Sugar-Derived Tricatenar Catanionic Surfactant: Synthesis, Self-Assembly Properties, and Hydrophilic Probe Encapsulation by Vesicles

Elodie Soussan,[†] Caroline Mille,[†] Muriel Blanzat,*[,†] Pascal Bordat,[‡] and Isabelle Rico-Lattes[†]

Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique, UMR CNRS 5623, Université Paul Sabatier, 31062 Toulouse Cedex 4, France, and Pierre Fabre Dermo-Cosmétique, 17 allée Camille Soula BP 74, 31322 Castanet Tolosan cedex, France

Received July 19, 2007. In Final Form: December 4, 2007

A new sugar-derived tricatenar catanionic surfactant (TriCat) was developed to obtain stable vesicles that could be exploited for drug encapsulation. The presence of the sugar moiety led to the formation of highly hydrophilic stoichiometric catanionic surfactant systems. The three hydrophobic chains permitted vesicles to form spontaneously. The self-assembly properties (morphology, size, and stability) of TriCat were examined in water and in buffer solution. Encapsulation studies of a hydrophilic probe, arbutin, commonly used in cosmetics for its whitening properties, were performed to check the impermeability of the vesicle bilayer. The enhancement of hydrophobic forces by the three chains of TriCat prevented surfactant equilibrium between the bilayer and the solution and enabled the probe to be retained in the aqueous cavity of the vesicles for at least 30 h. Thus, the present study suggests that this tricatenar catanionic surfactant could be a promising delivery system for hydrophilic drugs.

Introduction

The effectiveness of a drug is determined by its ability to migrate through the body and reach diseased tissue in therapeutically relevant amounts. Therefore, drug delivery systems designed to improve the pharmacological and therapeutic properties of drugs administered are one of the central topics of current therapeutic research.[1] Among several promising new drug delivery systems, drug encapsulation in vesicles is an advanced technology for delivering active molecules. Drugs entrapped in this kind of microstructure are temporarily protected against enzymatic and immunological reactions of the human body. Moreover, the toxicity of the drugs is reduced, their time of activity is increased, and these carriers can be designed to deliver the drugs to a specific diseased cell.

Among supramolecular architectures, mixtures of oppositely charged surfactants, so-called catanionic surfactants, are a growing area of research. These mixtures have been shown to spontaneously form several different types of surfactant aggregates, such as micelles of various forms and sizes, and particularly lamellar structures such as vesicles.[2−5] Thus, catanionic surfactants offer promise for the design of a new drug delivery system.

To this end, our laboratory first designed and developed catanionic bicatenar surfactants.[6−9] Accordingly, to enhance the hydrophobic interactions which are the driving forces of molecular aggregation in water, a new catanionic tricatenar surfactant,[10−12] TriCat, possessing three hydrocarbon chains, was designed. Furthermore, the association of the anionic and cationic moieties was improved over a wider pH range by introducing a phosphinic acid,[13−15] which is stronger than carboxylic acid. The strengthened association between the two moieties of the catanionic surfactant TriCat should lead to more stable and less permeable aggregates.[16]

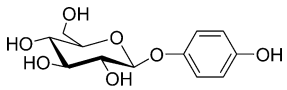


Figure 1. Chemical structure of arbutin.

Moreover, for recognition of a target cell, the strategy was to prepare sugar-grafted surfactants. Glycolipids are an important class of naturally occurring amphiphiles, which have been shown to be involved in diverse intercellular recognition events.[17] They are intimately involved in important phenomena such as interactions of cancer cells with hosts, cell−cell recognition,[18] the working of the immune system,[19] tissue growth and repair, and the interaction of cells with bacteria[20] or viruses,[21] since the

* To whom corrrespondence should be addressed. E-mail: blanzat@chimie.ups-tlse.fr. Telephone: (+33) 5-61-55-73-75. Fax: (+33) 5-61-55-81-55.

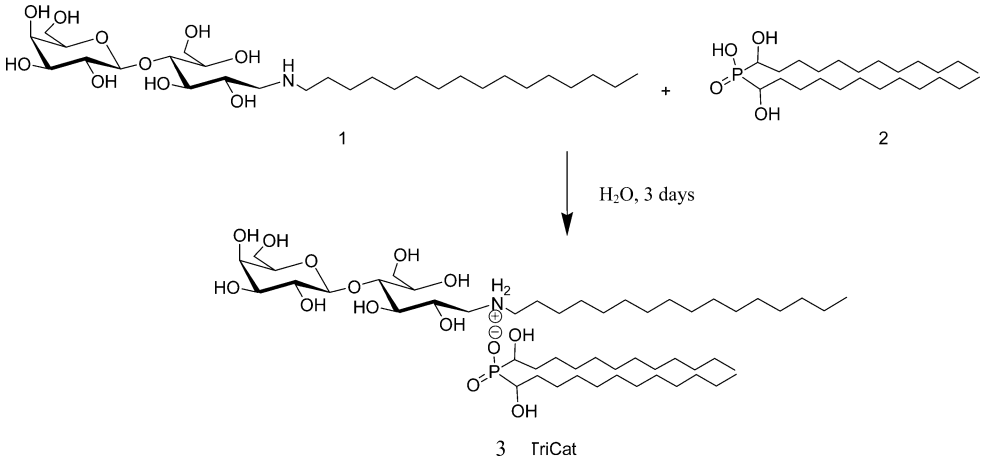
[†] Université Paul Sabatier.

[‡] Pierre Fabre Dermo-Cosmétique.

(1) Gregoriadis, G. *Trends Biotechnol.* **1995**, *13*, 527.
(2) Tondre, C.; Caillet, C. *Adv. Colloid Interface Sci.* **2001**, *93*, 115.
(3) Dubois, M.; Deme, B.; Gulik-Krzywicki, T.; Dedieu, J. C.; Vautrin, C.; Desert, S.; Perez, E.; Zemb, T. *Nature* **2001**, *411*, 672.
(4) Dubois, M.; Lizunov, V.; Meister, A.; Gulik-Krzywicki, T.; Verbavatz, J. M.; Perez, E.; Zimmerberg, J.; Zemb, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15082.
(5) Kaler, E. W.; Kamalakara Murthy, A.; Rodriguez, B. E.; Zasadzinski, J. A. N. *Science* **1989**, *245*, 1371.
(6) Pasc-Banu, A.; Stan, R.; Blanzat, M.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Labrot, T.; Oda, R. *Colloids Surf., A* **2004**, *242*, 195.
(7) Rico-Lattes, I.; Blanzat, M.; Franceschi-Messant, S.; Perez, E.; Lattes, A. *C. R. Chim.* **2005**, *8*, 807.
(8) Blanzat, M.; Perez, E.; Rico-Lattes, I.; Promé, D.; Promé, J. C.; Lattes, A. *Langmuir* **1999**, *15*, 6163.
(9) Blanzat, M.; Perez, E.; Rico-Lattes, I.; Lattes, A. *New J. Chem.* **1999**, *23*, 1063.
(10) Marques, E.; Khan, A.; Da Gracia Miguel, M.; Lindman, B. *J. Phys. Chem.* **1993**, *97*, 4729.
(11) Marques, E. F.; Regev, O.; Khan, A.; Lindman, B. *Adv. Colloid Interface Sci.* **2003**, *100*, 83.
(12) Soussan, E.; Blanzat, M.; Rico-Lattes, I.; Brun, A.; Teixeira, C.; Brezesinski, G.; Al-Ali, F.; Banu, A.; Tanaka, M. *Colloids Surf., A* **2007**, *303*, 55.
(13) Brun, A.; Albouy, D.; Perez, E.; Rico-Lattes, I.; Etemad-Moghadam, G. *Langmuir* **2001**, *17*, 5208.
(14) Brun, A.; Etemad-Moghadam, G. *Synthesis* **2002**, *10*, 1385.
(15) Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1998**, *63*, 7223.
(16) Chung, Y.-C.; Lee, H.-J.; Park, J.-Y. *Bull. Korean Chem. Soc.* **1998**, *19*, 1249.
(17) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978.
(18) Hakomori, S. *Pure Appl. Chem.* **1991**, *63*, 473.
(19) Rosen, M. J. *Chemtech* **1993**, 30.
(20) Bouguenec, C. L. *Int. J. Med. Microbiol.* **2005**, *295*, 471.

10.1021/la702171s CCC: $40.75
Published on Web 02/13/2008

Scheme 1. Synthesis of 1-*N*-Hexadecylammonium-1-deoxylactitol-bis(α-hydroxydodecyl)phosphinate (TriCat)



sugar moiety can influence the biological and molecular recognition properties. The presence of the sugar moiety also allows highly hydrophilic stoichiometric catanionic surfactant systems to form, which do not precipitate upon equimolar combination.[22] Moreover, the sugar moiety creates a thick hydrated barrier that should prevent the collapse of vesicle bilayers.[23]

The aim of the present work was first the synthesis of a new sugar-derived tricatenar catanionic surfactant (TriCat) and the study of its self-assembling properties. The entrapment inside TriCat vesicles was quantified using a fluorescent drug, arbutin (Figure 1), commonly used in cosmetics for its whitening properties.[24] These results were used to evaluate TriCat's capability to form stable vectors that could be exploited for drug delivery. All the work was also performed in a buffer solution to validate future biological applications.

Results and Discussion

N-Hexadecylamino-1-deoxylactitol **1** and bis(hydroxydodecyl)phosphinic acid **2** were synthesized according to standard procedures reported in the literature.[8,9,14] Product **1** was synthesized through a reductive amination of the hexadecylamine on α-lactose monohydrate. This sugar-derived compound **1** possesses surfactant properties: it forms micelle aggregates in water and decreases the surface tension of water to about 35 mN/m. The critical micelle concentration (CMC) has been evaluated by surface tension measurements to be 5×10^{-4} M.

The addition of hypophosphorous acid to dodecylaldehyde led to the formation of the bis-adduct **2** by an Abramov reaction. This product is not soluble in water.

TriCat (1-*N*-hexadecylammonium-1-deoxylactitol-bis(α-hydroxydodecyl)phosphinate) was synthesized via an acid−base reaction in water, by addition of the phosphinic acid **2** to a slightly cloudy aqueous solution of *N*-hexadecylamino-1-deoxylactitol **1**[25−36] (Scheme 1). The initial heterogeneous suspension turned to a viscous milky solution when the reaction was complete. The reaction was followed by pH measurements until it had stabilized.

The completion of the acid−base reaction was enabled by the hydrophobic effect between alkyl chains in water.[37] Proton transfer between the phosphinic acid and the amine produced a catanionic pair, characterized by Fourier transform infrared (FT-IR) spectroscopy. The characterization brought out the appearance of the typical $R_2PO_2^-$ stretching absorption band at 1045 cm^{-1} and also the disappearance of $R_2(OH)PO$ absorption bands at 1115 cm^{-1}, POH absorption bands at 941 and 2162 cm^{-1}, and NH absorption bands at 1654 cm^{-1}, which confirmed the completion of the acid−base reaction.

To identify interactions between this surfactant ionic pair, investigations based on TriCat molecular modeling were then carried out (Figure 2) in an aqueous medium. Hydrophobic chains tend to lie close to one another to minimize their contact with water. Two hydrogen bonds, between the hydrogens of NH_2^+ and the oxygens of $P(O)O^-$, were detected at distances of ∼1.89 and ∼1.84 Å (a typical hydrogen bond length in water). Thus, we can assume that water did not dissociate the ion pair because of the hydrophobic effect among the three chains. This model supports the molecular design idea of introducing three carbon chains to increase the association between the cationic and anionic units, leading to an ion pair associated system in water.

This model also provided an estimation of the TriCat geometry, which is believed to play a critical role in defining its supramolecular properties. The effective interfacial headgroup area of each part of the catanionic surfactant seems to be smaller than that for each individual surfactant because of the electrostatic attraction and the removal of hydration water as charges become neutralized.[38,39] Thus, the contribution of the three chains results in a molecule in which the hydrophobic character is as great as the hydrophilic one. According to the concept of Israelachvili,[40]

(21) Suzuki, Y.; Ito, T.; Suzuki, T.; Miyamoto, D.; Hidari, K. I.-P. J.; Guo, C.-T.; Kida, H.; Webster, R. G.; Chambers, T. M.; Kawaoka, Y. *Int. Congr. Ser.* **2001**, *1219*, 521.
(22) Vautrin, C.; Dubois, M.; Zemb, T.; Schmolzer, S.; Hoffmann, H.; Gradzielski, M. *Colloids Surf., A* **2003**, *217*, 165, Symposium C of the E-MRS 2002 Spring Meeting in Strasbourg, France.
(23) Zhu, J.; Yan, F.; Guo, Z.; Marchant, R. E. *J. Colloid Interface Sci.* **2005**, *289*, 542.
(24) Tomita, K.; Fukuda, M.; Kawasaki, K. *Fragrance J.* **1990**, *6*, 72.
(25) André-Barrès, C.; Madelaine-Dupuich, C.; Rico-Lattes, I. *New J. Chem.* **1995**, *19*, 345.
(26) Dupuy, C.; Auvray, X.; Petipas, C.; Anthore, R.; Costes, F.; Rico-Lattes, I.; Lattes, A. *Langmuir* **1996**, *12*, 3162.
(27) Fantini, J.; Hammache, D.; Delezay, O.; Yahi, N.; André-Barrès, C.; Rico-Lattes, I.; Lattes, A. *J. Biol. Chem.* **1997**, *272*, 7245.
(28) Garelli-Calvet, R.; Latge, P.; Rico, I.; Lattes, A. *Biochim. Biophys. Acta* **1992**, *1109*, 55.
(29) Garrigues, J.-C.; Perez, E.; Linas, M. D.; Rico-Lattes, I.; Seguela, J.-P.; Lattes, A. *J. Mycol. Med.* **1996**, *6*, 111.
(30) Latgé, P.; Rico, I.; Garelli, R.; Lattes, A. *J. Dispersion Sci. Technol.* **1991**, *12*, 227.
(31) Rico-Lattes, I.; Garrigues, J. C.; Perez, E.; André-Barrès, C.; Madelaine-Dupuich, C.; Lattes, A. *New J. Chem.* **1995**, *19*, 341.
(32) Rico-Lattes, I.; Gouzy, M. F.; Andre-Barres, C.; Guidetti, B.; Lattes, A. *Biochimie* **1998**, *80*, 483.
(33) Rico-Lattes, I.; Gouzy, M. F.; André-Barrès, C.; Guidetti, B.; Lattes, A. *New. J. Chem.* **1998**, *22*, 451.
(34) Rico-Lattes, I.; Lattes, A. *Colloids Surf., A* **1997**, *37*, 123.
(35) Bhattacharya, S.; Ghanashyam Acharya, S. N. *Chem. Mater.* **1999**, *11*, 3504.
(36) Bhattacharya, S.; Ghanashyam Acharya, S. N. *Langmuir* **2000**, *16*, 87.
(37) Soussan, E.; Pasc-Banu, A.; Consola, S.; Labrot, T.; Perez, E.; Blanzat, M.; Oda, R.; Vidal, C.; Rico-Lattes, I. *ChemPhysChem* **2005**, *6*, 2492.

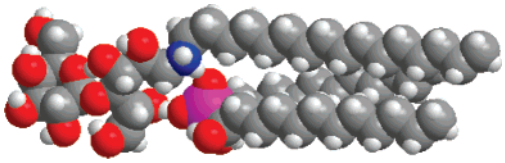


Figure 2. Molecular model of TriCat calculated in an aqueous environment with a H_2O thickness of 5 Å.

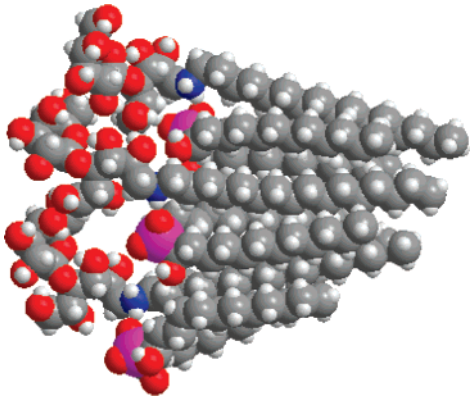


Figure 3. Molecular model of three molecules of TriCat in an aqueous environment with a H_2O thickness of 5 Å.

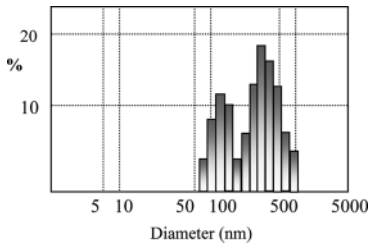


Figure 4. Size distribution of aggregates formed by TriCat (1×10^{-3} M) in aqueous solution at 25 °C.

the packing parameter relative to the cylindrical geometry of TriCat should drive the aggregation toward bilayers (possibly membranes or vesicles).

To characterize the intermolecular interactions resulting from a predictable aggregation of TriCat, a study was then carried out on three of these catanionic surfactants in water by molecular modeling. On the model of Figure 3, the catanionic surfactants are aggregated in water due to the hydrophobic effect. Intermolecular hydrogen bonds were also formed between the sugar moieties of the three surfactants. These two effects should lead to a spontaneous and stable aggregation of TriCat in water. Moreover, the aggregated surfactants tend to change their cylindrical morphology and to adopt truncated cone geometry in water. This geometry should drive vesicle formation in water.

Consequently, we first examined the self-assembly properties of TriCat surfactant in pure water. The critical aggregation concentration (CAC) of TriCat was determined by surface tension titration and found to be 3.5×10^{-5} M in water. Above the CAC, the size distribution of aggregates was analyzed by dynamic light scattering (DLS; Figure 4) and their shape was observed by transmission electron microscopy (TEM; Figure 5) and freeze fracture experiments (Figure 6).

Two different aggregate populations formed by TriCat were detected by DLS measurements. The first population was centered

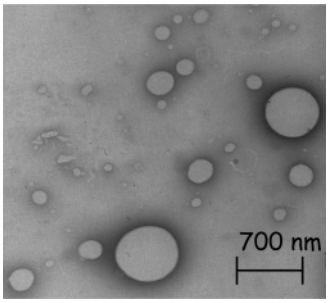


Figure 5. TEM micrograph obtained for TriCat (1×10^{-3} M) compound in aqueous solution.

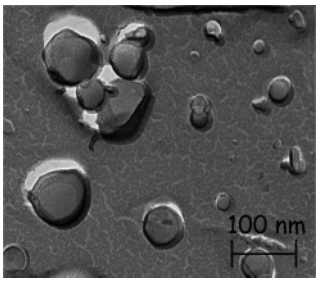


Figure 6. Freeze fracture micrograph obtained for TriCat (1×10^{-3} M) compound in aqueous solution.

at 150 nm (40%), and the second corresponded to larger objects, around 400 nm (60%).

TEM micrographs showed vesicles having diameters correlated with the size distribution obtained by DLS measurements. It was, therefore, necessary to ascertain the presence of vesicles by performing freeze fracture experiments, which do not require any contrast agent.

The micrograph presented in Figure 5 confirmed the spontaneous vesicle formation in water by self-assembly of TriCat surfactants. Moreover, these vesicles were unilamellar, since all of the aggregates presented only one bilayer[37] and not an onionlike structure as for multilamellar vesicles.[41] These catanionic vesicles were also fracturable, which is usual for vesicles formed by a bilayer. Indeed, the fracture propagates according to the interaction zones of weaker energy which correspond to the hydrophobic interactions between the two monolayers.

The stability of the aggregates was then determined by studying the behavior of these vesicles versus time.

DLS measurements (Figure 7) followed the stability of vesicles formed by the TriCat compound over time. The size distribution of the aggregates was stable for at least 75 h. Larger objects (~800 nm), probably resulting from the aggregation of these vesicles, then appeared rapidly, leading to precipitation of the catanionic system. The precipitate was observed by TEM (Figure 8) to investigate the origin of vesicle destabilization.

This micrograph displays vesicle aggregates. The precipitation of the system was due to a vesicle agglomeration which settled down with time. However, the presence of the lactose moiety created a thick hydrated barrier[23] which prevented vesicle fusion. Experiments are running to investigate the reversibility of this destabilization phenomenon.

Although the stability of the vesicle solution lasted only for a few days, this time could be improved to as long as 12 days by adding 30% in volume of glycerol. Moreover, this solution could be frozen for longer conservation without disrupting vesicles.

(38) Engberts, J. B.; Kevelam, J. *Curr. Opin. Colloid Interface Sci.* **1996**, *1*, 779.
(39) Fuduka, H.; Kawata, K.; Okuda, H. *J. Am. Chem. Soc.* **1990**, *112*, 1635.
(40) Israelachvili, J. N.; Mitchell, D. J.; Ninham, B. W. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 1525.
(41) Auguste, F.; Douliez, J.-P.; Bellocq, A.-M.; Dufourc, E. J.; Gulik-Krzywicki, T. *Langmuir* **1997**, *13*, 666.

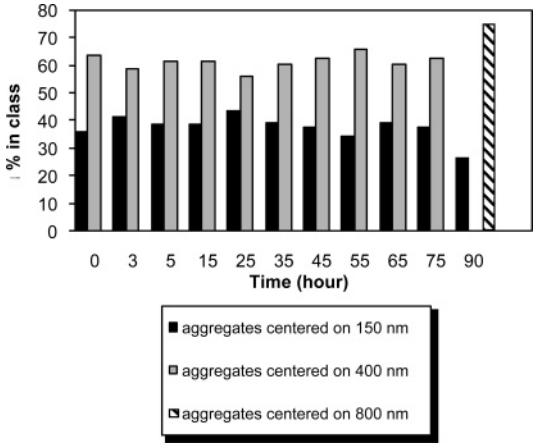


Figure 7. Vesicle stability studied by DLS measurements at 1×10^{-3} M TriCat at 25 °C.

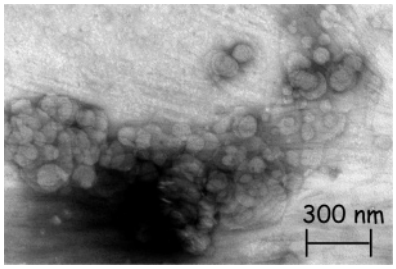


Figure 8. TEM micrograph obtained for TriCat (1×10^{-3} M) compound in aqueous solution after 20 days.

In conclusion, TriCat is one of the first catanionic surfactants to form vesicles upon equimolar combination.[42] The lactose moiety creates a thick hydrated barrier which compensates for the lack of electrostatic repulsive forces that are present at the vesicle surface at nonequimolar conditions. This gain in hydrophilicity is a great advantage when working with neutral vesicles.

When these physicochemical results (vesicle formation in water, stability for 3 days, and possibility of working in neutral conditions) are considered, it appears that TriCat is a good candidate for drug vectorization.

Encapsulation studies were carried out with arbutin, a hydrophilic (log $P = -0.58$), fluorescent ($\lambda_{em} = 319$ nm) dye chosen to accurately quantify the percentage of encapsulated molecules by fluorimetry measurements. Arbutin encapsulation was performed by directly building up the catanionic vesicles in an aqueous arbutin solution. The method chosen to determine the encapsulation percentage was based on a microdialysis technique. One of the two compartments of the dialysis cell was filled up with a mixture of TriCat and arbutin, while the other contained the same volume of pure water. The free arbutin (nonencapsulated) equilibrated between the initial solution and the pure water until an equal concentration was reached in both compartments. The cells containing arbutin in pure water were then titrated by fluorimetry measurements to calculate the quantity of arbutin entrapped.

The apparent encapsulation efficiency ϵ, explicitly the percentage of dye entrapped by the vesicles during their preparation, was found to be around 8% for a TriCat concentration of 1×10^{-3} M at 25 °C. To estimate the probe quantity which could bind to vesicle surfaces, microdialysis experiments were performed by adding probes after vesicle formation. They clearly showed that no probe bound to the vesicle surfaces. This result proves that TriCat has a certain capability to retain hydrophilic drugs in the aqueous cavity of the vesicles formed in water. In comparison with the bibliographic data, the encapsulation efficiency of the catanionic vesicles formed by TriCat in water is one of the best obtained under such conditions (at equimolarity, without residual salts).[39,43−46]

To check the impermeability of the bilayer, the encapsulation efficiency was determined versus time using the same microdialysis technique as described previously. Up to at least 30 h, the percentage of encapsulated arbutin remained at 8% with slight fluctuations of about 1%. A reason for these fluctuations could be simply experimental noise. Arbutin release by the vesicles would lead to a diffusion of half the arbutin toward the other compartment of the dialysis cell, which would drive a decrease in the encapsulation percentage over time.

To ensure the impermeability of the vesicles and thus that the equilibrium between the vesicle and the free monomeric surfactant was negligible, microdialysis experiments were performed. Surface tension experiments were carried out on the dialysis compartments which should normally contain only arbutin in water to quantify the monomeric surfactant ratio which could cross the dialysis membrane under osmotic forces. A surface tension of 72.8 mN/m was found for all the titrated solutions, which indicates that the TriCat concentration equilibrating across the dialysis membrane is lower than 1.8×10^{-7} M (detection limit of the TriCat concentration obtained by surface tension titration). This unexpected result can be explained by a shift of the equilibrium between the vesicle and the free monomeric species toward the aggregated forms, thus avoiding their diffusion through the dialysis membrane. This assumed mechanism could be explained by the formation of many hydrogen bonds between sugar headgroups in the aggregates (as shown by molecular modeling), by the introduction of a phosphinic acid (pK_a in aggregates is 5.4) stronger than a carboxylic one, and also by the enhancement of hydrophobic forces (with the three chains of TriCat). The strengthened association between the two moieties of the surfactant ensures vesicle impermeability and thus avoids the release of encapsulated molecules.

To separate the probe-containing vesicles from the free probes,[5] we then used a common dialysis technique. The mixture was placed in a semipermeable dialysis bag, which was put into a large volume of pure water. Only free arbutin diffused according to the concentration gradient through the membrane used and thus was separated from the vesicles. However, working with a large volume of pure water compared to that of the dialyzed solution generated a high osmotic pressure that could destabilize vesicles. To avoid this phenomenon, the separation was carried out with a pure water volume 40 times the dialyzed solution volume. To amplify elimination of the diffusible arbutin, this process was repeated several times in series. To confirm the stability of the arbutin-containing vesicles after separation from free arbutin, the size distributions of the aggregates before and after the dialysis series were then compared. The vesicle size distribution, centered on 150 and 400 nm, was identical before and after the separation. We concluded that aggregates were stable under the osmotic pressure generated by the series of dialyses. Moreover, the total concentration of the free probe after dialysis elimination was measured by fluorimetry. We then could deduce the total quantity of probe remaining encapsulated, which still corresponded to 8%. These results confirm our

(42) Menger, F. M.; Binder, W. H.; Keiper, J. S. *Langmuir* **1997**, *13*, 3247.
(43) Bhattacharya, S.; De, S.; Subramanian, M. *J. Org. Chem.* **1998**, *63*, 7640.
(44) Chung, Y.-C.; Lee, H.-J. *Bull. Korean Chem. Soc.* **1999**, *20*, 838.
(45) Fischer, A.; Hebrant, M.; Tondre, C. *J. Colloid Interface Sci.* **2002**, *248*, 163.
(46) Tondre, C.; Caillet, C. *Adv. Colloid Interface Sci.* **2003**, *93*, 115.

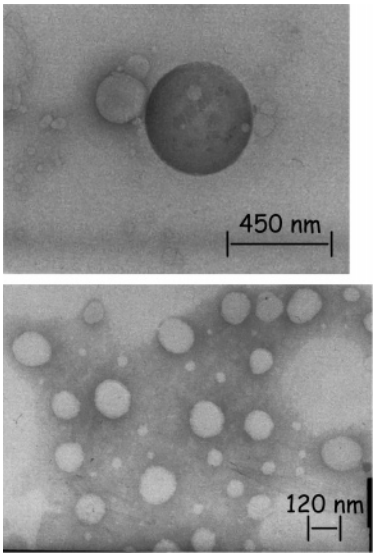


Figure 9. TEM micrographs obtained for TriCat compound (1×10^{-3} M) in buffer solution.

assumption that the vesicles do not rupture during dialysis elimination. The method of separation to obtain pure active-molecule-containing carriers was thus validated.

To assess the feasibility of biological applications, the self-assembly properties and encapsulation efficiency of TriCat vesicles were examined in a buffer solution ([NaCl] = 100 mM; $[PO_4^{2-}] = 7$ mM, pH = 7.45). First, surface tension measurements were carried out, and the critical aggregation concentration of TriCat was found to be 8.4×10^{-6} M in this buffer solution (3.5×10^{-5} M in water). According to McDevit and Long,[47] the energy required to create the volume needed to accommodate a solute in water is increased in electrolyte solutions, due to ion−water interactions. This augmentation causes an increase in the activity of the neutral electrolyte and hence increases its salting out. Equimolarity between anionic and cationic surfactants allows us to consider the catanionic system as a neutral solute. Thus, the McDevit−Long theory could explain the lower value of the CAC in the presence of NaCl.

The size distribution of TriCat aggregates, studied by DLS measurements, showed no significant difference whatever the medium ionic strength. These results were confirmed by TEM micrographs which showed the same vesicular geometry of TriCat autoassemblies in buffer solution as in water (Figure 9). Moreover, the stability over time of vesicles formed in buffer medium was comparable to the aggregate stability obtained in pure water.

The encapsulation efficiency of the vesicles formed by TriCat was also studied in phosphate buffer. Microdialysis experiments allowed us to conclude that the percentage of arbutin entrapped by the vesicles during their autoaggregation remained at 8%. The presence of salt did not have a significant influence on vesicle formation or on their encapsulation efficiency. Thus, all these results tend to prove that drug vectorization by TriCat vesicles in a biological medium seems to be a promising path to follow.

Conclusion

A new sugar-derived tricatenar catanionic surfactant, TriCat, has been designed and synthesized to obtain stable vesicles that could be exploited for drug vectorization. The aggregation properties and encapsulation efficiency of this catanionic surfactant were studied in pure water and also in phosphate buffer. Vesicles were formed by the self-aggregation of TriCat whatever the medium used. Moreover, an entrapment percentage of hydrophilic probes of 8% was determined whatever the conditions of vesicle formation (in water or in buffer solution). This encapsulation efficiency is one of the highest obtained with catanionic vesicles at surfactant equimolarity.[43,45,48] Moreover, TriCat displayed a capability to retain drugs in the aqueous cavity of the vesicles for at least 30 h, which is among the highest probe entrapment stabilities ever described for catanionic systems at equimolar conditions. The present study suggests that this tricatenar catanionic surfactant could be promising a new kind of delivery system where the drug is easily entrapped during spontaneous surfactant self-assembly in water.

Acknowledgment. The authors are grateful to Pierre Fabre Dermo-Cosmétique Laboratories, Vigoulet Auzil (France), and CNRS for their financial support. They would like to thank Dr E. Perez and Dr J.-C. Garrigues for their valuable contribution to this work.

Supporting Information Available: Experimental details, schematic of the microdialysis technique, and figure showing the emission and absorption spectra of arbutin. This material is available free of charge via the Internet at http://pubs.acs.org.

LA702171S

(47) McDevit, W. F.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773.

(48) Kondo, Y.; Uchiyama, H.; Yoshino, N.; Nishiyama, K.; Abe, M. *Langmuir* **1995**, *11*, 2380.