

Periodic minimal surface structures in bicontinuous lipid–water phases and nanoparticles

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Abstract

The accumulated evidence for the existence of periodic minimal surface (PMS) bilayer structure of the bicontinuous cubic phases in lipid–water systems is summarized. There are three fundamental PMS: the G, D, and P types. These three and no others have been observed in lipid–water systems. Due to the so-called Bonnet relation, the PMS structures are isometric conjugates to one another at coexistence, which determines the cubic axis ratio and water content at equilibrium. A number of lipid systems exhibiting coexisting cubic phases have been examined in relation to fulfilling the Bonnet relation. In all cases with known unit cell dimensions, the phases are Bonnet-related. This is regarded as strong evidence for their PMS structure. The phase transitions in relation to swelling and water content also fulfill the Bonnet relations. Aside from bulk phases with PMS structure, it has also been shown possible to produce nanoparticles with internal PMS structure. New developments enable the manufacturing of such particles with uniform size and internal structure, of interest in practical applications such as in vivo delivery of drugs.

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1. Introduction

It is now generally accepted that the bilayer of bicontinuous cubic lipid–water phases forms periodic minimal surface structures. A periodic minimal surface (PMS) has zero average curvature everywhere and is free from self-intersections. It divides space into two equal or chiral compartments. Studies of lipid–water systems have given evidence for the existence of three cubic PMS structures, with the lipid bilayer following the gyroid (G), diamond (D), and Schwarz primitive (P) surface (with the minimal surface equivalent to the bilayer midsurface). Their identification is usually based only on the observed space group. There is, however, no complete structure determination, and this type of structure has therefore occasionally been questioned. A recent paper on a glycolipid–water system, where two of these cubic space groups were identified [1], refers to the

PMS description as well as the rod system description. The accumulated evidence for the existence of PMS conformations of the lipid bilayer in lipid and water continuous (bicontinuous) cubic phases will therefore be summarized here. Such phases can be fragmented into nanoparticles: single crystals of finite periodicity formed by closing of the lipid bilayers towards an outside aqueous phase. Studies of their structure by cryotransmission electron microscopy (cryo-TEM) and a new method to prepare monodisperse particles will be described here. These nanoparticles are able to solubilize proteins and other peptides, providing new possibilities in drug delivery.

Already in 1976, Scriven put forward the idea “that bicontinuous structures may arise in fluids,” and he also included mesomorphic phases in his discussion [2]. In an experimental study of the aqueous glycerolmonooleate (GMO)–water system [3], the cubic region in the phase diagram was proposed to have space group Im3m and therefore the P type of minimal surface structure. Larsson et al. [4] had earlier shown that cubic phase samples obtained in the GMO–water were bicontinuous. This first

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space group determination was not correct, however, as the cubic region consists of two phases (Im3m representing a “common denominator” of the epitaxially related phases).

The first hard evidence for the existence of the minimal surface type of structure was the demonstration of the Bonnet transformation between the coexisting two cubic phases G and D in the GMO–water system, with these two phases being isometric conjugates to one another [5*] as further discussed below. The Bonnet relation represents an isometric transformation of a surface that leaves the intrinsic geometry intact, such as the Gaussian curvature (cf. [6**]). The volume content per surface area unit of Bonnet-related phases, however, is different as discussed below.

This initial work led to a more general introduction of curvature in the description of lipid–water structures (cf. [6**]).

2. Driving force of transitions at swelling of cubic minimal surface bilayer phases

The formation of different phases has for a long time been successfully rationalized by changes in molecular geometry expressed by the packing parameter (v/al , with the molecular volume= v , the length of the molecule= l , and the cross-section area at the water interface= a). The value is 1 in the lamellar liquid crystalline phase and somewhat larger in the PMS type of cubic phases, with the relation between their packing parameters (pp): $1 < G(\text{pp}) < D(\text{pp}) < P(\text{pp})$. At swelling of GMO in water at room temperature, the lamellar liquid crystalline phase is first formed and then the G-phase, indicating a successive increase of the disorder of the lipid molecules reflected by the increasing pp. Heating of the lamellar phase at a constant water composition, which also increases the lipid molecular disorder, can also result in a transition into the G-phase.

This increase in molecular disorder (reflected by changes of the packing parameter) cannot, however, be fulfilled during swelling of a particular minimal surface structure. On the contrary, the bilayer tends to get more and more planar. Swelling over a wide composition range should therefore be expected to lead to frustration in the bilayer packing. The transition into a Bonnet-related conjugate, such as $G \rightarrow D$ and $D \rightarrow P$ will reduce this frustration. Thus the phase transition sequence $G \rightarrow D \rightarrow P$ can be expected to occur within cubic regions with large water composition intervals.

3. The Bonnet relation

The origin of the Bonnet ratio is described in Ref. [7]. The first complete description of the GMO–water phase diagram was based on the fulfillment of the Bonnet relation between the coexisting cubic phases, as mentioned above

[5*]. Not only did the observed cubic axis ratio agree with the corresponding Bonnet ratio (1.58), but also the size of the two-phase region was consistent with the different volume content. Thus the normalized surface-to-volume ratio per lattice fundamental region according to Schoen [8] is 2.4533 and 2.4177 in the G and D surfaces, respectively. The theoretical water ratio estimated from this value was observed to be in reasonable agreement with the water compositions in the coexisting G and D phases of the GMO–water system.

The main features of the Bonnet relation between cubic phases, with the same distribution of Gaussian curvature along the surface structure unit, have already been described. The work by Hyde and Fogden [9**] revealed many significant features. Importantly it defined a very useful concept—the *Gaussian curvature inhomogeneity*:

$$\mu_2 = \langle K^2 \rangle / \langle K \rangle^2$$

The most homogeneous of all known surfaces are the G, D, and P surfaces with a value of μ_2 equal to 1.2188, which possibly explains why only these three types of structures out of all other periodic minimal surfaces have been identified experimentally. Furthermore they calculated the phase sequence versus water content from the elastic energy minimum. Schwarz and Gompper [10*] have also analysed the Gaussian curvature distribution, and they calculated the bending energy of seven different PMS. The free energy was found to be lowest in the G, D, and P surfaces (in that order). Furthermore they calculated the location in the phase diagram lauric acid/water/dilauroylphosphatidylcholine, which agreed well with the observations.

The analysis by Hyde and Fogden of “curvature frustration” [9**], involving a combination of the Gaussian curvature and the average curvature, demonstrated that a surface can appear to be close to a minimal surface (e.g., in electron micrographs) but still have pronounced deviations. This is probably a significant feature with regard to the formation of cubic phase particles (Cubosome®). The interior bilayer of such particle structures must be in hydrostatic equilibrium with the closed bilayer at the surface.

Besides the phase transitions observed in the GMO–water system, three other systems with Bonnet-related cubic phases were discussed [8]. One was a D–P transition with a Bonnet ratio of 1.28, and the other were G–D transitions. All showed cubic axis ratios at coexistence, which agreed within a few percent with the theoretical Bonnet ratios. The lauric acid/water/dilauroylphosphatidylcholine phase diagram mentioned earlier was determined by Templer et al. [11*], and they also found that the experimental a -axis ratios agreed with the Bonnet requirements. A further example of G–D transitions is observed for the di-dodecyl alkyl glucopyranosyl glycerol/water system [12*]. Additional Bonnet-related phases will be considered below.

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