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Note

Synthesis of 1-octadecyl 5-betainylamino-5-deoxy-β-D-fructopyranoside hydrochloride as a new long-chain cationic sugar-based surfactant

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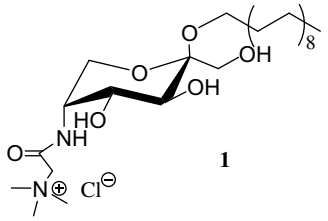
ABSTRACT

The synthesis of a novel long-chain cationic surfactant bearing a fructopyranoside polar head functionalized at the C-5 position by a natural glycine betaine residue through an amide linkage is described.

Long-chain cationic surfactants have become a very important class of industrial chemicals. These surface-active agents are based on plant oils or animal fats and they incorporate polar heads capable of being protonated in acidic media (e.g., amines) or bearing a permanent positive charge (such as quaternary ammonium salts).[1] They have many applications, which include fabric softeners, antistatic agents, organo-mineral clays, emulsifiers for uses in cosmetics or in road making applications, germicides, flotation chemicals, corrosion inhibitors and foam depressants.[2] In particular, as the use of cationic emulsifiers increases in cosmetology (hair care conditioning, skin care), there is a growing interest in the development of new cationic derivatives expanding the sensory options (powdery dry velvety feel, long-lasting skin moisturization) available by modifying the cationic moiety. Additionally, the consumer demand for healthy and environmentally friendly products coupled with a recent restrictive European regulation in terms of surfactant biodegradability[3] has prompted both industrial and academic research groups to propose new biocompatible and biodegradable cationic products. Within this context, sugar-based surfactants[4] derived from renewable plant resources gain increasing attention due to advantages with regard to performance, health of consumers and environmental compatibility compared to some standard products.[5] Sucrose and starch-based surfactants are well-established products and some cationic versions are already commercially available as for cationic alkyl polyglucosides (APGs).[6,7] Alkyl derivatives of fructose would also present similar potentialities since inulin and its monomer fructose may become economical starting materials, provided that an efficient alkylation method could become available.[8] The specific synthesis of glycopyranosides of D-fructose is not readily achieved. The Fischer-type glycosidation procedures frequently lead to complicated mixtures of furanosides and pyranosides, which require chromatographic separation.[8] In our group, we have developed a one-step stereocontrolled synthesis of alkyl D-fructopyranosides from totally unprotected D-fructose.[9] The objective of the study described here is the regioselective introduction of the natural cationic glycine betaine onto a D-fructopyranoside possessing one long C_{18} alkyl chain for the development of a novel biocompatible fructose-based cationic surfactant **1**.



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Long-chain C_{18} alkyl fructopyranoside **2** has been prepared in heterogeneous medium (THF) in order to avoid the oligomerization of unprotected D-fructose following the procedure developed in our group.[9] Glycosylation of 1-octadecanol by D-fructose was carried out in the presence of iron(III) chloride. The work-up of the reaction leading to the unprotected fructoside **2** appeared to be difficult (20%

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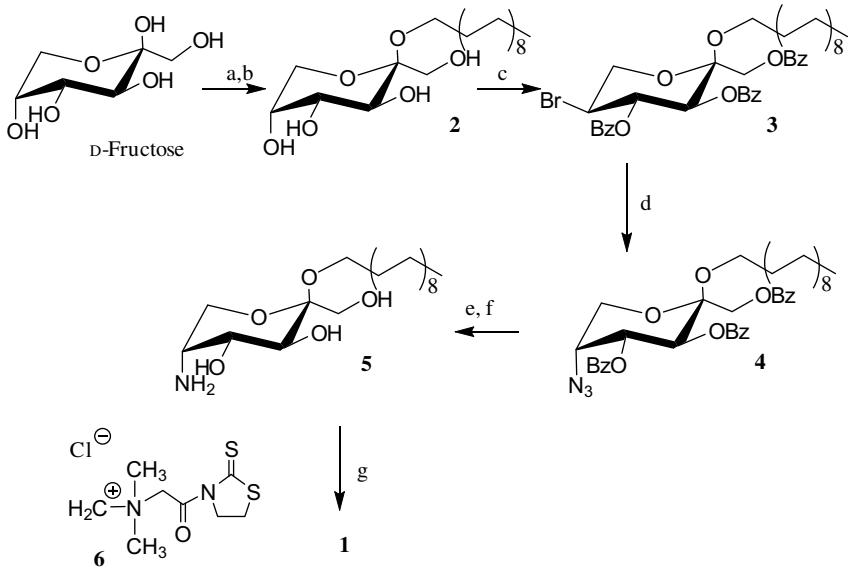

Scheme 1. Reagents and conditions: (a) 1-octadecanol, $FeCl_3$, THF, 20 °C, 6 h, then Ac_2O, Py, 20 °C, 20 h, 32%; (b) MeOH, Et_3N, H_2O, 99%; (c) PPh_3, CBr_4, Py, 0 °C to 80 °C, 16 h, then BzCl, Py, 20 °C, 5 h, 83%; (d) NaN_3, Me_2SO, 100 °C, 40 h, 90%; (e) MeONa, MeOH/$CHCl_3$, 20 °C, 7 h, 85%; (f) H_2, Pd/C, MeOH/$CHCl_3$ (1:1 v/v), 94%; (g) **6**, Et_3N, DMF, 50 °C, 2 h, 66%.

yield of isolated compound) since stable emulsions were formed, when the organic layer was washed with aqueous solutions. Acetylation was therefore performed in situ. For this purpose, the reaction mixture was quenched with an excess of pyridine and acetic anhydride (Scheme 1). After work up, the alkyl β-D-substituted peracetylated product was isolated by column chromatography in 30% yield. The formation of other isomers was not observed, and furthermore neither 5-(hydroxymethyl)furfural nor difructose dianhydrides were isolated in any significant amount.[10] Quasi-quantitative deprotection of the hydroxyl functions was performed by adding Et_3N and water in a 1:1 MeOH–$CHCl_3$ solution of peracetylated fructoside to furnish the unprotected octadecyl β-D-fructopyranoside **2**.

As glycine betaine esters were found to be highly pH-sensitive,[11] an amide linkage was considered for the introduction of the cationic moiety. The crucial step of the synthetic pathway consisted in taking advantage of the very special reactivity of alkyl fructosides for the regio- and stereoselective preparation of a fructoside monoazide. Treatment of octadecyl β-D-fructopyranoside **2** with PPh_3 (3.6 equiv) and CBr_4 (3.8 equiv) in pyridine at 80 °C for 16 h afforded 5-bromo-5-deoxy-α-L-sorbopyranoside.[12] After cooling, the reagent in excess was destroyed by the addition of methanol and once the solvent was removed under diminished pressure, the in situ benzoylation of the sorbopyranoside was performed by using benzoyl chloride in dry pyridine to afford the corresponding benzoylated derivative **3**. The protection of the hydroxyl groups was found to be necessary since the direct introduction of the azido group under standard conditions (NaN_3 or LiN_3 in DMF or Me_2SO) from the unprotected 5-bromo-5-deoxy-α-L-sorbopyranoside was unsuccessful. Indeed, the unprotected bromide was recovered, and only small amounts (<10%) of epoxide and/or N_3-epoxide opening derivatives were additionally obtained when using a large excess of LiN_3 (25 equiv) after stirring the reaction mixture at 100 °C for 4 days. The structure of **3** was evidenced by ^1H and ^{13}C NMR spectroscopies (Tables 1 and 2). This L-sorbopyranose derivative was shown to exist in a $^2C_5$ conformation in solution. This was confirmed by the magnitude of the $^3J_{3,4}$ coupling constant (9.9 Hz) which is characteristic of L-sorbopyranose derivatives.[13] Additionally, the presence of the bromine atom at the C-5 position was confirmed by ^{13}C NMR data (δ C-5 = 44.85 for **3** instead of 70.15 value for **2**).

The introduction of the nitrogen atom at C-5 was then carried out by a nucleophilic displacement of bromide in 5-bromo-5-deoxy-α-L-sorbopyranoside **3** using sodium azide in Me_2SO.[13] After heating at 100 °C for 40 h, benzoylated 5-azido-5-deoxy-β-D-fructopyranoside **4** was obtained in a good yield (90%). The inversion of configuration for carbon **5** was ascertained by the value of the coupling constant $^3J_{4,5}$ 3.8 Hz. A standard transesterification process under Zemplèn conditions (MeONa, MeOH) followed by hydrogenolysis (H_2, Pd/C) gave 5-amino-D-fructoside **5** in 80% yield. Finally, N-acylation of **5** was efficiently performed with the *N*-acyl thiazolidine-2-thione derivative **6** of glycine betaine in DMF in the presence of triethylamine.[14] Other stable activated derivatives of glycine betaine developed in our group[15] as *p*-nitrophenyl ester or amide resulting from the reaction of glycine betaine acyl chloride with 2-mercapto-5-methyl-1,3,4-thiadiazole could be also considered for the efficient introduction of the cationic moiety but they were not used in this study. The required cationic surfactant **1** was isolated in 66% yield after chromatography. The structure of **1** was fully confirmed by NMR spectroscopy (Tables 1 and 2) and high-resolution mass spectrometry. NMR data showed that the presence of the glycine betaine residue did not change the $^2C_5$ conformation of the fructopyranoside moiety ($^3J_{3,4}$ 9.9 Hz).

Preliminary surface tension measurements at 50 °C (to assure high water solubility) using a drop tensiometer (Tracker instrument, IT Concept) clearly revealed that cationic fructoside **1** diminished the surface tension (γ) at values characteristic to quite significant surfactant activities. Both critical micelle concentration (CMC = 0.095 mmol/L) and surface tension (γ_{CMC} = 37 mN/m) values were comparable to those obtained from novel long-chain glycine betaine esters and amides, which were recently developed in our group for road making applications.[11] The potential of this new cationic sugar-based surfactant for bitumen emulsifying applications and cosmetics is under investigation.

1. Experimental

1.1. General methods

All reagents were commercially available from Sigma or Acros and used without further purification. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled. TLC analyses were

Table 1
^{1}H NMR (400 MHz, δ values) and coupling constants (Hz) for compounds **1–5**

Compound	H-1a	H-1b	H-3	H-4	H-5	H-6a	H-6b	OCH_2CH_2	OCH_2CH_2	CH_2	CH_3
1[a,b,d]	3.75d	3.81 d (^3J 11.4)	3.79d	4.00dd (^3J 4.6, 9.9)	4.32m	3.64dd (^3J 1.5)	3.87dd (^3J 2.0 ^2J 12.2)	3.49–3.55m	1.56–1.64m	1.22–1.42m	0.89t (^3J 6.9)
2[a,b]	3.69d (^2J 11.4)	3.71–3.80m	3.88d ($^3J_{3,4}$ 9.9)	3.71–3.80m	3.86m	3.71–3.80m	3.87dd (^3J 1.8 ^2J 12.4)	3.41–3.53m	1.51–1.60m	1.19–1.35m	0.85t (^3J 7.1)
3[a,c,e]	4.29d	4.57d (^2J 11.9)	5.57d	5.98dd (^3J 9.9)	4.14ddd (^3J 5.6 ^3J 11.4)	3.94dd	4.00dd	3.47–3.69m	1.56–1.73m	1.12–1.48m	0.82t (^3J 6.6)
4[a,c,f]	4.39d	4.64d (^2J 11.9)	6.13d (^3J 10.4)	5.81dd (^3J 3.8)	4.34m	3.92dd (^3J 1.8)	4.05dd (^3J 1.5 ^2J 12.5)	3.54-3.73m	1.61-1.76m	1.18-1.49m	0.88t (^3J 6.8)
5[a,b]	3.74m	3.80d (^2J 11.1)	3.71d	4.00dd (^3J 4.6 9.9)	3.40–3.53m	3.74m	3.56dd (^3J 1.6 ^2J 13.2)	3.40–3.53m	1.50–1.61m	1.15–1.38m	0.85t (^3J 6.8)

[a] Signal multiplicities: d, doublet; t, triplet; m, multiplet.
[b] Recorded in $CDCl_3$/CD_3OD (1:1 v/v) and calibrated on the CD_3OD signal at 3.31 ppm.
[c] Recorded in $CDCl_3$.
[d] For compound **1**: δ $(CH_3)_3$ 3.36, δ CH_aH_bCO 4.17, δ CH_aH_bCO 4.22.
[e] For compound **3**: δ PhCO 7.14–7.90.
[f] For compound **4**: δ PhCO 7.23–8.01.

conducted on precoated non-activated plates (E. Merck 60 F_{254}), and compounds were visualized using a 5% soln of H_2SO_4 in EtOH followed by heating. For column chromatography, E. Merck 60 H (5–40 μm) Silica Gel was used. Melting point (mp) was determined on a Reichert microscope and is uncorrected. IR spectrum was recorded on a IRFT Nicolet 205 spectrometer. Optical rotation was measured on a Perkin–Elmer 341 polarimeter at 20 °C using a 1-dm cell. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C, respectively) in $CDCl_3$ or 1:1 $CDCl_3$/CD_3OD at 298 K. Chemical shifts are given in δ-units measured downfield from Me_4Si at 0 ppm using the residual solvent signal as secondary reference. HRFAB mass spectra were acquired on a MS/MS ZabSpec TOF Micromass spectrometer with 3-nitrobenzylic alcohol as the matrix.

1.2. 1-Octadecyl β-D-fructopyranoside (2)

To a suspension of D-fructose (12 g, 66.6 mmol) in dry THF (100 mL) was added 1-octadecanol (27.03 g, 99.9 mmol). Ferric chloride (32.44 g, 200 mmol) was then added in small portions after cooling the soln to 0 °C. The mixture was stirred at room temperature for 6 h under N_2 followed by the addition of dry pyridine (200 mL) at 0 °C. After stirring for 15 min at room temperature, Ac_2O (88 mL, 933 mmol) was introduced into the reaction mixture at 0 °C. The resulting soln was maintained at room temperature under vigorous stirring overnight before being diluted with CH_2Cl_2, washed with 5% aq HCl (until discoloration) and water (until neutral pH), successively. The organic layer was dried over $MgSO_4$ and concentrated under diminished pressure. Purification of the residue by column chromatography (4:1 petroleum ether–EtOAc) afforded peracetylated octadecyl β-D-fructopyranoside (12.10 g, 30%) as a white solid: mp 58–60 °C; $[\alpha]_D^{20}$ −69.6 (*c* 1, CH_2Cl_2); TLC (4:1 petroleum ether–EtOAc): R_f 0.24. HRFABMS: calcd for $C_{32}H_{56}O_{10}Na$, 623.3771; found, *m/z* 623.3771 $[M+Na]^+$. Anal. Calcd for $C_{32}H_{56}O_{10}$: C, 63.98; H, 9.40. Found: C, 64.21; H, 9.33. To a soln of this compound (9.01 g, 15 mmol) in MeOH (120 mL) and $CHCl_3$ (120 mL) were added Et_3N (20 mL) and water (20 mL). After stirring for 17 h at 35 °C, the solvent was removed under diminished pressure and the residue was chromatographed on silica gel (9:1 CH_2Cl_2–MeOH) to give the resulting unprotected octadecyl β-D-fructopyranoside **2** (6.42 g, 99% yield) as a white solid: mp 131–132 °C; $[\alpha]_D^{20}$ −75.4 (*c* 0.85, 1,4-dioxane), lit.[9] $[\alpha]_D^{20}$ −70 (*c* 1, 1,4-dioxane); TLC (9:1 CH_2Cl_2–MeOH): R_f 0.36. HRFABMS: calcd for $C_{24}H_{48}O_6Na$, 455.3349; found, *m/z* 455.3342 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{48}O_6$: C, 66.63; H, 11.18. Found: C, 66.25; H, 10.98.

1.3. 1-Octadecyl 1,3,4-tri-*O*-benzoyl-5-bromo-5-deoxy-α-L-sorbopyranoside (3)

To a soln of **2** (2 g, 4.6 mmol) in dry pyridine (70 mL) cooled to 0 °C were added successively in several portions PPh_3 (4.36 g, 16.6 mmol) and CBr_4 (5.83 g, 17.6 mmol). After stirring at 80 °C for 16 h, the reaction mixture was cooled to room temperature and the excess of reagent was destroyed by adding MeOH (20 mL). The solvent was removed under diminished pressure and benzoylation of the product was carried out in situ. To the residue were added slowly at 0 °C dry pyridine (50 mL) and benzoyl chloride (3.22 mL, 27.7 mmol). The resulting soln was maintained at room temperature for 5 h and it was spilled into icy water (50 mL) before adding CH_2Cl_2 (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under diminished pressure. The crude product was purified by silica gel (95:5 petroleum ether–EtOAc) to give the α-L-sorbopyranoside derivative **3** (3.09 g, 83%) as a colourless oil: $[\alpha]_D^{20}$ −25.8 (*c* 0.99, CH_2Cl_2); TLC (4:1 petroleum ether–EtOAc): R_f 0.58; IR (Nujol, cm^{-1}); *v* 707 (C–Br), 1130–990 (C–O), 1735 (C=O) and 1652–1559 (C=C) and

Table 2
^{13}C NMR (100 MHz, δ values) for compounds **1–5**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OCH_2CH_2	OCH_2CH_2	CH_2	CH_3
1[a,c]	63.29	101.62	71.13	70.30	52.52	62.97	62.14	31.03	23.54–32.91	14.23
2[a]	62.29	100.79	70.01	70.89	70.15	64.43	61.50	30.54	23.19–32.46	14.32
3[b,d]	63.18	98.98	72.93	73.09	44.85	63.60	61.74	29.87	22.77–32.00	14.22
4[b,e]	63.36	99.19	68.80	71.30	61.15	61.56	61.73	29.92	21.13–31.99	14.21
5[a]	61.96	101.21	68.79	67.65	52.99	60.30	61.82	30.49	23.15–32.44	14.32

[a] Recorded in $CDCl_3/CD_3OD$ (1:1 v/v) and calibrated on the CD_3OD signal at 49 ppm.
[b] Recorded in $CDCl_3$.
[c] For compound **1**: δ $(CH_3)_3$ 55.16, δ CH_2CO 66.38, δ CH_2CO 165.08.
[d] For compound **3**: δ *Ph*CO 7.128.27–133.25, δ PhCO 165.43–165.80.
[e] For compound **4**: δ *Ph*CO 7.128.28–133.60, δ PhCO 165.50–166.08.

3010–2790 (C–H). HRFABMS: calcd for $C_{45}H_{59}BrO_8Na$, 829.3291; found, *m/z* 829.3283 $[M+Na]^+$. Anal. Calcd for $C_{45}H_{59}BrO_8$: C, 66.91; H, 7.36. Found: C, 67.44; H, 7.34.

1.4. 1-Octadecyl 5-azido-1,3,4-tri-*O*-benzoyl-5-deoxy-β-D-fructopyranoside (4)

Sodium azide (2.96 g, 45.6 mmol) was added under N_2 to a stirred soln of **3** (3.07 g, 3.8 mmol) in dry Me_2SO (40 mL). The reaction mixture was stirred for 43 h at 100 °C. After cooling to room temperature, the soln was spilled into EtOAc (300 mL) and washed with water (3 × 300 mL). The organic layer was dried over $MgSO_4$ and concentrated under diminished pressure. The crude product was purified by silica gel chromatography. Elution with 19:1 petroleum ether–EtOAc gave the desired product **4** (2.64 g, 90%) as a colourless oil: $[\alpha]_D^{20}$ −22.6 (*c* 1.1, CH_2Cl_2); TLC (4:1 petroleum ether–EtOAc): R_f 0.54. HRFABMS: calcd for $C_{45}H_{59}N_3O_8Na$, 792.4200; found, *m/z* 792.4201 $[M+Na]^+$. Anal. Calcd for $C_{45}H_{59}N_3O_8$: C, 70.20; H, 7.72; N, 5.46. Found: C, 70.56; H, 7.91; N, 5.45.

1.5. 1-Octadecyl 5-amino-5-deoxy-β-D-fructopyranoside (5)

To a soln of **4** (2.6 g, 3.4 mmol) in dry MeOH (40 mL) and dry $CHCl_3$ (10 mL) was added a 0.3 M soln of MeONa in MeOH (5 mL). The mixture wax stirred for 7 h at room temperature, neutralized with an acidic resin (Amberlite IR 120), filtered and concentrated. The crude product was purified by silica gel chromatography, eluting with a mixture of 19:1 CH_2Cl_2–MeOH, to yield the corresponding unprotected azido compound (1.32 g, 85%) as a white powder: mp 70–72 °C; $[\alpha]_D^{20}$ −90.4 (*c* 0.44, CH_2Cl_2); TLC (4:1 petroleum ether–EtOAc): R_f 0.28. HRFABMS: calcd for $C_{24}H_{47}N_3O_5Na$, 480.3413; found, *m/z* 480.3415 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{47}N_3O_5$: C, 62.99; H, 10.35; N, 9.18. Found: C, 63.18; H, 10.33; N, 8.93. A soln of this compound (1.15 g, 2.5 mmol) in a mixture of MeOH (30 mL) and $CHCl_3$ (30 mL) was stirred in the presence of 10% Pd/C (400 mg) and under an atmosphere of hydrogen gas at room temperature for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under diminished pressure. The crude product was purified by silica gel chromatography (4:1 CH_2Cl_2–MeOH), to give the 5-aminodeoxy-fructopyranoside derivative **5** (1.01 g, 94%) as a white powder: mp 65–70 °C; $[\alpha]_D^{20}$ −59.6 (*c* 0.24, 41–59 CH_2Cl_2–MeOH); TLC (4:1 CH_2Cl_2–MeOH): R_f 0.30. HRFABMS: calcd for $C_{24}H_{50}NO_5$, 432.3689; found, *m/z* 432.3696 $[M+H]^+$.

1.6. 1-Octadecyl 5-betainylamino-5-deoxy-β-D-fructopyranoside chloride (1)

N-(*N*′,*N*′,*N*′-Trimethylammonium acetyl)thiazolidine-2-thione chloride **6**[14] (700 mg, 2.76 mmol) and Et_3N (277 μL, 1.97 mmol) were added to a soln of 5-amino-D-fructoside **5** (850 mg, 1.97 mmol) in dry DMF under N_2. The reaction mixture was stirred at 50 °C for 2 h. After removal of the solvent, the residue was flash chromatographed (6:3:1 then 5:3:2 EtOAc–*i*PrOH–H_2O) to afford **1** (739 mg, 66%) as a white solid: mp 200-220 °C; $[\alpha]_D^{20}$ −36.1 (*c* 0,42, 17:33 $CHCl_3$–MeOH). HRFABMS: calcd for $C_{29}H_{59}N_2O_6$, 531.4373; found, *m/z* 531.4362 $[M]^+$.

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