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Molecular organized systems with fluorinated compounds: from synthesis to biological applications

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Abstract

This review summarizes previous results obtained in synthesis, physicochemical studies and biological applications of fluorinated or semifluorinated compounds. In these series we prepared olefins from which we studied:

- the cycloaddition reaction with cyclopentadiene, and the aggregation properties of the obtained substituted norbornenes;
- the amidation reaction in formamide microemulsions;
- their ability to provide new formulations for blood substitutes or their applications in vitreous surgery.

We also prepared new surfactants having polar heads from lactose and glucose derivatives. An interesting phenomenon of gelification in formamide was observed with surfactants synthesized from gluconolactone.

Keywords: Molecular organized systems; Amphiphiles; Fluorinated olefins; Reactivity in microemulsions; Blood substitutes; Vitreous surgery

1. Introduction

Perfluorinated or semifluorinated hydrocarbons have special properties owing to the characteristics of the fluorine atom: particularly the hydrophobicity of the fluorinated chains and their segregation behavior towards perhydrogenated compounds. We have explored these properties in order to develop new syntheses and new applications in biology and medicine.

2. Synthesis and aggregation of semifluorinated hydrocarbons

One of the objectives of our laboratory has been the development of novel mixed fluorinated and hydrogenated molecules. Taking advantage of the properties of formamide, we prepared, by phase transfer catalysis, alkenes from aldehydes and perfluorinated Wittig reagents [1,2]. These last reagents: $Ph_3P^+–CH_2CH_2–R_FI^-$, insoluble in water, were very useful for the synthesis of mixed molecules and presented aggregation properties in solution in formamide [3]. Being surfactants in formamide and not in water, they attracted our attention to the properties of this organic polar solvent and the behavior of fluorinated compounds and fluoride anion in this liquid. Softer than water, it solvates fluoride less and the following chloride-fluoride exchange reaction

$$RCl + KF \rightarrow RF + KCl$$

catalyzed by ammonium salts, takes place with some formamide in place of water, faster and with better yields [4–6].

In order to investigate the synthesis of mixed derivatives, we attempted the preparation of bicyclo[2.2.1]hept-2-enes, mono and disubstituted with long perfluorinated groups: such compounds were also interesting monomers for the preparation of mixed polymers [7]. These derivatives were synthesized by a Diels–Alder reaction between cyclopentadiene and olefines with perfluorinated chains: $R_F–CH{=}CH_2$ and $R_F–CH{=}CH–R_F$ (Scheme 1). The ^{19}F spectra of these derivatives, in $CDCl_3$ at the probe temperature (23°C) differed considerably for different chain lengths R_F. We postulated that these differences could be attributed to intermolecular associations. Such associations were probably limited to segregation processes between the fluorinated and hydrogenated groups. This is a well known phenomenon in mixtures of perfluorinated and perhydrogenated compounds [8].

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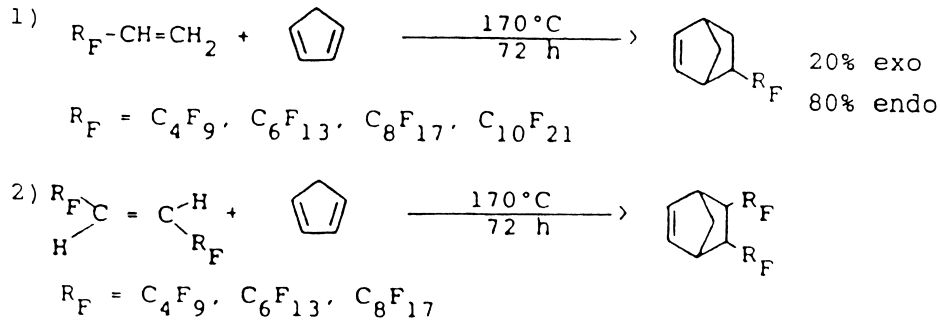


Scheme 1. Synthesis of substituted bicyclo[2.2.1]hept-2-enes.

This process leads to the association of the bicyclic derivatives which behave as amphiphilic molecules with a large hydrogenated head (bicyclomoiety) and a long perfluorinated tail. Associations of this type can lead to the formation of micelles (Fig. 1).

This hypothesis was confirmed by studying:

1. The effect of temperature: the micellar structures are sensitive to temperature. We carried out an investigation of the ^{19}F NMR spectrum of R_F monosubstituted norbornene in $CDCl_3$ at different temperatures and observed the destruction of the aggregate with liberation of free molecules when the solution was heated.
2. The effect of concentration: with R_F=C_4F_9, in the concentration range studied (0.4×10^{-7}–2×10^{-7} mol l^{-1} in $CDCl_3$), the association process appeared to persist.

On the same time, Turberg and Brady showed that semifluorinated hydrocarbons

CF_3–$(CF_2)_7$–(CH_2)–CH_3 and CF_3–$(CF_2)_7$–$(CH_2)_{15}$–CH_3

form reverse micelles in perfluorotributylamine and perfluorooctane, respectively [9]. They gave to these semifluorinated hydrocarbons the name of "primitive surfactants".

Their work and our own showed that

- the aggregation phenomenon in solution is general;
- the amphiphilic behavior only necessitates complementary parts in the molecule: one soluble in the solvent and the other not.

More recently, Binks et al. have studied the aggregation of semifluorinated alkanes (SFAs) in binary and ternary mixtures with hydrocarbon and fluorocarbon solvents. They showed that (SFAs) aggregate weakly in both hydrocarbon and fluorocarbon solvents [10].

Confirmation of the general character of the formation of aggregates was from the same group who has investigated the extent to which alkybenzenes exhibit surfactant properties in diiodomethane (DIM) as solvent: DIM has a high affinity for the benzene group and low affinity for the alkyl chain. So octylbenzene forms aggregates in DIM at concentrations higher than 5 mol%. [11]. Previously, we have been able to show that colloidal species were also formed by mixing two compounds (formamide and norbornene) in appropriate proportions [12].

3. Polymerization of substituted norbornenes

Fluorinated polymers have interesting properties: exceptional chemical inertness, strong water repellency, etc. we were interested to examine the polymerization by a methatetical reaction by the ring opening of the norbornene (Scheme 2).

With [$W(CO)_3$mesitylene] as catalyst, and $C_2H_5AlCl_2$ as cocatalyst, in the presence of oxygen at molar ratios: catalyst/olefin/cocatalyst/O_2 (1/50/4/6), we have been able to obtain polymers corresponding to ring opening of all the monomers in good yield.

The polymers obtained were elastomers and exhibited good water repellant properties on textile fibers.

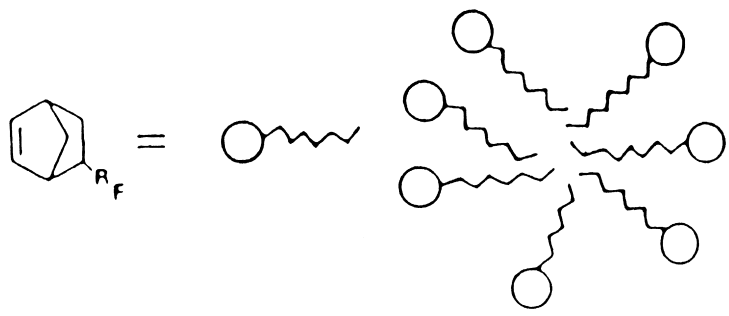
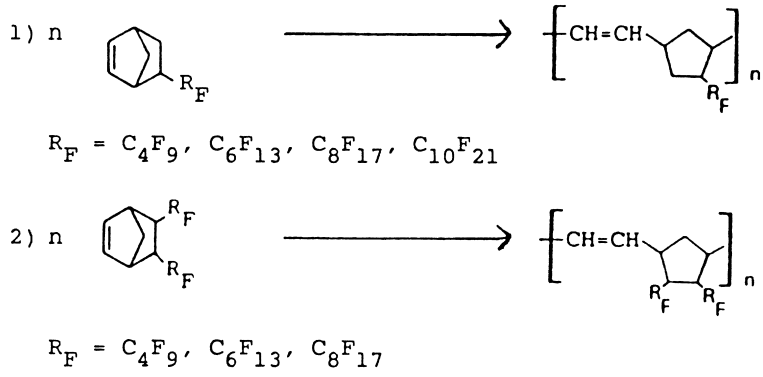


Fig. 1. Aggregation of perfluorinated substituted norbornenes.

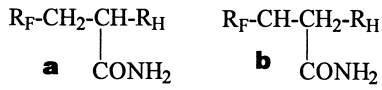


Scheme 2. Methatetic polymerization of substituted norbornenes.

4. Reactivity of compounds with long perfluorinated or semifluorinated chains

The above results have clearly shown the role of segregation between fluorinated derivatives and the corresponding hydrogenated ones. This segregation often accounts for the difficulty to carry out organic synthesis with perfluorinated compounds. Because there are many applications of such functionalized products essentially based on their surfactant properties, we tried to synthesize new series of molecules with an amide group as the polar head:

- with a single fluorinated chain: R_F–CH_2–CH_2–$CONH_2$;
- with a fluorinated and a hydrogenated chain:



They were synthesized by photoamidation of the corresponding olefins R_F–$CH=CH_2$ and $R_FCH=CH–R_H$.

For these synthesis, the method described by Elad and Rockach was selected [13]. By irradiation at 300 nm of a sample containing a mixture of olefin and formamide in the presence of acetone, the mixture being made homogeneous by addition of *tert*-butanol, hydrogenated olefins gave good yields of amide products. However, with perfluorinated olefins this method does not work. By modification of the method: use of large excess of *tert*-butanol (10-fold more dilute than normal) we get good yields of amide (up to 82%) [14].

With terminal olefins we only got the amidation on the terminal carbon, and essentially on the carbon bearing the alkyl group for the mixed olefins (regioisomer **a**).

The same reactions were carried out in a microscopically heterogeneous medium represented by a nonaqueous micro-

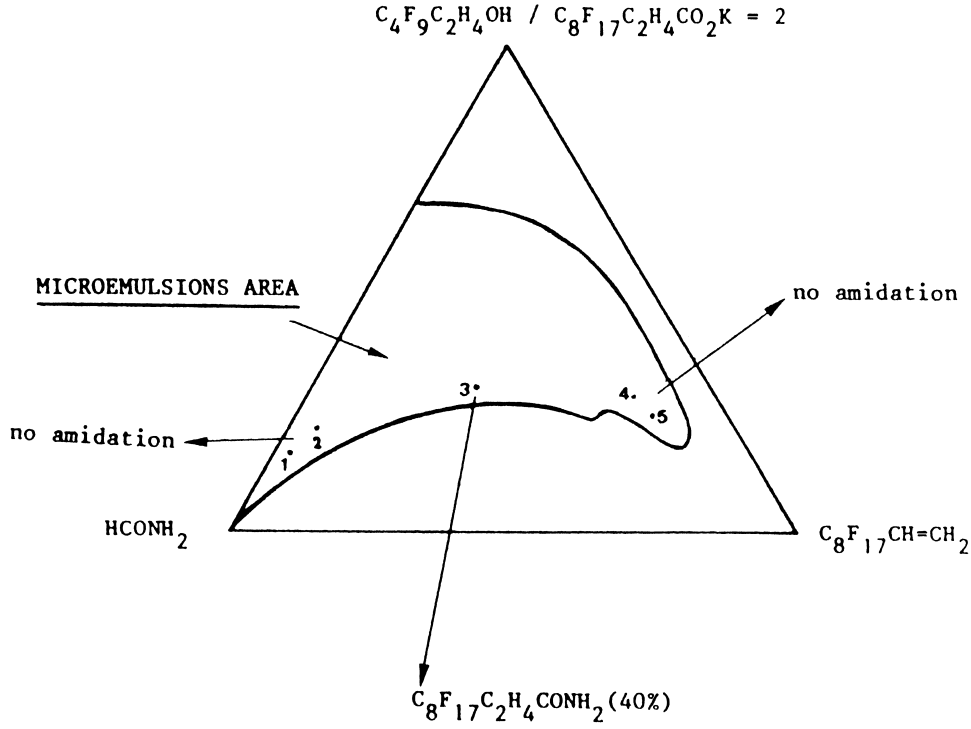


Fig. 2. γ Radiolysis of microemulsion systems ($HCONH_2$, $C_8F_{17}CH=CH_2$, $C_4F_9C_2H_4OH/C_8F_{17}C_2H_4CO_2K$=2).

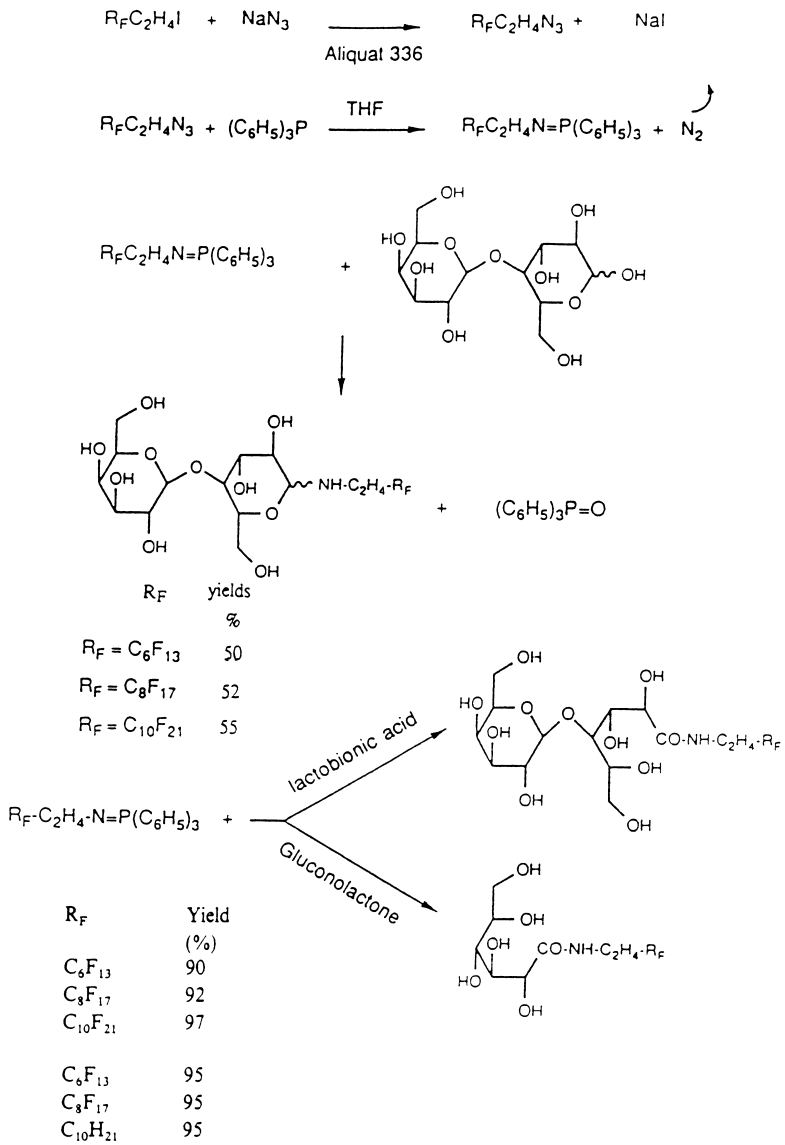
emulsion in which water is replaced by formamide, the olefin and the formamide being both reactants and constituents of the microemulsion (Fig. 2)

- with terminal olefin ($C_8F_{17}CH{=}CH_2$), the amidation, by γ radiolysis, takes place only in a bicontinuous microemulsion and not in direct or reverse micelles [15]. This result can be explained by the easy diffusion of the constituents in this structure. On the contrary the olefin diffuses little into the micellar media;
- with mixed olefin ($C_8F_{17}CH{=}CHC_{10}H_{21}$) amidation works very well in suitable microemulsions (up to 94%) and we obtained the opposite regioselectivity to that found in *tert*-butyl alcohol:
  - $\mathbf{a}/\mathbf{b} = 7.71$ in *tert*-butyl alcohol;
  - $\mathbf{a}/\mathbf{b} = 0.40$ in microemulsions.

This was interpreted in terms of the structure of the microemulsions which anchored the olefin in the interfacial film: the predominantly steric effects in *tert*-butyl alcohol are, thus, outweighed by polar effects in the microemulsions [16].

5. New formulations for blood substitutes

Perfluorocarbons combine high gas dissolving capacities with extreme chemical and biological inertness: they are good oxygen carriers in artificial blood and in liquid breathing. However, fluorocarbons are highly hydrophobic molecules. To solve the problem of their formulation, it is necessary to use the perfluorocarbons as an oil in water emulsion (O/W). To avoid instability of such emulsions and in order to have injectable "blood substitutes", microemulsions seem particularly attractive since they are fluid, transparent, thermodynamically stable microheterogeneous systems.



Scheme 3. Synthesis of fluorinated non-ionic surfactants.

However, production of a microemulsion with a perfluorinated oil requires the use of a fluorinated surfactant due to segregation between the fluorinated and hydrogenated chains [17]. In general, these surfactants are eliminated slowly from the organism, often being degraded to toxic fluoride ions. Much effort is now being put into the development of non-toxic fluorinated surfactants. This first strategy can be summarized as:

The development of biocompatible fluorinated surfactants to microemulsify perfluorinated oils.

In accord with this strategy, new synthesis of biocompatible non ionic fluorinated surfactants has been tried. In view of the above mentioned considerations, we felt that this approach was fraught with difficulties, and we also opted for an approach which can be summarized as:

The adaptation of the oil to a known biocompatible surfactant.

6. Synthesis of new fluorinated non-ionic surfactants derived from lactose and glucose

These derivatives were readily prepared in good yields in an aza-Wittig reaction from 2-(F-alkyl)ethylazides and the ose (lactose or glucose) or the corresponding acid or lactone (Scheme 3).

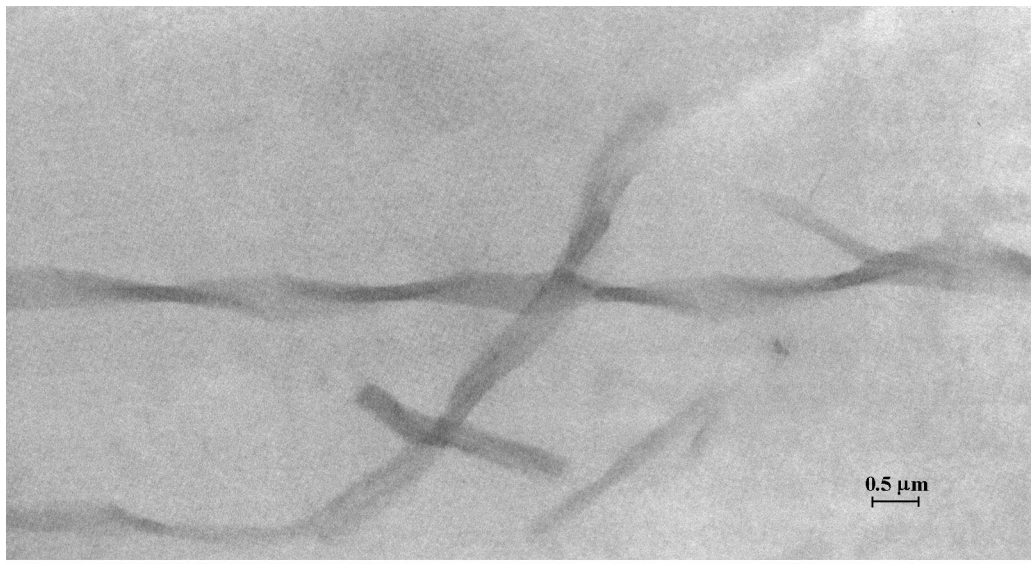
Fluorinated surfactants derived from lactose have good surfactant properties: CMC from 4.3×10^{-5} to 1.9×10^{-3} mol l^{-1}, and very low surface tensions at CMC: 15 mN m^{-1} in some cases. But, owing to the instability of analogs hydrocarbon surfactants, they are difficult to utilize in biocompatible formulation.Those derived from lactobionic acid have CMC near 10^{-4} mol l^{-1}, but the surface tension at the CMC is not low enough: they are not good surfactants [18].

7. Gelification in aqueous and formamide solution

N-fluoroalkyllactobionamides having an amide group gave gels in water solution after heating to 100°C and cooling at 0°C with concentrations from 10 to 30% (g ml^{-1}) depending on the length of the fluoroalkyl chain.

N-fluoroalkylgluconamides are insoluble in water, but it was possible to study their gelification properties in formamide after heating them at 155°C and cooling at 0°C: it was the first study of gels in formamide [19].

Electron microscopy analysis without contrast agent of these gels in formamide showed the presence of twisted lamellae of widths ranging from 50 to 120 nm and an infinite length with a helical pitch ranging from 160 to 600 nm. (Fig. 3).



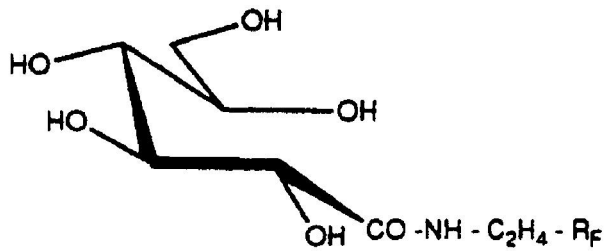


Fig. 3. Electron micrograph from negative staining method of 2% in formamide of *N*-perfluorodecyl gluconamide.

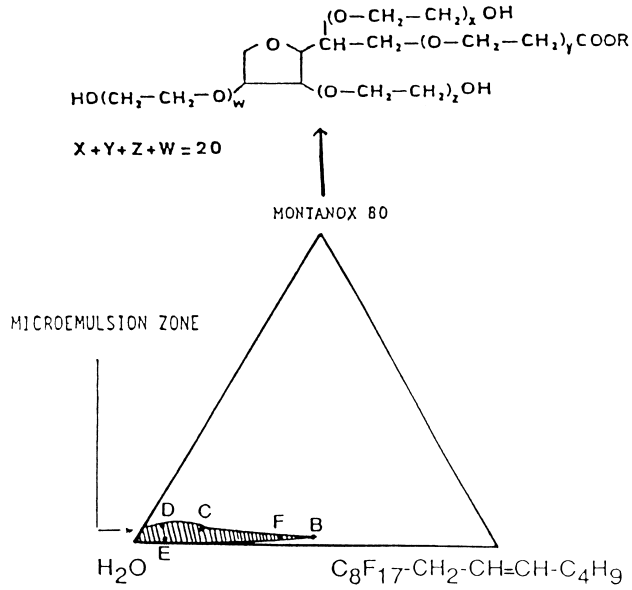


Fig. 4. Pseudoternary phase diagram of the system (H_2O-Montanox 80–C_8F_{17}–CH_2–CH=CH–C_4H_9).

8. Mixed oils and biocompatible surfactant

Some hydrogenated non ionic surfactants have been found to be biocompatible. We, thus, decided to test mixed oils sufficiently fluorinated to dissolve gas and be rapidly eliminated, but sufficiently hydrogenated to enable them to be microemulsified using biocompatible hydrogenated surfactants [20].

The mixed oil: $C_8F_{17}CH_2$–CH=CH–C_4H_9, is a good oxygen solvent [21]; it dissolves oxygen to as great an extent as F-decalin (43 ml/100 ml) with this oil we have been able to produce microemulsions. We optimized an aqueous system with a biocompatible surfactant, Montanox 80 (Fig. 4). This surfactant is used in the formulations of vaccines by the Institut Pasteur.

The diagram in Fig. 4 shows the microemulsion zone at 37°C (body temperature). The microemulsions are of the oil in water type, which are well suited for use as blood substitutes, since they are readily diluted in blood after intravenous administration [22]. Apart from microemulsion D, the others dissolved oxygen to a greater extent than Fluosol DA (Table 1).

It should also be noted that the theoretical values of oxygen solubility (taking into account the proportion of oil in the microemulsion) are much less than the measured values in microemulsions C, D and E which have true micellar structures. The excess of solubility was in fact 500%, indicating that the structure of the microemulsion increases their capacity to take up oxygen.

The toxicity of the microemulsions was tested after intraperitoneal injection in rats, and in mice after intravenous administration: the microemulsions appeared to be well tolerated [22]. These results show promise for the development of oxygen transporting compounds [23].

9. Application of mixed oils in vitreous surgery [24]

The use of perfluorocarbon liquids has facilitated the surgical management of complicated retinal detachment [25] and vitreous replacement is already used by some surgenous. However, retinal damage occurs when some such products are used as long-term vitreous replacements. Mechanical alteration due to pressure and chemical impurities has been suggested to explain this behavior.

Our study demonstrated that we readily obtained mixed oils, with high purity and high chemical stability. Moreover it is also possible to modulate the density of liquids by changing the relative lengths of the perfluorinated and perhydrogenated parts. This last property is very useful for surgeon who are able to choose the oil to adapt to the retinal damage. Formulations of purified mixed oils were tolerated by the eyes for a long time (more than 3 months) [26–28].

10. Conclusions

This paper is devoted to results concerning the synthesis and aggregation properties of perfluorinated and semi-fluorinated compounds. We have been able to prepare olefins with perfluorinated chains. These olefins react with cyclopentadiene to give substituted norbornenes which aggregate in $CDCl_3$ and give colloidal species similar to micelles.

By irradiation of olefins in formamide microemulsion, new series of amides have been obtained.

Table 1
Characteristics of microemulsions B, C, D and E (see Fig. 4)

Microemulsions	Composition of microemulsions (wt.%)					O_2 absorption (ml/100 ml)	
	$M \times 80$	Oil	H_2O	η (cp)	r (Å)	Measured	Calculated
B	2.6	48.7	48.7	70.0	–	23	17.0
C	5.5	16.6	77.8	1.1	64	32	5.4
D	7.15	7.15	85.7	1.1	36	9	2.3
E	1.3	9.1	89.6	0.9	43	21	2.8

Taking advantage of the lipophilicity of the chains we have synthesized new fluorinated non-ionic surfactants with sugar heads: an interesting phenomenon of gelification has been observed in formamide with some of these surfactants.

Biological properties of the mixed olefins have been explored in two applications: formulation of blood substitutes and surgical management of retinal detachment.

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