JOC Article

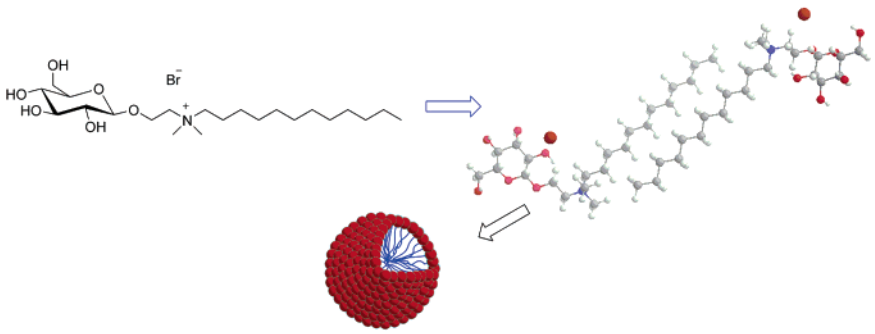
Synthesis and Properties of New Glucocationic Surfactants: Model Structures for Marking Cationic Surfactants with Carbohydrates

Pierluigi Quagliotto,*,† Guido Viscardi,† Claudia Barolo,† Domenico D'Angelo,† Ermanno Barni,† Carlotta Compari,‡ Elenia Duce,‡ and Emilia Fisicaro‡

Dipartimento di Chimica Generale ed Organica Applicata e Centro di Eccellenza NIS, Università di Torino, C.so Massimo d'Azeglio, 48, 10125 Torino, Italy, and Dipartimento di Scienze Farmacologiche, Biologiche e Chimiche Applicate, Università di Parma, Parco Area delle Scienze, 27A, 43100 Parma, Italy

pierluigi.quagliotto@unito.it

Received July 28, 2005



In this work, we report the synthesis of a new series of glucocationic surfactants, a class of surfactants we introduced very recently. The preparation of the surfactants is based on the synthesis of the 2-bromoethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, whose preparation was studied in order to improve yields and stereoselectivity of this key intermediate. These glucocationic amphiphiles were prepared and studied as a model of cationic surfactants marked with a carbohydrate moiety. The use of carbohydrates as markers on cationic lipids was recently introduced to induce recognition by specific receptors, present on the surface of cell membranes. The chemicophysical characterization of these model structures can give more insight on the aggregation behavior. Conductivity and surface tension measurements were performed in order to characterize the compounds from the amphiphilic point of view. The results showed a different effect of the glucosidic moiety on the cmc value with respect to the glucopyridinium cationic surfactants. The surfactants also showed the tendency to form premicellar aggregates in solution when the hydrophobicity is raised.

Introduction

In recent years, the field of cationic surfactants has attracted many applicative interests. Among them, the urge for cationic amphiphiles to be used in gene transfection, with the ultimate goal of gene therapy, is continuously growing.[1,2] Many cationic structures were prepared and tested for their ability to complex DNA and to allow it to cross over the cell membrane, until gene expression is achieved, giving rise to the so-called transfecting activity.[1−5] Some of these molecules were very effective, at least for the in vitro tests, to reach the market as products for molecular biology purposes. The last aim of these efforts is to reach enough information

† Università di Torino.
‡ Università di Parma.

(1) Miller, A. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 1768−1785.
(2) Kirby, A. J.; Camilleri, P.; Engberts, J. B. F. N.; Feiters, M. C.; Nolte, R. J. M.; Söderman, O.; Bergsma, M.; Bell, P. C.; Fielden, M. L.; Garcia Rodriguez, C. L.; Guédat, P.; Kremer, A.; McGregor, C.; Perrin, C.; Ronsin, G.; van Eijk, M. C. P. *Angew. Chem., Int. Ed.* **2003**, *43*, 1448−1457.
(3) Felgner, P. L.; Gadek, T. R.; Holm, M.; Roman, R.; Chan, H. W.; Wenz, M.; Northrop, J. P.; Ringold, G. M.; Danielsen, M. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7413−7417.
(4) Pedroso de Lima, M. C.; Simões, S.; Pires, P.; Faneca, H.; Düzgünes, N. *Adv. Drug. Deliv. Rev.* **2001**, *47*, 277−294.
(5) Meekel, A. A.; Wagenaar, A.; Kroeze, J. E.; Haadsma, P.; Bosgraaf, B.; Stuart, M. C.; Brisson, A.; Ruiters, M. H.; Hoekstra, D.; Engberts, J. B. F. N. *Eur. J. Org. Chem.* **2000**, 665−673.

10.1021/jo051579s CCC: $30.25
Published on Web 10/21/2005

to control the whole process in fine detail so that in vivo application, mainly gene therapy, can be available.

Many problems need to be overcome to reach this goal.[1,6−8] In fact, a comprehensive knowledge of the transfecting process is still lacking, and cooperation between medicine, pharmacology, biology, and chemistry is of outmost importance.

Also, great efforts are being made in the field of carbohydrate chemistry.[9−12] The collection of biochemical information about interactions involving carbohydrates is providing very important weapons for molecular biology to exploit, i.e., the chance to link an opportune saccharide or oligosaccharide structure to a cationic surfactant. This structure can be used to selectively "mark" a liposome in order to enhance both its chance of being recognized by a particular receptor and the transfecting ability toward only a well-defined target cell type.[13−16]

Recently, we introduced a new family of cationic surfactants: the glucopyridinium amphiphiles,[17] that can be envisaged as a particular case of the glucocationic surfactant class.

In such work, the presence of a gluco moiety in the cationic surfactant seemed to substantially depress the bacteriostatic activity, enabling us to say that these structures could be more biocompatible. This is a prerequisite for all structures to be used in biomedical applications, especially if they have to be used in substantial quantities as carriers for drugs or DNA. In this respect, a structure belonging to a series of catanionic gemini surfactants based on lactose showed good activity against HIV in in vitro studies.[18] This fact was related to the similarity of the polar group to the headgroup of GalCer, a glycolipid expressed on the surface of cells infected by HIV and recognized by the gp120 protein, which is typical of the AIDS virus.[19]

Most of the glucocationic compounds were mainly developed by Lattes and co-workers.[18,20,21] who explored the fascinating world of surfactants having several chiral centers and, in principle, lower toxicity and biological activity. The structures they prepared belong to the more general class of the catanionic surfactants, obtained by mixing two compounds, one bearing an acidic moiety and the other bearing a basic moiety, in a 1:1 ratio (or 1:2 ratio, giving gemini surfactants[18]) to give salts that showed unusual properties and sometimes high biological activity. Very few compounds were found, however, that contained in the same molecule the cationic and the glucose moieties connected with covalent bonds.[17,22−25]

In view of the development of more complex cationic lipid structures, we envisaged the synthesis of a model glucocationic series having a tunable hydrophobicity, due to both the hydrophobic chain and the presence/absence of the acetyl protection on the glucosyl hydroxyl groups.

The study of the amphiphilic behavior of these model structures could give some information on the effect of the different structural features on the aggregation process, trying to get evidence for structure−performance relationships. A glucose ring was chosen as the glycosyl moiety. This was connected to the cationic nitrogen by a short spacer, obtained by coupling the protected glucose to bromoethanol. A brief study of the different alternatives to the glucosylation of bromoethanol was performed to optimize the yields in preparing the intermediate 2-bromoethyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranoside (**1**).

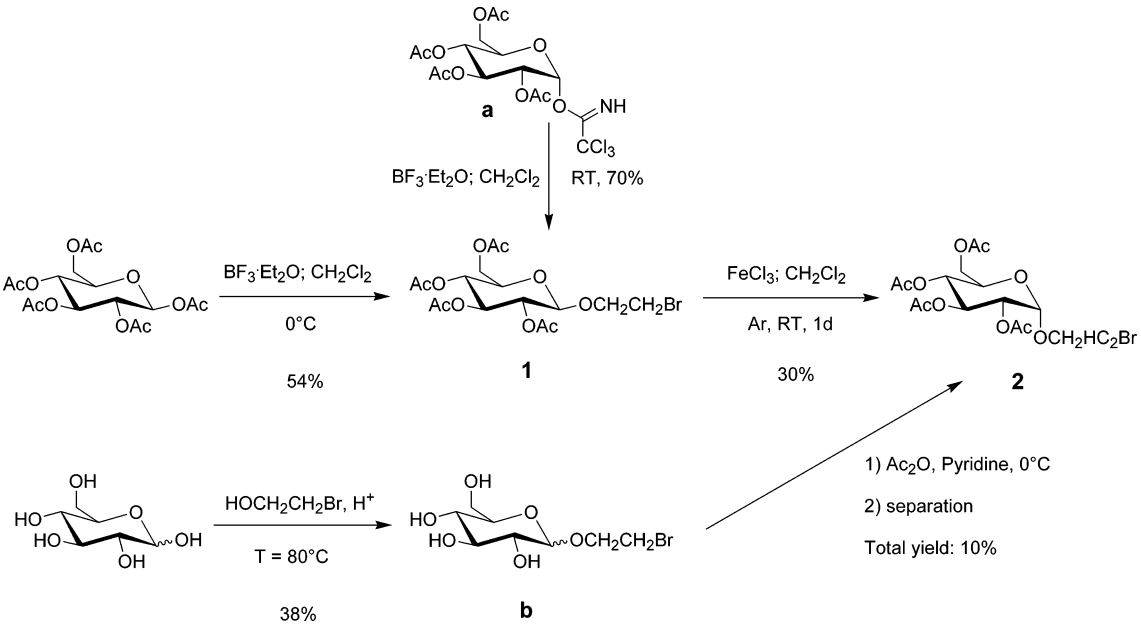
The amphiphilic behavior was determined by conductivity and surface tension measurements, showing peculiarities, namely premicellar aggregate formation in some cases.

Results and Discussion

Synthesis. To perform the synthesis of the glucocationic surfactants, by quaternization of the alkyldimethylamine, the 2-bromoethyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside **1** was needed as a key intermediate (Scheme 1). This compound was first synthesized by Dahmen et al.[26−29] by reaction of the pentaacetylglucose with bromoethanol and boron trifluoride etherate in dichloromethane. The yield was about 40%. With a careful application of their procedure, we obtained an improvement in the yield to 54%. The reaction was completely stereoselective, giving only the β-anomer. We also tried to improve the yield, preserving complete stereoselectivity control. The use of the Schmidt's glycosylation protocol,[10,11,30−32] involving a protected trichloroacetimidate glucosyl donor, namely the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyltrichloroacetimidate (compound **a**), gave an effective yield improvement from the 40% obtained with the peractylated glucose as a donor (or 54% obtained in our laboratory) to about 70%, preserving the total control of stereoselectivity. This is undoubtedly due to the effect of acetyl protection of the

(6) Lasic, D. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1685−1698.
(7) Lasic, D. D.; Papahadjopoulos, D. *Science* **1995**, *267*, 1275−1276.
(8) Hong, K.; Zheng, W.; Baker, A.; Papahadjopoulos, D. *FEBS Lett.* **1997**, *400*, 233−237.
(9) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173.
(10) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.
(11) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.
(12) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624.
(13) Huang, L.; Klibanov, A. L.; Mori, A.; Gao, X. *J. Liposome Res.* **1993**, *3*, 505−515.
(14) Remy, J.-S.; Kichler, A.; Mordvinov, V.; Schuber, F.; Behr, J.-P. *Proc. Natl. Acad. Sci. U.S.A.* **1995,** *92*, 1744−1748.
(15) Ferkol, T.; Perales, J. C.; Mularo, F.; Hanson, R. W. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 101−105.
(16) Liang, W.; Shi, X.; Deshpande, D.; Malanga, C. J.; Rojanasakul, Y. *Biochim. Biophys. Acta* **1996**, *1279*, 227−234.
(17) Viscardi, G.; Quagliotto, P.; Barolo, C.; Savarino, P.; Barni, E.; Fisicaro, E. *J. Org. Chem.* **2000**, *65* (24), 8197−8203.
(18) Blanzat, M.; Perez, E.; Rico-Lattes, I.; Prome, D.; Prome, J. C.; Lattes, A. *Langmuir* **1999**, *15*, 6163−6169.
(19) Faroux-Corlay, B.; Clary, L.; Gadras, C.; Hammache, D.; Greiner, J.; Santaella, C.; Aubertin, A. M.; Vierling, P.; Fantini, J. *Carbohydr. Res.* **2000**, *327*, 223−260.
(20) Pasc-Banu, A.; Blanzat, M.; Belloni, M.; Perez, E.; Mingotaud, C.; Rico-lattes, I.; Labrot, T.; Oda, R. *J. Fluorine Chem.* **2005**, *126*, 33−38.
(21) Rico-lattes, I.; Blanzat, M.; Franceschi-Messant, S.; Perez, E.; Lattes, A. *C. R. Chimie* **2005**, *8*, 807−814.
(22) Kirk, O.; Pedersen, F. D.; Fuglsang, C. C. *J. Surfactants Deterg.* **1998,** *1*, 37−40.
(23) Benvegnu, T.; Lecollinet, G.; Guilbot, J.; Roussel, M.; Brard, M.; Plusquellec, D. *Polymer Int.* **2003**, 52, 500−506.
(24) Guilbot, J.; Benvegnu, T.; Legros, N.; Plusquellec, D.; Dedieu, J. C.; Gulik, A. *Langmuir* **2001**, 17, 613−618.
(25) Montier, T.; Delepine, P.; Benvegnu, T.; Ferrieres, V.; Miramon, M. L.; Dagorn, S.; Guillaume, C.; Plusquellec, D.; Ferec, C. *Blood Cells Mol. Dis.* **2004**, *32*, 271−282.
(26) Dahmen, J.; Frejd, T.; Grönberg, G.; Lave, T.; Magnusson, G.; Noori, G. *Carbohydr. Res.* **1983**, *116*, 303−307.

SCHEME 1. Synthetic Pathways to Intermediate Compounds 1 and 2



hydroxyl group in the 2-position of glucose. The participation of this acetyl group in stabilizing the carbocation derived from the release of the trichloroacetimidate group gives an "acetoxonium" ion and forces the reaction with the alcohol toward the complete inversion of configuration.[11,33−35] The improvement in the synthesis of **1** showed that, in general, a careful synthetic project should be prepared to obtain both high yield and selectivity. In the case of carbohydrates one should bear in mind that both the right arrangement of the protecting groups and the activating group for glucosylation are of crucial importance.

In this case, the use of the well-known trichloroacetimidate was a quite easy and well performing choice. In fact, since their introduction in the early 1980s, these glucosyl donors showed excellent behavior in order to give high control of the selectivity, ascribed to a combination of Lewis acid, pattern of protection of the hydroxyl groups, and solvent effect. The broad application they found in the oligosaccharide preparation is the best demonstration of their synthetic power and versatility. A whole knowledge of the different properties of different glucosyl donors and protecting groups is of utmost importance to plain carbohydrate modifications.

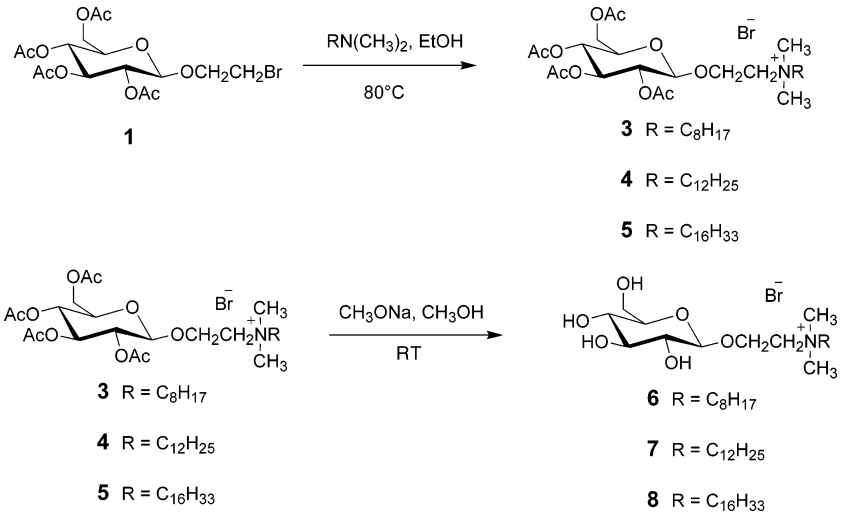
Also, the possibility to obtain the α-anomer **2** was studied. The first route we tried was not stereoselective. An anomeric mixture (compound **b**) was prepared from glucose and bromoethanol by reaction at 80 °C, using the same alcohol as the solvent.[22] The direct reaction of bromoethanol with glucose was not so high yielding, thus depressing the whole yield. The mixture was successively peracetylated with acetic anhydride in pyridine, and the anomers were separated by flash chromatography, obtaining, however, a very low yield (10%). By a simple NMR control, made on the anomeric protons, partial anomerization could be involved in the acetylation step. This fact could be the reason for the very low yield for compound **2**, even if the crude product to be acylated showed a greater quantity of α-anomer, as expected from this classic Fischer glucosylation step.

A second way was tried, by anomerization of **1** to **2** promoted by ferric chloride in dichloromethane. A literature method[36] showed that when the anhydrous ferric chloride was used to remove benzylic protections from sugars, the anomerization to the more stable α-anomer was occurring in a substantial yield. In addition, the authors showed that, in most cases (but not all) the acetyl protecting groups on the carbohydrate moiety were stable toward the ferric chloride. During our trials the reaction worked, but a decomposition of the starting compound was occurring. In our conditions, the reaction gave, after purification, a 30% yield in α-anomer (**2**). This fact did not guarantee a sufficient yield to exploit practically this way for the production of glucocationic surfactants having an α anomeric configuration. The results here obtained were not encouraging, and the synthesis of α-glucocationic surfactants will be attempted soon. However, the occurrence of the *β*-linkage for glucose in nature is practically ubiquitous, while the α-linkage is quite rare.

We prepared the surfactants **3**−**5** by reaction of **1** with the proper alkyldimethylamine in ethanol at reflux (Scheme 2). In approximately 2 days, the reaction reached completion and was stopped. The evaporation of the

(27) Magnusson, G.; Noori, G.; Dahmen, J.; Frejd, T.; Lave, T. *Acta Chem. Scand. B* **1981**, *35*, 213-216.
(28) Dahmen, J.; Frejd, T.; Magnusson, G.; Noori, G.; Carlström, A. S. *Carbohydr. Res.* **1984**, *127*, 15−25.
(29) Dahmen, J.; Frejd, T.; Magnusson, G.; Noori, G. *Carbohydr. Res.* **1983**, *114*, 328−330.
(30) Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343−1357.
(31) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1982**, *21*, 72−73.
(32) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249−1256.
(33) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213.
(34) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2214−2221.
(35) Schmidt, R. R.; Klotz, W. *Synlett* **1991**, 168−170.
(36) Ikemoto, N.; Kim, O. K.; Lo, L. C.; Satyanarayana, V.; Chang, M.; Nakanishi, K. *Tetrahedron Lett.* **1992**, *33*, 4295−4298.

SCHEME 2. Synthesis of the Glucocationic Surfactants 3−8



solvent yielded an oil that was purified by chromatography and several suspensions in petroleum ether to remove the last trace of the amine, giving a white powder.

The protecting groups were removed under the Zemplen[37] conditions (CH_3ONa in CH_3OH), giving the surfactants **6**−**8** (Scheme 2). While the compound **6** was isolated as an oil, compounds **7** and **8** were obtained as solids after flash chromatography and crystallization from dichloromethane/ethyl acetate. During the first purification attempts of the surfactants **6**−**8**, it was noticed that these products could induce gelation of hydrophobic organic solvents, like petroleum ether. Nice long filamentous structures in the bulk appeared, substantially enhancing the viscosity of the system.

Amphiphilic Characterization. Conductivity Measurements. The characterization of the surfactants was performed by conductivity and surface tension measurements.

Apart from surfactant **6**, for which the solubility was not high enough to permit us to obtain the cmc, all the surfactants were analyzed for the conductivity of their solutions. An example of the conductivity-related plots is reported in Figure 1 for compound **4**. Plots for each compound are included in the Supporting Information. The unexpected solubility behavior for compound **6** is worthy of more study, to be performed later.

The conductivity results are reported in Table 1. The critical micellization concentrations and the degree of counterion binding (i.e., the percentage of counterion tightly bound to the micelle in order to compensate for the repulsive force acting among the charged headgroups) were obtained. The cmc was taken as the intersection of the lines drawn from two ranges, pre- and postmicellar. A more precise method was recently proposed, using a nonlinear function based on the integral of the Boltzmann sigmoid, to fit the equivalent conductivity (κ) vs C data[38] (Figure 1a). This was particularly useful for those cases where the transition between the monomeric and the micellar state is very gradual. This happens for surfactants giving small micelles of low aggregation number and when the micellization is anticipated by the formation of premicellar aggregates such as the case of the gemini surfactants.[17,39]

A detailed discussion of the theory of the method has been reported elsewhere, along with its first application to the case of gemini surfactants.[17,38] Application of the two methods gave similar results. The ratio of the slopes of postmicellar and premicellar ranges (S_{post}/S_{pre}) gave the degree of micellar dissociation, α, and the degree of counterion binding, β, was estimated by $1 - \alpha$. The same slopes were obtained alternatively by nonlinear fit,[38,40] as fit parameters (called A_1 and A_2 in the original article) that were used in the same way to estimate α (equal to A_2/A_1) and β obtaining comparable results.

The cmc values are higher for the nonacetylated surfactants **7** and **8**, since they are less hydrophobic than the protected ones (**3**−**5**).

As an example, for the dodecyl chain, the unprotected compound **7** has a cmc four times higher than that of the acetylated compound **4**. The cmc trends for all the surfactants are logical, since the cmc decreases when the chain length is raised. For the hexadecyl chain pair (compounds **5** and **8**) there is no difference in the cmc. If one thinks that an unprotected glucose should add more hydrophilicity to the surfactant **8** one should expect a substantially higher cmc for it. The compound **5** is more hydrophobic and less soluble in water, while the ability of the glucose headgroups to form a hydrogen bonding network would stabilize the packing of the molecules in the micelle. Both those factors account for a decrease of the cmc. This should explain why two surfactants apparently different due to the hydrophilic/lipophilic balance show similar cmc.

The two hexadecyl surfactants **5** and **8** also show a discontinuity in the κ vs C plot at very low concentrations, which was already considered as an evidence of the formation of tight ion couples.[17,39] The corresponding degree of counterion binding agrees with this interpretation.

The analysis of the counterion binding data (β) reveals important information on the micellar structure. The

(37) Zemplen, G. *Chem. Ber.* **1927**, *60*, 1555−1564.
(38) Carpena, P.; Aguiar, J.; Bernaola-Galvan, P.; Ruiz, C. C. *Langmuir* **2002**, *18*, 6054−6058.
(39) Zana, R. *J. Colloid Interface Sci.* **2002**, *246*, 182−190.

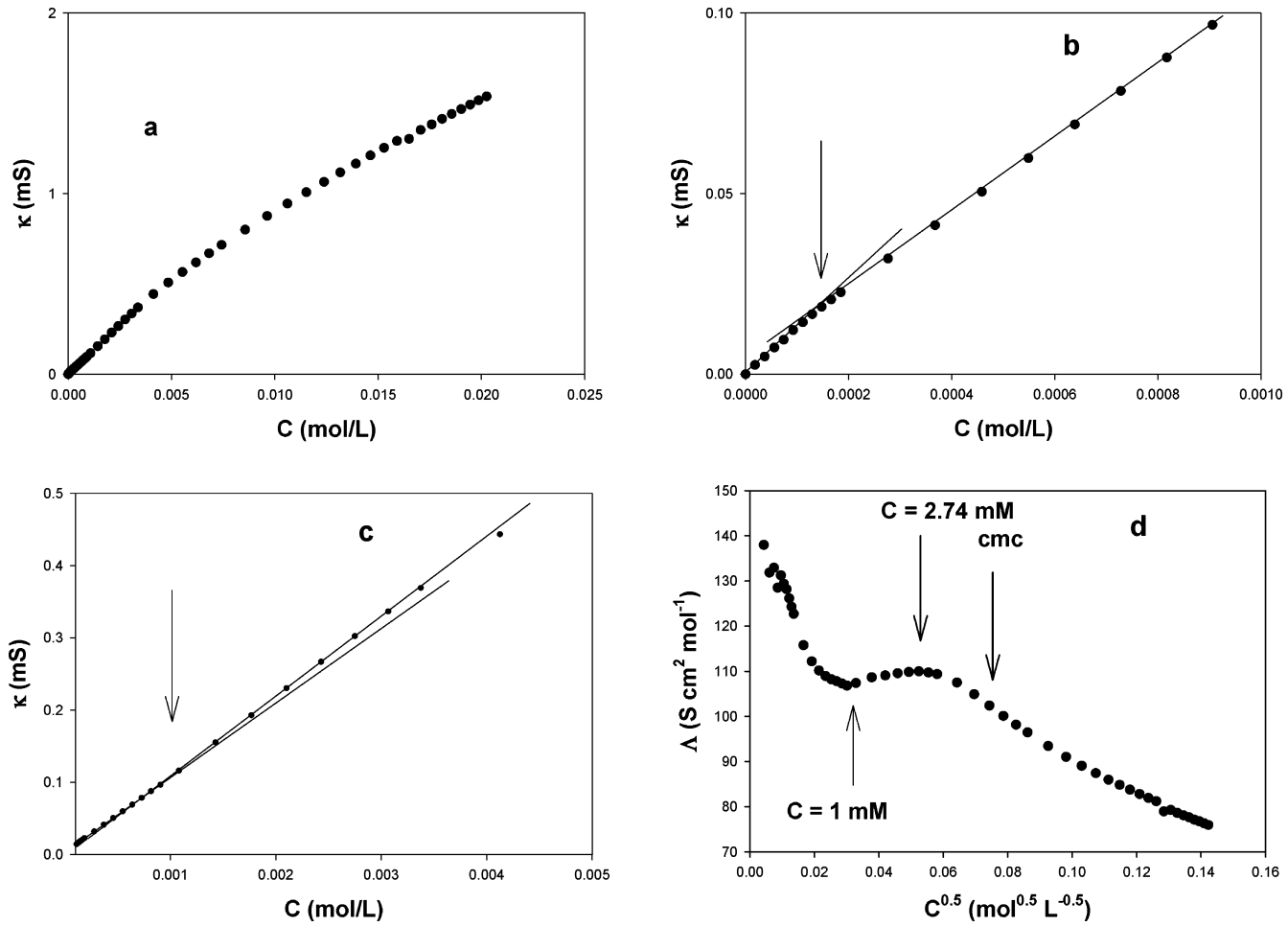


FIGURE 1. Specific conductivity vs C (a, full concentration range) (b and c, expanded regions: the arrows indicate peculiar points for the onset of: ion pair formation for b, and premicellar aggregates for c, where smaller points were drawn to let the reader to identify the crossing point of the two lines) and molar conductivity vs $C^{0.5}$ (d, the arrows indicate, from left to right, the onset of premicellar aggregate formation as in c, the concentration at which the maximum is attained, the cmc as determined in a, respectively) plots for compound **4**, taken as an example.

TABLE 1. Characterization of the Surfactants 3−8 by Conductivity Measurements

compd	cmc (mM)	β (%)	Λ vs $C^{0.5}$ plot shape
3	29.2	44	maximum
4	5.48	47	asynthotic/maximum
5	1.25	56	slight maximum
	0.18	38	
6	*a*		
7	21.3	71	asynthotic/maximum/normal
8	1.42	70	asynthotic/maximum/normal
	0.12	28	
DTAB[b]	15.80	77	normal
CTAB[b]	0.90	84	normal

[a] This product shows a solubility limit before attaining the theoretical cmc. [b] From ref 37.

acetylated compounds (surfactants **3**−**5**) show a low degree of counterion binding, around 50−60%. This is quite low for common cationic surfactants having a bromide counterion. However, it was shown that when the crowding around the charged ammonium site is increased, the β value is lower than normally expected.[17,41] This is due to the screening effect of the bulkier substituents on the nitrogen atom. The great dimension of the headgroup diminishes its surface charge density and its proneness to tightly bind a counterion. The lengthening of the hydrophobic chain cause an increase of the degree of counterion binding (see surfactants **3**-**5**) that agree with the behavior of the simple alkyltrimethylammonium surfactants DTAB (64 or 77%),[41−43] TTAB (74%),[42] and CTAB (79 or 84%).[41,42] Moreover, the deprotected surfactants **7** and **8** show nearly the same β value, that is sensibly higher than that of the acetylated products. As already anticipated, the hexadecyl surfactants **5** and **8** show a discontinuity at very low concentration, at which β is about 30−40%.

The conductivity data can also be reported as molar conductivity (Λ) vs $C^{0.5}$ plots. From those plots it is evident that those surfactants show peculiar behavior. All of the surfactants seem to have the same asymptotic trend at low concentration (Figure 1d). This is normally

(40) Quagliotto, P.; Viscardi, G.; Barolo, C.; Barni, E.; Bellinvia, S.; Fisicaro, E.; Compari, C. *J. Org. Chem.* **2003**, *68* (20), 7651−7660.

(41) Buckingham, S. A.; Garvey, C. J.; Warr, G. G. *J. Phys. Chem.* **1993**, *97*, 10236−10244.

(42) van Os, N. M.; Haak, J. R.; Rupert, L. A. M. *Physico-Chemical Properties of Selected Anionic, Cationic and Nonionic Surfactants;* Elsevier: Amsterdam, 1993.

(43) De Lisi, R.; Fisicaro, E.; Milioto, S. *J. Solution Chem.* **1988**, *17*, 1015−1041.

taken as a further evidence for the formation of tight ion couples.[17,40,44] The acetylated compounds **3**−**5** show the occurrence of a maximum in the plot (compound **4**, Figure 1d). Normally, the maximum is more evident when the hydrophobicity of the molecule is enhanced and is taken as a clear evidence of the formation of premicellar aggregates in solution.[39,45] The ion pairing is referring to the binding of a counterion to the oppositely charged surfactant ion. In this case, the partial neutralization of charges would result in a loss of conductivity, and both the κ vs C and the Λ vs $C^{0.5}$ plots would show a slight curvature toward the C axis. This was observed for the κ vs C plot in Figure 1b (at a $C = 0.1$ mM) and, with the asymptotic trend at low concentration in the Λ vs $C^{0.5}$ plot, gives evidence for ion couple formation. Besides, Zana showed in a qualitative way that the conductance of a dimer is higher than that of a monomer, provided that the arrangement of the monomers in the dimer is able to let it fully ionized.[39] One possibility is that two monomers form a dimer by coupling their hydrophobic chains and leaving the two headgroups far apart each other, at the edges of the dimer (like a bolaform structure).

Under those conditions, the dimer is (a) fully ionized, (b) a bit smaller that the simple sum of the volume of two surfactant monomers, and (c) would require less water to be "solvated". Consequently, its diffusion and migration ability in the solution would be faster and the conductivity of the dimer should be higher than that of the two surfactant monomers. Also, Pinazo et al.[45] evaluated this kind of behavior from a theoretical and quantitative point of view and obtained plots showing a maximum in the Λ vs $C^{0.5}$ plot. This discussion can be extended to the formation of oligomers, such as trimers, tetramers and so on, provided that they do not bind counterions in practice. As a practical result, the κ vs C plot should show in the low concentration premicellar range a slight curvature toward the κ axis. This was observed in Figure 1c for compound **4** at C of about 1 mM. In addition, Λ will increase with C, and the Λ vs $C^{0.5}$ plot will show an increase in Λ values. Increasing the concentration, the oligomers will further grow until their conductivity start to decrease since in order to keep the monomers together to form the aggregate they need to firmly bind a few counterions to diminish the cationic headgroup repulsion. This explains why in the Λ vs $C^{0.5}$ plots sometimes a maximum is shown (for compound **4**, in Figure 1d, at 2.74 mM, while the cmc for this surfactant is twice that value, 5.48 mM). For a detailed description of this phenomenon one should consult the two cited articles which account for both a qualitative−semiquantitative[39] and a more rigorous quantitative[45] description.

For products **3**−**5**, the maximum follows this trend when the chain becomes longer. In the case of compound **5**, it is also difficult to clearly detect the presence of the maximum, which would be probably detected by obtaining measurements at lower concentrations (this task is not easy[39,45]). However, an evident discontinuity in the plot is found at C lower than 0.1 mM, which does not correspond to the cmc obtained with the κ vs C plot which is found at 1.25 mM, but rather with the cmc data coming from the surface tension measurements (see below). The same occurs for compound **4**, and for the unprotected surfactants **7** and **8**. In particular, the hexadecyl compound **8** shows a behavior very similar to that of the corresponding acetylated product **5** at very low concentration, while the dodecyl surfactant **7** show a very slight maximum. Besides, those two products also show the normally expected discontinuity at a proper concentration that well correlate with the cmc as determined from the κ vs C plots.

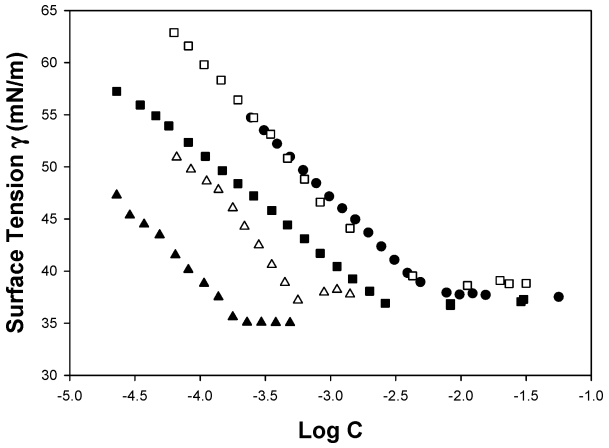


FIGURE 2. Surface tensions vs log C plot for the compounds **3** (●), **4** (■), **5** (▲), **7** (□), and **8** (△).

Surface Tension Measurements. The surface tension measurements performed on the surfactants gave the results reported in Figure 2 and in Table 2.

From this technique, the following parameters were determined: (i) critical micellar concentration; (ii) γ_{cmc}, i.e., the surface tension attained at the cmc; (iii) C_{20}, i.e., concentration at which the surface tension is decreased by 20 mN/m, a parameter measuring the adsorption efficiency, and its corresponding logarithm pC_{20}; (iv) Γ_{max}, i.e., the surface excess concentration, the maximum concentration of adsorbed species, attained at the cmc; (v) A_{min}, i.e., the minimum area that a molecule would occupy at the air−water layer in the condition of surface saturation, at the cmc; (vi) the cmc/C_{20}, i.e., a parameter that compare the micellization and the adsorption ability of the molecule. The cmc as determined by surface tension was found to be substantially lower than that obtained by conductivity for all samples. The ratio between the cmc obtained by conductivity and that obtained by surface tension falls in the range 2−8. The same ratio was previously introduced by Rosen et al.,[46] during a study on gemini *N*-acyl-β-alaninate surfactants, to evidence unexpected behaviors mainly linked to the formation of premicellar aggregates.

The general trend of the surface tension cmc follows the order shown above for the conductivity cmcs. A general agreement of the surface tension cmc with the maximum in the molar conductivity vs $C^{0.5}$ plots was found. This would account for the formation of premicellar aggregates in substantial quantity, so that no de-

(44) Fuoss, R. M.; Chu, V. F. *J. Am. Chem. Soc.* **1951**, *73* (3), 949−952.

(45) Pinazo, A.; Wen, X.; Perez, L.; Infante, M. R.; Franses, E. I. *Langmuir* **1999**, *15*, 3134−3142.

(46) Tsubone, K.; Arakawa, Y.; Rosen, M. J. *J. Colloid Interface Sci.* **2003**, *262*, 516−524.

TABLE 2. Characterization of the Surfactants 3−8 by Surface Tension Measurements

compd	cmc[a] (a) (mM)	cmc[b] (b) (mM)	ratio[c] b/a	γ_{cmc} (mN/m)	pC_{20}	Γ_{max} (mol cm^{-2})	A_{min} (Å^2)	cmc/C_{20}
3	5.78	29.2	5	37.75	3.400	1.06	157	14.5
4	2.63	5.48	2	36.97	4.061	0.90	184	30.3
5	0.21	1.25	6	35.06	5.021	1.11	150	21.7
6[d]								
7	2.82	21.3	8	38.98	3.414	1.28	130	7.3
8	0.51	1.42	3	39.06	4.194	1.32	125	8.0
DTAB[e]	14.45	15.80		36.4		1.40	77	
CTAB[e]	0.80	0.90		35.3		1.12	140	

[a] cmc obtained by surface tension. [b] cmc obtained by conductivity. [c] Ratio of the cmc conductivity/surface tension (see Rosen et al.[46]), approximation to unity. [d] This product shows a solubility limit (see Table 1 and text). [e] From the literature.[43,47]

crease of surface tension occurs between the formation of such aggregates and the formation of "regular" micelles. When the maximum in the Λ vs $C^{0.5}$ plot is attained the aggregates already started to grow, forming regular micelles (see Figure 1d for coumpond **4**, where the concentration at which the maximum is attained is in excellent agreement with the cmc obtained by surface tension). For this case, the interface is already saturated with surfactant near at the point of the onset of transformation of the premicellar aggregates in micelles. Since the conductance of the premicellar aggregates is higher than that of the simple surfactant ion (see above), they should stay in the solution bulk and probably are not adsorbed at the air−water surface.[39] In the equilibrium between bulk and surface, only the monomeric surfactant ions are involved. When the small aggregates start to form, the concentration of the surfactant at the interface remains practically constant, as well as the concentration of the monomeric surfactant in the bulk. All of the surfactants show this behavior.

The difference among the cmcs, as determined from surface tension, of acetylated (**3**−**5**) and non acetylated (**7**−**8**) surfactants is quite small. Once more, this is an indication of the different nature of the aggregate revealed by surface tension and conductivity measurements and its meaning is connected to the water solubility (for acetylated compounds **3**−**5**) and the hydrogen bonding network taking place among the free glucose moieties (for non acetylated compounds **7**−**8**) as features favoring micellization (see above). The limiting surface tension at the cmc, γ_{cmc}, is lower for compounds **3**−**5** than for products **7**−**8** and decreases with increasing the chain length. This is in accordance with the different hydrophobicity of the products, the more hydrophobic shows a better surface reduction behavior.

The C_{20} parameter decreases for compounds **3**−**5** with the order **3** > **4** > **5**, showing once more that to the higher hydrophobic character of the molecule corresponds an increased proneness to adsorb. Working with eqs 1 and 2, the excess surface concentration Γ_{cmc} and the minimum area at the air−water surface can be obtained.[48]

$$\Gamma_{cmc} = -\frac{1}{2.303nRT}\left(\frac{\partial\gamma}{\partial \log C}\right)_T \quad (1)$$

$$A_{min} = \frac{10^{16}}{\Gamma_{cmc}N_A} \quad (2)$$

In the above equations, R is the gas constant (8.3134 $\times$ 10^7 erg mol^{-1} K^{-1}), T the absolute temperature, n the Gibbs prefactor (i.e., the number of ions that originate in solution by dissociation of the surfactant and whose concentration change at the surface when changing the bulk solution concentration, assumed as 2 in our calculations), and N_A the Avogadro Number. In eq 1, the last right term is usually considered as the slope of the steep decrease of surface tension, taken at the cmc point. Strictly speaking, this term is the derivative of the γ vs log C plot, taken at the cmc.[49]

The areas thus derived can give information about the space that every molecule needs to accommodate to the air−water surface. By analysis of those minimum area data, it can be inferred that the acetylated surfactants **3**−**5** would occupy more space at the surface than that occupied by the nonacetylated compounds **7** and **8**. This is in accordance with the bulkier acetylated glucose present in the former series of amphiphiles. The final result is that a poor packing is found at the air−water surface. The bulkier protected glucose would also account for a lower binding of the counterion (shown above) and for a "loose" micellar structure (compounds **3**−**5**) which was sometimes referred to as "wet" micelles, since the poor packing would leave enough space for water to deeply enter the micellar interior. The nonacetylated amphiphiles **7** and **8** show a smaller area, in agreement with both the smaller structure of the unprotected glucose alone and the glucose hydrophilicity that require a completely different arrangement of this moiety in the adsorption layer. As shown before,[17] the more probable arrangement for glucose is in nearly complete contact with water, submerged in the water layer. From our results, nearly the same hypothesis can be done also for the acetylated glucose in surfactants **3**−**5**. As a result, a lower A_{min} value is expected, and this is what was found. A comparison could be performed with quite similar structure having pyridinium headgroups.[17] In this case the area for a β-glucopyridinium surfactant having a dodecyl chain is substantially smaller (50 Å^2) than that found for the corresponding product **7**. As a reference, the area found for β-(*n*-dodecyl)glucopyranoside is only 36 Å^2. A possible explication for this behavior could reside in different factors. First, the difference between the two structures is the presence of a dimethylenic spacer between the glucose and the nitrogen atom for compound **7**, which is absent in the pyridinium structure where the

(47) Moulik, S. P.; Haque, Md. E.; Jana, P. K.; Das, A. R. *J. Phys. Chem.* **1996**, *100*, 701−708.
(48) Rosen, M. J. *Surfactants and Interfacial Phenomena*, 2nd ed.; John Wiley & Sons: New York, 1989.
(49) Lunkenheimer, K. On the problem of surface chemical purity of surfactants—Phenomena, analysis, results, consequences, and prospects. In *Encyclopedia of Surface and Colloid Science*; Marcel Dekker: New York, 2002; pp 3739−3772.

glucose ring is directly attached to the pyridinium nitrogen. This spacer should give more conformational freedom to the structure **7** to arrange to the air−water surface. Second, but not less important, the presence of the positive charge makes the headgroups to repel each other, giving higher areas than that of the simple β-(n-dodecyl)glucopyranoside. The pyridinium ring could delocalize the positive charge and should not strongly repel similar molecules, thus permitting the establishing of a quite strong network of hydrogen bonds among the glucose hydroxyl groups. For compound **7**, the positive charge is localized on the ammonium nitrogen and should cause more repulsion among similar molecules. The area values agree with the proposed interpretation. The degree of counterion binding for surfactant **7** is slightly lower than that of the cited gluco-pyridinium surfactant, but the difference (71 for **7** vs 73% for the gluco-pyridinium surfactant) is too low to be taken as a reliable indicator to support the hypothesis. According with all those observations, however, the minimum area should be higher for the compound **7**, as we found. The higher conformational freedom due to the dimethylenic spacer could leave the glucose moiety to move quite freely in water, to be more highly hydrated with respect to the glucopyridinium surfactant and to occupy more space at the air−water surface, even if interacting with other glucose counterparts by hydrogen bonding.

Finally, the cmc/C_{20} parameter is high for the acetylated compounds in agreement with their higher hydrophobicity and with their stronger ability to adsorb than to micellize. Obviously, this parameter is expected to show lower values for the nonacetylated compounds (**7** and **8**) because of their higher polarity.

To obtain further insights in the structure−property relationships, surfactants **4** and **7** can be compared to their "unsubstituted" parent compound dodecyltrimethylammonium bromide (DTAB) and the same can be done for **5** and **8** with hexadecyltrimethylammonium bromide (CTAB). The presence of the acetylated glucose decreases the cmc (if we refer to the values of cmc determined by conductivity) for the dodecyl surfactant **4** to one-third of that of DTAB, while in the case of the hexadecyl chain (**5**) the cmc increases. The acetylated glucose moiety adds hydrophobicity to both the molecules, but the effect on the cmc is clearly evident only for surfactant **4**.

Generally, when the increase in hydrophobicity is located on the headgroup this phenomenon is less severe but, in the case of compound **5** vs CTAB, it seems quite appreciable. Since the cmc difference between DTAB and CTAB accounts for the behavior expected for adding four methylenes to the hydrophobic chain, we could roughly try to estimate the contribution of the acetylated glucose (and its spacer) attached to the positive headgroup to be similar to adding two methylenes to the main hydrophobic chain. When the same analysis is performed on the unprotected surfactants **7** and **8** against their respect parent compounds (DTAB and CTAB, respectively) the glucose moiety causes an increase in the cmc, in agreement with the hydrophilicity enhancement imposed by the sugar addition. Looking at the surface tension data, in particular at the A_{min} values, the DTAB show an area of 49−50 Å^2, and this demonstrates once more that the higher area obtained for **7** is probably mainly due to the conformational freedom of the glucose that makes the whole headgroup more hydrated. The different charge type, ammonium, concentrated on the nitrogen atom, or ring delocalized pyridinium (case shown above for a β-glucopyridinium dodecyl surfactant), and the glucose conformational freedom are essential in determining the area value. The higher positive charge density present on the ammonium center can act to separate the charged headgroups in the adsorbed layer giving, as a whole result, a much greater area for compound **7** with respect to the DTAB.

Conclusions

In this paper, the preparation of a new series of surfactants, belonging to the glucocationic class, was performed. The procedure here reported was simple and good yielding. The characterization of the surfactants was performed by conductivity and surface tension measurements. The conductivity measurements could be useful to evaluate the cmc of the surfactants and also showed peculiar behavior in the premicellar concentration range. In fact, the formation of both tight ion couples and premicellar aggregates was evidenced. In general, the increase in hydrophobicity seems to cause a higher tendence to form premicellar aggregates. The surface tension plots gave the expected break point, normally taken as an evidence of the cmc, at a concentration substantially lower than the cmc measured by conductivity. This was explained by the formation of surface-unactive premicellar aggregates. The molar conductivity plots showed a maximum when the premicellar aggregation occurs and this concentration is in reasonable agreement with the surface tension break point. Besides, those data seem to evidence that the premicellar aggregates are no more surface active, but they can grow toward the normal micelles, not affecting the surface tension behavior. Those peculiar behaviors, taken with other evidences coming out in the recent literature, shed more light on the complexity of the surfactant aggregation, showing that more studies and more information is needed to elucidate the structure−properties relationships in order to predict the solution behavior of these kindly named "schizophrenic molecules".

Experimental Section

General Procedures and Materials. Please refer to the Supporting Information section.

2-Bromoethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (1). Method A. Compound **1** was prepared according to a literature method.[26] However, due to the yield increase the detailed procedure is reported. A solution of penta-*O*-acetyl-β-D-glucopiranose (63.5 g, 0.16 mol) and 2-bromoethanol (13.9 mL, 0.19 mol) in dry dichloromethane (250 mL) was introduced in a 500 mL three-necked round-bottom flask, placed in the dark and fitted with a dropping funnel. The solution was cooled at 0 °C, and $BF_3{\cdot}Et_2O$ (100 mL, 0.81 mol) was added dropwise over a period of 80 min. The reaction was then stirred at 0 °C for 3 h and for 20 h at room temperature. The completion of the reaction was monitored by TLC (ethyl acetate−petroleum ether 30:70; R_f = 0.3). At the end, the reaction mixture was diluted with further dichloromethane (50 mL) and then poured into cold water (250 mL) with vigorous stirring. The organic layer was separated and washed repeatedly with water and saturated sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and concentrated on the rotary evaporator, and the resulting residue was purified by flash

chromatography on silica gel using ethyl acetate−petroleum ether (30:70) as solvent. A white crystalline solid was obtained, yield 39.97 g (54%).

Method B. Compound **a** (0.5 g., 1.02 mM) was dissolved at 25 °C in 25 mL of anhydrous dicholoromethane in a three-necked flask under Ar. 2-Bromoethanol (0.14 g., 0.079 mL, 1.12 mM) was added dropwise under stirring followed by boron trifluoride etherate (0.144 g., 0.129 mL, 1.02 mM). The reaction was left at room temperature. The reaction progress was monitored by TLC (silica gel, petroleum ether/ethyl acetate 70:30), until the starting material disappeared. The reaction was quenched by adding a 10% $NaCO_3$ aqueous solution, and the organic phase was extracted three times with 10% $NaCO_3$ aqueous solution and washed with water to neutrality. The organic phase was treated with $NaSO_4$ and filtered. The solvent was removed under reduced pressure, giving a yellow-brown thick oil.

Flash chromatography on column of silica gel and petroleum ether/ethyl acetate 70:30 as the eluent gave the pure product (0.33 g., 71% yield), which crystallized immediately from the eluted fractions: mp 119−120 °C; $R_f = 0.30$ on silica (petroleum ether/ethyl acetate 70:30); $[\alpha]^{25}_{578} = -12.5$ ($c = 0.78$ $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.99, 2.01, 2.05, 2.07 (4 s, 12H, 4 CH_3COO); 3.44 (m, 2H, CH_2Br); 3.69 (ddd, 1H, H_5); 3.80 (ddd, 1H, O*C*$H_{2a}$$CH_2Br$); 4.11 (dd, 1H, H_{6a}); 4.15 (dd, 1H, O*C*$H_{2b}$$CH_2Br$); 4.24 (dd, 1H, H_{6b}); 4.55 (d, 1H, H_1, $J_{1,2} = 7.69$ Hz); 5.00 (dd, 1H, H_2); 5.07 (t, 1H, H_4); 5.20 (t, 1H, H_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.5 (CH_3*C*O*O*); 170.1 (CH_3*C*O*O*); 169.3 (2 CH_3*C*O*O*); 100.9 (C_1); 72.5 (C_3); 71.8 (C_5); 70.9 (C_2); 69.7 (O*C*H_2), 68.2 (C_4); 61.7 (C_6); 29.8 (CH_2Br); 20.6 (2 *C*H_3-COO); 20.5 (2 *C*H_3COO); FT-IR (KBr) (cm^{-1}) 2962, 2884, 1752, 1432, 1370, 1224, 1042, 904, 834, 510; MS-ESI (*m/z*) calcd 455, found 477, 479 (M + Na^+). Anal. Calcd for $C_{16}H_{23}BrO_{10}$: C, 42.21; H, 5.09. Found: C, 42.27; H, 5.03.

2-Bromoethyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (2). Method A. In a first step, the anomeric mixture of 2-bromoethyl-D-glucopyranoside was prepared according to a literature method.[22] This material was directly used in the synthesis of the compound **2**. The anomeric mixture (0.68 g, 2.2×10^{-3} mol) was dissolved in pyridine (4 mL) and added dropwise in a three-necked flask containing a previously chilled (0 °C) pyridine (8 mL) solution of acetic anhydride (3.15 mL, 3.33×10^{-2} mol) under stirring. After 80 min, the mixture was allowed to return to room temperature and reacted for 4 h, when it was quenched with brine (50 mL). The product separated as an oil, and 15 mL of concd HCl wa added. The mixture was extracted with dichloromethane, washing the organic phase with $NaHCO_3$ solution until neutralization was attained. After drying with Na_2SO_4, evaporation of the solvent in vacuo gave a viscous oil which, by flash chromatography on silica (petroleum ether/ethyl acetate 70:30), furnished a pale yellow oil, yield (based on starting glucose) 10%.

Method B: Anomerization of Compound 1. Compound **1** (3 g, 6.59 mmol) was introduced in a three-necked round-bottom flask, dissolved in 20 mL of dichloromethane, and stirred under argon at room temperature. Anhydrous ferric chloride (5.3 g., 32.7 mmol) was quickly added to the reaction. The black solution was allowed to react overnight and quenched with water (20 mL). The organic phase was extracted three times with water, dried with $CaCl_2$, and evaporated, giving a dark brown oil. Flash chromatography on silica with petroleum ether/ethyl acetate 70:30 gave a colorless oil that solidified on prolonged standing. A white solid paste was obtained: yield 0.91 g (30%); $R_f = 0.21$ on silica (petrol ether/ethyl acetate 70:30); $[\alpha]^{25}_{578} = +112.52$ ($c = 0.558$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.99, 2.00, 2.06, 2.07 (4 s, 12H, 4 CH_3COO); 3.49 (t, 2H, CH_2Br); 3.82, 3.97 (2 sym quintets, 2H, O*C*H_2CH_2Br), 4.08−4.11 (m, 2H, H_5+H_{6a}); 4.20−4.24 (m, 1H, H_{6b}); 4.83 (dd, 1H, H_2); 5.04 (t, 1H, H_4); 5.13 (d, 1H, H_1, $J_{1,2} = 3.8$ Hz); 5.47 (t, 1H, H_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.6 (CH_3*C*O*O*); 170.2 (CH_3*C*O*O*); 170.0 (CH_3*C*O*O*); 169.6 (CH_3*C*O*O*); 96.0 (C_1); 70.8 (C_2); 69.9 (C_3); 68.8 (C_4); 68.5 (O*C*H_2), 67.7 (C_5); 61.9 (C_6); 29.8 (CH_2Br); 20.7 (2 *C*H_3COO); 20.6 (2 *C*H_3COO); FT-IR (KBr) (cm^{-1}) 2958, 1750, 1434, 1372, 1244, 1038, 904, 834, 756, 694, 602, 554, 524; MS-ESI (*m/z*) calcd 455, found 477, 479 (M + Na^+). Anal. Calcd for $C_{16}H_{23}BrO_{10}$: C, 42.21; H 5.09. Found: C, 42.25; H, 5.06.

***N*-[2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-octylammonium Bromide (3).** In a three-necked flask, compound **1** (10.49 g, 0.023 mol) was dissolved in anhydrous ethanol under argon. The mixture was warmed at reflux, and an ethanolic solution of *N*,*N*-dimethyloctylamine (3.21 g, 0.0204 mol) was added dropwise. After 24 h, a 10% excess of compound **1** was added, and the reaction was continued for further 24 h. The solvent was removed in vacuo, and the resulting viscous oil was purified by flash chromatography on basic alumina first with ethyl acetate and subsequently with ethyl acetate/methanol 80:20 and 50:50. The resulting viscous pale yellow syrup solidified on standing and was further purified from trace of the amine by suspension in petroleum ether and a small quantity of chloroform, under stirring. A white powder was finally obtained: yield 70%; mp 95−100 °C; $R_f = 0.05$ on silica (MAC methanol/acetic acid/chloroform 20:10:70); 0.17 on basic alumina (ethyl acetate/methanol 70:30); $[\alpha]^{25}_{578} = -12.12$ ($c = 0.775$, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 0.86 (t, 3H CH_3); 1.30 (m, 10H, 5 CH_2); 1.70 (m, 2H, N^+-CH_2-*C*H_2); 1.95, 2.01, 2.04, 2.07 (4 s, 12H, 4 *C*H_3-COO); 3.32(s, 3H, N^+CH_3); 3.35(s, 3H, N^+CH_3); 3.48 (t, 2H, N^+*C*H_2); 3.80 (m, 1H, H_5); 3.94 (ddd, 1H, OCH_2*C*$H_{2a}N^+$), 4.08−4.22 (m, 4H, OCH_2*C*$H_{2b}N^+$, $OCH_{2a}CH_2N^+$, 2H_6); 4.33 (dd, 1H, O*C*$H_{2b}CH_2N^+$); 4.66 (d, 1H, H_1, $J_{1,2} = 8.02$ Hz); 4.90 (dd, 1H, H_2); 5.02 (t, 1H, H_4); 5.08 (t, 1H, H_3); ^{1}H NMR (DMSO-d_6) δ (ppm) 0.88 (t, 3H CH_3); 1.29 (m, 10H, 5 CH_2); 1.66 (m, 2H, N^+-CH_2-*C*H_2); 1.95, 2.00, 2.03, 2.04 (4 s, 12H, 4 *C*H_3COO); 3.04 (s, 6H, 2 N^+CH_3); 3.30 (t, 2H, N^+*C*H_2); 3.57 (t, 2H, OCH_2*C*H_2N^+), 4.03−4.22 (m, 5H, O*C*$H_2CH_2N^+$, H_5, 2H_6); 4.82 (dd, 1H, H_2); 4.93−4.97 (m, 2H, H_1, H_4); 5.29 (t, 1H, H_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.4 (CH_3*C*O*O*); 169.7 (CH_3*C*O*O*); 169.3 (2 CH_3*C*O*O*); 100.1 (C_1); 72.2 (C_3); 72.0 (C_5); 70.8 (C_2); 67.9 (C_4); 66.0 (N^+*C*H_2); 63.5 (O*C*H_2), 62.9 (OCH_2*C*H_2N^+); 61.3 (C_6); 51.5 (2 N^+CH_3); 31.4, 29.0; 28.8; 26.0 (4 CH_2); 22.6 (N^+CH_2*C*H_2); 22.4 (CH_2); 20.7 (*C*H_3COO); 20.6 (*C*H_3COO); 20.4 (*C*H_3COO); 20.3 (*C*H_3COO); 13.9 (CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.1 (CH_3*C*O*O*); 169.6 (CH_3*C*O*O*); 169.3 (CH_3*C*O*O*); 169.2 (CH_3*C*O*O*); 98.9 (C_1); 72.0 (C_3); 70.8 (C_5); 70.6 (C_2); 68.1 (C_4); 64.1 (N^+*C*H_2); 62.6 (O*C*H_2); 62.2 (OCH_2*C*H_2N^+); 61.6 (C_6); 50.8 (N^+CH_3); 50.7 (N^+CH_3); 31.2, 25.8 (4 CH_2); 22.1 (N^+CH_2*C*H_2); 21.8 (CH_2); 20.6 (*C*H_3COO); 20.5 (*C*H_3COO); 20.5 (*C*H_3COO); 20.3 (*C*H_3COO); 14.0 (CH_3); FT-IR (KBr): cm^{-1} 2928, 2858, 1752, 1438, 1372, 1226, 1166, 1042, 910; MS-ESI: (*m/z*) calcd 612, found 532 (M − Br). Anal. Calcd for $C_{26}H_{46}BrNO_{10}$: C, 50.98; H, 7.57; N, 2.29. Found: C, 50.94; H, 7.59; N, 2.32.

***N*-[2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-dodecylammonium Bromide (4).** The same procedure described for product **3** was applied, giving a white powder: yield 60%; mp 90−93 °C; $R_f = 0.05$ on silica (MAC 20:10:70); 0.22 on basic alumina (ethyl acetate/methanol 70:30); $[\alpha]^{25}_{578} = -11.68$ ($c = 0.78$, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm) 0.87 (t, 3H CH_3); 1.26 (m, 18H, 9 CH_2); 1.65 (m, 2H, N^+−CH_2-*C*H_2); 1.95, 2.00, 2.03, 2.04 (4 s, 12H, 4 *C*H_3COO); 3.04(s, 6H, 2 N^+CH_3); 3.30 (t, 2H, N^+*C*H_2); 3.57 (t, 2H, OCH_2*C*H_2N^+); 4.03−4.22 (m, 5H, O*C*$H_2CH_2N^+$, H_5, 2H_6); 4.82 (dd, 1H, H_2); 4.93−4.97 (m, 2H, H_1, H_4); 5.29 (t, 1H, H_3); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.1 (CH_3*C*O*O*); 169.6 (CH_3*C*O*O*); 169.3 (CH_3*C*O*O*); 169.2 (CH_3*C*O*O*); 99.0 (C_1); 71.9 (C_3); 70.8 (C_5); 70.7 (C_2); 68.1 (C_4); 64.1 (N^+*C*H_2); 62.6 (O*C*H_2), 62.2 (OCH_2*C*H_2N^+); 61.6 (C_6); 50.8 (N^+CH_3); 50.7 (N^+CH_3); 31.4−25.8 (8 CH_2); 22.2 (N^+CH_2*C*H_2); 21.8 (CH_2); 20.6 (*C*H_3COO); 20.5 (2 *C*H_3COO); 20.3 (*C*H_3COO); 14.0 (CH_3); FT-IR (KBr) (cm^{-1}) 2926, 2856, 1751, 1464, 1372, 1224, 1042, 908; MS-ESI (*m/z*) calcd 668, found 588 (M − Br). Anal. Calcd for $C_{30}H_{54}NO_{10}Br$: C, 53.89; H, 8.14; N, 2.09. Found: C, 53.83; H, 8.19; N, 2.04.

***N*-[2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-hexadecylammonium Bromide (5).** The same procedure described for product **3** was applied, giving a white powder: yield 58.6%; mp 53−55 °C; $R_f = 0.05$ on silica (MAC 20:10:70); 0.29 on basic alumina (ethyl acetate/methanol 70:30); $[\alpha]^{25}_{578} = -16.01$ ($c = 0.82$, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm) 0.87 (t, 3H CH_3); 1.25 (m, 26H, 13 CH_2); 1.66 (m, 2H, N^+-CH_2-CH_2); 1.96, 2.01, 2.03, 2.04 (4 s, 12H, 4 CH_3COO); 3.04 (s, 6H, N^+CH_3); 3.30 (t, 2H, N^+CH_2); 3.57 (t, 2H, $OCH_2CH_2N^+$); 4.03−4.22 (m, 5H, $OCH_2CH_2N^+$, H_5, 2H_6); 4.83 (dd, 1H, H2); 4.93−4.97 (d, 1H, H1, H4); 5.30 (t, 1H, H3); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.1 (CH_3COO); 169.6 (CH_3COO); 169.3 (CH_3COO); 169.2 (CH_3COO); 99.0 (C_1); 71.9 (C_3); 70.8 (C_5); 70.7 (C_2); 68.1 (C_4); 64.1 (N^+CH_2); 62.6 (OCH_2), 62.2 ($OCH_2CH_2N^+$); 61.6 (C_6); 50.8 (N^+CH_3); 50.7 (N^+CH_3); 31.4−25.8 (12 CH_2); 22.2 ($N^+CH_2CH_2$); 21.8 (CH_2); 20.6 (CH_3COO); 20.5 (2CH_3COO); 20.5 (CH_3COO); 20.3 (CH_3COO); 14.0 (CH_3); FT-IR (KBr) (cm^{-1}) 2924, 2854, 1739, 1462, 1438, 1372, 1213, 1166, 1037, 910, 732, 700; MS-ESI (*m*/*z*) calcd 724, found 644 (M − Br). Anal. Calcd for $C_{34}H_{62}NO_{10}Br$: C, 56.34; H, 8.62; N, 1.93. Found: C, 56.36; H, 8.58; N, 1.99.

***N*-[2-(β-D-Glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-octylammonium Bromide (6).** In a three-necked round-bottom flask was dissolved product **3** (5 g, 8.16 mmol) in dry methanol (100 mL). Sodium methoxide (6.91 mequiv) was introduced, and the mixture was stirred at room temperature. Completion of the reaction was monitored by TLC (MAC 20:10:70). At the end of reaction ion exchanger Amberlite IR-120 was added (H^+-form, 1.57 g, 6.91 mequiv) under vigorous stirring. The mixture was filtered and the solvent was then evaporated in vacuo giving a brown-yellow syrup: yield 7.19 g (90%); $R_f = 0.05$ on silica (MAC 20:10:70); $[\alpha]^{25}_{578} = -18.5$ ($c = 0.53$, MeOH); ^{1}H NMR (D_2O; acetone as reference) δ (ppm) 0.80 (t, 3H CH_3); 1.26 (m, 10H, 5 CH_2); 1.73 (m, 2H, N^+-CH_2-CH_2); 3.08 (s, 6H, 2 N^+CH_3); 3.20−3.48 (m, 6H, H_2, H_3, H_4, H_5, N^+CH_2); 3.58 (t, 2H, $OCH_2CH_{2a}N^+$); 3.68 (dd, 1H, H_{6a}); 3.86 (dd, 1H, H_{6b}); 4.02−4.06 (m, 1H, $OCH_{2a}CH_2N^+$); 4.28−4.31 (m, 1H, $OCH_{2b}CH_2N^+$); 4.44 (d, 1H, H_1, $J_{1,2} = 7.87$ Hz); ^{13}C NMR (D_2O; acetone as reference) δ (ppm) 104.9 (C_1); 78.7 (C_5); 78.4 (C_3); 75.7 (C_2); 72.3 (C_4); 68.2 (N^+CH_2); 65.9 ($OCH_2CH_2N^+$), 65.7 (OCH_2); 63.4 (C_6); 54.1 (2 N^+CH_3); 33.7−24. 6 (6 CH_2); 16.1 (CH_3); FT-IR (KBr) (cm^{-1}) 2924, 2854, 1739, 1462, 1438, 1372, 1213, 1116; MS-ESI (*m*/*z*) calcd 444, found 364, (M − Br). Anal. Calcd from $C_{34}H_{62}NO_{10}Br$: C, 48.65; H, 8.62; N, 3.15. Found: C, 48.71; H, 8.69; N, 3.13.

***N*-[2-(β-D-Glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-dodecylammonium Bromide (7). Method A.** In a three-necked, round-bottom flask was dissolved the product **3** (10 g, 0.015 mol) in methanol (200 mL). The solution was chilled at 0 °C, and gaseous ammonia was introduced for about 1 h under stirring. The reaction was allowed to warm to room temperature and continued to stir until the starting material disappeared. The solvent was then evaporated in vacuo, and the resulting syrup was crystallized twice from dichloromethane/ethyl acetate. The crystals were recovered by filtration on a Büchner funnel, obtaining a slightly hygroscopic white powder.

Method B. The same procedure described for product **6** was applied. The resulting syrup was crystallized twice from dichloromethane/ethyl acetate. The crystals were recovered by filtration on a Büchner funnel, obtaining a slightly hygroscopic white powder: yield 100%; mp 184−188 °C; $R_f = 0.05$ on silica (MAC 20:10:70) $[\alpha]^{25}_{578} = -14.4$ ($c = 0.52$, MeOH); ^{1}H NMR (D_2O; acetone as reference) δ (ppm) 0.84 (t, 3H CH_3); 1.30 (m, 18H, 9 CH_2); 1.75 (m, 2H, N^+-CH_2-CH_2); 3.14 (s, 6H, 2 N^+-CH_3); 3.25 (t, 1H, H_2); 3.31 (t 1H, H_4); 3.48−3.37 (t, 4H, N^+CH_2, H_3, H_5); 3.69−3.58 (m, 3H, $OCH_2CH_2N^+$, H_{6a}); 3.88 (d, 1H, H_{6b}); 4.07 (m, 1H, $OCH_{2b}CH_2N^+$); 4.32 (m, 1H, $OCH_{2a}CH_2N^+$); 4.47 (t, 1H, H_1, $J = 7.87$ Hz); ^{13}C NMR DEPT (D_2O; acetone as reference) δ (ppm) 102.5 (C_1); 76.4 (C_5); 76.0 (C_3); 73.3 (C_2); 70.0 (C_4); 66.0 (N^+CH_2); 63.6 ($OCH_2CH_2N^+$), 63.4 (OCH_2); 61.1 (C_6); 51.7 (2 N^+CH_3); 32.1−25.6 (10 CH_2); 14.1 (CH_3); FT-IR (KBr) (cm^{-1}) 2922, 2854, 1464, 1416, 1374, 1160, 1074, 1044, 752; MS-ESI (*m*/*z*) calcd 500, found 420 (M − Br). Anal. Calcd from $C_{34}H_{62}NO_{10}Br$: C, 52.79; H, 9.26; N, 2.80. Found: C, 52.81; H, 9.21; N, 2.75.

***N*-[2-(β-D-Glucopyranosyl)ethyl]-*N*,*N*-dimethyl-*N*-hexadecylammonium Bromide (8).** The same procedure described for product **7** was applied (method B): yield 100%; mp 198−200 °C; $R_f = 0.05$ on silica (MAC 20:10:70); $[\alpha]^{25}_{578} = -26.57$ ($c = 0.56$, MeOH); ^{1}H NMR (D_2O; acetone as reference) δ (ppm) 0.85 (t, 3H CH_3); 1.30 (m, 26H, 13 CH_2); 1.76 (m, 2H, N^+-CH_2-CH_2); 3.17 (s, 6H, 2 N^+CH_3); 3.26 (t, 1H, H_2); 3.32 (t 1H, H_4); 3.49−3.41 (t, 4H, N^+CH_2, H_3, H_5); 3.69−3.65 (m, 3H, $OCH_2CH_2N^+$, $H6_a$); 3.87 (d, 1H, $H6_b$); 4.09 (m, 1H, OCH_{2b}-CH_2N^+); 4.34 (m, 1H, $OCH_{2a}CH_2N^+$); 4.49 (t, 1H, H_1, $J = 7.87$ Hz); ^{13}C NMR (D_2O; acetone as reference) δ (ppm) 103.0 (C_1); 77.0 (C_5); 76.6 (C_3); 73.8 (C_2); 70.5 (C_4); 66.7 (N^+CH_2); 64.3 ($OCH_2CH_2N^+$), 63.8 (OCH_2); 61.6 (C_6); 52.1 (2 N^+CH_3); 32.8−23.5 (14 CH_2); 14.7 (CH_3); FT-IR (KBr) (cm^{-1}) 2916, 2850, 1464, 1414, 1374, 1258, 1116, 1080, 1030, 922, 898, 724; MS-ESI (*m*/*z*) calcd 556, found 476, (M − Br). Anal. Calcd from $C_{34}H_{62}NO_{10}Br$: C, 56.10; H, 9.78; N, 2.52. Found: C, 56.08; H, 9.75; N, 2.57.

Acknowledgment. This work was supported by a contribution from the Consiglio Nazionale delle Ricerche (CNR), of the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, COFINLAB 2001—"Superfici ed Interfasi Nanostrutturate"), Italy, of the University of Torino (ex-60% funds), and of the University of Parma (FIL 2005). We are particularly grateful to Compagnia San Paolo (Torino, Italy) and the Fondazione Cassa di Risparmio di Torino for supplying laboratory equipment.

Supporting Information Available: General procedures, ^{1}H, ^{13}C, COSY, HETCOR, and HMQC NMR experiments for new compounds, specific conductivity vs *C* plots, and molar conductivity vs $C^{0.5}$ plots for all soluble surfactants. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051579S