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Review

THE USE OF TIN COMPOUNDS IN CARBOHYDRATE AND NUCLEOSIDE CHEMISTRY *

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Introduction

Tin, in both its inorganic and organometallic forms, reacts readily with a wide range of biologically important molecules, such as amino acids, steroids, carbohydrates and nucleosides. Since the first reported examples of tin-carbohydrate [1] and tin-nucleoside [2] derivatives in the early 1970's, there has been much interest in the chemistry, structure and applications of compounds of this type, and, in this article, the major developments in the field are reviewed.

Synthesis and structure

By far the most common organotin(IV) carbohydrate or nucleoside derivatives are the trialkylstannyl ethers and the dialkylstannylenes [3], in which the alkyltin group (usually n-butyltin) is linked to the pyranose or furanose ring via the hydroxylic oxygens, e.g. tributylstannyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (**1**). These compounds may be prepared [2–6] by refluxing a mixture of the bis(trialkyltin) oxide, trialkyltin hydroxide or dialkyltin oxide and the appropriate blocked sugar in toluene, with azeotropic removal of the water formed, or in methanol (Fig. 1; Schemes 1–3). The former solvent is usually employed for the synthesis of the trialkylstannyl ethers, since, in general, these are more readily hydrolysed in air than their dialkylstannylene counterparts.

In the case of sugar derivatives containing more than one unprotected hydroxyl group, partial tributylstannylation may be achieved, either by the use of bis(tributyltin) oxide [7,8] or by treatment of the diethylboryl ethers with tributyltin acetylacetonate [9], and partial dibutylstannylation by the use of dibutyltin oxide [5,10]. With these compounds, a valuable aid to assignment of the position of substitution is the appearance in the ^{13}C NMR spectra of $^{117,119}Sn$ satellites, arising from $^{2}J(^{117,119}Sn–O–^{13}C)$ and $^{3}J(^{117,119}Sn–O–^{13}C)$ couplings. An example of this coupling is shown in Fig. 2, which is the ^{13}C NMR spectrum of a mixture of **1** and its β-anomer **2** in toluene [8]. ^{119}Sn NMR studies have revealed [8] that the

* Dedicated to Professor G.E. Coates on the occasion of his 70th birthday.

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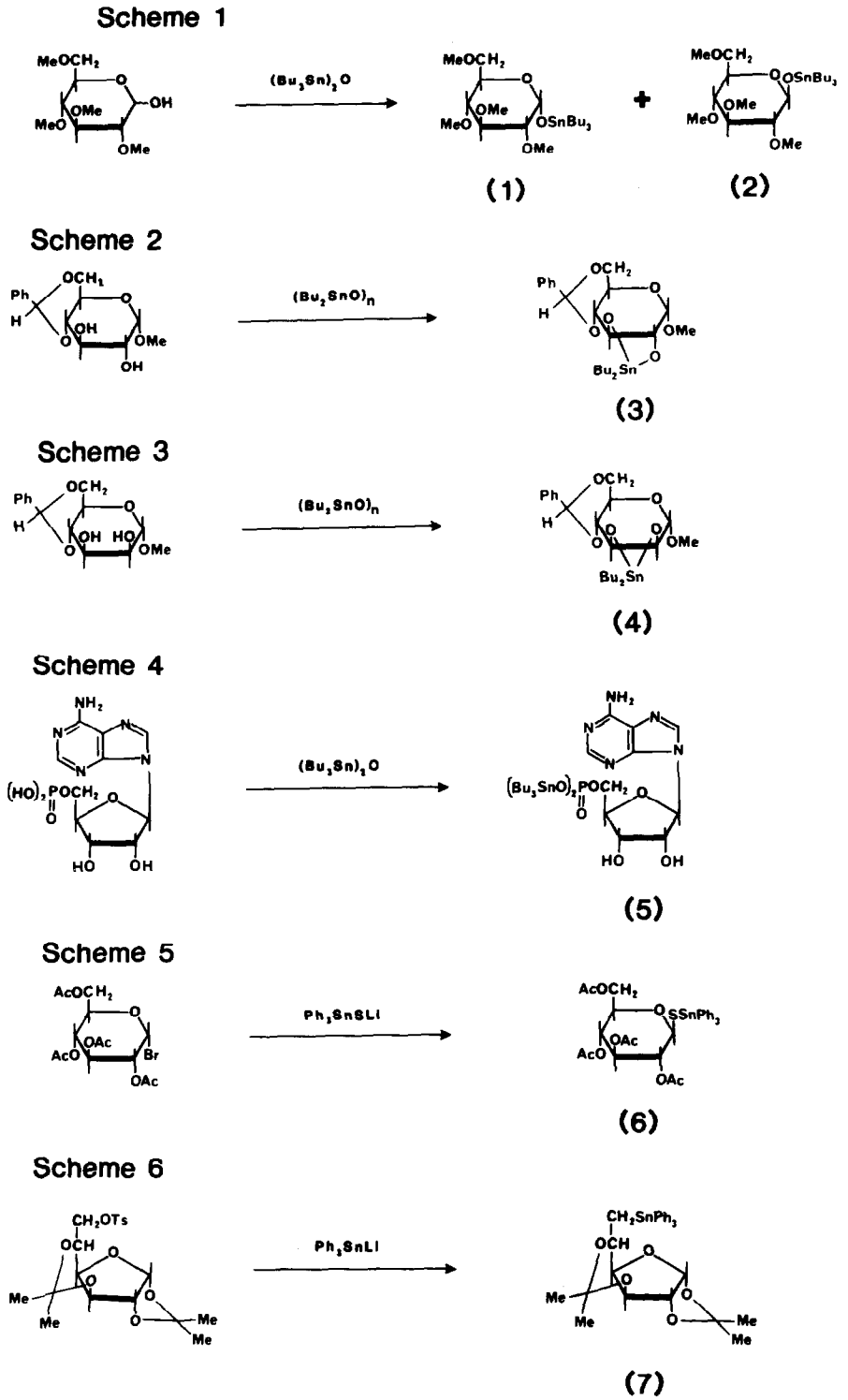


Fig. 1. Synthetic routes to organotin(IV) derivatives of carbohydrates and nucleosides [5,6,8,14,21,22].

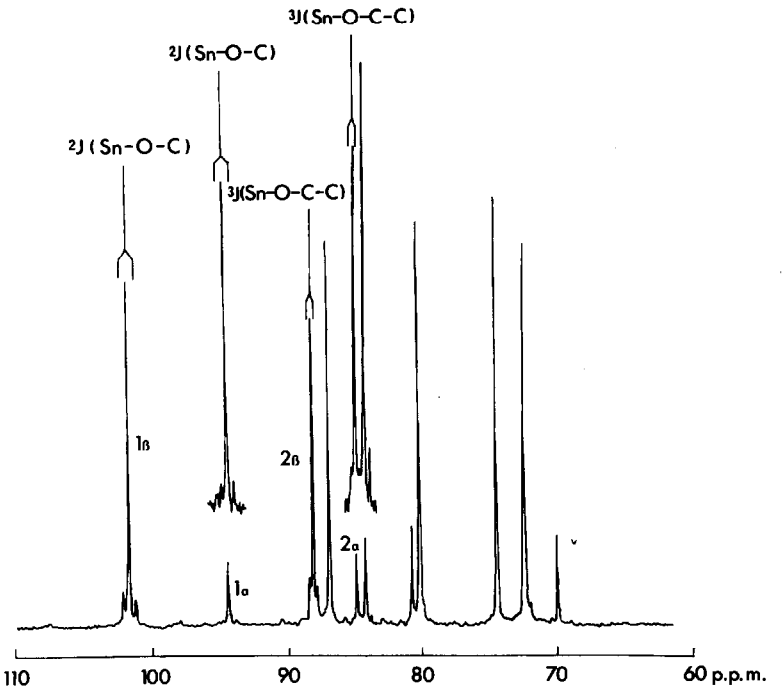
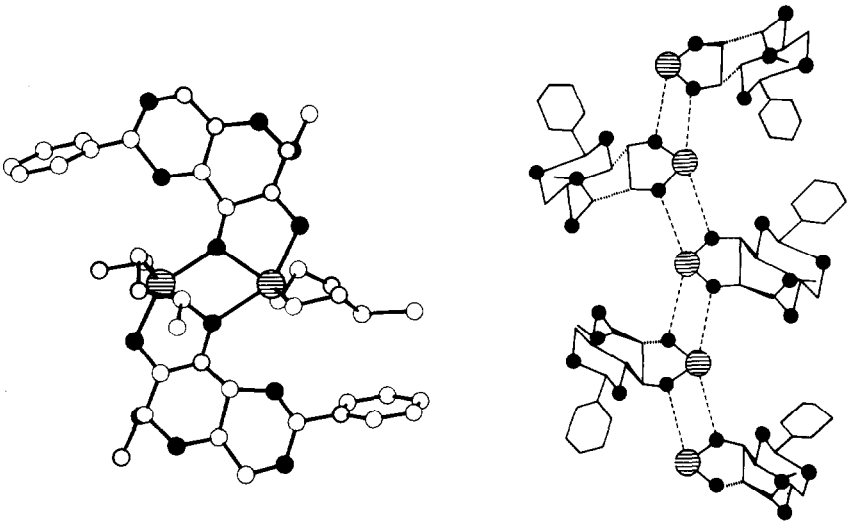


Fig. 2. ^{13}C NMR spectrum of tributylstannyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (**1**), and its β-anomer (**2**), in toluene [8]. The C(1) and C(2) resonances from each anomer are labelled.

tributylstannyl ethers exist in toluene solution as monomers containing a tetrahedral tin atom geometry and ^{119m}Sn Mössbauer spectroscopic investigations show [11] that this structure is preserved in the solid state at 80 K. In compounds such as **1**, the possibility of intramolecular coordination from the oxygen atom of a neighbouring methoxy group to the tin has been proposed [7,12], but this would appear to be ruled out by their high frequency ^{119}Sn NMR chemical shifts, $\delta(^{119}Sn)$ [8].

In contrast to the monomeric tributylstannyl ethers, the dialkylstannylene derivatives of carbohydrates and nucleosides are associated in the solid state. X-ray studies on methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**3**) [13] and the corresponding mannopyranoside (**4**) [14] have revealed that these are dimeric and pentameric respectively, in which both tin atoms in **3** are five-coordinate, and, in **4**, the metal is pentacoordinate in the two terminal moieties and hexacoordinate in the three medial units (Fig. 3). No coordination of the methoxy group to tin is observed. Self-association of the glucose derivative **3** is limited to dimerisation because of increased steric hindrance by the sugar group, as compared to the mannose compound **4** [14]. In line with this, structural studies on the cyclic dibutylstannylenes of 1,2-ethanediol [15] and 1,3-propanediol [16], in which there is little or no such steric hindrance, have shown that these form infinite ribbon polymers containing distorted octahedral tin atoms. Although no X-ray data have been reported on organotin derivatives of nucleosides, recent ^{119m}Sn Mössbauer studies [17] on a series of 2′, 3′-*O*-dialkylstannyleneribonucleosides are indicative of



(3) (4)

Fig. 3. Solid state geometries of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**3**) and methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**4**), adapted from refs. 13 and 14, respectively. Sn atoms are represented by striped circles; O atoms by black circles; the C atoms in **3** are white circles and in **4** are omitted.

a dimeric structure involving trigonal bipyramidal tin atoms, similar to **3**. Mössbauer parameters have also been reported [15] for compounds **3** and **4**.

^{119}Sn NMR investigations on dibutylstannylene derivatives of carbohydrates are in accord with the retention of their associated structure in solution, since compounds possessing the dimeric form **3** show [8,14,18] a single low frequency resonance, whereas the mannose pentamer (**4**) gives [14] several low frequency tin signals, indicating the presence of a number of tin-containing species and this suggests a range of oligomeric states. In the gas phase, it has been shown, using field desorption mass spectroscopy, that 2′,3′-*O*-dibutylstannylene-adenosine retains its dimeric structure [19].

In recent years, hydrolytically stable organotin carbohydrate and nucleoside derivatives containing Sn–O [5,20], Sn–S [21] or Sn–C [22,23] linkages to the sugar ring have been synthesised and the routes to these are illustrated by compounds **5–7** in Fig. 1; Schemes 4–6. There are, to our knowledge, no reports of monoalkyltin(IV) or organotin(II) derivatives of sugars.

The strongly Lewis Acid inorganic tin(IV) and tin(II) halides form a wide range of adducts with organic donor molecules [24,25] and, consequently, their interaction with carbohydrates and nucleosides involves coordination of the hydroxyl groups to the tin, rather than the formation of ethers (containing Sn–O–C bonds). The sugar may function either as a unidentate or bidentate donor ligand and this results in an octahedral geometry for the tin(IV) derivatives **8** and **9** and a distorted trigonal pyramidal structure for the tin(II) complexes **10**, (Fig. 4). These adducts are prepared by mixing stoichiometric proportions of the reactants in chloroform at room temperature, in the case of $SnCl_4$ [26,27], or by refluxing in methanol for the

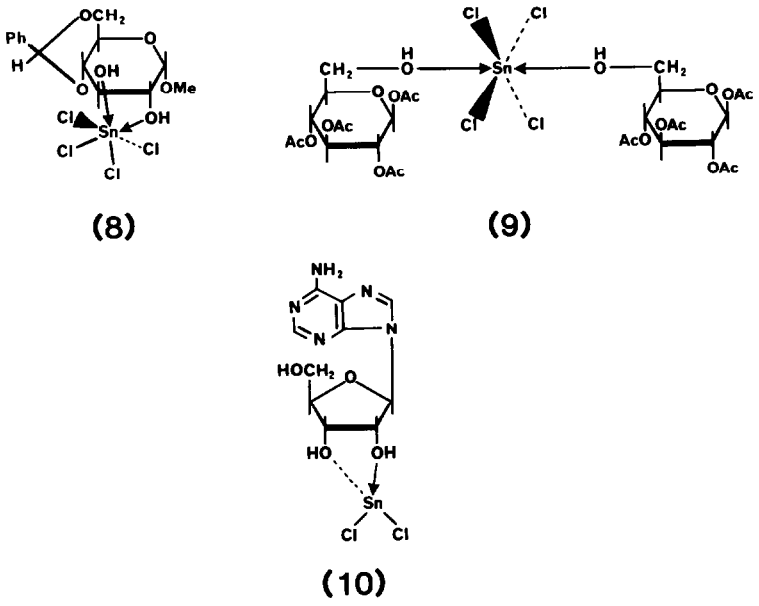


Fig. 4. Proposed structures [26–28] of inorganic tin(II) and tin(IV) derivatives of carbohydrates and nucleosides.

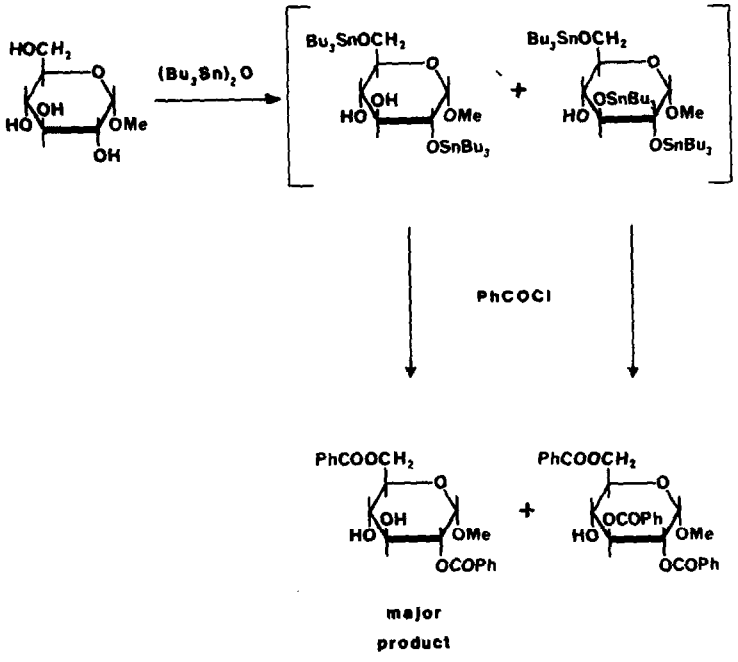
tin(II) chloride-nucleoside complexes [28]; the tin(IV) derivatives are hydrolysed rapidly in air, whereas the tin(II) compounds appear to be more stable. A recent paper has described [29] the synthesis of adducts of adenosine with two organotin chlorides, $Me_2SnCl_2 \cdot 2$(Adenosine) and $PhSnCl_3 \cdot 2$(Adenosine), and interestingly, in these complexes, ^1H NMR studies suggest that coordination is through the N(7) position of the adenine base, rather than via the hydroxyl groups.

In aqueous media, the alkali and alkaline earth metal salts form adducts with a wide range of sugars (many of which have been isolated in the solid state) and these involve donation to the metal from the hydroxyl groups [30]. Aqueous solution studies have indicated the existence of inclusion complexes between organotin(IV) compounds and β-cyclodextrin polymers [31] and similar adducts have been observed between inorganic tin(IV) salts and a series of mono- and di-saccharides [32], although these have not been isolated in the solid state. Further work on cyclodextrin-organotin inclusion compounds is reported to be in progress [33].

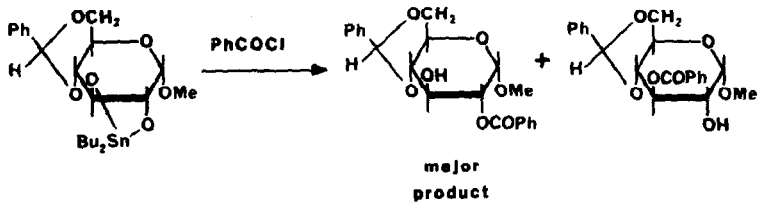
Intermediates in synthesis

By far the largest use of organotin [5,19] and inorganic tin derivatives of carbohydrates and nucleosides is their regioselective esterification, alkylation and arylation. It has been shown [2,7,12] that formation of a tributylstannyl ether results in an enhancement of the nucleophilicity of the oxygen atom compared to the original hydroxyl group. Thus, subsequent attack on the organotin intermediate by a suitable electrophilic reagent, e.g. benzoyl chloride [7], occurs selectively at the position of tributylstannylation, rather than at the other free hydroxyl groups (Fig. 5; Scheme 7). Additionally, the synthesis of partially protected 2-deoxyribonucleo-

Scheme 7



Scheme 8



Scheme 9

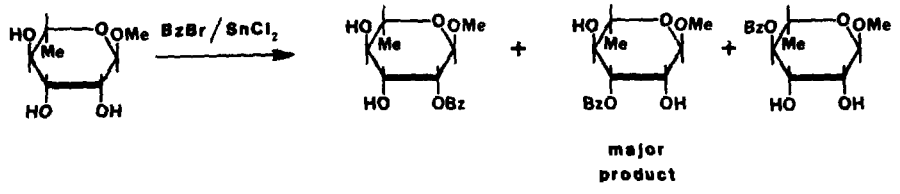


Fig. 5. Regioselective electrophilic attack involving tin-carbohydrate species [7,35,48].

tide dimers by the selective phosphorylation of hydroxyl functions activated with bis(tributyltin) oxide has been reported [34] recently.

The dibutylstannylene derivatives of sugars have also been utilized extensively as synthetic intermediates in compounds containing vicinal diol groups. David has proposed [19] that, in the dimeric structures, such as **3**, the oxygen atom involved in intermolecular coordination to the tin (O(3) in **3**) is less nucleophilic than the uncoordinated oxygen. Hence, in non-donor solvents, electrophilic attack occurs at the latter site [35] (Fig. 5; Scheme 8).

There have been a number of reports on the use of inorganic tin(II) salts, in catalytic amounts, to promote the selective methylation [36–43] (Table 1) and di- [44] or mono- [45–47] arylmethylation of carbohydrates and nucleosides with $CRR'N_2$ (where R and R′ = H or Aryl), usually in methanol, and benzylation [48], using benzyl bromide in ethyl acetate or acetonitrile. Since tin(II) compounds have a marked tendency to occupy a 3-coordinate pyramidal geometry [49], it is probable that only one of the hydroxyl groups is directly coordinated to the metal and that the second HO · · · Sn interaction is relatively weak, e.g. **10**. Consequently, the strongly coordinated hydroxyl moiety is selectively deactivated to electrophilic attack (by R^+). ^{13}C NMR studies [50] on an equimolar solution of tin(II) chloride and methyl α-L-rhamnopyranoside in acetone indicate a stronger interaction of the tin with C(2) compared to C(3), and, in line with this, selective benzylation of this monosaccharide with benzyl bromide, using $SnCl_2$ as a catalyst, occurs predominately at C(3) [48] (Fig. 5; Scheme 9). The interaction of tin(IV) halides with vicinal diols involves the formation of a neutral adduct, such as **8**, in which the HO → Sn donor bonds are likely to be symmetrically disposed in the octahedral tin(IV) environment. Consequently, it is unlikely that inorganic tin(IV) compounds will be able to selectively deactivate these hydroxyl groups in sugars.

Tin compounds, both organic and inorganic, have a number of other applications as synthetic intermediates in carbohydrate chemistry. The oxidative transformations of tributylstannyl ethers, using *N*-bromosuccinimide (NBS), and of dibutylstannylenes, with bromine, have been described. Ogawa and Matsui have shown [51] that treatment of a series of tributylstannyl ethers of monosaccharides with NBS in dry carbon tetrachloride produces dimeric esters (e.g. Fig. 6; Scheme 10), and David and Thiéffry found [52] that the action of bromine on a number of dibutylstannylenes gave the corresponding hydroxy-ketones (e.g. Fig. 6; Scheme 11).

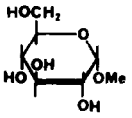
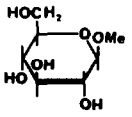
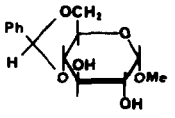
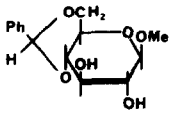
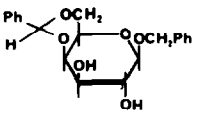
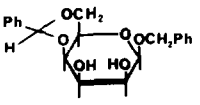
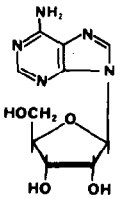
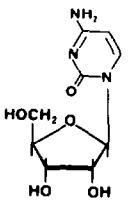
Several reactions have been reported using tin intermediates which involve the anomeric carbon atom of the sugar. Tin(IV) chloride has been used to promote the replacement of an acetoxy group in the β-anomeric position by an alkoxy moiety [53] (Fig. 6; Scheme 12). A special example of this type of reaction involves the formation of an internal ether linkage [26] (Fig. 6; Scheme 13). Ogawa and Matsui have shown that a convenient synthesis of glycosides [54] or thioglycosides [55] may be achieved by the reaction of tetra-*O*-acetyl-α-D-glucosyl bromide [54,55] or 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl acetate [55] with Bu_3SnOR or Bu_3SnSR, in the presence of a Lewis Acid, e.g. $SnCl_4$ (Fig. 6; Schemes 14 and 15 *). This

(Continued on p. 150)

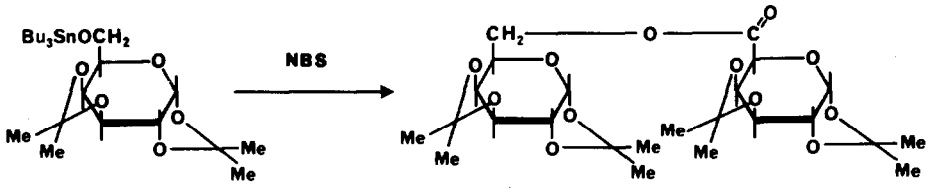
* The products of Scheme 15 in fact consist of an equimolar mixture of the α- and β-anomers in 95% yield.

TABLE I

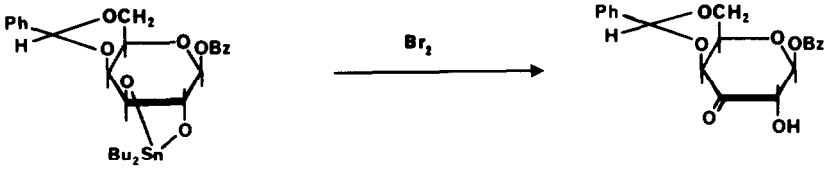
EXAMPLES OF THE PRODUCTS FORMED IN THE PARTIAL METHYLATION OF SUGARS USING THE $CH_2N_2/SnCl_2$ SYSTEM

Sugar	Reaction products			Reference
	2-O-methyl ether	3-O-methyl ether	2,3-di-O-methyl ether	
	—	74%	17%	36
	—	54%	48%	36
	4%	97%	trace	36
	34%	52%	trace	36
	91%	—	—	40
	—	89%	—	41
	38%	61%	—	38
	74%	15%	—	38

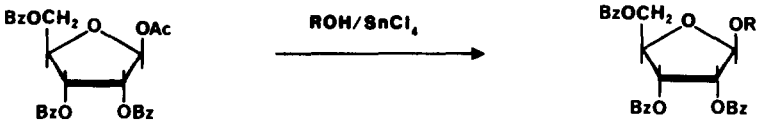
Scheme 10



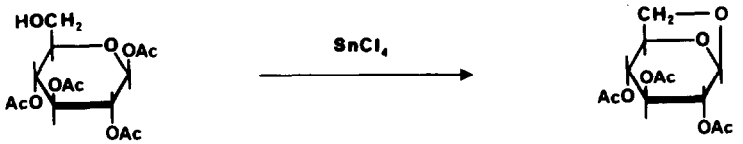
Scheme 11



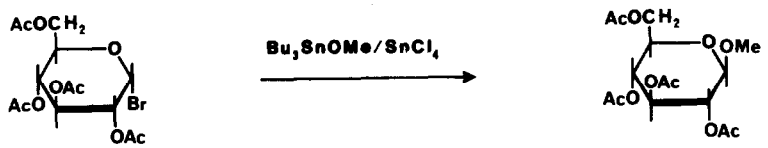
Scheme 12



Scheme 13



Scheme 14



Scheme 15

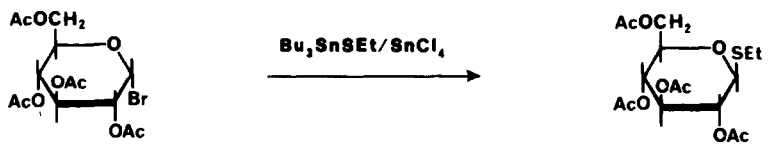


Fig. 6. Miscellaneous reactions [26,51–55].

procedure leads to higher yields of the desired products, through the enhanced nucleophilicity of the hydroxyl or thiol groups by trialkylstannylation of HOR or HSR.

Tin(II) chloride has been shown [56] to catalyse the reaction of D-fructose with 2,2-dimethoxypropane in 1,2-dimethoxyethane to form the acetal, 1,2,-*O*-isopropylidene-β-D-fructofuranose. Acetal formation was also observed [50] in the reaction of methyl α-L-rhamnopyranoside with acetone in the presence of $SnCl_2$, to give methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside.

Other applications

Triorganotin compounds, R_3SnX, where X = anionic radical, find extensive use in industry as biocides [57,58], their biological activity being primarily dependent upon the nature of the organic group (Table 2). A limited number of the simple triorganostannyl-sugar derivatives, i.e. where X is a carbohydrate or nucleoside residue, have been tested in this area, including possible applications as herbicides [1,59] bactericides [5,20,59] fungicides [5,20,59,60], algicides [20,59] and acaricides [59], but these have not yet reached commercialisation.

The diorganotin compounds, R_2SnX_2, are, in general, less toxic than their trialkyltin counterparts [57,58] and certain of these have shown promise as anti-tumour [61] and anti-leishmaniasis [62] drugs. In addition, dibutyltin dilaurate has been used for many years in anthelmintic preparations for poultry [58]. 2′3′-*O*-Dialkylstannylene derivatives of 5-fluorouridine have been claimed to reduce solid tumour size upon injection [63].

Carraher and his co-workers chemically modified cellulose, using a range of tri- and di-organotin chlorides, to form products which were reported [64] to show good fungicidal activity, as well as enhanced thermal properties.

In addition, sodium hydroxystannate, $Na_2Sn(OH)_6$, has been reported [65] to be effective as an insolubilising agent for starch and may therefore have applications in the paper industry.

An interesting application of carbohydrates in inorganic tin chemistry involves their ability to retard the oxidation and hydrolysis of tin(II) species. Tin(II) chloride, for example, has been found [27] to be stabilised against oxidation in methanol by methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, due to the formation of a weak donor complex of the type shown in Fig. 4. These properties were first

TABLE 2

DEPENDENCE OF BIOLOGICAL ACTIVITY OF TRIORGANOTIN COMPOUNDS ON THE NATURE OF THE ORGANIC GROUP FOR VARIOUS SPECIES

Species	R in most active R_3SnX compound
Insects	Me
Mammals	Et
Gram-negative bacteria	Pr
Gram-positive bacteria and fungi	Bu or Ph
Mites	cyclo-C_6H_{11} or $PhMe_2CCH_2$

exploited [66–68] in dental formulations containing tin(II) fluoride, since one of the major problems associated with the use of this salt is the instability of its aqueous solutions, which become turbid or cloudy on standing. However, the incorporation of highly water soluble polyhydroxylated compounds, such as sugars, into aqueous solutions of SnF_2 has been found to produce a marked stabilising effect, whereby the rate of hydrolysis is reduced [66]. Hence, although the use of this compound in toothpastes has declined in recent years, this trend may be reversed by the discovery that both aqueous and organic solutions of tin(II) salts are stabilised by the addition of these complexing agents.

Acknowledgements

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