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SOLUBILITY OF FLUOROCARBONS IN WATER AS A KEY PARAMETER DETERMINING FLUOROCARBON EMULSION STABILITY

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SUMMARY

The kinetics of particle size growth in emulsions of 14 fluorocarbons has been studied by means of photon correlation spectroscopy. It was assumed that Ostwald ripening is the mechanism of emulsion coarsening with time; solubility of fluorocarbons in water (about 10^{-6}– 10^{-10} ml/ml) being the key parameter determining fluorocarbon emulsion stabilities. The solubilities of fluorocarbons in water were calculated from the Ostwald ripening kinetics data and a solubility-fluorocarbon structure relationship was established. In a homologous series of normal chain fluorocarbons the solubility in water decreased by a factor of ~8.0 for each $-CF_2-$ group. For a given carbon number, ring formation and branching increased water solubility of the fluorocarbons. A correlation between fluorocarbon solubility in water and solvent cavity surface area was found which allows prediction of the fluorocarbon emulsion stability from the structure of the fluorocarbon.

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INTRODUCTION

It is well known that fluorocarbons (fully fluorinated hydrocarbons, tertiary amines and ethers) possess very low water solubility [1]. The detection limit of the conventional methods for determining solubilities ($\sim 10^{-7}$ ml/ml [2]) is already reached for the light liquid fluorocarbons; the only fluorocarbon with a known solubility value is gaseous tetrafluoromethane [1]. No attempts have been made to determine water solubilities of fluorocarbons by means of new GLPC based methods [3].

Theoretical estimations demonstrate that solubilities of organic liquids in water at a considerably lower level (up to $\sim 10^{-11}$ml/ml) determine submicron emulsion stability to so-called Ostwald ripening [4,5]. Ostwald ripening process arises as a consequence of Kelvin effect [6]. According to the Kelvin equation, smaller particles possess higher solubility in a given medium than larger ones:

$$\ln(C_{a}/C_{A}) = \frac{2\sigma V_{m}}{RT} (1/a - 1/A) \qquad (1)$$

where σ is the interfacial tension, V_m is the molar volume of a substance, a and A are the radii of the particles (a < A), C_a and C_A are solubilities of corresponding droplets in the medium. In a polydisperse system, because of the Kelvin effect smaller particles will dissolve (up to complete disappearance) and larger ones will grow in size at their expense. The possibility of this process was first indicated by Ostwald [7]; later the process was called Ostwald ripening.

The theory of the Ostwald ripening kinetics was proposed in modern form by Lifshitz and Slesov [8] and has been developed recently [9]. Estimates on the basis of the theory demonstrate that although a solubility increase due to the Kelvin effect is comparatively small (for submicron droplets the relative increase of the solubility is ~ 1%), the Ostwald ripening is sensitive to very low solubility values up to $C \sim 10^{-11}$ ml/ml.

The theory of Ostwald ripening allows one to calculate the rate of increase of the mean particle size in a system when some physical parameters of the emulsion are known (as has been mentioned before, it is essential to know the disperse phase solubility in the medium for this calculation). Recently [4,5] for hydrocarbon-in-water emulsions it has been demonstrated that the calculations with known solubility values [2,3] give the rates of particle size growth in the systems which are in fair agreement with experiment. Conversely, if the kinetics of the particle size growth in emulsions due to Ostwald ripening are known, the corresponding solubility values can be calculated. Therefore, the calculation of the solubility values from the particle size growth in emulsions can be considered as a method of solubility measurements with a very low detection limit.

There are some indications that the mechanism of coarsening with time of fluorocarbon emulsions-blood substitutes is Ostwald ripening [10-14]. According to our previous work [12], we believe that "insolubility" of fluorocarbons in water is not an arguement against the possibility of Ostwald ripening in these systems. Considerably lower solubility values ($\sim 10^{-8}$ -10^{-11} ml/ml) than those detected by GLPC would be sufficient for the observed Ostwald ripening rates in these systems.

In the present work it was assumed that the mechanism of emulsion coarsening with time is Ostwald ripening. Kinetics of particle size growth in emulsions of 14 fluorocarbons was studied and corresponding water solubilities were calculated from the kinetic data. The fluorocarbon structure/water solubility relationship was analyzed in terms of the solution theory model [15] proposed earlier for aqueous solutions of hydrocarbons . The results obtained allow us to evaluate water solubility of fluorocarbons (and the corresponding emulsion stability) on the basis of the molecular structure of fluorocarbons, including compounds that have not yet been synthesized .The correlation proposed can be applied to screening of fluorocarbons for their use as components of fluorocarbon emulsions-blood substitutes.

EXPERIMENTAL

Materials

Perfluoro-1-methyl-4-isopropylcyclohexane,perfluoro-1-methyl-4-tert-butylcyclohexane, and perfluorotricyclo[3.3.0.0]^{2,6}octane were synthesized according to methods published earlier [16,17]. All the other fluorocarbons: perfluoro-n-pentane, perfluoro-n-hexane, perfluoro-n-heptane, perfluoro-n-octane, perfluoro-2-methylpentane, perfluoro-2-methyl-3-isopropylpentane, perfluorodecalin, perfluoromethylcyclohexane, perfluoro-1,3- dimethylcyclohexane,perfluorotriethylamine, perfluorotripropylamine were commercially available products. Dialkylsubstituted cyclohexanes and perfluorodecalin were mixtures of trans- and cis- isomers. The purity of fluorocarbons and the relative amounts of isomers in mixtures were determined by GLPC. Column Carbopack H10612 (Supelco), l=2m, at T = 120÷200 C was used. Under these conditions complete resolution for cis- and trans- perfluorodecalin isomers and partial resolution of dialkylsubstituted perfluorocyclohexanes was attained.

Sodium dodecyl sulfate was synthesized according to [18] from chromatographically pure dodecanol. Then it was Soxhlet extracted with n-hexane to remove dodecyl alcohol after which it was twice recrystallised from doubly distilled water. An interfacial tension isotherm of SDS at the air-water interface was found to be close to the literature curve [19]. The Krafft point of the purified SDS (16^{o}C) coincided with the known value [20].

Doubly distilled deionized water with theoretical values of interfacial tension (71.8 dyne/cm) and electroconductivity (<3 10^{-6}Ohm^{-1}cm^{-1}) was used.

Methods

Emulsion preparation. The emulsions of fluorocarbons in 0.1M SDS solution with a volume fraction of the disperse phase ϕ = 0.1 were prepared ultrasonically by means of a dispergator - 'Sonicator W-375' (Heat Systems-Ultrasonics).The emulsions were sonicated in the pulse mode for 10 minutes (the working cycle amounting to 50%). In the preparation process cuvette containing an emulsion was cooled to a temperature of about~10^{o}C. For perfluorotricyclo-octane (melting point ~40^{o}C) the cuvette was heated up to ~60^{o}C and the dispersion was prepared in the same way as for all the other fluorocarbons. Just after preparation, the initial particle diameter in emulsions of all fluorocarbons was in the range from 67 to 148 nm except for perfluoro-n-pentane (211nm) and perfluorotricyclo-octane (440nm), see Table 1.

Particle size analysis and Ostwald ripening kinetic studies. The particle size analysis of emulsions was performed by means of a photon correlation spectrometer "Coulter N-4", model 9.2 (Coultronics).The scattering angle was $\theta = 90^{\circ}$. For processing of the correlation data the cumulants method was used [21] allowing determination of the mean diameter of the particles $\bar{d}_{inst}$ and polydispersity equal to the ratio of a variance to squared mean value for the decay time constant Γ: $\mu = \langle\Gamma^2\rangle/\langle\Gamma\rangle^2 - 1$.

The Ostwald ripening kinetics of fluorocarbon emulsions in 0.1M SDS solution was studied as follows. A 1-10 μl sample of the emulsion was diluted with 3 ml of water in a measuring cuvette; thereafter a particle size was measured for one minute. At appropriate time intervals samples of the emulsion were taken off and subsequent particle size measurements were done. The time interval between the dilution of the emulsion and the end of the measurement was kept constant (2 min).

The kinetics of the particle size growth were observed until the mean value of the diameter $\bar{d}_{inst}$ =200 nm was attained. For emulsions of different fluorocarbons this process required from several minutes to several months. For an emulsion of perfluoro-n-pentane and a dispersion of perfluorotricyclo-octane the Ostwald ripening rate was so high that at the moment of the first measurement of the particle size, $\bar{d}_{inst}$ was greater than 200 nm. For these systems the kinetics of particle size growth was observed until the value $\bar{d}_{inst}$=600 nm was reached. In this case the scattering angle was $\theta=29.7^{\circ}$.

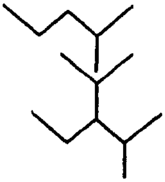
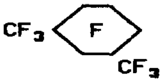
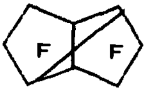
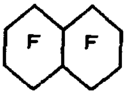
Additional details of the kinetic experiment (i.e. influence of the surfactant concentration on Ostwald ripening) will be published elsewhere.

In the course of the kinetic experiments sedimentation of the emulsions was negligible.

Interfacial tensions at the fluorocarbon-water and fluorocarbon-0.01M SDS solution interface were measured by the De Nyu

TABLE 1

Particle size data of fluorocarbon emulsions at 25°C

Fluorocarbon	Number (Fig.2)	Initial mean particle size, nm	Ostwald ripening rate, sm^3/s
$n\text{-}C_5F_{12}$	I	211	$1.4\cdot10^{-18}$
$n\text{-}C_6F_{14}$	II	104	$1.3\cdot10^{-19}$
$n\text{-}C_7F_{16}$		91.2	$1.7\cdot10^{-20}$
$n\text{-}C_8F_{18}$		67	$2.5\cdot10^{-21}$
	III	139	$2.1\cdot10^{-19}$
		89	$1,6\cdot10^{-21}$
	IV	148	$2\ 6\cdot10^{-19}$
	V	118	$3.6\cdot10^{-20}$
	VI	85.6	$1.4\cdot10^{-21}$
	VII	97.5	$3.6\cdot10^{-22}$
	VIII	440	$6.0\cdot10^{-19}$
	IX	121	$5.3\cdot10^{-21}$
$N(C_2F_5)_3$	X	93.4	$5.7\cdot10^{-20}$
$N(C_3F_7)_3$		86	$1.9\cdot10^{-22}$

method using a Fisher tensiometer; experimental error was ±1mN/m. All the fluorocarbons were passed repeatedly through a column of alumina before their use in interfacial tension measurements.

All the experiments were at 25±1°C.

Calculations of water solubilities of fluorocarbons from Ostwald ripening rates For calculations of the solubility C, ml/ml, the Lifshitz-Slesov equation with a correction coefficient $\gamma(\phi)$ taking into account the diffusional interaction of the particles at finite values of ϕ was used [9]:

$$C = \frac{9RT\omega}{8\sigma V_m D} \gamma(\phi)^{-1} K^{-3} \qquad (2)$$

where $\omega = \frac{d}{dt}(\bar{a}_{inst})^3 = \frac{1d}{8dt}(\bar{d}_{inst})^3$ is the Ostwald ripening rate, determined by straightening of the dependence of mean particle radius $\bar{a}_{inst}$ (or mean particle diameter $\bar{d}_{inst}$) on time in cubic coordinates, D is the diffusivity of the disperse phase substance in the medium, K is the ratio of an instrumental mean diameter $\bar{d}_{inst}$ determined by the cumulants method to its number average value. Calculations for a stationary size distribution function at $\phi = 0.1$ [9] analogous to ones carried out in [22] demonstrated that K ~1.18 for $\bar{d}_{inst} < 200$ nm.

The correction coefficient $\gamma(\phi)$ was assumed to be equal to $\approx$ 1.75 for $\phi = 0.1$ [9]. Diffusivities D were calculated with the Hayduk-Laudie equation [23] on the basis of the molar volume of hydrocarbons and viscosity of 0.1M SDS solution at 25°C η equal to 1.04 cP:

$$D = 13.26 \cdot 10^{-5} \cdot \eta^{-1.14} \cdot V_m^{-0.589}$$

Interfacial tensions were assumed to be equal to the values when the SDS concentration is equal to the CMC. Estimations of the depletion of the SDS solution due to adsorption at the hydrocarbon-water interface demonstrated that if a surface area per SDS molecule A = 50Å^2 [18] was assumed, a maximum depletion of the SDS solution in our experiments was equal to 0.03M , so the concentration of SDS in all our experiments remained greater than CMC (equal to 0.0082M [19]).

The accuracy of the estimations of the solubilities with the Eq (2) is fairly low. For aliphatic hydrocarbons the calculations would give an exaggeration of ~2.5 times by comparison with values measured by GLPC [4]. This exaggeration could be related to the Brownian motion of particles which was not accounted for in Ostwald ripening theories [8,9]. We believe that Eq (2) can predict relative changes of the solubility values (i.e. in homologous series) with a considerably greater accuracy (~30%).

Solvent cavities were calculated using the program [24]. For fluorocarbons possessing several conformations and/or having several steric isomers calculations were made for all the possible structures and averaging was performed as in [15]. Details of calculations will be published elsewhere.

RESULTS AND DISCUSSION

Interfacial tensions at the fluorocarbon-water and fluorocarbon-0.01M SDS solution interface (a slightly higher concentration than the CMC point of SDS) are presented in **Table 2**. For perfluoro-n-hexane, n-heptane and n-octane interfacial tensions at the fluorocarbons-water interface coincided with values known in the literature [25] within the limits of experimental error.

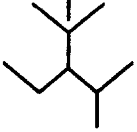
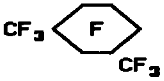
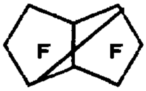
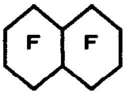
During the whole kinetic experiment all the emulsions possessed high and approximately constant monodispersity: μ = 0.04±0.02. For all the fluorocarbon emulsions the dependence of the mean particle diameter on time was readily linearized in the $\bar{d}^3_{inst}$ versus t coordinates, see Fig.1.

Using the least squares method, Ostwald ripening rates were calculated from the slopes of the corresponding lines and water solubilities of fluorocarbons were calculated, see **Tables 1 and 2**.

It is apparent that the values obtained are very low: S = $10^{-6} \div 10^{-10}$ mol/l. In homologous series of non-branched fluorocarbons, the solubility is lowered by a factor of ~8.0 for each $-CF_2-$ group, i.e. the increment of the free energy of dissolution $\Delta G^o = -RT\ln S$ is equal to ~5.05 kJ/mol for each added

TABLE 2

Physical properties of fluorocarbons at 25°C

Fluorocarbon	Purity,% (cis/trans)	S,mol/l	σ, mN/m SDS	σ, mN/m H_2O	TSA, $\AA^2$	Vm, cm^3/mol
n-C_5F_{12}	98	$4.0\circ10^{-6}$	18	55	335.8	177^4
n-C_6F_{14}	99	$2.7\circ10^{-7}$	20	55 $(56.1)^3$	372.5	201^4
n-C_7F_{16}	>99	$3.1\circ10^{-8}$	20	55 $(56.1)^3$	-	224^4
n-C_8F_{18}	>99	$3.8\circ10^{-9}$	20	56 $(56.0)^3$	-	253^4
	97	$5.0\circ10^{-7}$	18	56	357.5	201
	97	$2.5\circ10^{-9}$	19	55	-	255
	97	$6.7\circ10^{-7}$	17	54	356.8	197^4
	73(50/50)^1	$7.7\circ10^{-8}$	18	54	377.5	216
	>99(28/72)	$2.2\circ10^{-9}$	19^2	$-^2$	436.7	253
	>99(14/86)	$5.1\circ10^{-10}$	19	57	444.9	280
	>99	$2.2\circ10^{-6}$	18^2	$-^2$	364.6	144
	95(50/50)	$9.9\circ10^{-9}$	18	55	408.8	238
$N(C_2F_5)_3$	>99	$1.2\circ10^{-7}$	18	53	373.6	214
$N(C_3F_7)_3$	94	$2.8\circ10^{-10}$	18^2	-	-	285

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[1] impurity - mixture of 1,2- and 1,4- isomers.
[2] for these compounds the available amount was not sufficient for interfacial tension measurements. The data presented are approximations. [3] [25] [4] [26].

TABLE 3

Fluorocarbon structure - water solubility correlation

Element of structure		Water solubility
Carbon number		↘ 8.0 times
At the same carbon number:	tertiary branching	↗ 1.6 times
	quaternary branching	↗ 4.0 times
	six-membered ring	↗ 6.8 times
	nitrogen (tertiary amines)	↘ 2.0 times

$-CF_2-$group. Thus, in terms of hydrophobicity, $-CF_2-$ group is equivalent to ~1.75 $-CH_2-$ groups. Rings and branching in fluorocarbon structures (for the same carbon number) increase water solubility of fluorocarbons. Actually, the presence of a six membered ring increases solubility ~6.8 times; tertiary branching ~1.6 times; quaternary branching - ~4.0 times, see **Table** 3.

These results are in good agreement with GLB studies of fluorinated surfactants. According to [27,28], the increment of the free energy of dissolution is equal to 5.27-5.37 kJ/mol for each added $-CF_2-$ group and branching decreases fluorocarbon 'tail' hydrophobicity.

The presence of a nitrogen atom in the fluorocarbon structure leads to slight (~2 times) decrease in fluorocarbon solubility in comparison with normal chain fluorocarbons possessing the same carbon number. This is a specific feature of perfluorinated amines; it is well known that non-perfluorinated tertiary amines have much higher solubilities than the corresponding hydrocarbons.

Increase in water solubility in the presence of rings and branching of solute molecules has been demonstrated earlier for saturated hydrocarbons [2]. This effect can be explained in terms of a model relating water solubility to the surface area of the solvent cavity large enough to accommodate the solute molecule [15,24]. It has been found that the same linear

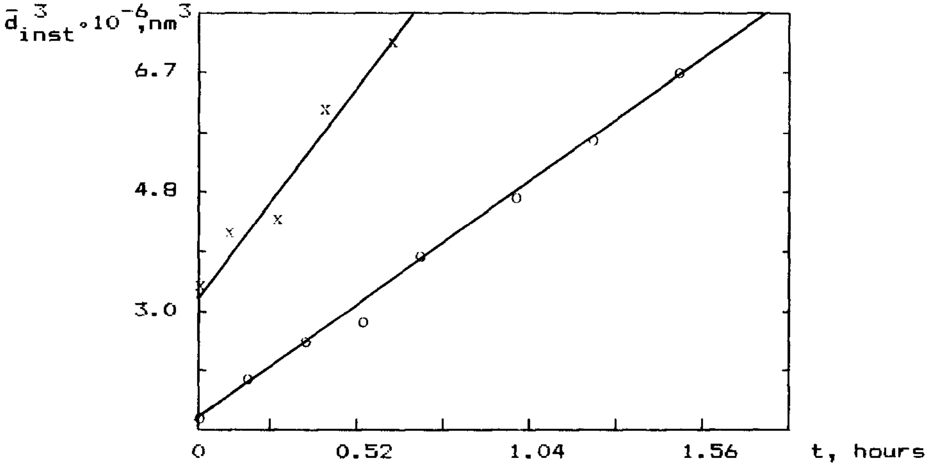

Fig. 1. Kinetics of Ostwald ripening in fluorocarbon emulsions. o perfluoro-n-hexane; x - perfluoromethylcyclohexane.

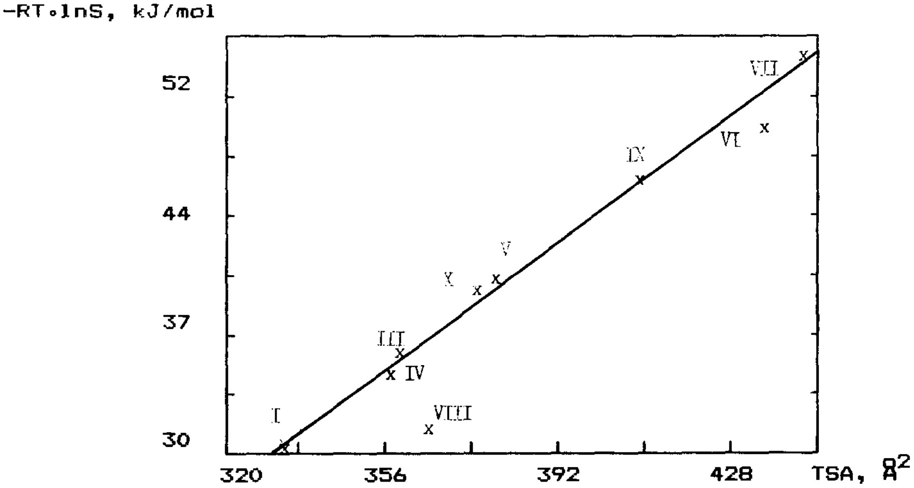

Fig.2. Correlation of the free energy of dissolution with the solvent cavity surface area for fluorocarbons. For abbreviations see Table 1.

correlation (with different values of coefficients) can also be applied to fluorocarbons:

$$-RT\ln S = 0.20\ TSA - 37.3 \qquad (3)$$

where TSA is the cavity area, Å^2 (see Table 2), $-RT\ln S$ is the free energy of dissolution, kJ/mol. The respective linear regression data are presented in Fig.2. Using equation (3) it is then possible to estimate solubility of fluorocarbons in water (and the corresponding emulsion stability) only from the molecular structure of fluorocarbons.

LIST OF SYMBOLS

σ - the interfacial tension

V_m - the molar volume of fluorocarbon

C and S - the solubility of fluorocarbon in water, ml/ml and mol/l, respectively

D - the molecular diffusivity of fluorocarbon in medium

ΔG^o - the free energy of dissolution

ϕ - the volume fraction of particles in emulsion

$\gamma(\phi)$ - the correction coefficient in equation for absolute rates

t - the time

a, A - the radius of particle

$\bar{a}$ - the number average radius

$\bar{a}_{inst}$ - the instrumental value of average radius determined by the PCS method

d, $\bar{d}$, $\bar{d}_{inst}$ - the same for diameter

$K = \bar{a}_{inst}/\bar{a}$

$\omega = \frac{d}{dt}(\bar{a}_{inst})^3$

Γ - the decay constant of the autocorrelation function

μ - the second cumulant of the autocorrelation function

θ - the scattering angle

η - the viscosity of medium

R - the universal gas constant

T - the absolute temperature

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