

chemical shifts, the frequencies of the asymmetric CO stretches $\bar{\nu}_{\text{CO}}(f_{1u})$ are given in Table 1, because Raman spectra have so far not been reported for the two carbonylate anions. For the remaining four molecular species from $[\text{W}(\text{CO})_6]$ to $[\text{Ir}(\text{CO})_6]^{3+}$ complete vibrational data are available.^[10, 20–23]

The trend shown by the f_{1u} vibrations, that the CO bond strength increases with increasing formal charge of the metal, is quantified by the increasing stretching force constants f_{CO} (Table 1). The value of the force constant for $[\text{Ir}(\text{CO})_6]^{3+}$ ($20.8 \times 10^2 \text{ Nm}^{-1}$) is only slightly below that for $[\text{Hg}(\text{CO})_2]^{2+}$ ($21.0 \times 10^2 \text{ Nm}^{-1}$)^[12] and that for HCO^+ ($21.3 \times 10^2 \text{ Nm}^{-1}$).^[5] The ^{13}C chemical shift of $\delta = 121$ is the lowest that has been measured for carbonyl complexes. The rather smooth trend in both $\bar{\nu}_{\text{CO}}(f_{1u})$ and ^{13}C chemical shifts illustrates that for the six isostructural and isoelectronic (d^6) $[\text{M}(\text{CO})_6]$ species π back donation gradually decreases with a concomitant increase in σ donation as the formal charge on the metal gradually increases from -2 to $+3$. For $[\text{Ir}(\text{CO})_6]^{3+}$, π back bonding makes only a small, insignificant contribution to the Ir–CO bonding. A similar correlation can be made for carbonyl derivatives of iridium where $\bar{\nu}_{\text{CO}}$ for terminal CO groups increases from 1642 cm^{-1} for $[\text{Ir}(\text{CO})_3]^{3-}$ ^[4] to 2295 cm^{-1} for the a_{1g} mode of $[\text{Ir}(\text{CO})_6]^{3+}$. Both trends clearly demonstrate the great versatility of the CO ligand, which coordinates to metallic centers of formal charges from -3 to $+3$ form stable metal carbonyl species.

As more cationic carbonyl complexes like $[\text{M}(\text{CO})_6]^{2+}$ ($\text{M} = \text{Ru}, \text{Os}$)^[10], $[\text{Ir}(\text{CO})_5\text{Cl}]^{2+}$, and $[\text{Ir}(\text{CO})_6]^{3+}$ become known, together with accurate structural and vibrational data, and as smooth correlations between the formal charge on the metal and the bonding characteristics in the CO ligands emerge, it becomes increasingly obvious that any arbitrary subdivision using vague terms like “classical” and “nonclassical (σ -only)” carbonyl complexes as proposed sometime ago for the thermally unstable $[\text{Ag}(\text{CO})_n]^+$ ($n = 1, 2$) species^[24] is incorrect, inappropriate, and unnecessary. The first metal carbonyl derivative $[\text{Pt}(\text{CO})_2\text{Cl}_2]$ reported in 1868^[25] with an average $\bar{\nu}_{\text{CO}}$ value of 2175 cm^{-1} [well above that (2143 cm^{-1}) for free CO ^[26]] would be assigned “nonclassical”, which is in our view absurd.

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Achieving Stable, Reverse Water-in-Fluorocarbon Emulsions**

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Macroemulsions are thermodynamically unstable systems that tend to separate irreversibly into the component phases upon aging. Their kinetic stability can, however, be increased by counteracting the processes by which they break down, that is, coalescence and molecular diffusion (Ostwald ripening).^[1] Preparing stable water-in-fluorocarbon “reverse” emulsions is a stimulating challenge from both fundamental and applied standpoints.

Fluorocarbons are unique due to the extreme position of fluorine in the Periodic Table.^[2] Liquid fluorocarbons display very

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weak intermolecular (van der Waals) interactions, and this results in the lowest possible associative character.^[3] Water-in-fluorocarbon emulsions are thus a most unnatural combination of the least associated of liquids with one of the most strongly associated ones. Their formation and stabilization presuppose that very high interfacial tensions have been overcome.

Molecular diffusion was shown to be the predominant mechanism of particle size increase in direct, fluorocarbon-in-water emulsions.^[4] We have now found that the same mechanism is effective for water-in-fluorocarbon emulsions. According to the Lifshitz–Slyozov equation [Eq. (a)]^[5] that describes this

$$v = d(\bar{a}^3)/dt = 8\gamma_i CDV_m/9RT \quad (a)$$

mechanism, the rate v of particle volume increase (\bar{a} = average radius of the particle) over time t through molecular diffusion is proportional to the molar volume of the dispersed phase (V_m), to the interfacial tension γ_i between continuous and dispersed phase, and to the solubility and diffusivity coefficients (C and D) of the dispersed phase in the continuous phase.

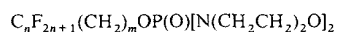
Molecular diffusion of water through the continuous fluorocarbon phase in a reverse water-in-fluorocarbon emulsion is expected to be faster than that of the same fluorocarbon through water, on two accounts: 1) although no data appear to be available on mutual solubilities of water and fluorocarbons, water should be more soluble in the fluorocarbon than vice versa because of its smaller molar volume and the easier formation of holes capable of hosting the water molecules in the loosely associated fluorocarbon. According to Hildebrand's theory, the solubility of water in a fluorocarbon is actually expected to be higher by several orders of magnitude than that of the same fluorocarbon in water, as it varies exponentially with the molar volume.^[6] 2) The diffusivity of water in the fluorocarbon should also be larger than that of the fluorocarbon in water as indicated by the Hayduk–Laudie equation, although the difference is not expected to be as great.^[7] Coalescence of water droplets in a fluorocarbon phase should be favored by the large difference in densities and by the higher fluidity of the fluorocarbons utilized here relative to that of water.

In spite of these unfavorable premises we have prepared stable water-in-fluorocarbon emulsions with submicrometer particles and a narrow size distribution. The key to meeting this challenge lay in the selection of an effective surfactant system. Because the continuous phase is fluorinated, the surfactant needs to have definite affinity for fluorocarbons, and hence needs to be fluorinated. A number of single- and double-chain perfluoroalkyl surfactants, among those that have been synthesized in this laboratory in recent years,^[8] were therefore screened. Their modular molecular design allows stepwise modifications of their hydrophilic, lipophilic, and fluorophilic properties, which, in turn, have a considerable impact on their ability to form and stabilize colloidal systems.

Potential applications of reverse fluorocarbon emulsions can be envisaged in pulmonary administration of drugs and other agents. The agents to be delivered (which include surfactants, antibodies, antioxidants, steroids, nucleic acids, vasoactive agents, and cytotoxic drugs) are usually insoluble in fluorocarbons in significant amounts. Contrary to the presently investigated dispersions of micronized solid drugs in liquid fluorocarbons,^[9] water-in-fluorocarbon emulsions should allow uniform, reproducible distribution of the agents, including to the deeper parts of the lungs; this presupposes, however, that emulsion stability has been achieved. Controlled release and reduced toxicity are also expected; in the hydrocarbon series, for example, water-in-oil emulsions of doxorubicin that allowed

controlled delivery of the drug have been prepared, and fewer side-effects were experienced than with dispersions of solids.^[10]

Perfluorooctyl bromide and perfluorooctylethane were chosen for this study, because they satisfy the criteria required for liquid breathing, a procedure investigated for treatment of acute respiratory distress. The former compound is in Phase II/III clinical trials for this procedure;^[11] its fluorocarbon-in-water emulsions are in Phase II clinical trials as injectable oxygen carriers (blood substitutes).^[12] The emulsifying agent utilized for the reverse fluorocarbon emulsions was eventually selected from a homologous series of fluorinated surfactants (FnCmDMP) derived from dimorpholinophosphate.^[13]



FnCmDMP; $n = 4, 6, 8, 10$ and $m = 2, 5, 11$

FnCmDMP are indeed highly fluorophilic; the potential for spontaneous formation of membranes with low curvature is indicated by the presence of elongated rather than spherical self-assemblies when dispersed in water.^[14] Various spacer (m) and fluorocarbon chain lengths (n) were investigated. The best results, that is, the obtention of stable emulsions with small droplet size and long shelf-life, were achieved with F8C11DMP. It is noteworthy that no stable reverse emulsions could be prepared with the phospholipids used to prepare direct fluorocarbon-in-water emulsions, nor with the hydrocarbon dimorpholinophosphate $C_{15}H_{31}OP(O)[N(CH_2CH_2)_2O]_2$.

The preparation of the reverse fluorocarbon emulsions involved first the dispersion of the perfluoroalkylated surfactant in the fluorocarbon, followed by the addition of the aqueous phase, which may contain an active component. Emulsification was initiated with a low-energy mixer and completed with a high-pressure mechanical homogenizer. A series of water-in-fluorocarbon emulsions was thus prepared with water contents ranging from 1 to 30% v/v.

A typical example of a reverse emulsion containing perfluorooctyl bromide (95% v/v), NaCl (2.5% solution in water; 5% v/v), and F8C11DMP (2% w/v) was prepared as follows: F8C11DMP (40 mg) was dispersed in perfluorooctyl bromide (1.9 mL) by gentle stirring. The aqueous 2.5% solution of NaCl (0.1 mL) was added to the fluorocarbon phase, and the mixture was shaken by hand. The resulting coarse pre-emulsion was homogenized under high pressure (Emulsiflex B3, Avestin, 4.1×10^7 Pa, 12 cycles); the temperature was maintained below 40 °C.

The final emulsion was highly fluid and bluish. The average particle diameter, as measured by photosedimentation (Horiba Capa 700) immediately after preparation, was $0.15 \pm 0.01 \mu\text{m}$; this emulsion was stable enough to withstand heat sterilization conditions (121 °C, 15 min, 15 N m^{-2}) without significant particle size increase ($0.16 \pm 0.02 \mu\text{m}$). As an alternative, the emulsion can also be filtered through a $0.22 \mu\text{m}$ sterilizing membrane without detectable change ($0.15 \pm 0.01 \mu\text{m}$). The reverse nature of the water-in-fluorocarbon emulsion is unequivocally supported by the high fluidity (comparable to that of the fluorocarbon), by the absence of electrical conduction, and by the fact that the emulsions can easily be diluted with a fluorocarbon but not with water. The possibility of having reverse surfactant vesicles was excluded by an epifluorescence microscopy experiment in which 5,6-carboxyfluorescein was incorporated into the aqueous phase ($2 \times 10^{-3} \text{ M}$); it clearly showed uniformly fluorescent droplets rather than the fluorescent rim that was seen in the case of reverse vesicles.^[15] Furthermore, as much as 30% by weight (45% by volume) of water can be incorporated into our reverse emulsions, with a surfactant/water ratio as low as 0.03

by weight, which is definitely incompatible with the formation of reverse vesicles.

The shelf stability of the reverse fluorocarbon emulsions was monitored at 25 °C by photosedimentation. After about 4.5 months, the average particle diameter of the above emulsion was still only $0.27 \pm 0.02 \mu\text{m}$, and the particle size distribution remained reasonably narrow as shown in Figure 1. That the

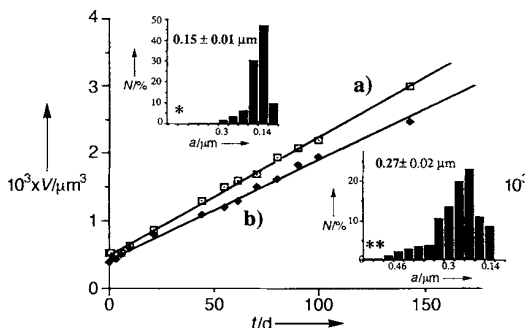


Fig. 1. Linear variation with time of the average volume V of water droplets at 25 °C in a reverse water-in-fluorocarbon emulsion (95% v/v perfluorooctyl bromide, 5% v/v saline, 2% (perfluorooctyl)undecyldimorpholinophosphate F8C11DMP) after heating at 121 °C for 15 min (a) and after filtration on a 0.22 μm sterilizing membrane (b). Insets: Size distribution histograms measured for the heated emulsion immediately after preparation (*) and after 140 days at 25 °C (**). N = percentage of particles with radius a . The quoted values give the average radii \bar{a} .

mechanism of particle growth in reverse fluorocarbon emulsions is molecular diffusion is strongly indicated by the following findings: a) the average volume of the water droplets increases linearly with time, as seen in Figure 1 for both heated and filtered emulsions; b) the distribution function, that is, the ratio a_i/\bar{a} of particle radius a_i to the mean radius \bar{a} , is time-invariant;^[4, 5] and c) the addition of NaCl contributes to stabilizing the emulsions by reducing the solubility of water in the fluorocarbon.

A series of drugs, including antibiotics (doxycycline, gentamycin, erythromycin), vasoactive bronchodilators (epinephrine, tolazoline), mucolytic agents (acetyl cysteine), antituberculosis agents (ethambutol, pyrazinamide), cholinergic (acetylcholine chloride), glucocorticoid (prednisone), and anti-tumor agents (cyclophosphamide), could be incorporated into such reverse fluorocarbon emulsions without inducing significant loss of stability.

For example, a reverse fluorocarbon emulsion otherwise formulated as in the example given above was prepared by adding 0.1 mL (5% v/v) of an aqueous solution of tolazoline (3% w/v in a 2.5% aqueous solution of NaCl). The average particle size, as measured by photosedimentation was 0.15 μm after preparation, 0.17 μm after heat-sterilization, and 0.23 μm after a month at 25 °C.

Preliminary toxicity data on water-in-fluorocarbon emulsions are encouraging. Intravenous administration of a dispersion of F8C11DMP in NaCl (0.9% solution) showed no acute toxicity at concentrations as high as 2 g kg^{-1} body weight in mice (limit of protocol; all ten animals treated survived) indicating an i.v. LD₅₀ value greater than 2 g kg^{-1} . Intraperitoneal administration of the same compound dispersed in perfluorooctyl bromide yielded an i.p. LD₅₀ value around 4 g kg^{-1} . In the case of F8C2DMP all ten animals survived a 2 g kg^{-1} body weight dose i.p. No hemolytic activity was detected either for these surfactants. A reverse emulsion (perfluorooctyl bromide,

95% v/v; NaCl 0.9% in water, 5% v/v; F8C11DMP, 1% w/v) was injected intraperitoneally into 10 mice (25 mL kg^{-1} body weight); after one month all the animals were still alive; no significant perturbation in their growth or behavior was observed during this period.

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