Biochimie 94 (2012) 11–25

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Controlling phospholipid self-assembly and film properties using highly fluorinated components – Fluorinated monolayers, vesicles, emulsions and microbubbles

Marie Pierre Krafft*

Systèmes Organisés Fluorés à Finalités Thérapeutiques (SOFFT), Institut Charles Sadron (CNRS UPR 22), Université de Strasbourg, 23 rue du Loess, 67034 Strasbourg Cedex 2, France

ARTICLE INFO

Article history:
Received 29 April 2011
Accepted 19 July 2011
Available online 28 July 2011

Keywords:
Fluorosurfactant
Fluorocarbon
Molecular film
Monolayer
Vesicle
Emulsion
Microbubble
Self-assembly

ABSTRACT

Use of fluorinated components instead or along with standard phospholipids in film, vesicle, bubble and emulsion engineering, can cause drastic modifications of the formation processes, structure and dynamics, and functional behavior of these systems. Perfluoroalkyl chains provide a powerful driving force for self-assembly and ordering. They allow, for example, obtainment of thermally stable vesicles from single-chain phosphocholine derivatives, tubules from non-chiral amphiphiles, faceted vesicles with fluid bilayer membranes, exceptionally stable and narrowly dispersed emulsions and microbubbles. Contact of a monolayer of DPPC with a fluorocarbon gas modifies the monolayer's phase behavior, suppressing the liquid expanded/liquid condensed transition. Phospholipid absorption kinetics at an air/water interface can be substantially accelerated, and the equilibrium interfacial tension reduced by exposure to a fluorocarbon gas. Perfluoroalkyl chains induce nanocompartmentation in films and membranes, allowing, for example, polymerization within vesicular membranes. Vesicles involving highly fluorinated components generally exhibit stability, permeability, fusion and recognition characteristics, different from those of their hydrogenated analogues. Drastic stabilization can be gained for phospholipid-coated emulsions through a co-surfactant effect of (perfluoroalkyl)alkyl diblocks. Stable, size-controlled, narrowly dispersed populations of microbubbles have been obtained using fluorinated wall and/or internal gas components, allowing progress in the understanding of microbubble physics, and open new application perspectives.

1. Introduction

1.1. Scope

This short survey[1] concerns *phospho*lipid-based molecular self-assemblies, including films, membranes, vesicles, emulsions and microbubbles in which at least one component is highly fluorinated. It intends to show, using a non-exhaustive series of examples, how perfluoroalkyl chains (C_nF_{2n+1}, *F*-chains)[2] or components (*F*-components) can profoundly modify the properties and behavior of phospholipids (PLs) in such assemblies, and how they can serve as tools to control the characteristics and functions of PL-based colloids and interfaces. Of particular significance is the powerful capacity for *F*-chains and *F*-components to promote self-assembly. Recent reviews on the latter topic can be found in [1–3].

1.2. Some basic properties of perfluoroalkyl chains relevant to self-assembly and phospholipid property control

F-chains experience feebler intermolecular (van der Waals) interactions than their hydrogenated counterparts, primarily related to lesser polarizability of the fluorine atom as compared to hydrogen. Their unique combination of extreme hydrophobic and pronounced lipophobic characters causes fluorinated amphiphiles (*F*-amphiphiles) to segregate and form stable nano- and micro-sized self-assemblies [1,2]. In these assemblies, *F*-chains tend to be oriented towards gases or fluorocarbons (*FC*s) rather than

* Tel.: +33 3 88 41 40 60; fax: +33 3 88 40 41 99.
E-mail address: krafft@ics.u-strasbg.fr.
URL: http://www-ics.u-strasbg.fr/

[1] Based in part on a lecture given at the 7th Lipidomics Congress in Biarritz in October 2010.

[2] The italized, *F*- (for perfluoro or perfluorinated) short notation will be used throughout this paper to designate perfluoroalkyl (*F*-alkyl) moieties and, by extension, constructs (e.g. *F*-vesicles) made from *F*-alkylated components. The *H*- notation will designate their hydrocarbon counterparts (e.g. *H*-alkyl, *H*-vesicles) [1]. Fluorocarbons and hydrocarbons will be designated as *FC*s and *HC*s, respectively.

0300-9084/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.biochi.2011.07.027

towards other organic or aqueous media. *F*-chains and *F*Cs display much lower surface tensions than *H*-chains and *H*Cs (e.g. 11 mN m^{-1} for *F*-hexane vs. 18 mN m^{-1} for hexane). Another feature of *F*-chains that contributes to their capacity to generate organization at the molecular level stems from their helical configuration, higher rigidity and much larger cross-section (~30 $Å^2$) as compared to *H*-chains (~20 $Å^2$). Phase separation of *F*-chains from *H*-chains induces formation of distinct micro- or nanometer size compartments (or sub-layers) within micelles, monolayers, membranes and colloids comprising *F*-amphiphiles; these compartments tend to exclude non-like solutes [3]. Also noteworthy in this context are the high volatility of *F*Cs relative to molecular weight, and their very low solubility in water.

1.3. (F-alkyl)alkyl diblocks

The simple (*F*-alkyl)alkyl diblocks $C_nF_{2n+1}C_mH_{2m+1}$ (*FnHm*) proved to be particularly useful tools for phospholipid behavior control. Although devoid of hydrophilic head group, these compounds are amphiphilic since the opposing blocks display markedly different affinities, one being fluorophilic and lipophobic, the other lipophilic and fluorophobic, resulting in definite surfactant activity (e.g. they allow emulsification of *H*Cs in *F*Cs) or co-surfactant activity (as in *F*C emulsion stabilization; Section 5). They are amphisteric since the two moieties have different cross-sections, conformations and spatial requirements. They are also amphidynamic in the sense that the two moieties experience different types of motions and different activation energies [3].

2. Controlling phospholipid interfacial film and membrane properties

Phospholipid monolayers, bilayers and multilayers play a foremost role in living organisms as well as in many technical and engineering issues. This section provides examples of interplay of PLs with *F*Cs and *F*-amphiphiles at interfaces.

2.1. Controlling the phase behavior of phospholipids by contact with a fluorocarbon gas — Relevance to lung surfactant function

An exemplar illustration of the impact that *F*-compounds can have on PL behavior is provided by the capacity of simple *F*C gases (e.g. C_8F_{18}, $C_8F_{17}C_2H_5$, $C_8F_{17}Br$), when contacted with dipalmitoylphosphatidylcholine (DPPC) monolayers, to completely inhibit the formation of the normally expected liquid condensed (LC) phase upon compression (Fig. 1A) [4,5]. Moreover, contact with an *F*C gas can achieve complete dissolution of LC domains already formed (Fig. 1B). Suppression of the LC phase of DPPC was confirmed by small angle X-ray scattering experiments that showed disappearance of the two peaks characteristic of this phase (Fig. 2) [5].

The ability to maintain a monolayer of DPPC in its liquid expanded (LE) phase is directly relevant to respiration in superior animals. Indeed, DPPC, the main component of the native lung surfactant, is inadequate as a lung surfactant replacement because, in the absence of appropriate proteins, it forms rigid monolayers upon compression (i.e., during expiration) that contain semi-crystalline LC domains, thereby hindering effective re-spreading of the phospholipid on the alveolar surface during inspiration. Treatment with *F*Cs could help cope with native lung surfactant deficiency. Experimentation on premature rabbits demonstrated a significant increase in alveolar tidal volume (from 20 to 140 μL within 50 min) following pulmonary administration of an emulsion of $C_8F_{17}Br$ (0.4 g *F*C/kg body weight) stabilized with $C_6F_{13}C_{10}H_{21}$ and emulsified with egg yolk phospholipids (EYP), indicating recovery of effective surfactant activity.

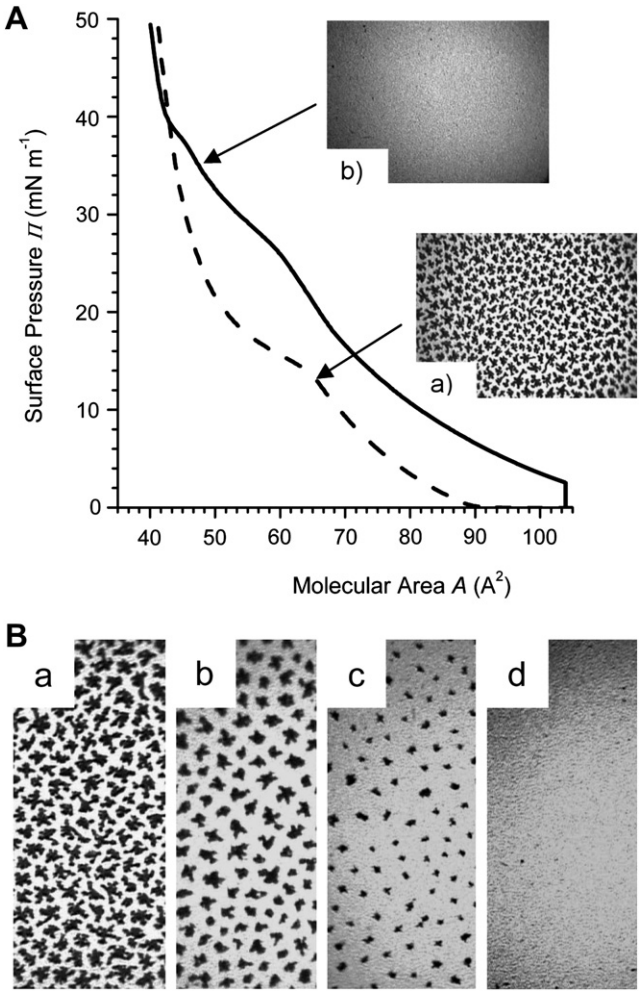

Fig. 1. A) Compression isotherms of a Langmuir monolayer of DPPC at the N_2/water interface with (solid line) and without (dashed line) saturation of N_2 with *F*-octyl bromide; in the latter case, formation of the normally expected LC phase is completely inhibited; fluorescence microscopy images: the rigid semi-crystalline LC domains (a) are no longer seen when the *F*C is present (b). Similar alterations are obtained with C_8F_{18} or $C_8F_{17}C_2H_5$ [5]. B): Dissolution of the LC domains in a DPPC monolayer compressed at 13 mN m^{-1} on water under N_2 at 26 °C. The fluorescent dye (NBDC6-HPC) is preferentially soluble in the disordered regions of the monolayer; therefore, the LE regions appear bright, and the semi-crystalline LC domains are dark. At time t_0 (fluorescence image a) the N_2 atmosphere above the monolayer was saturated with *F8H2*; after 5 min, the LC domains had completely disappeared and the monolayer was totally fluidized (d) [31].

Monolayers of DPPC, when exposed to an *F*C gas, also become significantly less sensitive to the deleterious effect of albumin [6]. This protecting effect could be interesting for the management of the acute respiratory distress syndrome (ARDS), which is often accompanied by the infiltration of albumin and other proteins in the alveoli, where they have a damaging delipiding effect.

This example shows that the phase behavior of films of a PL can be drastically modified by simple contact with minute amounts of an *F*C gas diluted in the atmosphere.

2.2. Co-surfactant effect of a non-amphiphilic fluorocarbon on phospholipids

Subsequently, we investigated the kinetics of adsorption of a series of PLs at the interface between an aqueous solution or dispersion of the PL (dioctanoylphosphatidylcholine (DiC_8-PC), dilaurylphosphatidylcholine (DLPC), dimyristoylphosphatidylcholine (DMPC) and DPPC, and a gas phase containing *F*-hexane (PFH) by