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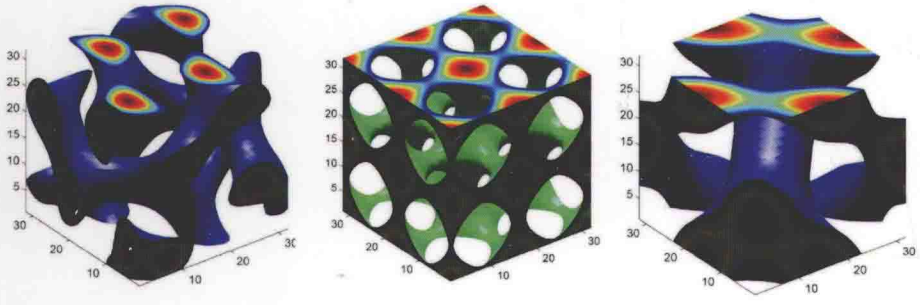
SELF-ASSEMBLED SUPRAMOLECULAR ARCHITECTURES

Lyotropic Liquid Crystals



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PREFACE

Lyotropic liquid crystals make up one of the most outstanding examples of complex fluids based on components as simple as water, lipids, surfactants, platelets, and rodlike particles. These also are some rare cases in which complex fluids are spontaneously found at the thermodynamic equilibrium. What is then the driving force behind this unique self-organization? And how can the specific features of these resulting materials be exploited in the various disciplines of applied and fundamental sciences? This is a question of primary importance since the relevance of lyotropic liquid crystals spans today fields ranging from biology to nanotechnology, from cosmetics to food technologies. Despite their apparent simplicity, these materials remain challenging systems that need to be understood at the molecular level. Water, which is the most frequently used solvent in lyotropic liquid crystals, adds up dramatically to the complexity of the systems, as the hydrogen bonds among water molecules and the resulting clusters of water molecules, already provide this solvent most of the features common to structured fluids. When polar lipids are mixed with water, the selectivity in the partition coefficient of water with the hydrophilic and hydrophobic parts of the lipids leads to structured fluids of complex topologies and intricate architectures organized in the few nanometer-length scales. These heterogeneities and their organization determine to a very great extent the final properties of lyotropic liquid crystals and can then be exploited for encapsulation, templating, diffusion, release, reactions, or confinement in a multitude of possible applications.

Recently, researchers are devoting much of their efforts to better understand how to manipulate the lyotropic liquid crystals and to be able to increase the lattice parameter values, to elongate and to enlarge the aqueous channels in order to use these systems as solubilization reservoirs for food additives, supplements, bioactives, and drugs.

The modified lyotropic liquid crystals (LLCs) show very significant potential to serve as microreactors, template systems for interfacial crystallization, and more.

It is our believe that the recent progress made in the last decade will bring us to a new area in which LLCs will be used in the pharmaceutical, cosmetic, and food industries as major carriers of bioactives.

This book tackles the topic of LLCs from both the fundamental and applied perspectives. The first part of the book discusses our current fundamental understanding of lyotropic liquid crystals, with emphasis on lipid-based

systems and rodlike solvent dispersions, whereas the second part of the book tackles the applications landscape, with special emphasis on drug delivery applications.

In Chapter 1, Mezzenga describes the physics of self-assembly of lyotropic liquid crystals from a thermodynamic point of view, introducing recent concepts such as self-consistent field theory, to understand the structural and physical properties of these systems; the chapter also touches on the current understanding of transient states associated with order–order transitions.

Herrera and Rey, in Chapter 2, present a comprehensive review of the rheology and properties of nematic phases, including calamitic and discotic micellar solutions and wormlike micelles. Their review examines verifiable rheological liquid crystal models for lyotropic nematics highlighting the mechanisms that control orientation behavior under shear, anisotropic viscoelasticity, and non-Newtonian behavior.

In Chapter 3, Kolev, Aserin, and Garti focus on the topological properties of the columnar hexagonal phase and are critically looking at—and summarizing—the available theoretical and mathematical aspects and the most fundamental aspects of the columnar reverse hexagonal mesophase.

Chapter 4 by Hartley and Shen provides a comprehensive review of the available experimental characterization methods of lyotropic liquid crystalline systems, spanning small-angle neutrons and X-ray scattering, nuclear magnetic resonance, positron annihilation lifetime spectroscopy, electron and atomic force microscopy, and neutron reflectivity.

In Chapter 5, Yaghmur and Glatter discuss the phase diagram, emulsification procedures, structural and physical properties of LLCs confined in small nanoparticles dispersed in water. They focus on monoglyceride-based systems and also touch on potential applications of these formulations in the area of food colloids and dispersions.

Kulkarni and Glatter, in Chapter 6, review the hierarchical organization of lyotropic liquid crystals from the lipid length scale up to the macroscopic organization of emulsified liquid crystalline systems, with special emphasis on their end-use applications in dispersed systems in the form of oil-in-water emulsions, high internal phase emulsions, and gels.

Chapter 7, by Amar-Yuli, Aserin, and Garti, is a review of the current strategies available for the use of LLCs as templates for the synthesis and alignment of nanostructured materials. The chapter reviews carefully the templating effects in both inorganic and organic materials throughout the main classes of available lyotropic mesophases.

Libster, Aserin, and Garti, in Chapter 8, open the discussion on the use of LLCs as drug delivery vehicles. The different intrinsic diffusion of guest molecules as a function of the mesophase structure are discussed in details, and different means available to tune this diffusion are discussed, considering both external stimuli and "doping" strategies, such as the use of membrane piercing agents.

Chapter 9, by Boyd and Fong, is a discussion of the different types of external stimuli to induce a release of drugs on demand. Recent developments in the field are carefully reviewed and external stimuli such as temperature, pH, and light are discussed in details.

Chang and Nylander (Chapter 10) discuss the problem of dealing with nonlamellar lyotropic liquid crystalline nanoparticles, mostly hexasomes and cubosomes, at interfaces and surfaces. The chapter provides a state of the art on the techniques available to detect the adsorption and structures of these nanoparticles at interfaces, their formation, and implications for biological interfaces and drug delivery.

Chapter 11, by Géral and colleagues, concludes the book by providing a practical direct example of the relevance of lyotropic liquid crystalline nanoparticles, by discussing their use as nanocarriers for targeting of cells expressing brain receptors. The chapter screens self-assembled lipid systems suitable for the encapsulation of neurotrophic peptides and demonstrate their potential in targeting neuronal therapetic applications.

To summarize, the present book gathers an impressive set of contributions by leading scientists in the area, overarching the entire framework in which lyotropic liquid crystals are today investigated worldwide; this is done by moving from a very fundamental perspective into the possible practical applications area of these materials. Such a contribution was missing from available literature, and it is in the scope of this book to timely fill this gap. It is to be hoped that this outstanding set of reports will not only serve scientists working in the field but will also become an inspiring source for younger scientist generations and also serve students in their education process in the area of nanosctructured self-associating soft materials.

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CONTENTS

CHAPTER 1

Physics of Self-Assembly of Lyotropic Liquid Crystals

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Abstract

We review recent advances in the understanding of self-assembly principles in lipid-based lyotropic lipid crystals, from the original rationalization achieved using the critical packing parameter up to recent, more sophisticated thermodynamics approaches, such as the self-consistent field theory, which can be efficiently used to minimize the total free energy of a lipid–water system and identify stable mesophases. We highlight the importance of reversible hydrogen bonding as one of the key parameters ruling the self-assembly in these systems and examine the implications this may have also in real applications. We finally discuss the current understanding on the dynamics of phase transitions and review the status of the art on current atomistic approaches to investigate the relaxation dynamics in these systems.

Self-Assembled Supramolecular Architectures: Lyotropic Liquid Crystals, First Edition. Edited by Nissim Garti, Ponisseril Somasundaran, and Raffaele Mezzenga.

1.1 INTRODUCTION

The term *lyotropic liquid crystals* generally refers to systems in which any form of liquid crystallinity is induced or affected by the presence of a solvent. The simplest form of lyotropic liquid crystal is the nematic phase, which is given by the nonisotropic orientation of rigid particles or molecules, called mesogens. In what follows we shall focus on lyotropic liquid crystals of superior order and, in particular, in those observed in surfactants (surface-active agents) in the presence of water, with special emphasis on lipid–water systems. Disregarding other forms of aggregation of lipids in water to consider only those characterized by a periodic order, lipids most frequently found to form lyotropic liquid crystals are neutral lipids such as monoglycerides or phospholipids (Krog, 1990). These two systems have in common one or two fatty acid tails and a polar head with total neutral charge (in the case of phospholipids most often the positive and negative charges are present in stoichiometric ratio; one talks then about zwitterionic lipids). These structured fluids are periodically organized on the nanometer length scale and have been known for half a century since the pioneering work of Luzzati and Husson (1962). One particular feature that is breathing new life into these systems is the fact that, when redispersed in excess water, some specific liquid crystalline structures can be maintained. This makes them particularly suitable for food, pharmaceutics, and cosmetic applications (Fong et al., 2009; Mezzenga et al., 2005a; Mohammady et al., 2009; Yaghmur and Glatter, 2009). Additionally, in their bulk form, they have been used as nanoreactors to run and control regioselective reactions (Garti et al., 2005; Vauthey et al., 2000) due to the environment constituted by a very large lipid–water interfacial area. The most frequently found structures in lipid–water lyotropic liquid crystals are the isotropic fluid (L_{II}), the lamellar phases (L_α or L_C depending on whether the alkyl tail is amorphous or has crystallized), inverted columnar hexagonal cylinders (H_{II}), and bicontinuous double gyroid (Ia3d), double diamond (Pn3m), and primitive (Im3m) cubic phases (de Campo et al., 2004; Mezzenga et al., 2005b; Qiu and Caffrey, 2000). The presence of charges on the lipid–water interface tends to disrupt the interface, and, thus, lyotropic liquid crystals, with a great nonzero total charge, are rarely found. Nonetheless, cationic and anionic surfactants have been used as doping agents for these systems, to engineer other phases or to displace boundaries in the phase diagram (Borne et al., 2001). Finally, a new class of lyotropic liquid crystals has recently emerged, that is, the macromolecular amphiphilic systems: the most common, Pluronics, is formed by a diblock copolymer with one hydrophilic (generally polyethyleneoxide, PEO) and one hydrophobic (generally polypropyleneoxide, PPO) blocks, so that in the presence of water a strong partitioning effect leading to self-assembly and microphase segregation of the two blocks is found.

Figure 1.1 shows a typical example of a phase diagram for a commercial form of monoglyceride, monolinolein, in the presence of water. Remarkably, several transitions are found within a few degrees of temperature or small

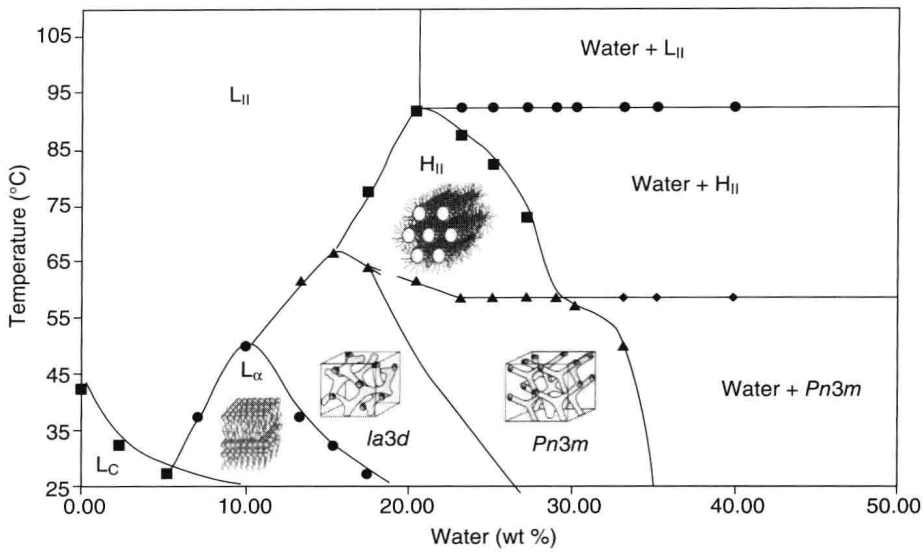

Figure 1.1 Phase diagram of a monolinolein–water system, with a schematic sketch of the different liquid crystalline phases found in the various regions of the phase diagram. [Reproduced with permission from Mezzenga et al. (2005a).]

percentage changes in the composition. Below, we will briefly review the state of the art on the driving forces for the order–order transitions among different mesophases and the order–disorder transitions of a mesophase into the isotropic micellar fluid.

1.2 CRITICAL PACKING PARAMETER

Without any doubt, the simplest, the easiest, and the most diffuse approach to the rationalization of the different structures found in the lyotropic liquid crystals is based on the concept of the critical packing parameter (CPP), a criterion developed originally by Israelachvili and colleagues (Israelachvili, 1991; Israelachvili et al., 1976). The CPP is a geometrical value consisting of the ratio between the volume of the hydrophobic lipid tail, v, and the product of the cross-sectional lipid head area, A, and the lipid chain length, l. Following the changes of the CCP, one can approximately predict order–order transitions associated with the change in the curvature of the water–lipid interface. Figure 1.2 gives a schematic overview of the correspondence between various mesophases and their corresponding CCP.

The CCP predicts essentially two classes of morphologies. For a value of CCP $v/(Al) < 1$ "oil-in-water" morphologies are expected, which correspond to the so-called direct liquid crystalline phases in which the polar heads are

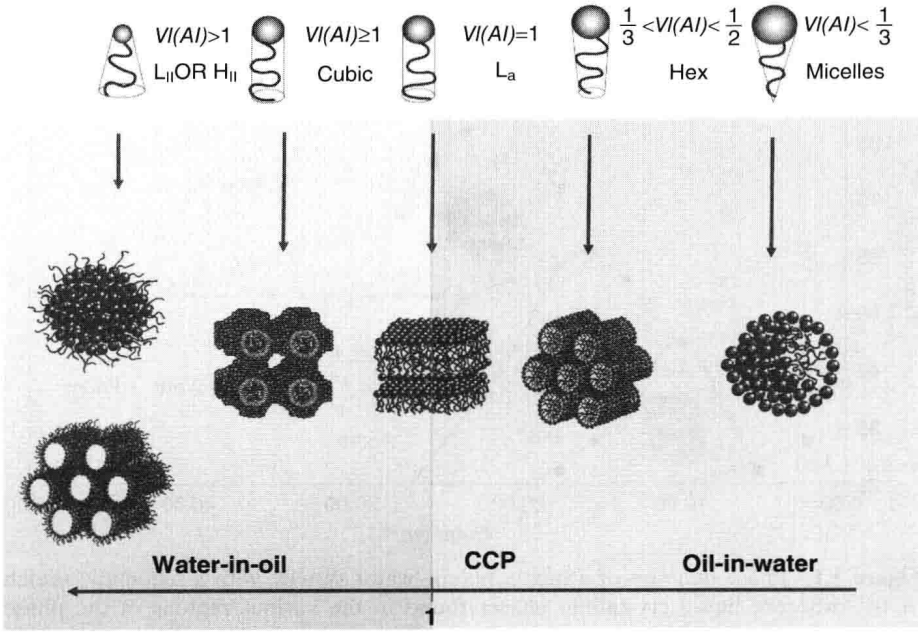

Figure 1.2 Relationship between the critical packing parameter (CCP) and the expected morphology in lyotropic liquid crystals.

forming a convex interface against water. On the other hand, for $v/(Al) > 1$, a phase inversion occurs and "water-in-oil" morphologies are found, with concave lipid head surfaces against the water. The flat interfaces, corresponding to the L_α lamellar phase are found for $v/(Al) = 1$. More in details, inverted micelles/inverted hexagonal, inverted cubic phases, lamellar, hexagonal phases, and direct micelles are expected when the CPP has a value of $v/(Al) > 1$, $v/(Al) \geq 1$, $v/(Al) \approx 1$; $\frac{1}{3} < v/(Al) < \frac{1}{2}$, and $v/(Al) < \frac{1}{3}$, respectively (Israelachvili et al., 1991; Jonsson et al., 2001).

The CPP has been widely employed to predict and rationalize differences observed among liquid crystalline phases and can capture some of the physical changes. For example, changes occurring on CCP with temperature and composition can be understood to some extent. Increases in temperature leads to partial breaking of hydrogen bonds, with the number of water molecules hydrating the polar heads of the lipids, and this leads to an increase of the CPP because it decreases the effective head area. This can well explain the cubic-to-hexagonal transition, for example (Qiu and Caffrey, 2000). Similar arguments can be used to explain the L_α to cubic transition induced by temperature raises. However, other transitional changes, such as the concentration-induced lamellar $\rightarrow$ cubic transition remains unexplained by the application of the CCP concepts. The concept of the CPP is limited to a qualitative interpretation of the phase diagrams and cannot be used to bring insight into the structural

complexity of these mesophases, nor on the physical mechanisms regulating their self-assembly behavior.

1.3 ANALOGIES AND DIFFERENCES BETWEEN LIPIDS AND BLOCK COPOLYMERS

Alternative approaches can be taken in order to develop a physical understanding of lyotropic liquid crystals. A good starting point is to draw analogies and differences with another important organic self-assembling system, that is, block copolymers.

Block copolymers bear many similarities to surfactants. As for lipids, they are also formed by two blocks attached into the same amphiphilic molecule. If the two blocks differ enough in chemical composition, they will induce a microphase segregation into nanostructured morphologies spanning a few nanometers in periodicity (Bates and Fredrickson, 1999). The types of structures found are also very similar: lamellar, columnar hexagonal, and bicontinuous cubic (Ia3d) phases are present in both classes of materials. The Pn3m bicontinuous cubic phase, which is missing for a pure diblock copolymer phase diagram, can be recovered when additional components are added. Indeed, when comparing the morphologies from the two classes of materials, one must realize that since the water–lipid system is a two-component system, for direct comparison with block copolymers one should take the case of a block copolymer plus a second component compatible with one of the two constitutive blocks of the copolymer. This second component, be it a solvent or a homopolymer, has the role to mimic water in the lipidic mesophases. Figure 1.3 shows the phase diagram of a hypothetical diblock copolymer, with a graphic of the morphologies found.

Beside this encouraging start, some important differences should be mentioned. Let us take a classical diblock copolymer system: Onset of microphase separation occurs when the segregation power, χN, where χ is the Flory–Huggins parameter and N the polymerization degree of the entire block copolymer, is of the order of $\approx$10 or more (Leibler, 1980). By adding the third block mimicking the role of water, small perturbations on this threshold criterion can be expected, without, however, changing it significantly. Because typical polymer pairs typically have an unfavorable χ of $\approx$0.1 or less at room temperature, this indicates that in order to observe microphase separation at standard temperatures the polymerization degree must be 100 or more.

In the case of lipids, the scenario is very different. The Flory–Huggins parameter of the polar versus unipolar species can be estimated by measuring the activity of alkanes partitioning in water at room temperature, which indicates values of the order of 3 for χ (Mezzenga et al., 2005a). This represents such a high unfavorable mixing enthalpy that microphase segregation between the polar head (plus water) and the hydrophobic tail occurs at much lower polymerization degrees.

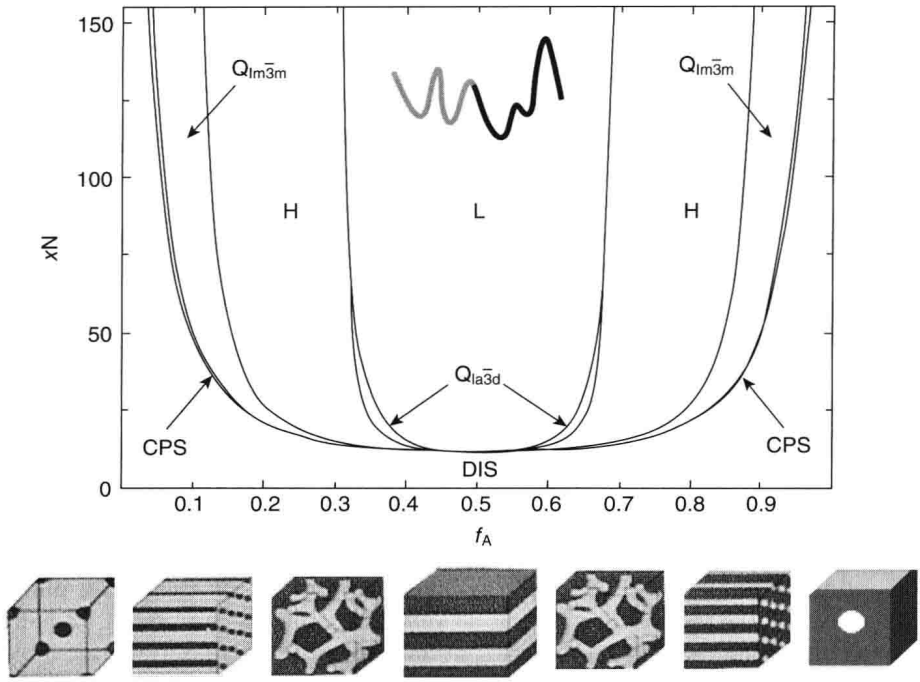

Figure 1.3 Theoretical phase diagram for a diblock copolymer system [Readapted with permission from Matsen and Bates (1996). Copyright 1996, American Chemical Society.]

This explains why microphase segregation in lipid–water mixtures is nearly always observed. Therefore, the loss of entropy in packing together the different lipid molecules is always small compared to the enthalpic gain driving microphase segregation, and self-assembly is driven nearly entirely by enthalpy gain. These concepts are summarized in Figure 1.4.

Another important difference between block copolymers and lipids is the sequence of phases found, for example, on a isothermal, concentration-titrating experiment. Matsen has formulated a theoretical phase diagram for an A–B block copolymer plus an A homopolymer pair (Matsen, 1995a,b), which is exactly the system needed to draw direct comparisons with the lipid–water system of interest.

Consider the arrow in Figure 1.5 in which the phase diagram of such a system, an A–B diblock copolymer, is reported as a function of the block copolymer volume fraction of block A, f, versus the volume fraction ϕ of the additional homopolymer A. Upon adding the homopolymer A, the system goes through spheres, hexagonal, gyroid, and lamellar, which is also referred to as a "normal" sequence since the curvature is progressively decreasing as a consequence of the increasing overall A fraction. The analog experiment