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When detergent meets bilayer: Birth and coming of age of lipid bicelles

Ulrich H.N. Dürr [1], Ronald Soong [2], Ayyalusamy Ramamoorthy *

Biophysics and Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055, USA

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* Corresponding author. Tel.: +1 734 647 6572; fax: +1 734 615 3790.
E-mail address: ramamoor@umich.edu (A. Ramamoorthy).
[1] Current address: INFAI GmbH, Gottfried-Hagen-Str. 60-62, 51105 Cologne, Germany.
[2] Current address: Department of Physical and Environmental Science, University of Toronto, Toronto, Canada.

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1. Introduction

Lipids spontaneously form bilayered structures when brought into an aqueous environment. This is the foundation in the architecture of biological cell membranes. However, lipid bilayers do not lend themselves easily to common biophysical studies; be it of the bilayer itself or of embedded membrane proteins. Detergents, on the other hand, form small aggregates known as micelles that readily solubilize membrane proteins and are well-suited for numerous biophysical methods. However, they are not excellent models of biological membranes as they may denature the structure of a protein and the curvature of the micelle may impose a non-native protein folding. When lipid and detergent meet in an aqueous environment, entities with wholly different properties are formed: lipid bicelles. Bicelles are made of patches of lipid bilayers that are either encircled or perforated by detergent 'rims'. They combine the advantages of both components alone (micelle and lipid bilayer), namely being good models for a biological membrane and having advantageous properties for biophysical experiments. An additional advantage of certain bicelle preparations is their tendency to macroscopically align when brought into a magnetic field. This fact has been exploited not only in the high-resolution structural and dynamics studies of membrane proteins, but also for globular proteins using nuclear magnetic resonance (NMR) experiments.

Fig. 1 gives a graphical introduction to the two types of bicellar phases most commonly employed. At a high detergent concentration and low temperatures, isotropically tumbling disk-like aggregates are formed, the so-called isotropic bicelles (Fig. 1B). At a high lipid concentration and in certain temperature ranges, extended bilayered lamellae are formed that are perforated or delimited by detergent, and have the potential for magnetic alignment (Fig. 1D). Cryo-transmission electron microscopy (TEM) micrographs (A, C) of bicelles taken from the literature [1] are also included in Fig. 1.

Since their first description in 1988, the great potential of bicelles in the study of membrane proteins and proteins in general has been realized. A steady stream of remarkable insights and applications has emerged that is still growing in size. In the present contribution, we will give an introduction to the properties of lipid bicelle phases with an emphasis on NMR experimental measurements. In addition, we will discuss some of the most exciting recent applications of bicelles in the structural and dynamic studies of membrane proteins.

2. Different types of model membranes used in NMR studies

2.1. Vesicles

Lipid membranes and membrane proteins have been investigated by NMR spectroscopy for more than 40 years. Numerous types of membrane samples and preparation protocols have been developed. An overview of the most popular ones is depicted in Fig. 2. The choice of a certain type of sample depends on the task in hand. The simplest type of lipid bilayer sample is formed spontaneously when pure lipids are mixed with a buffer. In this case, multilamellar vesicles (MLVs) are formed, which are approximately spherical aggregates up to tens or thousands of μm in diameter where large numbers of lipid bilayers are stacked in the fashion of an onion. Fig. 2A gives a simple schematic idea. By means of sonication, or by extrusion through the pores of suitable membrane filters, MLV samples can be converted into small unilamellar vesicles (SUVs, Fig. 2B) made up of small spheres consisting of only a single lipid bilayer. The size or size distribution of SUVs is governed by the preparation method employed and is usually much more homogeneous when filter extrusion is employed [2–4].

For use in conventional NMR spectroscopy, vesicle samples have a drawback: they do not reorient fast on the NMR time scale, hence the anisotropic NMR interactions (chemical shift anisotropy, dipolar coupling, quadrupolar coupling) dominate the spectra. This is in stark contrast to systems usually investigated in solution-state NMR spectroscopy, where fast molecular reorientation makes anisotropic interactions collapse to an average isotropic value. A situation of fast isotropic tumbling can be recreated in detergent micelles (Fig. 2E) which do not form bilayers and, hence, give unreliable environments for mimicking membrane conditions and may not always preserve the membrane protein structure and function. Alternatively, anisotropic NMR interactions can be suppressed by

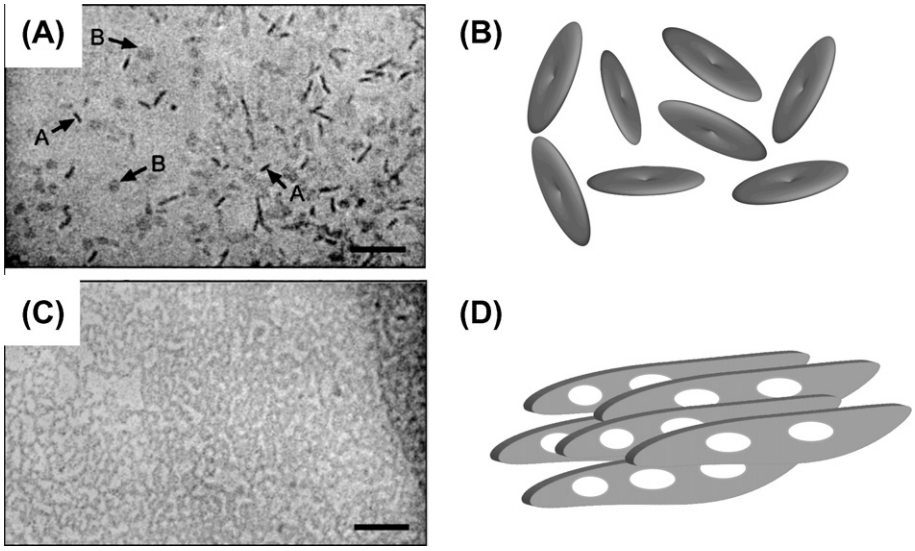

Fig. 1. Lipid bicelles are supramolecular aggregates that are formed when appropriate amounts of lipids and detergents are mixed in an aqueous environment. The size and phase of bicellar aggregates depend on the [lipid]:[detergent] ratio as well as on the temperature. Two fundamentally different phases of bicellar preparations have proven highly useful in the study of protein structure using NMR spectroscopy: isotropic bicelles rapidly tumble freely and are formed at a high detergent concentration (A and B). At low detergent concentrations extended bilayered lamellae are formed (C and D), that spontaneously align macroscopically in a magnetic field. Cryo-TEM micrographs (A and C) are reproduced from the literature [1]. Micrograph (A) contains arrows marked A and B that point to disk-like bicelles viewed from the side and the top, respectively.