



Self-assembly of different single-chain bolaphospholipids and their miscibility with phospholipids or classical amphiphiles



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ABSTRACT

A variety of bolalipids with a single long alkyl chain and two identical headgroups self-assemble in aqueous solutions into helical entangled nanofibers leading to the formation of a hydrogel. An increase in temperature usually leads to the break-up of the fiber structure into micellar aggregates. In this paper the question is addressed whether bolalipids of different lengths or different headgroup structures can form mixed fibers. Also, the stability of the fiber aggregation of bolalipids in mixtures with phospholipids forming lamellar bilayers is discussed. Here, the question whether single-chain bolalipids can be incorporated into phospholipid bilayers to stabilize bilayer membranes is important, as possibly lipid vesicles used for drug delivery can be improved. Finally, the stability of the fiber aggregate against solubilisation by common surfactants was studied. The paper addresses the question which type of aggregate structure dominates the self-assembly of bipolar and monopolar amphiphiles in aqueous suspension.

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1. Introduction

Bolalipids with two chains connecting both headgroups occur in many archaeobacterial membranes and serve as membrane stabilizing

molecules due to their chemical structure traversing the membrane [1–10]. The question whether single-chain bolalipids can also be used in stabilizing lipid bilayers is of great interest. Single chain bolalipids are much easier to synthesize and can be varied in a systematic way for optimization of membrane properties. In many cases monolayer membranes are formed by short chain bolaamphiphiles with not too large headgroups [8,11–16]. However, symmetrical bipolar phospholipids (bolalipids) composed of one long alkyl chain and two large

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polar headgroups show packing frustration due to the mismatch between the cross-sectional areas of the alkyl chain and the headgroups. Therefore, they do not form lamellar aggregate structures in water but self-assemble in aqueous solutions in the form of helical nanofibers with a fiber cross-section corresponding to the length of the bolamphiphile [17–19]. The alkyl chains of the bolalipids are extended in an all-*trans* conformation and the packing of the molecules is such that they are slightly twisted to each other leading to a helical structure of the nanofibers. The fibers can reach a length of several micrometers and are relatively stiff due to the fact that the alkyl chains are in an all-*trans* conformation. The fibers become entangled and can also form “cross-links” by contacts of exposed hydrophobic surfaces of the fibers. These effects then lead to the formation of a hydrogel with properties intermediate to those formed by worm-like micelles and those found for more crystalline nanofibers [18–20]. Fig. 1 shows schematically how these bolalipids aggregate to form long fibers with a diameter corresponding roughly to the length of the molecule. Coarse grain simulations have shown that the surface of the nanofiber cannot be completely covered by the polar groups, but that grooves are present where hydrophobic surface of the chains is exposed to water. This could be confirmed by high resolution AFM of single fibers [21,22].

While this nanofiber structure is surprisingly common for many bolalipids with a long single alkyl chain, also other types of aggregates can be formed. Under certain conditions micellar aggregates and also lamellar structures can be detected [23,24]. Systematic investigations have shown that the type of aggregate structure observed depends on the chemical structure of the bolalipid, particularly the length of the alkyl chain and the modification of the chain by introduction of hetero-atoms, triple bonds, or phenyl rings. In addition, the ratio of the cross-sectional area of the headgroup and the chain, and the presence of attractive interactions via hydrogen bonds between the headgroups are important [19,20,25–32]. In many cases, the nanofiber is the stable aggregate form at a low temperature and heating of the system leads to a disruption of the fibers into small micellar-like aggregates, which show an additional transition at a higher temperature into a different form of micellar aggregate with increased disorder of the chain [18,23,33]. The structure of these micellar aggregates are at present still unclear. Fig. 2 shows in the middle part cryo electron microscopic images of the micellar aggregates formed at a high temperature and the fiber structures present at room temperature.

On the left hand side of Fig. 2 the thermotropic behavior of a bolalipid suspension is exemplified by the DSC curve at the top and the change in the CH₂-stretching band frequency as a function of temperature at the bottom. In the DSC curve, the fiber to micelle I transition is indicated by the large endothermic transition, while the change in micellar aggregate structure is accompanied by a broad transition at a higher temperature (micelle I–micelle II transition). The IR-spectroscopic data show that the wavenumber of the antisymmetric stretching band increases in two steps indicating that the chains become disordered when the fibers transform into micelles and that a further fluidization of the chains occur during the micelle I–micelle II transition [18,19].

When the chain length of the bolalipid is increased, the temperatures of the transitions observed in the aqueous solution increase as expected due to the increase in the hydrophobic and the van der Waals interactions between the chains.[27] Fig. 3 shows as an example the chemical structure of single-chain bolalipids with different chain lengths used for this purpose and the diagram of the transition temperatures as a function of chain length.

As bolalipids are not necessarily useful in their pure form, the mixing behavior of single-chain bolalipids with other molecules of similar chemical structure and with membrane forming phospholipids have to be known to find the optimal properties regarding the mismatch in chain length and volumetric properties for the formation of membranes with enhanced mechanical stability. In Fig. 4 these differently shaped molecules are schematically shown. On the left hand side are bolalipids with different headgroup sizes, different chain lengths or different chain structure and conformation. On the right hand side of the figure monopolar amphiphiles such as phospholipids with two chains, single alkyl chain surfactants or amphiphilic molecules with a rigid ring structure, such as cholesterol and its derivatives, are shown.

In this paper we will therefore focus first on the mixing behavior of single-chain bolalipids with other bolalipids having different chain structures and different headgroups to elucidate the stability regime of the nanofibers with respect to temperature and mixing with other bolalipids. Then we will describe the mixing properties of bolalipids with monopolar amphiphiles forming either lamellar phases, such as phospholipids, or micellar aggregates such as alkyl chain surfactants. Finally, the influence of a membrane stabilizing molecule, such as cholesterol, on the mixing properties in ternary systems containing bolalipids, phospholipids and cholesterol will be described.

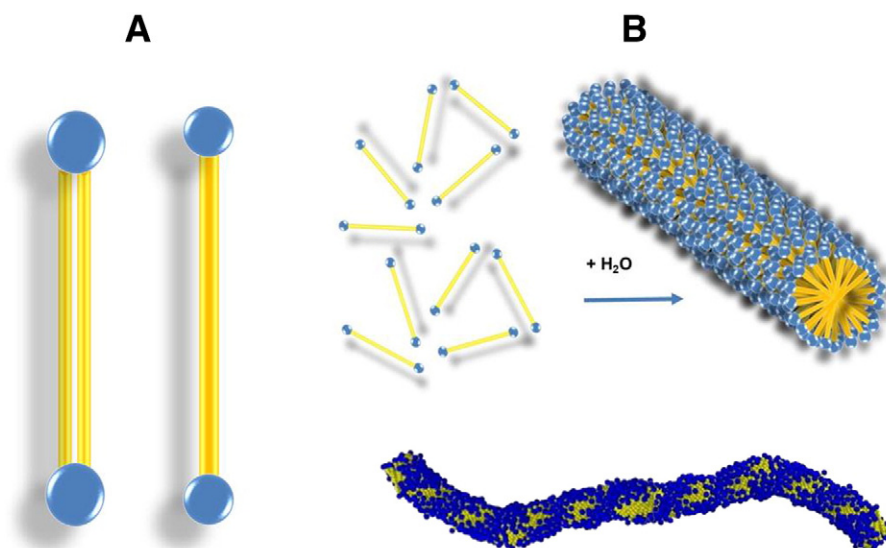


Fig. 1. A: Schematic drawing of a natural bolalipid with two hydrophobic chains connecting the two polar groups and a synthetic single-chain bolalipid. B: Scheme showing the aggregation of single-chain bolalipids into fibers and the helical fiber structure with the hydrophobic grooves obtained by coarse grain simulations at the bottom [21,22].

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