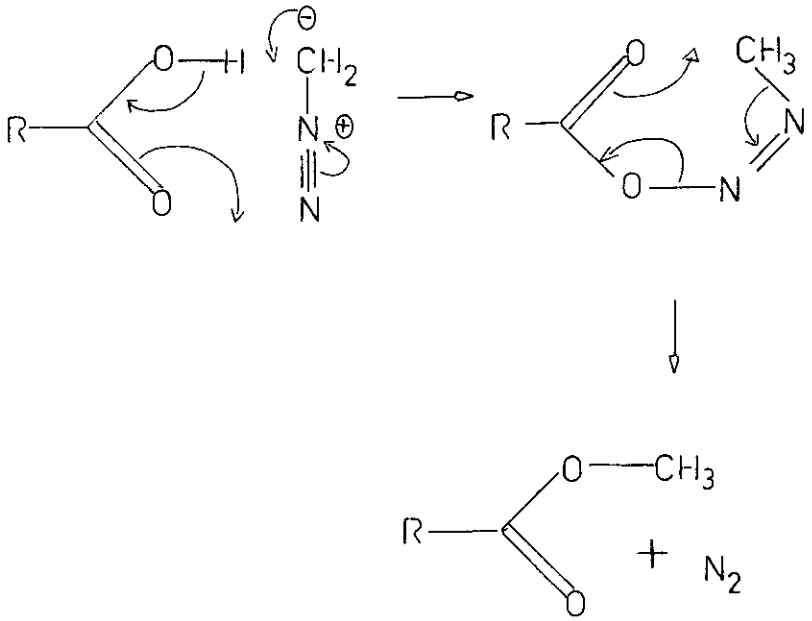
The protonated diazoalkane species, $R\text{-}CH_2\text{-}N_2^{(+)}$ can react with chloride ions, liberated in the formation of the 2-stanna-1,3-dioxolane system, to form the alkyl chloride $R\text{-}CH_2\text{-}Cl$. This alkyl chloride was not the effective alkylating agent however, as has been demonstrated by the above-described reaction of the intermediate (17) with benzyl bromide, as then the 'normal' selectivity would have been observed.

The other alkylating agent to consider was the carbonium ion, $R\text{-}CH_2^{(+)}$, which could be formed by loss of nitrogen from $R\text{-}CH_2\text{-}N_2^{(+)}$. Again, the carbonium ion $R\text{-}CH_2^{(+)}$ would not be expected to react differently than benzyl bromide, with a nucleophile and certainly the decomposition of $CH_3\text{-}N_2^{(+)}$ to $CH_3^{(+)}$ would not be expected to occur with ease, if at all.

The third alkylating agent to consider was $R\text{-}CH_2\text{-}N_2^{(+)}$. This alkylating (electrophilic) agent can be attacked by a nucleophile at either of <u>two</u> sites. An Sn2-like attack at carbon would result in a simple alkylating process, similar to that observed with simple alkyl halides, but an attack at the nitrogen would yield an intermediate which could further react as an alkylating agent. This is shown in scheme 2.

The more nucleophilic oxygen, O-2, would be expected to be the first attacking nucleophile, leading to the formation of the entity (20), which could rearrange through a 6-membered transition state to the alkylated complex (21). The complex (21) could then act as a base in converting more of the initially formed tin-diol complex (A) to intermediate (17), which would then go through the processes outlined.

This mechanism, scheme 2, reconciled all the features of the known reactions of diols with diazoalkanes in the presence of metal ions (salts) as catalysts[17]. The metal ion will clearly influence the rate and selectivity of the reaction by (a) determining how acidic the protons of the initially formed diol-metal ion complex are; (b) determining how available the lone pairs of the oxygen atoms are, for actions as nucleophiles, here phenomena such as 'back-bonding', and a high electronegativity of the metal ion will inhibit the nucleophilic process, and (c) by determining the sizes of the steric factors encountered by the approaching electr-



SCHEME 3

ophile, this depending on the coordination pattern at the metal atom.
This type of mechanism might also be followed in the alkylation of carboxylic acids by diazoalkanes, as shown in scheme 3.
If the gross features of the mechanism, proposed to rationalise the diazoalkane/tin salt/diol alkylations are correct, then these reactions truly complement the alkylation processes done using alkyl halides. The known efficacious alkylation methods using alkyl halides are (a) the phase transfer method[3]; (b) the reactions involving dibutyltin oxide[10,11], and (c) the process described herein, i.e. the diol/sodium hydride/dimethylformamide/$SnCl_2.OH_2O$ method. It should be obvious that those diols which are alkylated by one of the three methods above with alkyl halides and which show marked selectivity in their reactions, because of a marked difference in the nucleophilicities of the reacting oxygens, will show marked inverse selectivity in the diazoalkane/tin salt process.
The β- and γ-effects enable the selectivity of the alkyl halide alkylations to be predicted, and so too the selectivity of the diazoalkane-tin salt alkylations.

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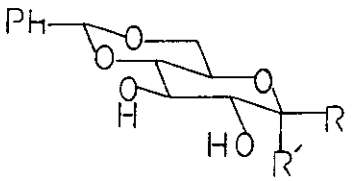
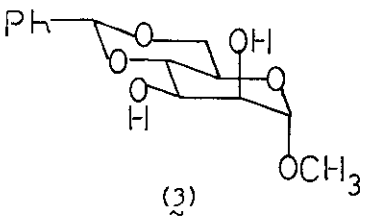
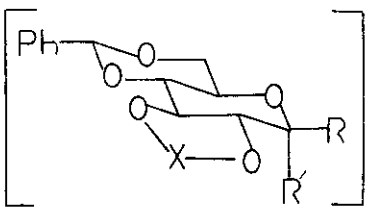


(1) R : OR, R' : H

(2) R : H, R' : OR



(3)



(4) R : OR, R' : H, X : H

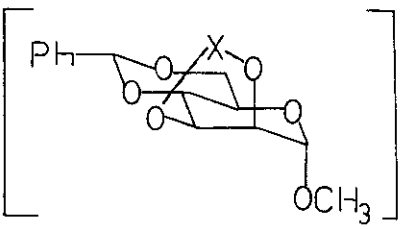
(5) R : H, R' : OR, X : H

(11) R : H, R' : OCH_3, X : Bu_2Sn

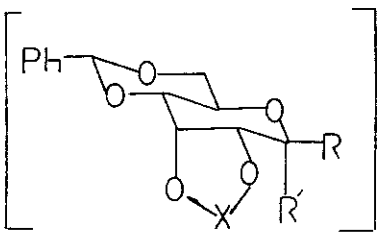
(16) R : OCH_3, R' : H, X : Bu_2Sn

(17) R : H, R' : OCH_3, X : Sn

(18) R : OCH_3, R' : H, X : Sn



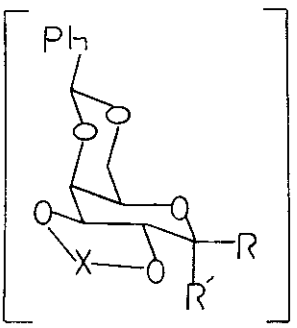
(6) X : H



(7) R : OR, R' : H, X : H

(8) R : H, R' : OR, X : H

(12) R : H, R' : OCH_3, X : Bu_2Sn



(9) R : OR, R' : H, X : H

(10) R : H, R' : OR, X : H

(13) R : H, R' : OCH_3, X : Bu_2Sn

(19) R : OCH_2Ph, R' : H, X : Sn

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