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REGIOSELECTIVE SYNTHESIS OF SUCROSE MONOESTERS AS SURFACTANTS

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ABSTRACT

A highly regioselective conversion of sucrose into 6-*O*-acyl derivatives is reported. First sucrose was transformed into the dibutyltin acetal, thus enhancing the nucleophilicity at the C-6 oxygen and restricting the subsequent acylation reaction. The surface activity properties of the sucrose monoesters obtained were determined and compared with those of commercially available ionic and non-ionic surfactants.

INTRODUCTION

Most of the surfactants produced by the chemical industry are based on petrochemicals. A number of efforts to use carbohydrates, especially sucrose, as bulk raw materials for synthesis of non-ionic surfactants have been reported.[1-5] Their amphiphilic behavior is caused by the presence of the hydrophilic free hydroxyl groups and a hydrophobic alkyl chain. Unique properties, such as the surfactant being nontoxic, skin-compatible, non-polluting and biodegradable, are of major importance considering their wide range of applications.

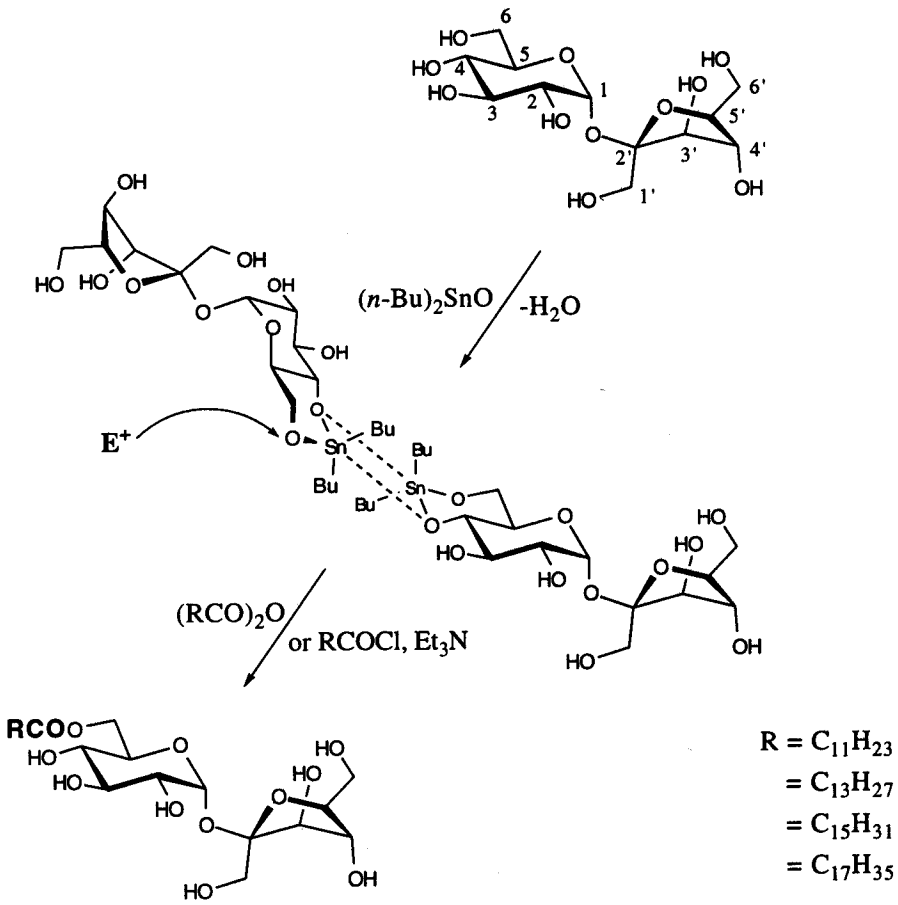
Most of the approaches in this field have been directed to the preparation of fatty acid esters of monosaccharides and disaccharides.[6-23] Attempts to acylate saccharides, directly with activated fatty acid derivatives, often involves non-specific reactions leading to mixtures of mono-, di- and tri-esters that are inherently difficult to separate. Despite the large numbers of application for such mixtures, selective reactions that distinguish between the hydroxyl groups of sucrose, a readily available disaccharide, and result in defined products would be valuable. In modifying sucrose, attention has been focused on regioselective reactions at the three primary hydroxyl groups. Selective acylation of unprotected sugars has been accomplished by enzymatic approaches,[24] under Mitsunobu conditions[25,26] and by a method recently introduced by Plusquellec and coworkers.[27,28] However, these methods depend on the availability of enzymes, the tedious activation of the acyl component, and can result in complex reaction mixtures. Chemical reactions that preferentially acylate the primary hydroxyl groups of sucrose in a single high yielding step represent an attractive alternative approach. Thus, the standard procedure for the preparation of specific sucrose esters requires suitable, partially protected sucrose derivatives, thereby necessitating a number of cumbersome protection and deprotection steps.

We have recently demonstrated that sucrose can be regioselectively benzoylated in excellent yields at the 6-*O*-position by exploiting a dibutylstannylene intermediate.[29] This manuscript reports the extension of this methodology for the direct, one-pot, regioselective synthesis of 6-acyl esters of sucrose. The surface activity of these sucrose-based fatty acid esters were measured and compared to those values obtained for commercially available ionic and non-ionic surfactants.

RESULTS AND DISCUSSION

Reactions, isolation and characterization: Di-*n*-butyltin oxide is known to form dibutylstannylene acetals with eqimolar amount of diols or polyols.[30] The products obtained have enhanced nucleophilicity at one of the stannylene acetal bound oxygen atoms, resulting in a high regioselectivity in a concomitant reaction of a stannylene acetal complex with electrophilic agents.[31] These dibutylstannylene acetals are generally considered to exist as dimers in both the solid state[32] and in solutions (shown by ^{119}Sn NMR spectroscopy).[33,34]

In this study we applied a dibutylstannylene based approach for the synthesis of 6-*O*-lauryl-, 6-*O*-myristyl-, 6-*O*-palmityl- and 6-*O*-stearyl-sucrose. First sucrose was converted to a dibutylstannylene acetal by refluxing with one equivalent of di-*n*-butyltin



Scheme

oxide in methanol. The resulting acetal was reacted directly with the anhydrides of the fatty acids in *N,N*-dimethylformamide (DMF) at room temperature (see *Scheme*). In all cases, after 48 h a single product was obtained. This high regioselectivity suggested that sucrose has formed preferred six-membered stannylene acetal (the five-membered ring would involve the *trans* vicinal diols in the pyranoid or furanoid moieties). The anhydride-derived acyl species affords an electrophilic substitution at the primary C-6-position in the six-membered stannylene intermediate. The regioselectivity is different from that observed for formation of the 2-*O*-esters of some other α-D-hexopyranosides *via* dibutylstannylene acetals.[35] Presumably the reason for the observed regioselectivity is the overall conformation of sucrose in solution in which the C-2-oxygen of the glucose moiety acts as

Table 1. Regioselective esterification of sucrose.

Ester	Method[a]	Time (h)	Yield of monoesters at the specific position in sucrose[b] 6-*O*	3-*O*
Lauryl	**A**	48	64	0
		96	66	5
	B	48	68	0
		96	70	3
Myristyl	**A**	48	58	0
		96	60	4
	B	48	60	0
		96	61	3
Palmityl	**A**	48	51	0
		96	52	4
	B	48	53	0
		96	55	3
Stearyl	**A**	48	46	0
		96	47	4
	B	48	47	0
		96	47	2

a. **A**, *n*-Bu_2SnO; $(RCO)_2O$. **B**, *n*-Bu_2SnO; RCOCl, Et_3N.
b. Percent after column chromatography of the reaction mixture.

an acceptor for a strong intramolecular hydrogen bond with the C-1'- or C-3'-hydroxyl groups of the fructose moiety.[36-38]

When the acetal was treated at room temperature with equimolar amounts of acyl chloride and triethylamine, the 6-*O*-acylsucrose was isolated in slightly higher yield (Table 1). Prolonged reaction times (3 or more days) led to the regioselective formation of the 3-*O*-monoacylated sucrose derivative, as a byproduct obtained in a low yield (appr. 2-5%). This suggests that the formation of five-numbered cyclic dibutylstannylene acetal with a vicinal diol occurs with the advancement of reaction time. This "secondary" regioselection can be explained by fact that in the case of the six-membered tin-acetal one of the bulky *gem*-di-*n*-butyl groups is forced into an unfavorable axial position, whereas in the formation of the five-membered stannylene ring such a strain is avoided. A similar

rationale is used to explain the tendency of acetone to form a five-membered 1,3-dioxolane ring and benzaldehyde to form a six-membered 1,3-dioxane.[39] Unfortunately, this hypothesis can not be confirmed due to the hydrolytic sensitivity of the tin-acetals. Alternatively, acyl migration might also afford the 3-*O*-monoacyl sucrose derivative. Acyl migration in partially protected carbohydrates is frequently observed in acidic, basic, and neutral media.[28,40,41] In most cases, isomerization tends to proceed from the oxygen atom of a secondary hydroxyl group to the oxygen atom of a primary hydroxyl group and occasionally between two secondary hydroxyl groups. The migration of an acyl group from the primary 6-*O*- position to the secondary 3-*O*- position is considerably less likely.

A major importance of this regioselective sucrose-monoderivatization method described is the simple work-up procedure. The sequence for isolation, of pure reaction product, consists of selective extraction of the organotin compounds, selective sedimentation of the unreacted sucrose and crystallization of the desired surfactant. This simple approach is an attractive one for the commercial downstream processing of prepared surfactants using this approach.

The structures of the reaction products were established primarily from their ^{1}H NMR spectra in perdeuterated dimethylsulfoxide, containing 5% of perdeuterated methanol (in this solvent system no micelle formation was observed). Homonuclear spin decoupling technique or COSY experiments were used to confirm the assignment of the signals of nuclei that are mutually coupled (Table 2).

Generally in comparison with sucrose, the 6-*O*-acyl derivatives show a down-field shift for the AB resonances (part of an ABX spin system), corresponding to the signals of both protons at C-6. The 3-*O*-acyl compounds show a similar shift for the doublet of doublets (dd) corresponding to H-3. Irradiation of this signal caused the collapse of the dd's of H-2 and H-4 unequivocally assigning the position of the acyl group in the sucrose moiety.

Surface activity of the esters synthesized: Sucrose fatty acid esters with more than 11 carbon atoms on the alkyl chain have polymorphic phase behavior and display surfactant properties. In aqueous solution, at a specific certain concentration, known as the critical micellar concentration (CMC), these molecules aggregate in micelles. This value is of practical importance as it defines the minimal concentration of surfactant required to solublize a hydrophobic molecule in water. The most frequently used methods for determination of CMC are based on direct surface tension measurements[48] or on the observation that solubilization, of a hydrophobic dye in a surfactant solution, occurs only if micelles are present. The concentration of dissolved dye can then be determined in a spectrophotometer.[49]

Table 2. ^{1}H NMR Assignments for the carbohydrate moiety of sucrose monoacylates

	6-*O*-Lauryl	6-*O*-Myristyl	6-*O*-Palmityl	6-*O*-Stearyl	3-*O*-Stearyl
H-1	5.17 (d) $J_{1,2}$=3.8	5.16 (d) $J_{1,2}$=3.7	5.18 (d) $J_{1,2}$=3.6	5.15 (d) $J_{1,2}$=3.7	5.22 (d) $J_{1,2}$=3.7
H-2	3.21 (dd) $J_{2,3}$=9.1	3.18 (dd) $J_{2,3}$=9.6	3.20 (dd) $J_{2,3}$=9.9	3.20 (dd) $J_{2,3}$=9.7	3.36 (dd) $J_{2,3}$=10.0
H-3	3.49 (dd) $J_{3,4}$=9.1	3.48 (dd) $J_{3,4}$=9.6	3.48 (dd) $J_{3,4}$=9.9	3.47 (dd) $J_{3,4}$=9.7	5.00 (dd) $J_{3,4}$=10.0
H-4	3.07 (dd) $J_{4,5}$=9.1	3.05 (dd) $J_{4,5}$=9.6	3.06 (dd) $J_{4,5}$=9.9	3.06 (dd) $J_{4,5}$=9.7	3.30 (dd) $J_{4,5}$=10.0
H-5	3.89 (mm)	3.86 (m)	3.90 (ddd) $J_{5,6a}$=1,3	3.86 (m)	3.75 (m)
H-6_a	4.23 (dd) $J_{a,b}$=10.3; $J_{5,6a}$=1.0	4.21 (dd) $J_{a,b}$=11.7; $J_{5,6a}$=1.1	4.22 (dd) $J_{a,b}$=11.6	4.20 (dd) $J_{a,b}$=11.1; $J_{5,6a}$=0.9	3.50-3.60 (m)
H-6_b	4.02 (dd) $J_{5,6b}$=5.7	3.99 (dd) $J_{5,6b}$=6.0	4.01 (dd) $J_{5,6b}$=5.8	3.99 (dd) $J_{5,6b}$=5.6	
H-1'$_{a,b}$	3.39 (s)	3.37 (s)	3.38 (s)	3.38,3.35(dd) $J_{a,b}$=12.0	3.39 (s)
H-3'	3.38 (d) $J_{3',4'}$=7.6	3.86 (d) $J_{3',4'}$=8.2	3.87 (d) $J_{3',4'}$=8.0	3.86 (d) $J_{3',4'}$=8.1	3.89 (d) $J_{3',4'}$=8.2
H-4'	3.73 (dd) $J_{4',5'}$=7.6	3.71 (dd) $J_{4',5'}$=7.6	3.73 (dd) $J_{4',5'}$=8.0	3.74 (dd) $J_{4',5'}$=8.0	3.76 (dd) $J_{4',5'}$=8.2
H-5'	3.60 (m)	3.59 (m)	3.59 (m)	3.58 (m)	3.50-3.60 (m)
H-6'$_{a,b}$	3.56 (m)	3.57 (m)	3.56 (m)	3.56 (m)	3.50-3.60 (m)

The CMC of the sucrose monoesters was independent of the method of measurement that was used (Table 3). Both tensiometer and dye solubilization methods gave CMC values within 10% of one another. The CMC values measured for the sucrose monoesters were over an order of magnitude lower than the CMC of commercially prepared ionic and non-ionic surfactants (Table 3). These results suggest that the series of sucrose monoesters prepared in this study warrant further investigation as potentially valuable commercial surfactants.

Table 3. Surface-activity characteristics of synthesized esters and of some commercial surfactants.

	CMC (30° C) [mol/L]			
Compound	Method 1[a]	Method 2[b]	Lit. Values	σ_{min} [mN/m]
6-*O*-Laurylsucrose	5.14×10^{-4}	5.31×10^{-4}		32.7
6-*O*-Myristylsucrose	0.88×10^{-4}	0.71×10^{-4}		30.9
6-*O*-Palmitylsucrose	1.74×10^{-5}	1.81×10^{-5}		33.9
6-*O*-Stearylsucrose				
$C_{12}H_{25}SO_3Na$ [42]			1.2×10^{-3}	33.0
$C_{14}H_{23}SO_3Na$ [43]			2.5×10^{-3}	---
$C_{12}H_{25}OSO_3Na$ [44]			8.6×10^{-3}	32.5
$C_{14}H_{23}OSO_3Na$ [45]			2.1×10^{-3}	37.2
$C_{10}H_{21}$-$(CH_2CH_2O)_8$-H [46]			1.0×10^{-3}	36.0
$C_{12}H_{25}$-$(CH_2CH_2O)_8$-H [47]			0.72×10^{-4}	34.0
Octyl-β-D-glucopyranoside[47]			25.3×10^{-3}	---
Octyl-β-D-thioglucopyranoside[47]			9.0×10^{-3}	---
Hecamag[47]			19.6×10^{-3}	---

a. Determined from surface tension using de Nöuy ring.
b. Measured by colorimetric method.

EXPERIMENTAL

General methods. Sucrose was dried under vacuum before use. All reagents and solvents were purchased from Aldrich (Milwaukee, WI). DMF was anhydrous grade. All reactions were monitored by TLC on aluminum sheets, Silica Gel 60 F254 (E. Merck, Darmstadt) and detected by dipping the plates into staining solution (1.0 g cerric ammonium sulfate and 24.0 g ammonium molybdate in 31 mL sulfuric acid, 470 mL water) then heating. The elution system was 4:1 chloroform - methanol. Flash chromatography was performed on Silica Gel 60 (230-400 mesh Aldrich) using solvent

system 9:1 chloroform - methanol. Optical rotations were measured with a Perkin Elmer 141 polarimeter at 22 °C. ^{1}H NMR spectra were recorded at 25 °C on a Varian Unity 500 MHz spectrometer and chemical shifts are given in ppm from tetramethylsilane as internal standard (for the solvent system used see Results and Discussion). Surface tension was determined using a Fisher Model 21 Tensiomat at 30 °C (Method 1). The colorimetric CMC determination used uniformly pre-coated plastic balls that were purchased from Pro Chem, Inc. (Rockford, IL) (Method 2).[49] The absorption of the dye was measured at 612 nm on Shimadzu UV-160.

General procedures. Method A: A mixture of 5 g (14.6 mmol) sucrose, 3.76 (15.1 mmol) di-*n*-butyltin oxide and 75 mL methanol was refluxed for 3 h. The clear solution was concentrated *in vacuo* to dryness. The resulting white crystals were further dried by evaporation of 75 mL of added anhydrous toluene three times, then 30 mL DMF was added under inert gas. The clear, colorless solution was cooled to 4 °C and treated with 15.1 mmol of fatty acid anhydride. The mixture was stirred at ambient temperature for 48 h. The organotin compounds were separated from the reaction mixture by extracting two times with 100 mL petroleum ether. Then the reaction mixture was concentrated *in vacuo* to dryness and the last traces of DMF were removed by co-evaporation with 100 mL of *n*-heptane. After adding 150 mL of acetone and storing at 6 °C for 12 h the unreacted sucrose was precipitated and filtered off. To the clear acetone solution was added petroleum ether until the solution became slightly turbid. After equilibrating for 12 h at 6° C the crude reaction product was isolated by filtration and then recrystallized from acetone - petroleum ether. After prolonged reaction times (96 h) the reaction mixture was directly concentrated to dryness and subjected to flash chromatography.

Method B: The tin acetal of sucrose, prepared in accordance with Method A, was dissolved in 25 mL of DMF and 2.1 mL (15 mmol) triethylamine. After cooling to 4 °C the mixture was treated with 15 mmol of fatty acid chloride dissolved in 10 mL of DMF. The reaction mixture was then handled as indicated in Method A.

β-D-Fructofuranosyl 6-*O*-lauryl-α-D-glucopyranoside. Yield, Table 1; Rf 0.35; $[\alpha]_D$ + 35.0 (*c*1,MeOH); mp 118-120 °C; ^{1}H NMR, Table 2.

Anal. Calcd for $C_{24}H_{44}O_{12}$: C, 54.95; H, 8.45. Found: C, 54.65; H, 8.25.

β-D-Fructofuranosyl 6-*O*-myristyl-α-D-glucopyranoside. Yield, Table 1; Rf 0.38; $[\alpha]_D$ + 50.1 (*c*1, MeOH); mp 109-110 °C; ^{1}H NMR, Table 2.

Anal. Calcd for $C_{26}H_{48}O_{12}$: C, 56.50; H, 8.75. Found: C, 56.39; H, 9.01.

β-D-Fructofuranosyl 6-*O*-palmityl-α-D-glucopyranoside. Yield, Table 1; Rf 0.42; $[\alpha]_D$ + 48.6 (*c*1, MeOH); mp 107-108 °C; ^{1}H NMR, Table 2.

Anal. Calcd for $C_{28}H_{52}O_{12}$: C, 57.91; H, 9.03. Found: C, 57.58; H, 9.00.

β-D-Fructofuranosyl 6-*O*-stearyl-α-D-glucopyranoside. Yield, Table 1; Rf 0.49; $[\alpha]_D$ + 45.1 (*c*1, MeOH); mp 92-94° C; ^{1}H NMR, Table 2.

Anal. Calcd for $C_{30}H_{56}O_{12}$: C, 59.19; H, 9.25. Found: C, 58.84; H, 8.91.

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