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SYNTHESIS OF C_7-C_{16}-ALKYL MALTOSIDES IN THE PRESENCE OF TIN(IV) CHLORIDE AS A LEWIS ACID CATALYST

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ABSTRACT. The synthesis of C7- to C16-alkyl maltosides in the presence of tin(IV) chloride as Lewis acid catalyst was performed. The characterization of the products and theoretical investigation of the crucial step in the synthesis were carried out. The preparation of the β-maltosides required reaction time of 1 h, and that of the α-maltosides was 72 h. The side products were the α-D-maltosidechloride and 2-hydroxy-β-maltoside, respectively. The PM3 calculation confirmed the formation of the kinetically controlled β-product.

KEY WORDS: Maltose, Synthesis of maltosides, Tin(IV) chloride, PM3

INTRODUCTION

Maltose is a disaccharide, which is used in huge amounts in the candy industry. In contradistinction to e.g. glucose, which is able to crystallize even in the presence of impurities in high concentrations, maltose is not able to crystallize, and thus to be further purified, unless the maltose used as a starting material exhibits a purity above 90%. This is one of the reasons why maltose is a valuable raw material in the candy industry. Maltose is also used as an active component of intravenous injection liquids intended for provision of sugar for patients, as a component in frozen deserts, in the baking and brewing industry, for production of maltitol which can be used as a sweetening agent, etc [1]. By introducing different substituents in a molecule of maltose, compounds with a variety of physico-chemical properties are obtained. For this reason modified sugars have extensive spectrum of applications.

It is known that alkyl polyglycosides exhibit a wide range of physical and functional properties which make them suitable for use as biodegradable surfactants, detergents and emulsifiers. n-Octyl β-D-glucopyranoside and other similar compounds have been successfully used in the crystallization of membrane proteins [2]. The first synthesis of these compounds was performed by Noller and Rockwell [3] who used a rather complicated procedure of Koenigs and Knorr [4]. According to this procedure sugars were first peracetylated and then converted to the acetobromo sugars. The alkyl group was introduced by performing a reaction of the desired alcohol with the brominated peracetate in the presence of silver oxide, and deacetylation was accomplished by a treatment with sodium methoxide. Modifications of this procedure [5] led to simplified preparations of alkyl glycosides with increased yields. Boether [6] reported later an alternative synthesis of alkyl glycosides involving a double alcohol interchange in the presence of an acid catalyst. Glucose was first converted to methyl glycoside, then to butyl glycoside, and finally to the desired alkyl glycoside. In 1974 Boettner [7] successfully prepared several alkyl glycosides and alkyl oligosaccharide mixtures, directly from glucose and higher molar mass alcohols, by carefully controlling the removal of water during the reaction. Longer-chain alkyl biosides are widely used as nonionic surfactants [8] and are known to form liquid crystalline phases [9]. They are used as sugar acceptors for enzymatic glycosylation [10]

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and as the lipophile-carrying head-moiety of artificial bioactive sugar clusters [11]. Several biosites are probe-guests combining to receptor proteins [12] and artificial receptors [13, 14]. Some long-chain alkyl maltosides enhance the nasal insulin absorption [15] and the bioavailability of calcitonin [16].

There are three main categories of methods for synthesizing glycosides and glucuronides (**1** + **2** → **3**, Figure 1). These are the following categories: (a) the Koenigs-Knorr reaction (**1**, where X = halogen) and its modifications [4, 17, 18, 19], (b) reactions catalyzed with Lewis acids [20-22] (**1**, X = OAc), and (c) reactions where HO-1 of the starting derivative is unsubstituted (**1**, X = OH). Category (c) includes methods in which HO-1 is initially converted into a more reactive species [23-28), and those which involve a Lewis acid catalyst [29]. In our previous investigations, syntheses of alkyl glycosides were performed, where starting compounds were glucose and alcohols [30-32].

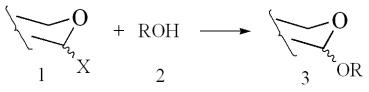


Figure 1. General scheme for synthesizing glycosides.

In this paper we present the synthesis of C7- to C16-alkyl maltosides in the presence of tin(IV) chloride as Lewis acid catalyst, as well as the characterization of the products, and theoretical investigation of the crucial step in the synthesis.

EXPERIMENTAL

Dry column chromatography. Merck silica gel 60 (particle size 0.046-0.060 mm; toluene (Merck, Germany) and ethyl acetate (Merck, Germany) as eluent).

Thin layer chromatography (TLC). Merck TLC plates (silica gel 60 F_{254}, layer thickness 0.2 mm). The spots were visualized by spraying with 10% sulfuric acid in ethanol (carbohydrates) and 1% anisaldehyde and 2% sulfuric acid in glacial acetic acid (non-carbohydrate compounds), and subsequent heating.

NMR spectra. ^{1}H (500 MHz) and ^{13}C NMR (126 MHz) spectra were measured on a Bruker DRX 500 instrument (Germany) in $CDCl_3$ with TMS as internal standard, or DMSO-d_6 with DSS as internal standard. All solvents were purified by distillation (dichloromethane from calcium hydride).

D-maltose (Fluka, Switzeland) (10 mmol) was treated with anhydrous sodium acetate (10 mmol) and acetic anhydride (12.5 mL) at 100 ºC for 4 h, and worked up as usual [33] to give the β-anomer of the peracetylated saccharide.

The β-D-maltose-octaacetate (6.71 g, 10 mmol) was dissolved in anhydrous dichloromethane (100 mL) and stirred for 1-2 h with molecular sieves 0.4 nm (4 g) under an argon atmosphere. The solution was treated with tin(IV) chloride (1.2 mL, 10.25 mmol), and immediately treated with the alcohol component (11 mmol) dissolved in anhydrous dichloromethane (20 mL).

The preparation of the β-maltosides required reaction time of 1 h, and that of the α-maltosides was 72 h. After the required time, the mixture was poured into the saturated sodium hydrogen carbonate solution (100 mL), the organic layer separated, and the aqueous phase extracted with dichloromethane (3 x 40 mL). The combined organic phases were washed twice with water (2 x 40 mL), filtered over Celite, and evaporated in vacuum. The resulting syrup was purified by dry column chromatography (silica gel 60, Merck, toluene/ethyl acetate 9:1).

The side products in the preparation reactions of β- and α-maltosides were the α-D-maltosidechloride and 2-hydroxy-β-maltoside, respectively. The acetylated alcohol was a side product in both cases. The side products were isolated from the reaction mixtures in small amounts.

The resulting material was deacetylated by treatment with 2 mL of methanol : triethylamine : water (2:1:1) at room temperature for 24 h.

Yields. 50-65% based on the starting saccharide for the three stage process, including purifications. The following products were obtained: a = 1-methyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; b = 1-buthyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; c = 1-heptyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; d = 1-octyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; e = 1-(2-ethyl-1-hexyl)-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; f = 1-nonyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; g = 1-decyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; h = 1-undecyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; i = 1-dodecyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; j = 1-tetradecyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-α-D-glycopyranoside; k = 1-hexadecyl-2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyrano-syl)-α-D-glycopyranoside (Figure 2).

RESULTS AND DISCUSSION

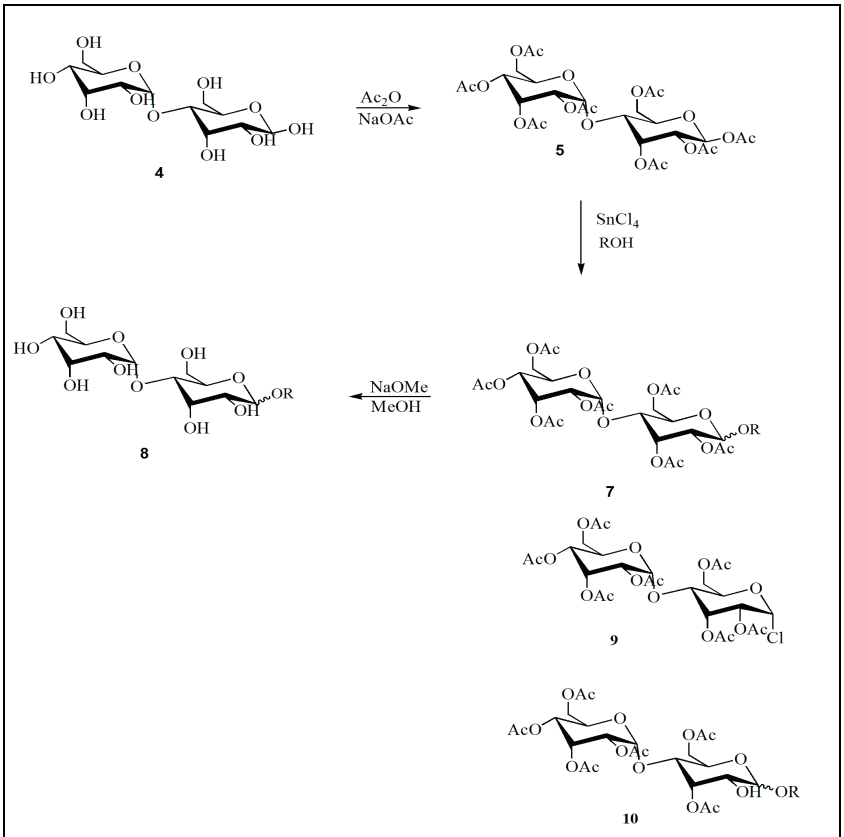
It is known that methyl β-D-glucopyranoside can be prepared from penta-*O*-acetyl-β-D-glucopyranose under Lewis acid catalysis [20]. This procedure was later modified to provide l,2-*trans*-linked disaccharides [34-36].

Bearing this in mind, we performed the glycosylation of β-peracetylated maltose derivative with different fatty alcohols in the presence of tin(IV) chloride as a Lewis acid catalyst (Figure 2). A treatment of maltose **4** with acetic anhydride and molten anhydrous sodium acetate at 120 °C gave exclusively the β-octaacetate **5**. The reaction of **5** in dichloromethane with fatty alcohols and tin(IV) chloride at room temperature under anhydrous conditions lead to the product **7,** and side products **9** and **10**. Similar results were also obtained in the case with other Lewis acids, such as antimony-pentachloride. Over the reaction time of 1 h *trans*-linked maltosides in moderate yields (about 60%) were obtained. Besides that β-D-maltoside acetylated alcohol (ROAc) and α-D-maltosidechloride **9** are formed as side products. An extension of reaction time led to increasing yields of α-glucosides, due to anomerization. Besides that α-D-maltoside ROAc and small amounts of 2-hydroxymaltoside **10** are produced as side products.

Following chromatographic purification, the peracetylated products **7** were deesterified with the mixture of methanol : triethylamine : water (2:1:1), and the anomers were separated on a strong basic ion exchange resin to give α- and β-maltosides **8**. The characterization of the major products (α- and β-maltosides **8**) was performed by means of ^{1}H-NMR and ^{13}C-NMR spectroscopy. The spectra are in agreement with the assigned structures (Tables 1 and 2).

When we examine the structures of the side products **9** and **10,** the results support an assumption that this reaction proceeds *via* dioxalenium ion **6** and orthoester **7a** as intermediates (Figure 3). Similar conclusions were made by Hanessian and Banoub, who prepared 1,2-orthoesters under conditions similar to those used in this work [37]. Under these reaction conditions, the acetoxy group leaves **5**, and the remaining oxocarbonium intermediate is

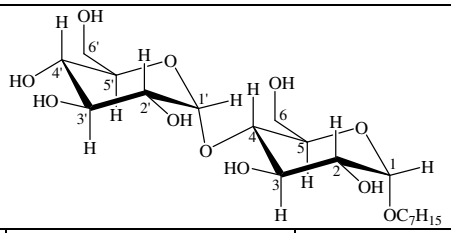
stabilized by the neighboring 2-acetoxy group to give the 1,2-acetoxonium intermediate **6**. It is supposed that the intermediate **6** can react with alcohols in two ways (Figure 3): the alkoxy group can attack electropositive carbon atom of the acetoxy group (pathway **a**), or C1 of maltose (pathway **b**). In the pathway **a**, the intermediate **7a** is formed, whereas in the pathway **b** a trans opening of **6** is obtained, yielding **7b**. Intermediate **7a** can be transformed into **7b** by an intramolecular rearrangement. The formation of the β-product **7b** is kinetically controlled and occurs at lower temperatures and short reaction times. In contrast, with extended reaction times and higher temperatures, an *in situ* transformation into the thermodynamically favored α-maltoside **7b** is observed.



	R	Yield (%)		R	Yield (%)		R	Yield (%)
a	CH_3	57.2	**e**	$CH_2CH(C_2H_5)C_4H_9$	58.6	**i**	$C_{12}H_{25}$	51.3
b	C_4H_9	64.7	**f**	C_9H_{19}	59.0	**j**	$C_{14}H_{29}$	54.8
c	C_7H_{15}	58.7	**g**	$C_{10}H_{21}$	54.3	**k**	$C_{16}H_{33}$	50.2
d	C_8H_{17}	63.2	**h**	$C_{11}H_{23}$	53.8			

Figure 2. General reaction scheme for synthesis of alkyl-(α and β)-D-maltosides. a-k represent fatty alcohols used in the reaction.

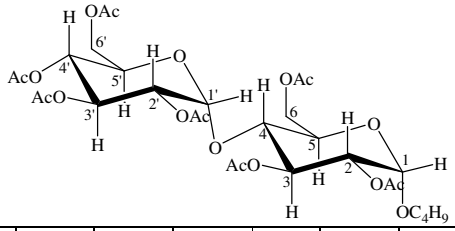
Table 1. ^{1}H NMR ($CDCl_3$, 500 MHz) data of acetylated α- and β-maltosides **8c**[a].



Proton	Compound **8cα**	Compound **8cβ**
H-1	4.96 d (3,9)	4.45 d (7.9)
H-2	4.87 dd (3.9, 10.2)	4.99 dd (7.9, 10.2)
H-3	5.53 dd (9.4, 10.2)	5.23 dd (9.4, 10.2)
H-4,4'	5.07 dd (9.4, 10.3)	5.09 dd (9.4, 10.3)
H-5,5',6a,6a'	4.00 m	4.05 m
H-2'	4.73 dd (3.9, 10.2)	4.67 dd (3.9, 10.2)
H-3'	5.41 dd (9.4, 10.2)	5.12 dd (9.4, 10.2)
H-6b,6b'	4.25 m	4.26 m
H-1a''	3.44 dt (9.6, 10.5, 6.9) A part of ABX_2 spectra	3.49 dt (9.6, 10.5, 6.9) A part of ABX_2 spectra
H-1b''	3.69 dt (9.6, 10.5, 6.9) B part of ABX_2 spectra	3.89 dt (9.6, 10.5, 6.9) B part of ABX_2 spectra
$OCOCH_3$	2.01, 2.03, 2.07, 2.10, 2.14, 5 s	2.01, 2.03, 2.07, 2.10, 2.14, 5 s
H-2''	1.63 m	1.58 m
$-(CH_2)_n-$	1.27 m	1.26 m
$-(CH_2)_n-CH_3$	0.88 t (6.4)	0.88 t (6.4)

[a]Chemical shifts (in ppm) relative to TMS (= 0 ppm) as internal standard are given outside the parentheses; coupling constants *J* (in Hz) are given in the parentheses. Abbreviations: *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet.

Table 2. ^{13}C-NMR($CDCl_3$, 126 MHz) data of thermodynamically favored α-maltosides **7b** (**a-k**).



Carbon	**7b a**	**7b b**	**7b c**	**7b d**	**7b e**	**7b f**	**7b g**	**7b h**	**7b i**	**7b j**	**7b k**
1	95.2	95.3	95.5	95.3	95.5	95.4	95.4	95.3	95.4	95.2	95.2
2	69.7	69.7	69.9	69.7	69.7	69.8	69.8	69.7	69.6	69.6	69.6
3	72.3	72.3	72.6	72.4	72.4	72.5	72.6	72.4	72.6	72.3	72.2
4	72.4	72.7	72.8	72.8	72.8	72.9	72.8	72.6	72.7	72.6	72.7
5	68.2	68.2	68.3	68.1	68.2	68.3	68.3	68.1	68.3	68.0	68.0
6	62.5	62.6	62.7	62.6	62.6	62.7	62.7	62.6	62.8	62.5	62.5
1'	96.3	95.1	95.3	95.1	95.3	95.3	95.3	95.1	95.3	95.0	95.0
2'	69.0	69.0	69.3	69.1	69.1	69.2	69.2	69.1	69.2	69.0	68.9
3'	71.1	71.1	71.4	71.2	71.3	71.3	71.4	71.2	71.3	71.0	71.0
4'	67.2	67.2	67.4	67.2	67.3	67.4	67.3	67.2	67.3	67.1	67.2
5'	67.7	67.7	67.9	67.8	67.8	67.9	67.9	67.7	67.9	67.7	67.7
6'	61.2	61.2	61.3	61.2	61.2	61.3	61.3	61.2	61.3	61.1	61.1
1''	53.3	68.2	68.7	68.4	69.7	68.6	68.7	68.5	68.7	68.3	68.3

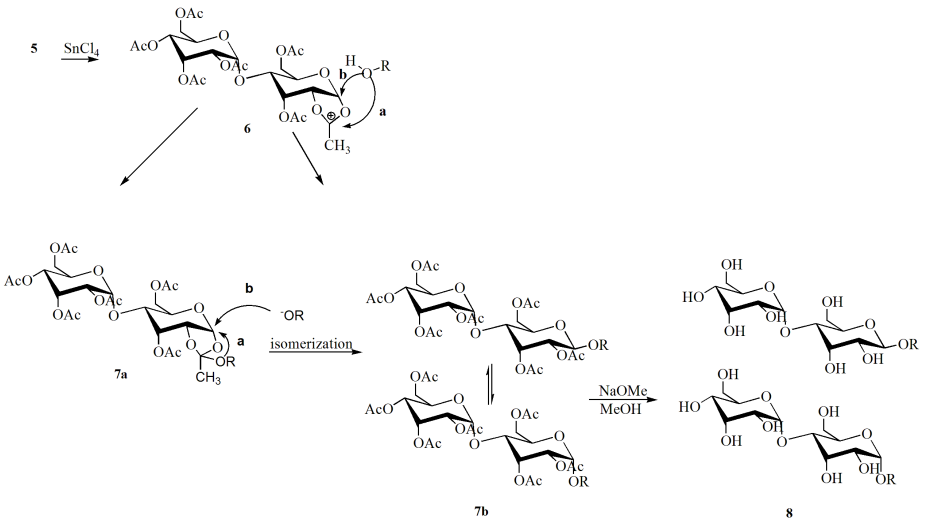


Figure 3. Reaction mechanism for the synthesis of alkyl-(α and β)-D-maltosides.

Since the transformation of the compound **5** *via* intermediate **6** is crucial for the synthesis, it was a subject of theoretical investigation. The species **5**, **6**, and **7** were optimized by means of PM3 Hamiltonian [38-40], using Spartan'02 program [41] package (Spartan'02 Wavefunction). The optimized geometry of **6** is presented in Figure 4. The geometry of cyclic oxocarbonium intermediate is significantly different in comparison to the structure of **5**. For instance, the C1-C2 and C2-O bonds in **6** are somewhat shorter than the corresponding bonds in **5**. In addition, the bond between oxygen atom of acetoxy group and C1 is almost formed.

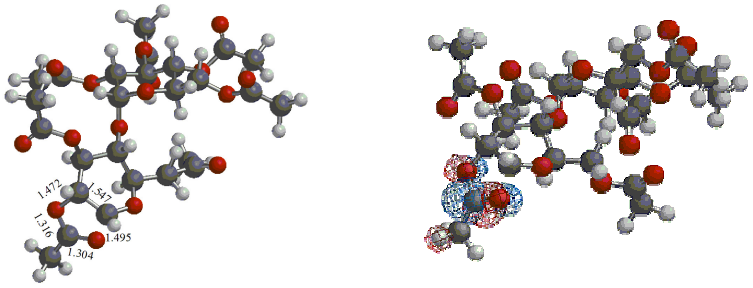


Figure 4. The optimized geometry of the 1,2-acetoxonium intermediate **6** with some important bond lengths in Å, (left) and its LUMO (right). Dark gray, red and light gray balls represent carbon, oxygen and hydrogen atoms, respectively.

The NBO analysis of this intermediate shows that the positive charge is distributed between C1 and the carboxylic carbon of the acetoxy group (the NBO charges values of these C atoms amount to 0.210 and 0.443). The HOMO-LUMO analysis shows that the greatest contribution to the LUMO comes from the C atom of the acetoxy group (Figure 4). Both NBO and HOMO-LUMO analyses indicate that the carboxylic carbon of the acetoxy group is the main reactive site for the next step of the reaction. Thus, one can conclude that pathway **a** is more favorable

than pathway **b** (Figure 3). The intermediate **7a** can react with another alkoxy anion, or it can undergo intramolecular rearrangement yielding **7b** in both cases.

For the next step of the reaction both reaction paths were investigated. Our calculations revealed that intramolecular rearrangement is more favorable by 3.7 kcal/mol than the reaction of 7a with another alkoxy anion. This implies that the intramolecular rearrangement is the next step of the reaction. Obviously, an attack of the acetoxy anion is possible only from β side of 7a. The main reason lies in the fact that α-side in 7a is protected by steric hindrance. As a consequence, the kinetically controlled β-product is formed. This finding is in perfect agreement with the experimental results.

CONCLUSIONS

The reactions of fatty alcohols and maltose catalyzed with tin(IV) chloride as Lewis acid are performed in moderate yields. The formation of the β-products occur easily, after only 1 h. Due to anomerization, the β-products are converted into α-isomers after 72 h. Semiempirical investigation shows that the reason for the formation of β-products in the beginning of the reaction lies in the fact the the α-side in **7a** is protected by steric hindrance. The calculation results of the semiempirical investigation are in perfect agreement with the experimental results.

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