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Synthesis of unsymmetrical saturated or diacetylenic cationic bolaamphiphiles

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ABSTRACT

This work presents the synthesis of novel unsymmetrical bolaamphiphiles bearing a sugar residue and a cationic glycine betaine moiety connected to both ends of a C_{22} or C_{32} oligomethylene bridging chain possessing or not a diacetylenic unit. Preliminary transmission electron microscopy (TEM) studies revealed the polymorphism of these bola lipids with regard to their self-assembled morphologies in water depending on the presence or not of the diacetylenic functionality and on alkyl chain length.

Unsymmetrical bolaamphiphiles are original classes of surface-active molecules that have been found as cell-membrane components of methanogenic and thermoacidophilic archaea.[1–3] These bipolar amphiphiles are characterized by the presence of two different hydrophilic end groups connected by a hydrophobic spacer that has one or two alkyl chains. These materials often self-assemble into monolayer lipid membranes (MLMs) that are more tightly packed and less permeable than standard bilayer membranes.[4] Unsymmetrical bola lipids with polar head groups of different sizes may exhibit an unsymmetrical or a symmetrical type arrangement depending on a parallel or antiparallel molecular packing within the monolayer as shown in Figure 1.[2] Another interest of the bolaamphiphiles is their capability to adopt various conformations in supramolecular assemblies, that is, U-shaped and stretched conformations.[5] The aggregate morphologies of bolaamphiphiles include vesicles and lamellae, disks, rods, tubules, ribbons and fibres in a micro- and nanometer range.[6] Despite the continuing emergence of novel synthetic structures and original highly ordered assemblies,[7,8] fundamental studies to establish the relationship between the morphology of the self-organized systems and the chemical structure of unsymmetrical monomers remain to be carried out. Over the past decade, the results obtained from synthetic molecules have demonstrated the existence of complex relationships between chain composition, spacers and head groups that considerably influence the structure of their supramolecular aggregates.[5,9,10]

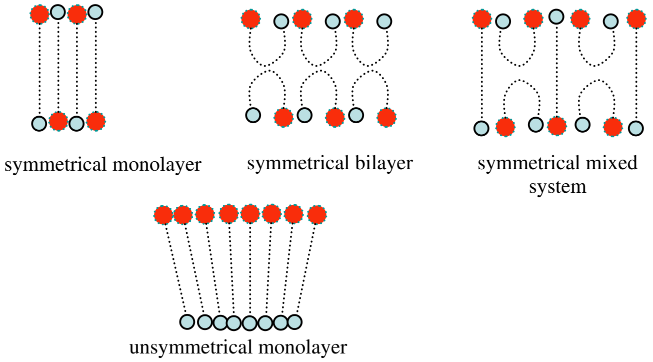

Figure 1. Symmetrical and unsymmetrical membranes based on unsymmetrical bolaamphiphile lipids.

Consequently, the rational design of well-defined functional bolaamphiphiles continues to be challenging in order to analyze the mechanisms involved in molecular self-assembly and to develop new advanced materials.

We had previously reported the self-assembly behaviour of the unsymmetrical bolaamphiphile **1** bearing a neutral glycosidic polar head and an electropositive ammonium group at the opposite end

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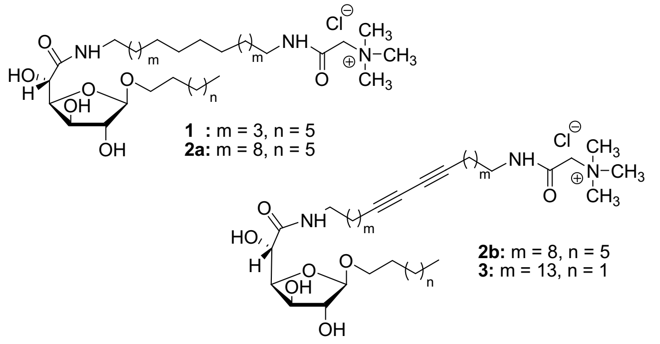
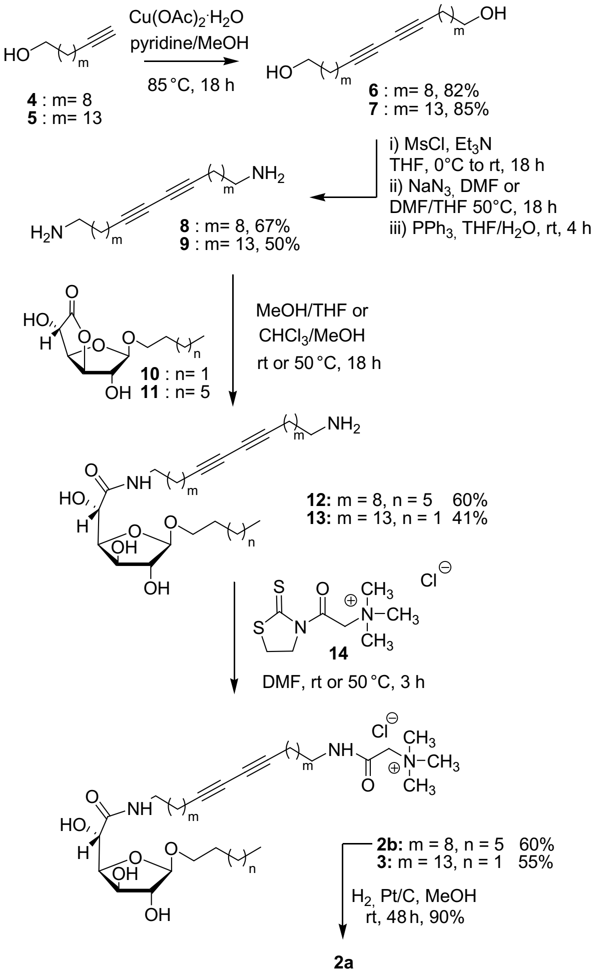


Figure 2. Structural formula for saturated and diacetylenic bolaamphiphiles **1**–**3**.

of a dodecamethylene bridging chain (Fig. 2).[11,12] An additional octyl chain was also introduced at the anomeric site of the carbohydrate. It self-assembled spontaneously in water to form vesicles or disks with a transmembrane organization, depending on temperature. We herein describe the synthesis of a new series of unsymmetrical bolaamphiphiles **2a,b** and **3** with longer chains of 22 and 32 carbon atoms for the bridging chain, and 4 or 8 carbon atoms for the alkoxy group at the anomeric site of the D-glucurone moiety (Fig. 2). The incorporation of a diacetylene unit into the centre of the main hydrocarbon chain of compounds was envisaged to maximize the chance of proper alignment of diacetylenes in different packing arrangements. This known phenomenon is due to the π–π stacking interactions that favour the alignment of diacetylene bearing bolaamphiphiles.

Bolaamphiphiles **2a,b** and **3** were obtained through a straightforward synthetic pathway based upon the sequential introduction of the D-glucurone headgroup and the cationic glycine betaine moiety onto α,ω-diamines as previously described for the preparation of the saturated C_{12} bridging chain containing bola lipid **1**.[11] Central to the synthesis of all these novel bolaamphiphiles was the preparation of diacetylenic diamines **8** and **9** (Scheme 1). Acetylenic alcohols **4** and **5** were coupled in the presence of cupric acetate in a methanol/pyridine mixture to give the 11,13-diyne-1,22 diol **6** and 16,18-diyne-1,32 diol **7** in 82% and 85% yields, respectively (Scheme 1). The non-commercially available ω-tetradecynol **5** was accessible from 7-hexadecynol by ‘zipper’ isomerization of the alkyne to the terminal position in superbase medium.[13] α,ω-Diols **6** and **7** were then converted into the corresponding diamines 8 and **9** in a three-step procedure involving (1) a mesylation of the diols by mesyl chloride, (2) a condensation of sodium azide in DMF at 50 °C (C_{22} derivative) or in DMF/THF (5:1) at 60 °C (C_{32} derivative) and (3) a Staudinger reduction with PPh_3 in THF/H_2O (Scheme 1). Diamines **8** and **9** were thus obtained in good yields (50–67%, 3 steps).

Having the α,ω-diamines in hand, anomerically pure butyl and octyl β-D-glucofuranurono-6,3-lactones **10** and **11** were prepared in satisfactory yields (60–63%) according to a previously described procedure from our laboratory.[11] Treatment of these lactones with 1.5 equiv of the diamines **8** and **9** at room temperature in CH_3OH/THF (C_{22} derivative) or in $CH_3OH/CHCl_3$ (C_{32} derivative) provided the glucuronamides **12** and **13** resulting from monoacylation of the diamine, in 41% to 60% yields (Scheme 1). *N*-Acylations of the glycosylated monoamines **12** and **13** were efficiently performed with the *N*-acyl thiazolidine-2-thione derivative **14** of glycine betaine affording the required unsymmetrical bolaamphiphiles **2b** and **3** in 55–60% yield. The C_{22} saturated derivative **2a** was efficiently obtained by a platine-catalyzed hydrogenation of the diacetylenic compound **2b**. All the required bolaamphiphiles **2a,b** and **3** were isolated after chromatography on silica gel and gel filtration on Sephadex (G-10 or LH-20).[14]



Scheme 1. Synthesis of saturated and diacetylenic bolaamphiphiles **2a**,**b** and **3**.

In Cryo-TEM, the aqueous dispersion of unsaturated C_{22} bolaamphiphile **2b** revealed vesicles that varied in size and depending of the ultrasound bath temperature. Indeed, when the sample was sonicated at 65 °C, compound **2b** assembled into vesicles with a 100 nm average diameter (Fig. 3a). In contrast, smaller vesicles were visualized in cryo-TEM when the sample dispersion was sonicated at ambient temperature (Fig. 3b). The saturated C_{22} compound **2a** provided after sonication at ambient temperature or at 65 °C, preferentially tubular-like structures (Fig. 3c), and some rare vesicles with a mean diameter of 100 nm were additionally observed when the preparation was carried out below 40 °C. Additional confirmation of the tubule morphology assumed by bolalipid **2a** was obtained by freeze fracture electron microscopy (FFEM)[11] in a more concentrated sample (Fig. 3e and f). The micrographs are characterized by spherical multilamellar membrane systems that suggest the formation of enrolled layers of molecules around a hollow centre (diameter range between 100 and 200 nm).[15,16]

For compound **3** that contains a 32-carbon diacetylenic polymethylene bridging chain and a butyl chain at the anomeric position of the sugar head, cryo-TEM showed the presence of a filament network with a very thin diameter (2–5 nm) (Fig. 3d). Self-assembling of the compound **3** was further achieved by exposing 3–4 mg of the sample in water at different concentrations, and after heating at 100 °C, the dispersions were then cooled to room temperature. A translucent stable hydrogel was formed for relatively high concentrations ($\geqslant 16.5$ mg mL^{-1}) and a viscous liquid or a solution