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Fluorous micro- and nanophases with a biomedical perspective

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Abstract—Fluorinated components useful for organizing space at the molecular, nanometer and micrometer scales include perfluorocarbons, perfluoroalkylated surfactants and perfluoroalkyl/alkyl diblock amphiphiles. Perfluoroalkyl moieties, being lipophobic as well as highly hydrophobic, add a new dimension to the hydrophobic segregation effect. Fluorinated amphiphiles, therefore, have an enhanced tendency to self-assemble in various media into stable, highly organized fluorinated colloids, thus generating organized nanometer-size fluorous phases, i.e. fluorous domains with at least one dimension in the nanometer range. Such fluorous nanophases are found in variously shaped micelles, Langmuir films, and bilayer membranes, as in vesicles, tubules and other molecular self-assemblies. Micron-size fluorous phases are present in diverse colloids that comprise liquid, solid and gaseous perfluorocarbons, such as in emulsions, microemulsions, multiple emulsions, microbubbles, gels and dispersions. Continuous or dispersed fluorous, hydrocarbonous and aqueous phases can be present simultaneously. Research on colloidal systems involving highly fluorinated components and destined for biomedical uses (injectable O_2 carriers, contrast agents, drug delivery systems and other devices) has generated a wealth of data. These data are analyzed here from the perspective of the formation, structure and behavior of fluorous nano- and microphases in colloidal systems. Fluorocarbons and fluorinated amphiphiles allow the formulation of an array of multicomponent, multiphase compartmented colloidal systems and nano-objects with various architectures, differential solubility and diffusibility characteristics, and other properties, and exclusion zones that have potential as microreservoirs, microreactors and templates useful for reaction, morphology and functionality control well beyond their initial biomedical purpose. © 2002 Published by Elsevier Science Ltd.

This paper offers an assessment, from the angle of fluorous micro- and nanophase formation, structure and behavior, of data generated during research conducted on fluorinated colloids (*F*-colloids)‡ primarily destined for use in medicine and biology (Table 1). While very few *F*-colloids have undergone pharmaceutical development yet, such research has resulted in a wealth of novel, highly fluorinated components, self-assemblies and other colloidal systems, formulations, evaluations, and data. Selection of the components, and target properties of these colloids (or phase-separated systems) were largely determined by the specific criteria and constraints relevant to the intended biomedical uses. These criteria and constraints included, in particular, the components' pharmacokinetic profile, especially when intravascular administration was contemplated.[1,2] Further constraints were dictated by the need for large-scale manufacture, extended shelf-life, user friendliness, abidement by good manufacturing practice and regulatory rules, and other practical considerations. However, the concepts developed, observations made and conclusions reached during these studies should be valid for and applicable to other fluorinated systems and in other circumstances. Because of the projected use, the level of purity and definition of the components were generally high and well controlled. The unique and intriguing characteristics of fluorinated compounds and colloidal systems will undoubtedly continue to inspire original research, likely leading to novel applications in the medical and other fields. Highly fluorinated components and colloidal systems provide indeed molecular tools for the creation of compartmented micro- and nano-phases and nano-objects that can result in confinement zones, exclusion zones, reservoirs, microreactors, templates, etc. They should be useful for controlling phase behavior, transition temperatures, solubilities, segregation, separation, protection, reaction rates, catalytic effects, product morphology, etc. The author believes in the heuristic value of critically comparing research approaches that have different purposes, yet overlap somewhat, either conceptually, methodologically or in materials (molecules, phases) used; this can generate mutual interest, developing intuition, and opening new perspectives.

Keywords: bilayer; blood substitute; diagnosis; drug delivery; emulsion; fluorinated colloid; fluorinated surfactant; fluorophilic; fluorous phase; hydrophilic; langmuir monolayer; lipophilic; nano-objects; oxygen carrier; perfluoroalkyl chain; perfluorocarbon; phase separation; self-assembly; tubule; ultrasound contrast; vesicle.

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‡ In this paper, the IUPAC-authorized *italicized* prefixal symbol *F*-, meaning perfluoro, as in *F*-alkyl=perfluoroalkyl, will, by extension, be used to designate entities (*F*-chains, *F*-amphiphiles, *F*-surfactants, *F*-vesicles and *F*-colloids) that comprise a highly fluorinated moiety or phase, responsible for significant effects, different from those found for hydrocarbon (HC) analogs. Mirroring this representation, the prefix *H*- (as in *H*-alkyl) will be used for unambiguous designation of HC counterparts.

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Table 1. Examples of colloids with fluorous micro- or nanophases destined for biomedical uses

Dispersed phase (inside)	Water (solvents)	Gazeous FC+N_2	Liquid FC	Liquid FC	Water	Water	Liquid HC	Solid particles
Surfactant film (interface)	*F*-surfactant (*H*-surfactant +F*n*H*m* diblock)	Phospholipids	Phospholipids (+diblock)	*F*-surfactant	*F*-surfactant	Diblock	Diblock	*F*-surfactant
Continuous phase (outside)	Water (solvents)	Water	Water	Water	FC	FC	FC	FC, HFA
	↓	↓	↓	↓	↓	↓	↓	↓
F-colloid	Lamellar phases micelles vesicles, tubules	Osmotically stabilized microbubbles	FC-in-water emulsion	HIPRE gel	Entangled elongated micelle gel	W-in-FC reverse emulsion	HC-in-FC apolar emulsion	Suspension
Biomedical potential	Controlled drug delivery	Contrast echosonography	O_2-delivery (blood substitute)	Topical delivery barrier creams		Drug delivery to the resiratory tract		

Biomedical applications of *F*-colloids include delivery of drugs, including oxygen (as in blood substitutes), and other bioactive materials and markers, and contrast agents. However, fluorocarbon-in-water emulsions and microemulsions for oxygen delivery will only be briefly alluded to in this analysis since their design, preparation, structure, properties, in vivo behavior, and applications have been recently reviewed extensively.[2–4] Likewise for gels[5] and liquid crystals[6] with a fluorinated phase. Neat fluorocarbons, fluorinated polymers and copolymers, solid fluorinated materials, and mesophases as such, are excluded from the scope of this paper. The references cited are primarily intended to provide background information, illustration and literature sources, and cannot be exhaustive, as so many groups have actively contributed to research on fluorinated colloids in the recent years.

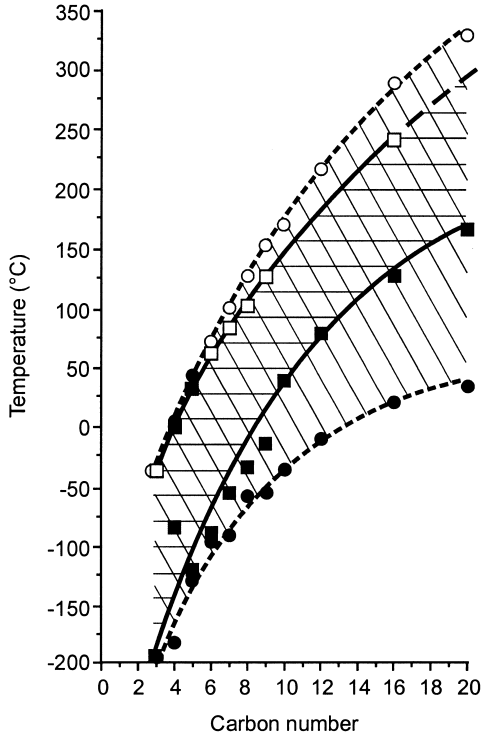


Figure 1. Boiling points (open signs) and melting points (filled signs) of *F*-*n*-alkanes (squares) as compared to *H*-*n*-alkanes (circles) of three and more carbon atoms. The liquid domain is narrower for the former compounds and barely widens when the number of carbon atoms increases. Adapted from F. Giulieri, Thesis, Nice 1995, with permission.

1. Specific properties of highly fluorinated fluid materials relevant to use in medicine and biology

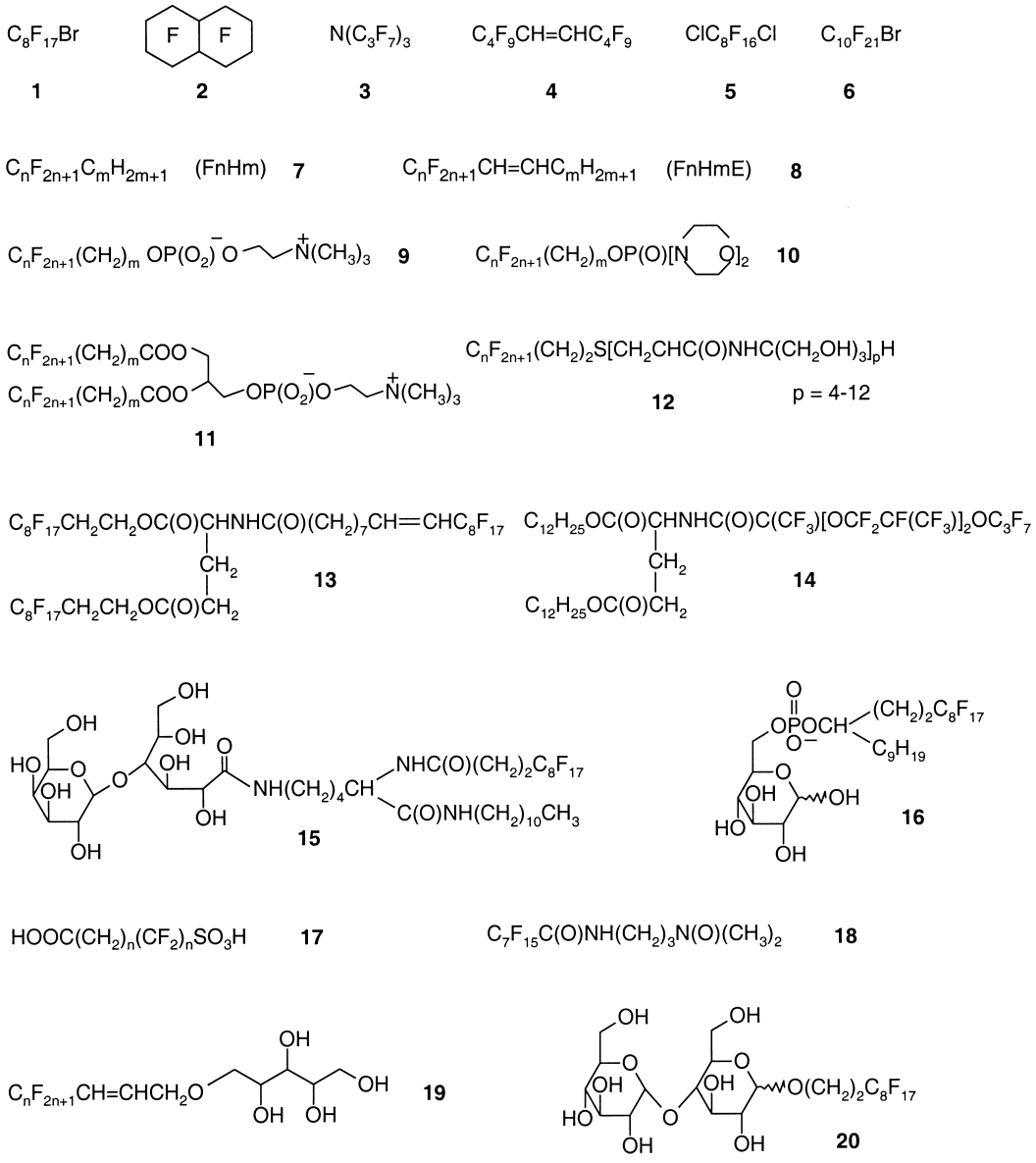
Introducing fluorine in a molecule tends to generate novel behavior, unmatched performance, and potential for discrimination and separation. The attributes that single out the element fluorine include the combination of high ionization potential and electronegativity, and low polarizability. Fluorine is larger than hydrogen (van der Waals radius estimated at 1.47 vs 1.20 Å, respectively) and as space filling as oxygen, yet is less polarizable than the latter.[7,8] Finally, fluorine is a valuable probe for structure determination due to favorable X-ray scattering and NMR properties. On the other hand, the low refractive indexes of *F*-chains, close to that of water, result in poor contrast, thus limiting the effectiveness of light-scattering techniques.

1.1. Perfluoroalkyl chains: bulkier, stiffer, hydrophobic and lipophobic

Perfluoroalkyl chains (*F*-chains) are bulkier than alkyl chains (*H*-chains) (cross-sections of around 30 and 20 $Å^2$, respectively), have a helical structure (rather than a planar 'zigzag' structure) and are more rigid than alkyl chains. The mean volume of CF_2 and CF_3 groups are estimated as 38 and 92 $Å^3$ vs 27 and 54 $Å^3$ for CH_2 and CH_3, respectively.[9,10] CF_3 is substantially larger than $CH(CH_3)_2$ and only marginally smaller than $C(CH_3)_3$.[11] Conformational freedom is strongly reduced (trans/gauche interchange energy of 4.6 vs 2.0 kJ mol^{-1} for *F*- and *H*-chains, respectively) and, consequently, the occurrence of gauche defects at equilibrium, which facilitates stacking and ordering.[12–15]

F-chains are considerably more hydrophobic than *H*-alkyl chains, and have the unique attribute of being lipophobic (or oleophobic or solvophobic) as well. These differences promote self-aggregation, molecular organization, phase separation and the exclusion of non-highly fluorinated solutes. Being strongly electron-withdrawing, *F*-alkyl chains can create or amplify a dipole and locally increase the polarity of the molecules in which they are incorporated. The surface potential of *F*-alkylated fatty acids adsorbed on water was strongly negative, while it is positive for non-fluorinated fatty acids.[16] Substitution of the terminal CH_3 of stearic acid by CF_3 caused the surface potential measured on monolayers of these acids to change from +275 to −915 mV.[17] Similar differences were found

Table 2. Examples of fluorinated components used for preparing fluorinated colloids



between *F*-lipids of type **11** and their *H*-analogs.[18a] Also, *F*-alkanoic acids are more extensively dissociated in water than *H*-alkanoic acids, *F*-alcohols are substantially more acidic then *H*-alcohols, while *F*-alkyl diethers and *F*-alkyl tertiary amines generally lose essentially all basicity. *F*-alkyl halides can undergo a unique type of 'halogen bonding' with heteroatom-containing hydrocarbons, thus generating original supramolecular networks.[18b,c]

The thermal stability and chemical inertness of *F*-chains reflect a combination of the strength of the C–F bond (the strongest single bond known in organic chemistry), low polarizability and electroattracting character of fluorine (which reinforces the C–C backbone), and of the repellent, compact electron shield that protects the molecule against the approach of reagents. Resistance of *F*-chains to metabolism may be an advantage when enzymatic material is present. The large difference in molecular weight (MW; 1 CF_2=50) between consecutive homologous *F*-alkyl chains greatly facilitates the separation of *F*-alkylated compounds having different fluorine contents.[19]

1.2. Perfluorocarbons: gas-like liquids

In sharp contrast with their strong intramolecular bonds, FCs display very low intermolecular cohesiveness, as low polarizability of fluorine results in much lower van der Waals interactions between pairs of CF_2 groups than between pairs of CH_2 groups.[20] Consequently, liquid FCs behave like nearly ideal, gas-like fluids.[10,21] Lesser chain flexibility is reflected by higher melting points and Krafft points, and lesser van der Waals interactions (hence lesser cohesive energy density) by lower boiling points (barely higher than those of noble gases with comparable MW) than for the corresponding HCs, resulting in a narrower liquid phase domain (Fig. 1). As compared to HCs, FCs are also characterized by higher vapor pressures relative to their molecular mass, exceptional chemical and

biological inertness, low refractive index and high compressibility, high gas solubilities (relative to water), low surface tensions, high fluidity and spreading coefficients, high density, low dielectric constants, and magnetic susceptibilities comparable to that of water. These strongly interrelated properties are the basis for the potential of FCs in medicine.[2,22,23] However, due to biological constraints (especially excretion rates), very few liquid FCs have undergone pharmaceutical development; these include primarily *F*-octyl bromide **1**, *F*-decalin **2**, *F*-tripropylamine **3**, bis-(*F*-alkyl)ethene **4** and *F*-α,ω-dichlorooctane **5** (Table 2). Needless to say that the properties listed above have also been used to advantage in fluorous biphasic chemistry.[24–27] Gaseous and volatile FCs or FC derivatives are used as propellants and in injectable gaseous microbubbles (Section 3.2).

The mixing of FCs and HCs is highly non-ideal.[28–30] The Hildebrand parameter δ, which is related to the cohesive energy density of the solvents and reflects their alikeness, range in the following order: δ fluorocarbons$<\delta$ hydrocarbons$\ll\delta$ water. In order for two fluids to be mutually soluble, they need to have similar δ values. The δ values of FCs are typically close to 6 hildebrands ($cal^{1/2}\ cm^{-3/2}$), as compared to 5.7 for O_2, 7–9 for hydrocarbons, and 23.4 for water. FCs and HCs with seven carbon atoms or more are not miscible at room temperature.

On the other hand, *F*-alkyl chains and FCs are definitely CO_2-philic.[31] The solubility of standard gases in FCs is well documented.[3,26,32] The enhanced solubility of FCs in liquid and supercritical CO_2 (as well as the large solubility of gaseous CO_2 in FCs) are noteworthy as they indicate an alikeness of the two media; the existence of specific interactions between the two species appears unlikely, but is still controversial.[33] The fact that stable microemulsions of an aqueous phase in both supercritical CO_2[34–36] and fluorous continuous phases[37–39] can be obtained using *F*-surfactants further illustrates the analogy of FCs with CO_2. Likewise for the obtaining of effective CO_2-philic catalysts by grafting *F*-chains onto ligands.[40] Self-association through hydrogen bonding of *F*-alkylated (hence CO_2-philic) compounds into rods and three-dimensional networks led to gelification of CO_2 and, upon removal of CO_2, in free-standing foams with micron-size cells.[31]

1.3. Fluorinated amphiphiles: a potent driving force for self-assembly and discrimination

Grafting *F*-alkyl chains to molecules 'drives' the amphiphilic character of these molecules to extremes. Fluorinated surfactants (*F*-surfactants) display properties or performances that can usually not be attained with standard surfactants. They are particularly valuable when extreme surface activity, extreme hydrophobicity, high fluorophilicity, and resistance to high temperatures, aggressive chemical or biological environments and detergent activity are needed.[41]

F-surfactants are more surface-active than their HC counterparts, both in terms of effectiveness and efficiency. They decrease the surface tension of water from 72 to typically 15–20 $mN\ m^{-1}$ vs 25–40 $mN\ m^{-1}$ for HC analogs. They can reduce the FC/water interfacial tension to very low values, on the order of 1 $mN\ m^{-1}$ or less. Efficiency is illustrated by critical micellar concentrations in water (CMC, which depends primarily on the hydrophobicity of the tail[42]) that are typically one to two orders of magnitude lower than for HC analogs. Therefore, *F*-surfactants can usually be used in much smaller amounts than non-fluorinated surfactants, partially compensating for higher cost. The CMC values for *F*-alkylated surfactants are often considered roughly equivalent to those of *H*-alkylated analogs with a 50–60% longer chain (reflecting the difference in volume of *F*- vs *H*-chains or, more precisely, the volume of the cavity that they create in water).[9,43] However, precaution should be exercised when applying this rule to amphiphiles with partially fluorinated chains, since an *F*-chain tends to reduce the contribution of an *H*-spacer to the adsorption and micellization energies.[44] The enhancement of surface activity brought by *F*-chains can be lost as a result of apparently minor structural modifications; it suffices, for example, of one residual hydrogen atom in terminal position of an otherwise perfluorinated chain to cause a strong decrease in surface activity.[45] Hydrophobic interactions between the *F*-chains of *F*-amphiphiles can lead to association into dimers and micelles.[46]

F- and *H*-surfactants generally display limited miscibility. When co-dissolved in water, they tend to form separate micelles.[47] When present simultaneously in bilayer membranes, they form phase-separated domains[48,49–51] The unique combination, for *F*-alkyl chains, of extreme hydrophobic character and, additionally, of lipophobic character, provides a powerful driving force for *F*-amphiphiles to collect at interfaces, and to self-assemble into discrete molecular organizations when dispersed in water and other solvents (Section 2). However, the *F*-alkyl chains need generally to be longer than four carbon atoms for the increase in hydrophobic interactions to override the weaker cohesiveness among *F*-alkyl chains and promote self-aggregation. Well-organized films, bilayers, vesicles, tubules and fibers are then generated, with stability and properties generally unmatched by their HC analogs—when they exist! *F*-amphiphiles also allowed engineering of numerous types of novel ternary *F*-colloids and manipulation of the morphology and properties of these colloids (Sections 2 and 3). Mixing between *F*- and *H*-amphiphiles and colloid morphology can be controlled to some extent by using hybrid amphiphiles having both *F*- and *H*-chains.[49,51–53]

A variety of novel *F*-surfactants have been synthesized as part of an extensive effort aimed at providing well-defined and pure, highly surface-active components usable in pharmaceuticals and determining the impact of the *F*-chains on phase behavior, structure of colloids formed, and physicochemical and biological properties.[22,54,55] These surfactants are neutral, anionic, cationic or zwitterionic, single- or double-tailed, with tails of variable length, identical or not, and include a large diversity of hydrophilic head groups. A modular molecular design was elected that allowed stepwise variation and adjustment in hydrophilic, lipophilic and fluorophilic characters, size and shape, chemical functions available for derivatization, etc. The polar heads, often derived from natural products, included diverse types of polyols, anhydropolyols, mono- and

disaccharides, amino acids, amine oxides, phosphoramides, diverse phospholipids, as well as telomers with a variable number of hydrophilic tris(hydroxymethyl)aminomethyl groups. Diverse spacers and junction units were used to link the head and tail groups together. Drugs can be directly bound, using a labile linker, to the amphiphile, which is then expected to function as a prodrug. Bioactive molecules, targeting devices and markers can be grafted simultaneously, for example onto small amphiphilic telomers.[56] Synthetic strategies were chosen that provided well defined, pure compounds. Examples of such *F*-surfactants are collected in Table 2 and Refs. 55,57–59. Further recent examples of *F*-surfactants include numerous *F*-amphiphiles derived from carbohydrates and polyols,[59,60] aminoacids and peptides,[61] lipids,[62] dimeric (gemini) surfactants,[53] bola-form compounds (two polar heads for one *F*-chain),[63] surfactants with a 'reverse' HC–FC–polar head sequence,[64–66] amphiphilic fluorinated copolymers (or 'polysoaps'),[67] gel-forming *F*-alkyl-end-capped amphiphilic oligomers and cooligomers,[46,68,69] polymeric *F*-surfactants for use in emulsion polymerization in liquid and supercritical CO_2,[70] etc. Numerous fluorinated monomers and initiators, telomers, polymers and copolymers with fluorinated groups in the backbone or as side-chains have also been made available.[71]

In spite of substantially higher surface activity, the hemolytic activity of *F*-surfactants was consistently found to be lower than that of their *H*-counterparts, and was often entirely suppressed.[23,72] Acute toxicity is apparently not increased by the presence of *F*-alkyl chains. Acute lethal doses, LD_{50}, of several grams per kilogram body weight have been reported for certain *F*-alkylated phosphatidylcholines of type **11** and tris(hydroxymethyl)acrylamidomethane telomers **12** in mice.[23,57,58] However, contrary to FCs, our understanding of the pharmacology of *F*-surfactants is still rudimentary. With few exceptions,[73] their absorption, distribution, metabolism and excretion characteristics remain to be determined, as well as their sub-acute and chronic toxicity. The ability of *F*-surfactants to influence protein adsorption to particles and phagocytic uptake of particles was demonstrated.[74,75]

1.4. Fluorocarbon–hydrocarbon diblocks: fluorophilic/lipophilic amphiphiles

F-alkyl/*H*-alkyl diblock compounds, such as, for example, $C_nF_{2n+1}C_mH_{2m+1}$ (F*n*H*m*) **7** and $C_nF_{2n+1}CH{=}CHC_mH_{2m+1}$ (F*n*H*m*E) **8**, provide unique building blocks for colloidal systems. These compounds are amphiphiles with a fluorophilic moiety and a lipophilic moiety. Therefore, these diblocks can play, with respect to fluorous and hydrocarbonous phases, a role similar to that played by standard surfactants at a water/hydrocarbon interface, hence appear to be particularly relevant to fluorous biphasic chemistry. *F*-alkyl/*H*-alkyl diblocks can have strong dipole moments (primarily due to the CH_2–CF_2 dipole), and surface tensions and dielectric constants higher than those of both the totally fluorinated and the totally hydrogenated analogs.[10] Mixed fluorinated/hydrogenated compounds can indeed have significant polar character and physical properties quite different from those of their HC or FC counterparts. The synthesis of *F*-alkyl/*H*-alkyl diblocks is straightforward.[76–78] They form micelles when dispersed in a HC and reverse micelles in a FC, however with low aggregation numbers.[79,80] The diblock F12H14 demonstrated the formation of highly condensed monolayers at a pentadecane/air surface.[81] A Gibbs film, i.e. a crystalline monolayer of diblocks, appears to form at the surface of solutions of *F*-alkyl/*H*-alkyl diblocks in *H*-alkanes.[82] *F*-alkyl/*H*-alkyl diblocks are capable of reducing the surface tension of HCs,[82,83] and of modifying the interfacial tension between a FC and water.[84] They were also shown to further reduce the tension between FCs and water in the presence of an interfacial phospholipid monolayer.[84] The adsorption of sodium laurate at an *F*-octyl bromide/water interface increased when F*n*H*m*E diblock **8** was added to the fluorous phase.[85] The minimum surface area occupied by the surfactant at the interface decreased from 50 to 38 $Å^2$ for F4H10E, reflecting a better structuration of the interfacial film. Likewise, incorporation of a diblock in a FC-in-water emulsion emulsified with egg phospholipids reduced the area occupied by the phospholipids at the surface of the droplets.[86] Partition measurements of diblocks **8** (n/m=0.6–1.3) between FCs **1**, **2** or **4** and hexadecane indicated no marked preference for either phase.[87]

From the biological standpoint, the data presently available indicate a behavior close to that of FCs, including absence of effect on cell cultures, very low acute toxicity, absence of metabolism, and excretion rate dependent on block sizes.[23,88] Diblocks thus appear to benefit from simplified pharmacology, hence may have a serious advantage over *F*-surfactants from the standpoint of pharmaceutical development.

F-alkyl/*H*-alkyl diblocks have provided effective emulsifiers for the preparation of HC-in-FC emulsions, and their combination with other amphiphiles can result in novel structural arrangements or significant modification of the behavior of *F*-colloids (Sections 2 and 3). When used in conjunction with appropriate non-fluorinated surfactants they can provide strong stabilization of FC-in-water emulsions[88] and allow close control of particle size (i.e. of fluorous microdomain size) over a wide range.[89] Addition of diblocks to a fluorous phase increases the solubility of lipophilic material. Addition to mixtures of FCs and HCs improves the miscibility between the two media. When present in a liposomal membrane, *F*-alkyl/*H*-alkyl diblocks impart to this membrane some of the properties obtained with hydrophilic/fluorophilic *F*-surfactants (Section 2). Diblock molecules have also been used as the dispersed phase of microemulsions in water.[90]

1.5. Fluorophilic/lipophilic/hydrophilic characters: extending the hydrophobicity scale

The low polarizability of fluorine as compared to hydrogen, and larger surface presented by *F*-alkyl chains vs *H*-alkyl chains concur in providing enhanced hydrophobicity. The incremental changes in the free energy of adsorption for the transfer of a CF_2 group from water to the air/water interface or to an FC/water interface are about twice those of a CH_2 group.[20,91] The free energy of transfer of a CH_2 group from an HC to an FC phase, and of a CF_2 from an FC to an HC phase, are about one third of the energy needed to transfer a CH_2 from an HC to water.[80] If one draws a hydrophobicity

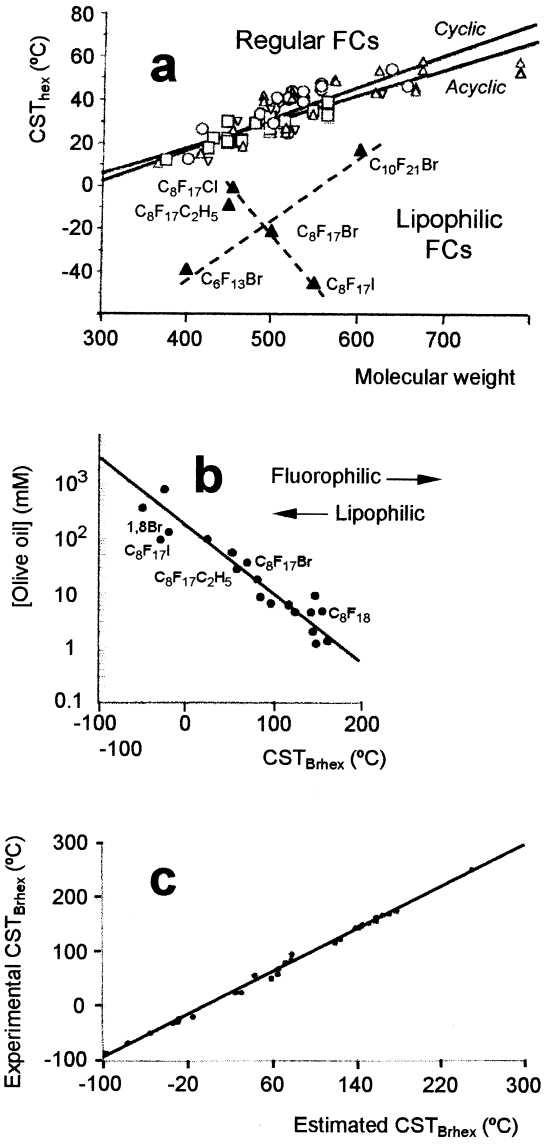


Figure 2. Assessing the lipophilicity of fluorocarbons. (a) Correlation between CST_{hex} and molecular weight for a variety of regular ((△) acyclic, (○) monocyclic, (□) bicyclic, (▽) tricyclic) and lipophilic (▲) PFCs. A lower CST corresponds to higher lipophilicity; doted lines indicate trends observed for the more lipophilic FCs (from Ref. 3 with permission); (b) correlation between CST_{Brhex} and olive oil solubility (from Ref. 98 with permission); and (c) experimentally determined CST_{Brhex} values vs. those determined via a group contribution model (from Ref. 98 with permission).

scale (or a fluorophilicity scale), *F*-alkyl chains are located well beyond *H*-chains on the hydrophobic side.[92] The enhanced hydrophobicity of *F*-chains has been related primarily to their larger surface area.[42,93]

The fluorophilic/lipophilic balance happens to be the most critical criterion for selecting a FC for intravascular use, as it largely determines the rate of excretion of the FC from the body.[1,2] This is because the rate-determining step in the elimination process is the dissolution of the FC into lipid carriers in the blood.[94] Lipid solubility also largely determines membrane permeability and tissue distribution and accumulation. Hence, the long-standing interest of the blood substitute research community in measuring and predicting the solubility of FCs in lipids. The lipophilicity of a FC was first assessed by measuring its critical solution temperature in *n*-hexane (CST_{hex}, the temperature at which equal volumes of the FC and hexane form a single isotropic phase).[95–97] The organ half-life (and CST_{hex}) of regular, non-lipophilic FCs was essentially an exponential function of MW, reflecting the decreasing lipid solubility generally attached to increasing molecular volume of the solute (Fig. 2(a)). Neither connectivity (cyclization or branching) nor the presence of heteroatoms had any significant effect on organ retention.[1,96,97] *F*-octyl bromide was selected for use as an injectable oxygen carrier because of organ half-life shorter than for other FCs of similar MW. Its enhanced excretion rate was assigned to the lipophilic character induced by the presence of the well-exposed, polarizable terminal bromine atom. The CST_{hex} of $C_8F_{17}Br$ is around −24°C, i.e. about 25°C lower than that of C_8F_{18} (in spite of higher molecular weight) and about 50°C lower than that of *F*-*N*-methyldecahydroisoquinoline ($C_{10}F_{19}N$), an earlier candidate oxygen carrier with similar MW. Measurement of CST in *n*-bromohexane (CST_{Brhex}) was subsequently proposed in order to allow more convenient and more accurate determination of the lipophilic character of the more lipophilic FCs.[98] Fig. 2(b) illustrates the relation between CST_{Brhex} and olive oil solubility for a range of FCs. It indicates, for example, that the effect of one Br on the solubility in olive oil is essentially equivalent to that of two Cl and almost comparable to that of a C_2H_5 group, and that the effect of two terminal Br is equivalent to that of one I. An empirical group contribution model was developed that provided accurate prediction of CST_{Brhex} for a variety of FCs (Fig. 2(c)).[98]

The relative polarity of a solvent was conveniently characterized by a spectral polarity index (P_s) based on UV–visible observation of an *F*-alkylated dye that is soluble in a wide range of solvents, including highly non-polar fluorinated ones.[10,99] The very low P_s values of FCs, the lowest of all solvents, reflect the non-polar character of these materials. On the other hand, P_s values higher than those of their HC counterparts, as found for some partially fluorinated compounds and for fluorinated alcohols, reveal higher polarity/dipole moments. Partition coefficients for reactants, catalysts and products between fluorous and non-fluorous phases directly reflect the relative fluorophilicity and lipophilicity of these compounds, and are of great practical value to those who practice chemistry in fluorous biphasic media. Numerous partition coefficients have been measured in the recent years as fluorous chemistry was taking momentum,[24–27] but, at this point, there exists no satisfactory way of predicting such coefficients. The atypically large solubility in FCs of the shorter carboxylic acids was explained by the formation of hydrogen-bound dimers; moreover, very large amounts of formic acid (which is very poorly soluble in FCs) could be dragged along into a fluorous phase using CF_3COOH; however, in the presence of an aqueous phase, these acids partition highly preferentially into the aqueous phase.[100] The effect of structure of a fluorinated solvent on water solubility and fluorophilicity (or hydrophobicity) has been highlighted.[101,102] Cyclization and branching significantly decrease the water solubility of FCs. It has also been noted that the solubility of acetic acid in $C_4F_9CH{=}CHC_4F_9$ **4** was an order of magnitude larger than in *n*-C_8F_{18}.[100] The latest developments in terms of

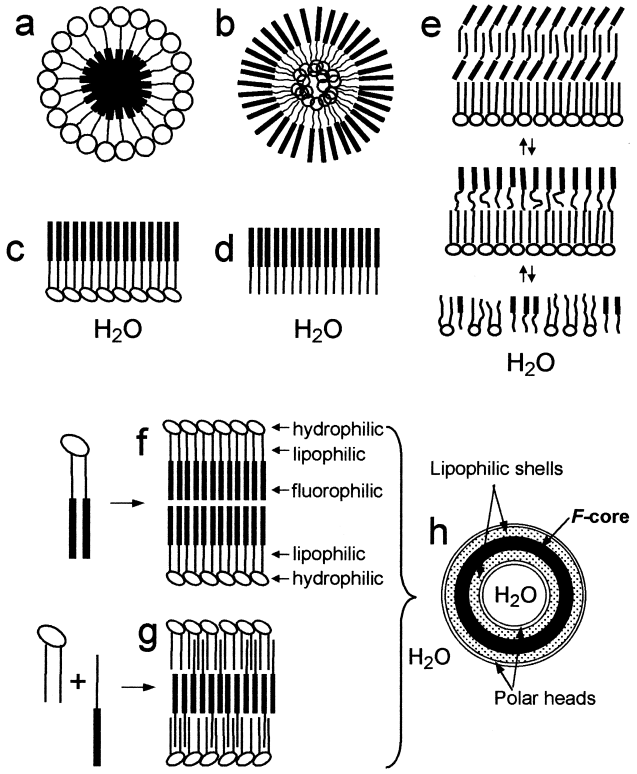


Figure 3. Examples of fluorous nanophases involving F-amphiphiles: (a) in a micelle, (b) in a reverse micelle, (c) in a Langmuir film of a 'complete' F-surfactant, (d) in a Langmuir film of an F-alkyl/H-alkyl diblock, (e) reversible vertical segregation within a Langmuir film made of phospholipids and F-alkyl/H-alkyl diblocks (see Ref. 127), (f) bilayer membrane made from a double-tailed F-amphiphile, (g) bilayer membrane made from a complementary mixture of a standard phospholipid and an F-alkyl/H-alkyl diblock, (h) schematic representation of the fluorinated core that characterizes F-vesicles and F-tubules. In the membranes (f)–(h), the central hydrophobic and lipophobic F-core is flanked by two lipophilic HC shells, then by hydrophilic outer layers of polar heads (see Ref. 57).

quantifying the fluorophilicity of a given molecule has used molecular descriptors and neural network analysis to predict P_s values and fluorous partition coefficients for molecules much more complex than those used in blood substitute research.[102] The solvent extended surface and the calculated Hildebrand solubility parameter were among the top most effective molecular descriptors in predicting fluorophilicity. However, for practical reasons, only the latter parameter was used for a rough estimation of fluorophilicities within a given family of compounds.

F-alkylation is obviously key to the practice of fluorous biphasic chemistry. *F*-alkylation was also used to immobilize biomolecules (e.g. proteins) onto FC surfaces for applications in affinity chromatography, enzyme immobilization for bioprocessing and analytical and clinical chemistry, biosensors, immunodiagnostic and other assays.[103]

2. Nanometer-size fluorous domains

This section concerns self-assemblies (also known as organized molecular systems) of *F*-amphiphiles having at least one dimension in the nanometer range. The limited miscibility and lack of geometric compatibility of *F*-chains with non-highly fluorinated moieties generally results in phase separation and the formation of nanometer-size fluorous domains, whether in micelles, in two-dimensional monolayers or bilayers, or within discrete three dimensional constructs (Fig. 3).

2.1. Micelles

Both theory and experimentation indicate that with the stiffer, more voluminous *F*-amphiphiles, disk-like micelles and rod-like cylindrical micelles are favored over spherical micelles.[9,103a,104] The formation of long rod-like micelles of *F*-amphiphiles in water can profoundly affect the rheologic behavior of their solutions.[104,105] In line with the enhanced compressibility of FCs as compared to HCs, micelles of *F*-alkanoates were more compressible than those made from related *H*-alkanoates.[106] The simpler *F*-alkyl/*H*-alkyl diblocks, below a certain transition temperature, form gel phases in HCs and other solvents that appear to be made of microfibrils.[77,107–109] Above the transition temperature, micellar aggregates are obtained.[79] Diblocks also form aggregates in fluorinated solvents[109] (as well as in CO_2[110]). In such solvents, the usual hydrophobic effects are replaced by lipophobic effects and fluorophobic effects. Generation of worm-like entangled micelles of hydrated surfactants within a continuous fluorous phase, is a likely mechanism for the formation of gels from associations of *F*-alkyl/*H*-alkyl diblocks, phospholipids and water in FCs.[111] Such gels have potential topical uses as low friction, gas-permeant, repellant barrier creams. *F*-surfactants also form micelles in liquid CO_2 in which the *F*-chains are located on the outer side (i.e. CO_2 side).[70] FC-in-water microemulsions, which can be considered as swollen micelles, are mentioned in Section 3, along with ternary systems.

When co-dispersed in water, *F*- and *H*-amphiphiles tend to form two kinds of micelles, rich in one or the other amphiphile, due to the lipophobicity of the *F*-chains.[47,112,113] Polymeric micelles with two types of mutually incompatible hydrophobic microdomains, one fluorous, the other hydrocarbonous, attached to the same water-soluble polymeric backbone were obtained by terpolymerization of the water-soluble acrylamide monomer with two mutually incompatible polymerizable *F*- and *H*-surfactants.[114] These materials displayed two CMCs, reflecting the coexistence of the two distinct types of micelles. Likewise, segregation of *F*- and *H*-microdomains, coexisting within the hydrophobic core of polymeric micelles, was evidenced in terpolymers of *N*-isopropylacrylamide, and 1*H*,1*H*-*F*-octyl and *N*-(*n*-octadecyl)-*N*-[4-(1-pyrenyl)butyl] group-substituted isopropylacrylamides.[115] The *F*-chains were shown to affect the association of the *H*-chains.

2.2. Two-dimensional arrangements—Langmuir films

F-amphiphiles tend to form well-ordered, dense and stable Langmuir monolayers on a water surface (see, for example Refs. 12,16,48,116–120). The rate of adsorption of a series of sugar-derived *F*-alkylated amphiphiles decreased with increased hydrophobicity.[60] Film close packing is facilitated by the reduced number of kinks present in *F*-alkyl vs *H*-alkyl chains. However, *F*-chain rigidity and orientation favor hexagonal phases over rectangular phases, the later being favored with *H*-amphiphiles due to stronger

intermolecular interactions. Langmuir monolayers of *F*-amphiphiles display much higher collapse pressures than those made from analogous *H*-amphiphiles, reflecting higher stability.[48,121] When the hydrophobic tail essentially consists of an *F*-chain (with no or only a very short *H*-spacer) and the polar head is small (e.g. *F*-alkanoic acids), the liquid phase is limited or absent.[117] Langmuir films of *F*-amphiphiles are usually characterized by higher cristallinity than those obtained from their HC analogs, in line with enhanced stiffness of *F*-chains.[118] High intrinsic film density is reflected by the close-to-perpendicular orientation of the *F*-amphiphiles to the film surface.

Within a monolayer of *F*-amphiphiles having a mixed hydrophobic moiety made of an *F*-chain and an *H*-spacer, the *F*-tails are more ordered than the *H*-spacer.[12] When the area available per molecule slightly exceeds that corresponding to close packing, the homogeneous ordered monolayer breaks up into an inhomogeneous array of condensed islands within which order and collective low tilt angle are preserved, and a dilute disordered phase.[12,13] *F*- and *H*-amphiphiles, when present together within films and membranes, tend to form separated domains.[48,50] In multibilayer films made of mixed *F*- and *H*-amphiphiles the *F*-component is concentrated preferentially near the film surface.[50]

F-alkyl/*H*-alkyl diblocks also organize in Langmuir films.[83,122,123] The orientation of the diblock is, however, not yet fully established. Even standard, non-amphiphilic *F*-alkanes, such as, for example, $C_{20}F_{42}$, form stable ordered monolayers at the surface of water;[124] such behavior was subsequently seen with *H*-alkanes one and a half times longer.[125]

The chemical inertness of *F*-chains allowed preparation of stable, insoluble films of *F*-polyethers on the surface of concentrated sulfuric, nitric and phosphoric acids.[126] Spreading was suggested to be driven by hydrogen bonding between ether oxygens and/or fluorines and the acid, causing the *F*-alkyl ethers to lie down on the acid's surface at monolayer coverage.

A unique vertical, pressure-induced phase separation phenomenon was recently observed upon compression of Langmuir films made of combinations of standard phospholipids and *F*-alkyl/*H*-alkyl diblocks **7** (n=8, m=16).[127] Depending on diblock/dipalmitoylphosphatidylethanolamine (DPPE) ratio and surface pressure, either a monolayer or a bilayer of diblocks was formed on top of a DPPE-only monolayer (Fig. 3(e)). The phenomenon was fully reversible.

Fluorinated films are also present in emulsions when the surfactant system involves fluorinated components (Section 3). Coating of the surface of sugar-persubstituted dendrimers with an anionic *F*-amphiphile generates hydrophobic interactions and aggregation between dendrimers.[128]

2.3. Lamellar phases and bilayer membranes made from *F*-amphiphiles

When dispersed in water at low concentrations, *F*-amphiphiles tend to form large domains of lamellar Lα phases made of stacked bilayers rather than the L_1 micellar phase usually found with *H*-amphiphiles, reflecting lesser water solubility and higher stiffness of *F*-chains.[9,43,104,129] *F*-amphiphiles in lamellar phases tend to have substantially higher melting temperatures than HC analogs.[51] Bilayer membranes are also found in *F*-vesicles, tubules and other discrete self-assemblies. Formation of *F*-vesicles from *F*-surfactants has been pioneered primarily by Kunitake[51,130] and Ringsdorf.[48,131] Numerous molecular self-assemblies of *F*-surfactants were subsequently elaborated in the author's former laboratory for the purpose of determining the impact of *F*-chains on the formation, structure and properties of such self-assemblies and for application to the delivery of drugs and other bioactive agents.[23,57,58] 'Non-polar' amphiphiles with one *F*-chain and two *H*-chains, such as **13**, form bilayer assemblies in FCs.[132] Amphiphiles with two *F*-chains and one *H*-chain, such as **14**, formed stable bilayers that gave tubule-, tape- and rod-like self-assemblies in benzene or chlorocyclohexane.[133] The primary driving force for self-association was determined to be enthalpic in nature and due to limited miscibility between *F*-chains and solvent.

Planar fluorinated black lipid membranes made from combinations of phospholipids and *F*-alkyl/*H*-alkyl diblocks have been briefly mentioned, that were exceptionally long-lived and sturdy, with capacitances two to three times larger than in the absence of the diblock component.[23]

(i) *Readily formed, stable fluorinated vesicles*. *F*-chains exacerbate the driving force for amphiphiles to aggregate. Thus, even single-chain, short (typically 10 C atoms) *F*-amphiphiles, when dispersed in water and other solvents, can provide discrete self-assemblies of various shapes and structures. For example, the *F*-alkylated phosphocholine derivative **9** (n=8, m=2), depending on concentration, temperature, energy input and time, provided stacked bilayers, small unilamellar vesicles (SUVs), multilamellar vesicles (MLVs), long flexible fibers, globules and giant vesicles; in sharp contrast, dispersions of the *H*-analog of **9** yielded nothing more organized than micelles.[134] Vesicles were also obtained from *F*-alkylated single-chain ethoxylated alcohols.[135] Some *F*-alkylated glycolipids (e.g. **15**) provided vesicles, stacked disk-like assemblies, tubules and helical aggregates.[136]

The enhanced propensity for self-aggregation and increased membrane stability provided by *F*-tails is also strikingly illustrated by the fact that formation of *F*-vesicles from single chain *F*-amphiphiles (e.g. **9**) in water, does not require any supplementary intermolecular associative forces to promote and maintain tight molecular packing.[134,137] These *F*-vesicles withstood heat sterilization at 121°C and showed only little changes in particle size distribution after 3 months at 40°C. This difference in behavior of *F*- vs *H*-amphiphiles is in accordance with the higher packing parameter of the former, as defined by Israelachvili.[138]

Numerous SUVs and MLVs made from amphiphiles having two or three hydrophobic tails, one at least being fluorinated, including *F*-alkylated phospholipids such as **11**, glycolipids such as **15** and galactophospholipids **16**, have been reported (for reviews, see Refs. 23,57–59). Formation

of vesicles rather than micelles occurred consistently for shorter hydrophobic tails when these tails are fluorinated. The thermal resistance and shelf stability of *F*-vesicles was generally much higher than for vesicles made from analogous *H*-amphiphiles. Very stable vesicles, mostly SUVs, were also obtained from fluorinated dimeric (gemini) surfactants, while their HC analogs formed elongated cylindrical micelles; coexistence of branched cylindrical micelles and some SUVs was seen with hybrid surfactants having an *F*- and an *H*-chain.[53] Further vesicles were obtained from bolaamphiphiles with a central fluorinated segment[139] and from 'semi-gemini' amphiphiles with one terminal *F*-chain and two polar heads.[63]

An alternative means of preparing *F*-vesicles consists in combining standard *H*-amphiphiles (e.g. phospholipids) with linear mixed *F*-alkyl/*H*-alkyl diblocks.[140] When incorporated in the bilayer membrane, these diblocks confer to vesicles some of the properties found for vesicles made from regular (complete) *F*-surfactants, including increased stability (for example, liposomes made from dimyristoylphosphatidylcholine (DMPC) and diblock F4H10E became heat sterilizable), reduced membrane permeability and fusion kinetics; they can also affect the vesicle's behavior in a biological milieu.

(ii) *A highly hydrophobic and lipophobic fluorous film within the bilayer membrane*. Bilayer membranes made from *F*-amphiphiles are uniquely characterized by the presence of a well-organized hydrophobic internal fluorinated core, typically 1–2 nm thick, usually flanked by lipophilic shells and hydrophilic external shells (Fig. 3(f)–(h)).[57] The contact between the fluorophilic, lipophilic and hydrophilic zones should tend to be minimum, likely reducing the jutting that normally exists between fatty tails within phospholipid membranes, with possible repercussions on the conformation and orientation of the polar groups, hence, possibly on in vivo particle recognition.[141] Due to the difference in cross-section between *F*- and *H*-alkyl chains, the packing within the lipidic shells formed by the HC spacers is expected, from data on monolayers, to be rather loose.[16] The presence of the *F*-core and relatively loose packing of the *H*-spacers were confirmed by X-ray diffraction experiments showing high electron density in the central part of multibilayers made of *F*-amphiphiles of type **11**.[18]

The presence of the *F*-core within its bilayer membrane profoundly modifies a vesicle's thermotropic and lyotropic behavior, usually provides improved thermal stability, significantly lowers membrane permeability and slows down the release of encapsulated material. Additionally, it can modify the particle's behavior in vivo or in a biological medium. The properties of *F*-vesicles made from a range of *F*-amphiphiles have been reviewed extensively.[58] In brief, the reversible crystal-to-liquid crystal (or gel-to-fluid) phase transition usually found for bilayers of amphiphiles (which reflects the cooperative transition of the hydrophobic chains from an ordered to a disordered state) can be significantly affected by the presence of *F*-chains. Increased ordering is reflected by higher transition temperatures (T_c), provided the *F*-chains are longer than about six carbons. Thus, T_c increases very markedly if one terminal C_8F_{17} chain is present in all the hydrophobic chains of a double- or triple-chain amphiphile. For example, two C_8F_{17} chains in phospholipid **11** (n=8, m=4) caused an increase in T_c of ca. 45°C with respect to a close *H*-analogs, DMPC;[142] introduction of only one *F*-chain had the opposite effect. C_6F_{13} chains have little effect on T_c, while C_4F_9 chains tend to decrease T_c, indicating that, in this case, the increased hydrophobic effect is insufficient to compensate for the lower cohesive attraction between *F*-chains as compared to *H*-chains. Differences in T_c between *F*- and *H*-bilayers reflect indeed the competing effects of *F*-chains on packing characteristics: on one hand, an increase in order, rigidity and hydrophobic interactions, which increases T_c ant ΔH and ΔS values for the transition, and, on the other hand, increased packing disorder and fluidity due to weaker lateral van der Waals forces and larger steric repulsion between *F*-chains as compared to *H*-chains, which lowers these values. The latter effect still prevails with C_4F_9 chains, while the former definitely predominates with C_8F_{17} and longer chains. The smaller ΔH and ΔS values found for the gel-to-fluid phase transition of *F*-bilayers vs their *H*-analogs, indicate that there is little reorganization of the *F*-moieties at T_c.[51] The phase transition is actually preceded by the melting of the *F*-chain; each portion of this chain melting separately and (in contrast with *H*-chains) over a large temperature range, reflecting lesser cooperativity. The differences of packing of *F*-amphiphiles in *F*-membranes between gel and fluid states appear to be smaller than for *H*-membranes due to the superior intrinsic ordering and rigidifying effects of the *F*-chains,[58] in other words, the 'fluid' state may not be really fluid. The *F*-chains of *F*-alkylated phospholipids **11**, and their length, had an important rigidifying effect on the membrane of *F*-vesicles in their fluid state, especially near the membrane's surface.[143]

In terms of membrane dynamics, *F*-vesicles have a lesser tendency to undergo fusion than analogous *H*-vesicles or exchange components with them. The initial rate of Ca^{++}-induced fusion of *F*-vesicles made from phosphatidylserine (PS) and F6H10 was an order of magnitude slower than when PS was alone; contrary to the later case, this rate was independent from Ca^{++} concentration for the *F*-vesicles.[144] Flip–flop processes can occur, for example of hydrocarbon spin labels into the fluorinated domain in vesicles made from bolaamphiphile **17**, which, due to the immiscibility of *F*- and *H*-chains, forms vesicles with a fluorinated outer semimonolayer and a hydrocarbon inner semimonolayer.[145]

Endowing the liposomal membrane with the uniquely high hydrophobicity of FCs is expected to reduce membrane permeability and hinder the release of non-fluorinated encapsulated materials. This was confirmed by release experiments of entrapped hydrophilic, lipophilic and amphipathic drugs, drug models and dyes from vesicles made of various *F*-alkylated phospholipids, glycophospholipids and other *F*-amphiphiles.[49,57,58] In the fluid state, *F*-vesicle membranes formed a significantly more efficient barrier to the permeation of 5,6-carboxyfluorescein (CF) than any of their fluid HC counterparts, primarily reflecting the lower solubility and diffusibility of CF through the *F*-core of the membrane. CF permeability decreased, as expected, with increasing *F*-tail or *H*-spacer length. In the gel state, the *F*-core did not have any significant effect on CF permeation.

Use of amphiphiles with one *F*-chain and one *H*-chain generally gave poor results in terms of vesicle leakage. An increase in *F*-alkyl chain length, hence in lipophobicity and membrane ordering, in vesicles made from *F*-alkylated phosphatidylcholines of type **11**, resulted in a dramatic decrease in permeability to the lipophilic/hydrophilic paramagnetic probe TEMPO (2,2,6,6-tetramethyl-1-piperidyloxy).[142] The *F*-core was not a barrier (in the absence of Na^+) to remote loading of doxorubicin (Dox), an amphipathic anticancer drug whose encapsulation into liposomes can be mediated using transmembrane ammonium sulfate or pH gradients.[146] However, the Dox-loaded liposomes were less stable with respect to loss of content than some conventional liposomes in the presence of Na^+ ions. The latter ions, due to an exchange with protons, induce a raise in internal pH, hence in deprotonated, neutral form of Dox, which diffuses more easily through membranes than the protonated Dox. The unfavorable membrane permeability to H^+ and Na^+ increased with fluorine content. Consequent to high H^+/Na^+ permeability, leakage of Dox was accelerated in a physiological buffer or in human serum.[146]

Vesicles made of DMPC and F*n*H*m* displayed significantly reduced permeability with respect to those made from DMPC alone.[147] Likewise, equimolar mixtures of *F*-alkylated phosphocholine **9** and F8H2 yielded vesicles with substantially reduced membrane permeability as compared to vesicles made from **9** only.[148] In this case, the hydrophobicity-driven cohesion of the *F*-chains of the two components likely leads to reconstituting a pseudo-double-tailed amphiphile and to tighter packing of the membrane. The rate of release of CF from vesicles of PS and F6H10 was 40 times slower than when PS was alone.[144]

Interestingly, the modification of the internal structure of the bilayer membrane can have significant repercussions on the vesicle's behavior in vivo or in a biological milieu. Thus, the stability of fluid *F*-vesicles with respect to encapsulated material was reduced when incubated in human serum, and extent of reduction depended on polar head group.[52,149] It is noteworthy that *F*-vesicles made from fluorinated phospholipids of type **11** in a gel or semi-gel state displayed higher encapsulation stability in serum than in a physiological buffer, possibly due to the suppression of packing defects by serum components.[149] The intravascular persistence of vesicles of **11** was several times larger than those of similarly sized liposomes made from distearoylphosphatidylcholine (DSPC) or DSPC and cholesterol, and was essentially dose-independent,[150] probably meaning that the lipophobic internal core had repercussions on the adsorption of opsonizing proteins onto the vesicles' surface. Introduction of diblocks of type **7** into the membrane of liposomes made of DMPC or dipalmitoylphosphatidylcholine (DPPC) has resulted in a dramatic reduction of the rate of hydrolysis of the phospholipids by pancreatic phospholipase A_2.[151] For a given phospholipid fatty chain length there was a precise minimal *H*-alkyl chain length in the diblock for this rate reduction to occur; the effect was not observed in the absence of an *F*-alkyl segment, demonstrating a key role in structuring the bilayer membrane. These observations indicate that surface behavior, including interactions with peptides and proteins and in vivo recognition could be modulated by changes made *inside* the membrane.

(iii) *Tubules and fibers*. Hollow microtubules and other fibers made from rolled-up bilayers were obtained from diverse *F*-amphiphiles in various media. The presence of a chiral center is generally deemed necessary for the inception of the rolling-up of tubules, and hydrogen bonds are usually involved in their formation as well.[152,153] By exception, robust fluorinated tubules were obtained from non-chiral, non-hydrogen bonding single-chain *F*-amphiphiles such as **10**,[154] questioning the commonly accepted understanding of tubule formation. These *F*-tubules converted into *F*-vesicles when heated and back to tubules upon cooling.[155–158] Tubules are more stable and better organized than the vesicles in which they convert upon heating. The fact that HC analogs of **10** only formed micelles further demonstrates the powerful structuring and stabilizing effect of *F*-chains. Tubule length and diameter can be adjusted by varying the amphiphile's molecular structure or the tubule's preparation conditions.[159] Tubules were also obtained from anionic double-tailed glucolipids of type **15**; when an *F*-chain was present, tubule diameter was an order of magnitude smaller than when both chains were *H*-chains.[155] The *F*-chain also increased the vesicle-tubule transition temperature. pH dependence was, in this case, indicative of the formation of hydrogen bonds between the phosphate group and a hydroxyl group of the saccharide. Tubule formation was favored over vesicle formation at high pH when the polar heads are less hydrated. Helical fibers, several microns in length, were obtained from *F*-alkylated glycolipids **15** and **16**.[136,155] *F*-tubules and fibers were also grown in ethanol, dimethylsulfoxide, formamide and dimethylformamide,[63,160] and CO_2.[31]

The structure and dynamics of *F*-surfactant films and membranes are currently being investigated using combinations of techniques involving isothermal compression, small angle X-ray scattering, grazing incidence X-ray diffraction or reflectivity, cryotransmission electron microscopy, atomic force microscopy, surface potential measurements, pendant drop interfacial tension analysis, etc.[121,127,157]

3. Micron- and sub-micron-size fluorous phases

Diverse colloids with dispersed fluorous phases, and colloids with aqueous or hydrocarbonous phases dispersed within a fluorous phase have been elaborated that were destined for medical uses, but may as well provide microreservoirs, microreactors, templates and other reaction control devices.

3.1. Emulsions with fluorous dispersed phases—gas transport

Extensive research and development efforts have been devoted to designing, preparing and investigating FC-in-water emulsions for in vivo oxygen delivery (blood substitutes).[2–4] Briefly, reasons for developing blood substitutes include insufficient blood collection to meet the augmenting needs of an aging population; the reluctance that has developed against allogeneic (donor) blood transfusion; the realization that banked blood is less effective then fresh blood; evidence that donor blood may reduce the immune responsiveness of the organism; and the possibility of providing

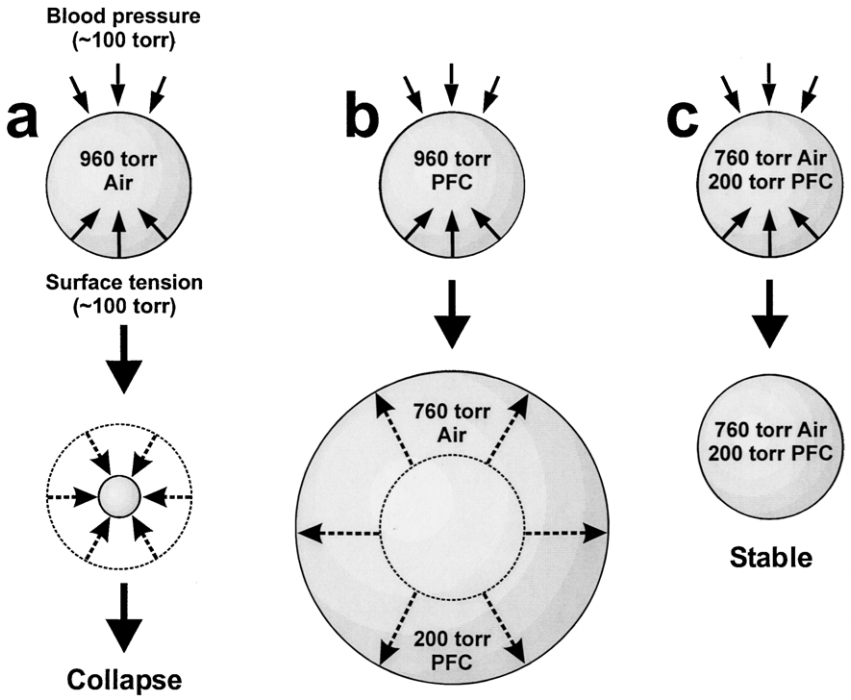


Figure 4. Stabilizing gaseous microbubbles in an aqueous phase. (a) Air-filled microbubbles collapse when injected in the blood stream under the combined action of surface tension and arterial blood pressure; (b) bubbles containing only a fluorocarbon gas grow in the vasculature as air diffuses in the bubble, until osmotic equilibrium with blood gases is reached; (c) in osmotically stabilized bubbles, the partial pressure of the fluorocarbon gas counterbalances surface pressure and blood pressure, thus stabilizing the bubble at a predetermined size.

the developing countries with an alternative to blood transfusion. Injectable FC emulsions are expected to offer an effective means of delivering oxygen to tissues in patients undergoing surgery, to help bridge the time gap between a sudden critical need (as in trauma) for increased tissue oxygenation and transfusion of compatible blood, and to help mitigate the increasingly frequent blood shortages. Further expected uses for FC-based O_2 carriers include local organ perfusion as for treating myocardial infarction and stroke, sensitization of tumors to radio and chemotherapy, organ preservation for transplantation, and uses as research tools. Novel ligand-targeted FC emulsions are being developed that could combine site-directed imaging and drug delivery.[161]

One of the major challenges in the development of injectable FC-in-water emulsions was to counteract molecular diffusion (Ostwald ripening), which is the principal mechanism responsible for particle size growth over time in such emulsions. Several solutions for emulsion stabilization were devised that can be applied to FC emulsions destined for other uses. The solubility and diffusibility of the FC in the aqueous phase (two of the factors that determine molecular diffusion rate) have been reduced by adding a secondary, higher MW FC. Slightly lipophilic FCs were selected in order to mitigate the increase in organ retention that normally accompanies an increase in MW.[162] This solution was retained for developing *Oxygent*™ (Alliance Pharmaceutical Corporation, San Diego), a submicronic (about 0.16 μm in average) 60%-concentrated emulsion of *F*-octyl bromide **1**, emulsified with egg phospholipids and stabilized with *F*-decyl bromide **6**, that is in Phase III clinical evaluation for use in surgical patients.[2,163]

F-surfactants provide another effective means of stabilizing FC emulsions. *F*-surfactants allowed, for example, increasing the stability of an *F*-decalin emulsion from days to years.[3] Incorporation of appropriate *F*-alkyl/*H*-alkyl diblocks in the surfactant system also resulted in substantial emulsion stabilization.[164] The fit between emulsifier and diblock is then critical. Thus, incorporation of *F*-alkyl-*H*-alkyl diblocks provided very effective stabilization of FC emulsions when phospholipids were the emulsifier,[3] while combination with poloxamers (e.g. Pluronic® F68) was insufficient to effectively stabilize an *F*-decalin emulsion.[165] Incorporation of diblock F6H10 increased the proportion of egg phospholipids associated with *F*-octyl bromide droplets relative to that present in the form of free vesicles dispersed in the aqueous phase.[86] Tighter packing of the phospholipid film was reflected by reduced surface area of the polar heads. The stabilization effect may possibly result from a reduction in interfacial tension, an effect of the diblocks on interfacial film organization (dowel effect), and/or an increased local concentration of the heavier, molecular diffusion-repressing lipidic material in the neighborhood of the lipidic interface.

High internal phase ratio emulsions (HIPRE), consisting of up to 99% FC have been obtained from a wide range of FCs, from low-boiling hydrofluoroalkanes to high-boiling polycyclic FCs, using the *F*-alkylated amine oxide surfactant **18**. These materials can have very high viscosities and provide highly stable clear, solid gels. Their structure is made of micron-size polyhedral fluorous domains enclosed within a thin hydrated film of the surfactant.[166] Dispersion in water (the continuous phase) generates a standard FC-in-water emulsion.

3.2. Gaseous fluorocarbon-loaded microbubble dispersions in water: effective sound reflectors

Micron-size injectable gas bubbles containing a gaseous perfluorochemical (i.e. gas emulsions) have been developed as contrast agents for ultrasound imaging.[167,168] These agents are actually the first large market-size FC-based products to have been commercialized. The ideal intravascular reflector for ultrasound signals should be highly compressible, about 5 μm in diameter, have a soft, easily deformable shell, provide a long imaging window, and should preferably not contain proteinous material from animal source. It is also primordial that the microbubbles do not grow in the circulation.

The reason for the presence of a perfluorochemical gas in the microbubbles is their very poor water solubility (at least an order of magnitude lower than for HC analogs).[101,169] In the absence of perfluorochemical, micron-size air bubbles, when injected in the vasculature, dissolve rapidly in the blood under the combined actions of the blood pressure and the Laplace pressure generated by surface tension (Fig. 4(a)). On the other hand, a microbubble filled only with a FC gas will expand in the circulation because the gases dissolved in the blood will be drawn into the bubble until the FC is diluted to an osmotic equilibrium composition (Fig. 4(b)). Such droplet growth in the circulation is not desirable and may actually constitute a dose-limiting factor. It can be avoided by loading the bubble with just the amount of FC vapor needed to counterbalance the surface tension and blood pressure forces that push the gases inside the bubble towards dissolution (Fig. 4(c)).[170,171] Once equilibrium is reached, the rates of diffusion of the water-soluble gases in and out of the bubble are equal. The FC used as an osmotic stabilizing agent must combine low water solubility and high saturated vapor pressure at body temperature.[171] Examples of effective FCs for stabilizing gaseous microbubbles include *n*-C_6F_{14}, $CF_3(OCF_2)_3OCF_3$ and $CF_3(OCF_2CF_2)OCF_3$.[172]

Imagent® (formerly known as Imavist™), an ultrasound contrast agent based on the above concept (Alliance Pharmaceutical Corporation) is formulated as a heat-sterilized spray-dried powder comprising hollow, amorphous and porous microspheres under a nitrogen-diluted *F*-hexane atmosphere. The microspheres are made of DMPC, hydroxyethylstarch (a wall-forming agent), a poloxamer (a wetting agent), sodium chloride and a phosphate buffer (for tonicity and pH control). Upon dispersion in water, a phospholipid monolayer forms that traps the gas mixture present in the headspace inside a microbubble. The gas and phospholipid film are both highly compressible, making them highly echogenic. Extended intravascular persistence, hence a long imaging window, is achieved as a gas osmotic equilibrium is established between the *F*-hexane-containing gas mixture inside the bubble and the gases dissolved in the blood. The amount of FC in the gas mixture was calculated to provide bubbles about 4–5 μm in diameter in the circulation, yet ensure that these bubbles could not grow in vivo, but rather shrink slowly over time. The persistence time of the microbubbles in the blood stream is controlled by their eventual dissolution rather than clearance by the reticuloendothelial system.[172] *F*-hexane ultimately leaves the body through the lungs. Under similar conditions, a microbubble made of pure gaseous FC would double in diameter.

Several types of FC-based ultrasound contrast agents have been developed in the past few years. The first one to have been marketed, *Optison*® (Molecular Biosystems, Inc., San Diego, CA) consists of a suspension of *F*-propane microspheres, 2.0–4.5 μm in diameter, with a shell made of human albumin.[173] *Definity*® (DuPont Pharmaceutical Co., North Billerica, Ma),[174] another *F*-propane microbubble dispersion, 1–3.3 μm in diameter, but with a phospholipid coating, has been licensed in 2001 in the United States. *Imagent*, the microbubble product osmotically stabilized with *F*-hexane, awaits licensure, as well as *SonoVue*® (Bracco, Milan, Italy),[175] which uses SF_6 as the poorly water soluble perfluorochemical within a PEG membrane. A phase shift phenomenon, i.e. the fact that *F*-pentane is liquid at room temperature and gaseous at body temperature, was the basis for developing an injectable *F*-pentane emulsion stabilized by an *F*-surfactant (Sonus Pharmaceuticals, Bothel, WA);[176] this product was, however, abandoned, possibly because bubble formation and bubble size growth in the circulation were difficult to control.

Ultrasound contrast agents are useful when contrast between tissues is insufficient to allow safe, conclusive diagnosis. Blood, for example, is a poor sound reflector. Ultrasonography therefore provides only limited information on the cardiovascular system, blood flow and organ perfusion. The above contrast agents have all demonstrated left ventricular opacification and significant improvement in endocardial border delineation, hence assessment of cardiac function, compared to standard ultrasound procedures. Further clinical studies are ongoing to evaluate the ability of these agents to assess myocardial perfusion and improve detection of blood flow abnormalities and of solid tumors in the liver, kidney, breast and prostate.[177–179] Ligand-directed microbubbles offer the potential for detection of specific pathologic tissues and site-specific drug and gene delivery.[161] Microbubbles with appropriate surface ligands may, for example, facilitate targeting and delivery of thrombolytic agents.[180] Enhanced transgene expression in the myocardium of rats using microbubbles with an adenovirus gene vector attached has also been reported.[181]

3.3. Dispersions within a continuous fluorous phase—pulmonary drug delivery

FCs offer a fluid, rapidly spreading inert vehicle for the delivery of drugs, lung surfactant, vaccines, genes and other bioactive material to and through the respiratory tract. However, very few agents (besides gases) are soluble in this medium, hence the interest of colloidal systems with a fluorous continuous phase incorporating aqueous, oily or solid phases (Fig. 5). Both hydrophilic and lipophilic materials can thus be dispersed within an FC carrier.

The challenge in producing reverse (i.e. water-in-FC) emulsions (Fig. 5(a)) was to stabilize a dispersion of water droplets in one of the most water-repellent media that exists. Additionally, molecular diffusion of water through the continuous phase is facilitated by the low cohesive forces in liquid FCs. Highly stable reverse emulsions and

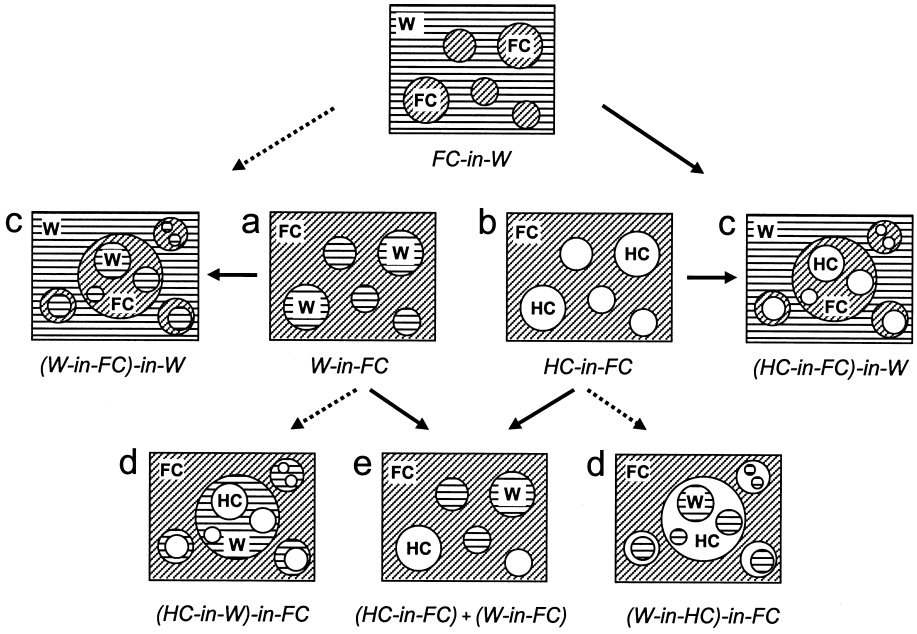


Figure 5. Examples of (a) reverse water-in-FC emulsion, (b) apolar HC-in-FC emulsion, (c) multiple emulsions within an aqueous continuous phase, and (d) and (e) multiple emulsions within a fluorous continuous phase. Full-line arrows indicate the first emulsification step; doted arrows the second.

microemulsions (i.e. thermodynamically stable reverse emulsions), ranging from ca. 10–500 nm in size, have nevertheless been obtained using highly fluorophilic surfactants such as the (*F*-alkyl)alkyldimorpholinophosphates **10**.[39,182] Water-in-FC emulsions could be loaded with a range of drugs, including antibacterial, bronchodilating, mucolytic, tuberculostatic, cholinergic, and antineoplastic agents, without loss of stability. Release of CF from the water droplets was much slower than from water-in-HC oil emulsions.[183]

Stable HC-in-FC emulsions (i.e. emulsions of one apolar phase in another apolar phase; Fig. 5(b)) have also been produced.[184] The amphiphile used to prepare and stabilize them included the simple *F*-alkyl/*H*-alkyl diblocks. Dodecane has, for example, been dispersed in *F*-octyl bromide using F6H10 as the emulsifier. Antibiotics, corticosteroids and antitumor agents have been incorporated in such emulsions.

Combinations of the procedures established for obtaining direct, reverse and apolar emulsions allowed the preparation of diverse novel types of multiple emulsions, including compartmentalized liquid media with three distinct, nonmiscible phases: a fluorous, a hydrocarbonous and an aqueous phase, the continuous phase being aqueous (Fig. 5(c)) or fluorous (Fig. 5(d) and (e)). An internal lipidic phase can, for example, be separated from the external aqueous phase by an intermediate fluorous layer.[23] Fluorophilic, lipophilic and hydrophilic agents can be loaded simultaneously and separately in such emulsions.

4. Colloids with fluorinated phases as molecular tools

4.1. Nanometer-size fluorous compartments

Micelles, Langmuir films, vesicles and other molecular constructs with nanometer size fluorous phases have potential uses in chemistry, physics, biology and medicine, a few examples of which will be mentioned here. This potential is still largely unexplored.

Catalytic hydrolysis of phenyl esters within fluorinated micelles, using hydroxamates as the catalyst, demonstrated enhanced selectivity when both the substrate and the catalyst were *F*-alkylated.[185] *F*-octanesulfonate formed micellar solutions in a highly polar concentrated lithium perchlorate/acetonitrile solution, providing a reaction system for enhanced efficiency in anodic electron-transfer and intermolecular cycloaddition.[186] Self-assemblies of poly(ethylene glycols) (PEG) with *F*-alkyl chains at both ends recently provided hydrogels with controlled surface erosion characteristics.[187] Phase behavior could be modulated by varying *F*-alkyl chain length relative to PEG length, resulting in single-phase behavior, sol-gel coexistence, or precipitation. Mechanical and erosion properties of the hydrogels could thus be tailored for use as implantable drug-release depots.

Langmuir monolayers can be used to induce nucleation of three-dimensional crystals from molecules and ions present in the subphase, for investigating interactions between crystal surface and solvent, and for generating supramolecular architectures at an air–solution interface.[125] *F*-surfactants have been rationally designed for the purpose of two-dimensional crystallization of soluble membrane proteins at an air–water interface. Such crystallization has been promoted by insertion of an *F*-alkyl segment between a receptor ligand and a lipidic tail.[188] The *F*-alkyl segments stabilize the monolayer of *F*-amphiphile against solubilization by the detergent used for protein solubilization. Fluidity necessary for allowing crystallization to occur is provided by branched terminal HC chains. The *F*-alkyl segment also forces a lipophilic ligand to stay exposed on the aqueous side of the monolayer, while in the absence of this segment, the ligand

tends to bury itself in the lipidic region of the monolayer and is ineffective.[189] Monolayers of steroidal *F*-alkylated amphiphiles with cellobiose or maltose hydrophilic heads exhibited pressure-area behavior related to, respectively, specific and non-specific interactions with the enzyme cellulase present in the sub-phase.[190]

Langmuir–Blodgett films have potential as tools for tailoring supramolecular assemblies with specific architectures and properties, and materials with modulated composition on the nanometer scale. These colloids could lead to composites, catalysts and functional devices such as sensors and optical, microelectronic nd electrooptical devices; they can also be used for passivation of surfaces, etc.[191–193] The fact that stable organization into films and bilayers can be obtained with *F*-amphiphiles that are significantly shorter (typically 10 carbons vs 15 for *H*-amphiphiles) than their *H*-analogs means that thinner films, membranes and Langmuir Blodgett multilayers can be obtained that have enhanced thermal stability, and may have improved dielectrical and other properties.[194,195] Immobilization by casting of composite multibilayers of both *F*- and *H*-amphiphiles provided transparent films with enhanced gas permeation (promoted by the *H*-amphiphile) and preferential selectivity for oxygen as compared to nitrogen (determined by the *F*-amphiphile).[50] CF_3-rich nanostructured coatings with remarkably low, adjustable surface energies were prepared from complexes formed by *F*-amphiphiles and poyelectrolytes.[196] The mesomorphous structures obtained are essentially multi-lamellar, sometimes perforated; columnar discotic phases were also seen. Applications are found primarily in low-friction, protective and anti-soiling (including anti-graffiti) coatings. Development of command surfaces, i.e. surfaces whose surface energies can be changed by an external stimulus such as a laser beam, is also envisaged.

Catalytic reactions supported on bilayer matrices can depend on the gel or fluid state of the membrane, as well as on the distribution of the reacting species within the bilayer. Phase separation resulted in considerably faster hydrolysis of *F*-alkylated vs *H*-alkylated phenylesters in a non-fluorinated bilayer in the presence of an *F*-alkylated histidine derivative, owing to the concentration of the substrate and catalyst in the FC domains.[49]

F-vesicles may find uses for targeting and delivery of drugs, prodrugs, contrast agents, immunoactive material, genetic material, etc. Like for other vesicles, they may, as needed, be fitted with markers, targeting devices, or rendered p*H*-, pressure-, or temperature-sensitive, or be surface modified, as for example, with PEG strands to prevent access to the vesicle's surface and hinder in vivo recognition and clearance from circulation. The fact that little energy is usually needed to induce the formation of *F*-vesicles may be advantageous when the material to be encapsulated is fragile.

Lateral phase separation of *F*- and *H*-amphiphiles within bilayer membranes has been used to 'drill' holes in liposomes, thus mimicking a process that is believed to take place when an activated macrophage attacks a tumor cell.[131] Therefore, phase-separated liposomes that had labile domains of non-polymerizable, cleavable or soluble *F*-lipids (or *H*-lipids) embedded in a stable matrix of polymerized *H*-lipids (or *F*-lipids, respectively) were prepared. 'Uncorking' of the labile domains was achieved by cleavage or dissolution of the labile domains. Formation of phase-separated microdomains of *F*-alkylated crown ethers within an HC membrane resulted in ca. 20 times faster transport of K^+ through the membrane than with *H*-alkylated crown ethers, and, contrary to the HC carrier, nearly complete suppression of transport below T_c, thus providing near ideal temperature-regulation for K^+ transport.[197]

Most compounds are excluded from fluorous nanodomains, yet allow diffusion of small molecules and ions, offering a means for diffusion control. On the other hand, the HC shells that flank the *F*-core within the bilayer of an *F*-vesicle can host and confine lipophilic material. Segregation within the lipophilic shells of *F*-vesicles made of phospholipid **11** provided an appropriately shaped confinement microreactor for the polymerization of a lipophilic monomer into spherical microcapsules, a goal that had not been achieved with *H*-vesicles.[198] Use of fluorous solvents during solid-phase organic synthesis, by excluding the reagents, led to their concentration in the polymer beads, resulting in substantially accelerated reactions.[199]

Possible applications evoked for tubular self-assemblies include elaboration of new components for microelectronics, models of natural tubules and enzyme clefts, microcontainers for the controlled release of active agents, and applications in catalysis and separation systems.[200,201] *F*-components could provide additional stability, sturdiness and control over aggregation dimension and properties.

Tagging of substrates with *F*-alkyl chains of different length allowed the synthesis of mixtures (libraries) of compounds, followed by straightforward chromatographic separation (deconvolution) of individual final products, thus combining the advantages of mixture synthesis and the ease of separation of molecules having different fluorine content, hence MW.[202] *F*-surfactants are also increasingly used in analytical techniques.[203] Chromatographic techniques using *F*-alkylated phases can also be listed under this heading.

4.2. Micron-size fluorous compartments

Emulsions with fluorous phases can provide microreservoirs and microreactors for reaction control. Fluorous phases are particularly apt at serving as reservoirs for gases. An FC affinity emulsion allowed extraction of an enzyme from yeast.[204] FC emulsions also provide tools for the engineering of other particulate systems. For example, FC-in-water emulsions have been used to produce hollow and porous microparticles for non-invasive delivery of bioactive agents to the respiratory tract.[205,206] The procedure involves spray-drying of a mixture of an FC-in-water/phospholipid emulsion with a solution of the active component and, optionally, hydroxyethylstarch. During the process, evaporation of water first leaves a shell made of bioactive agent, starch and phospholipid on the FC droplets' surface; subsequent evaporation of the FC 'blows' holes in this shell. The resulting free-flowing powder consists of amorphous microparticles (*PulmoSpheres*™, developed by Alliance

Pharmaceutical Corporation), about 4–7 μm in diameter with pore diameters on the order of 50–300 nm, that have small aerodynamic diameters, which facilitates their delivery and uniform distribution in the lung. These particles can be delivered to the respiratory tract as dry powders or as suspensions in non-aqueous solvents, including propellants for metered dose inhalers (e.g. hydrofluoroalkanes, HFAs) and liquid biocompatible FCs (e.g. *F*-octyl bromide). They form very stable 'homodispersions' in FCs and HFAs where the dispersed and continuous phases are identical, thus reducing the attractive forces between particles and the difference in density between particles and carrier medium. The particles release their content when exposed to an aqueous environment such as, for example, a mucosa. Excellent aerosolization efficiency and dose uniformity were obtained for albuterol sulfate, cromolyn sodium, and formoterol fumarate microspheres.[206] Formulation and functional integrity of immunoglobulins in *PulmoSpheres* for local and systemic delivery via the respiratory mucosa has been demonstrated and may be used to trigger or modulate immune response.[205] Inhaleable tobramycin and budesonide formulations (as dry powders) and an albuterol formulation (suspended in an HFA) in *PulmoSpheres* are presently in clinical trials (Inhale Therapeutic Systems, Inc., San Carlos, CA).[207] Instillation in the lungs of a dispersion of a gentamicin/*PulmoSphere* formulation in *F*-octyl bromide is also being investigated.[208]

Emulsion polymerization of fluorinated monomers has been used to produce polymerized *F*-colloids with specific properties. For example, *F*-monomers with refractive indices close to that of water, allowed preparation of optically transparent aqueous dispersions, glasses and crystals of *F*-colloids that were used as models for studying the structure and dynamics of colloidal systems and may be useful as optical filters and switching devices.[209–211]

Water-in-FC microemulsions provide size-controlled, insulated zones for confinement of material to be studied. They have allowed investigation of the perturbation of water dynamics as a function of confining size.[212] The stretching frequencies of water were seen to depend strongly upon confining size. Confinement for investigation of individual proteins and other material appears possible using such systems.

The totally apolar HC-in-FC emulsions, besides their potential for pulmonary delivery and controlled release of lipophilic material, may be useful for confining and protecting water-sensitive reactants and products.

5. Perspectives

F-chains provide unique tools whenever surface properties and self-assembly into functional organized molecular systems and nano-objects are critical. They allow extending the range of many physical properties to extremes that cannot be reached with *H*-chains. In particular, *F*-chains offer the ultimate in terms of hydrophobic character. In addition, they tend to phase-separate from *H*-chains, thereby providing an enhanced driving force for compartmented self-assembly. Beyond their potential in medicine, primarily as controlled delivery systems for gases and other bioactive material and as contrast agents, FCs, *F*-amphiphiles (including *F*-alkyl/*H*-alkyl diblocks) and *F*-colloids constitute unique, modular building blocks for programming the 'self'-assembly of molecules and controlling the structure and properties of these self-assemblies. They provide versatile molecular tools for engineering space at the micro- and nanometer scale, especially when extreme segregation between fluorous, hydrocarbonous and aqueous nano- and micrometer-size compartments is desired.

The presence of *F*-chains can impact considerably on colloid formation, structure and morphology, usually increasing their stability, reducing their membrane permeability, modulating their physical properties, including phase transition temperatures, permeation rates and selectivity, and affecting their behavior in a biological milieu. Such effects can often be achieved with compounds that are structurally simpler (shorter, single-tailed, non-chiral, non-hydrogen bonding) than the standard *H*-amphiphiles.

Many non-medical applications could obviously benefit from the specific characteristics induced by *F*-chains and *F*-colloids, including the formulation, dispersion, encapsulation, spatial compartmentation, segregation, confinement and exclusion of diverse material. *F*-colloids could help protect sensitive agents, control reaction kinetics and catalysis, help modulate membrane-supported reactions, serve as matrices for elaborating nano-objects with specific morphologies, allow possibly for colloidal imprint synthesis, control surface coating, provide model membranes and confinement zones for physical studies, and participate in the engineering of nanosize composite devices for microelectronics optics, electrooptics, etc. Fluorous phases have a specific vocation to serve as microreservoirs for gaseous reagents or markers (e.g. NO, Xe). *F*-colloids can provide sturdy templates for the elaboration, possibly after polymerization or metalation, of new solid microcompartmented or microporous nanosystems useful for controlled release of reactants and catalyzers, and as molecular sieves. They can separate, at the nanometer level, domains that need to be treated (e.g. polymerized) separately. They may offer the possibility of combining the potential of fluorous phase chemistry with that of template synthesis. Assessing whether micron-size FC-stabilized sound reflectors embedded in a reaction medium could help enhance and control ultrasound-driven reactions would also be interesting.

F-amphiphiles may face the problem of acceptance in pharmaceuticals, especially when large amounts are needed, due to the many unknowns that overshadow their toxicity and pharmacology. Unless a dramatic improvement in effectiveness or a specific biological activity is found for an *F*-amphiphile vs a non-fluorinated component in a given circumstance, it is doubtful that the lengthy and costly efforts needed to remove these unknowns will be spent. Such considerations do obviously not apply to non-medical or extracorporeal uses (e.g. possibly, as colloidal templates for tissue growth).

F-alkyl/*H*-alkyl diblocks behave with respect to fluorous

and hydrocarbonous phases in a similar way as standard surfactants behave at aqueous/hydrocarbonous interfaces. They represent simple building blocks for producing and stabilizing colloids with fluorous phases, and provide an effective means of modulating the physical and biochemical properties of these colloids. A definite advantage of these diblocks is their greater simplicity and chemical and biological inertness as compared to the usual surfactants.

The diversity of components and structures available allows manipulation of the physical and biological characteristics of *F*-colloids over a wide range. *F*-colloids thus appear to stand at the cross-roads of many disciplines, and may have, among other area of interest, a potential for promoting colloidal fluorous phase chemistry.

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