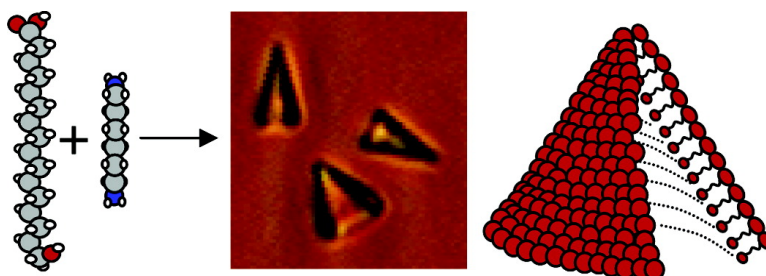


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J. Am. Chem. Soc., **2005**, 127 (45), 15694-15695 • DOI: 10.1021/ja0560478 • Publication Date (Web): 21 October 2005

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Self-Assembly of Hollow Cones in a Bola-amphiphile/Hexadecylamine Salt Solution

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Lipids are well-known to exhibit a broad polymorphism in aqueous solution,¹ including micelles, bilayers, hexagonal phases, etc. Bilayers can fold under various shapes forming supramolecular assemblies, the stability of which is governed by the thermodynamics of surfactant self-assembly.^{2–4} This includes the membrane bending energy, the cohesive energy between molecules within the aggregates, and the way by which the system closes the supramolecular structure to prevent the formation of edges.⁵ For instance, vesicles or sponge phases form to prevent the occurrence of such bilayer edges. An alternative to this is to incorporate in the system lipids capable of forming half a micelle at the bilayer boundaries as in the case of bicelles.⁶ In the same way, in salt free catanionic disks or icosahedra,^{7,8} edges, and pores, respectively, can form via electrostatic repulsions of the polar head surfactants. Conical structures have not hitherto been observed in surfactant or lipid systems. Cones were observed in the biomineralization process under control of block copolymers.⁹ This topology is also known to occur in graphite.^{10,11} The carbon sheet folds using a route other than that of lipid bilayers in order to decrease the energy at the edges.¹⁰ This originates from the 6-fold symmetry ($p6$) of the hexagonal carbon lattice. By introducing a disclination¹² in the carbon network (n -gonal defects), the sheet can fold in a conic shape, decreasing the number of atoms at the edges and, then, the energy of the system. The conical core of the HIV was modeled in the same way¹³ since the protein forming capsids are arranged in hexameric rings having the $p6$ symmetry.¹⁴

Dilute mixtures of a bola-amphiphile and diamine are constituted of such self-assembled cones of micrometer size and can be produced in a simple way in large quantities. The samples from 0.1 to 1% (amount of lipid) were prepared using protonated α,ω -hexanediamine and ω -hydroxyl palmitic acid in ultrapure water (see Supporting Information). This lipid mixture can be viewed either as a catanionic system^{7,8} or as a salt of fatty acid, the diamine playing the counterion.^{15,16} Both of these molecules are known as bola-amphiphiles since they possess a polar head at the extremities of their hydrophobic part^{17,18} (Figure 1a). The 1% sample produced a turbid gel of membranes at room temperature (Figure 1b). Upon increasing the temperature, the dispersion became isotropic at around 60 °C, probably forming micelles. The phase transitions were monitored as a single peak by differential scanning calorimetry (see Supporting Information). At room temperature, the ν_{CH} band on the FTIR spectrum recorded on an ATR crystal¹⁹ was 2848 cm^{-1} , indicating that the fatty acid alkyl chains are in the all-trans conformation,²⁰ that is, the membranes are in the gel state. Wide-angle X-ray scattering exhibited a single thin peak at $2\theta = 22^\circ$ (Figure 2) with no shoulders characteristic of the rotator phase.^{21,22} This shows that the bola-fatty acids are arranged in a regular hexagonal lattice with a distance between lipids of 4.1 Å. This value is similar to that obtained in a catanionic system forming disks⁸ and confirms that the fatty acid chains are frozen in the membrane. The diamine does not penetrate the membrane and remains at the

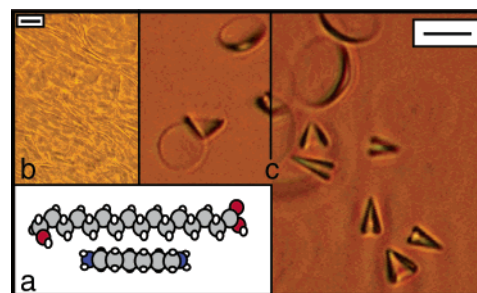


Figure 1. Molecular structure of the bola-amphiphiles (a) and phase contrast microscopy of a 1 and 0.1% dispersions, (b) and (c), respectively. The bar represents 10 μm .

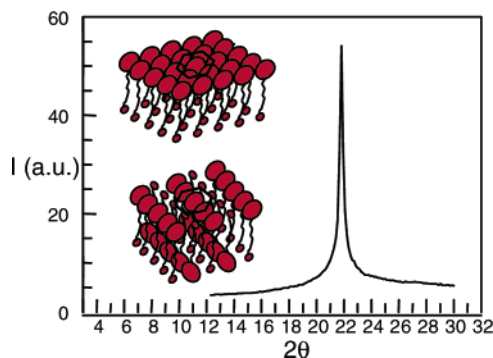


Figure 2. Wide-angle X-ray scattering data for a 1% dispersion. The arrangement of bolas is sketched on the left. For the sake of clarity, the diamine is not shown.

interface as a salt of the fatty acid. The membrane forms a monolayer as expected from bola-amphiphiles,^{17,23} and this was demonstrated in the case of the glycerol derivative of ω -hydroxyl palmitic acid.²⁴ Moreover, that fatty acid belongs to the class of unsymmetrical bolas which can form either symmetrical or unsymmetrical membranes²³ (Figure 2), the latter can fold in tubular shapes according to the curvature of the membrane.

Samples at a 0.1% amount of lipid appeared markedly different than those at higher concentration. Upon cooling from the micellar phase, an iridescent dispersion formed at room temperature after a short period of rest. Heating ensures re-dissolution, and aggregates can be restored by cooling again. Together with tubes and flat disks, cones were observed by phase contrast microscopy (Figure 1c). The apex angle varied from a cone to another one through the sample, and this point is further examined. The size of the cones was 5 μm on average, much larger than that of capsid virion¹³ and graphite,¹⁰ which is a few tens of nanometers. Upon a 10 time dilution of a 1% sample at room temperature, no cones formed but rather dislocated pieces of membranes (not shown). This reveals that cones can only form by the introduction of defects when the monolayer grows upon cooling and are not the result of the lamellar swelling limit, the routes of which have been well described

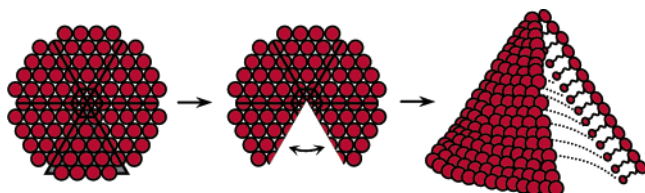


Figure 3. Sketch of the lipid arrangement in the monolayer sheet from an upper view and a 60° disclination yielding to the formation of a cone having an n -gonal (here a pentagon) at the apex.

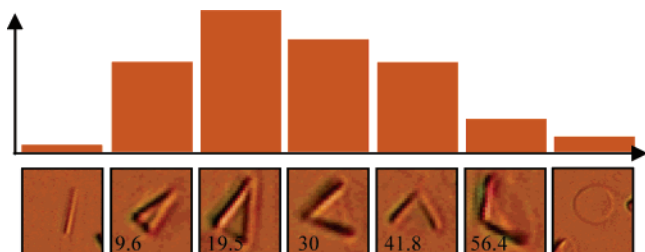


Figure 4. Frequency histogram representing the occurrence of the tubes, the five types of cones (angle indicated in degrees), and disks, from the left to the right, respectively. The width of each microgram is $10\ \mu\text{m}$.

elsewhere.²⁵ As in the case of graphite¹⁰ and HIV,¹³ it is likely that the formation of cones originates from the lipid regular hexagonal lattice by introducing disclinations¹² as defects. Disclination may be created by cutting off n sectors of 60° ($1 < n < 6$) in the membrane following the $p6$ symmetry (Figure 3) and by joining the two cut edges. This leaves an n -gonal defect at the apex of the cone. For $n = 1$, a pentagon is formed, for $n = 2$ a square, and so on. A cone can also be obtained by introducing n pentagons at some distance from each other (see Supporting Information). Among the two configurations that the monolayer can adopt (Figure 2), only the unsymmetrical one has the $p6$ symmetry. Interestingly, one side of the monolayer is stabilized by the formation of hydrogen bonds through the hydroxyl groups of the bola-fatty acid.

The molecular shape is then the determinant for the final structure of the aggregate as is usually the case for the lipid polymorphism.^{1,2} If both polar heads of the bola exhibit a marked different volume, this is expected to induce a strong curvature in the unsymmetrical monolayer. Then, the most stable structure is a tube, as previously observed for unsymmetrical monolayers made of glyco-bolas.²³ Then, the diamine salt of ω -hydroxyl palmitic acid exhibits the ideal shape for the unsymmetrical monolayer to bend in a conic structure. Such disclinations yield to five types of cones having an apex angle quantified^{12,26} according to $\alpha_n = \arcsin(1 - n/6)$, which gives $\alpha_1 = 9.6^\circ$, $\alpha_2 = 19.5^\circ$, $\alpha_3 = 30^\circ$, $\alpha_4 = 41.8^\circ$, and $\alpha_5 = 56.4^\circ$. These are all present through the 1000 cones observed in our samples. Cones having an apex angle $\alpha_n \pm 15\%$ were gathered, and the result is depicted in Figure 4 as a frequency histogram. The occurrence of disks and tubes, which correspond to $n = 0$ and 6, respectively, is also reported. Their relative frequency of occurrence is weak since tubes exhibit a strong curvature and disks have a high edge energy.

Clearly, cones having smaller angles, that is, a high number of pentagonal defects (or n -gonal with n high), are a majority. As in the case of graphite,¹⁰ this means that entropy plays a dominating role in the distribution of disclinations within the cone. This is determined at the nucleation stage since, as in the case of icosahedra,⁷ cones occur upon crystallization of the surfactant alkyl chains while crossing the chain melting transition. In our system, there is no possibility for covering the edges of the lipid sheets when it grows up upon cooling. This represents a high energetic cost on the order of $\pi\gamma Dd$, where γ is the oil–water surface tension,

d is the monolayer thickness, and D the sheet disk diameter (Figure 3).^{2,27} For a cone having an apex angle 2α and a side length $L = D/2$ (Figure 3), this value is reduced to $\pi\gamma Dd \sin(\alpha)$. The final cone apex angle is then a balance between the defect and bending energies and the reduction of the surface edges exposed to the solvent.

Thus, it is presently shown that there exists a novel route for the stabilization of lipid aggregates as cones. Cones are composed of unsymmetrical monolayers made of a diamine salt of ω -hydroxyl palmitic acid with the hydroxyl group pointing toward the hollow interior of the cone. There are, however, minimal conditions for this to occur. The formation of cones in a lipid system is inherent with the arrangement of lipids on a regular hexagonal lattice having a $p6$ symmetry. This most probably implies that bola-amphiphiles are used since both lipid sheets in a bilayer are uncorrelated. The bola-alkyl chains have to be frozen, and its molecular shape is determinant. Finally, the lipid system must not contain any surfactant capable of forming half a micelle that is susceptible of stabilizing edges or pores. This should help the search for other lipid systems capable of forming cones in solution. Mixtures of an unsymmetrical bola-amphiphile and a diamine can produce aggregates similar in shape to viruses and graphite.

Acknowledgment. The author would like to thank B. Pontoire for the X-ray experiments, and J. Davy for the DSC.

Supporting Information Available: Sample preparation, DSC data, and n pentagonal defects. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0560478