Synthesis and Interfacial Properties of Sugar-Based Surfactants Composed of Homo- and Heterodimers

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ABSTRACT: Dimeric sugar-based amphiphiles were synthesized starting from D-glucose and a commercial mixture of dodecyl and tetradecyl alcohols by a simple procedure. Three different spacers (glutaryl, succinyl, and terephthaloyl) were used to link the sugar moieties through *O*-2 or *O*-6. Dimeric compounds are composed by mixtures of homodimers (C-12/C-12) and heterodimers (C-12/C-14). The interfacial properties of these nonionic gemini surfactants are described.

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Gemini surfactants characterized by the presence of two polar heads, charged or uncharged, and two hydrophobic chains linked by a spacer were introduced in the early 1990s.

These important structural differences give this type of surfactants unprecedented and better interfacial properties in comparison with the traditional surfactants (1,2).

One of the latest applications of gemini surfactants is in molecular biology as a potential agent in gene therapy, and their properties as a vehicle for gene delivery into cells (transfection) have been reported (3,4). Interesting syntheses of gemini surfactants using carbohydrates as starting material have been reported in the literature (5–12).

Conversely, alkyl glycosides are monomeric nonionic surfactants. Natural alkyl glycosides are biosynthesized as glycolipids by microorganisms from rhamnose or sophorose. They are prepared on an industrial scale from fatty alcohols and carbohydrates, and they are gradually replacing other nonionic surfactants derived from petrochemicals. Due to their excellent biodegradability and the absence of toxic effects, food elaboration, polymer manufacture, and solubilization of biological membranes are some of the wide spectrum of applications of alkyl glycosides (13).

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Abbreviations: CI, chemical ionization; CMC, critical micellar concentration; DMF, dimethyl formamide; FAB, fast atom bombardment; HPTLC, high-pressure thin-layer chromatography; HRMS, high-resonance mass spectrometry; IR, infrared; NMR, nuclear magnetic resonance; UV, ultraviolet.

The interesting properties of gemini surfactants supported the design and synthesis of a new series of amphiphilic molecules, composed of two long alkyl glucosides linked by different rigid and flexible spacers. Initially, butyl glucosides were used as starting materials (14–16).

In the present work, the synthesis of four different gemini derivatives using a commercial mixture of dodecyl and tetradecyl alcohols is reported. Their interfacial properties are discussed in comparison with those of previously prepared gemini surfactants from D-glucose and pure long-chain alcohols.

EXPERIMENTAL PROCEDURES

General methods. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded using a Bruker spectrometer at 200.13 MHz and 50.14 MHz, respectively, in $CDCl_3$ or CD_3OD. High-pressure thin-layer chromatography (HPTLC) was carried out on precoated glass plates (0.1 mm) of silica gel 60 F-254; detection was performed by exposure to ultraviolet (UV) light and by spraying the plate with 5% (vol/vol) H_2SO_4 in ethanol followed by heating. Infrared (IR) spectra were recorded with a Fourier transform spectrometer. Melting points are uncorrected. Chemical ionization (CI) and fast atom bombardment (FAB) mass spectra were obtained with a JMS-700 spectrometer.

Determination of interfacial properties. Air-water surface tensions were measured at 25°C in a specially adapted tensiometer based on the bubble pressure method (17,18). Calibration was performed against a range of standard liquids (19); excellent agreement with literature values was found (20). Critical micellar concentration (CMC) was determined by extrapolation of plots of surface tension vs. log concentration. All compounds exhibited the typical plots, with an abrupt change in slope at the zone corresponding to the CMC. Other interfacial properties were calculated according to known methods (21).

Dodecyl/tetradecyl α-D-glucopyranoside (1). Compound **1** was prepared from D-glucose and a commercial mixture of dodecyl/tetradecyl alcohols (7:3) by a reported procedure (14–16). Colorless oil (21% yield). HPTLC (SiO_2): R_f = 0.47 (EtOAc/MeOH, 5:1, vol/vol). $[\alpha]_D$ +77.1° (*c* 0.9, MeOH). IR (film) ν_{max} (cm^{-1}): 3,404.0 (OH), 2,916.4 (CH_2), 1,035.7

(CH_2O). ^1H NMR (200.1 MHz, methanol-*d*), δ (ppm): 4.66 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 3.73–3.14 (m, 8 H, H-2, H-3, H-4, H-5, H-6a, H-6b, CH_2O), 1.52 (m, 2 H, CH_2), 1.20 (bs, 19 H, CH_2), 0.80 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ (ppm): 100.0 (C-1), 75.1 (C-3), 73.5 (C-2, C-5), 71.8 (C-4), 69.1 (CH_2O), 62.6 (C-6), 33.0, 30.7, 30.6, 30.4, 27.3, 23.6 (CH_2), 14.4 (CH_3). High-resonance mass spectrometry (HRMS) (CI) *m/z* calcd. ($C_{18}H_{37}O_6$) 349.2590, found 349.2580 [M + H]$^+$. HRMS (CI) *m/z* calcd. ($C_{20}H_{41}O_6$) 377.2903, found 377.2910 [M + H]$^+$.

Dodecyl/tetradecyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (2). Trityl chloride (4.95 g, 17.73 mmol), Et_3N (3.6 mL, 25.83 mmol), and DMAP (4-dimethylaminopyridine; 90 mg, 0.74 mmol) were added to a solution of **1** (2.02 g, 5.80 mmol) in dimethyl formamide (DMF) (20 mL) at room temperature. The mixture was stirred for 48 h at 40°C and then water-ice (1:1) was added (40 g). The crude was extracted with CH_2Cl_2 (2 × 50 mL) and the organic phase was washed with NH_4Cl (1 × 50 mL) and brine (1 × 50 mL), dried (Na_2SO_4), and concentrated under diminished pressure to leave the trityl derivative as a pale yellow gum. Benzyl bromide (2.50 mL, 20.88 mmol) and sodium hydride (650 mg, 15.00 mmol) were added to a stirring solution of crude trityl derivative in DMF (28 mL) at 0°C. The resulting mixture was slowly allowed to warm to room temperature and stirred for 24 h, and then MeOH (4 mL) was added to quench the reaction. The organic mixture was diluted with chloroform (40 mL) and washed with brine (4 × 20 mL), dried (Na_2SO_4), and concentrated under diminished pressure to leave the benzyl-trityl derivative as a yellow gum. Pyridinium chloride (150 mg, 1.30 mmol) was added to a stirring solution of the tribenzyl trityl derivative in ethanol (25 mL) at room temperature. The mixture was refluxed for 2 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography column, eluting with a solvent gradient of EtOAc (10–15%) in cyclohexane to afford the tribenzyl glucoside **2** as pale yellow oil (910 mg, 55% yield). HPTLC (SiO_2): R_f = 0.39 (cyclohexane/EtOAc, 75:25, vol/vol). $[\alpha]_D$ +35.5° (*c* 1.3, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,486.7 (OH), 2,933.7 (CH_2), 1,070.7 (C-O, ether), 741.6, 702.1 (Ph). ^1H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.33–7.23 (m, 15 H, H_{ar}), 5.02–4.61 (m, 7 H, CH_2Ph, H-1), 4.01 (t, 1 H, $J_{3,4}$ = 9.2 Hz, H-3), 3.72–3.46 (m, 6 H, H-2, H-4, H-5, CH_2CH_aO, H-6a, H-6b), 3.38 (dt, 1 H, J = 6.9 Hz, J_{gem} = 9.6 Hz, CH_2CH_bO), 1.62 (m, 2 H, CH_2), 1.26 (bs, 19 H, CH_2), 0.88 (t, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 138.9–138.2 (C_{ar}), 128.4–127.5 (C_{ar}), 96.8 (C-1), 81.9 (C-3), 80.3 (C-2), 77.6 (C-4), 75.6, 75.0, 73.1 (CH_2Ph), 70.7 (C-5), 68.3 (CH_2O), 61.9 (C-6), 31.9 (CH_2), 29.6, 29.4, 26.1 (CH_2), 19.2 (CH_2), 13.8 (CH_3). HRMS (CI) *m/z* calcd. ($C_{39}H_{58}O_6N$) 636.4264, found 636.4257 [M + NH_4]$^+$. HRMS (CI) *m/z* calcd. ($C_{41}H_{62}O_6N$) 664.4577, found 664.4608 [M + NH_4]$^+$.

General procedure for the preparation of protected gemini surfactants linked through O-6. Succinyl chloride (18 μL, 0.16 mmol) and Et_3N (45 μL, 0.32 mmol) were added to a stirring solution of **2** (0.25 mmol) in toluene (0.5 mL) at 0°C. The resulting mixture was slowly allowed to warm to room temperature and stirred for 24 h, then more succinyl chloride (18 μL, 0.16 mmol) and Et_3N (7 μL, 0.06 mmol) were added, and the mixture was stirred at room temperature for 16 h. The crude product was purified by preparative TLC (silica gel) using cyclohexane/EtOAc (75:25, vol/vol) to afford the protected gemini surfactant as a colorless syrup.

General procedure for deprotection of gemini surfactants linked through O-6. A solution of the benzylated gemini surfactant (0.060 mmol) in EtOAc/MeOH (1:1, vol/vol, 12 mL) was hydrogenated (4 atm) at room temperature over 10% Pd/C for 6 h. The mixture was filtered through a celite pad and concentrated under diminished pressure to afford the gemini surfactant.

1,4-Bis-[6-O-(dodecyl/tetradecyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid)] succinate (3). Colorless oil (72 mg, 38% yield). HPTLC (SiO_2): R_f = 0.55 (cyclohexane/EtOAc, 75:25, vol/vol). $[\alpha]_D$ +26.9° (*c* 1.0, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 2,920.7 (CH_2), 1,740.7 (CO), 735.6, 697.9 (Ph). ^1H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.33–7.25 (m, 30 H, H_{ar}), 5.11–4.51 (m, 14 H, CH_2Ph, H-1, H-1'), 4.26 (m, 4 H, H-6a, H-6'a, H-6b, H-6'b), 3.99 (t, 2 H, $J_{3,4}$ = 9.1 Hz, H-3, H-3'), 3.82 (m, 2 H, H-5, H-5'), 3.61–3.35 (m, 8 H, H-2, H-2', H-4, H-4', CH_2O), 2.57 (s, 4 H, CH_2COO), 1.59 (m, 4 H, CH_2), 1.26 (bs, 38 H, CH_2), 0.87 (t, 6 H, J = 7.0 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 172.0 (COO), 138.6–138.2 (C_{ar}), 128.6–127.7 (C_{ar}), 96.8 (C-1, C-1'), 82.1 (C-3, C-3'), 80.3 (C-2, C-2'), 77.8 (C-4, C-4'), 75.7, 75.1, 73.2 (CH_2Ph), 68.7 (C-5, C-5'), 68.4 (CH_2O), 63.4 (C-6, C-6'), 32.0 (CH_2), 29.7, 29.6, 29.5, 29.2, 29.0 (CH_2), 28.9 (CH_2COO), 26.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3). HRMS (CI) *m/z* calcd. ($C_{82}H_{114}O_{14}N$) 1,336.8239, found 1,336.8223 [M + NH_4]$^+$. HRMS (CI) *m/z* calcd. ($C_{84}H_{118}O_{14}N$) 1,364.8552, found 1,364.8464 [M + NH_4]$^+$.

1,4-Bis-[6-O-(dodecyl/tetradecyl α-D-glucopyranosid)] succinate (4). Colorless gum (28 mg, 44% yield). HPTLC (SiO_2): R_f = 0.63 (EtOAc/MeOH, 9:1, vol/vol). $[\alpha]_D$ +74.3° (*c* 1.4, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,408.0 (OH), 1,737.8 (CO), 1,055.0 (C-O, ether). ^1H NMR (200.1 MHz, methanol-*d*), δ (ppm): 4.80 (d, 2 H, $J_{1,2}$ = 4.0 Hz, H-1, H-1'), 4.43 (dd, 2 H, $J_{5a,6a}$ < 1.0 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6a, H-6'a), 4.26 (dd, 2 H, $J_{5,6b}$ = 6.0 Hz, H-6b, H-6'b), 3.77–3.26 (m, 12 H, H-2, H-2', H-3, H-3', H-4, H-4', H-5, H-5', CH_2O), 2.70 (s, 4 H, CH_2COO), 1.69 (m, 4 H, CH_2), 1.34 (bs, 38 H, CH_2), 0.94 (t, 6 H, J = 6.2 Hz, CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ(ppm): 173.8 (COO), 100.2 (C-1, C-1'), 75.1 (C-3, C-3'), 73.5 (C-2, C-2'), 72.0 (C-5, C-5'), 71.2 (C-4, C-4'), 69.4 (CH_2O), 65.3 (C-6, C-6'), 33.1, 30.8, 30.6, 30.5 (CH_2), 30.0 (CH_2COO), 27.4, 23.7 (CH_2), 14.5 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{40}H_{74}O_{14}Na$) 801.4976, found 801.5004 [M + Na]$^+$. HRMS (FAB) *m/z* calcd. ($C_{42}H_{78}O_{14}Na$) 829.5289, found 829.5272 [M + Na]$^+$.

1,5-Bis-[6-O-(dodecyl/tetradecyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid)] glutarate (5). Colorless oil (42 mg, 36% yield). HPTLC (SiO_2): R_f = 0.50 (cyclohexane/EtOAc, 75:25, vol/vol). $[\alpha]_D$ −33.6 (*c* 1.6, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 2,925.2 (CH_2),

1,739.6 (CO), 735.6, 696.2 (Ph). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.35–7.26 (m, 30 H, H_{ar}), 5.13–4.53 (m, 14 H, CH_2Ph, H-1, H-1'), 4.27 (m, 4 H, H-6a, H-6'a, H-6b, H-6'b), 4.03 (t, 2 H, $J_{3,4}$ = 9.4 Hz, H-3, H-3'), 3.85 (m, 2 H, H-5, H-5'), 3.64–3.38 (m, 8 H, H-2, H-2', H-4, H-4', CH_2O), 2.38 (t, 4 H, J = 6.4 Hz, CH_2COO), 1.95 (m, 2H, CH_2CH_2COO), 1.62 (m, 4 H, CH_2), 1.28 (bs, 38 H, CH_2), 0.89 (t, 6 H, J = 6.8Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 172.5 (COO–), 138.9–136.0 (C_{ar}), 128.6–127.7 (C_{ar}), 96.8 (C-1, C-1'), 82.1 (C-3, C-3'), 80.3 (C-2, C-2'), 77.8 (C-4, C-4'), 75.8, 75.1, 73.1 (CH_2Ph), 68.7 (C-5, C-5'), 68.4 (CH_2O), 63.2 (C-6, C-6'), 33.1 (CH_2COO), 32.0 (CH_2), 29.7, 29.5, 26.3, 22.8 (CH_2), 20.1 (CH_2CH_2COO), 14.2 (CH_3). HRMS (CI) *m/z* calcd. ($C_{83}H_{116}O_{14}N$) 1,350.8396, found 1,350.8308 $[M + NH_4]^+$. HRMS (CI) *m/z* calcd. ($C_{85}H_{120}O_{14}N$) 1,378.8709, found 1,378.8562 $[M + NH_4]^+$.

1,5-Bis-[6-O-(dodecyl/tetradecyl α-D-glucopyranosid)] glutarate (6). Colorless gum (19 mg, 62% yield). HPTLC (SiO_2): R_f = 0.57 (EtOAc/MeOH, 9:1, vol/vol). $[\alpha]_D$ +58.1° (*c* 0.9, MeOH). IR (film) ν_{max} (cm^{-1}): 3,415.3 (OH), 1,739.7 (CO), 1,053.1 (C-O, ether). ^{1}H NMR (200.1 MHz, methanol-*d*), δ (ppm): 4.81 (d, 2 H, $J_{1,2}$ = 4.0 Hz, H-1, H-1'), 4.41 (dd, 2 H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6a, H-6'a), 4.22 (dd, 2 H, $J_{5,6b}$ = 6.0 Hz, H-6b, H-6'b), 3.83–3.25 (m, 12 H, H-2, H-2', H-3, H-3', H-4, H-4', H-5, H-5', CH_2O), 2.46 (t, 4 H, J = 7.3 Hz, CH_2COO), 1.98 (m, 2 H, CH_2CH_2COO), 1.67 (m, 4 H, CH_2), 1.32 (bs, 38 H, CH_2), 0.92 (t, 6 H, J = 6.9 Hz, CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ (ppm): 174.4 (COO), 100.2 (C-1, C-1'), 75.1 (C-3, C-3'), 73.5 (C-2, C-2'), 72.0 (C-5, C-5'), 71.2 (C-4, C-4'), 69.4 (CH_2O), 65.0 (C-6, C-6'), 34.1 (CH_2COO), 33.0, 30.8, 30.6, 30.5, 27.4, 27.0, 23.7 (CH_2), 21.4 (CH_2CH_2COO), 14.4 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{41}H_{76}O_{14}Na$) 815.5133, found 815.5111 $[M + Na]^-$. HRMS (FAB) *m/z* calcd. ($C_{43}H_{80}O_{14}Na$) 843.5446, found 843.5477 $[M + Na]^+$.

Dodecyl/tetradecyl 4,6-O-benzylidene-α-D-glucopyranoside (7). α,α-Dimethoxytoluene (1.4 mL, 9.53 mmol) and camphorsulfonic acid (220 mg, 0.86 mmol) were added to a stirring solution of **1** (2.53 g, 7.11 mmol) in chloroform (35 mL) at room temperature. The mixture was refluxed for 4 h and then cooled at room temperature. Na_2CO_3 (900 mg) was added, and the organic mixture was stirring for 30 min at 80°C. The solid was filtered and then concentrated under diminished pressure. The residue was recrystallized from methanol/water to afford the benzylidene derivative **7** as a white solid (1.96 g, 62% yield). HPTLC (SiO_2): R_f = 0.46 (cyclohexane/EtOAc, 1:1, vol/vol). $[\alpha]_D$ +73.9° (*c* 1.0; $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,384.0 (OH), 2,922.6 (CH_2), 1,051.1 (C-O, ether), 758.0, 700.1 (Ph). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.50–7.30 (m, 5 H, H_{ar}), 5.52 (s, 1 H, C*H*Ph), 4.86 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.26 (dd, 1 H, $J_{5,6a}$ = 4.0 Hz, $J_{6a,6b}$ = 9.1 Hz, H-6a), 3.91 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.81–3.40 (m, 6 H, H-2, H-4, H-5, H-6b, CH_2O), 1.61 (m, 2 H, CH_2), 1.27 (bs, 19 H, CH_2), 0.88 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 137.1 (C_{ar}), 129.2–126.2 (C_{ar}), 101.8 (CHPh), 98.7 (C-1), 81.0 (C-4), 72.9 (C-2), 71.9 (C-3), 68.9 (C-6), 68.7 (CH_2O), 62.5 (C-5), 31.9 (CH_2), 29.6, 29.4, 29.3, 26.1 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (CI) *m/z* calcd. ($C_{25}H_{41}O_6$) 437.2903, found 437.2899 $[M + NH_4]^+$. HRMS (CI) *m/z* calcd. ($C_{27}H_{45}O_6$) 465.3216, found 465.3256 $[M + NH_4]^+$.

Dodecyl/tetradecyl 4,6-O-benzylidene-2,3-O-dibutylstannylidene-α-D-glucopyranoside (8). A mixture of **7** (170 mg, 0.38 mmol), toluene (16 mL), and dibutyltin oxide (100 mg, 0.40 mmol) in a conical flask adapted with a small air condenser was placed in a microwave oven (119 W). The oven was turned on for 1 min, and after 30 s, it was turned on again for 1 min. The sequence was repeated 10 times; the IR spectrum indicated the end of the reaction. After solvent evaporation, the stannylidene derivative was used in the next reaction without further purification.

General procedure for the preparation of protected gemini surfactants linked through O-2. Succinyl chloride (23 µL, 0.20 mmol) and Et_3N (52 µL, 0.36 mmol) were added to a stirring solution of **8** (234 mg) in toluene (0.7 mL) at 0°C. The resulting mixture was stirred for 20 min. The crude product was purified by preparative TLC (silica gel) using cyclohexane/EtOAc (75:25, vol/vol) to afford the protected gemini surfactant as a colorless syrup.

1,4-Bis-[2-O-(dodecyl/tetradecyl 4,6-O-benzylidene-α-D-glucopyranosid)] succinate (9). Colorless oil (107 mg, 65% yield). HPTLC (SiO_2): R_f = 0.20 (cyclohexane/EtOAc, 8:2, vol/vol). $[\alpha]_D$ +118.0° (*c* 1.1, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,469.7 (OH), 2,923.9 (CH_2), 1,739.7 (CO), 756.1, 698.2 (Ph). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.52–7.31 (m, 10 H, H_{ar}), 5.54 (s, 2 H, C*H*Ph), 5.03 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 4.77 (dd, 2 H, $J_{2,3}$ = 9.5 Hz, H-2, H-2'), 4.27 (dd, 2 H, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 9.1 Hz, H-6a, H-6a'), 4.20 (t, 2 H, $J_{3,4}$ = 9.5 Hz, H-3, H-3'), 3.85 (dd, 2 H, $J_{5,6b}$ 4.4 Hz, H-6b, H-6b'), 3.78–3.61 (m, 4 H, CH_2CH_aO, H-5, H-5'), 3.54 (t, 2 H, H-4, H-4'), 3.40 (dt, 2 H, J = 6.6 Hz, J_{gem} = 9.9 Hz, CH_2CH_bO), 2.74 (s, 4 H, CH_2COO), 1.57 (m, 4 H, CH_2), 1.32 (bs, 38 H, CH_2), 0.88 (t, 6 H, J = 6.6 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 171.8 (–COO), 137.1 (C_{ar}), 129.1–126.3 (C_{ar}), 101.9 (CHPh), 96.4 (C-1, C-1'), 81.3 (C-4, C-4'), 74.3 (C-2, C-2'), 68.9 (C-3, C-3'), 68.6 (C-6, C-6'), 68.5 (CH_2O), 62.2 (C-5, C-5'), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2COO), 26.0, 22.6 (CH_2), 14.0 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{54}H_{82}O_{14}Na$) 977.5602, found 977.5625 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{56}H_{86}O_{14}Na$) 1,005.5915, found 1,005.5948 $[M + Na]^+$.

1,5-Bis-[2-O-(dodecyl/tetradecyl 4,6-O-benzylidene-α-D-glucopyranosid)] glutarate (10). Colorless oil (102 mg, 62% yield). HPTLC (SiO_2): R_f = 0.23 (cyclohexane/EtOAc, 8:2, vol/vol). $[\alpha]_D$ +98.1° (*c* 1.0, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,479.4 (OH), 2,924.8 (CH_2), 1,739.5 (CO), 752.2, 698.4 (Ph). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 7.49–7.30 (m, 10 H, H_{ar}), 5.53 (s, 2 H, C*H*Ph), 5.03 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 4.77 (dd, 2 H, $J_{2,3}$ = 9.5 Hz, H-2, H-2'), 4.27 (dd, 2 H, $J_{5,6a}$ = 4.0 Hz, $J_{6a,6b}$ = 9.5 Hz, H-6a, H-6a'), 4.17 (t, 2 H, $J_{3,4}$ = 9.2

Hz, H-3, H-3'), 3.83 (dd, 2 H, $J_{5,6b}$ = 4.4 Hz, H-6b, H-6b'), 3.78–3.59 (m, 4 H, H-5, H-5', CH_2CH_aO), 3.53 (t, 2 H, H-4, H-4'), 3.39 (dt, 2 H, J = 6.6 Hz, J_{gem} = 9.9 Hz, CH_2CH_bO), 3.07 (bs, 2 H, OH), 2.50 (m, 4 H, CH_2COO), 2.03 (m, 2 H, CH_2CH_2COO), 1.57 (m, 4 H, CH_2), 1.32 (bs, 38 H, CH_2), 0.88 (t, 6 H, J = 6.6 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 172.7 (COO), 137.1 (C_{ar}), 129.1–126.2 (C_{ar}), 101.8 (CHPh), 96.5 (C-1, C-1'), 81.4 (C-4, C-4'), 73.7 (C-2, C-2'), 68.9 (C-3, C-3'), 68.5 (C-6, C-6'), 68.4 (CH_2O), 62.1 (C-5, C-5'), 32.5 (CH_2COO), 31.9 (CH_2), 29.6, 29.3, 26.0, 22.6 (CH_2), 20.1 (CH_2CH_2COO), 14.0 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{55}H_{84}O_{14}Na$) 991.5759, found 991.5790 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{57}H_{88}O_{14}Na$) 1,019.6072, found 1,019.6088 $[M + Na]^+$.

– *Bis-[2-O-(dodecyl/tetradecyl 4,6-O-benzylidene-α-D-glucopyranosid)] terephthalate (11).* Colorless oil (74 mg, 58% yield). HPTLC (SiO_2): R_f = 0.42 (cyclohexane/EtOAc, 8:2, vol/vol). $[\alpha]_D$ + 96.7° (*c* 0.8, $CHCl_3$). IR (film) ν_{max} (cm^{-1}): 3,344.0 (OH), 2,924.8 (CH_2), 1,724.3 (CO), 761.6, 730.0, 698.3 (Ph). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ (ppm): 8.16 (s, 4 H, H_{ar}), 7.54–7.33 (m, 10 H, H_{ar}), 5.58 (s, 2 H, CHPh), 5.17 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 5.05 (dd, 2 H, $J_{2,3}$ = 9.5 Hz, H-2, H-2'), 4.38 (t, 2 H, $J_{3,4}$ = 9.5 Hz, H-3, H-3'), 4.32 (dd, 2 H, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 9.9 Hz, H-6a, H-6a'), 3.93 (dd, 2 H, $J_{5,6b}$ = 4.4 Hz, H-6b, H-6b'), 3.78 (t, 2 H, H-4, H-4'), 3.73–3.58 (m, 4 H, H-5, H-5', CH_2CH_aO), 3.39 (dt, 2 H, J = 6.6 Hz; J_{gem} = 9.9 Hz, CH_2CH_bO), 2.50 (bs, 2 H, OH), 1.56 (m, 4 H, CH_2), 1.28 (bs, 38 H, CH_2), 0.87 (t, 6 H, J = 6.6 Hz, CH_3). ^{13}C NMR (50.1 MHz, $CDCl_3$), δ (ppm): 165.3 (COO), 137.0, 133.7 (C_{ar}), 129.8–128.3, 126.3 (C_{ar}), 102.0 (CHPh), 96.5 (C-1, C-1'), 81.5 (C-4, C-4'), 74.5 (C-2, C-2'), 68.8 (C-3, C-3'), 68.6 (C-6, C-6', CH_2O), 62.1 (C-5, C-5'), 31.9, 29.6, 29.3, 29.2, 26.0, 22.6 (CH_2), 14.0 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{58}H_{82}O_{14}Na$) 1,025.5602, found 1,025.5590 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{60}H_{86}O_{14}Na$) 1,053.5915, found 1,053.5878 $[M - Na]^+$.

General procedure for deprotection of gemini surfactants linked through O-2. A solution of the protected gemini surfactant (0.070 mmol) in EtOAc/MeOH/HOAc (2:1:1, by vol, 14 mL) was hydrogenated and worked up as described for gemini surfactants linked through *O*-6.

1,4-Bis-[2-O-(dodecyl/tetradecyl α-D-glucopyranosid)] succinate (12). Colorless oil (42 mg, 95% yield). HPTLC (SiO_2): R_f = 0.48 (EtOAc/MeOH, 25:1, vol/vol). $[\alpha]_D$ +79.9° (*c* 1.9, MeOH). IR (film) ν_{max} (cm^{-1}): 3,421.4 (OH), 2,923.1 (CH_2), 1,733.8 (CO), 1,049.2 (C-O, ether). ^{1}H NMR (200.1 MHz, methanol-*d*), δ (ppm): 5.00 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 4.62 (dd, 2 H, $J_{2,3}$ = 9.9 Hz, H-2, H-2'), 3.89 (dd, 2 H, $J_{3,4}$ = 8.8 Hz, H-3, H-3'), 3.83–3.69 (m, 6 H, H-4, H-4', H-6a, H-6'a, H-6b, H-6'b), 3.63 (m, 2 H, H-5, H-5'), 3.44 (dt, 4 H, J = 6.6 Hz, J_{gem} = 9.9 Hz, CH_2O), 2.75 (s, 4 H, CH_2COO), 1.97 (bs, 4 H, OH), 1.62 (m, 4 H, CH_2), 1.34 (bs, 38 H, CH_2), 0.94 (t, 6 H, J = 6.6 Hz; CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ (ppm): 173.7 (COO), 97.2 (C-1, C-1'), 75.4 (C-2, C-2'), 73.5 (C-3, C-3'), 72.4(C-5, C-5'), 71.8 (C-4, C-4'), 69.1 (CH_2O), 62.5 (C-6, C-6'), 33.0, 30.8, 30.5 (CH_2), 29.9 (CH_2COO), 27.3, 23.7 (CH_2), 14.4 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{40}H_{74}O_{14}Na$) 801.4976, found 801.4991 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{42}H_{78}O_{14}Na$) 829.5289, found 829.5273 $[M + Na]^+$.

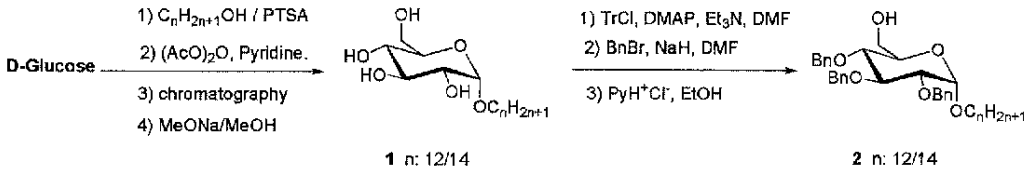
1,5-Bis-[2-O-(dodecyl/tetradecyl-α-D-glucopyranosid)] glutarate (13). Colorless oil (55 mg, 99% yield). HPTLC (SiO_2): R_f = 0.50 (EtOAc/MeOH, 25:1, vol/vol). $[\alpha]_D$ +83.9° (*c* 0.8, MeOH). IR (film) ν_{max} (cm^{-1}): 3,431.2 (OH), 2,924.1 (CH_2), 1,733.8 (CO), 1,034.7 (C-O, ether). ^{1}H NMR (200.1 MHz, methanol-*d*), δ (ppm): 5.00 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 4.62 (dd, 2 H, $J_{2,3}$ = 9.9 Hz, H-2, H-2'), 3.88 (dd, 2 H, $J_{3,4}$ = 8.8 Hz, H-3, H-3'), 3.79–3.69 (m, 6 H, H-4, H-4', H-6a, H-6'a, H-6b, H-6'b), 3.61 (m, 2 H, H-5, H-5'), 3.45 (dt, 4 H, J = 4.4 Hz; J_{gem} = 9.1 Hz, CH_2O), 2.52 (t, 4 H, J = 7.0 Hz, CH_2COO), 2.04–1.96 (m, 6 H, CH_2CH_2COO, OH), 1.62 (s, 4 H, CH_2), 1.34 (bs, 38 H, CH_2), 0.94 (t, 6 H, J = 6.6 Hz, CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ (ppm): δ 174.3 (COO), 97.1 (C-1, C-1'), 75.1 (C-2, C-2'), 73.5 (C-3, C-3'), 72.4 (C-5, C-5'), 71.8 (C-4, C-4'), 68.9 (CH_2O), 62.5 (C-6, C-6'), 33.9 (CH_2COO), 33.0, 30.8, 30.5, 30.4, 27.3, 23.7 (CH_2), 21.3 (CH_2CH_2COO), 14.4 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{41}H_{76}O_{14}Na$) 815.5133, found 815.5092 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{43}H_{80}O_{14}Na$) 843.5446, found 843.5427 $[M - Na]^+$.

Bis-[2-O-(dodecyl/tetradecyl-α-D-glucopyranosid)] terephthalate (14). Colorless oil (52 mg, 90% yield). HPTLC (SiO_2): R_f = 0.43 (EtOAc/MeOH, 25:1, vol/vol). $[\alpha]_D$ +62.7° (*c* 2.4, MeOH). IR (film) ν_{max} (cm^{-1}): 3,420.9 (OH), 1,717.3 (CO), 1,030.7 (C-O, ether), 732.9 (Ph). ^{1}H NMR (200.1 MHz, methanol-*d*), δ (ppm): 8.19 (s, 4 H, H_{ar}), 5.12 (d, 2 H, $J_{1,2}$ = 3.7 Hz, H-1, H-1'), 4.83 (dd, 2 H, $J_{2,3}$ = 9.9 Hz, H-2, H-2'), 4.02 (dd, 2 H, $J_{3,4}$ = 8.8 Hz, H-3, H-3'), 3.83–3.64 (m, 6 H, H-6a, H-6'a, H-6b, H-6'b, CH_2CH_aO), 3.50–3.36 (m, 6 H, H-4, H-4', H-5, H-5', CH_2CH_bO), 1.53 (m, 4 H, CH_2), 1.28 (bs, 38 H, CH_2), 0.90 (t, 6 H, J = 6.6 Hz, CH_3). ^{13}C NMR (50.1 MHz, methanol-*d*), δ (ppm): 166.7 (COO), 135.4, 130.8 (C_{ar}), 97.1 (C-1, C-1'), 76.1 (C-2, C-2'), 73.6 (C-3, C-3'), 72.5 (C-5, C-5'), 71.8 (C-4, C-4'), 68.9 (CH_2O), 62.5 (C-6, C-6'), 33.0, 30.7, 30.4, 27.2, 23.7 (CH_2), 14.4 (CH_3). HRMS (FAB) *m/z* calcd. ($C_{44}H_{74}O_{14}Na$) 849.4976, found 849.4986 $[M + Na]^+$. HRMS (FAB) *m/z* calcd. ($C_{46}H_{78}O_{14}Na$) 877.5289, found 877.5250 $[M + Na]^+$.

RESULTS AND DISCUSSION

Alkyl α-D-glucopyranosides were easily obtained by a well-established procedure: Fischer glycosylation, acetylation, chromatographic separation, and deacetylation (14–16). Following this protocol, dodecyl/tetradecyl-α-D-glucopyranoside (1) was obtained using a commercially available alcohol mixture (C_{12}/C_{14}, 7:3 ratio) as starting material.

The sequence tritylation-benzylation-detritylation (Scheme 1) gave the dodecyl/tetradecyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2). These three steps can be performed without intermediate purification; only workup procedures were included between each reaction, and the overall preparation requires a unique final chromatographic purification.



SCHEME 1. PTSA, *p*-toluenesulfonic acid; DMAP, 4-dimethylaminopyridine; TrCl, trityl chloride; DMF, dimethylformamide; PyH^+Cl^-, pyridinium chloride.

This simple synthetic strategy allowed us to prepare a dimeric compound reacting **2** with succinyl dichloride and triethylamine in toluene (compound **3**). Final smooth catalytic hydrogenation lead to 1,4-bis-[6-*O*-(dodecyl/tetradecyl α-D-glucopyranosid)] succinate (**4**) (Scheme 2).

The product composition was analyzed by mass spectrometry. It is important to point out that the dimer C_{14}/C_{14} was not detected. The major component of product **3** was, as expected, the C_{12}/C_{12} dimer (m/z 1,336.8 $[M + NH_4]^+$), arising from the major component of the alcohol mixture. The minor dimer obtained, as shown by MS, was a non-symmetric molecule, composed of a C_{12} monomer connected to a C_{14} monomer (m/z 1,364.8 $[M + NH_4]^+$). After deprotection of benzyl groups, signals at m/z 801.5 (C_{12}/C_{12}, $[M + Na]^+$) and 829.5 (C_{12}/C_{14}, $[M + Na]^+$) were detected on MS spectra of compound **4**. The dimers C_{12}/C_{12} and C_{12}/C_{14} could not be separated by chromatographic methods, and the mixture was analyzed for interfacial properties as a unique sample.

From compound **2**, an additional dimeric compound was prepared using glutaryl dichloride leading to protected dimer **5**, and the final gemini surfactant 1,5-bis-[6-*O*-(dodecyl/tetradecyl α-D-glucopyranosid)] glutarate (**6**) (Scheme 2). This compound was prepared to study the effect of the spacer chain length on interfacial properties.

Previous results (22) on gemini surfactants prepared from butyl α-D-glucopyranoside suggested that a change in the position of linking from *O*-6 to *O*-2 leads to products with improved interfacial properties.

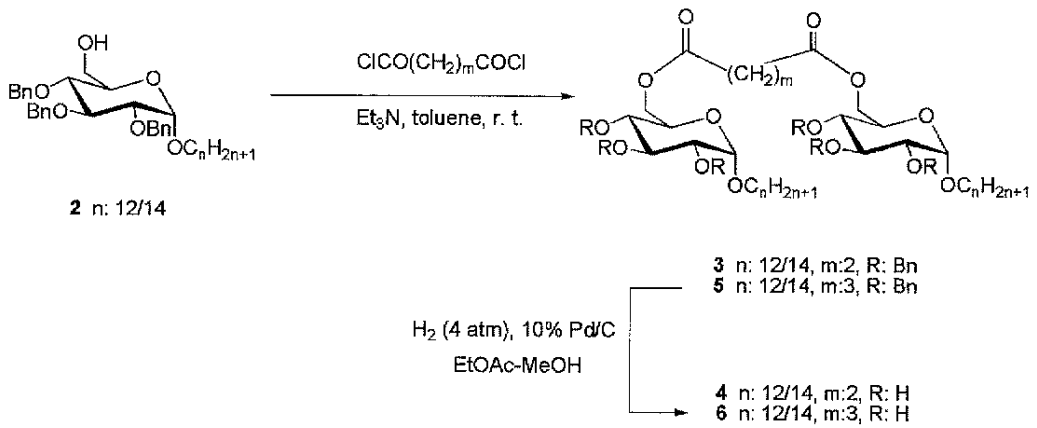
The same strategy was applied as was previously developed (14–16) for butyl α-D-glucopyranoside to compound **1**. Thus, positions 4 and 6 of starting glucoside **1** were protected as the benzylidene derivative **7**, and the 2-hydroxyl was activated through the stannylidene **8** (Scheme 3).

When compound **8** was reacted in parallel with succinyl, glutaryl, and terephthaloyl dichlorides, the dimers **9**, **10**, and **11** were isolated (Scheme 4). After hydrogenation 1,4-bis-[2-*O*-(dodecyl/tetradecyl α-D-glucopyranosid)] succinate (**12**), 1,5-bis-[2-*O*-(dodecyl/tetradecyl α-D-glucopyranosid)] glutarate (**13**), and bis-[2-*O*-(dodecyl/tetradecyl α-D-glucopyranosid)] terephthalate (**14**), respectively, were obtained. The rigid aromatic spacer was used only for the dimer linked through *O*-2, because the corresponding *O*-6 dimer previously prepared from butyl-α-D-glucopyranoside was insoluble in water, whereas the isomeric *O*-2 dimer was soluble (14–16,22).

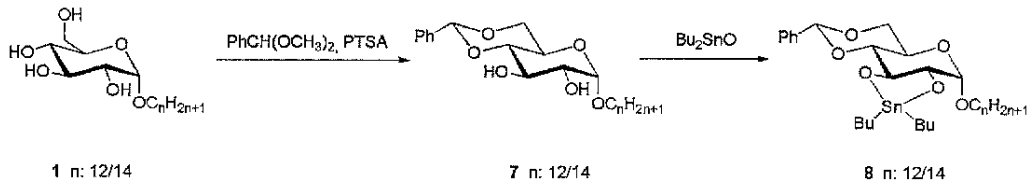
Dimeric compounds **6**, **12**, **13**, and **14** showed by MS that they are composed by mixtures of homodimers (C_{12}/C_{12}) and heterodimers (C_{12}/C_{14}), as observed for compound **4**.

This new family of sugar-based surfactants was analyzed for its interfacial properties, as shown in Table 1. Short-chain dimers obtained from butyl α-D-glucopyranoside as well as medium- and long-chain dimers obtained from octyl, dodecyl, and tetradecyl α-D-glucopyranosides are included for comparison (22). Properties of the terephthaloyl derivative **14** could not be determined because it was water-insoluble.

Conversely, a synergistic effect was observed (23) when dodecyl/tetradecyl glucoside (**1**) was employed as starting material in comparison with pure dodecyl glucoside and tetrade-

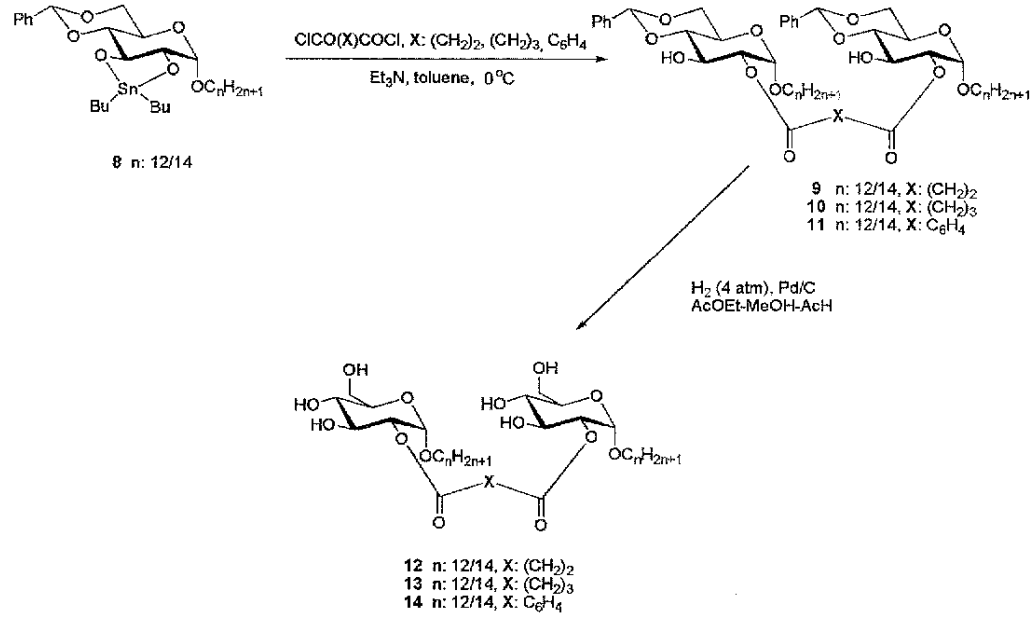


SCHEME 2



1 n: 12/14 **7** n: 12/14 **8** n: 12/14

SCHEME 3



8 n: 12/14

9 n: 12/14, X: $(CH_2)_2$
10 n: 12/14, X: $(CH_2)_3$
11 n: 12/14, X: C_6H_4

12 n: 12/14, X: $(CH_2)_2$
13 n: 12/14, X: $(CH_2)_3$
14 n: 12/14, X: C_6H_4

SCHEME 4

cyl glucoside derivatives, as shown in Table 1. Synergistic effects have been previously reported for anionic surfactants in surface tension reduction, especially when mixed with nonionic surfactants (21).

A synergistic effect is displayed when the CMC in aqueous medium of any mixture of two surfactants is smaller than that of either individual surfactant. It is apparent that synergism in surface tension reduction effectiveness can occur only when the attractive interaction between the two surfactants in the mixed monolayer at the aqueous solution–air interface is stronger than that in the mixed micelle in the solution phase. The relation between synergism in the fundamental

TABLE 1
Interfacial Properties of Alkyl Glucoside-based Gemini Surfactants[a]

Alkyl chain	Spacer (linkaged)	Compound	CMC (mM)	γ_{CMC} (mN/m)	$\Delta G°_{mic}$ (kJ/mol)	$\Delta G°_{ads}$ (kJ/mol)	pC_{20}	CMC/C_{20}	HLB
4	Succinyl (O-2)		2.0	44.4	−25.3	−35.5	2.9	1.6	16.8
4	Glutaryl (O-2)		3.1	51.7	−24.3	−34.2	2.4	1.5	16.2
4	Terephthal. (O-2)		9.7	47.1	−21.4	−33.2	2.2	1.5	15.3
4	Succinyl (O-6)		8.7	46.7	−22.2	−34.7	2.5	2.2	16.8
4	Glutaryl (O-6)		9.6	40.5	−20.7	−32.3	2.3	2.9	16.2
8	Succinyl (O-6)		1.8	39.1	−25.7	−36.8	3.0	1.9	13.5
12	Succinyl (O-6)		3.4	46.7	−24.0	−34.9	2.6	1.3	11.6
14	Succinyl (O-6)		2.6	54.4	−24.7	−33.3	2.5	0.8	10.8
12/14	Succinyl (O-6)	4	1.3	41.7	−26.4	−40.0	3.3	2.5	11.4
12/14	Glutaryl (O-6)	6	1.6	37.2	−25.9	−38.7	3.3	2.8	11.4
12/14	Succinyl (O-2)	12	1.8	45.5	−25.6	−37.8	2.9	1.5	11.4
12/14	Glutaryl (O-2)	13	2.4	42.5	−24.9	−36.5	2.9	1.7	11.4

[a]CMC, Critical micelle concentration; γ_{CMC}, surface tension at CMC; $\Delta G°_{mic}$, Gibbs energy of micellization; $\Delta G°_{ads}$, Gibbs energy of adsorption; pC_{20}, $-\log C_{20}$ where C_{20} = concentration of surfactant to reduce 20 dyn/cm the surface tension of the solution; HLB, hydrophilic lipophilic balance.

properties of mixed monolayer formation at an interface or mixed micelle formation in solution and synergism in various practical applications of surfactants is still a relatively unexplored area. Some studies have explored this area, but much remains to be known (24).

Compound **4** is not exactly a mixture of 1,4-bis-[6-*O*-(dodecyl α-D-glucopyranosid)] succinate and 1,4-bis-[6-*O*-(tetradecyl α-D-glucopyranosid)] succinate, but a mixture of the former and a heterodimer C_{12}-succinyl-C_{14}. Nevertheless, the supposition of synergistic effect still applies, because compound **4** is in fact composed by two different dimeric compounds.

Compounds **4** and **6** with succinyl and glutaryl as spacer, respectively, and linked through *O*-6 have shown almost the same CMC value (1.3 mM and 1.6 mM), and these values are 7-fold lower than those of compounds prepared from butyl α-D-glucopyranoside (22) (7.2 and 13.1 mM, respectively; see Table 1). The change in the linkage position of the carbohydrate moiety from *O*-6 to *O*-2 produces a relatively small effect in the CMC values in contrast with the results obtained for the butyl series. In these short-chain dimers, a decrease in CMC values has been observed for the 2-*O*-linked derivatives that was explained on the basis of a more ordered conformation (22).

The Gibbs energy of micellization (ΔG^{o}_{mic}) and the Gibbs energy of adsorption (ΔG^{o}_{ads}) were almost identical in both series. Similar behavior was observed in pC_{20} values and CMC/C_{20} values.

The fact that no significant differences were observed in the interfacial properties of *O*-6 and *O*-2 linked dimers suggests that it is not necessary to perform selective protection of hydroxyl groups of the sugar moiety, and the synthesis can be simplified.

The highest CMC value was observed for the butyl derivative and the lowest for the dodecyl/tetradecyl derivative (**4**, Table 1). Disappointingly, the CMC of this compound was only slightly lower than the CMC of the octyl derivative. Thus, for long-chain dimers the CMC values observed are relatively high. In monomeric surfactants, the CMC values decrease continuously with the addition of a methylene group to the alkyl chain, but when the number of carbon atoms approaches 16, this effect is no longer observed. For long chains, there is a transition to a coiled state over certain chain lengths, as a result of hydrophobic bonding between parts of the chain itself (self-coiling) (25). For dimeric surfactants, the number of carbon atoms at which the coiled state is reached could be lower, because of the presence of two alkyl chains. An alternative explanation might be the formation of submicellar aggregates such as dimers or tetramers (26,27).

Another possible explanation of the experimental results may be based on the modification observed in the interfacial properties of conventional anionic surfactants when the polar head is moved from the normal position (at the end of the molecule) to the center (28). The shift of the polar head from the end to the middle of the surfactant molecule is the reason for the loss of effectiveness. Gemini surfactants with long alkyl chains (**4**, **6**, **12**, **13**, and **14**) have their polar heads relatively close and centered compared with the sugar-based gemini surfactants with butyl chain as hydrophobic moiety. These sugar-based dimers can be considered as surfactants with 24–26 carbon atoms in their hydrophobic tails and one big polar head in the middle of the structure. Therefore, the water network distortion produced by the gemini surfactants will be a consequence of the alkyl moieties and will be independent of the hydrophilic moieties present in the molecule. Under the conditions described in this study, the occurrence of premicellar aggregates and self-coiling is highly probable. Moreover gemini surfactants with long alkyl chains are less soluble than their butyl counterparts because the great polar head present in the center of this kind of molecule produces a smaller effect on the solubility of the surfactant. In the butyl series (14–16,22), the relative position of the two polar heads is adequate for a gemini surfactant. Conversely, for longer alkyl chains, the two sugar moieties are too close with the short spacers used, and the whole molecule can be seen macroscopically as a monomeric surfactant carrying only one polar head and two alkyl chains.

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