Journal of Fluorine Chemistry, 51 (1991) 335–347

Received: August 31, 1990; accepted: November 14, 1990

PERFLUORODIMORPHOLINOALKANES AS STABILIZING ADDITIVES IN PERFLUOROCARBON-EMULSIONS

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SUMMARY

The interfacial behaviour of perfluorodecalin in contact with water was investigated in relation to added perfluorodimorpholinoalkane. An equation was found for calculating the interfacial tension curves. A new theory on the stabilizing effect of perfluorodimorpholinoalkanes in emulsions of perfluorodecalin was developed taking into account the interfacial tension and stability curves. Perfluorodimorpholinoalkanes might be called 'Interfacial Active Compounds' (IFACs) because of their behaviour at the water/perfluorodecalin interface.

INTRODUCTION

Emulsions of perfluorocarbons (PFCs) are known to have properties which make them interesting as physiological oxygen-transport fluids [1 - 3]. However, one inherent problem of PFC-emulsions of the first generation, e.g. Fluosol-DA, is that they are not stable at room temperature and have only a short shelf-life time. The search for stable PFC-emulsions is, therefore, an important step towards their biomedical application.

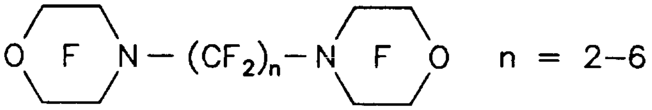
Higuchi and Misra [4] have presented a theoretical analysis of emulsion instability by considering model systems. They

0022-1139/91/$3.50

commented on the stabilizing effect of an added third component. Davis et al. [5] used PFCs as a third component in a n-hexane/water system and explained the stabilizing effect of the third component as resulting from a reduction in the vapour pressure of the oil phase in accordance with Raoult's law. They transferred their results to PFC-emulsions in that they stabilized emulsions of F-decalin in water with Pluronic F-68 as surfactant with perfluorinated saturated polycyclic hydrocarbons. They called these polycycles, 'higher boiling point oil additives' (HBPO-additives) [6, 7, 8]. At the same time, Kabal'nov et al. [9, 10, 11] demonstrated the accuracy of the concept of Ostwald Ripening as a coarsening process for emulsions of PFCs, using a theory developed by Lifshits and Slezov.

RESULTS AND DISCUSSION

We synthesized F-dimorpholinoalkanes of type I where n = 2-6 by using electrochemical fluorination (ECF) [12] and investigated their behaviour as the third component in emulsions of F-decalin.



(I)

Figure 1 shows interfacial tension curves of F-decalin in contact with water in relation to the added F-dimorpholinoalkane. As can be seen, the curves have a steep decline at the beginning. This indicates that the molecules of the dissolved material are enriched at the interface, as pointed out by Wolf [13].

With regard to the results of Marwedel [14] we were able to find an equation for calculating the curves in Fig. 1 (interfacial tension data are given in Table 1). This equation is

$$\log \gamma = a \cdot c^{1/k} + b \tag{1}$$

where γ is the interfacial tension, c the concentration of

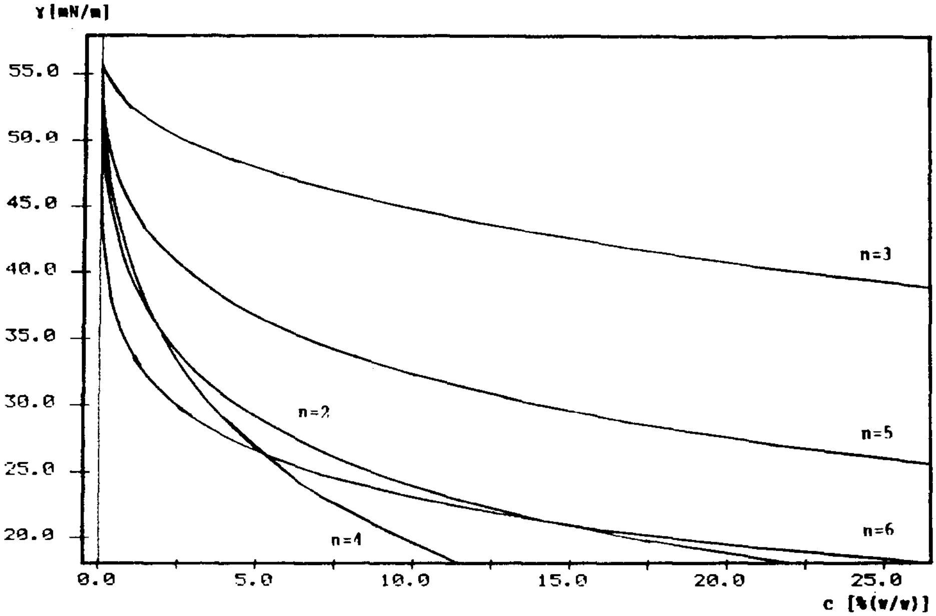


Fig. 1. Interfacial tension of perfluorodecalin/water vs. concentration of perfluorodimorpholinoalkane.

TABLE 1

Interfacial tension data of mixtures of F-decalin/F-dimorpholinoalkane in contact with water

Perfluorodimorpholino-									
ethane		propane		butane		pentane		hexane	
γ	c	γ	c	γ	c	γ	c	γ	c
57.5	0.00	57.4	0.00	56.4	0.00	56.5	0.00	56.6	0.00
55.8	0.01	55.0	0.04	53.5	0.01	54.9	0.01	48.5	0.01
55.4	0.12	54.1	0.13	53.0	0.10	54.4	0.11	45.5	0.04
44.1	0.52	53.1	1.10	46.9	0.50	49.8	0.56	38.0	0.45
40.0	1.03	51.1	2.15	39.6	1.01	46.2	1.09	34.2	1.06
33.3	2.02	50.2	3.12	34.1	2.06	42.2	2.09	30.9	2.14
32.2	3.10	49.8	4.14	31.6	3.06	40.0	3.11	27.6	3.16
29.6	4.14	47.1	5.15	30.8	4.06	37.8	4.10	25.9	4.11
29.1	5.14	43.0	10.13	19.4	9.49	36.4	5.10	25.7	5.09
25.2	10.05	41.2	17.59			32.2	10.08	23.0	10.10
21.0	14.56	39.8	26.74			28.5	16.19	22.3	14.16
19.3	18.16					27.7	19.91	20.9	17.67
						26.4	23.07		
						25.4	26.18		

γ =Interfacial tension
c =concentration of F-dimorpholinoalkane in F-decalin in %(w/w)

F-dimorpholinoalkane in F-decalin (% w/w) and k a whole number between 1 and 10. Table 2 contains the values for F-dimorpholinoalkanes where n = 2-6. Figure 2 shows a linearisation of the curves of Fig. 1 based on the example of F-dimorpholinoethane.

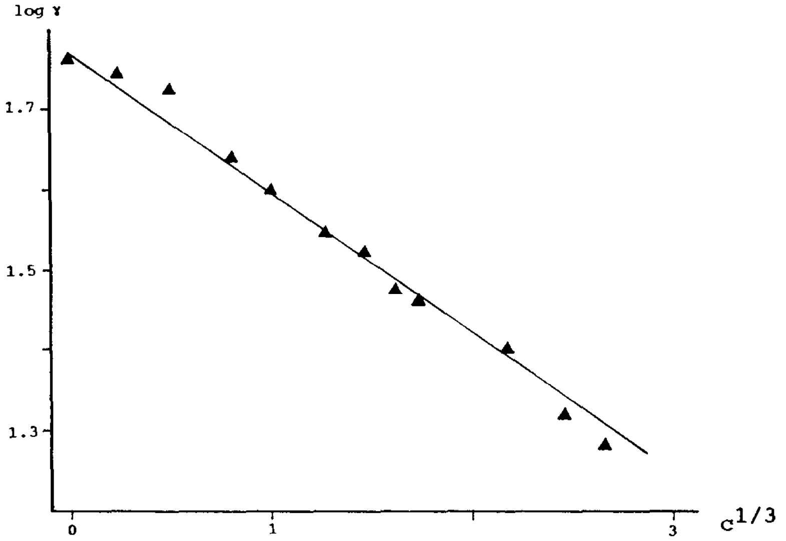


Fig. 2. Plot of log γ versus $c^{1/3}$ for perfluorodimorpholinoethane in perfluorodecalin.

TABLE 2

Constants of equation 1 and area per molecule at the interface F-decalin/water for F-dimorpholinoalkanes

F-DIMORPHOLINO-	k	a	b	Γ [mole/m^2]	AREA/MOLECULE [Å^2/molecule]
ETHANE	3	-0.19	1.90	$2.76 \cdot 10^{-6}$	60
PROPANE	2	-0.03	1.75	$2.01 \cdot 10^{-6}$	82
BUTANE	2	-0.15	1.76	$2.67 \cdot 10^{-6}$	62
PENTANE	3	-0.12	1.78	$2.67 \cdot 10^{-6}$	62
HEXANE	4	-0.22	1.75	$1.93 \cdot 10^{-6}$	86

Figure 3 shows interfacial tensions of F-dimorpholinoalkane solutions in F-decalin versus the logarithm of concentration %(w/w). From the slope of the linear part of the curves we obtained the surface excess Γ by applying eqn. 2 :

$$\Gamma = -1/(RT)\ (d\ \gamma/d\ \ln c) \qquad (2)$$

in mole/m^2 where c is the concentration of F-dimorpholinoalkane in F-decalin. Table 2 also contains values of area per molecule obtained from eqn. 2. The curves in Fig. 3 are similar to these of PFC/water with Proxanol, an EO/PO-block polymer, as surfactant (15). This is another indication of the enrichment of F-dimorpholinoalkanes at the interface. Because of this phenomenon we designate F-dimorpholinoalkanes 'Interfacial Active Compounds' (IFACs).

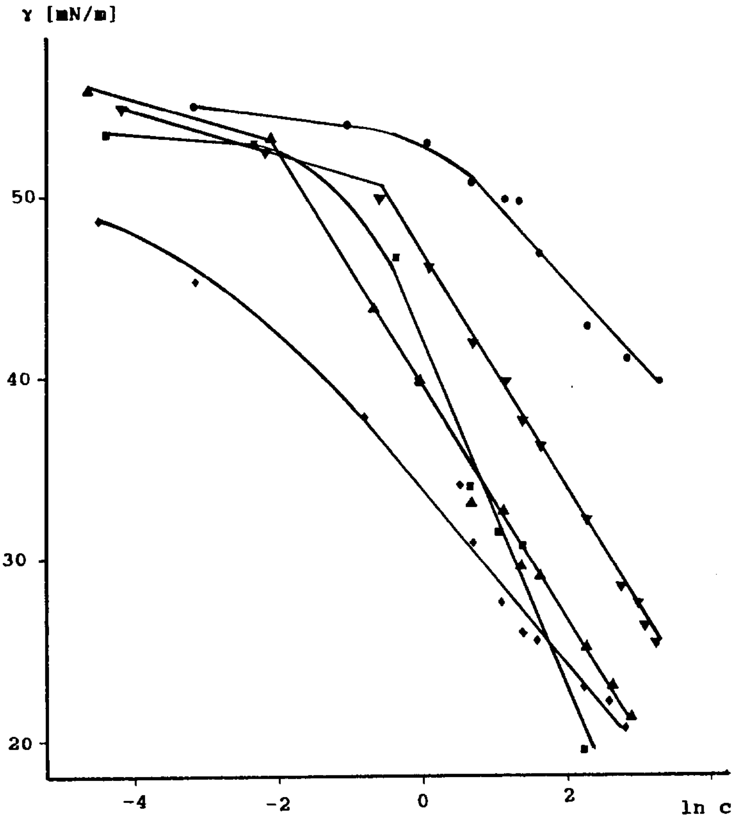


Fig. 3. Plot of interfacial tension vs. ln of concentration for perfluorodimorpholinoalkanes in perfluorodecalin.
▲ n=2; ● n=3; ■ n=4; ▼ n=5; ◆ n=6

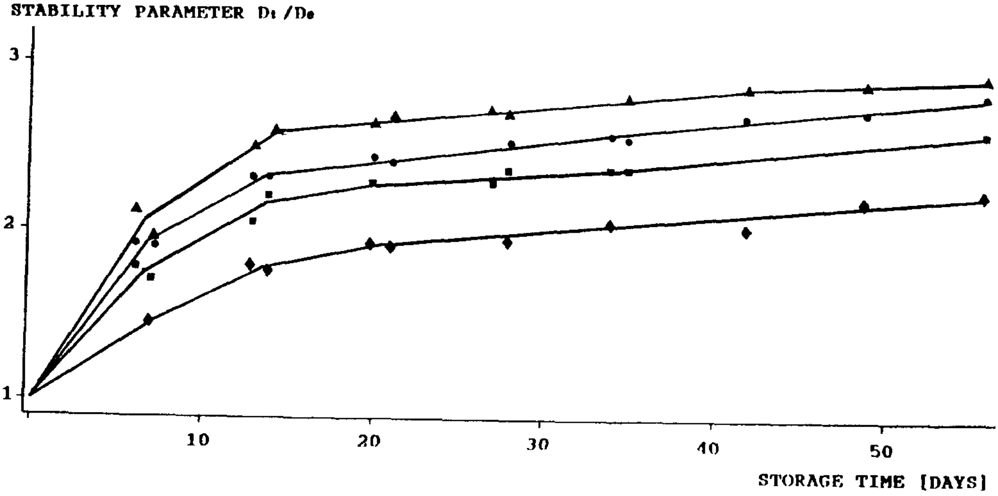


Fig. 4. Relative stability of perfluorodecalin emulsions stabilized with varying amounts of perfluorodimorpholinoethane.
▲ 0.1 %(w/v); ● 0.5 %(w/v); ■ 1.0 %(w/v); ◆ 2.0 %(w/v)

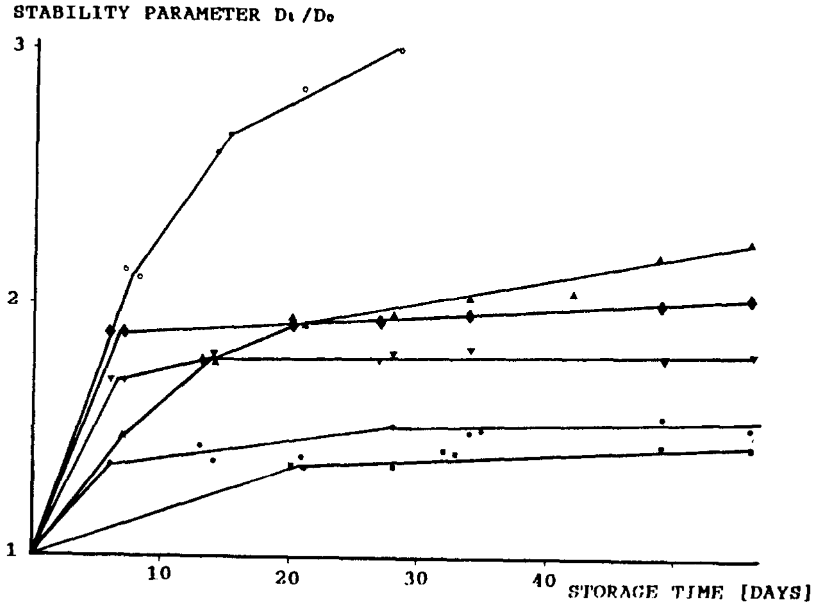


Fig. 5. Relative stability of perfluorodecalin emulsions stabilized with 2 %(w/v) perfluorodimorpholinoalkane.
○ control; ▲ n=2; ● n=3; ■ n=4; ▼ n=5; ◆ n=6

The stabilizing effect of these IFACs on emulsions of F-decalin is illustrated in Figs. 4 and 5. Changes in stability parameter D_t/D_0 plotted against storage time for different amounts of F-dimorpholinoethane in F-decalin are given in Fig. 4. The stability parameter is defined by considering the ratio of the measured diameter after storage to that immediately upon preparation. The stabilizing effect increases with the amount of IFAC. In Fig. 5, a plot of the stability parameter of different IFACs at the same concentration in F-decalin and the plot for pure F-decalin are given. Figure 5 shows that IFACs differ in their stabilizing effects.

Before introducing our own theory we want to consider the two previous theories which assume Ostwald-Ripening to be the coarsening mechanism for PFC-emulsions. Davis et al. [5] explain the effect of the third component as follows: the third component has a lower vapour pressure than the predominant oil. This added material slightly reduces the vapour pressure of the perfluorocarbon bubbles, as defined by Raoult's law. The lower boiling PFC-molecules now move from the smaller bubbles to the larger ones. Thus the third component is enriched in the small bubbles. According to Raoult's law the reduced vapour pressure balances the higher vapour pressure of the small bubbles (Kelvin effect). In a later paper [7], they stated that for PFC-emulsions stabilized with higher boiling point oils (HBPOs) the stabilizing effect is directly related to boiling point and hence molecular weight. We think the statement that the reduction of vapour pressure is directly related to molecular weight is a disturbing feature of this theory. This theory of Davis et al. is also questioned by Kabal'nov et al. [9]. Russian groups [9, 10, 15, 16] have proved that the third component influences the transcondensation rate. The common transcondensation rate can be represented as follows:

$$\omega = \frac{1}{\frac{\varphi_a}{\omega_a} + \frac{\varphi_b}{\omega_b}} \tag{3}$$

where ω_a and ω_b are the transcondensation rates of the individual components and φ_a and φ_b are the volume fractions of the components in the disperse phase. Their emulsions obeyed the

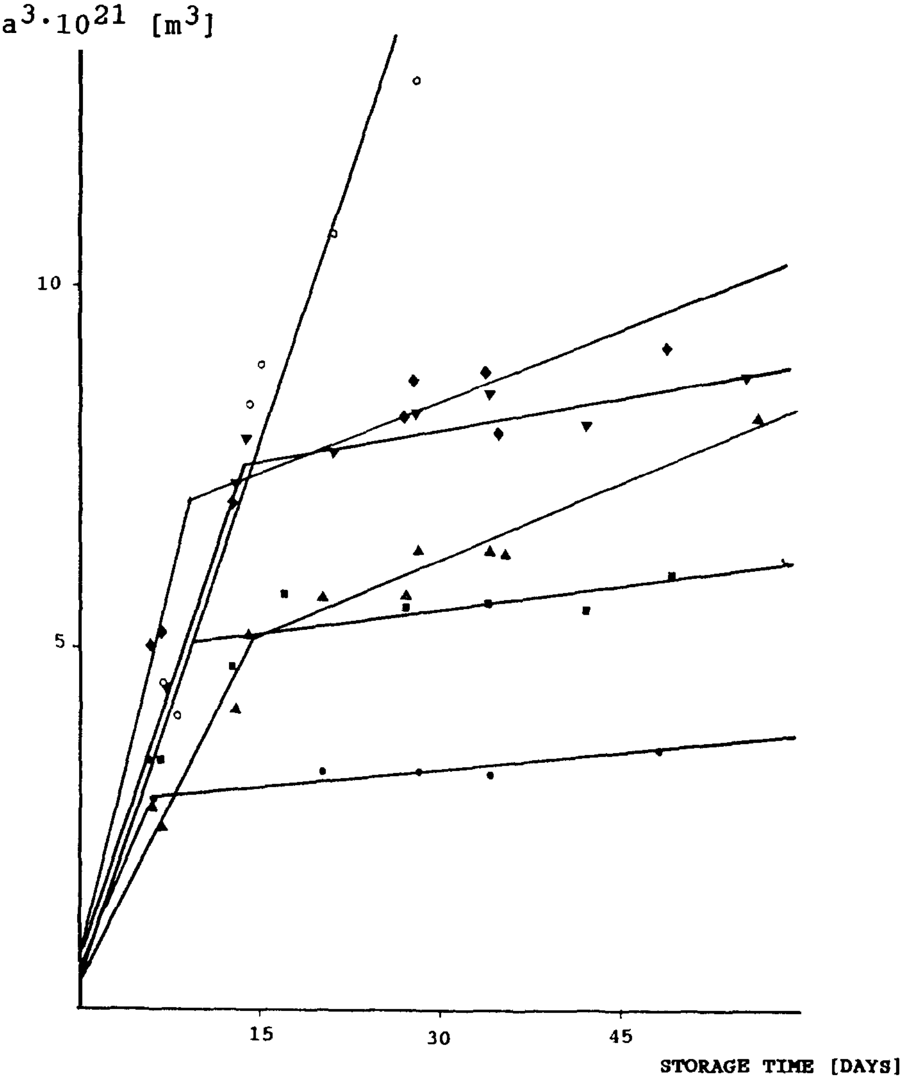


Fig. 6. Cube of mean radius of particles as a function of time for emulsions of perfluorodecalin with 1 %(w/v) of various IFACs stabilized by Pluronic F-68.
○ control; ▲ n=2; ● n=3; ■ n=4; ▼ n=5; ◆ n=6

TABLE 3

Rates of increase of the cube of mean radius of particles in emulsions of F–decalin with added F–dimorpholinoalkanes, in relation to nature and quantity of IFAC

IFAC F–DIMORPHOLINO–	TRANSCONDENSATION RATE [m^3/s]							
	0.1 % (w/v)		0.5 % (w/v)		1.0 % (w/v)		2.0 % (w/v)	
	ω_1	ω_2	ω_1	ω_2	ω_1	ω_2	ω_1	ω_2
ETHANE	$6.4\cdot10^{-27}$	$1.1\cdot10^{-27}$	$4.9\cdot10^{-27}$	$1.1\cdot10^{-27}$	$3.5\cdot10^{-27}$	$8.0\cdot10^{-28}$	$2.3\cdot10^{-27}$	$8.0\cdot10^{-28}$
PROPANE	$5.8\cdot10^{-27}$	$7.5\cdot10^{-28}$	$6.1\cdot10^{-27}$	$2.0\cdot10^{-28}$	$4.5\cdot10^{-27}$	$1.8\cdot10^{-28}$	$1.7\cdot10^{-27}$	$1.6\cdot10^{-28}$
BUTANE	$7.9\cdot10^{-27}$	$2.0\cdot10^{-27}$	$7.5\cdot10^{-27}$	$1.4\cdot10^{-27}$	$4.9\cdot10^{-27}$	$2.7\cdot10^{-28}$	-----	$1.2\cdot10^{-28}$
PENTANE	$8.3\cdot10^{-27}$	$1.7\cdot10^{-27}$	$8.4\cdot10^{-27}$	$3.2\cdot10^{-27}$	$5.9\cdot10^{-27}$	$3.4\cdot10^{-28}$	$4.6\cdot10^{-27}$	$1.2\cdot10^{-28}$
HEXANE	$1.0\cdot10^{-28}$	$1.3\cdot10^{-27}$	$9.6\cdot10^{-27}$	$1.6\cdot10^{-27}$	$7.9\cdot10^{-27}$	$7.3\cdot10^{-28}$	$5.8\cdot10^{-27}$	$1.7\cdot10^{-28}$

F–DECALIN $\omega=5.3\cdot10^{-27}$

Lifshits-Slezov-theory which means that the cube of the mean radius of the particles increases linearly with time as given in equation 4

$$\omega = \frac{d\,(a)^3}{d\,t} = \frac{8\,\gamma\,V_m\,C\,D}{9\,R\,T} \qquad (4)$$

where a is the mean radius of the particles, γ is the interfacial tension, V_m is the molar volume of substance of the dispersed phase, and C and D are the solubility and diffusion coefficient of the disperse-phase substance in the dispersion medium.

In our theory we assume Ostwald-Ripening to be the mechanism of emulsion degradation. We demonstrated this for a control emulsion consisting of 20 %(w/v) F-decalin and 4 %(w/v) Pluronic F-68. We found a transcondensation rate of $0.5 \cdot 10^{-26}$ m^3/s. This is in close agreement with the value of $1 \cdot 10^{-26}$ m^3/s published by Kabal'nov et al. [9] for F-decalin with 1 % (w/v) Proxanol P-268 as surfactant.

A plot of the cube of the average radius of PFC bubbles versus storage time for our emulsions stabilized by IFACs and our control emulsion is shown in Fig. 6. It can be seen that the graphs consist of two different linear parts. Each linear part obeys eqn. 4. Table 3 shows the obtained values of transcondensation rates.

In PFCs, the carbon skeleton is completely surrounded by fluorine atoms and the heteroatoms are masked by perfluoroalkyl groups. Because of this, PFCs are chemically inert. PFCs have been regarded as ideal liquids being fully miscible with one another. Our findings lead, however, to the conclusion that IFACs are enriched at the interface F-decalin/water and that they form a retaining film at the interface as suggested by Sharts et al. [17] for perfluoroalkyl substituted steroids when used as coemulsifying agents for Pluronic F-68. This retaining film reduces Ostwald-Ripening by hindering the transmission of F-decalin from the bubble into water. The closer the retaining film is packed the better is the stabilizing effect of an IFAC. This explains the increasing stabilizing effect as further amounts of IFAC are added. The differences in absolute stabilizing effect correspond qualitatively with k in eqn 1.

The smaller k the better is the stabilizing effect of the IFAC.

Table 3 shows that the transcondensation rate ω_2, as seen in the second part of the growth curve, decreases as increasing amounts of IFAC are added. The transcondensation rate ω_2 seems to have a limit at $1.5 \cdot 10^{-28}$ m^3/s, but F-dimorpholinoethane will probably reach this value only at higher concentrations. This, too, can be explained by the retaining film theory. After the retaining film has been formed, F-decalin is no longer in direct contact with the interface. It has to diffuse through the retaining film to leave the bubble. Decisive for the stabilizing effect of the IFAC is the time needed to form the retaining film. The shorter the time emulsions grow at transcondensation rate ω_1, the better is the stabilizing effect. In view of the above, F-dimorpholinopropane and F-dimorpholinobutane are the most effective IFACs.

It should be mentioned that the approach of Pertsov et al. [16] is valid only for non-surface-active third components. Kabal'nov et al. [10] proved this approach for F-decalin/F-tributylamine and we can confirm their conclusions. The interfacial tension of F-decalin/F-tributylamine in contact with water shows no strong curvature and is nearly linear between 0 and 30 %(w/w) F-tributylamine. In this case there is no action of an IFAC.
However, perfluoroperhydrophenanthrene $C_{14}F_{24}$ used by Davis et al. and Sharma et al. [6, 7, 8] shows behaviour analogous to F-dimorpholinoalkanes. Perfluoroperhydrophenanthrene must, therefore, be regarded as an IFAC.

There are two ways of stabilizing PFC-emulsions by the use of a third component. One, is by statistical distribution of the third component in the oil phase. In this way, the transcondensation rate is given by eqn. 3 as is the case for F-tributylamine/F-decalin. The other is by forming a retaining film by addition of interfacial active PFCs, being enriched at the interface and retaining Ostwald-ripening. Our F-dimorpholinoalkanes are typical IFACs.

EXPERIMENTAL

F-decalin was purchased from Fluka, Pluronic F-68 from Serva. F-dimorpholinoalkanes were obtained by ECF of CH-analogous starting materials [12].

Interfacial tensions were measured at 20 °C on a Krüss interfacial tensiometer K 8 based on the Lecomte du Nouy method, using a rigid platinum ring.

Emulsions were prepared by sonication using a Braun Melsungen Labsonic 2000.

In a typical experiment, 2 g of F-decalin, 0.4 g of Pluronic F-68 and 0.1 g (1 % (w/v)) F-dimorpholinopropane and water to a total of 10 ml were sonicated at output 170 units for 5 minutes. During sonication the mixture was cooled with an ice/salt bath.

Particle size was measured by photon correlation spectroscopy on an autosizer IIc from Malvern Instruments. Emulsions were stored at 4 °C.

ACKNOWLEDGEMENT

We would like to thank the Bundesministerium für Forschung und Technologie, F.R.G. for the financial support.

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