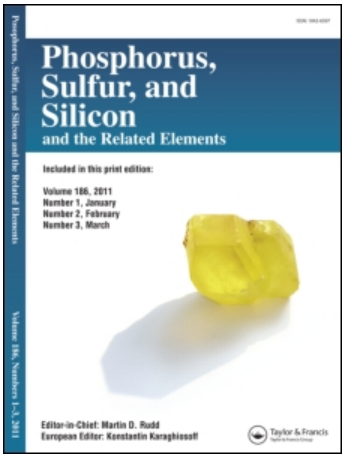

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CHOLESTEROL INHIBITS MELITTIN-INDUCED MEMBRANE DISRUPTION. A PHOSPHORUS SOLID STATE NMR STUDY

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^{31}P solid state NMR has been utilized in order to monitor the influence of cholesterol, a major component of plasma membranes, on melittin-induced membrane disruption. The bee venom melittin is a basic and amphiphilic peptide of 26 amino acids well known for its ability to destabilize pure zwitterionic and negatively charged phospholipid bilayers in producing small supramolecular structures [1,2]. The study was carried out on dipalmitoylphosphatidylcholine (DPPC), at pH=7.5, and on dimyristoylphosphatidic acid (DMPA), at pH=4.2 and 7.5-8.2, in the presence (30%) and absence of cholesterol, as a function of temperature and melittin concentration.

Taking advantage of the sensitivity of ^{31}P-NMR lineshapes to the vesicle size, experiments with DPPC or DMPA/melittin molar ratios, R_i, greater than 20 exhibit two-phase spectra, *i.e.* a narrow component superimposed on the usual lamellar-type powder pattern. These narrow resonances have been assigned to small supramolecular structures (discs of 200-400 Å diameter, in the gel phase, and large unilamellar vesicles of 2000-4000 Å size) undergoing fast isotropic tumbling [2] and provide a means to quantitate the destruction of wide extended multilayers.

Spectral simulations afforded a measure of the amount of each phase, *i.e.* the percentage of small structures and that of non-pertubed bilayers. It appears clearly that the presence of cholesterol in DPPC systems considerabily diminishes the amount of melittin-driven membrane reorganization. Similar results have been obtained with DMPA, independently of the electric charge at the interface. These results nicely reflect the well known cholesterol-induced membrane cohension [3], which couterbalances the destabilization promoted by melittin.

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[2] Dufourc E.J., Smith I.C.P. and Dufourcq J. (1986) *Biochemistry*, 25, 6448

[3] Léonard A., Dufourc E.J.(1991) *Biochimie*, 73, 1295-1302

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CHOLESTERYL-POLYSACCHARIDE COVERED LIPOSOMES. MECHANISMS OF CHOLESTEROL MOIETY ANCHORING INTO THE EGG-PHOSPHATIDYLCHOLINE MONOLAYERS

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Polysaccharide coating enhances liposome stability, and acting as a sensory device may provide targetability to specific cells and tissues.

Surface physico-chemical methods such as surface pressure and surface potential were used to elucidate the anchoring mechanism of cholesterol substituted pullulan (CHP) and cholesterol substituted amylopectin (CHA) in egg phosphatidylcholine monolayers. It has been considered that a phospholipid monolayer modelises the lipid bilayer of a liposome since two phospholipid monolayers makes up a liposome membrane.

The obtained data reveal the ability of both polysaccharide derivatives to penetrate the lipid monolayer. Although CHA is able to more effectively penetrate the lipid monolayer than CHP, it compensates the surface potential of the monolayer to a higher degree than does CHP. This would explain why liposomes covered with cholesterol substituted amylopectin exhibit lower stability relative to those covered with cholesterol substituted pullulan. Models of phospholipid-CHP and phospholipid-CHA orientation at the monolayer-water interface are proposed (Figure 1).

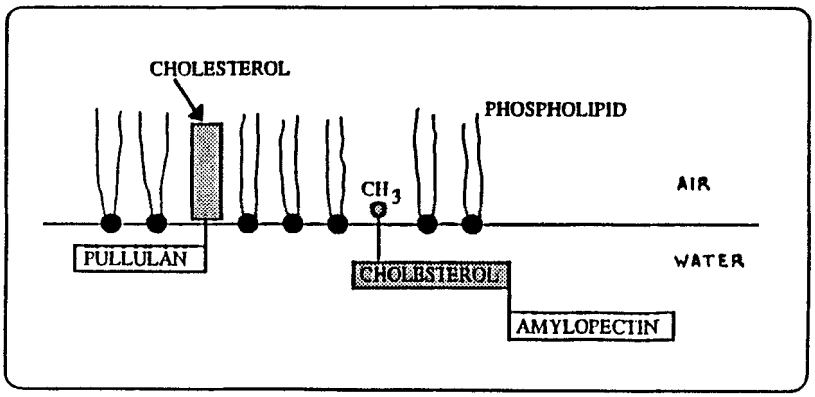

Figure 1: Model of cholesterol bearing polysaccharide anchorage into egg-PC monolayers

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SYNTHESIS, PHYSICOCHEMICAL AND BIOLOGICAL EVALUATION OF NEW *F*-ALKYLATED AMPHIPHILIC SINGLE-CHAIN ANALOGS OF PHOSPHOLIPIDS .

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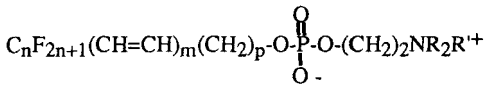
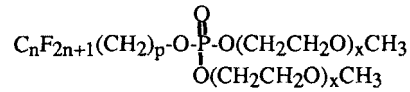
The key characteristics (particle size, shelf life, intravascular persistence, biodistribution, response to phagocytosis...) of injectable fluorocarbon emulsions are largely determined by the nature of the surfactant(s) which constitute the external aspect of the emulsion's droplets. In order to better control these characteristics, we have synthesized new *F*-alkylated amphiphiles with various perfluoroalkyl tails, hydrocarbon spacers (satured or not) and natural phosphorylated head groups including phosphocholine (**1-4**) or synthetic ones such as phosphodiester of poly(ethyleneglycol) methyl ether (**5-8**).



	n	m	p	R_2R'
1	6	0	5	Me_3
2	6	1	3	Me_3
3	8	0	5	Me_3
4	8	0	5	Me_2Et



	n	p	x
5	8	2	2
6	8	2	7
7	8	5	7
8	8	5	16

These compounds were obtained by a simple effective route (one pot, two steps) which is based on the direct phosphorylation of the *F*-alkylated alcohol with phosphorus oxytrichloride, followed by condensation with choline tosylate or the appropriate poly(ethyleneglycol) methyl ether.

The surfactant's physicochemical properties (surface activity, emulsifying efficiency) and biological behavior (effect on cell cultures, hemolytic activity and toxicity in mice) will be presented. These results will be discussed with regard to the modular structure of the compounds (perfluoroalkyl tail and hydrocarbon spacer chain length and size, charge and hydrophilicity of the head group) in order to establish structure/property relationships especially where their emulsifying properties and biocompatibility are concerned.

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SYNTHESIS OF D-GLYCOSYLPHOSPHODIESTERS OF LINEAR OR BRANCHED (PERFLUOROALKYL)ALKANOLS : TWO SYNTHETIC APPROACHES.

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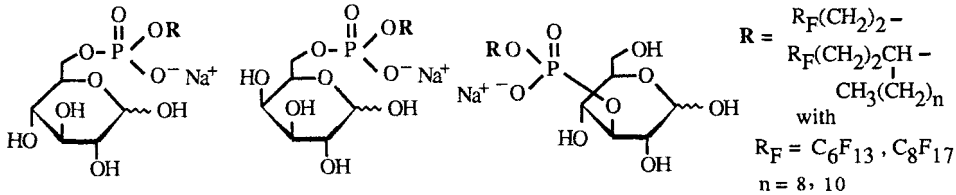
The administration of oxygen *in vivo* with the help of fluorocarbon emulsions is a challenge with considerable potential in medecine. A significant drawback of the injectable emulsions known-to-date is their lack of versatility in terms of their adaptibility to specific therapeutic indications, a primary reason for this situation being the lack of available biocompatible fluorophilic surfactants.

Therefore, we have developped new anionic amphiphiles with a phosphate ester junction between the fluorophilic-lipophilic tail and the sugar-based hydrophilic head. In view of the results previously obtained with neutral perfluoroalkylated surfactants having an ether or ester junction, such surfactants were expected to be efficient either alone or in conjunction with egg yolk phospholipids (EYP), the only well-accepted injectable surfactant presently available.



The selection of a suitable phosphorylating method is crucial but seldom straightforward because of the many different, often contradictory factors which must be taken into consideration when designing the reaction conditions. Two approaches (3 steps) were used: one employing the activation of the intermediate perfluoroalkyl phosphorodichloridate by triazole, the other involving a H-phosphonate, starting from phosphorus oxychloride and phosphorus trichloride, respectively. Purification was easier for the first route whereas the second one did not require an excess of the (perfluoroalkyl)alkanols.

Some of these perfluoroalkylated surfactants were tested as emulsifiers, either alone or in conjunction with EYP, and give significantly more stable emulsions than does EYP alone. Preliminary biocompatibility tests indicate that intravascular use may be possible. It is noteworthy for example that they are not hemolytic even at high concentrations.