Regiospecific Synthesis of New Methyl Sulfoglucopyranoside-Based Surfactants: Nucleophilic Displacement of a Cyclic Sulfate

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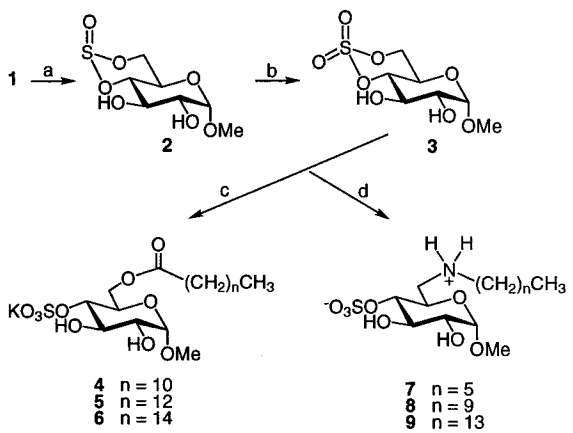
Abstract. A two-step regiospecific synthesis of a new class of anionic and amphoteric methyl α-D-glucopyranoside-based surfactants is described. Reaction of methyl α-D-glucopyranoside with thionyl chloride followed by oxidation of the resulting sulfite afforded the corresponding methyl α-D-glucopyranoside 4,6-cyclic sulfate in high yield. Nucleophilic displacement of this cyclic sulfate by different fatty acids and amines led to the corresponding methyl 6-*O*-acyl- or 6-amino-6-deoxy-4-sulfoglucopyranosides in very good yields. These newly synthesized sulfoglucopyranoside-based surfactants displayed low critical micelle concentration (CMC) values.

Key words: cyclic sulfates, anionic surfactants, amphoteric surfactants

Most of the surfactants produced by the chemical industry are based on petrochemicals. A number of efforts to use carbohydrates as bulk raw materials for synthesis of non-ionic surfactants have been reported.[1] Their amphiphilic behavior is caused by the presence of the hydrophilic free hydroxyl groups and a hydrophobic alkyl chain. Unique properties, such as non-toxicity of the surfactant, skin compatibility, environmental compatibility and biodegradability suggest a wide range of applications for sugar-based surfactants. Most of the approaches in this field have been directed to the preparation of fatty acid esters of mono- and disaccharides.[2,3] Recently, we described the synthesis of anionic and amphoteric sulfosucrose-based-surfactants through a protected sucrose 4,6-cyclic sulfate.[4] Cyclic sulfates undergo regioselective nucleophilic substitutions when reacted with *O*-nucleophiles,[4–8] *S*-nucleophiles,[6–9] halide nucleophiles,[8,10,11] *C*-nucleophiles,[6,12] and *N*-nucleophiles.[4,7,8,13] Cyclic sulfates are readily prepared through the oxidation of cyclic sulfites, which are obtained in very good yield by reaction of diols with thionyl chloride.[6] Carbohydrate cyclic sulfates are usually synthesized from a suitable protected carbohydrate precursor.[4,14] Attempts to synthesize cyclic sulfates of unprotected sugars with sulfuryl chloride and pyridine have been reported.[15] However, the reaction has never been clean and several side products were isolated. Only 1,2-cyclic sulfites of unprotected glucose, galactose and mannose have been synthesized using *N,N'*-thionylimidazole.[16] These cyclic sulfites were reportedly unstable and were used in situ in the reaction with azide. The present manuscript reports the synthesis of a cyclic sulfate of methyl α-D-glucopyranoside **1** containing unprotected hydroxyl groups, and its subsequent nucleophilic displacement by fatty acids and amines. New surfactants were obtained having improved surface activity properties compared to the values reported for commercially available ionic and non-ionic surfactants.

Synthesis of a methyl α-D-glucopyranoside cyclic sulfate relied on the two-step procedure described in the Scheme. Reaction of methyl α-D-glucopyranoside **1** with thionyl chloride ($SOCl_2$) and pyridine in DMF:ethyl acetate (v/v 1:1) at room temperature for 1.5 h afforded the corresponding 4,6-cyclic sulfite **2** in 70% yield, after purification on silica gel (Table 1). The position of the cyclic sulfite as well as the configuration of the sulfoxide group was determined by ^1H NMR.[4] The significant deshielding[17] of H-4 and H-6a indicates (i) a 4,6-cyclic sulfite and (ii) the axial configuration of the sulfoxide group. The equatorial isomer was not formed under these reaction conditions. Oxidation of **3** in acetonitrile:water (v/v 1:1.5) using sodium periodate ($NaIO_4$) with a catalytic amount of ruthenium(III) chloride ($RuCl_3$) led to the 4,6-cyclic sulfate **3** in 82% yield.



(a) $SOCl_2$ (1.05 + 0.52 equiv), pyr (2.05 + 1.02 equiv), DMF, EtOAc, r.t., 1.5 h; (b) $RuCl_3$ (cat.), $NaIO_4$ (2 equiv), $CH_3CN:H_2O$ (1.0:1.5), r.t., 1 h, (c) $CH_3(CH_2)_nCO_2H$ (1.2 equiv), K_2CO_3 (1.2 equiv), DMF, 70 °C, 3 h; (d) $CH_3(CH_2)_nNH_2$ (1.2 equiv), DMF, 80 °C, 18 h.

Scheme

Reaction of the cyclic sulfate **3** in DMF with a slight excess of lauric acid and potassium bicarbonate for 3 h at 70 °C afforded the methyl 6-*O*-lauroyl-4-*O*-sulfo-α-D-glucopyranoside **4** in 85% yield. The 4-position of the *O*-

sulfonation was confirmed by acid-catalyzed hydrolysis of the sulfo group in **4**. The ^{1}H NMR spectrum of the resulting product showed a large upfield shift for H-4 ($\Delta\delta$ = –0.95 ppm) while H-5, H-6a and H-6b were moderately shifted ($\Delta\delta$ = +0.13, –0.12 and –0.07 ppm, respectively), compared to the corresponding chemical shifts of the lauroyl-sulfo compound **4**. These observations indicated that the hydrolysis compound was the methyl 6-*O*-lauroyl-α-D-glucopyranoside, thus confirming the sulfate position at *O*-4. The same reaction performed with myristic and palmitic acids under identical conditions led to the 6-*O*-myristoyl- and 6-*O*-palmitoyl-4-*O*-sulfo derivatives **5** and **6** in 91% and 87% yield, respectively (Scheme).

Reaction of the cyclic sulfate **3** with a slight excess of hexylamine, decylamine or tetradecylamine in DMF at 80 °C for 17 h, led to the corresponding amphoteric 6-deoxy-6-

Table 1 Yields and Physical Characteristics of Compounds **2–9**

Compounds	Yields (%)	$[\alpha_D]^{24}$	mp (°)	HRFABMS	IR (cm^{-1})	^{1}H NMR (500 MHz) (Solvent), *J* (Hz)
2	70	+ 135 (c 2, MeOH)	163–165	Calcd. 263.021[a] Found 263.0202	1031 (O_2SO), 2832 (OCH_3), 3200–3600 (OH)	($CDCl_3$) δ 3.48 (s, 3 H, OMe), 3.57 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.3, H-2), 3.83 (t, 1 H, $J_{3,4}$ 9.5, H-3), 3.98 (m, 1 H, H-5), 4.02 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, $J_{6a,b}$ 10.1 Hz, H-6b), 4.51 (t, 1 H, $J_{4,5}$ 9.6, H-4), 4.63 (t, 1 H, $J_{5,6a}$ < 1.0, H-6a), 4.76 (d, 1 H, H-1).
3	82	+ 131 (c 1, MeOH)	160–162	Calcd. 279.0150[a] Found 279.0153	1035 and 1220 (O_2SO_2), 2837 (OCH_3), 3200–3500 (OH)	($CDCl_3$): 3.46 (s, 3 H, OMe), 3.53 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.3 Hz, H-2), 3.88 (t, 1 H, $J_{3,4}$ 9.3, H-3), 4.14 (m, 1 H, H-5), 4.41 (t, 1 H, $J_{4,5}$ 9.8, H-4), 4.56–4.62 (m, 2 H, $J_{6a,b}$ 10.4, H-6a, H-6b), 4.77 (d, 1 H, H-1).
4	85	+ 62 (c 1, MeOH)	215–217 (d)	Calcd. 455.1951[b] Found 455.1953	1034 (OSO_3^-), 1420–1460 and 2910–2960 (CH_2 and CH_3), 1725 (OC(O)R), 3200–3500 (OH)	(CD_3OD): δ 0.90 (t, 3 H, CH_3), 1.23–1.38 (m, 16 H, 8 CH_2), 1.63 (quint., 2 H, $C(O)CH_2CH_2$), 2.35 (t, 2 H, $C(O)CH_2$), 3.42 (s, 3 H, OMe), 3.54 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.8, H-2), 3.84 (m, 1 H, H-5), 4.00 (t, 1 H, $J_{3,4}$ 9.5, H-3), 4.17 (dd, 1 H, $J_{4,5}$ 8.9, H-4), 4.26 (dd, 1 H, $J_{5,6b}$ 6.2, $J_{6a,b}$ 12.1, H-6b), 4.41 (t, 1 H, $J_{5,6a}$ 2.1 Hz, H-6a), 4.68 (d, 1 H, H-1).
5	91	+ 62 (c 1, MeOH)	207–209 (d)	Calcd. 483.2264[b] Found 483.2267	Signals identical to those of **4**	(CD_3OD): δ 0.89 (t, 3 H, CH_3), 1.25–1.35 (m, 20 H, 10 CH_2), 1.62 (quint., 2 H, $C(O)CH_2CH_2$), 2.35 (t, 2 H, $C(O)CH_2$); other signals identical with those of **4**.
6	87	+ 77 (c 1, MeOH)	204–206 (d)	Calcd. 511.2577[b] Found 511.2574	Signals identical to those of **4**	(CD_3OD): δ 0.89 (t, 3 H, CH_3), 1.22–1.38 (m, 24 H, 12 CH_2), 1.61 (quint., 2 H, $C(O)CH_2CH_2$), 2.35 (t, 2 H, $C(O)CH_2$); other signals identical with those of **4**.
7	53	+ 116 (c 0.5, MeOH)	amorphous glass	Calcd. 356.1379[b] Found 356.1382	Signals identical to those of **9**	(CD3OD): δ 0.89 (t, 3 H, CH_3), 1.25–1.43 (m, 6 H, 3 CH_2), 1.75 (quint., 2 H, NCH_2CH_2), 3.01 (t, 2 H, NCH_2); other signals identical with those of **9**.
8	51	+ 74 (c 1, MeOH)	194–196 (d)	Calcd. 412.2005[b] Found 412.2002	Signals identical to those of **9**	(CD_3OD): δ 0.90 (t, 3 H, CH_3), 1.25–1.37 (m, 14 H, 7 CH_2), 1.72 (quint., 2 H, NCH_2CH_2), 3.02 (t, 2 H, NCH_2); other signals identical with those of **9**.
9	54	+ 74 (c 1, v/v 1:1 MeOH: $CHCl_3$)	209–212 (d)	Calcd. 468.2631[b] Found 468.2627	763 and 1660 (NH_2^+), 1035 (OSO_3^-), 1420–1460 and 2910–2960 (CH_2 and CH_3), 3200–3500 (OH)	(CD_3OD): δ 0.89 (t, 3 H, CH_3), 1.25–1.43 (m, 22 H, 11 CH_2), 1.75 (quint., 2 H, NCH_2CH_2), 3.01 (t, 2 H, NCH_2), 3.30 (dd, 1 H, $J_{5,6b}$ 6.3, $J_{6a,b}$ 13.3, H-6b), 3.42 (dd, 1 H, $J_{5,6a}$ 3.1, H-6a), 3.38 (s, 3 H, OMe), 3.55 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.6, H-2), 3.86 (t, 1 H, $J_{3,4}$ 9.3, H-3), 3.94 (m, 1 H, H-5), 4.11 (dd, 1 H, $J_{4,5}$ 8.2, H-4), 4.75 (d,1 H, H-1).

a Mass calculated for $[M+Na^+]^+$;
b Mass calculated for $[M-H]^-$

hexylamino-, 6-deoxy-6-decylamino- and 6-deoxy-6-tetradecylamino-4-*O*-sulfo derivatives **7**, **8** and **9** in 53%, 51% and 54% yield, respectively. No other regioisomers were detected by TLC or by ^{1}H NMR spectroscopy.

Into aqueous solution, at a specific concentration known as the critical micelle concentration (CMC), surfactant molecules aggregate in micelles. This CMC value is of practical importance since it is the minimal concentration of surfactant required to solubilize hydrophobic molecules in water. Our laboratory recently demonstrated that a colorimetric method for CMC determination[18] was useful for the accurate analysis of sucrose-based surfactants.[2–4] This dye solubilization method was used to determine the CMC of the sulfated surfactants. The newly synthesized water soluble acylsulfo and aminosulfo products **4**, **5**, **6** and **7**, displayed excellent surface-activity (Table 2). The CMC values measured for the acylsulfo derivatives **4**, **5** and **6** of 0.43, 0.067 and 0.034 mM respectively, were 1–3 orders of magnitude lower than those of commercially prepared ionic surfactants, the palmitoyl derivative showing the highest surface activity (Table 2). As expected, the CMC values decrease with acyl chain length. Amphoteric derivative **7** displayed a CMC value comparable to commercial surfactants while compounds **8** and **9** were insufficiently water soluble to determine their CMC values.

New *O*-acyl-*O*-sulfo and amino-*O*-sulfoglucopyranoside-based surfactants have been synthesized by nucleophilic displacement of the methyl α-D-glucopyranoside 4,6- cyclic sulfate with fatty acids and amines. These new anionic surfactants display very good surface active properties with CMC values from one to three orders of magnitude lower than those of commercial anionic surfactants. They are readily prepared using inexpensive renewable starting materials in high yield and in only 2 reaction steps without the requirement of hydroxyl protection. These derivatives should be biodegradable and thus, may have commercial applications as surfactants.

^{1}H NMR spectra were recorded at 25 °C, in deuterated solvent on a Varian Unity 500 MHz spectrometer. Chemical shifts were recorded in ppm (δ) and coupling constants in Hz, relative to TMS as internal standard. The ^{1}H NMR spectra were fully assigned by the use of single-frequency decoupling. Optical rotations were measured with a Jasco P-1020 polarimeter. Thin-layer chromatography (TLC) was performed using E. Merck plates of silica gel 60 with fluorescent indicator. Visualization was effected by spraying plates with Von's reagent (1.0 g ceric ammonium sulfate and 24.1 g ammonium molybdate in 31 mL sulfuric acid and 470 mL water) followed by heating at 140 °C. Flash chromatography was conducted with silica gel (230–430 mesh, E. Merck). Anhyd DMF, EtOAc, pyridine and methyl α-D-glucopyranoside were from Aldrich. The colorimetric CMC determination[18] used uniformly pre-coated plastic balls that were purchased from Pro Chem, Inc. (Rockford, IL). The absorption of the dye was measured at 612 nm on Shimadzu UV-60. All the sulfoglucopyranoside derivatives were hygroscopic, preventing their elemental analysis. The purity and identity of these surfactants were assessed based on the absence of extraneous signals in their ^{1}H NMR spectra and on the expected molecular ion by high resolution mass spectrometry.

Methyl α-D-Glucopyranoside 4,6-Cyclic Sulfite 2

To a solution of methyl α-D-glucopyranoside (1.0 g, 5.15 mmol) in anhyd DMF/EtOAc (v/v 1:1, 12 mL) under N_2, $SOCl_2$ (0.39 mL, 5.41 mmol) and anhyd pyridine (0.87 mL, 10.81 mmol) were added. After 45 min at r.t., $SOCl_2$ (0.18 mL, 2.52 mmol) and anhyd pyridine (0.43 mL, 1.25 mmol) were added. After an additional 45 minutes, the mixture was neutralized by addition of Et_3N and the solvent evaporated in vacuo. Purification by chromatography on silica gel ($MeOH/CHCl_3$ v/v, 1:15) afforded **2** (865 mg, 70%) as a white solid.

Methyl α-D-Glucopyranoside 4,6-Cyclic Sulfate 3

To a solution of **2** (62 mg, 0.26 mmol) in a mixture H_2O/CH_3CN (v/v 1:1.5, 2.5 mL), $RuCl_3$ (catalytic amount, 5 mg) and $NaIO_4$ (110 mg, 0.51 mmol) were added. After 1 h at r.t. the mixture was concentrated in vacuo. Purification by chromatography on silica gel ($MeOH/CHCl_3$ v/v, 1:9) afforded **3** (54 mg, 82%) as a white solid.

Methyl 6-*O*-Acyl-4-*O*-sulfo α-D-Glucopyranoside Derivatives 4–6; General Procedure

To a solution of **3** (50 mg, 0.19 mmol) in anhyd DMF (4 mL) maintained under N_2, K_2CO_3 (1.2 equiv) and the fatty acid (1.2 equiv) were added. The mixture was heated at 70 °C for 3 h. After cooling to r.t., the mixture was filtered through Celite and evaporated in vacuo. Purification by chromatography on silica gel ($CHCl_3/CH_3OH$ v/v, 4:1) afforded the corresponding 6-*O*-acyl-4-*O*-sulfo α-D-glucopyranoside derivatives.

6-Alkylamino-6-deoxy-4-*O*-sulfo α-D-Glucopyranoside Derivatives 7–9; General Procedure

To a solution of **3** (50 mg, 0.19 mmol) in anhyd DMF (4 mL) maintained under N_2, the fatty amine (1.2 equiv) was added. The mixture was heated at 80 °C for 17 h and evaporated in vacuo. Purification by chromatography on silica gel ($CHCl_3/CH_3OH$ v/v, 4:1) afforded the corresponding 6-alkylamino-6-deoxy-4-*O*-sulfo α-D-glucopyranoside derivatives.

Acidic Hydrolysis of 4

Compound **4** (10 mg, 0.022 mmol) in solution in THF (1 mL), was reacted with 50% aq H_2SO_4 (3 drops) for 30 min at r.t. After neutralization with sat. aq $NaHCO_3$, the mixture was extracted with $CHCl_3$ (3 x 3 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered and evaporated.

Table 2 CMC Values of Compounds **4–9** and Commercially Available Surfactants

Compounds	CMC	
	mmol/L	mg/L
4	0.43	210
5	0.067	35
6	0.034	20
7	3.0	1200
8	ns	ns
9	ns	ns
$C_{10}H_{21}OC_2H_4SO_3Na$[19]	15.9	4600
$C_{12}H_{25}SO_3Na$[19]	12.4	3400
$C_{12}H_{25}OSO_3Na$[19]	7.94	2300
$C_{12}H_{25}OC_2H_4OSO_3Na$[19]	3.91	1300
Octyl β-D-glucopyranoside[20]	25.1	7400

The CMC values determined for **4–9** and the CMC values reported from the literature were measured at 25 °C for aqueous solutions of the surfactants.

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