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Synthesis and Surface and Antimicrobial Properties of Novel Cationic Surfactants

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Received April 25, 2000

A series of surfactants with tuned polarity were prepared, including a new class of compounds: gluco-pyridinium surfactants. Pure anomers were obtained by chromatographic separation. The conductivity and surface tension of surfactant solutions in water were measured, and provided interesting information regarding their aggregation behavior. Peculiarities were observed in the premicellar range. Tensidic parameters correlated with antimicrobial activity. A few parameters, mainly the hydrophobicity of the headgroup, may play a role in finding more efficient antimicrobial structures.

Introduction

Although cationic surfactants comprise only a small portion of the surfactant market, their importance in practical applications continues to grow. They are used in antibacterials,[1,2] liquid crystals,[3] oil recovery,[4] road repair,[5] mineral flotation,[6] protection of metals from corrosion,[7] and other aspects of materials science.[8] Both fundamental and applied studies on cationic surfactants have been reported.[1,2,4,9−12] Among the cationic surfactants, pyridinium salts are a peculiar class, and their surface properties and characteristics have been thoroughly studied. In particular, Engberts and co-workers have extensively studied the behavior of 1-alkyl-4-alkylpyridinium iodides,[13−16] a set of surfactants which have also captured our interest. Furthermore, compounds with a tail at nitrogen have found practical use in the delivery of DNA into cells.[17]

The aims of the present work were (i) to synthesize new cationic surfactants with headgroups of tuned polarity, (ii) to determine their surface properties, and (iii) to evaluate their antibacterial properties, with the goal of identifying a relationship between surface and biological properties.

The growing importance of alkylpolyglucosides as surfactants,[18] and their excellent ecological properties,[19,20] have suggested the synthesis of a new class of compounds, i.e., gluco-cationic surfactants. Therefore, a glucose moiety was inserted in the surfactant molecule, thus modifying the headgroup polarity.

Experimental Section

General Procedures and Materials. Melting points were taken on a hot plate equipped with a microscope and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6, using the DMSO signal as a reference (2.52 ppm, ^{1}H), except for compounds **3**α and

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10.1021/jo0006425 CCC: $19.00 © 2000 American Chemical Society
Published on Web 10/28/2000

3β, whose NMR spectra were recorded in D_2O using HCOONa as an internal reference. UV spectra were recorded in ethanol 95%. Optical rotations were measured at 20 °C and 578 nm. TLC was performed on silica gel 60 F_{254} plates using as eluents (A) BAW: butanol/acetic acid/water 40:10:50 (organic phase), (B) chloroform/methanol/acetic acid 85:10:5, and (C) chloroform/methanol/acetic acid 70:20:10. Chromatographic purification was carried out by flash chromatography (FC)[21] or medium-pressure liquid chromatography (MPLC) using the eluents B and C shown above for TLC. A strong anionic exchanger and a weak anionic exchanger were used. The silica gel for FC and for MPLC were 40−63 and 15−40 μm, respectively. The glassware was carefully dried, assembled, and purged with argon. 4-Methylpyridine, 4-methylquinoline, undecyl bromide, dodecyl bromide, 1,3-dibromopropane, and triethylamine were carefully distilled before use. Benzyldimethyldodecylammonium bromide (**7**) was freeze-dried and repeatedly crystallized from acetone. 4-Dodecylpyridine and 3-bromopropyltriethylammonium bromide were synthesized as described in the literature.[22−24] MilliQ-purified water (conductivity: 0.05 μS; surface tension: 72.8 mN/m) was used for anionic exchange and in the surface tension and conductivity measurements.

4-(*n*-Dodecyl)-*N*-(*N*′-(3-propyl)triethylammonium)pyridinium Dibromide (1). 4-(*n*-Dodecyl)pyridine (147 g, 0.59 mol) and 3-bromopropyltriethylammonium bromide[24] (18 g, 0.059 mol) were dissolved in 400 mL of dry acetone, refluxed under magnetic stirring for 7 h, and then kept overnight at room temperature. The crude solid was collected and repeatedly crystallized from 2-butanone. Yield: 27.6 g (85%). White solid. Mp: 182−184 °C. R_f: 0.23 (eluent A). UV (ethanol): λ_{max} 256 nm, logϵ 3.63. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, CH_3), 1.21 (t, 9H, 3 CH_3), 1.26 (broad, 18H, 9CH_2), 1.67 (m, 2H, CH_2-CH_2Py), 2.33 (m, 2H, $CH_2CH_2N^+C_5H_5$), 2.91 (t, 2H, CH_2Py), 3.29 (m, 8H, 4 CH_2N^+), 4.65 (t, 2H, $CH_2N^+C_5H_5$), 8.10 (d, 2H, 2Hβ), 9.07 (d, 2H, 2Hα). FAB/MS: (glycerol), 389 [M − H]$^+$. Anal. Calcd for $C_{26}H_{50}Br_2N_2$: C, 56.73; H, 9.15; N, 5.09. Found: C, 56.42; H, 9.29; N, 5.23.

***N*-(Tetra-*O*-acetyl-α-D-glucopyranosyl)-4-dodecylpyridinium Bromide (2α) and *N*-(Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-4-dodecylpyridinium Bromide (2*β*). Method A.** α-Acetobromoglucose (20 g, 0.048 mol), phenol (19.28 g, 0.204 mol), and 4-(*n*-dodecyl)pyridine (14 g, 0.056 mol) were dissolved in 160 mL of dry acetonitrile. The solution was kept under an argon atmosphere, stirred and refluxed for 4 h, and then kept overnight at room temperature. A white solid, isolated by filtration, was identified as 4-(*n*-dodecyl)pyridinium hydrobromide. The solution was evaporated under vacuum to give a brown syrup. The syrup was washed well with diethyl ether and purified by FC on silica gel, using a gradient elution from acetone to acetone/methanol 4:1. The resulting yellow-orange oil (21.9 g, yield: 71%) was identified as a mixture of **2**α and **2**β in a ratio of 20:80, as measured by integration of the anomeric NMR peaks (**2**α 6.27 ppm, **2**β 6.73 ppm).

Method B. 4-(*n*-Dodecyl)pyridine (40 g, 0.161 mol) and didodecyldimethylammonium bromide (11.10 g, 0.024 mol) were heated at 65 °C and stirred under an argon atmosphere. When the ammonium salt was completely dissolved, α-acetobromoglucose (10 g, 0.024 mol) was added. The solution was kept at the same temperature for 6 h, after which time a solid had separated. The solid was collected by filtration, washed with diethyl ether, and dissolved in acetone (300 mL). The white residue, identified as a mixture of didodecyldimethylammonium bromide and 4-(*n*-dodecyl)pyridinium hydrobromide, was filtered off. Acetone was removed under vacuum and the resulting syrup was purified by FC on silica gel with acetone and acetone/methanol 9:1. The resulting yellow-orange oil (11.35 g, yield: 72%) was identified as a mixture of **2**α and **2**β in a ratio of 80:20.

Method C. 4-(*n*-Dodecyl)pyridine (6.92 g, 0.028 mol) and α-acetobromoglucose (10 g, 0.024 mol) were dissolved in 50 mL of dry acetonitrile. The solution was heated at reflux with stirring under an inert atmosphere (argon) for 6 h, and the crude product was then worked up as indicated in method A. The resulting yellow-orange oil (11.02 g, 70%) consisted of an equimolecular mixture of **2**α and **2**β.

The anomeric mixtures resulting from methods A−C were separated quantitatively either by FC or by MPLC on silica gel (column diameter 7 cm; column height 20 cm for FC and 35 cm for MPLC). The eluent B was used. After evaporation of the solvents, the samples were dissolved in chloroform/methanol and precipitated with diethyl ether, and this procedure was repeated. The resulting solids were freeze-dried and stored in a desiccator.

2α. R_f: 0.59 (eluent A); 0.43 (eluent B). Mp: 155−157 °C. UV (ethanol): λ_{max} 256 nm, log ϵ 3.59. $[\alpha]^{20}_{578} = +25.2°$ (c = 0.68, methanol). ^{1}H NMR (DMSO-d_6) (H_1−H_6 refers to glucosidic protons, assigned by ^{1}H−^{1}H COSY experiment): δ 0.87 (t, 3H, CH_3), 1.27 (broad, 18H, 9CH_2), 1.69 (m, 2H, CH_2CH_2-Py$^+$), 1.91, 2.07, 2.11, 2.19 (4 singlets, 3H each, 4 CH_3CO), 2.94 (t, 2H, CH_2Py$^+$), 4.45 (t, 2H, H_6), 4.73 (m, 1H, H_5), 5.01 (q, 1H, H_4), 5.22 (t, 1H, H_3), 5.54 (t, 1H, H_2), 6.73 (d, $J_{1,2}$ = 2.93 Hz, 1H, H_1), 8.12 (d, 2H, 2Hβ), 9.07 (d, 2H, 2Hα). FAB/MS: (glycerol), 578 [M]$^+$. Anal. Calcd for $C_{31}H_{48}BrNO_9$: C, 56.53; H, 7.35; N, 2.13. Found: C, 56.80; H, 7.06; N, 2.08.

2*β*. R_f: 0.63 (eluent A), 0.34 (eluent B). Mp: 113−115 °C. UV (ethanol) λ_{max} 256 nm, log ϵ 3.63. $[\alpha]^{20}_{578} = -16.5°$ (c = 0.83, methanol). ^{1}H NMR (DMSO-d_6) (H_1−H_6 refers to glucosidic protons, assigned by ^{1}H−^{1}H COSY experiment): δ 0.86 (t, 3H, CH_3), 1.27 (broad, 18H, 9 CH_2), 1.68 (m, 2H, CH_2CH_2-Py$^+$), 1.88, 2.00, 2.04, 2.07 (4 singlets, 3H each, 4 CH_3CO), 2.95 (t, 2H, CH_2Py$^+$), 4.21 (m, 2H, H_6), 4.43 (m, 1H, H_5), 5.42 (t, 1H, H_4), 5.65−5.55 (m, 2H, H_2+H_3), 6.27 (d, $J_{1,2}$ = 7.93 Hz, 1H, H_1), 8.15 (d, 2H, 2Hβ), 9.19 (d, 2H, 2Hα). FAB/MS: (glycerol), 578 [M]$^+$. Anal. Calcd for $C_{31}H_{48}BrNO_9$: C, 56.53; H, 7.35; N, 2.13. Found: C, 56.49; H, 7.26; N, 2.16.

4-(*n*-Dodecyl)-*N*-(α-D-glucopyranosyl)pyridinium Bromide (3α) and 4-(*n*-Dodecyl)-*N*-(*β*-D-glucopyranosyl)pyridinium Bromide (3*β*). The equimolecular mixture **2**α/**2**β or the purified anomers (9.0 g, 0.014 mol) were dissolved in 50% aqueous ethanol (180 mL). Hydrobromic acid 48% was added (12 g, 8.05 mL). The solution was heated at 50 °C and stirred for 3 days. The solution was then evaporated under vacuum, and excess hydrobromic acid was removed by dissolving the crude product in water and eluting the solution through a weak basic ionic exchanger (Duolite A-368; 5−10 equiv with regard to the hydrobromic acid) using water as an eluent. By evaporation under vacuum and subsequent freeze-drying, a fluffy pale yellow solid was obtained (5.30 g, yield: 79%). However, this was highly hygroscopic and rapidly changed to a wax. The two anomers were separated by the same procedures as for **2**α and **2**β using the eluent (C). The anomer **3**α, which was waxlike, did not melt at a definite temperature.

3α. R_f: 0.32 (eluent C). UV (ethanol): λ_{max} 256 nm; log ϵ 3.59. $[\alpha]^{20}_{578} = +21.1°$ (c = 0.59, methanol). ^{1}H NMR (D_2O): δ 0.88 (t, 3H, CH_3), 1.30 (broad, 18H, 9 CH_2), 1.73 (m, 2H, CH_2-CH_2Py$^+$), 2.93 (t, 2H, CH_2Py$^+$), 3.77 (t, 1H), 3.88 (m, 2H), 4.08 (t, 1H), 4.33 (q, 1H), 6.44 (d, $J_{1,2}$ = 3.66, 1H, H_1), 7.99 (d, 2H, 2Hβ), 9.04 (d, 2H, 2Hα). ^{13}C NMR (D_2O): δ 166.57, 143.97, 129.54, 92.73, 80.55, 74.51, 72.33, 70.78, 62.46, 37.74, 34.14, 32.09, 32.06, 32.00, 31.67, 31.61, 31.47, 25.37, 24.79, 16.03. FAB/MS: (glycerol), 410 [M]$^+$. Anal. Calcd for $C_{23}H_{40}BrNO_5$: C, 56.32; H, 8.22; N, 2.86. Found: C, 56.04; H, 8.35; N, 2.88.

3*β*. R_f: 0.24 (eluent C). Mp: 132−134 °C. UV (ethanol) λ_{max} 256 nm, log ϵ 3.61. $[\alpha]^{20}_{578} = +18.8°$ (c = 0.63, methanol).^{1}H NMR (D_2O): δ 0.86 (t, 3H, CH_3), 1.28 (broad, 18H, 9 CH_2), 1.77 (m, 2H, $CH_2CH_2Py^+$), 3.0 (t, 2H, CH_2Py^+), 3.65−4.10 (m, 5H), 5.72 (d, $J_{1,2}$ = 8.24, 1H, H_1), 8.01 (d, 2H, 2Hβ), 8.86 (d, 2H, 2Hα).^{13}C NMR (D_2O): δ 167.33, 143.27, 129.23, 96.23, 81.21, 77.00, 75.58, 70.28, 61.99, 37.36, 33.64, 31.54, 31.48, 31.16, 31.04, 30.93, 24.30, 15.53. FAB/MS: (glycerol), 410 [M]$^+$.

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Anal. Calcd for $C_{23}H_{40}BrNO_5$: C, 56.32; H, 8.22; N, 2.86. Found: C, 56.34; H, 8.21; N, 2.80.

4-(*n*-Dodecyl)-*N*-methylpyridinium Bromide (4). To a solution of 5 g of 4-(*n*-dodecyl)pyridine (0.020 mol) in 20 mL of benzene, heated at reflux and stirred, was added methyl iodide (28.68 g, 12.6 mL, 0.20 mol) dropwise. After 6 h, the solution was allowed to cool to room temperature. A yellow solid was recovered, washed with petrol ether and crystallized first from acetonitrile and then from acetone. Yellow crystals were obtained (yield 4.2 g, 54%). R_f: 0.34 (eluent A). Mp: 120−121 °C (lit.[3] mp 112.8−113.1 °C). UV (ethanol): λ_{max} 256 nm, logϵ 3.35. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, CH_3), 1.27 (broad, 18H, $9CH_2$), 1.66 (m, 2H, $CH_2CH_2Py^+$), 2.88 (t, 2H, CH_2Py^+), 4.30 (s, 3H, $N^+ - CH_3$), 8.01 (d, 2H, 2Hβ), 8.87 (d, 2H, 2Hα). FAB/MS: (glycerol), 262 $[M]^+$. Anal. Calcd for $C_{18}H_{32}IN$: C, 55.53; H, 8.28; N, 3.60. Found: C, 55.25; H, 8.41; N, 3.49.

4-(*n*-Dodecyl)-*N*-methylpyridinium iodide (30 g, 0.077 mol) was dissolved in water and eluted through a column containing about 200 g of a strong anionic exchanger which had been previously conditioned with 10% aqueous NaBr. The eluates were evaporated under vacuum to give a waxy solid which was freeze-dried and crystallized from 2-butanone. White crystals were obtained (yield 12.8 g, 49%). R_f: 0.34 (eluent A). Mp: 115−117 °C (lit.[16] mp 106.1−109 °C). UV (ethanol): λ_{max} 256 nm; log ϵ 3.60. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, CH_3), 1.27 (broad, 18H, $9CH_2$), 1.66 (m, 2H, $CH_2CH_2Py^+$), 2.87 (t, 2H, CH_2-Py^+), 4.30 (s, 3H, CH_3), 8.00 (d, 2H, 2Hβ), 8.89 (d, 2H, 2Hα). FAB/MS: (glycerol), 262 $[M]^+$. Anal. Calcd for $C_{18}H_{32}BrN$: C, 63.15; H, 9.42; N, 4.09. Found: C, 62.91; H, 9.49; N, 3.94.

***N*-(*n*-Dodecyl)-4-methylpyridinium Bromide (5).** 4-Methylpyridine (46.57 g, 0.5 mol) and 1-bromododecane (162.01 g, 0.65 mol) were dissolved in toluene (300 mL). The solution was stirred under reflux for 12 h and then transferred to a 3 L beaker. Diethyl ether (1 L) was added to the cooled solution with stirring. The resulting solid was recovered, washed with diethyl ether, and freeze-dried. The product was crystallized from 2-butanone (yield 165.3 g, 97%). R_f: 0.36 (eluent A). Mp: 69−71 °C. UV (ethanol) λ_{max} 256 nm; logϵ 3.60. ^{1}H NMR (DMSO-d_6): δ 0.90 (t, 3H, CH_3), 1.30 (broad, 18H, $9CH_2$), 1.94 (m, 2H, $CH_2CH_2N^+C_5H_5$), 2.68 (s, 3H, CH_3), 4.61 (t, 2H, $CH_2N^+C_5H_5$), 8.07 (d, 2H, 2Hβ), 9.04 (d, 2H, 2Hα). FAB/MS: (glycerol), 262 $[M]^+$. Anal. Calcd from $C_{18}H_{32}BrN$: C, 63.15; H, 9.42; N, 4.09. Found: C, 63.22; H, 9.45; N, 4.04.

***N*-(*n*-Dodecyl)-4-methylquinolinium Bromide (6).** 1-Bromododecane (67.83 g, 0.272 mol) was heated at 120 °C with stirring. 4-Methylquinoline (32.49 g, 0.227 mol) was then added dropwise with stirring over 3 h. The solution was refluxed for 20 h. After being allowed to cool to room temperature, the sticky, crude product was dissolved in acetone and precipitated with diethyl ether. The resulting bluish solid (87.5 g, yield 98%) was repeatedly dissolved in acetone and precipitated with diethyl ether. A white powder was obtained (yield 42.7 g, 48%, after purification). R_f: 0.41 (eluent A). Mp: 95−96 °C. UV (ethanol): λ_{max} 236, 316 nm, logϵ 4.62, 3.92. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, CH_3), 1.24 (broad, 18H, $9CH_2$), 1.95 (m, 2H, $CH_2CH_2N^+C_{10}H_7$), 3.02 (s, 3H, CH_3), 5.01 (t, 2H, $CH_2N^+C_{10}H_7$), 8.05 (t, 1H, H_4), 8.08 (d, 1H, H_2), 8.27 (t, 1H, H_5), 8.57 (d, 1H, H_3), 8.62 (d, 1H, H_6), 9.42 (d, 1H, H_1). FAB/MS: (glycerol), 312 $[M]^+$. Anal. Calcd from $C_{22}H_{34}BrN$: C, 67.34; H, 8.37; N, 3.57. Found: C, 67.40; H, 8.34; N, 3.57.

Surface Tension Measurements. Surface tension was measured on a digital tensiometer 25 ± 0.1 °C, following the method of Wilhelmy.[25] The glassware used was carefully cleaned with chromosulfuric acid, washed thoroughly with MilliQ-purified water and burned on a flame. The surfactant solution was eluted through a cartridge filled with octadecyl silica gel to avoid contamination by more surface-active impurities, according to the procedure proposed by Rosen and co-workers.[26,27a] Surface tension was measured at 15-min intervals until constant values were attained.

Conductivity Measurements. Conductivity was measured on a conductivity meter equipped with a conductivity cell with a cell constant of 0.943 cm^{-1}. The solutions were thermostated in the cell at 25 ± 0.1 °C for at least 15 min and stirred with a magnetic device. Surfactant concentrations were varied by adding 20−50 μL portions of a concentrated solution of the surfactant. Concentrations were corrected for volume changes.

Results

Synthesis and Characterization of the Cationic Surfactants. The compounds synthesized in this work are shown in Chart 1. Compound **1** is a bisquaternary salt that was prepared by introducing 3-bromopropyltriethylammonium bromide to 4-dodecylpyridine.

The synthesis of compound **4**, which has been previously described,[14,16,28] was slightly modified, mainly to avoid the use of gaseous methyl bromide.

Compound **5** was synthesized by refluxing 4-methylpyridine and n-dodecyl bromide in toluene. The same method was used to obtain 1-dodecyl-4-methylquinolinium bromide (**6**). The addition of 4-methylquinoline to warm dodecyl bromide limited the decomposition of the base.

The glucosurfactants **3**α/**3**β and their acetylated precursors **2**α/**2**β were obtained by reacting 4-dodecylpyridine with α-acetobromoglucose.[29] This reaction was previously investigated, and following Lemieux and coworkers,[30−32] the mode of action is depicted in Scheme 1. The diastereoselective synthetic pathways described by Lemieux, when applied to the more hydrophobic 4-(*n*-dodecyl)pyridine, did not give satisfactory results due to the loss of diastereoselectivity. However, when the highly hydrophobic didodecyldimethylammonium bromide was used as a source of bromide anions, the **2**α anomer was appreciably enriched (**2**α/**2**β = 80:20). Similarly, using acetonitrile as a solvent in the presence of phenol, the yield of the β-anomer was enhanced (**2**α/**2**β = 20:80).

The separation of the two diastereoisomers is described in detail in the Experimental Section.

Compounds **2**−**3** remained quite stable throughout purification (neither hydrolysis nor anomerization occurred).

The NMR spectra were easily assigned, except for those of the gluco compounds **2**α, **2**β, **3**α, and **3**β. The NMR spectra of **2**α and **2**β were assigned to the respective anomers on the basis of the coupling constant values[31] ($J_{1,2}$ = 2.93 Hz for **2**α and $J_{1,2}$ = 7.93 Hz for **2**β). Compounds **3**α and **3**β were studied by both ^{1}H and ^{13}C NMR. The anomeric configuration was assigned on the basis of both the coupling constants in the ^{1}H spectra[31] ($J_{1,2}$ = 3.66 Hz for **3**α and $J_{1,2}$ =8.24 Hz for **3**β) and the chemical shift of the anomeric carbon in the ^{13}C spectra[33] (C_1 = 92.73 ppm, for **3**α and C_1 = 96.23 ppm, for **3**β). Compounds **2**α, **2**β and **3**α (**3**β gave a total superimposi-

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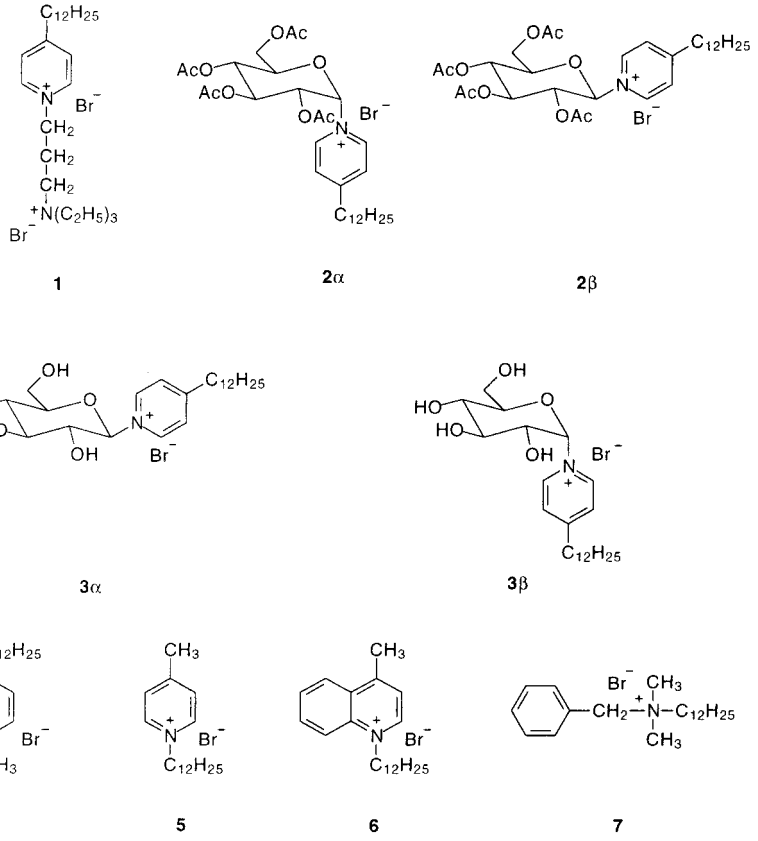
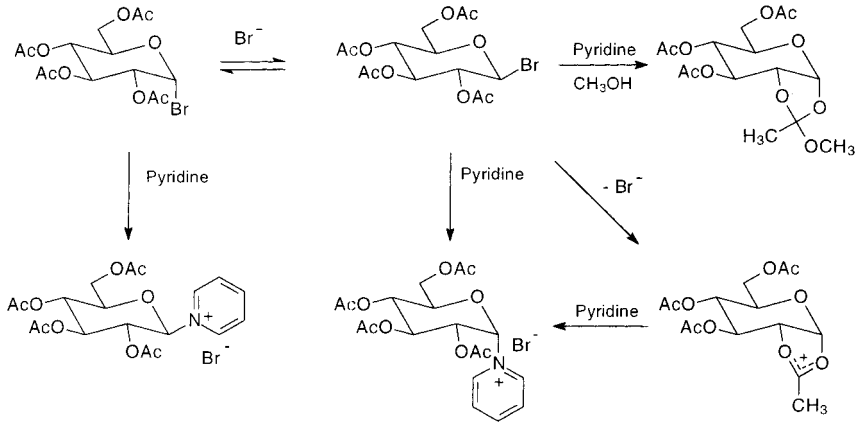
Chart I. Compounds Synthesized in the Present Work



Scheme 1. Reactivity of α-Acetobromoglucose toward the Quaternization of Pyridine



tion of the glucosidic portion) were further characterized by COSY experiments. Details for **2***β* are given in the Supporting Information.

Surface Properties. The surface properties of **1**, **3**α, **3***β*, **4**, **5**, **6** and **7**, with **7** used as a reference standard, were determined by surface tension and conductivity measurements. To obtain a careful measurement of the surface tension, the protocol described by Rosen et co-workers[26,27a] was applied, which involves the use of octadecyl silica gel cartridges to purify solutions before measurement. Very small quantities of more hydrophobic (with respect to the target surfactant) surface-active impurities readily affect the measured value of the surface tension, to give an incorrect plot of γ vs logC, in which a minimum[27a,b] occurs near the micellization point. From the plots of surface tension against the logarithm of the molar concentration, using Gibbs law (formula 1) and the treatment of data described by Rosen et al.[26]

$$\Gamma = \frac{1}{2.303nRT}\left(\frac{\partial\gamma}{\partial \log C}\right)_T \qquad (1)$$

the following parameters were obtained (Table 1): (i) cmc, the critical micellar concentration; (ii) Γ, the maximum surface concentration; (iii) A_{min}, the minimum surface area per molecule; (iv) pC_{20} i.e., the efficiency of surface tension reduction measured by the negative log of the molar concentration of the surfactant required to produce a decrease in surface tension of 20 mN/m; and (v) π_{cmc}, i.e., the effectiveness of the surface tension reduction, measured by the surface pressure attained at cmc. The parameter cmc/C_{20}, which compares micellization and adsorption phenomena, was also calculated. Finally, Table 1 also shows the results of the conductivity measurements: the value of cmc and the degree of

Table 1. Tensidic Parameters for 1−7 at 25 °C

compd	cmc[a] (mM)	β[a] (%)	β[a,b] (%)	cmc[c] (mM)	γ_{lim}[c] (mN/m)	Γ[c] (mol/Å^2) ($\times 10^{-10}$)	A_{min}[c] (Å^2)	pC_{20}[c]	C_{20}[c] (mM)	cmc/C_{20}[c]
1	9.8	90		9.5	49.7	2.96[d]	56[d]	2.10	7.94	1.20
						1.98	84[e]			
3α	4.1	49	43	4.1	38.3	4.51	37	2.68	2.11	1.96
	0.39	10		0.40	66.1	1.49	111			
3*β*	4.8	73	69	5.2	39.9	3.31	50	2.67	2.12	2.44
	0.32	13		0.33	66.7	1.15	145			
4	4.2[f]	80	77	4.7	39.7	2.94	56	2.72	1.91	2.45
	0.051	17								
5	9.1	79	74	8.8	40.7	2.43	68	2.50	3.15	2.79
	0.28	20		0.32	64.5	1.67	100			
6	4.9	68	57	4.3	42.3	1.96	85	2.83	1.48	2.88
	0.27	26		0.10	65.4	0.61	271			
	0.12	9		0.019	68.5	0.31	541			
7	5.3	80	74	5.5	34.9	2.69	62	2.84	1.44	3.86
	0.30	23		0.25	65.0	1.40	118			

[a] From conductivity measurements. [b] Calculated neglecting the first change in slope (see text). [c] From surface tension measurements. [d] Calculated from formula **1** assuming $n = 2$. [e] Calculated from formula **1** assuming $n = 3$. [f] cmc = 4.95 mM and $\beta = 71\%$ (30 °C), taken from ref 14.

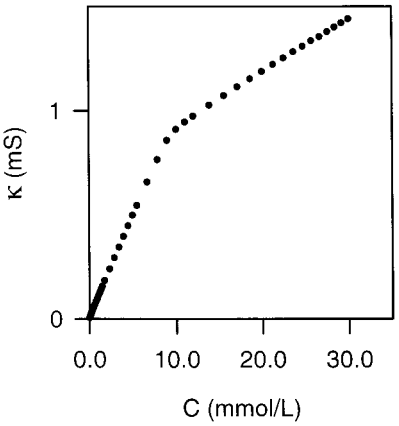


Figure 1. Specific conductivity vs *C* plot for 1-dodecyl-4-methylpyridinium bromide (**5**) at 25 °C.

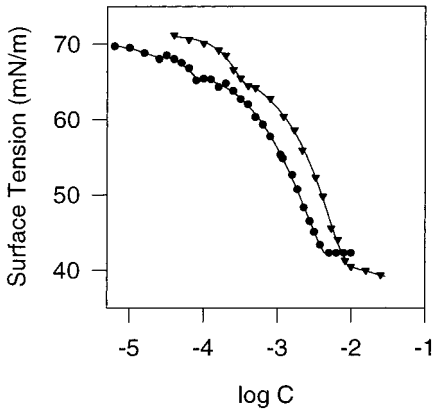


Figure 2. Surface tension vs log *C* plots for **4** (▼) and **6** (●).

counterion binding, β, taken as the ratio of the slopes of the conductivity vs concentration curve, above and below the cmc.[34]

The curves of specific conductivity, κ vs C, show the expected behavior for dodecyl cationic surfactants (Figure 1). A closer look at the trends at concentrations below the cmc shows a small change in slope, which normally occurs at a concentration of about 1 order of magnitude (or more) below the cmc for the compounds under investigation (except **1**). Consequently, the β value must be calculated by dividing the slope above the cmc by the slope below the first change in slope.[35a] Since this behavior was not revealed by conductivity measurements in earlier studies on pyridinium surfactants,[13−16,26,28,35b] the values of β computed in the usual way, i.e., when the first change in slope is neglected, are also shown for comparison.

The surface tension data are given in Table 1 and the curves for **5** and **6**, as examples, are shown in Figure 2. The γ vs log *C* plots for all of the products (except for **1**) show one (or two, for **6**) peculiarity at a concentration lower than the cmc. The cmc values, as extrapolated from γ vs log *C* plots, are consistent with those determined by conductivity. On the other hand, the peculiarities at low concentrations found in conductivity experiments sometimes do not closely agree with those found in surface tension measurements. This is not surprising, since the two techniques monitor aggregation by considering very different properties: interfacial for tensiometry and bulk for conductivity. Furthermore, when working at a low concentration range, the measurements are affected by a higher error.

Antimicrobial Properties. Cationic surfactants generally show antimicrobial activity. Devinsky and coworkers sought to determine quantitative structure/activity relationships between the antimicrobial activities and micellar properties of variously modified quaternary ammonium surfactants.[36−39] With a decrease in cmc, both the germicidal activity and protein-binding ability of quaternary ammonium salts increased.[36,37] Compounds with a cmc value of 1×10^{-2} to 1×10^{-4} M were active, regardless of whether the surfactant was monomeric or polymeric.

Measurements of antimicrobial activity were made using three bacterial strains, *Escherichia coli*, *Staphy-*

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Table 2. C log P and Antimicrobial Values (mg/mL) of the Surfactants Prepared in This Work According to BS 6471

		microorganism		
compd	*C* log *P*[a]	*Escherichia coli*	*Pseudomonas æruginosa*	*Staphylococcus aureus*
1	0.42	5.70	*b*	5.50
3α	2.72	0.88	5.50	0.12
3*β*	2.72	2.50	8.30	0.93
4	2.12	0.12	0.45	0.16
5	2.12	0.82	0.20	0.15
6	3.50	0.08	0.20	0.20
7	3.18	0.85	0.80	0.62

[a] Calculated by MacLogP.[41] [b] The antimicrobial value exceeded the highest measurable value according to the BS6471 method (10 mg/mL).

lococcus aureus, and *Pseudomonas æruginosa*, following the British protocol BS 6471[40] to determine the antimicrobial value of quaternary ammonium compounds in disinfectant formulations. The results of the antimicrobial tests are reported in Table 2. The antimicrobial power of benzyldimethyldodecylammonium bromide **7** is shown as a reference. Benzalkonium chloride, which is structurally similar to **7** but differs with regard to the length of the hydrophobic tail ($C_{10}-C_{14}$) and the counterion, is commonly used in disinfectant formulations[1].

Considering that the standard deviation for tests of this type is about ±40%, we can classify the products as being less, equally or more active than the standard **7**. With regard to the three different microorganisms, these three the sets are, for *E. coli:* **1**−**3*β*** < **3α**-**5**−**7** < **4**−**6**; for *P. æruginosa:* **1**−**3α**-**3*β*** < **4**-**7** < **5**−**6**; and for *S. aureus:* **1** < **3*β***−**7** < **3α**-**4**−**5**−**6**, which shows that compounds **4**−**6** are generally more active.

The log *P* parameter, i.e., the logarithm of the partition coefficient between *n*-octanol and water, is widely used to quantify the lipophilicity of a molecule. Following the fragmental approach of Leo and Hansch[42−44] and using MacLogP software,[41] the *C* log *P* data shown in Table 2 were calculated.

Discussion

During the cmc measurements by conductivity, peculiarities were detected at very low concentrations, and the significance of these peculiarities is under study. Abid et al.[35b] and Parreira et al.[45d] reported a similar behavior, for bolaform surfactants, and gemini surfactants, respectively. However, the Λ vs $C^{1/2}$ plots they reported did not show any discontinuity. The behavior at low concentration showed a clear deviation from linearity (i.e., the theoretical Onsager's slope for 1:1 salts), and the Λ value increased very rapidly when the concentration decreased. This abnormal behavior has often been found in bolaform bis-cationic compounds[35b−c] and has been attributed to the formation of a tight ion-pair. Taking compound **5** as an example, its *β* value of 20% at the first discontinuity can sustain this hypothesis. As far as the present compounds are concerned, this appears to be the first time that this phenomenon has been systematically found in a series of surfactants other than bolaform or geminis.

The bis-cationic surfactant **1** had the highest cmc value. In fact, the second positive charge makes the headgroup too hydrophilic, and thus less prone to adsorb at the surface, which inhibits the aggregation. The *β* value obtained for **1** is unusually high for cationic surfactants bearing bromide. Similar effects were reported by Zana et al.[45a] for a series of gemini surfactants, where a *β* value of 78% was obtained for a surfactant with two dodecyl hydrophobic chains and two quaternary ammonium charges, separated by three methylene groups (12−3−12 bromide) and also by Esumi et al.[45b] (*β* of 81% for a 12−2−12 bromide surfactant). The *β* value dropped when the length of the spacer was increased. *β* values of 71−77% were also found for pyridinium and quaternary ammonium bromide surfactants.[34,46] Our findings support strong binding of the counterion, which can be explained if we consider that the hydrophilic part of **1** can fold enough to strongly bind one bromide ion between the two different positive charges. The higher hydrophilicity of this compound is responsible for both the weak reduction of the surface tension and the adsorption at the air/water boundary, as shown by the pC_{20} value (2.21). Surfactant **1** does not show any discontinuity at a concentration below the cmc, in either the conductivity or the surface tension plots. In the first row of Table 1, Γ was computed using $n = 2$ in formula (1), whereas in the second row $n = 3$ was adopted, thus giving two possible values for A_{min}: 56 Å^2 ($n = 2$) and 84 Å^2 ($n = 3$). The hypothesis involving binding of one of the counterions[35a] suggests that $n = 2$ as confirmed by recent studies.[47] This behavior at the air/water interface indicates a high packing of molecules, which stand almost vertically at the surface.

The gluco-cationic surfactants **3α** and **3*β*** could be related to their uncharged counterparts, i.e., alkylpolyglucosides, a class of surfactants that recently entered the market under the trade name APG. They show a low cmc, similar to compounds with less hydrophilic headgroups (e.g., **4** and **6**). In APG, the glucose promotes aggregation[18] by creating a "hydrogen-bonding net" among the sugar moieties, as shown in smectic phases.[48] They display low cmc values, as exemplified, by *β*-(*n*-dodecyl)-glucoside[17,49] (cmc = $1.9 \cdot 10^{-4}$ M). The cmc values of the glucosurfactants considered here fall in the range that is usual for cationic amphiphiles (cmc **3α** = $4.1 \cdot 10^{-3}$ M, **3*β*** = $5.2 \cdot 10^{-3}$ M), which is at the lower edge of dodecyl cationic surfactants considered below (compounds **4** and **6**). This different behavior can be explained in terms of the balance between the aggregating effect of the glucose units and the repulsive effect of the positively charged rings. In addition, the area at the air/water interface follows the trend observed above for cmc. *β*-(n-Dodecyl)-

(40) British Standard BS 6471: British Standard Method for the *Determination of the antimicrobial value of QAC disinfectant formulations*.

(41) MacLogP (BioByte Corp.) version 2.5, incorporating the *C* log *P* algorithm, designed by A. Leo.

(42) *log P and Parameter Database: A Tool for the Quantitative Prediction of Bioactivity*. Pomona College Medicinal Chemistry Project, Comtex Scientific Corporation, New York, 1983.

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glucoside requires a minimum surface area of 36 Å^2, whereas **3**β requires 50 Å^2. The effect of anomerism is also worth considering, not neglecting further comparisons with APG. Although the data for α-(n-dodecyl)-glucoside, at 25 °C are unavailable, since it is insoluble in water under these conditions, the data for dodecylmaltosides[18] (cmc $\alpha = 1.5 \cdot 10^{-4}$ M, $\beta = 2.0 \times 10^{-4}$ M; β is 33% greater than α) agree with those of the glucocationics (cmc **3**α $= 4.1 \times 10^{-3}$ M, **3**$\beta = 5.2 \times 10^{-3}$ M; β is 25% greater than α). Also, the difference in cmc between **3**α and **3**β may be closely related to their different conformational arrangement in solution,[31] showing that **3**α is more prone than **3**β to form a "hydrogen bonding net", in agreement with their minimum areas (see Table 1). Further anomeric differences (**3**α vs **3**β) include (i) the formation of a better packed film of **3**α at the air/water boundary (minimum area, **3**α = 37 Å^2, **3**β = 50 Å^2), (ii) the changes in slopes, at very dilute concentration, in both conductivity and surface tension plots, and (iii) the abnormally low value of the degree of counterion binding shown by **3**α ($\beta = 43\%$), probably due to the formation of very small aggregates.[35,36,45d]

The remaining cationic surfactants **4**−**6** are alkylpyridinium and quinolinium bromides, whereas **7**, the conventional reference compound, is a benzalkonium bromide. A first interesting comparison involves the structural isomers **4** and **5**, in which the methyl and *n*-dodecyl groups change roles, thus modifying the structure of the headgroup and the hydrophobic moiety.

Molecules of **4** show a more marked order of packing (i.e. the formation of a compact film), as evidenced by a better effectiveness in reducing the surface tension (γ_{lim}: **4** = 39.7 mN/m, **5** = 40.7 mN/m), by a better adsorption efficiency (pC_{20}: **4** = 2.7, **5** = 2.5), and by a lower surface area at the air/water boundary (A_{min}: **4** = 56 Å^2, **5** = 68 Å^2). Compound **4** also shows a lower, nearly halved, cmc value (cmc: **4** $= 4.7 \times 10^{-3}$ M, **5** $= 8.8 \times 10^{-3}$ M). These data can be explained by the different location of the positive charge on the micelles. Provided the molecules in the aggregate are completely extended, **5** would have its positive charge deeper in the micelle, thus imposing a flatter arrangement of the pyridinium ring at the micellar surface and requiring, for a more favorable contact with water, a larger occupied area, which agrees with that calculated from the slope of γ vs log *C* plots (even if referring to the air/water interface).

With regard to antimicrobial properties, a general trend was observed. Compound **1** is the least active, followed by the glucosurfactants **3**α and **3**β, which are only moderately active. Their behavior could be related to the higher polarity of the polar head, compared to the standard **7**. Compounds **4**, **5**, and **6** are more active than product **7**.

Taking *Escherichia coli* as an example, the introduction of polar moieties on the pyridinium head (**1**, **3**α, **3**β) reduces antimicrobial activity. This could be due to modification of the lipophilic/hydrophilic balance imposed by the added moiety and is well reflected by the cmc value in a homologous series (**3**α-**3**β, **4**−**5**−**6**). Moreover, the mode of action of quaternary ammonium compounds has been ascribed to their adsorption onto membranes.[38,50] Consequently, surfactants **1** and **3**β are too hydrophilic to show good activity. Compounds **3**α and **5**, which show antimicrobial values similar to compound **7** are, in fact, more hydrophobic. Interestingly, **4** and **5**, which differ only with regard to the positional isomerism of the dodecyl and methyl moieties, show different behaviors for both cmc and antimicrobial values. Finally, compound **6**, which is the most hydrophobic due to the presence of a large quinoline ring (which more efficiently disperses the positive charge), shows the best activity.

The calculation procedure in *C* log *P*[41−44] cannot account for small differences in structure and hydrophobicity (such as between **3**α-**3**β and **4**−**5**). Nevertheless consistent results were found regarding (i) the least active compound **1** (*C* log *P* 0.42), (ii) the most active compound **6** (*C* log *P* 3.50), and (iii) the reference compound **7** (*C* log P 3.18).

With regard to the other bacterial strains, allowing for minor exceptions, *P. æruginosa*, due to its Gram-negative nature, is, as expected, more resistant to quaternary ammonium compounds, whereas *S. aureus* is more easily attacked.

In conclusion, these results indicate that the polarity of the cationic head, plays a crucial role in microbiological activity. In particular, in subsets of closely similar compounds, i.e., the pyridinium and quinolinium surfactants **5** and **6**, and the glucosurfactants **3**α and **3**β, a lower cmc (which is related in turn to the hydrophobicity of the headgroup), is associated with greater antimicrobial power.

Conclusions

This study was devoted to the synthesis, purification, characterization and determination of the surface and biological properties of a set of cationic surfactants. A new class of gluco-cationic surfactants, in the glucopyridinium series, was synthesized, and diastereomeric surfactants were successfully separated.

The surface properties and related parameters (critical micellar concentration, counterion binding, minimum required area, efficiency, effectiveness) were influenced by structural differences, as seen for both the series as a whole and subsets of structural isomers.

Diastereomeric gluco-pyridinium surfactants showed interesting differences in surface properties, which were less marked than those observed in the corresponding alkylglycosides surfactants, due to the strong effect of the charged pyridinium ring.

In antimicrobial tests, gluco-cationic surfactants, which are expected to be more environmentally friendly, showed moderate activity. A surfactant with a quinolinium headgroup showed the best antibacterial performance, even compared to a more popular agent. The hydrophobicity of the entire molecule appeared to be a reliable guideline for predicting antibacterial behavior.

Acknowledgment. This work was supported by a contribution from the Consiglio Nazionale delle Ricerche (CNR), Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, and by COFIN 98 - Molecular systems for transport and activation of oxygen. We gratefully acknowledge Compagnia di San Paolo (Torino, Italy) for supplying laboratory equipment.

Supporting Information Available: The glucosidic portion of the ^{1}H−^{1}H COSY NMR experiment for **2**β is reported to help the assignment of the above hydrogens. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0006425

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