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REGIOSELECTIVE ENHANCEMENT OF THE NUCLEOPHILICITY OF THE HYDROXYL GROUPS IN METHYL α-L-RHAMNOPYRANOSIDE BY COMPLEXATION WITH TIN(II) CHLORIDE

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ABSTRACT

A tentative mechanism for complexation, and a possible model of a tin(II)chloride–methyl glycoside intermediate complex, have been established largely from analysis of methyl ethers formed on methylation of methyl α-L-rhamnopyranoside and its monomethyl ethers by diazomethane in the presence of a catalytic amount of tin(II) chloride in selected solvents. The complex is mainly formed through displacement of molecules of the donor solvent coordinated to a tin(II) atom by the favorably *cis*-disposed, hydroxyl groups of the sugar moiety. The spatial arrangement of the hydroxyl groups plus the distribution of atomic charges at the individual oxygen atoms of hydroxyl groups of the methyl glycoside were found to be the main factors responsible for the selectivity observed. The effect of selected solvents on the stability and/or ability to participate in the formation of the foregoing intermediate complex could not be satisfactorily clarified.

INTRODUCTION

The selective methylation of glycosides[1–3] and nucleosides[4–6] with diazomethane in the presence of a catalytic amount of tin(II) chloride dihydrate shows that the catalyst exhibits remarkably high specificity towards certain hydroxyl groups. Thus far, however, little has been reported[6–8] on the nature of this specificity and about the possible mechanism of complexation of tin(II) chloride with a sugar residue. On the basis of their latest findings, Dudycz *et al.*[9] have proposed a common pathway for the activation of hydroxyl groups in selected sugars and their derivatives in methanolic solutions containing tin(II) chloride, prior to methylation with diazomethane. The activation appears to involve the respective 2-stanna-1,3-dioxolane and 2-stanna-1,3-dioxane intermediates.

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Our studies on regioselective methylation of methyl α-L-rhamnopyranoside (**1**) and its monomethyl ethers by diazomethane in the presence of a catalytic amount of tin(II) chloride in selected solvents have brought forth valuable information concerning complexation of tin(II) chloride with the methyl glycoside. The results have enabled us to propose a tentative mechanism for activation of the hydroxyl groups in sugars that differs from that published by Dudycz *et al.*[9]. Part of these findings has already been utilized in the selective monobenzylation[10] of **1** and its 4-*O*-benzyl derivative. The latest n.m.r. studies[11] on the complexation of tin(II) chloride with **1** and its monomethyl ethers have brought forth additional evidence supporting the mechanism of complexation presented.

Further details regarding the complexation are given herein.

RESULTS AND DISCUSSION

A catalytic amount of tin(II) chloride considerably enhances the reactivity of certain hydroxyl groups in glycosides towards diazomethane. Thus, analysis of the products of such a methylation of **1** and its monomethyl ethers may indicate formation of an intermediate tin(II) chloride–sugar complex, and its coordination sites. Results of methylation of **1** and methyl 2-, 3-, and 4-*O*-methyl-α-L-rhamnopyranoside (**2**, **3**, and **4**) in methanol (Table I) served to confirm a known fact[6-8] that a free diol system of restricted steric dimensions, acting as a bidentate chelate ligand, is the most favorable arrangement for the formation of an intramolecular complex with a tin(II) atom.

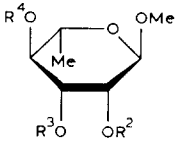
The products of methylation of **1** suggest two different ways for activation of the hydroxyl group through complexation with tin(II) chloride. Considering complexation at HO-2 and HO-3, the initial products of methylation should be compounds **2** and **3**. The latter compound cannot participate in subsequent methylation because of reasons already mentioned, in contrast to compound **2**, which is capable of further complexation at HO-3 and HO-4, thus giving rise to methyl 2,3- and 2,4-di-*O*-methyl-α-L-rhamnopyranoside (**5** and **6**).

Initial complexation at HO-3 and HO-4 should afford compounds **3** and **4** on methylation. Further complexation of **4** at HO-2,3 would yield the respective methyl 3,4- and 2,4-di-*O*-methyl-α-L-rhamnopyranosides (**7** and **6**). Inspection of

TABLE I

YIELDS OF METHYL ETHERS AFTER METHYLATION IN METHANOL

Starting compound	*Mol%*				
	2	*3*	*5*	*6*	*7*
1		62.4	25.1	8.5	4.0
2	trace		77.3	22.7	
3		100.0			
4				27.8	72.2



	R^2	R^3	R^4
1	H	H	H
2	Me	H	H
3	H	Me	H
4	H	H	Me
5	Me	Me	H
6	Me	H	Me
7	H	Me	Me

Table I reveals differences in the yields of methylated products with respect to the sites of coordination. Methylation of **1** indicates preferential formation, and probably also better stability, of the tin(II) complex at HO-2 and 3, mainly from the preponderance of **5** among the dimethyl ethers. If the complexation at HO-3 and HO-4 had been favored or would at least have equalled the complexation at HO-2 and HO-3, a higher yield of **7** would have been expected. Methylation of **4** and **2** also gave some indications in this respect, as reaction with the former proceeded more readily. The observed favored complexation of tin(II) chloride with HO-2 and 3 has been noted in the selective monobenzylation[10] of **1**, and also in recent n.m.r. studies[11].

Thus, the steric arrangement of hydroxyl groups and, in addition, the distribution of atomic charges at each group, could be the main factors influencing the selectivity observed. The X-ray structure[12] of α-L-rhamnose shows the O-2–O-3 and O-3–O-4 distances to be 278.3 and 289.0 pm, respectively. The hydroxyl groups are gauche disposed, with O-2–C-2–C-3–O-3 and O-3–C-3–C-4–O-4 dihedral angles of 59.4 and 61.4°, respectively. For complexation with tin(II) chloride, it is necessary for the hydroxyl groups to be ~280–300 pm apart. Such an arrangement may readily be reached by a small change of the ring form. It appears that the flexible *cis*-diol system in the compounds under study is a sterically more favorable one for coordination with a tin(II) atom than the HO-3,4 group. Evidence to support this idea is a local C-2–C-3 flattening[11] of the pyranose ring by ~10° upon complexation of **1** with tin(II) chloride. With compound **2**, no noticeable changes in the coupling constants could be observed.

Methylation studies clearly demonstrated preferential alkylation of HO-3 by the carbocation in all solvents studied (see later), indicating the highest electron density at this group. CNDO/2 quantum chemical calculations[13] for **1**, confirmed this assumption and afforded a complete picture of the atomic-charge distribution (Fig. 1). The geometry was taken from the crystal structure of α-L-rhamnose[12] and the methoxyl group was in the most stable, gauche disposition towards O-5.

Considering that the determining factor for alkylations of the hydroxyl group is the formation of a complex, the calculated CNDO/2 electron distribution in **1** may be used for qualitative prediction of the hydroxyl-group reactivity. Application of the generalized polyelectronic perturbation theory to the donor–acceptor interaction yielded the fundamental equation, consisting basically of two terms, an electrostatic term and a covalent one[14]. The electrostatic term always favors the in-

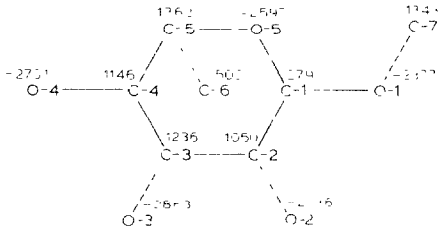
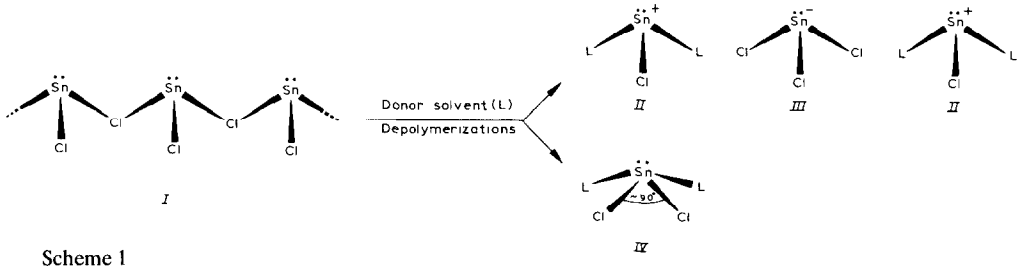


Fig. 1 Distribution of net atomic charges (in 10^{-4}eV) on selected atoms in **I**

teraction of the atoms carrying the highest opposite charges. On the other hand, the covalent term is optimized when the interaction involves a donor center carrying the highest electron density and an acceptor center having the largest positive hole. In our example, the charge on oxygen and the electron density of the hydroxyl groups in the highest occupied molecular orbital will be the determining factors, as the acceptor ($SnClL_2^+$, see later) is the same. It follows from the charge distribution in **I** (Fig. 1) that the highest negative charge is located on O-3 and therefore, this atom is the most readily complexed one from the electrostatic viewpoint. Although the charge at O-2 is higher than at O-4, the difference is not sufficient to make any definite conclusions concerning the preference in coordination to a tin(II) atom. However, some difference can be found in the electron-density localization in the highest occupied molecular orbital. If the electron density at O-2, O-3, and at O-4 atoms is compared, its localization decreases as follows: O-3 > O-2 > O-4. Thus, the second covalent term favors O-2 to O-4 in coordination with a tin(II) atom. The data presented here are qualitative only, as a more-precise, quantitative report would have required both calculations of the electron distribution and the structure of the whole complex, which are not currently possible

In order to understand better the mechanism of complexation between tin(II) chloride and methyl glycosides, it is useful to consider some details of the behavior of tin(II) chloride in various solvents. X-Ray analysis[15,16] has shown that crystalline, anhydrous tin(II) chloride, $(SnCl_2)_n$, consists essentially of polymeric chains of bent $SnCl_2$ units (Scheme 1, *I*). According to the donor solvent (L) used, the reagent is depolymerized[17] on dissolution in essentially two ways, with the formation of various solvated species[18,19], having, for example, the following compositions: $SnClL_2^+$ (ref. 20), $SnCl_3^-$ (ref. 21) (Scheme 1, *II* and *III* respectively), or $SnCl_2L$ (as in the crystalline hydrate[16] of $SnCl_2 \cdot 2H_2O$). Exceptionally, species of the type $SnCl_2L_2$ (Scheme 1, *IV*) may also occur[22-24]. The stereochemistry of tin(II) compounds differs considerably from those of tin(IV), which favor tetrahedral or octahedral geometries. The differences in oxidation numbers and geometries are connected, among other factors, with distinct properties of these compounds as Lewis acids.

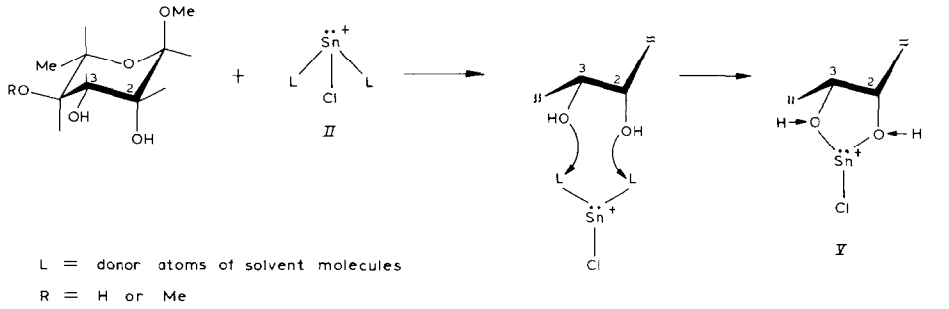
Measurements of electrical conductivity[25] have also indicated the presence of the aforementioned species in tin(II) chloride solutions. Thus, solutions of tin(II)



Scheme 1

chloride in methanol, ethanol, 2-propanol, acetone and acetonitrile show detectable electrical conductivity, and it may be assumed that they contain $SnClL_2^+$ and $SnCl_3^-$ species. On the other hand solutions of tin(II) chloride in tetrahydrofuran and 1,4-dioxane are not electrically conductive, thereby indicating the presence of $SnCl_2L_2$ or $SnCl_2L$ complexes.

At present little is known[18,19] concerning the factors influencing stabilities of such species in solutions. The bond strength of the coordinated solvent-molecules to a tin(II) atom evidently depends on the solvent used[26,27]. Some secondary reactions may also take place in these solutions. For example, if amines[24] or diazomethane[9] are present in solutions of tin(II) chloride in alcohols, they react with the hydrogen chloride generated during alcoholysis and the corresponding solvated tin (II) alkoxides are formed.



Scheme 2

Both the bond strength of the coordinated solvent molecules to a tin(II) atom and the stereochemistry of the species created should significantly influence the subsequent displacement reaction shown in Scheme 2. By analogy with other substitution reactions, formation of a tin(II) chloride–methyl glycoside complex (*V*) may take place only under conditions when the bond strengths of coordinated solvent molecules in *II* are weaker than the newly formed bonds with the hydroxyl groups, and the mutual distance of donor atoms of the coordinated solvent molecules is approximately the same as that of two vicinal hydroxyl groups suitably disposed in the sugar. Such a situation occurs in species of type *II* (L = methanol, ethanol, 2-propanol, acetone, acetonitrile, and so on). As *III* does not contain molecular ligands capable of effecting a displacement reaction, coordination with

the sugar molecule cannot take place and the tin derivative is, therefore, catalytically inactive. The nature of catalytic activity of the species of type *IV* (L = 1,4-dioxane) is not quite clear as yet.

Following methylation, the donor properties of the resultant OMe groups are lower than those of the free OH groups and they are thus not capable of coordinating a tin(II) atom in complex *V* in most of the solvents given. Complex *V* is, therefore, split off and the coordination sphere of tin(II) is filled with the solvent molecules, and the regenerated complex *II* enters a further catalytic cycle.

In contrast to the findings reported here, Dudycz *et al.*[7] have not considered the chemical role of a solvent in the catalytic process. In our opinion, an alkoxide ligand has a function analogous to that of chloride, and thus is not involved directly in activation of the hydroxyl group. This is evident from the fact that the catalytic process also takes place in aprotic (nonalcoholic) solvents, in which an alkoxide ion cannot be formed.

The aforementioned considerations led us to perform the methylation in selected solvents and to determine the influence of solvent on the distribution of methylated products and consequently on the complexation as well. In all solvents listed in Table II, preferential complexation at HO-2,3 of **1** could be inferred, again mainly from the preponderance of **5** among the dimethyl ethers. Acetone was the only solvent in which a moderate increase of the complexation at HO-3,4 could be observed. Evidence for this was a relatively high proportion of **7** in the mixture, a product that could only result from the enhanced initial activation of these two groups. The results revealed little solvent dependence in the selectivity of the methylation reaction. It may thus be assumed that such a vigorous reagent as diazomethane does not discriminate between fine distinctions of the degree of activation of the respective hydroxyl groups in various solvents and consequently, also between those concerning the stability of the intermediate tin(II) chloride–methyl glycoside complex. Slight activation of the hydroxyl groups is sufficient for the methylation reaction to proceed to completion.

Nevertheless, interesting results were obtained upon methylation of **3** with diazomethane in diethyl ether and 1,4-dioxane. In both solvents, compounds **5**

TABLE II

METHYLATION OF **1** IN VARIOUS SOLVENTS

Solvent	*Mol%*			
	3	5	6	7
Methanol	62.4	25.1	8.5	4.0
2-Propanol	62.8	24.8	8.3	4.1
Acetone	56.0	24.0	9.0	11.0
Acetonitrile	62.3	23.6	9.4	4.7
Tetrahydrofuran	64.9	21.5	8.6	5.0
1,4-Dioxane	55.5	27.3	12.4	4.8

(45.7, 20.4%), **7** (traces, 2.6%) and starting **3** (54.3, 77.0%) were detected after reaction. This fact clearly shows that solvents coordinated only weakly to tin(II) may even be displaced by a diol system in which one of the hydroxyl groups was substituted. However, both steps, namely displacement and subsequent coordination to tin(II) do not proceed to the extent observed with free hydroxyl groups, judging from the yields of methylated products. Furthermore, the distribution of dimethyl ethers again confirmed favored complexation at O-2 and O-3. As **3** was not methylated in other solvents mentioned here, it follows that they are probably coordinated more strongly to a tin(II) atom than are diethyl ether and 1,4-dioxane.

The findings here provide new information concerning the mechanism of the regioselective enhancement of the nucleophility of the sugar hydroxyl groups by tin(II) chloride, and some general conclusions may be drawn. Further experimental data are needed on the complexation as a basis for more-widespread application of tin(II)-catalyzed reactions in synthetic carbohydrate chemistry.

EXPERIMENTAL

All solvents used were purified and dried. Anhydrous tin(II) chloride was prepared as described elsewhere[10]. Compounds **2** and **3** were prepared by methylation (methyl iodide and silver oxide in *N*,*N*-dimethylformamide) of methyl 3,4- and 2,4-di-*O*-benzyl-α-L-rhamnopyranosides[10] and subsequent hydrogenolysis of the products over a palladium catalyst. Compound **4** was synthetized according to Butler *et al.*[28]. The identities and purities of the methyl ethers were proved after their conversion into the corresponding alditol acetates and analysis by g.l.c.–m.s.[29].

Methylations with diazomethane were performed as follows. To solutions of compounds **1**–**4** (5 mg of each) in selected solvents (2 mL) containing tin(II) chloride (1–5 mmol.dm^{-3}), ~0.6M diazomethane [from *N*-nitrosomethylurea[30]] in dichloromethane was added slowly at room temperature until a yellow color persisted. After 30 min, the mixtures were evaporated to dryness, chloroform (250 μL) was added to each sample, and the resulting solutions were then directly injected into the g.l.c. column. G.l.c. was performed with a Hewlett–Packard Model 5711 A chromatograph, with a column (200 × 0.32 cm) of 5% (w/w) of BDS on 80–100 mesh Gas-Chrom Z, at a programmed temperature-range of 130° (16 min) to 200° at 2°/min.

Large-scale methylations in the presence of tin(II) chloride (1–5 mmol.dm^{-3} of solution) afforded essentially the same yields and distribution of methyl ethers. No differences were observed whether or not the reactions were conducted with exclusion of oxygen.

REFERENCES

1 M. ARITOMI AND T. KAWASAKI, *Chem. Pharm. Bull. (Tokyo)*, 18 (1970) 677–686.
2 G. J. F. CHITTENDEN, *Carbohydr. Res.*, 43 (1975) 366–370.
3 G. J. F. CHITTENDEN, *Carbohydr Res*, 52 (1976) 23–29.

4 M J ROBINS AND S R NAIK, *Biochim Biophys Acta*, 246 (1971) 341–343
5 M J ROBINS, S R NAIK, AND A S K LEE, *J Org Chem*, 39 (1974) 1891–1899
6 M J ROBINS, A S K LEE, AND F A NORRIS, *Carbohydr Res* 41 (1975) 304–307
7 P J SMITH, *Chem Ind (London)*, (1976) 1025–1029
8 G J F CHITTENDEN, *Carbohydr Res*, 91 (1981) 85–88; and references cited therein
9 L DUDYCZ, A KOTLICKI, AND D SHUGAR, *Carbohydr Res*, 91 (1981) 31–37
10 R TOMAN, J ROSIK, AND M ZIKMUND, *Carbohydr Res*, 103 (1982) 165–169
11 J ALFOLDI, R TOMAN, AND C PECIAR, *Carbohydr Res*, 105 (1982) 258–265
12 R C G KILLEAN, J I LAWRENCE AND V C SHARMA, *Acta Crystallogr, Sect B*, 27 (1971) 1707–1711
13 J A POPLE AND D L BEVERIDGE, *Approximate Molecular Orbital Theory*, McGraw–Hill, New York, N Y, 1970
14 G KLOPMAN, in G KLOPMAN (Ed), *Chemical Reactivity and Reaction Paths*, Wiley, New York, 1974, pp 55–165
15 J M VAN DEN BERG, *Acta Crystallogr*, 14 (1961) 1002–1003
16 R E RUNDLE AND D H OLSON, *Inorg Chem*, 3 (1964) 596–598
17 J H R CLARKE AND C SOLOMONS, *J Chem Phys*, 47 (1967) 1823–1826
18 J D DONALDSON, *Progr Inorg Chem*, 8 (1967) 287–356
19 J A ZUBIETA AND J J ZUCKERMAN, *Progr Inorg Chem*, 24 (1978) 251–475
20 R H HERBER AND A E SMELKINSON, *Inorg Chem*, 17 (1978) 1023–1029
21 L A WOODWARD AND M J TAYLOR, *J Chem Soc*, (1962) 407–410
22 P F R EWINGS, P G HARRISON AND J T KING, *J Chem Soc, Dalton Trans* (1975) 1455–1458
23 E HOUGH AND D G NICHOLSON, *J Chem Soc, Dalton Trans*, (1976) 1782–1785
24 J S MORRISON AND H M HAENDLER, *J Inorg Nucl Chem*, 29 (1967) 393–400
25 M ZIKMUND AND S RAPIOVA, unpublished results
26 V GUTMANN, *Coordination Chemistry in Non-Aqueous Solutions*, Springer-Verlag, Vienna, 1968
27 S AHRLAND, in J J LAGOWSKI (Ed), *The Chemistry of Nonaqueous Solvents* Vol VA, Academic Press, New York and London, 1978, pp 1–62
28 K BUTLER, P F LLOYD AND M STACEY, *J Chem Soc*, (1955) 1531–1536
29 H BJORNDAL, C G HELLERQVIST, B LINDBERG, AND S SVENSSON, *Angew Chem Int Ed Engl*, 9 (1970) 610–619
30 J O DEFERRARI, E G GROS AND I M F THIEL, *Methods Carbohydr Chem*, 6 (1972) 365–367