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A Novel Class of Nonionic Microemulsions: Fluorocarbons in Aqueous Solutions of Fluorinated Poly(oxyethylene) Surfactants

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Abstract: Infinitely stable nonionic microemulsions have been prepared from a ternary mixture of water, fluorocarbon (e.g., perfluorodecaline), and a perfluoroalkylpoly(oxyethylene) surfactant of appropriate hydrophile–lipophile balance (HLB). The synthesis of pure monodisperse surfactants is therefore a prerequisite for these investigations. Self-emulsification (without any cosurfactant) was observed within certain ranges of temperature and of surfactant-to-fluorocarbon mass ratio. Microemulsions were stable (under certain conditions) on dilution with water. Ternary-phase diagrams were drawn for a few systems (microemulsion domains only), allowing us to point out some general trends about structural factors and the effect of additives in line with those previously enunciated by Shinoda et al. for the analogous hydrogenated solutions. Solubilization of fluorocarbon can be brought up to 50 wt %; this results in exceptionally high solubility of gases into microemulsions. Small-angle neutron-scattering (SANS) measurements show aggregation numbers of about 2000 and droplet sizes of ca. 100 Å; there are also indications for a monodispersity of droplet sizes which is maintained on aqueous dilution.

An outstanding property of fluorocarbons, as compared to hydrocarbons, is their higher solubility of gases.[2-5] This property has suggested a probable utility of fluorinated liquids as *oxygen carriers* in artificial blood and liquid breathing.[6-11] The study of this solubility is the general purpose of a research project planned in this laboratory some years ago. The first series of investigations was devoted to solutions of molecular oxygen[5,12-14]—and, later on, of nitric oxide[15]—in pure fluorocarbons. As a second step, our objective was to demonstrate the feasibility of aqueous microemulsions of fluorocarbons.[16,17] Severe requirements have to be fulfilled for this purpose.

(1) The solubilization of the three components involved, fluorocarbon, surfactant, and water, should be spontaneous, and the clear solution thus obtained should be infinitely stable within a given temperature range (including 37 °C for biomedical purposes).

(2) Microemulsions must also be stable with respect to aqueous dilution; this means that the ternary mixture should remain one phase when infinitely diluted with water.

(3) The total amount of solubilized fluorinated compounds should be as high as possible to ensure a maximum solubility of gases.

(4) The surfactant should be of the nonionic type.

(5) According to Fujita et al.,[18] the size of the droplets of O/W emulsions or microemulsions should be less than 0.1–0.4 μm for biomedical purposes.

Many additional requirements are necessary for biomedical applications: chemical inertness, biological acceptance, industrial feasibility,[11] etc. We shall, however, restrict attention to conditions 1–5 in the following, which are those relevant to the physicochemist. Commercial solutions for circulatory replacement or perfusion of isolated organs[19,20] are in fact macroemulsions obtained by prolonged high-pressure homogenization of a ternary mixture of fluorocarbon (usually perfluorodecalin), hydrogenated surfactant (pluronics—members of a family of poly(oxyethylene)–poly(oxypropylene) polymers[21]—or purified yolk phospholipids[22]), and water. The macroemulsion is not infinitely stable and should be freshly prepared and stored in the cold.

To our knowledge, fluorinated microemulsions seem to have been quoted only once in the literature.[23] In this work, the authors described one example of fluorocarbon dispersion by means of a volatile halogenofluorocarbon and a mixture of hydrogenated and fluorinated nonionic surfactants. The mixture became clear after stirring and heating and remained limpid after evaporation of the halogenofluorocarbon. However, the incorporation of fluorocarbon, and therefore the solubility of oxygen, was relatively low, and the size of aggregates, which is fundamental to characterize microemulsions, was not determined. Another patent[24] claims for clear "autoemulsions" by using a mixture of polydisperse

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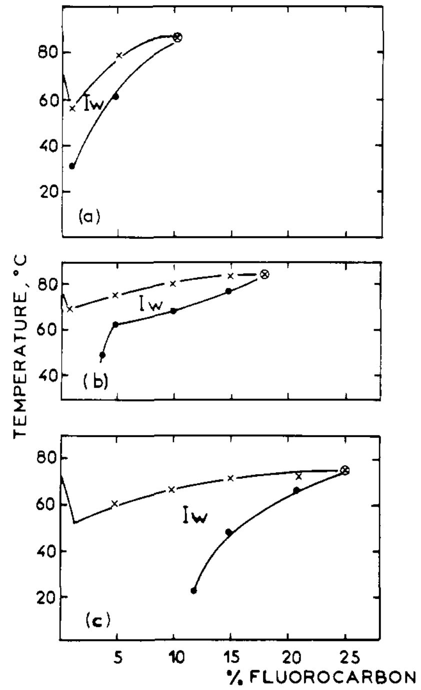

Figure 1. Partial phase diagrams of the $H_2O/C_6F_{13}CH{=}CHC_6F_{13}$ (a), $H_2O/C_8F_{17}C_2H_5$ (b), and $H_2O/C_6F_{13}CH{=}CH_2$ (c) systems containing 10 wt % $C_6F_{13}C_2H_4(OC_2H_4)_{\sim 14}OH$ as a function of the temperature. Cloud-point curve is indicated by X, solubilization curve indicated by O, and PIT indicated by ⊗. Realm I_W is the oil-swollen micellar solution according to Shinoda.[26,27]

fluorinated poly(oxyethylene) surfactants, ones with a high-hydrophobic character and others with a high-hydrophilic character, respectively. These solutions, as well as others using also poly(oxyethylene) surfactants,[25] seem to behave like macroemulsions, and they do not appear to have brought further improvements to the solutions already developed by the Green Cross Corp.

Investigations currently performed in this laboratory demonstrate the feasibility of highly fluorinated microemulsions, using for this purpose monodisperse well-defined fluorinated poly(oxyethylene) surfactants with an appropriate hydrophile–lipophile balance (HLB) value. Conditions 1–5 can be satisfied by selecting appropriate pairs of surfactant and fluorocarbon and determining the convenient mass ratios of components. No cosurfactant was required in the experiments. Microemulsions were unambiguously characterized by the size of aggregates from small-angle neutron-scattering experiments.

Strategy for Obtaining Fluorinated Microemulsions

As a starting point let us anticipate that nonionic fluorinated poly(oxyethylene) surfactants of the general type $C_mF_{2m+1}(CH_2)_p(OC_2H_4)_nOH$ behave quite similarly to their fully hydrogenated analogues, $C_{m+p}H_{2m+2p+1}(OC_2H_4)_nOH$. According to Shinoda and co-workers,[26-28] aqueous microemulsions can be obtained from water-rich ternary mixtures of hydrocarbon, surfactant, and water when the temperature is maintained between two limiting values, the solubilization and the cloud-point (CP) temperatures (lower and upper limits, respectively). These two temperatures, plotted as a function of the hydrocarbon concentration for a given surfactant concentration (typically 1–10 wt %) (Figure 1), give rise to the solubilization and cloud-point curves, respectively. The area comprised between the two curves corresponds to aqueous microemulsions, also called Winsor IV solutions;[29] their structure is generally described as aqueous solutions of detergent micelles swollen with oil, the so-called O/W Schulman microemulsions.[30,31] The cloud point was primarily defined in the absence of hydrocarbon, in which case it depends only on the mass fraction of dissolved surfactant. The cloud-point curve then represents the solubility curve of micelles in water. This curve exhibits a flat minimum following a sharp decrease when the mass fraction of detergent is increased from typically 0–1% (see, e.g., Figure 2). This lower consolute point is generally called the cloud point of the surfactant. CP temperature is modified when oil is added to the binary surfactant–water mixture. For aliphatic hydrocarbons, CP and solubilization curves are ascending curves which join together at the phase-inversion (PIT) or HLB temperature.[26-28] At this temperature three phases may coexist as the result of an easy passage from W/O-to-O/W type emulsions. The solubilization of hydrocarbons then exhibits a maximum at the PIT. In other words, the solubilization is large when the PIT of the selected nonionic surfactant is close to the desired temperature, e.g., 37 °C for most biomedical applications.

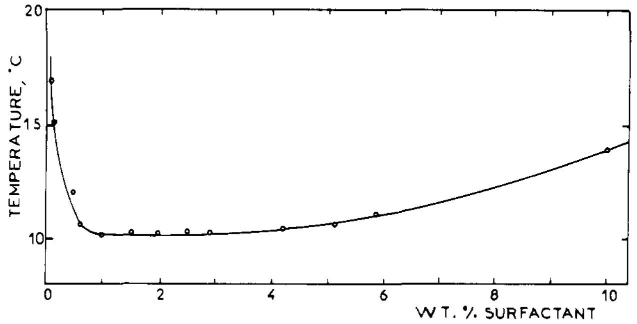

Figure 2. Liquid–liquid solubility curve (cloud-point curve) of the pure $C_6F_{13}CH_2(OC_2H_4)_6OH/H_2O$ system.

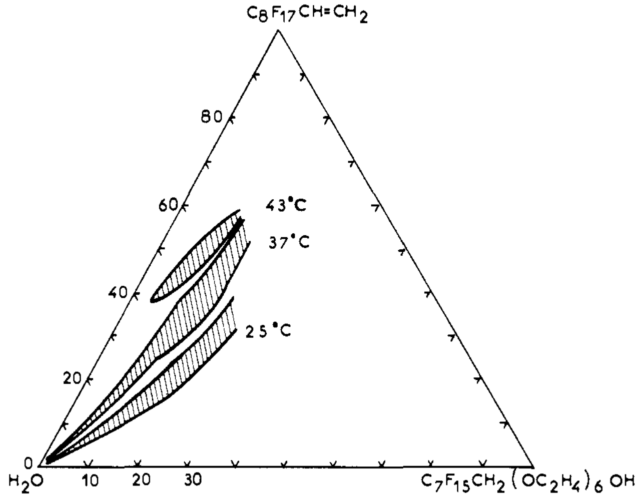

Figure 3. Phase diagram of the system $H_2O/C_8F_{17}CH{=}CH_2/C_7F_{15}CH_2(OC_2H_4)_6OH$ at 25, 37, and 43 °C (microemulsion region only, hatchured area).

Both CP and PIT temperatures are sensitive to structural factors in a parallel manner.[26-28] The effect of increasing hydrophobic or hydrophilic chain lengths of the emulsifier is a depression or an elevation, respectively, of both CP and PIT. The influence of added hydrocarbons on the PIT seems to be related to the mutual solubility of the hydrocarbon and the emulsifier: the more soluble the hydrocarbon for a definite nonionic surfactant, the lower is the phase-inversion temperature.

An equivalent representation of these results uses ternary diagrams (water–oil–surfactant) in which are plotted the boundaries between the different phases. If we restrict attention to the region

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of aqueous microemulsions, it may be said[32,33] that such a region does exist in the vicinity of the water corner along the water-to-surfactant axis for temperatures below the PIT. As the temperature approaches the PIT, a new solubility area develops, covering a sectorial region from the aqueous corner (see Figure 3). If the temperature T is raised beyond the PIT, the solubility area detaches from the aqueous corner and constitutes an isolated island parallel to the water-to-oil axis. The second situation only ($T \leq$ PIT) is appropriate for our purposes. A continuous straight line may be drawn in this case from the aqueous corner up to the hydrocarbon-rich extremity of the sector; this shows that an oil-rich microemulsion may be infinitely diluted with water at this temperature without observing any phase separation.

In conclusion, an essential problem is to bring the PIT of the investigated fluorinated systems within the desirable temperature domain, i.e., from about 25 to 40 °C. We are then led to compare the hydrophobic character of fluorocarbon chains with that of the corresponding hydrocarbon chains. Our first experiments used commercial polydisperse poly(oxyethylene) surfactants, $C_6F_{13}C_2H_4(OC_2H_4)_nOH$, with $n \sim 11.5$ (**1**) or 14 (**2**). The first method to evaluate the hydrophile–lipophile balance (HLB) character of a detergent is to consider its critical micelle concentration (cmc) in aqueous solution. According to Lange,[34] cmc values (in mol dm^{-3}) depend on the number of ether units, n, according to the formula

$$\log \text{cmc} = A + Bn$$

with $B = 0.128$. Using the cmc values we measured for detergents **1** and **2**, 4.48 and 6.12 × 10^{-4} M, respectively, we found $B = 0.125$ for fluorinated ethers. This shows that the influence of ether units over HLB and cmc is almost identical for fluorinated and hydrogenated surfactants. The difference then lies in the hydrophobic moiety of the detergent. Shinoda et al.[35,36] have shown that the cmc values of fluorinated ionic surfactants, namely perfluorinated C_6–C_{12} carboxylates, correspond to those of their hydrogenated analogues, containing 1.5 times more carbons. This rule seems to hold for the nonionic surfactants presently investigated. Thus, the cmc of $C_{12}H_{25}(OC_2H_4)_{12}OH$ is of the same order of magnitude (1.4 × 10^{-4} M at 23 °C[34]) as that of surfactant **1** (4.48 × 10^{-4} M). The same is true for the cmc values of $C_mF_{2m+1}CH_2(OC_2H_4)_5OH$, m = 6 or 7 (35 and 4.8 × 10^{-5} M, respectively[37]), compared to those of $C_mH_{2m+1}(OC_2H_4)_5OH$, m = 10 or 12 (86.0 and 5.8 × 10^{-5} M, respectively[28,38]). This difference of hydrophobicity between hydro- and fluorocarbons is also reflected in the empirical increments used by Davies[39] to compute HLB values of surfactants. The increments assigned to methylene and methyl units are 1.8 times smaller than those assigned to the corresponding perfluorinated units, −0.475 against −0.870. We may infer from these few data that *the behavior of nonionic fluorinated detergents should be similar to that of their hydrogenated analogues possessing a lipophilic chain 1.5–1.8 times longer*. In fact, these predictions were not fully verified as far as the cloud-point properties are concerned. Thus, we found an approximate CP temperature of 75 °C in 10 wt % aqueous solutions of **2**. According to the above rule, this value should compare to the CP temperature of $C_{10}H_{21}(OC_2H_4)_{14}OH$. This temperature has not been measured in the literature; however, the CP temperature of $C_{10}H_{21}(OC_2H_4)_6OH$ is known (60 °C), as well as the effect of additional oxyethylene units, namely an elevation of CP temperature by ca. 10 °C per unit (on the basis of CP temperatures of 27, 39, and 57.5 °C for $C_{12}H_{25}(OC_2H_4)_nOH$, n = 6, 7, or 8, respectively[28]). A CP temperature of ca. 140 °C is thus anticipated for the hydrogenated homologue of emulsifier **2**. We are then led to the conclusion that *CP temperatures of fluorinated nonionic surfactants are clearly lower than expected on the basis of comparative cmc measurements*.

This rule holds for ternary mixtures. This is shown on the Shinoda-type diagrams of Figure 1, representing the CP and solubilization curves of each of the three fluorocarbons ($C_6F_{13}CH{=}CHC_6F_{13}$ (**3**), $C_8F_{17}C_2H_5$ (**4**), and $C_6F_{13}CH{=}CH_2$ (**5**)) in 10 wt % aqueous solutions of **2**. The intersection of these curves yield the PIT and the maximum solubilization ($z_{\max}$) of each fluorocarbon in a one-phase solution. These exploratory experiments resulted in the important conclusion that less hydrophilic surfactants than those commercially available were necessary to obtain clear microemulsions at moderate temperature. PIT and $z_{\max}$ values are respectively increased and decreased as the chain length of the solubilized fluorocarbon is itself increased, PIT and $z_{\max}$ = 74 °C and 25%, 84 °C and 17%, and 85 °C and 10% for **5**, **4**, and **3**, respectively. This comparison also points to the necessity of using low-molecular weight fluorocarbons for a high solubilization. If due attention is also paid to volatility requirements, the fluorocarbons recommended to prepare artificial blood substitutes all contain ten carbon atoms, typically perfluorodecalin or bis(perfluoro-*n*-butylethylene).[11]

These observations led us to synthesize surfactants of the general formula $C_mF_{2m+1}(CH_2)_p(OC_2H_4)_nOH$, with m = 6 or 7, p = 1, and n = 4, 5, or 6. These compounds were designated by the sequence of integers *mpn*, e.g., 615 for $C_6F_{13}CH_2(OC_2H_4)_5OH$. Clear microemulsions with droplet size less than 500 Å (0.05 μm) were effectively obtained by simply mixing water, emulsifier, and fluorocarbon at 25–40 °C. The alternative procedure using pseudoternary mixtures of water, fluorocarbon, surfactant, and cosurfactant (in fact a mixture of two surfactants of different hydrophobicities,[24] such as **1** and $C_6F_{13}CH_2(OC_2H_4)_2OH$) was abandoned, as we observed that the dispersions were very turbid and difficult to prepare (sonication of the mixture was required) and that their stability was poor. Moreover, it has been established[40] that the solubilization of the analogous hydrocarbons in water is larger when the nonionic surfactant is monodisperse than when the distribution of hydrophilic chain lengths is broad. This was a second point which prompted us to devise efficient synthesis of monodisperse fluorinated surfactants.

Experimental Section

Materials. Polyethers **1** and **2** (polydisperse compounds) and pure fluorocarbons were generously supplied by the PCUK Co. and by Professors Cambon and Riess. Polyethers 614, 613, 616, 715, and 716 were prepared according to procedures described in previous publications[41,42] (see also below). Perfluorodecalin is a commercial product (Ventron) containing both cis and trans isomers.

Cmc Values. They were determined according to the procedure described by Ross and Olivier[43] by using UV–visible spectroscopy of added iodine. In the presence of micelles, an absorption band appears at lower wavelengths, 360–400 nm instead of 450–500 nm for iodine aqueous solutions. Plots of the optical density as a function of the surfactant concentration exhibit a strong discontinuity for the cmc value.

Cloud-Point and Solubilization Curves. Liquid–liquid solubility curve (cloud-point curve) of the pure $C_7F_{15}CH_2(OC_2H_4)_6OH$–$H_2O$ system was determined point by point by preparing aqueous solutions containing from 0.1 to 10 wt % surfactant. Aliquots (1–2 cm^3) were enclosed in small capped vials immersed in a thermostated bath. The temperature was progressively raised until the solution became turbid. The uncertainty range could be decreased up to ±0.1 °C. Solutions were examined between crossed polarizers and showed no anisotropy. Cloud-point and solubilization curves of ternary mixtures were determined by using solutions containing a given mass fraction (10%) of surfactant **2** added with increasing amounts of fluorocarbon **3**, **4**, or **5**. The cloud point was detected visually on varying the temperature by the turbidity of the solution and the solubility limit by the onset of solubilizate droplets. The

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Table I. Physicochemical Data Used in SANS Measurements

Scattering Lengths (*b*) of Atoms, 10^{-12} cm[46]
C, 0.662; D, 0.667; F, 0.574; H, 0.372; O, 0.575

Scattering Lengths (b_W), Molecular Volumes (v_W), Scattering Length Densities (Q_W) in H_2O/D_2 Mixtures

H_2O wt % molar fraction	100	70	65	60	41	0
	1.0	0.7216	0.6735	0.6250	0.4357	0
b_W, 10^{-12} cm	−0.169	0.4093	0.5095	0.6102	1.003	1.909
v_W, 10^{-23} cm^3	2.998	3.000	3.001	3.001	3.003	3.007
Q_W, 10^{10} cm^{-2}	−0.564	1.364	1.697	2.033	3.341	6.348

Molecular Weights (*M*), Densities (*d*), Molecular Volumes (*v*), Scattering Lengths (*b* and *Q*) of Fluorinated Compounds

		surfactant 716		
	$C_8F_{17}CHCH_2$ (FC)	whole molecule (S)	hydrophilic moiety A	hydrophobic moiety B
M, g mol^{-1}	446.7	664.4	281.32	383.08
d	1.66	1.425	1.00[a]	2.071[b]
v, 10^{-23} cm^3	4.46	7.74	4.67	3.071
b, 10^{-12} cm	15.26	16.16	3.00	13.16
Q, 10^{10} cm^{-2}	3.42	2.09	0.642	4.28

[a] Assumed value. [b] Computed value assuming $v_S = v_A + v_B$ or $M_S/d_S = M_A/d_A + M_B/d_B$.

accuracy was of ±2–3 °C for the more dilute solutions and was better than 1 °C in the vicinity of the PIT temperature where the microemulsion domain is very narrow in the representation of Shinoda (Figure 1).

Ternary Diagrams. Aqueous solutions containing given quantities of surfactant are progressively added with fluorocarbon and are placed in a thermostated bath at a constant temperature (generally 25 or 37 °C). After each addition, the aspect of the solution is observed: number, nature, and approximate volumes of phases. The domain of clear microemulsions up to the water corner of the diagram only was explored in this work. Each series of experiments of the type described above is equivalent to exploring a straight line that originates from the fluorocarbon corner in the triangular diagram water–surfactant–fluorocarbon. Solutions were left for equilibration at least for 24 h before observation was completed. The domains of microemulsion in the diagrams were determined for the systems $C_8F_{17}CH{=}CH_2$/716/H_2O (at 25, 37, and 43 °C), perfluorodecaline/615/H_2O (at 25 and 37 °C), and perfluorodecalin/715 or 615/H_2O (at 37 °C), respectively.

Small-Angle Neutron-Scattering (SANS) Measurements. Neutron-scattering experiments were performed by using the 2.83-m (source to detector) SANS D17 instrument at the Laue Langevin Institute (ILL), Grenoble. Scattered intensities were recorded in the *q* range 0.008–0.1 Å^{-1}, $q = (4\pi/\lambda)\sin\theta$ where 2θ is the scattering angle and λ is the wavelength of neutrons (12.0 Å). The samples were contained in a cylindrical cell of 1-mm path length mounted on an automatic and thermostated (25 ± 0.2 °C) cell holder.

The solutions investigated were prepared by progressively diluting a mixture of surfactant 716 and fluorocarbon $C_8F_{17}CH{=}CH_2$ with an H_2O/D_2O mixture. Five microemulsions were used whose representative points are all located on a straight line from the aqueous corner of the ternary diagram water/716/$C_8F_{17}CH{=}CH_2$ (Figure 10). The molar ratio of fluorocarbon to surfactant was thus maintained at a fixed value, $\alpha = 2.05$, throughout these experiments. The mass percentage of the dispersed phase (surfactant and fluorocarbon) ranged from 37 to 7.5%. The sectorial region of microemulsions in the ternary diagram becomes so narrow in the vicinity of the aqueous corner that temperature fluctuations of the thermostated bath resulted in uncontrolled phase separations, thus preventing investigations on more dilute solutions. Composition of the H_2O/D_2O mixture ranged from 70 to 32 wt % H_2O, allowing us to vary the scattering length[44–47] of the solvent (b_w) from 0.417 to 1.200 × 10^{-12} cm. When standard procedures[43,44] were used, the measured intensities were corrected for scattering due to the solvent and the quartz cell, for extinction and uncoherent scattering. The coherent scattered intensity per unit volume was then calculated on the absolute scale. Computations used the physicochemical data of Table I. Scattering lengths, b_i, where i = FC, S, A, B, or P, for fluorocarbon and surfactant molecules, for the hydrophilic and hydrophobic moieties (A or B) of S, and for the whole particle (P), were computed from atomic coherent scattering lengths. Scattering length densities, $Q_i = b_iN_{AV}/V_i$, were obtained as the ratio of the above b_i values to the corresponding molecular volumes, $v_i = V_i/N_{AV}$ (V_i, molar volumes; N_{AV}, Avogadro's number). The number of scattering particles per unit volume, $N_P = N_S/N$, was computed by assuming an average aggregation number (*N*) and neglecting the very small amount of monomeric surfactant molecules (cmc values are very low; see above). N_S is the number of surfactant molecules per unit volume

$$N_S = N_{AV}z_S/M_SV$$

and therefore

$$N_P = \frac{N_{AV}z_S}{M_SVN} \tag{1}$$

where z_S and M_S are the mass fraction and the molar weight of surfactant and *V* is the specific volume of the solution, $V = z_S/d_S + z_W/d_W + z_{FC}/d_{FC}$ (z_i and d_i denote the mass fractions and the densities of the pure components i, i = S, W, or FC, of the ternary mixture, assuming ideal solutions).

Oxygen Solutions. The oxygen content in saturated solutions under ordinary pressure is measured by using a Van Slyke apparatus.[49]

Synthesis of Fluorinated Surfactants

Poly(oxyethylene) perfluoroalkyl surfactants $C_mF_{2m+1}CH_2(OC_2H_4)_nOH$ are generally prepared by a Williamson-type reaction between a fluoroalcohol ($C_mF_{2m+1}CH_2OH$) and ethylene oxide. This method, however, results in an uncontrolled polyaddition of ethylene oxide and a broad distribution of oligomers of variable rank *n*. This prompted us to consider alternative synthetic procedures in which a perfluoroalkyl alcohol is grafted onto an oligo(ethylene glycol), $H(OC_2H_4)_nOH$, of definite length. These methods have been described in previous publications.[41,42] They are briefly summarized here for the sake of completeness. The symmetry of the ethylene glycol unit toward etherification was removed by either activating or deactivating one of the terminal hydroxyls. The first variant (path 1 in Scheme I) used an intermediate monooxyphosphonium salt of the appropriate poly(ethylene) glycol ($n = 4$–6), which was then made to react with the alcoholate $C_mF_{2m+1}CH_2O^-Na^+$. The second variant (path 2) used the monobenzyl or trityl ether of the appropriate poly(oxyethylene) glycol, $H(OC_2H_4)_nOR$, R = $PhCH_2$ or Ph_3C. Monoethers were obtained at the exclusion of diethers by a phase-transfer reaction between an aqueous H_2O + NaOH and an organic RCl + glycol phase. The protecting group was removed by catalytic hydrogenation. The final products were carefully

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Scheme I

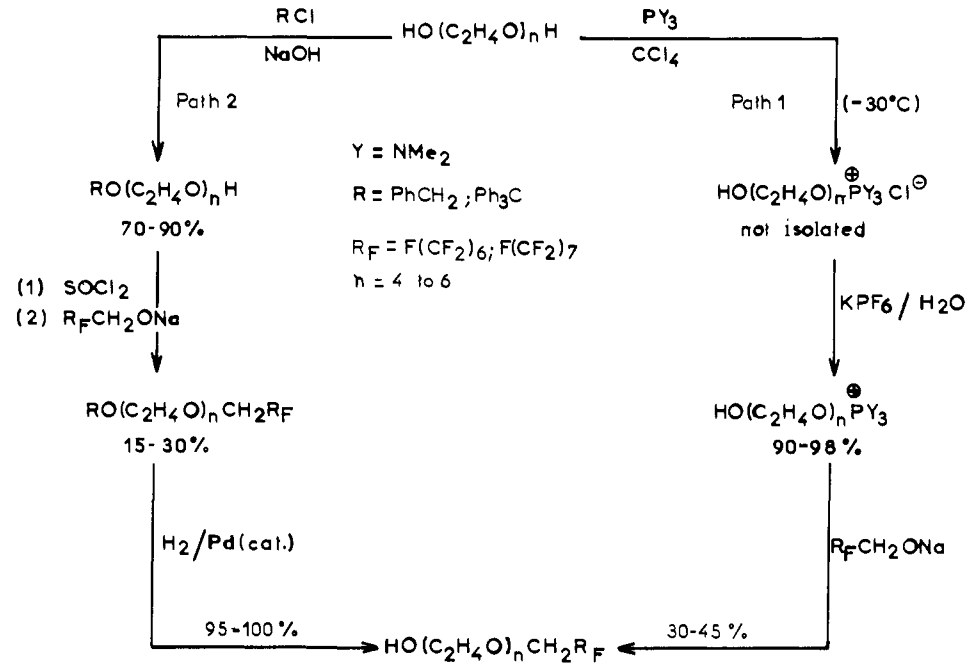

Table II. Formulation of Infinitely Stable Fluorinated Microemulsions (Typical Examples at 37 °C, Specifying the Nature and the Masses of the Components of the Ternary Mixture Water/Fluorocarbon/Surfactant)

No.	aqueous soln	fluorocarbon	surfactant
1	5.2 g of H_2O^a	3.5 g of $C_8F_{17}CH{=}CH_2$	1.3 g of 716[b]
2	5.7 g of Ringer's lactate[c]	3.3 g of $C_8F_{17}CH{=}CH_2$	1.0 g of 716
3	5.3 g of H_2O	3.8 g of $C_{10}F_{18}$ (perfluorodecalin)	0.9 g of 715
4	2.88 g of H_2O	4.16 g of $C_{10}F_{18}$	0.96 g of 715
5	7.5 g of H_2O	1.2 g of C_7F_{16}	1.3 g of 716
6	7.0 g of H_2O	1.8 of $C_{10}F_{18}$	1.2 g of 715
7	6.0 g of H_2O	2.5 g of $C_{10}F_{18}$	1.5 g of 615
8	5.6 g of Ringer's lactate	2.9 g of $C_{10}F_{18}$	1.5 g of 615
9	6.5 g of plasmion[d]	1.9 g of $C_{10}F_{18}$	1.6 g of 716
10	6.7 g of H_2O	1.5 g of $C_{10}F_{18}$	1.8 g of 716
11	6.92 g of Ringer's lactate	1.82 g of $C_8F_{17}CH_2CH_3$	1.26 g of 716

[a] Masses are referred to 10 g of the ternary mixture. [b] For nomenclature, see the text. [c] Ringer's lactate solution: 6 g of NaCl, 3.1 g of sodium lactate, 0.4 g of $CaCl_2$, $6H_2O$, 0.4 g of KCl per liter. [d] Commercial trademark (Laboratories Roger Bellon, Paris): plasmion is a blood plasma substitute composed of 30 g of modified fluid gelatin in 1:1 Ringer's lactate solution.

purified by chromatography on silica gel. Their purity was checked by centesimal analysis and IR and NMR spectroscopy. Surfactants with $m = 6$ or 7 and $n = 4$–6 were prepared in this way with overall yields (with respect to initial poly(ethylene) glycol) ranging from 10 to 40%.

Surfactant Aqueous Solutions

The solubility curve of compound 616 (Figure 2) exhibits a lower consolute point at 10.2 °C, the cloud-point temperature (T_{CP}), for 0.5–1 wt % surfactant. At temperatures below T_{CP}, the solution is perfectly clear and isotropic. No lyotropic phase was detected up to 10 wt % surfactant. Compound 616 has the larger HLB number in the series of surfactants prepared and is therefore expected to have the higher CP temperature. In fact, all detergents except 616 were found to be insoluble (as a one-phase solution) even when the temperature was lowered down to the freezing point of water. This indicates that the cloud points of all these surfactants but 616 are located below 0 °C, thus confirming the CP temperature elevation mentioned above from fluorinated surfactants to their hydrogenated homologues (e.g., 10.2 °C for 616 against 60 °C[49] for $C_{10}H_{21}(OC_2H_4)_6OH$). One may even wonder whether the optimum solubilization of fluorocarbons in aqueous solutions of the newly synthesized surfactants is not to occur at temperatures outside the desired interval of 25–40 °C, since the PIT and CP temperatures were close to each other in our preliminary experiments where $n \sim 11$ and 14. The fact that this was *not* the case (see below) is in line with the observation[50] that the temperature difference between the cloud points of a series of hydrogenated poly(oxyethylene) nonyl–phenyl ethers measured in the absence of, or saturated with hexadecane, amounts to ca. 60 °C when $n = 6.2$ and to 10 °C only when $n = 14$.

Microemulsions of Fluorocarbons

These investigations aim primarily at establishing the conditions which are necessary for solubilization of large amounts of fluorocarbons in water under the form of microemulsions at temperatures close to 37 °C. The exploration of ternary diagrams was consequently limited to water-rich domains, using three fluorocarbons, perfluorodecalin (**6**), 9*H*,9*H*,10*H*-perfluoro-*n*-dec-1-ene ($C_8F_{17}CH{=}CH_2$, **7**), and 9*H*,9*H*,10*H*,10*H*,10*H*-perfluoro-*n*-decane ($C_8F_{17}C_2H_5$, **8**), associated with one of the three surfactants 615, 715, or 716. Thorough examination of ternary diagrams, especially investigating regions of inverse micelles, is currently performed in this laboratory.[51,52]

Microemulsions are simply obtained by adding the three components together and shaking them by hand. Exact formulations[17] of a few systems are given for convenience in Table II. Microemulsions are perfectly clear and isotropic. Their viscosity, η, is moderately high and very sensitive to temperature, e.g., $\eta = 49.1$ and 20.2 cP at 28 and 37 °C, respectively, for a microemulsion containing 25 and 24 wt % of **6** and 615, respectively. Clear

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Table III. Solubilization Ranges (Upper and Lower Limits) of Fluorocarbons (wt %) at 37 °C in Various Systems

system	initial wt % surfactant 15	20	25
$H_2O/716/n\text{-}C_7H_{16}$	7-12%		
$H_2O/614/C_{10}F_{18}$	microemulsions at $T < 37$ °C		
$H_2O/715/C_{10}F_{18}$		37-49%	
$H_2O/615/C_{10}F_{18}$		22-28%	
$H_2O/716/C_{10}F_{18}$		9-16%	
$H_2O/616/C_{10}F_{18}$	microemulsions at $T > 37$ C		
plasmion[a]/716/$C_{10}F_{18}$		14-20%	
$H_2O/715/C_8F_{17}CH{=}CH_2$	microemulsions at $T <37$ °C		
$H_2O/716/C_8F_{17}CH{=}CH_2$	22-34%	27-43%	32-48%
$H_2O/716/C_4F_9CH{=}CHC_4F_9$			8-25%
plasmion[a]/716/$C_8F_7CH{=}CH_2$	microemulsions at $T <37$ °C		
Ringer's lactate[a]/716/$C_8F_{17}CH{=}CH_2$		30-36%	
Ringer's lactate[a]/716/$C_8F_{17}C_2H_5$		14-22%	

[a] See Table II.

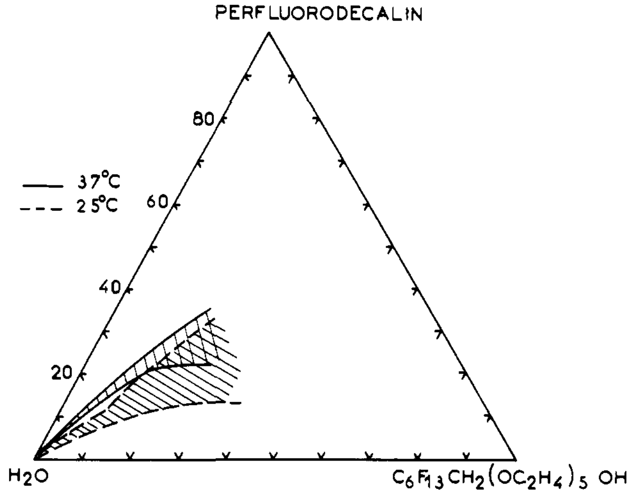

Figure 4. Phase diagram of the system H_2O/perfluorodecalin/$C_6F_{13}CH_2(OC_2H_4)_5OH$ at 25 and 37 °C (microemulsion region only, hatchured area).

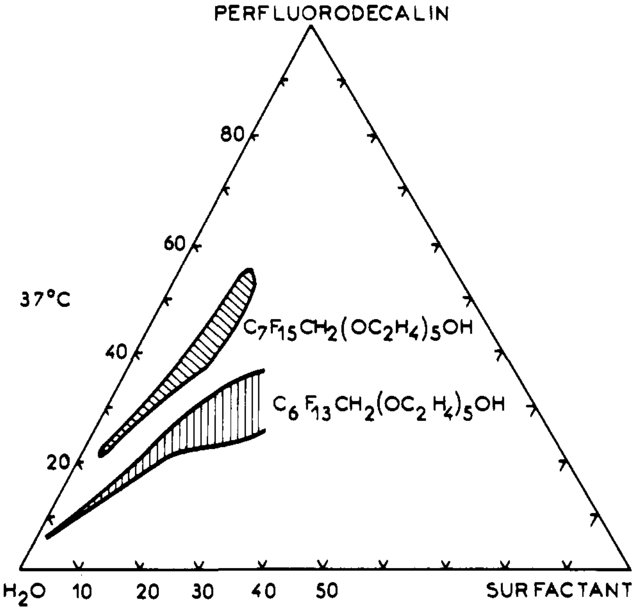

Figure 5. Phase diagrams of the systems H_2O/perfluorodecalin/$C_7F_{15}CH_2(OC_2H_4)_5OH$ and H_2O/perfluorodecalin/$C_6F_{13}CH_2(OC_2H_4)_5OH$ at 37 °C (microemulsion region only, hatchured area).

microemulsions are transformed into turbid solutions if they are heated above the cloud-point curve; they separate into O/W droplets if they are cooled below the solubilization curve. These transformations are fastly reversible and can be effected in a short period of time, thus allowing to store these solutions at any temperature before use. Fluorinated microemulsions seem to be infinitely stable in time; some of them have been prepared without suffering any alteration for more than 1 year.

First indications on properties related to solubilization of fluorocarbons are given in the following: effects of the temperature, of the poly(oxyethylene) and fluorocarbon chain lengths of surfactants, of the nature of solubilizates, and of additives. In many cases, comparisons were carried out by using only a section of the microemulsion sectorial corner along a straight line originating from the fluorocarbon apex in the ternary diagram (see, e.g., Figure 6). This was simply achieved by adding small incremental amounts of fluorocarbon to an aqueous 15-20 wt % solution of the surfactant until, and then as long as, a clear solution is observed (Table III).

Influence of the Temperature. The domains for aqueous microemulsions are shown for a typical system, $C_8F_{17}CH{=}CH_2$/716/water, on the ternary diagram of Figure 3. Large quantities of fluorocarbons can be solubilized in the vicinity of 37 °C. As the temperature is raised, the position of the microemulsion sector gets closer to the water-to-fluorocarbon side of the diagram; i.e., solubilization gets more efficient for higher temperatures. The microemulsion domain is a continuous sector attached to the water corner for temperatures of 25-37 °C; this means that solutions may be diluted without phase separation. At higher temperature (43 °C), the isotropic area transforms into an island very close to the water-to-fluorocarbon side, in complete analogy with the case of hydrogenated compounds.[32,33] At this temperature, solutions cannot be diluted with water or fluorocarbon. The HLB temperature (or PIT) of this system is therefore close to ca. 45 °C, showing a surprisingly high temperature difference between the cloud point of the binary solution of surfactant in water and the PIT of the ternary mixture. Moreover, the two sectorial regions for microemulsions at 25 and 37 °C do not overlap so that a microemulsion obtained at 25 °C cannot be raised to 37 °C and vice versa. A much better situation can be obtained with a few systems, e.g., perfluorodecalin/615/water, for which stable microemulsions have been obtained spanning a temperature range from 10° to 45 °C (Figure 4).

Effects of HLB on Solubilization. Let us consider two systems using the same fluorocarbon, perfluorodecalin, and two detergents which differ only by the length of the hydrophobic chain, e.g., 715 and 615. The microemulsion regions at 37 °C consist of a sectorial corner for the first system (Figure 5) and of an island shifted toward the water-perfluorocarbon axis for the second system. This means that the HLB temperature of the second system is closer to 37 °C and, therefore, that surfactant 715 is less hydrophilic than 615, as expected from the increased length of the hydrophobic moiety of the molecule. With detergent 614 no microemulsion can be obtained at temperatures higher than 20 °C; this shows that this compound is the less hydrophilic of the series. At the other end, surfactant 616 proved to be the more hydrophilic of the series; HLB temperatures for solutions containing 15-20 wt % detergent were found higher than 70 °C, i.e., 60 °C above the lower consolute point of binary aqueous solutions of 614 (see above). Among the series of poly(oxyethylene) surfactants, $C_mF_{2m+1}CH_2(OC_2H_4)_nOH$, only those corresponding to the three combinations of subscripts, $m = 6$ and $n = 5$, and $m = 7$ and $n = 5$ or 6, were convenient for our purposes. We may further classify these three surfactants by considering diagrams such as those of Figure 5 or by simply using the section of the sectorial corner of the microemulsion region by a straight line originating from the fluorocarbon corner, as explained above. Each section, for a given initial surfactant mass fraction, yields two limiting values of the mass fraction of the added fluorocarbon.

Table IV. HLB Values of Surfactants $C_mF_{2m+1}CH_2(OC_2H_4)_nOH$ according to Davies (HLB_D) or Griffin (HLB_G)

m	*n*	HLB_D	HLB_G
6	4	4.52	7.34
6	5	4.85	8.31
6	6	5.18	9.15
7	5	3.98	7.64
7	6	4.31	8.46

The detergents are then arranged in the sequence of increasing values of the concentration ranges thus determined for each system (Table III); this reflects the order of increasing hydrophilicities to be

$$614 < 715 < 615 < 716 < 616$$

Hydrophilicities are also reflected in the HLB values deduced from the formulas of Davies[39]

$$\mathrm{HLB} = 7 - 0.870n - 0.475 + 0.33m + 1.9$$

or of Griffin[53]

$$\mathrm{HLB} = \frac{44.05n + 17}{50 + 50m + 44.05n} \times 20$$

HLB values deduced from Griffin's formula (Table IV) can be arranged along the same sequence as the one reported above, while inversions in the sequence of Davies values are observed for pairs of surfactants containing six or seven fluorinated carbons, thus casting some doubt on the structural increments used in this method (−0.870, −0.870, −0.475, +0.33, and +1.9 for CF_3, CF_2, CH_2, C_2H_4O, and OH groups, respectively). To conclude this section, all these observations are in close agreement with those of Shinoda et al,[26] concerning the behavior of the analogous hydrogenated poly(oxyethylene) surfactants. Another important conclusion is the absolute necessity for using monodisperse surfactants due to the high sensitivity of phase diagrams to relatively small variations of the HLB.

Nature of the Solubilizate. Some interesting conclusions may be drawn from the few data presently available.

(a) The PIT is higher for systems using perfluorodecalin, a cyclic fluorocarbon, than for systems using an open chain C_{10} fluorocarbon. This is illustrated by the fact that stable microemulsions can be obtained at 37 °C with the system H_2O/715/perfluorodecalin and that this is impossible with the system $H_2O/715/C_8F_{17}CH{=}CH_2$. This point is also clear from a comparison of the mean positions of the concentration ranges from the cross sections displayed in Table III (the higher position in the wt % scale corresponding to PIT's closer to 37 °C). Finally, recent experiments[54] show that the PIT's for microemulsions using 8 wt % aqueous solutions of surfactant 614 or 615 or 616 are respectively decreased from 37 to 0 °C, 70 to 30 °C, and 100 to 62 °C when $C_8F_7CH{=}CH_2$ is substituted to perfluorodecalin as the third component.

(b) The presence of an unsaturation seems to be favorable to a higher solubilization of the fluorocarbon, as it results from the comparison of the two systems, $C_8F_{17}CH{=}CH_2$/716/Ringer's lactate and $C_8F_{17}CH_2CH_3$/716/Ringer's lactate. The recent proposal of using perfluorooctylethylene to prepare potential blood substitutes[11] is also convenient in this respect.

(c) Finally, it can be safely extrapolated from these results that any fluorocarbon seems to be able to give rise to a stable microemulsion within convenient temperature and concentration ranges by selecting the appropriate fluorocarbon–fluorinated-surfactant pair.

Effect of Additives. There is yet a necessity for a systematic study of the influence of the addition of electrolytes and macromolecular compounds on the stability of this new class of microemulsions. However, some exploratory experiments clearly demonstrate that there is no fundamental change to the conclusions drawn in the above paragraphs when electrolytic aqueous solutions are substituted to water. This is shown by comparing cross sections for systems using binary 20 wt % mixtures of surfactant 716 (Figure 6 and Table III) with either pure water or Ringer's lactate solution (aqueous solution containing 6 g of NaCl, 3.1 g of sodium lactate, 0.4 g of $CaCl_2$, $6H_2O$, and 0.4 g of KCl per liter) or Plasmion solution (aqueous solution containing 30 g of fluid modified gelatin, 5.38 g of NaCl, 0.14 g of $MgCl_2$, 0.37 g of KCl, and 3.36 g of sodium lactate per liter). As expected from the consideration of the analogous hydrogenated systems, cross sections in the ternary diagrams are shifted toward higher percentages of fluorocarbon with addition of electrolytes, thus showing a decreased apparent hydrophilicity of the surfactant, in line with a depression of the cloud point (themselves reflecting the structure-breaking effects of ions on the water structure). This is also illustrated by the fact that the fluorocarbon–surfactant pair, $C_8F_{17}CH{=}CH_2$/716 may yield stable microemulsions at 37 °C with pure water (in which case PIT > 37 °C) and that this becomes unfeasible when Plasmion is substituted to water (in which case PIT < 37 °C).

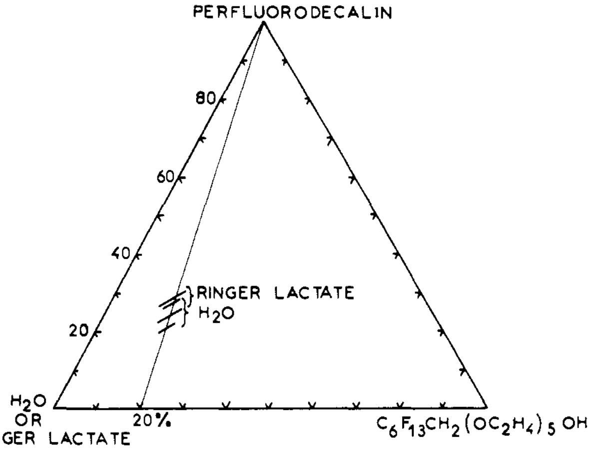

Figure 6. Cross sections of the microemulsion regions in the systems H_2O/perfluorodecalin/$C_6F_{13}CH_2(OC_2H_4)_5OH$ and H_2O/perfluorodecalin/Ringer's lactate solution at 37 °C for a constant 4:1 surfactant-to-water ratio.

Structure of Microemulsions

Neutron scattering is one of the most convenient methods to study the structure of microemulsions which contain particles of 50–500 Å. As far as interparticle effects are negligible, the scattered intensity by a sample containing well-defined monodisperse particles may be written as[45,46]

$$I(\mathrm{q}) = KN_{\mathrm{p}}g^2P_{\mathrm{N}}(\mathrm{q}) \qquad (2)$$

where $g = (Q_{\mathrm{P}} - Q_{\mathrm{W}})V_{\mathrm{p}}$, $P_{\mathrm{N}}(\mathrm{q})$ is the scattering form factor, and K is a calibration constant. In the limit of zero scattering angle, the scattering form factor approaches unity so that

$$I(\mathrm{o}) = KN_{\mathrm{AV}}(Q_{\mathrm{p}} - Q_{\mathrm{W}})^2V_{\mathrm{p}}^2/NM_{\mathrm{S}}V \qquad (3)$$

(introducing eq 1 into eq 2).

The interest of using H_2O–D_2O mixtures in the so-called *variable contrast method* is to be able to continuously vary the scattering length of the solvent between two limiting values, $b_{H_2O} = -0.169$ and $b_{D_2O} = 1.909 \times 10^{-12}$ cm, assuming that the structure of microemulsions remains unchanged to a large extent whatever the deuterium ratio in the aqueous solution may be. A complete extinction of the scattered intensity, $I(\mathrm{o})$, may be obtained when the scattering length density, Q_{W}, of the H_2O–D_2O mixture is made equal to Q_{p}. The occurrence of a sharp extinction involves that all particles exhibit the same Q_{p} value, thus ruling out the presence of droplets of variable composition. If we admit that droplets consist of a fluorocarbon core surrounded by a monolayer of surfactant molecules with a uniform area per polar head, this is equivalent to excluding a broad polydispersity of droplet sizes. On an experimental point of view, sharp extinction is also equivalent to obtaining a perfect linearity in plots of $\epsilon(I(\mathrm{o}))^{1/2}$

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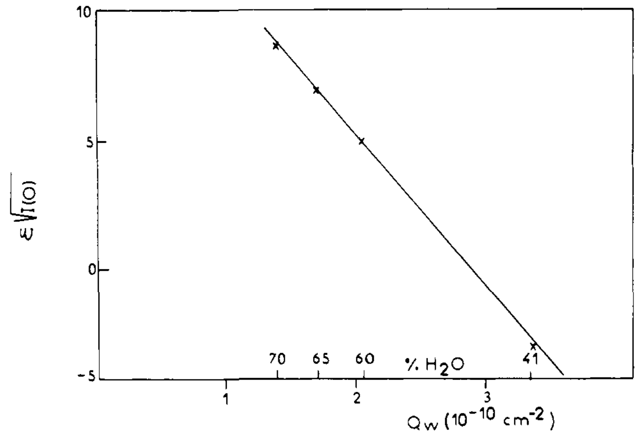


Figure 7. Plot of the square root of zero angle scattered intensity $\epsilon\sqrt{I}(\mathrm{o})$ vs. the scattering length density Q_W of the H_2O-D_2O mixture for the system water/$C_8F_{17}CH{=}CH_2$/$C_7F_{15}CH_2(OC_2H_4)_6OH$ at 25 °C (microemulsion **5** in Figure 10, 7.5 wt % dispersed phase, fluorocarbon and surfactant in the molar ratio α = 2.05).

Table V. Zero Angle Absolute Scattered Intensities and Guinier Apparent Gyration Radii for a Ternary $(H_2O/D_2O)/C_8F_{17}CH{=}CH_2/C_7F_{15}CH_2(OC_2H_4)_6OH$ Solution as a Function of H_2O Weight Percentage in H_2O/D_2O Mixtures (or of the Corresponding Scattering Length Density, Q_W)

H_2O wt %	70	65	60	41
Q_W, 10^{10} cm^{-2}	1.364	1.697	2.033	3.341
I(o)	74	48.5	25.5	94
R_G, Å	67	64	60	96

vs. Q_W (ϵ = 1 or −1, according to whether $Q_p > Q_W$ or $Q_p < Q_W$) which is maintained in the vicinity of $Q_W = Q_p$. This is illustrated in the graph of Figure 7 which is relative to the ternary mixture H_2O/716/$C_8F_{17}CH{=}CH_2$ (see Experimental Section and Tables I and V). The intercept with the Q_W axis yields the scattering length density of the particles, $Q_p = 2.843 \times 10^{10}$ cm^{-2}.

This value is in line with the one expected for a composite particle consisting of a collection of identical surfactant molecules, each one associated with α molecules of fluorocarbon

$$Q_p = N_{Av} b_p / v_p \tag{4}$$

where $b_p = b_S + \alpha b_{FC}$ and $v_p = v_S + \alpha v_{FC}$. Introducing the data of Table I into eq 4 yields $Q_p = 2.810 \times 10^{10}$ cm^{-2}, in excellent agreement with the experimental value quoted above.

The slope of the line in Figure 7 yields the ratio $V_p/N^{1/2}$ and, in turn, the apparent aggregation number N = 2100 ± 100, making the usual assumption that $V_p = Nv_p$. Each droplet may then be pictured as a *fluorinated core* (1) in Scheme II containing the hydrophobic moieties B of ca. 2100 surfactant molecules surrounding a pool of ca. 4300 fluorocarbon molecules, itself surrounded by a concentric *hydrogenated layer* (2) containing the hydrophilic moieties A of 2100 surfactant molecules. Assuming spherical droplets and taking into consideration the molecular volumes reported in Table I allows us to compute the internal radius R_1 = 84.7 Å of the fluorinated core. This corresponds to an average area per polar head, $\sigma = 4\pi R_1^2/N$ = 43 Å^2. A similar computation yields the external radius of the droplets R_2 = 94.4 Å. This value is, however, too small to account for the presence of hydrophilic chains A oriented perpendicular to the inner fluorinated core. Limiting conformations of the poly(oxyethylene) units are meander or zigzag chains[55] whose lengths (L_1 and L_2) may be estimated from bond lengths and bond angles as L_1 = 11 Å and L_2 = 21 Å. This means that the external radius R_2 is comprised between two limiting values of ca. 96 and 106 Å.

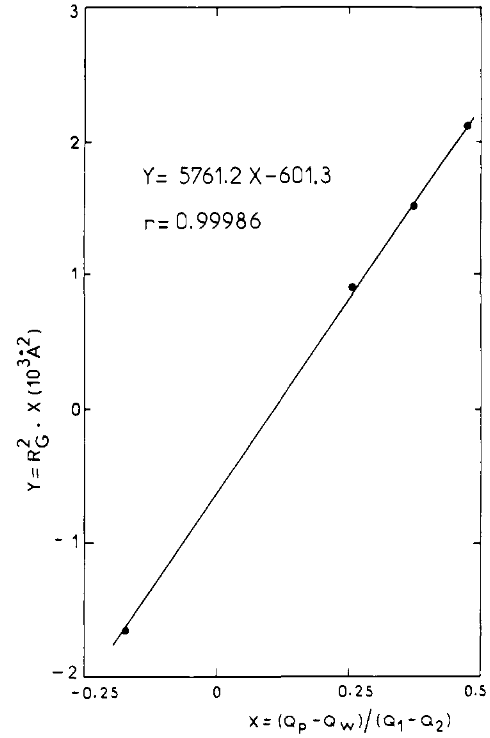
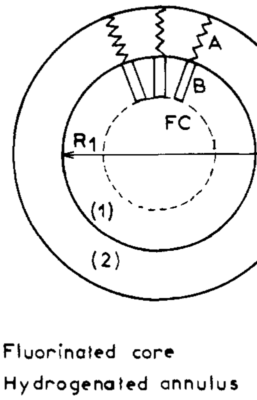


Figure 8. Plot of R_G^2X vs. X ($X = (Q_p - Q_W)/(Q_1 - Q_2)$) (see text) for the same microemulsion as in Figure 7.

Scheme II



These values can be compared with those deduced from Guinier's plots[56] of log I(q) vs. q^2, which yield the apparent gyration radius R_G, as far as interparticle interactions are neglected. For a heterogeneous particle composed of a fluorinated core (1) surrounded by a hydrogenated layer (2), each one with their own molecular volumes (v_1, v_2) and scattering length densities (Q_1, Q_2), R_G can be expressed as[45,46,57,58]

$$R_G^2 = \frac{3}{5}\,\frac{(Q_1 - Q_2)v_1R_1^2 + (Q_2 - Q_W)v_2R_2^2}{(Q_1 - Q_2)v_1 + (Q_2 - Q_W)v_2} \tag{5}$$

where $v_1 = v_B + \alpha v_{FC}$, $v_2 = v_1 + v_A$ (Table I), $Q_1 = (b_B + \alpha b_{FC})/v_1$, and $Q_2 = b_A/v_A$. Equation 5 may be recast under the form[59]

$$Y = R_2^2X + v_1(R^2_1 - R^2_2)/v_2 \tag{6}$$

where $X = (Q_p - Q_W)/(Q_1 - Q_2)$ and $Y = 5R_G^2X/3$. A linear plot of Y vs. X is effectively observed (Figure 8) by using the experimental data of Table V. This allows us to compute R_2 = 98.0 Å from the slope and R_1 = 90.6 Å from the intercept. *These*

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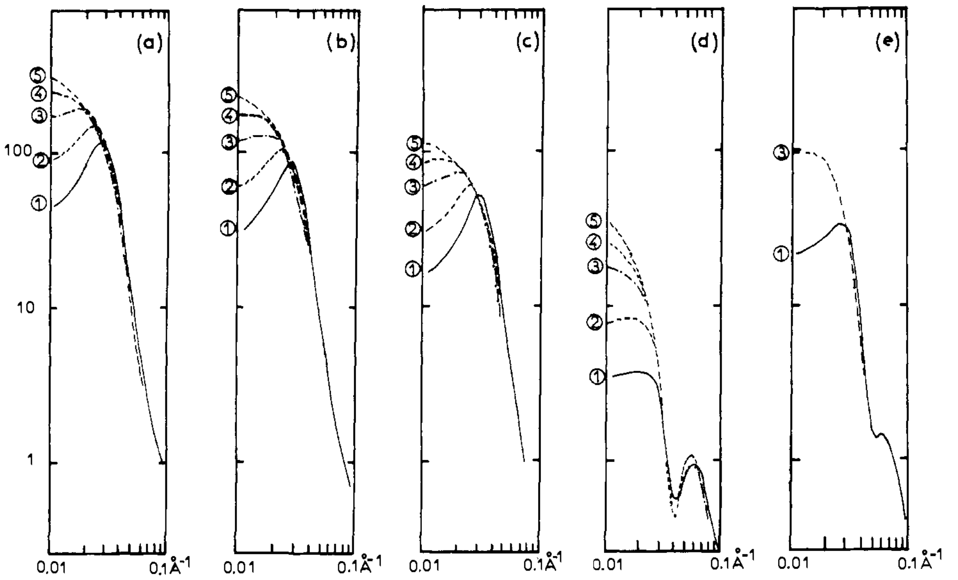

Figure 9. Normalized scattered intensities (I/z_S) in arbitrary units as a function of the scattering vector q, for microemulsions **1**–**5** of Figure 10 at 25 °C and various compositions of the H_2O–D_2O mixtures, H_2O % = 70 (a), 65 (b), 60 (c), 41 (d), and 32 (e). Note the coincidence of all curves for $q > \sim 0.035$ Å^{-1}.

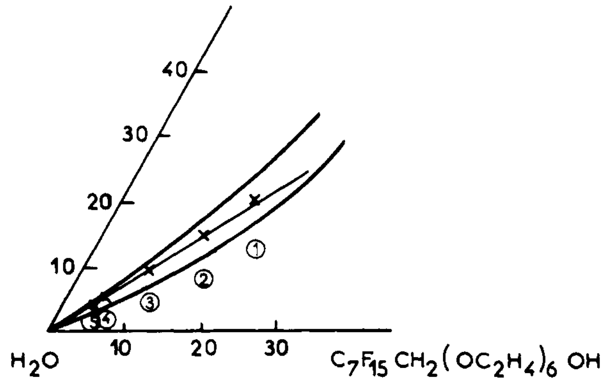

Figure 10. Enlargement of the aqueous corner of the microemulsion sector of the phase diagram of Figure 3 (25 °C) showing the five microemulsions used in neutron-scattering experiments.

two values are in reasonable agreement with those predicted above in spite of nonnegligible interparticle interaction effects on R_G.

In fact, more refined treatments are necessary to take into account the true value of N, the possibility of nonspherical droplets, the insertion of water molecules into the hydrophilic chain, the penetration of fluorocarbon molecules into the surfactant layer, and the existence of various conformations of the hydrophilic and hydrophobic chains of surfactant molecules. The exploration of the so-called intermediate domain ($q > \sim 0.04$ Å) is also necessary to study concentrated solutions where interparticle interactions strongly vitiate the results obtained for zero scattering angle. A salient feature of investigations at higher concentrations is a nearly perfect coincidence of experimental plots of $I(q)/z_S$ vs. q^{-1} in the intermediate q region ($q > 0.035$ Å) (Figure 9) when a concentrated microemulsion is progressively diluted with increasing amounts of a given H_2O–D_2O mixture (Figure 10) whatever the H_2O:D_2O ratio may be. This observation means that *droplets remain approximately identical in size and form on dilution* (at least up to 5 vol % dispersed phase) and that consequently *the conclusions drawn above for the more dilute solution* (7.5 wt % or 5 vol %) *also hold for the more concentrated ones.* These curves may also be compared with theoretical curves so as to adjust all the parameters stated above. Detailed reports on these treatments are deferred to further publications. Let us, however, mention here that the orders of magnitude given for spheroidal droplets are not fundamentally altered in these treatments. Complete analyses of series of curves such as those of Figure 9 are shown in effect to be compatible with aggregation numbers of ca. 2500 and an ellipsoidal form (~200 × 500 Å) of droplets, which also incorporate up to 27 water molecules per surfactant molecule.

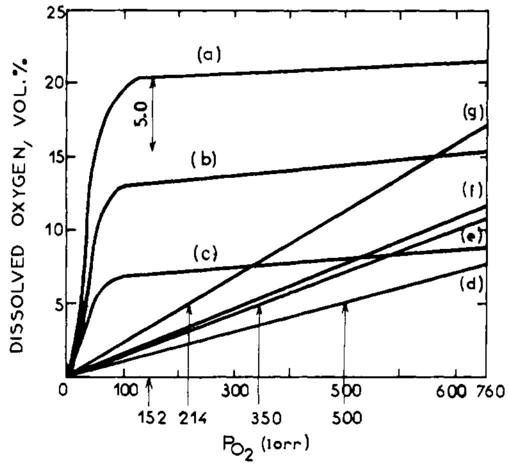

Figure 11. O_2 dissociation curves of whole blood (Hct 45%, curve a) (Hct = haematocrit), diluted blood (Hct 15% and 30%, b and c), Fluosol-DA 20% and 35% (d and e) (from ref 19 and 11), and microemulsions **1** (f) and **4** (g). The oxygen volume (5 vol %) necessary for human breathing is shown for convenience with the corresponding uptake pressure p_{O_2} for whole blood, Fluosol-DA 20% and 35%, and microemulsion **4**.

Solubility of Gases

The solubility of oxygen was determined for two typical microemulsions (**1** and **4** in Table II), prepared from two different surfactants (716 or 715, respectively) and fluorocarbons ($C_8F_{17}CH{=}CH_2$ and perfluorodecalin). The solubility at 37 °C for an oxygen pressure p_{O_2} = 760 torr amounts to 12.2 and 17.7 vol %, respectively, i.e., to 12.2 and 17.7 cm^3 of gaseous oxygen per 100 cm^3 of liquids **1** and **4**. Compared to the solubilities of the pure fluorocarbons (40.6 and 41.7 cm^3, respectively), these values are roughly proportional to the volume fraction of fluorinated substrates (fluorocarbon and hydrophobic moiety of the surfactant) in the liquids, approximately 0.3 and 0.45 for microemulsions **1** and **4**. This shows that the fluorinated core of the microemulsion droplets behaves like a pool of pure fluorinated liquids toward solubilization properties. An important point for practical purposes is *the high content of oxygen dissolved in microemulsion 4, which approaches the solubility in blood (20 vol %)*. This value is clearly larger than those reported for the commercial Fluosol emulsions from the Green Cross Corp.[19]

(Figure 11). It should, however, be recalled that an essential difference between blood and fluorinated liquids lies in the mechanism of dissolution, which is purely physical in the latter case (Henry's law is obeyed) and which results from O_2 binding to hemoglobin in the second case (hence a sigmoid shape of the uptake curve, cf. Figure 11). The uptake and release of oxygen is completely reversible, however, in both blood and fluorinated liquids, and the rate of exchange is very fast as shown by stopped-flow UV experiments.[20,60] As natural blood can release 5 vol % oxygen only in human breathing, this means that a similar release from fluorinated liquids involves an oxygen uptake of 5 vol %. This requires in turn a pressure of oxygen in touch with the liquid of about 500 and 350 torr for Fluosol DA 20% and 35% and of only 214 torr for microemulsion **4**, thus approaching in this case the partial pressure of oxygen in ordinary air (152 torr).

Conclusion

The pure surfactants synthesized in this work have allowed us to show the possibility of obtaining a novel class of true microemulsions (droplets less than 500 Å) using one nonionic surfactant only. These microemulsions are simply prepared by selecting appropriate surfactant-fluorocarbon pairs and mixing them in adequate molar ratio to an aqueous solution. High solubilization of fluorinated compounds are therefore possible, allowing in turn a high solubility of gases in the fluorinated microemulsion. On a fundamental point of view, a novel class of nonionic microemulsions is now available for all those working in this area. The structure of these aqueous microemulsions (in the water-rich region of the ternary-phase diagram) has been greatly elucidated by means of SANS experiments. A vast field of research seems now to be opened concerning the formulation of other fluorinated microemulsions along the lines of this work, the study of ternary-phase diagrams in their entirety with the corresponding structural determinations, and the numerous chemical and biochemical applications of these new materials.

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Registry No. 614, 82695-52-1; 615, 82576-80-5; 616, 82695-53-2; 715, 60331-77-3; 716, 82576-81-6; $C_6F_{13}CH{=}CHC_6F_{13}$, 56523-43-4; $C_8F_{17}C_2H_5$, 77117-48-7; $C_6F_{13}CH{=}CH_2$, 25291-17-2; $C_8F_{17}CH{=}CH_2$, 21652-58-4; $C_{10}F_{18}$, 306-94-5; oxygen, 7782-44-7.

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Microwave Spectra, Electric Dipole Moment, and Molecular Structure of *trans*-1,2-Difluoroethylene Oxide

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Abstract: The microwave spectra of the normal, oxygen-18, dideuterated, and carbon-13 isotopic species of *trans*-1,2-difluoroethylene oxide were assigned to determine the molecular structure. The partial r_s parameters are r(CO) = 1.395 (8) Å, r(CC) = 1.436 (4) Å, r(CH) = 1.098 (4) Å, and r(CF) = 1.363 (4) Å and θ(HCF) = 110.5 (4)° and θ(CCO) = 59.01 (42)°. The electric dipole moment was found to be 1.115 (3) D. The CC and CO ring bonds are shorter in *trans*-1,2-difluoroethylene oxide than in the corresponding cis isomer. However, the CF bond is longer in the trans form than in the cis isomer. The orientation of the HCF moiety with respect to the ring plane is very similar in the two isomers. These results are related to several theoretical studies of the 1,2-difluorocyclopropanes and 1,2-difluoroethylene oxides which predict the effect of fluorine substituents upon the molecular structure and the relative stabilities of the isomer pairs.

A number of experimental[3-5] and theoretical[6,7] studies of fluorinated cyclopropanes have provided data related to the effect of fluorine substitution upon the geometries. While the experimental data base is limited, the theoretical work has explained the observed structural effects[6,7] and also has offered a rationalization of an anomaly in the so-called "cis effect" for the 1,2-difluorocyclopropanes.[7] In this case, the trans isomer is more stable than the cis form[8] in spite of the fact that in the related unsaturated pair, 1,2-difluoroethylene, the cis form is more stable than the trans.[9]

Considerably less is known about the effect of fluorine substitution upon the structures of fluorinated oxiranes. A microwave study of the previously unknown compound, *cis*-1,2-difluoroethylene oxide, provided the first experimental structure of a fluorinated oxirane.[10] Recently, the geometry of perfluoroethylene oxide was determined by employing microwave techniques.[11] Both the CC and CO ring bonds in these oxiranes shorten relative to ethylene oxide.[10,11] These results are in contrast to theoretical predictions for 1,2-difluorocyclopropanes and 1,1,2,2-tetra-

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