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Synthesis and Vesicle Formation of Ethyl 2-[2′-(F-alkyl)ethyl] 2-alkyl Malonic Acid Disodium Salts

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A series of new di-anionic perfluoroalkylated amphiphiles with mixed F-alkyl/alkyl long chains and a malonic acid disodium salt head group has been synthesized. Among these new F-alkyl-containing amphiphiles, some were found to self-assemble in stable vesicles by hand shaking in water at room temperature. The vesicular aggregates were viewed by freeze-fracture electron microscopy and measured with photon correlation spectroscopy. Surface-activity of all amphiphiles was also investigated. Their CMCs were in particular determined from curves giving surface tension *versus* concentration.

Keywords: Malonic acid; Perfluoroalkylated amphiphile; Surface activity; Critical Micellar Concentration; Spontaneous vesicles

INTRODUCTION

In the field of biomedical applications, vesicles have become the microparticle systems which are the most studied and used as drug carriers [1]. They are composed of an amphiphilic bilayer which acts as a chemical, mechanical and electrical barrier capable of entrapping an internal aqueous solution and separating it from the external medium. The intrinsic properties of vesicles governing the microencapsulation efficiency are the vesicle size and the nature of membrane components. The vesicle size can be well tailored during preparation [2]; the membrane components are mainly amphiphiles with the schematic structure shown in Table I. Vesicle formation usually requires amphiphiles with two hydrophobic chains and considerable mechanical energy such as sonication or pressure filtration [3-5]. But the single-chain amphiphiles which usually form micelles in water can aggregate into vesicles under sonication if they contain a special element of order such as a rigid spacer [6] or a fluorocarbon segment [7] in the hydrophobic tail. If single-chain amphiphiles are submitted to intermolecular interactions such as hydrogen bonding [8-11] or pairing of oppositely charged amphiphiles [12-19], they are capable of self-assembly into vesicles but in the absence of sonication. Vesicles could be also prepared by sonication of hyperextended

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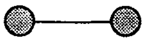
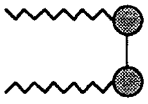
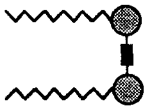
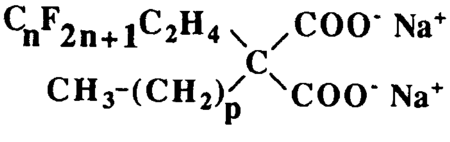
TABLE I Main schematic structures of amphiphiles forming the bilayer of vesicles

Structure	Amphiphile	Reference
	Single-tailed	[12–15, 17–20]
	Single-tailed	[16]
	Double-tailed	[5–7]
	Double-tailed	[5–7]
	Bolaform	[8, 9]
	Bolaform	[8, 9]
	Gemini	[10, 11]
	Gemini	[10, 11]



$$\begin{array}{c} C_nF_{2n+1}C_2H_4\diagdown\ \ \diagup COO^- Na^+ \\ C \\ CH_3\text{-}(CH_2)_p\diagup\ \ \diagdown COO^- Na^+ \end{array}$$

4 a-m

FIGURE 1 Structure of 2-alkyl 2-[2′-(F-alkyl)ethyl] malonic acid disodium salts.

amphiphiles composed of a very long hydrocarbon tail and polyammonium head groups [20] or gemini surfactants [21–25] and bolaamphiphiles [26]. In this work we describe the synthesis and colloïdal properties of new amphiphiles combining two structural elements promoting the bilayer formation: a double-tail and a fluorocarbon segment. It is known that the amphiphiles containing fluorinated moieties exhibit a better tendency to self-assemble when dispersed and sonicated in water in contrast with their hydrogenated analogs. Their unique aggregation properties are induced by fluorinated end groups. Thus the replacement of hydrogenated chains by fluorinated chains leads to strong hydrophobic interactions and to the formation of a rigid hydrophobic and lipophobic area within the bilayer. In preceding works we reported the formation of vesicles from a large variety of double-chain amphiphiles containing fluorinated moieties [27–30], but in all the cases the vesicular aggregates were obtained under sonication. In this paper we show that it is possible to generate vesicles only by hand shaking perfluoroalkyl group-containing malonic-type dicephalic and double-tailed amphiphiles. The molecular structure of these new fluorinated amphiphiles and their corresponding bilayered structure are shown in Figure 1. In contrast with gemini surfactants, both tails and both carboxylic heads groups are linked to the same carbon atom C_2 of malonic acid.

RESULTS AND DISCUSSION

Synthesis

The synthesis of diethyl esters of 2-[2′-(F-alkyl)ethyl] malonic acid **1a–m** used as a starting material has been reported elsewhere [31]. Diethyl esters of 2-alkyl 2-[2′(F-alkyl)ethyl] malonic acid **2a–m** were prepared from the alkylation reaction of one equivalent of compounds **1a–m** with an equivalent of alkyl bromides in presence of sodium ethoxide generated beforehand by addition of sodium in anhydrous ethanol. In the next step the 2-alkyl 2-[2′-(F-alkyl)ethyl] malonic acids **3a–m** were obtained after hydrolysis of the diethyl ester intermediates **2a–m** in an ethanolic KOH solution followed by acidification. Finally the disodium salts of 2-alkyl 2-[2′-(F-alkyl)ethyl] malonic acids **4a–m** were obtained by neutralization of diacids **3a–m** with an aqueous NaOH solution or by saponification of diesters **2a–m** with an anhydrous ethanolic NaOH solution.

These different reactions are summarized in Figure 2. Tables II to IV give the yields and physical characteristics of compounds **2a–m**, **3a–m** and **4a–m**.

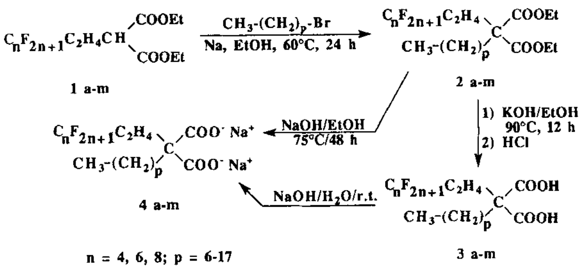


FIGURE 2 Synthesis of 2-alkyl 2-[2′-(F-alkyl)ethyl] malonic acid disodium salts.

Surface-active Properties

Table IV shows the surface and interfacial tensions of amphiphiles **4a–m** and their

TABLE II Yields and physical characteristics of esters **2a–m**

Compound	n(C_nF_{2n+1})	p	Eb (°C/mm Hg)	$n^{20}D$	Yields[a] (%)
2a	4	11	$120/2.8 \cdot 10^{-2}$	1.3891	75
2b	6	6	$100/3.0 \cdot 10^{-2}$	1.3793	88
2c	6	7	$115/2.8 \cdot 10^{-2}$	1.3840	75
2d	6	8	$120/2.8 \cdot 10^{-2}$	1.3866	75
2e	6	9	$100/2.5 \cdot 10^{-2}$	1.3867	85
2f	6	10	$114/2.5 \cdot 10^{-2}$	1.3905	76
2g	6	11	$115/2.4 \cdot 10^{-2}$	1.3951	75
2h	6	12	$125/2.4 \cdot 10^{-2}$	1.3968	79
2i	6	13	$135/2.3 \cdot 10^{-2}$	1.3982	83
2j	6	15	$160/2.3 \cdot 10^{-2}$	1.4214	88
2k	6	16	$165/2.3 \cdot 10^{-2}$	1.4430	78
2l	6	17	$150/2.2 \cdot 10^{-2}$	solid[b]	80
2m	8	11	$140/2.5 \cdot 10^{-2}$	1.3891	75

[a] Yields of isolated pure products.
[b] Solid as paste.

TABLE III Yields and physical characteristics of acids **3a–m**

Compound	n (C_nF_{2n+1})	p ($CH_3(CH_2)_p$-)	F[a] (°C)	Yields[b] (%)
3a	4	11	66	89
3b	6	6	111	91
3c	6	7	109	92
3d	6	8	106	89
3e	6	9	104	86
3f	6	10	100	87
3g	6	11	96	90
3h	6	12	94	92
3i	6	13	90	88
3j	6	15	88	87
3k	6	16	86	87
3l	6	17	85	89
3m	8	11	121	87

[a] Melting points are uncorrected.
[b] Yields of isolated pure products.

TABLE IV Yields, Surface and interfacial tensions, and CMC of amphiphiles **4a–m**

Compound	$n(C_nF_{2n+1})$	$p(CH_3(CH_2)_p-)$	Yields[a] (%)	γ_s[b] [mN/m]	γ_i[b] [mN/m]	CMC mol/l
4a	4	11	89	26.0	11.0	$7.8 \cdot 10^{-3}$
4b	6	6	90	24.4	18.9	$2.9 \cdot 10^{-3}$
4c	6	7	91	19.7	20.3	$11.1 \cdot 10^{-3}$
4d	6	8	92	17.8	10.8	$5.75 \cdot 10^{-3}$
4e	6	9	95	19.0	13.3	$2.3 \cdot 10^{-3}$
4f	6	10	90	18.8	2.4	$1.2 \cdot 10^{-3}$
4g	6	11	92	18.0	1.4	$9.0 \cdot 10^{-4}$
4h	6	12	90	18.7	/	$6.5 \cdot 10^{-4}$
4i	6	13	92	21.2	/	$6.3 \cdot 10^{-4}$
4j	6	15	95	25.4	4.8	$5.0 \cdot 10^{-4}$
4k	6	16	92	24.7	3.0	$2.45 \cdot 10^{-4}$
4l	6	17	92	28.0	6.1	$1.5 \cdot 10^{-4}$
4m	8	11	90	19.5	6.4	$8.8 \cdot 10^{-4}$

[a] Yields of isolated pure products.

[b] Surface and interfacial tensions are measured at 21.0 ± 0.1°C from aqueous solutions containing 0.1% w/w of amphiphile.

corresponding Critical Micellar Concentration (CMC) experimentally determined by curves giving surface tension (mN/m) *versus* concentration (mole/l). The results show that the increase of F-alkyl chain lengths results in a decrease of their CMC values: $7.8\,10^{-3}$ mole/l for **4a** (C_4F_9, $C_{12}H_{25}$), $9.0\,10^{-4}$ mole/l for **4g** (C_6F_{13}, $C_{12}H_{25}$) and $8.8\,10^{-4}$ for **4m** (C_8F_{17}, $C_{12}H_{25}$). When the F-alkyl chain is C_6F_{13} and the alkyl chain length increases (**4b** to **4l**), a decrease of CMC values is observed; as a result there is a gain in hydrophobicity which is essentially pronounced when we compare the CMC values of **4b** (C_6F_{13}, C_7H_{15}): $2.9\,10^{-3}$ mole/l and **4l** (C_6F_{13}, $C_{17}H_{35}$): $1.5\;10^{-4}$ mole/l.

Formation and Characteristics of Vesicles

The vesicle-forming amphiphiles described in this paper allow the formation of membranes with a discontinuous internal lipophobic fluorinated core as shown in Figure 3. This fluorinated core within the vesicle membrane is interesting since it constitutes an efficient barrier for the release of entrapped water-soluble compounds. The vesicular solutions were easily prepared simply by stirring the amphiphiles **4b**, **4d**, **e**, **4g**, **h** and **4k**, **m** in water. We also tried to apply the technique of ultrasonics to the amphiphilic dispersions but we could not improve the formation of vesicles. The vesicle dispersions of amphiphiles **4b**, **4d**, **e**, **4g**, **h** and **4k–m** were studied by Freeze-Fracture Electron Microscopy (FFEM). Freeze-fracture replicas show only micelles for amphiphilic dispersion of **4b**, vesicles for amphiphilic dispersion of **4d**, **e**, **4g**, **h**, **4k**, **l** (Figs. 4 to 9) crystals and vesicles for amphiphilic dispersion of **4m** (Fig. 10). The

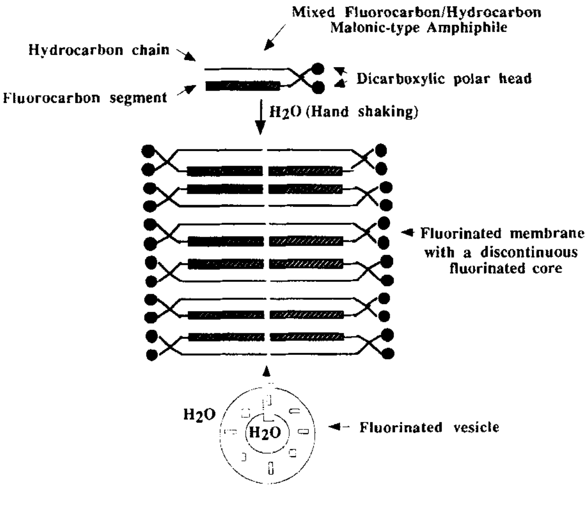


FIGURE 3 Schematic membrane structure of vesicles containing a discontinuous internal lipophobic fluorinated core.

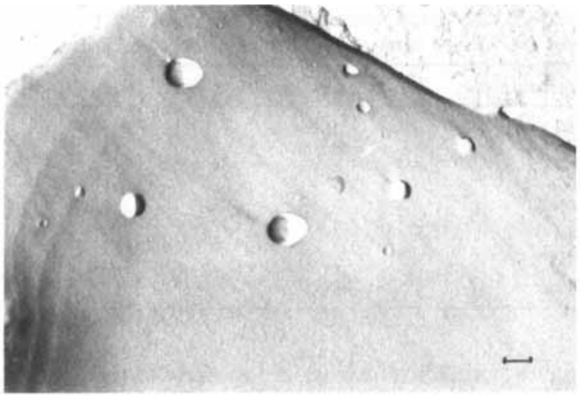


FIGURE 4 Freeze fracture electron micrograph of **4d** vesicular solution. Bar length is 100 nm.

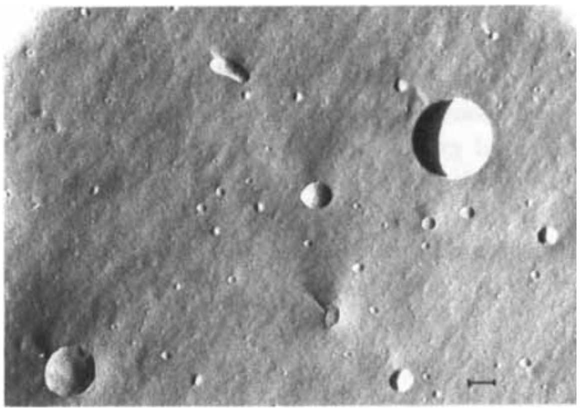


FIGURE 5 Freeze fracture electron micrograph of **4e** vesicular solution. Bar length is 100 nm.

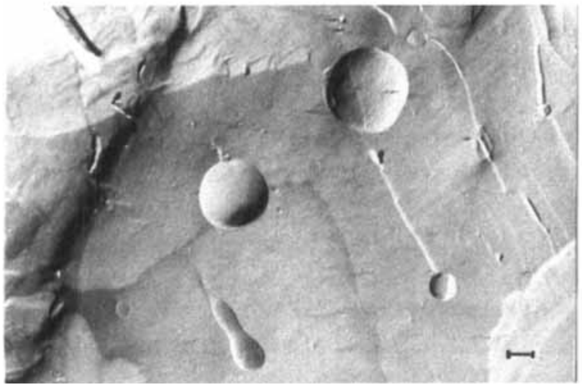


FIGURE 6 Freeze fracture electron micrograph of **4g** vesicular solution. Bar length is 100 nm.

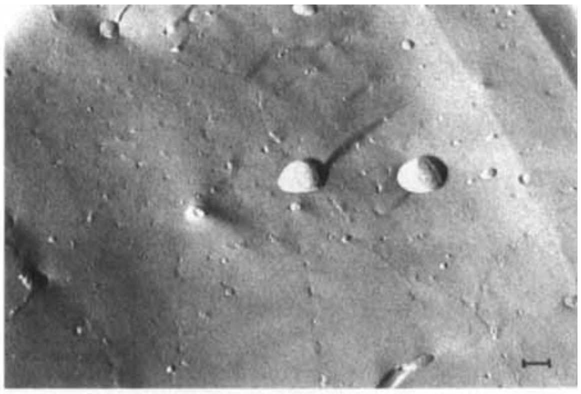


FIGURE 7 Freeze fracture electron micrograph of **4h** vesicular solution. Bar length is 100 nm.

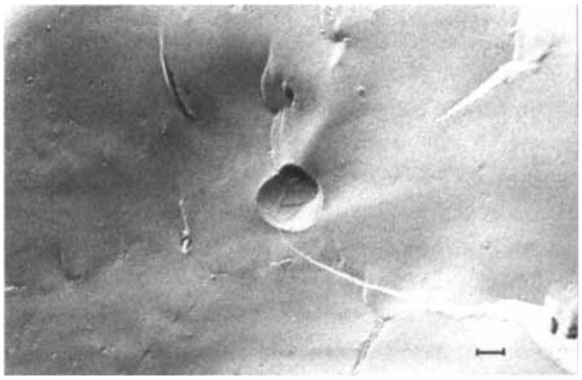


FIGURE 8 Freeze fracture electron micrograph of **4k** vesicular solution. Bar length is 100 nm.

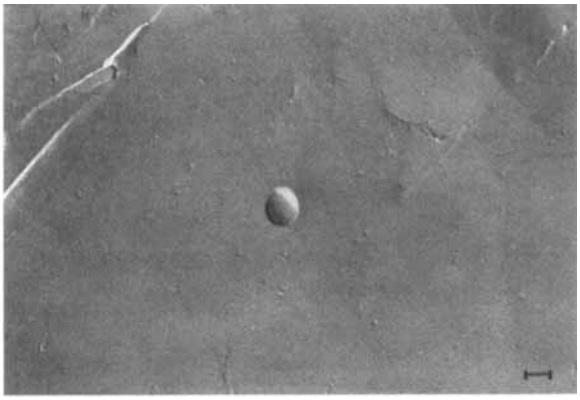


FIGURE 9 Freeze fracture electron micrograph of **4l** vesicular solution. Bar length is 100 nm.

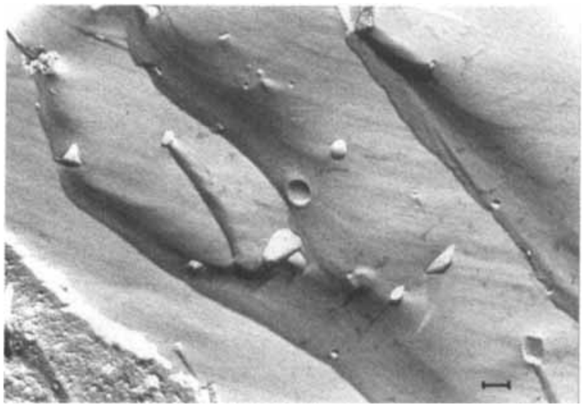


FIGURE 10 Freeze fracture electron micrograph of **4m** vesicular solution. Bar length is 100 nm.

compound **4b** is unable to produce hydrophobic interactions strong enough to form vesicles. In literature a similar behaviour was found for some linear cationic double-chain amphiphiles. In particular Kunitake showed that the formation of vesicular systems by sonication of cationic dialkyldimethyl ammonium bromides or anionic dialkyl sulfonate, phosphate and carboxylate, is only possible when the skeleton of each hydrocarbon chain contains at least 10 carbon atoms [32]. In the case of amphiphile **4b**, neither chain contains more than 8 carbon atoms. The vesicles formed from amphiphiles **4d, e**, **4g, h**, **4k, l** and contaminated by some micelles are spherical and unilamellar. Their mean size was determined by Photon Correlation Spectroscopy (PCS). The aggregates formed from amphiphiles **4d**, **4h**, **4k**, **4l**, **4m** exhibit a monomodal size-distribution. In contrast the sizes of vesicles formed from amphiphiles **4e** and **4g** are distributed according to a bimodal curve. The mean diameters and polydispersity index of vesicles formed from amphiphiles **4d, e**, **4g, h** and **4k – m** are displayed in Table V.

TABLE V Mean diameters and polydispersity index of vesicles formed from amphiphiles **4d, e**, **4g, h** and **4k – m**

Amphiphile	Diameter [nm]	Polydispersity index
4d	197.8	0.29
4e	381.4	0.30
4g	357.0	0.49
4h	369.8	0.28
4k	81.4	0.32
4l	200.6	0.31
4m	488.0	0.30

Vesicle Stability

When the vesicular dispersions were examined after 3 months, we did not observe crystallization, flocculation, precipitation or increasing of the vesicles' mean diameter. Their strong colloïdal stability is due to the nature of the dicarboxylic head group. Usually the high negative charge of the vesicle's surface gives rise to a large electrical double layer repulsion as well as a large hydration layer repulsion [33]. Thus vesicles are prevented from approaching each other and flocculating. Because of the expected hardness of the two carboxyl functions, the head groups will be strongly hydrated and as a result the counter-ion binding will be low. In addition, the dicarboxyl group was expected to improve the packing of the hydrophilic heads through hydrogen bonding and to increase the stability of vesicles simply formed by hand shaking.

MATERIALS AND METHODS

Diethylmalonate and n-bromoalkanes were purchased from Aldrich. IR spectra were obtained on a Bruker IFS 45 spectrophotometer. The uncorrected melting points were determined with a Büchi apparatus. ^1H NMR and ^{19}F NMR spectra were obtained in deuterated chloroform on a Bruker WH 200 spectrometer at 200 MHz (tetramethylsilane as internal reference) and 188.3 MHz (fluorotrichloromethane as internal reference), respectively. Elemental analysis was performed by the CNRS central facilities in Vernaison (France). Surface tension measurements (γ_S) were performed by a tensiometer from Krüss employing the Lecompte Du Noüy ring method at 21.0 ± 0.1°C. The interfacial tensions γ_i of amphiphiles solutions were determined in relation to cyclohexane solutions by the same technique at 21.0 ± 0.1°C.

General Synthetic Procedures

Diethyl 2-alkyl 2-[2'-(F-alkyl)ethyl] Malonates 2a–m

10 ml absolute ethanol is slowly added to sodium ($2.2 \cdot 10^{-2}$ mol) under nitrogen. When all the sodium has been consumed, diethyl 2-(F-alkyl)ethyl malonates **1a–m** ($2 \cdot 10^{-2}$ mol) are added dropwise while stirring. The limpid solution obtained is heated at 40°C for 10 minutes. Then alkyl bromides ($2 \cdot 10^{-2}$ mol) are added dropwise, and the mixture is heated at 60°C for 24 hours. After cooling, the solvent is removed. 10 ml of water is poured in and the mixture is extracted with 3 × 60 ml of diethylether. The organic phase is washed with water, dried with Na_2SO_4. After evaporation of the diethyl ether and distillation under vacuum in the presence of a small amount of phosphoric anhydride, the compounds **2a–m** are obtained as oils (*cf.* Tab. II).

Diethyl 2-dodecyl 2-[2'-(F-butyl)ethyl] Malonate 2a

IR (Film) v (cm^{-1}) 1747 and 1734 (C=O), 1300-1100 (C-F). ^1H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz) 0.87 (t, 3H, CH_3, J = 6.8); 1.25 (s, 26H, 2-OCH_2CH_3 and $-(CH_2)_{10}CH_3$); 1.80–2.25 (m, 6H, $-(CH_2)_2C_4F_9$ and $-CH_2(CH_2)_{10}-$); 4.21 (q, 4H, $-OCH_2CH_3$, J = 7.1). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) −81.1 (3F, CF_3); −115.3 (2F, 1-CF_2); −124.8 (2F, 2-CF_2); −126.5 (2F, 3-CF_2). Element. Anal. ($C_{25}H_{39}F_9O_4$): Calculated: C 52.26; H 6.84; F 29.75; found: C 52.81; H 7.01; F 29.98.

Diethyl 2-dodecyl 2-[2'-(F-hexyl)ethyl] Malonate 2g

IR (Film) v (cm^{-1}) 1747 and 1734 (C=O), 1300-1100 (C-F). ^1H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz) 0.87 (t, 3H, CH_3, J = 6.8); 1.25 (s, 26H, 2-OCH_2CH_3 and $-CH_2(CH_2)_{10}-$); 1.80–2.25 (m, 6H, $-(CH_2)_2C_6F_{13}$ and $-CH_2(CH_2)_{10}-$); 4.21 (q, 4H, $-OCH_2CH_3$, J = 7.1). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) −81.3 (3F, CF_3); −115.2 (2F, 1-CF_2); −122.4 (2F, 2-CF2); −123.4 (2F, 3-CF_2); −123.8 (2F, 4-CF_2); −126.6 (2F, 5-CF_2). Element. Anal. ($C_{27}H_{39}F_{13}O_4$): Calculated: C 48.07; H 5.82; F 25.34; found: C 48.53; H 5.98; F 25.68.

Diethyl 2-dodecyl 2-[2'-(F-octyl)ethyl] Malonate 2m

IR (Film) v (cm^{-1}) 1747 and 1734 (C=O), 1300-1100 (C-F). ^1H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz) 0.88 (t, 3H, CH_3, J = 6.8); 1.26 (s, 26H, 2-OCH_2CH_3 and $-(CH_2)_{10}CH_3$); 1.80–2.25 (m, 6H, $-(CH_2)_2C_8F_{17}$ and $-CH_2(CH_2)_{10}-$); 4.21 (q, 4H, $-OCH_2CH_3$, J = 7.1). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) −81.2 (3F, CF_3); −115.2 (2F, 1-CF_2); −122.3 (4F, 2-3-CF_2); −123.2 (2F, 4-CF_2); −123.8 (2F, 5-CF_2); −126.6 (2F, 6-7-CF_2). Element. Anal. ($C_{29}H_{39}F_{17}O_4$): Calculated: C 44.96; H 5.07; F 22.07; found: C 45.12; H 5.80; F 22.68.

2-alkyl 2-[2'-(F-alkyl] Malonic Acids 3a–m

Ground potassium hydroxyde ($2 \cdot 10^{-2}$ mol) is added to a solution of diethyl 2-alkyl 2-[2'-(F-alkyl)ethyl] malonates **2a–m** ($5 \cdot 10^{-3}$ mol) in 10 ml of absolute ethanol. The mixture is stirred and heated at 90°C overnight. After evaporation of the solvent the mixture is acidified with 30 ml of HCl 36–37%. Then, 30 ml of diethyl ether is slowly added and the mixture is stirred at room temperature for 1 hour. 30 ml of water is added and the mixture is extracted with 3 × 60 ml of diethyl ether. The organic phase is washed with 2 × 40 ml of water. The ethereal phase is dried and evaporated; the compounds **3a–m** are obtained as solids after purification by filtration on silica column (eluent: diethylether) (*cf.* Tab. III).

2-dodecyl 2-[2′-(F-butyl)ethyl] Malonic Acid 3a

IR (Film) v (cm^{-1}) 3400 (OH), 1703 (C=O), 1300-1100 (C-F). ^{1}H NMR (CDCl$_3$/TMS) δ (ppm), J (Hz) 0.87 (t, 3H, CH$_3$, J = 6.7); 1.26 (s, 20H, —(CH$_2$)$_{10}$CH$_3$); 1.80–2.25 (m, 6H, —(CH$_2$)$_{22}$C$_4$F$_9$ and —CH$_2$(CH$_2$)$_{10}$CH$_3$); 9.61 (s, 2H, 2-COOH). ^{19}F NMR (CDCl$_3$/CFCl$_3$) δ (ppm) −81.6 (3F, CF$_3$); −115.5 (2F, 1-CF$_2$); −124.7 (2F, 2-CF$_2$); −126.6 (2F, 3-CF$_2$). Element. Anal. ($C_{21}H_{31}F_9O_4$): Calculated: C 48.65; H 6.02; F 32.97; found: C 48.92; H 6.67; F 33.22.

2-dodecyl 2-[2′-(F-hexyl)ethyl] Malonic Acid 3g

IR (Film) v (cm^{-1}) 3400 (OH), 1703 (C=O), 1300-1100 (C-F). ^{1}H NMR (CDCl$_3$/TMS) δ (ppm), J (Hz) 0.87 (t, 3H, CH$_3$, J = 6.7); 1.26 (s, 20H, —(CH$_2$)$_{10}$CH$_3$); 1.80–2.25 (m, 6H, —(CH$_2$)$_2$C$_6$F$_{13}$ and —CH$_2$ (CH$_2$)$_{10}$CH$_3$); 9.75 (s, 2H, 2-COOH). ^{19}F NMR (CDCl$_3$/CFCl$_3$) δ (ppm) −81.4 (3F, CF$_3$); −115.3 (2F, 1-CF$_2$); −122.5 (2F, 2-CF$_2$); −123.5 (2F, 3-CF$_2$); −123.7 (2F, 4-CF$_2$); −126.7 (2F, 5-CF$_2$). Element. Anal. ($C_{23}H_{31}F_{13}O_4$): Calculated: C 44.66; H 5.05; F 39.93; found: C 44.99; H 5.71; F 40.31.

2-dodecyl 2-[2′-(F-octyl)ethyl] Malonic Acid 3m

IR (Film) v (cm^{-1}) 3400 (OH), 1703 (C=O), 1300-1100 (C-F). ^{1}H NMR (CDCl$_3$/TMS) δ (ppm), J (Hz) 0.87 (t, 3H, CH$_3$, J = 6.7); 1.26 (s, 20H, —(CH$_2$)$_{10}$CH$_3$); 1.80–2.25 (m, 6H, —(CH$_2$)$_2$C$_8$F$_{17}$ and —CH$_2$(CH$_2$)$_{10}$CH$_3$); 8.45 (s, 2H, 2-COOH). ^{19}F NMR (CDCl$_3$/CFCl$_3$) δ (ppm) −81.4 (3F, CF$_3$); −115.3 (2F, 1-CF$_2$); −122.5 (2F, 2-3-CF$_2$); −123.4 (2F, 4-CF$_2$); −123.7 (2F, 5-CF$_2$); −126.7 (2F, 6-7-CF$_2$). Element. Anal. ($C_{25}H_{31}F_{17}O_4$): Calculated: C 41.75; H 4.34; F 44.95; found: C 42.10; H 4.89; F 45.32.

2-alkyl 2-[2′-(F-alkyl)ethyl] Malonic Sodium Salts 4a–m

- Method involving the neutralisation of corresponding diacids **3a–m**: 2-alkyl 2-[2′-(F-alkyl) ethyl] malonic acids **3a–m** ($2 \cdot 10^{-3}$ mol) are dissolved in 40 ml of distilled water and 8 ml of a NaOH solution (0.5 M). The mixture is stirred at room temperature until complete consumption of the starting diacids, *i.e.*, for 3 to 6 days (the reaction is followed under Gas Chromatography) The mixture is extracted with 2 × 20 ml of diethyl ether. The compounds **4a–m** are obtained after evaporation of the water phase and drying in vacuum (*cf.* Tab. IV).
- Method involving the saponification of corresponding diesters **2a–m**: ground potassium hydroxyde ($2 \cdot 10^{-3}$ mol) is added to a solution of 2-alkyl 2-[2′-(F-alkyl)ethyl] malonic acid ($2 \cdot 10^{-3}$ mol) in 10 ml of absolute ethanol. The mixture is stirred and heated at 75°C for 48 hours. The compounds **4a–m** are obtained as white powders after evaporation of the solvent, washing with diethyl ether and dying in vacuum (*cf.* Tab. IV).

Preparation of Vesicle Dispersions

The vesicle dispersions were prepared by simple stirring of 200 mg of amphiphile **4a–m** in 10 ml of deionized Millipore water at room temperature for 30 minutes.

Freeze Fracture Electron Microscopy (FFEM)

The vesicle dispersions were observed under Freeze-Fracture Electron Microscopy in accordance with the published procedures [34]. The samples were fractured at −150°C and shaded by platinum at an angle of 45°C. The platinum/carbon replicas were examined with a Philips EM 301 electron microscope.

Photon Correlation Spectroscopy (PCS)

The mean size of vesicles was determined by Photon Correlation spectroscopy [35]. The measurements were carried out at 25°C and at a scattering angle of 90°C with an Autosizer IIC spectrometer from Malvern Instruments Ltd.

CONCLUSION

The stable fluorinated vesicles produced from disodium salts of mixed-chain alkyl/F-alkyl malonic acids [36] reviewed here, may validly be used as new colloïdal systems for drug delivery. The facility with which these fluorinated amphiphiles self-assemble without energy supply, should be an advantage where the agents designed for being entrapped in the vesicular aggregates are fragile proteins or genetic materials. This work shows that the formation of vesicles is not pH dependent as in the case of dicarboxylic acid-based single-chain amphiphiles such as dipotassium dodecene succinate reported in literature [37]. The vesicle formation of malonate-type double-chain amphiphiles mainly depends on the total hydrophobicity of both their chains alkyl/F-alkyl and the nature of their bulky group.

References

[1] Lasic, D. D. (1993). *Liposomes from Physics to Applications*, Elsevier, Amsterdam.

[2] New, R. R. C. (1990). *Liposomes: A Practical Approach*, IRL Press, Oxford.

[3] Fendler, J. H. (1982). *Membrane Mimetic Chemistry*, Wiley-Interscience, New-York.

[4] Kunitake, T. (1992). *Angew. Chem. Int. Ed. Engl.*, **31**, 709.

[5] Ringsdorf, H., Schlarb, B. and Venzmer, J. (1988). *Angew. Chem. Int. Ed. Engl.*, **27**, 113.

[6] Kunitake, T., Okahata, Y., Shimomura, M., Yasunami, S. and Takarabe, K. (1981). *J. Am. Chem. Soc.*, **103**, 5401.

[7] Krafft, M. P., Giulieri, F. and Riess, J. G. (1994). *Colloïds Surf.*, **84**, 113.

[8] Gebicki, J. M. and Hicks, M. (1973). *Nature*, **232**, 3243.

[9] Hargreaves, W. R. and Deamer, D. W. (1978). *Biochemistry*, **17**, 3759.

[10] Morigaki, K., Dalavalle, S., Walde, P., Colonna, S. and Luisi, P. L. (1997). *J. Am. Chem. Soc.*, **119**, 292.

[11] Walde, P., Wessicken, M., Rädler, U., Berclaz, N., Conde-Frieboes, K. and Luisi, P. L. (1997). *J. Phys. Chem.*, **101**, 7390.

[12] Kaler, E. W., Murthy, A. K., Rodriguez, B. E. and Zasadinski, J. A. N. (1992). *J. Phys. Chem.*, **96**, 6698.

[13] Safran, S. A., Pincus, P., Andelman, D. and Macintosh, F. C. (1991). *Phys. Rev.*, **43**, 1071.

[14] Szönyi, S., Cambon, A., Watzke, H. J., Schurtenberger, P. and Wehrli, E., In: *Structure and Conformation of Amphiphilic Membranes*, Lipowski, R., Richter, D. and Kremer, K. (Eds.), *Springer Proceedings in Physics*, Springer-Verlag, Berlin, 1992, **66**, 198.

[15] Ambühl, M., Bangerter, F., Luisi, P. L., Skrabal, P. and Watzke, H. J. (1993). *Langmuir*, **9**, 36.

[16] Zhao, G. X. and Yu, W. L. (1995). *J. Colloïd Interf. Sci.*, **173**, 159.

[17] Ristori, S., Appell, J. and Porte, G. (1996). *Langmuir*, **12**, 686.

[18] Marques, E. F., Regev, O., Khan, A., Miguel, M. G. and Lindman, B. (1998). *J. Phys. Chem. B*, **102**, 6746.

[19] Bergmeier, M., Hoffmann, H., Witte, F. and Zourab, S. (1998). *J. Colloïd Interf. Sci.*, **203**, 1.

[20] Menger, F. M. and Yamasaki, Y. (1993). *J. Am. Chem. Soc.*, **115**, 3840.

[21] Danino, D., Talmon, Y. and Zana, R. (1995). *Langmuir*, **11**, 1448.

[22] Rosen, M. J. and Song, L. D. (1996). *J. Colloïd Interf. Sci.*, **179**, 261.

[23] Jaeger, D. A. and Brown, E. L. G. (1996). *Langmuir*, **12**, 1976.

[24] Sommerdijk, N. A. J. M., Hoeks, T. H. L., Synak, M., Feiters, M. C., Nolte, R. J. M. and Zwanenburg, B. (1997). *J. Am. Chem. Soc.*, **119**, 4338.

[25] Bhattacharya, S. and De, S. (1995). *J. Chem. Soc., Chem. Commun.*, p. 651.

[26] Fuhrhop, J. H., David, H.-H., Mathieu, J., Liman, U., Winter, H.-J. and Boekema, E. (1986). *J. Am. Chem. Soc.*, **108**, 1785.

[27] Trabelsi, H., Szönyi, S., Gaysinski, M., Cambon, A. and Watzke, H. J. (1993). *Langmuir*, **9**, 1201.

[28] Jouani, M. A., Szönyi, S., Trabelsi, H., Dieng, S. Y., Cambon, A. and Watzke, H. J. (1995). *Supramol. Sci.*, **2**, 117.

[29] Jouani, M. A., Szönyi, S., Wehrli, E. and Cambon, A. (1999). *J. Liposome Research*, **9**, 95.

[30] Guittard, F., Cambon, A. and Chang, P. (1995). *J. Fluorine Chem.*, **74**, 131.

[31] Lucas, P., Jouani, M. A., Trabelsi, H. and Cambon, A. (1998). *J. Fluorine Chem.*, **92**, 17.

[32] Kunitake, T. (1992). *Angew. Chem. Int. Ed. Engl.*, **31**, 709.

[33] Israelachvili, J. N. (1992). *Intermolecular and Surface Forces*, Academic Press, London.

[34] Müller, M., Meister, N. and Moor, H. (1980). *Mikroscopie* (Wien), **36**, 129.

[35] Chong, C. S. and Colbow, K. (1976). *Biochim. Bioph. Acta*, **436**, 260.

[36] Trabelsi, H. and Cambon, A. (1996). *Patent MC*, No. 2334.

[37] Imae, T. and Trend, B. (1991). *Langmuir*, **7**, 643.