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Macrocyclic Sugar-Based Surfactants: Block Molecules Combining Self-Aggregation and Complexation Properties**

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There is a rise in interest in the rational design of new surfactants that possess various chemical or biological functionalities and self-assemble into tunable and predictable

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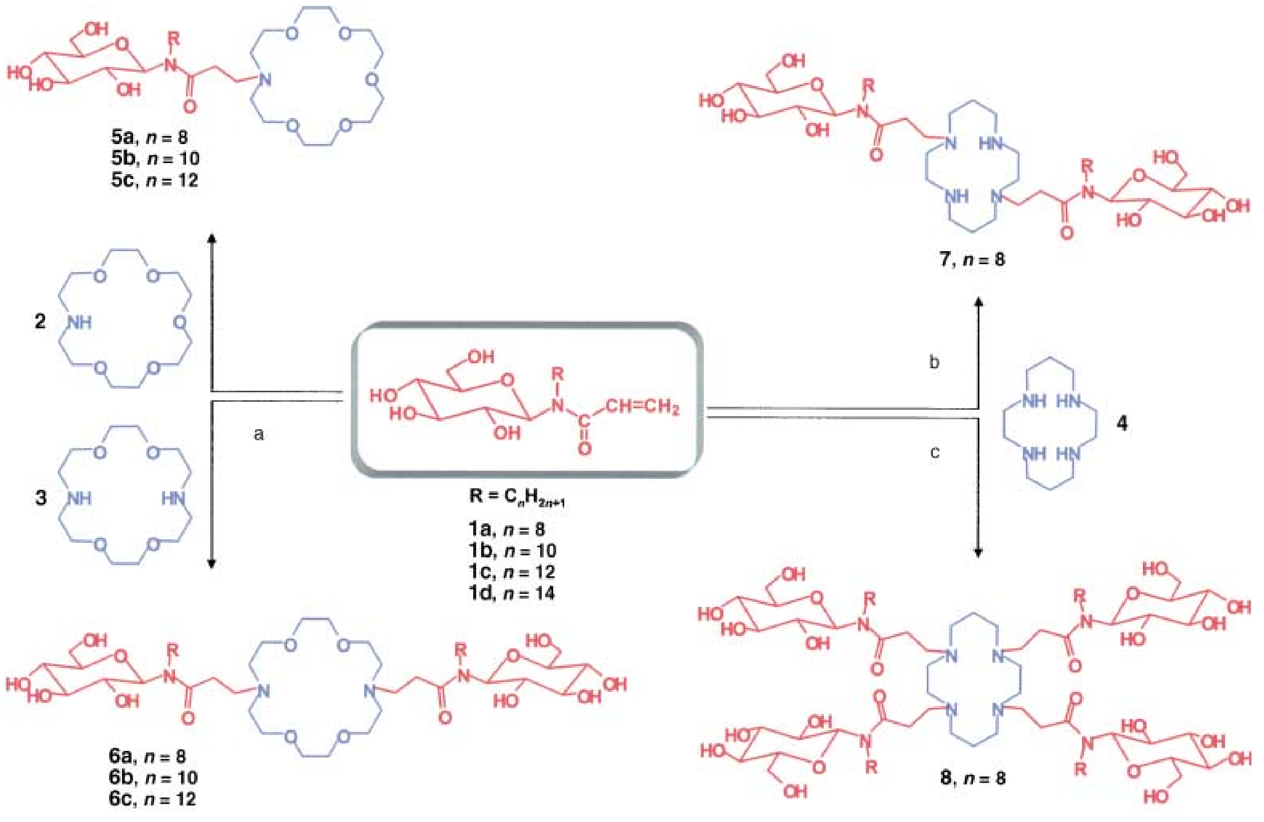
aggregate structures. In the past few years new amphiphiles (many of which are chiral and derived from peptides or carbohydrates) have been proved to be promising scaffolds for nanometer-sized structures and mimics of natural materials.[1,2] On the other hand, it is now well known that micelles and other supramolecular assemblies can enhance the rates of chemical reactions as well as the regio- and/or stereoselectivity, especially when functional surfactants are used.[3,4] Chelating surfactants and amphiphilic metal complexes are attracting considerable attention as catalysts for several types of reactions,[3–5] including enantioselective ones,[3,6] as well as in separation technology.[1,7] The main difficulty in dealing with surfactants that have recognition properties is in the profound change associated with the binding of the guest. The complexation often completely changes the solubility and aggregation behavior of metal-binding surfactants in an unpredictable way.[5,8,9] We have previously observed that micelles of a peculiar gemini sugar-based surfactant with a macrocyclic spacer were surprisingly not altered by the binding of cations.[10] In this paper we show that this is general for a whole family of novel amphiphiles consisting of one or more sugar-based surfactant units covalently linked to a macrocyclic residue; these amphiphiles combine independent predictable self-aggregation behavior and tunable complexation properties. The bulky sugar-based surfactant units impose the curvature and, hence, the morphology of the aggregates irrespective of the macrocycle. On the other hand, the sugar headgroups provide a dominating water-solubilization and thereby minimize the effect of ion association on the micellization.

A series of novel amphiphilic macrocycles is readily prepared by a one-step procedure, depicted in Scheme 1, from surfactant units which include a reactive group that permits the covalent linkage to various macrocyclic residues. *N*-alkylglucosylacrylamides **1a–d**, with octyl to tetradecyl tails, are a family of reactive nonionic sugar-based surfactants which exhibit properties very close to conventional alkylglucosides.[11] Moreover, they contain an acrylamide group that acts as a Michael acceptor and undergoes nucleophilic addition of azamacrocycles in aqueous medium (Scheme 1).

Two types of macrocycles, with different cation binding selectivities,[12] have been used: aza[18]crown-6 (compounds **2** and **3**) and cyclam (compound **4**). Crown derivatives **5** and **6**, with one or two surfactant units, are prepared from **2** and **3**, respectively. Amphiphilic crowns with octyl to dodecyl chains are soluble in water.[13,14] Soluble cyclam derivatives **7** and **8**, with two or four surfactant blocks, are obtained from **4** and the octyl precursor **1a**.[14,15]

Herein, we focus on the self-aggregation and complexation properties of cyclam/**1a** derivatives (**7**, **8**) and aza[18]crown-6/**1c** derivatives (**5c**, **6c**). As expected from the molecular structures, the cation-binding capacity and selectivity of the macrocycles are retained after the linkage of one or several surfactant moieties. As illustrated in Figure 1, electrospray mass spectra show that amphiphilic crowns **5c** and **6c** form complexes with alkali cations with a marked



Scheme 1. Synthesis of sugar-based macrocyclic surfactants. a) **1**/**2** = 4:1, **1**/**3** = 5:1, MeOH/H_2O (3:2)/NMe_4OH (0.04 M), 25 °C, 7 days; yields: 65 (**5a**), 80 (**5b**), 86 (**5c**), 60 (**6a**), 70 (**6b**), 77% (**6c**). b) **1a**/**4** = 5:1, H_2O/NaOH (0.1 M), 25 °C, 15 h; 90% yield. c) **1a**/**4** = 10:1, MeOH/H_2O (2:1)/NaOH (0.06 M), 40 °C, 2 weeks, 70% yield. For experimental details and structural characterization, see the Supporting Information.

selectivity for potassium and sodium cations, like their parent crowns **2** and **3**.[12,14,16] Cyclam **4** is a well-known ligand that exhibits a very high affinity for cupric ions;[12] its derivatives **7** and **8** with two and four surfactant units, respectively, also give stable complexes with Cu^{II} ions, with characteristic absorptions at 640 and 670 nm, close to the absorptions of other N-substituted cyclam–copper complexes.[17] The stability constants of the complexes, although not determined precisely, are high ($\log K > 6$), with quantitative complexation even at low copper concentrations (10^{-4} M).[14]

Table 1: Microstructural characteristics of the micelles.

Cmpd.	N_{Ag}[a]	N_S[b]	β[c]	Aggregate shape and size
8				
free[d]	8	32	<0.01	prolate micelles[e]
Cu complex[f]	9	36	<0.01	17/55 Å
7				
free[d]	17	34	<0.1	prolate micelles[e]
Cu complex[f]	20	40	<0.1	16/60 Å
1a	38	38		prolate micelles 17/55 Å
5c				
free[d,g]	66	66	<0.1	prolate micelles[e]
Na complex[h]	60	60	<0.1	25/78 Å
6c				
free[d,g]	35	70	<0.01	prolate micelles[e]
Na complex[h]	33	66	<0.15	25/76 Å
1c	>800	>800		cylinders 21/500 Å

[a] N_{Ag} = Aggregation number (average number of molecules per micelle) ±10%. [b] N_S = average number of sugar-based surfactant units per micelle. [c] β = Dissociation ratio of counterions, defined by $\beta = Z_{eff}/Z_{str}$, where the effective charge Z_{eff} is the charge at the origin of electrostatic repulsions between micelles and Z_{str} is the structural charge. [d] At pH 7.5. [e] Similar size and shape, average dimensions R/L (see Figure 2). [f] In the presence of one equivalent of $Cu(NO_3)_2$. [g] The pH value was adjusted by addition of HNO_3. Similar aggregates are formed at pH 7.5 and pH 5.[14] [h] In the presence of one equivalent of $NaNO_3$.

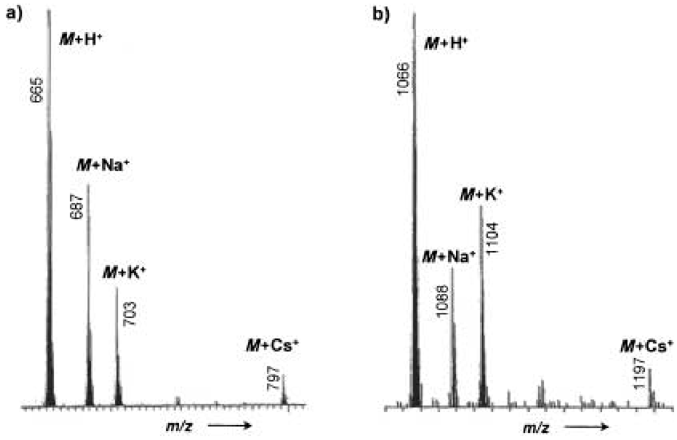


Figure 1. Electrospray mass spectra for a) **5c** and b) **6c** in the presence of one equivalent of alkali cations. [cage] = [NaBr] = [KNO_3] = [CsCl] = 10^{-2} M in CH_3CN/H_2O (80:20).

The characteristic properties of any surfactant are 1) a well-defined critical micelle concentration (CMC) and 2) self-aggregation in the form of small stable micelles.[18] Cage molecules with two or four surfactant moieties behave like oligomeric or so-called gemini surfactants[19] and have low CMC values compared with their precursors: the CMC values of **7**, **8**, and **6c** are 0.14, 0.6, and 0.01 mM, respectively, to be compared with 12 and 0.14 mM for **1a** and **1c**.[14] On the other hand, **5c** with only one surfactant block has a CMC value of 0.2 mM, a value of the same order of magnitude as that of its precursor **1c**. Micellar microstructures have been determined by combined small-angle X-ray and neutron scattering on the absolute scale.[10,20,21] The microstructural characteristics of aggregates formed by the surfactant cage molecules, their complexes, and the starting surfactants are given in Table 1. All of the macrocyclic surfactants studied self-aggregate in water into small prolate micelles with a lipophilic core consisting of hydrocarbon chains and a hydrophilic shell containing the cages and the hydrated sugar moieties (Figure 2).[22] The complexation does not affect the self-aggregation: in every case, the aggregates formed by the free cages and their complexes with $Cu(NO_3)_2$ or $NaNO_3$ are

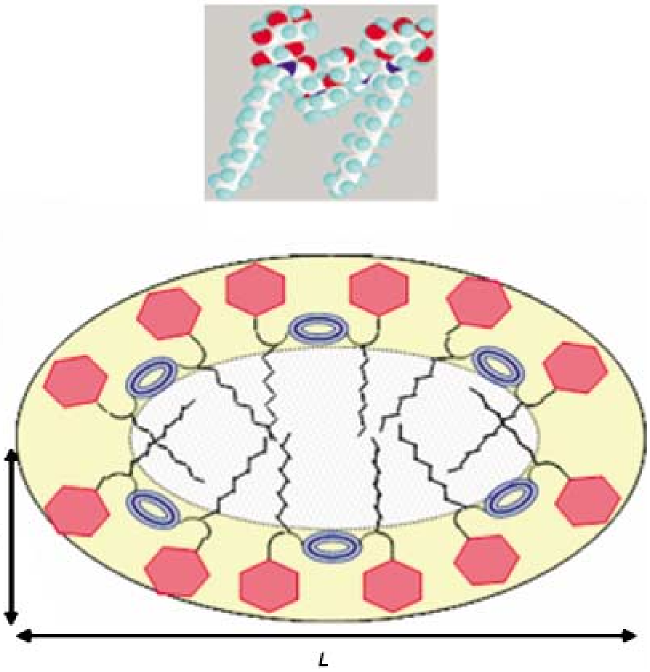


Figure 2. Schematic representation of prolate micelles (cross-section, bottom) and scaled CPK molecular model of **6c** (top).

similar in shape and size.[23] A tight association of the counteranions within the sugar-rich shell may account for a screening of the positive charges of the complexes and, hence, for the resulting low effective charge of the micelles.[24]

Moreover, as illustrated by the SANS and SAXS spectra shown in Figure 3, molecules of a given family form similar aggregates. The aggregation numbers of crowns **5c** and **6c** are about 30–35 and 60–65, respectively: the number of dodecyl sugar-surfactant blocks per micelle, about 60–70, is roughly constant regardless of the substitution pattern of the cage. Similar trends are observed for cyclam derivatives: **7** and **8** form comparable aggregates that contain about 35–40 surfactant blocks. The number of surfactant units per micelle increases as the length of the aliphatic chain increases, as for conventional surfactants.[18] The self-aggregation process is governed by geometrical constraints, and the surfactant packing parameter, p, may be used to compare Gibbs energies of the different possible self-assemblies. This parameter p, defined as $p = V/al$ where V is the hydrophobic volume of the chains, l is the chain length, and a is the cross-sectional headgroup area, is a useful tool to predict the aggregate morphology.[25] Since the macrocycle moieties lie in the polar shell,[22] V/l is set by the surfactant unit **1**. Accordingly, amphiphiles of the same family (that is, a given macrocycle and a given surfactant unit) self-assemble into identical aggregates whatever the number of surfactant residues per cage.[26] Remarkably, the cyclam derivatives **7** and **8** and their precursor **1a** form micelles comparable in size and shape and which contain the same number of surfactant blocks per micelle (≈35–40). In this case, a medium-size cage tethered with a medium-tail surfactant, a is set by the bulky sugar headgroups, and the self-aggregation is entirely governed by the precursor chosen.[26] On the other hand, the linkage of azacrowns to the dodecyl surfactant **1c** converts long cylinders (with high aggregation number) into small ellipsoidal micelles for macrocyclic derivatives **5c** and **6c**. A contribution of the large macrocycle to the polar headgroup and the resulting increase of the area per molecule account for the reduction of the size of the micelles.[25,26]

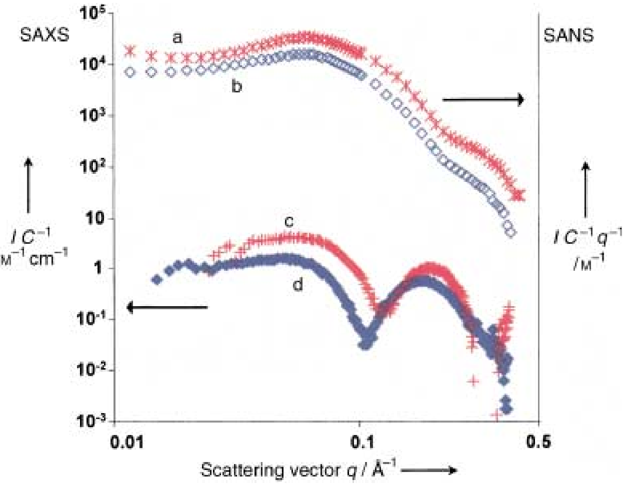


Figure 3. SANS spectra of globular micelles of a) **6c** and b) **5c**. SAXS spectra of globular micelles of c) **6c** and d) **5c**. $[\mathbf{5c}] = 9.4\times10^{-2}$ M, $[\mathbf{6c}] = 3.1\times10^{-2}$ M, D_2O, pH 5. Similar spectra are obtained at pH 7.5.[14]

In conclusion, this strategy based on surfactant units is a straightforward and versatile method which gives access to a series of glycosylated macrocyclic amphiphiles with complexation and self-aggregation properties controlled independently by the nature of the cage and the nature of the surfactant unit. This first example of full control of self-aggregation of functional surfactants by assembling building blocks, where each block carries out its designed task, is hoped to be general, provided that surfactant units with bulky nonionic polar headgroups are used. The potential of these new chiral amphiphilic macrocycles for use in enantioselective metal-catalyzed reactions in aqueous micellar media is currently under investigation.

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[9] The size and shape of the aggregates as well as the Gibbs energy of micellization in water are controlled by the equilibrium between lateral repulsions (electrostatic and steric repulsions) and the water–oil contact energy: D. F. Evans, D. J. Mitchell, B. W. Ninham, *J. Phys. Chem.* **1984**, *88*, 6344–6348. In most reported metallomicelles, the binding of ions imparts a charge and modifies the area per headgroup in large amounts.

[10] The small-angle scattering study of **7**, with and without CuF_2, is described in: L. Arleth, D. Posselt, D. Gazeau, C. Larpent, T. Zemb, K. Mortensen, J.-S. Pedersen, *Langmuir* **1997**, *13*, 1887–1896.

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[13] All of these compounds exhibit a surfactant behavior with CMC values in the 10^{-5}–10^{-3} M range. Their solubilities in water are in the range 0.01–0.05 M.

[14] For synthesis and characterization of the surfactant cage molecules (structural characterization, complexation, solubility in water, CMC values), procedures used to determine micellar microstructures, SAXS and SANS spectra, and analyses, see the Supporting Information.

[15] Compound **8** is obtained in a water–methanol medium. Compound **7** precipitates when the reaction is performed in water. The solubility of **7** and **8** in water is about 0.02–0.03 M. Di- and tetrasubstituted cyclam derivatives with longer chains are poorly soluble in water. Alternatively, mono- and disubstituted cyclam derivatives can be prepared selectively in organic media as described in: H. Fensterbank, J. Zhu, D. Riou, C. Larpent, *J. Chem. Soc. Perkin Trans. 1* **1999**, 811 – 815; H. Fensterbank, P. Berthault, C. Larpent, *Eur. J. Org. Chem.* **2003**, 3985 – 3990.

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[20] The known molecular volumes in the micellar state are such that micellar mass and charge (Z_{eff}), as well as number of water molecules per surfactant embedded in the effective volume of a micelle, can be determined by simultaneously fitting X-ray (SAXS) and neutron-scattering (SANS) spectra.[10,14,21]

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[22] The resolution of the X-ray scattering experiments is sufficient to allow determination of the partition of the macrocyclic ring in between the polar and apolar region of the micelle if the measured q-range is extended to 0.6 Å^{-1}.[14] For all the free and metalated amphiphiles studied here, the macrocycle is located mainly in the polar shell. The average percentage of the macrocycle that contributes to the apolar part of the micelles (x) does not exceed 10–15 % for **5c** and **6c** in pure water or in the presence of sodium nitrate (fitting parameter $x = 0.1$). For the cyclam derivatives **7** and **8**, the whole cage is located in the polar region (fitting parameter $x = 0$), with or without copper nitrate.

[23] The nature of the associated anion seems to have little effect on micellization since we found that metallomicelles of **8** with CuF_2,[10] $Cu(CF_3SO_3)_2$, and $Cu(CH_3CO_2)_2$ are quite similar in size, shape, and low effective charge.

[24] Comparable binding of anions by polyglycosylated hydrophobic macrocycles in water has been observed. The anions are incorporated in the clustering oligosaccharide pools of hosts through hydrogen bonding and the authors stated that "the saccharide clusters act as a macrosolvent for anions": O. Hayashida, M. Kato, K. Akagi, Y. Aoyama, *J. Am. Chem. Soc.* **1999**, *121*, 11 597 – 11 598. Adsorption of hydroxide ions to the surface of aggregates of sugar-based gemini surfactants was recently proposed to be responsible for a surface-charge reversal: M. Johnsson, A. Wagenaar, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **2003**, *125*, 757 – 760; M. Johnsson, A. Wagenaar, M. C. A. Stuart, J. B. F. N. Engberts, *Langmuir* **2003**, *19*, 4609 – 4618. Independently of specific sugar–anion interactions, an enhanced solubility of anions in the carbohydrate shell, as well as a stabilization of ion pairs within the polar shell, may also account for the observed low effective charge of our metallomicelles.

[25] The prediction of p (optimal value which minimizes bending energy) is $p \leq 1/3$ for spherical micelles, $1/3 < p \leq 1/2$ for cylindrical micelles and $1/2 < p \leq 1$ for vesicles or bilayers: D. J. Mitchell, B. W. Ninham, *J. Chem. Soc. Faraday Trans. 2* **1981**, *77*, 601 – 629; J. N. Israelachvili, D. J. Mitchell, B. W. Ninham, *J. Chem. Soc. Faraday Trans. 2* **1976**, *72*, 1525.

[26] We found values of $p \approx 0.3$–0.35 for **7** and **8**, $p \approx 0.33$ for **1a**; $p \approx 0.3$ for **5c** and **6c**, and $p \approx 0.5$ for **1c**.