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Synthesis and self-assembly of novel fluorous cationic amphiphiles with a 3,4-dihydro-2(1*H*)-pyridone spacer

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ABSTRACT

The synthesis of fluorous (highly fluorinated) 3,4-dihydro-2(1*H*)-pyridone-5-carboxylate cationic amphiphiles have been described, where the dihydropyridone serves as a spacer and either a pyridinium bromide or a triphenylphosphonium bromide form the polar cationic head group. The in water self-assembled aggregates have been observed by atomic force microscopy (AFM) and dynamic light scattering (DLS).

1. Introduction

The 3,4-dihydropyridone is a convenient scaffold for attaching cationic head groups and fluorous long chain esters for the construction of cationic amphiphiles. Also it is relatively straight forward to synthesize from Meldrum's acid as the second dicarbonyl component in a Hantzsch-like reaction [1,2] and recently by employing microwaves the yields have been boosted substantially [3]. The 2-pyridones possess interesting pharmacological properties such as reverse transcriptase inhibition of human immunodeficiency virus-1 (HIV-1) [4,5]. Milrinone, Amrinone [6] and their analogs are cardiotonic agents for the treatment of heart failure. They have also been reported to possess antitumor [7,8], antibacterial [9] and other biological activities [10–12].

Previously Hyvonen et al. [13] have tested a series of symmetrical cationic amphiphilic double-charged didodecyl 1,4-dihydropyridine-3,5-dicarboxylate derivatives (1,4-DHP), which have self-associating properties in aqueous media forming liposomes with a mean diameter in the 50–130 nm range. The aim of this present study is to combine the properties of DHP derived cationic compounds with the stability imparted by fluorous groups and to synthesize novel charged fluorous 6-methyl-3,4-dihydro-2(1*H*)-pyridone-5-carboxylates which are 1,4-DHP analogs having a single alkyl ester group. The formation of bilayers and vesicles usually requires bicaudal (double chain) amphiphiles but, organized supramolecular systems can be obtained from a single pure monocaudal nonrigid amphiphile by reinforcing the *hydrophobic interactions* in the surfactant film through the use of a highly perfluorinated tail, without recourse to classical steric effects or intermolecular associations [14]. The force of this self-assembling capacity is, illustrated by the ability of single chain *F*-surfactants to form stable vesicles rather than micelles in water and as a rule, films and membranes made of *F*-surfactants are more stable than those of their hydrogenated analogs [15].

2. Results and discussion

The 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecanol was synthesized using perfluorooctyliodide in a radical reaction with 3-buten-1-ol initiated by sodium dithionite and deiodinated with tributyltin according to a literature procedure [16]. This alcohol was further reacted with 2,2,6-trimethyl-4H-1,3-dioxin-4-one in refluxing *p*-xylene. The xylene was evaporated under reduced pressure and the residual oil was purified by silica gel flash chromatography using 10% ethylacetate in hexane as eluent to furnish the fluorous acetoacetate **1** as a white waxy solid in good yield Scheme 1.

The fluorous 3,4-dihydropyridone-5-carboxylate was synthesized employing a four component reaction developed by Suarez et al. [17], which involves using Meldrum's acid, a β-ketoester, and benzaldehyde in the presence of ammonium acetate in acetic acid as solvent, providing the dihydropyridone in reasonable yields.

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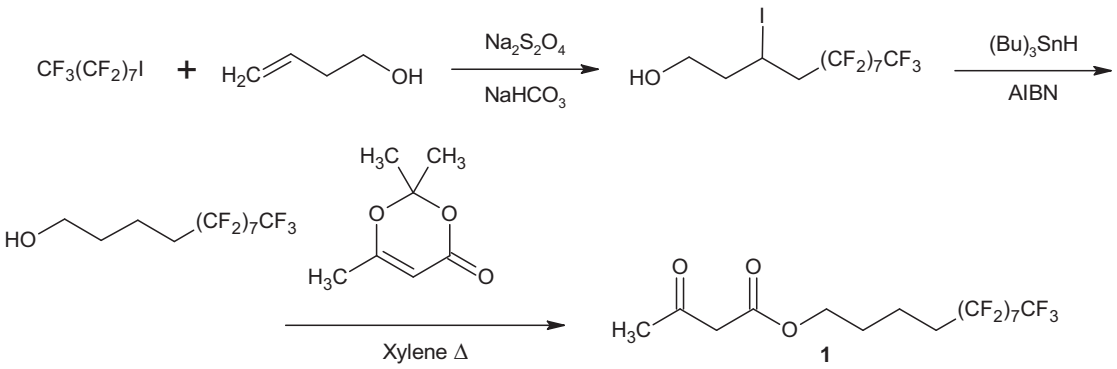
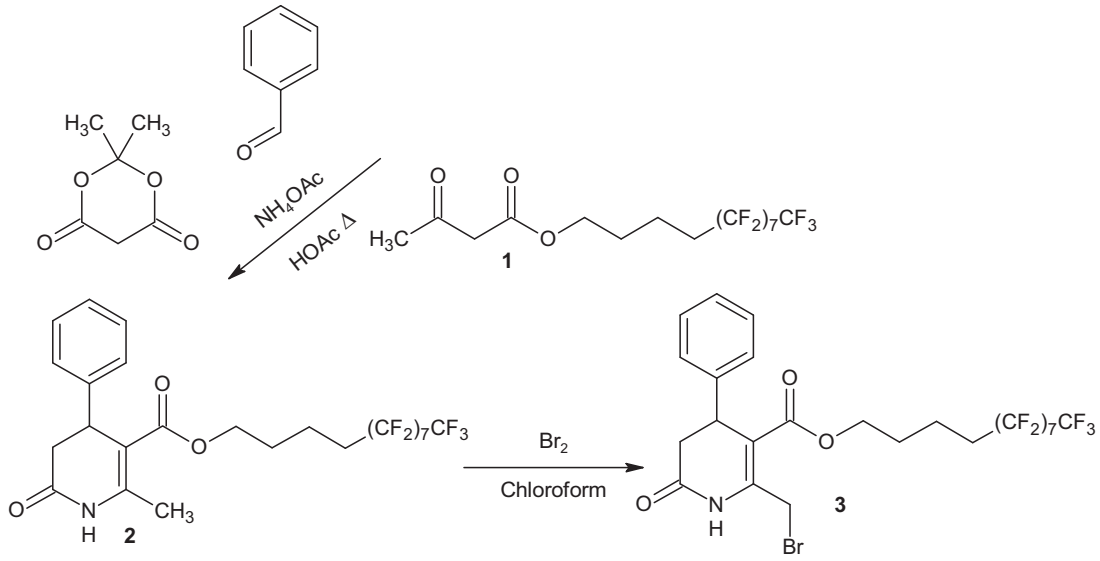


Scheme 1. Synthesis of a fluorous acetoacetate.



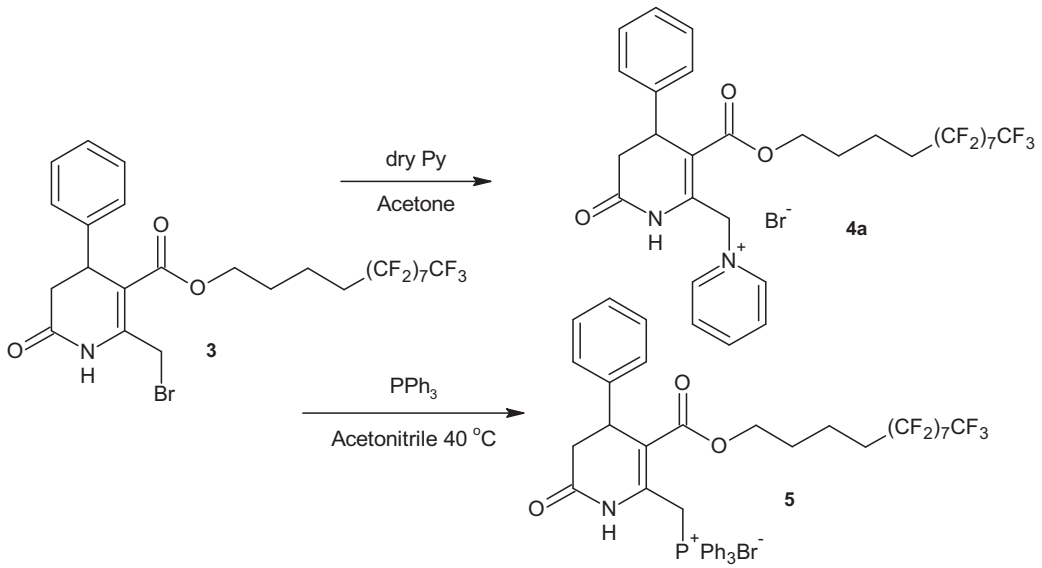
Scheme 2. Four component synthesis of 3,4-dihydropyridone and bromination of the 6-methyl group with bromine.

Thus by using the fluorous acetoacetate **1** as the β-ketoester Scheme 2, and after refluxing in glacial acetic acid for 6.5 h the reaction contents was poured in ice-water giving an orange syrup which after extraction with ethyl acetate and recrystallization from ethanol furnished the fluorous 3,4-dihydropyridone-5-carboxylate **2** as a yellow powder in 31% yield. Unlike the methyl ester dihydropyridones which give yields of around 60%, the fluorous ester seems to somehow interfere with the reactive centers in the reaction mixture reducing the yield quite substantially. The bromination of the 6-methyl group of 4-aryldihydropyridones described in the literature has been accomplished with *N*-bromosuccinimide (NBS) in refluxing chloroform for 10–14 h [17]. Although the 6-bromomethyl compound was not isolated its presence as intermediate was suggested by the subsequent lactonization producing γ-lactone fused 3,4-dihydropyridones. Another report on the 6-methyl group bromination utilized bromine in chloroform and irradiation with a 500 W lamp [18], in this case only the crude compound was isolated and not further characterized. In our case the 6-methyl group was brominated by dissolving the dihydropyridone in chloroform and simple drop-wise addition of a bromine chloroform solution with stirring. The reaction took place readily as indicated by the rapid discoloration of the bromine solution. After solvent removal the compound was dissolved in methanol and allowed to slowly crystallize in the dark, providing the light yellow compound **3** in 72% yield which could be fully characterized.

The bromine of 6-bromomethyl-3,4-dihydropyridone (**3**) was substituted with pyridine in dry acetone by stirring at room temperature overnight. The precipitated solids were filtered and washed with ethyl ether providing a white powder of the pyridinium bromide **4a** in 79% yield. The dodecyl ester analog **4b** of **4a** was also synthesized for comparison and its synthesis will be reported elsewhere. The substitution with triphenylphosphine was accomplished by warming in dry acetonitrile for 2 h when noticeable amounts of the triphenylphosphonium bromide **5** precipitated as a yellowish solid in 82% yield Scheme 3.

The determination of the structures of the synthesized compounds **1**–**5** were accomplished on the basis of 1D-^{1}H, ^{13}C, ^{19}F, ^{31}P and 2D-NMR ^{1}H-^{1}H, ^{19}F-^{19}F and ^{1}H-^{13}C spectra recorded in chloroform-d1 solution. The ^{1}H, ^{13}C, ^{19}F and ^{31}P chemical shifts are in full agreement with the proposed structures.

Atomic force microscopy (AFM) and dynamic light scattering (DLS) were employed to observe the self-assembly of compounds **4a**, **4b** and **5**. The samples were prepared in a dilute (0.03%, w/v) aqueous dispersion by sonication using a probe type sonicator. Compounds **4a** and **4b** were readily soluble in water and were sonicated for only 5 min but, compound **5** was quite insoluble and needed 25 min sonication for full dispersion. Using a longer sonification time, it is possible to obtain nanoparticles with a narrow size distribution, while after a short sonification time nanoparticles were quite different in their sizes and shapes. For AFM observation freshly cleaved mica plates were dipped into the solution and kept for 30 s to allow the nanoaggregates to stick to



Scheme 3. Synthesis of fluorous 3,4-dihydropyridone cationic amphiphiles.

the negatively charged surface. The mica samples were dried at room temperature and observed by AFM in tapping mode. AFM is a well established method for the characterization of nanoscale drug delivery systems (DDS) [19], enabling the direct observation of very small objects without the need of cumbersome and potentially contaminating sample preparation. Tapping mode AFM allows the investigation of soft samples with minimal sample alteration with a lateral resolution of several nanometers and height resolution of 0.1 nm [20]. Compound **5** formed nanoaggregates with a diameter of approximately 150 nm and height of 20 nm at the specified preparation conditions Fig. 1. Compounds **4a** and **4b** also formed similar aggregates but, the AFM images which we have obtain to date are not of publishable quality.

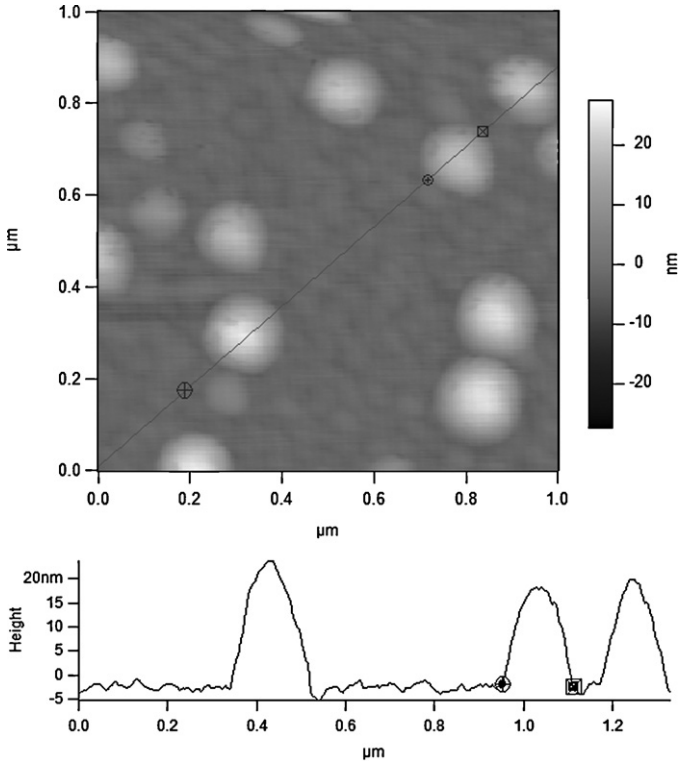


Fig. 1. AFM image of the self-assembled structures of fluorous 3,4-dihydropyridone triphenylphosphonium bromide amphiphile (**5**) adsorbed on a mica surface from aqueous solution with the corresponding height profiles (bottom).

This is consistent with the observations of Damas et al. that fluorinated surfactants with even a single chain can form bilayer aggregates or vesicles, although this is usually unfavorable for single chain hydrocarbon ones [21] however, since compound **4b** being the nonfluorinated analog of **4a**, also formed similar nanoaggregates it warrants further research on the nature of the aggregates formed, which could be provided by freeze-fracture electron microscopy. The hydrodynamic diameters of the nanoparticles (NPs) suspended in water were determined by DLS, Fig. 2 and the values are presented in Table 1. The advantages of DLS are rapidity of analysis, no requirement for calibration, and sensitivity [22].

The mean diameter represents the average diameter of all nanoaggregates in the sample and the most expected diameter depicts the diameter of the main population (or tip of the peak) of the nanoaggregate sample. The NPs from compound **4a** had the largest hydrodynamic diameter or approximately 250 nm and the nonfluorinated analog **4b** had a smaller diameter of approximately 165 nm. Both of the compounds formed NPs in a relatively narrow size distribution range. For the phosphonium amphiphile **5** two populations of NPs were observed, one at about 90 nm and the other at 395 nm diameters in approximately 3:1 ratio (Table 1, entry 3). Since micelle diameters are usually not more than about 30 nm these NPs could not be micelles, they could be liposomes or some other nanoaggregates but, without freeze-fracture electron microscopy it cannot be proved conclusively. There is a slight

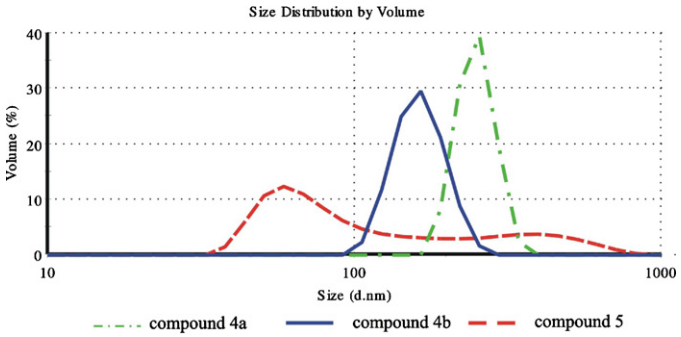


Fig. 2. Representative dynamic light scattering spectrum of NPs obtained from compounds **4a**; **4b** and **5** in distilled water.

Table 1
Characteristic hydrodynamic diameters of NPs determined by DLS.

Nr.	Comp.	DLS			
		Most expected $d_{[H]}$, nm		Mean $d_{[H]}$, nm (%)	
		Peak 1	Peak 2	Peak 1	Peak 2
1.	**4a**	255	–	249 (100)	–
2.	**4b**	164	–	164 (100)	–
3.	**5**	59	396	87 (75)	395 (25)

diameter size discrepancy between the AFM and DLS methods as observed for compound **5**. This could be due to the fact that DLS is performed on NPs in water which makes them fully hydrated, whereas, in AFM the samples are dried on a mica slide surface which may influence the size and shape of NPs. The polydispersity of the sample for compound **5** is explained by recognizing that DSL measures average size ranges whereas AFM visualizes only a small number of NPs.

3. Experimental

3.1. General

All reagents were purchased from Aldrich, Acros, Fluka or Merck and used without further purification. TLC was performed on 20 cm × 20 cm Silica gel TLC-PET F_{254} foils (Fluka). The one-dimensional ^{1}H (400 MHz), ^{19}F (376.2 MHz), ^{31}P (161.86 MHz) and ^{13}C (100.61 MHz) and two dimensional ^{1}H–^{1}H COSY, ^{19}F–^{19}F COSY, ^{13}C–^{1}H HMBC, ^{13}C–^{1}H HSQC NMR spectra of compounds were recorded on a Varian-Mercury BB 400 MHz. The ^{1}H–^{13}C-HMBC spectra were recorded with the evolution time of 62.5 s delay for the generation of long-range correlations. For all two dimensional ^{13}C–^{1}H HMBC, ^{13}C–^{1}H HSQC spectra 4096 × 1024 data matrix was used, which ensured τ_{2max} = 100 ms for ^{1}H and τ_{2max} = 50 ms for ^{13}C along the F1 and F2 axes, correspondingly. In order to improve the signal-noise ratio, the data matrix before Fourier transformation was zero-filled twice and multiplied with a cosine function. The chemical shifts of the hydrogen and carbon atoms are presented in parts per million and referred to the residual signals of the $CDCl_3$ solvent 7.25 (^{1}H) and 77.0 ppm (^{13}C) ppm respectively. The chemical shifts of fluorine and phosphorus atoms were referred to internal software standards $CFCl_3$ and H_3PO_4 correspondingly. Mass spectral data were determined on an Acquity UPLC system (Waters) connected to a Q-TOF micro hybrid quadrupole time of flight mass spectrometer (Micromass) operating in the ESI positive or negative ion mode on an Acquity UPLC BEH C18 column (1.7 μm, 2.1 mm × 50 mm) using a gradient elution with acetonitrile/phosphate buffer (pH 2.2; 0.05 M) in water (10:90 by volume) at a flow rate of 1 mL/min. Peak areas were determined electronically with a DP-800 (GBC Scientific Equipment). Melting points were determined on an OptiMelt (SRS Stanford Research Systems). The nanoaggregates were prepared by dispersing the compounds in water using a Cole Parmer probe type ultrasonic processor CPX 130W, U.S.A. and observed with MFP-3D-BIO™ atomic force microscope in dynamic mode using Olympus AC240TM tips. The characteristics of the formed nanoaggregates were determined by the Dynamic Light Scattering technique (DLS). For DLS measurements, we employed a Zetasizer Nano instrument. Nano–Nano S90: size range 1 nm–3 μm. Laser 633 nm and software of Malvern Instruments Ltd.

3.2. 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluorododecyl 3-oxobutanoate (1)

5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluorododecanol 6.45 g (0.0131 mol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one 1.86 g (0.0131 mol) in 50 mL *p*-xylene were heated in an oil bath and stirred at 160 °C for 2 h. The solvent was removed on a rotary evaporator to give 6.89 g of a light yellow oil. The oil was purified by a silica gel column using EtOAc/hexane as eluent 800 mL 5% and 500 mL 10% in EtOAc, the fractions were monitored on silica TLC plates with phosphomolybdic acid developer. Fractions with Rf = 0.1 were collected and concentrated to give 4.43 g 64% yield of oil which solidified, to a white powder, mp 76–79 °C. ^{1}H NMR, 400 MHz ($CDCl_3$): δ = 4.17 (t, $^{3}J_{HH}$ = 6.2 Hz, 2H, $OC\underline{H}_2$), 3.46 (s, 2H, $COC\underline{H}_2CO$), 2.21 (s, 3H, $COC\underline{H}_3$), 2.10 (m, 2H, $C\underline{H}_2CF_2$), 1.63–1.73 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_2CF_2$). ^{13}C NMR, 100.61 MHz ($CDCl_3$): δ = 200.26 ($\underline{C}O$), 167.02 ($\underline{C}OO$), 121–108 (six m, 8$\underline{C}F_2$'s), 64.47 ($O\underline{C}H_2$), 49.91 ($CO\underline{C}H_2$), 30.39 (t, $^{2}J_{CF}$ = 22.5 Hz, $CH_2\underline{C}F_2$), 30.04 (s, 3H, $\underline{C}H_3$), 27.90 ($OCH_2\underline{C}H_2$), 16.91 ($\underline{C}H_2CH_2CF_2$). ^{19}F NMR, 376.2 MHz ($CDCl_3$): δ = −80.99 (t, $^{3}J_{FF}$ = 9.67 Hz, 3F, $\underline{C}F_3$), −114.58 (m, 2F, $CH_2C\underline{F}_2$), −121.81 (m, 2F, $CH_2CF_2C\underline{F}_2$), −121.06 (m, 4F, $C\underline{F}_2C_2F_5$ and $CH_2C_2F_4C\underline{F}_2$), −122.86 (m, 2F, $CF_3C\underline{F}_2$), −123.61 (m, 2F, $C\underline{F}_2C_3F_7$), −126.27 (m, 2F, $C\underline{F}_2C_4F_9$). LC–MS: MS(+ESI) *m*/*z* (relative intensity): 599 ([M+Na]$^{+}$ 100) actual $C_{16}H_{13}F_{17}O_3$ MW 576.25.

3.3. 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluorododecyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (2)

An RB flask fitted with a water cooled condenser and a $CaCl_2$ guard tube was charged with Meldrum's acid 1.03 g (7.2 mmol), benzaldehyde 0.76 g (7.2 mmol), the above perfluoroalkyl acetoacetate (**1**) 4.13 g (7.2 mmol), ammonium acetate 0.83 g (10 mmol), and 12 mL glacial acetic acid. The reaction mixture was stirred magnetically and heated to reflux in an oil bath for 6.5 h, after which the heating was stopped and left stirring overnight. The reaction mixture was poured into ice water and extracted with 3× 50 mL EtOAc, and washed with brine, dried with Na_2SO_4 filtered and concentrated on the rotary evaporator to a light brown mass and after addition of 10 mL EtOH was left in the ice box to crystallize. The crystals were filtered on a sintered glass frit funnel and washed with cold EtOH to yield a light yellow compound 1.59 g 31% yield with Rf = 0.36 on a silica TLC in 9:7:1 chloroform:petroleum ether:acetone under UV light mp 114–120 °C. ^{1}H NMR, 400 MHz ($CDCl_3$): δ = 7.53 (br s 1H, N$\underline{H}$), 7.26 (t, $^{3}J_{HH}$ = 7.8 Hz, 2H, m-Ph), 7.19 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H, p-Ph), 7.15 (d, $^{3}J_{HH}$ = 7,8 Hz, 2H, o-Ph), 4.23 (dm, $^{3}J_{HH}$ = 8.1 Hz, 1H, $C_4\underline{H}$), 4.11 and 4.03 (dt, $^{2}J_{HH}$ = 11.5 Hz, $^{3}J_{HH}$ = 6.0 Hz, 2H, AB-sys, $OC\underline{H}_2$) 2.71 (dd, $^{2}J_{HH}$ = 16.5 Hz, $^{3}J_{HH}$ = 8 Hz, $C_5\underline{H}_A$), 2.94 (ddd, $^{2}J_{HH}$ = 16.5 Hz, $^{3}J_{HH}$ = 2 Hz, $^{4}J_{HH}$ = 0.9 Hz, $C_5\underline{H}_B$), 2.43 (s, 3H, $C\underline{H}_3$), 1.96 (m, 2H, $C\underline{H}_2CF_2$), 1.59 (m, 2H, $OCH_2C\underline{H}_2$), 1.47 (m, 2H, $C\underline{H}_2CH_2CF_2$).^{13}C NMR, 100.61 MHz ($CDCl_3$): δ = 170.04 (C_6), 166.65 ($\underline{C}OO$), 146.40 (C_2), 141.95 (i-Ph), 128.79 (m-Ph), 127.05 (p-Ph), 126.50 (o-Ph), 120–108 (six m, 8$\underline{C}F$'s), 106.84 (C_3), 63.21 $O\underline{C}H_2$), 38.23(C_4), 38.16(C_5), 30.50 (t, $^{2}J_{CF}$ = 23 Hz, $\underline{C}H_2CF_2$), 28.10 ($OCH_2\underline{C}H_2$), 19.23 ($\underline{C}H_3$), 16.93 ($\underline{C}H_2CH_2CF_2$). ^{19}F NMR ($CDCl_3$): δ = −80.76 (t, $^{3}J_{FF}$ = 10.4 Hz, 3F, $C\underline{F}_3$), −114.4 (m, 2F, $CH_2C\underline{F}_2$), −121.72 (m, 2F, $CH_2CF_2C\underline{F}_2$), −121.91 (m, 4F, $C\underline{F}_2C_2F_5$ and $CH_2C_2F_4C\underline{F}_2$), −122.69 (m, 2F, $CF_3C\underline{F}_2$), −123.51 (m, 2F, $C_3F_7C\underline{F}_2$), −126.1 (m, 2F, $C_4F_9C\underline{F}_2$). LC–MS: MS(+ESI) *m*/*z* (relative intensity): 728 ([M+Na]$^{+}$ 100) actual $C_{25}H_{20}F_{15}NO_3$ MW 705.40.

3.4. 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluorododecyl 2-(bromomethyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (3)

The above dihydropyridone (**2**) 0.71 g (1.0 mmol) was dissolved in 5 mL chloroform. While stirring magnetically 0.7 mL of a 0.232 g/mL Br_2 solution in chloroform (1.0 mmol) was added dropwise and the flask was stoppered and stirred 30 min. Then the flask contents were transferred to a 100 mL round bottom flask with an

additional chloroform wash and the solvent was removed on a rotary evaporator (foaming) and dissolved in about 1 mL MeOH and left to crystallize in the dark. The precipitated solid was filtered after 3 days as a light yellow solid powder 0.57 g, 72% yield and mp 100–104 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ = 7.95 (br s 1H, NH), 7.28 (t, $^3J_{HH}$ = 7,8 Hz, 2H, m-Ph), 7.21 (t, $^3J_{HH}$ = 7.8 Hz, 1H, p-Ph), 7.15 (d, $^3J_{HH}$ = 7,8 Hz, 2H, o-Ph), 4.88 (d, $^2J_{HH}$ = 11.2 Hz, 1H, CH_ABr), 4.57 (dd, $^2J_{HH}$ = 11.2 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, CH_BBr), 4.26 (dd, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 1.8 Hz, C_4H) 4.15 and 4.07 (two dt, $^2J_{HH}$ = 11.3, $^3J_{HH}$ = 6.1 Hz, 2H, OCH_2) 2.95 (dd, $^2J_{HH}$ = 16.5, $^3J_{HH}$ = 8.3, C_5H_A), 2.72 (ddd, $^2J_{HH}$ = 16.5, $^3J_{HH}$ = 2.1, $^4J_{HH}$ = 0.9, C_5H_B), 1.96 (m, 2H, CH_2CF_2), 1.60 (m, 2H, OCH_2CH_2), 1.47 (m, 2H, $CH_2CH_2CF_2$). ^{13}C NMR 100.61 MHz ($CDCl_3$): δ = 169.60 (C_6), 165.57 (COO), 144.46 (C_2), 141.01 (i-Ph), 129.02 (m-Ph), 127.38 (o-Ph), 126.44 (o-Ph), 120–108 (six br.m, 8CF's), 109.41 (C_3), 63.95 OCH_2), 38.33(C_4), 38.04 (C_5), 30.34 (t, $^2J_{CF}$ = 22.5 Hz, CH_2CF_2), 27.93 (OCH_2CH_2), 26.16 (CH_2Br), 16.90 ($CH_2CH_2CF_2$). ^{19}F NMR 376.2 MHz ($CDCl_3$): δ = −80.78 (t, $^3J_{FF}$ = 10.4 Hz, 3F, CF_3), −114.34 (m, 2F, CH_2CF_2), −121.73 (m, 2F, $CH_2CF_2CF_2$), −121.91 (m, 4F, $CF_2C_2F_5$ and $CH_2C_2F_4CF_2$), −122.71 (m, 2F, CF_3CF_2), −123.51 (m, 2F, $C_3F_7CF_2$), −126.1 (m, 2F, $C_4F_9CF_2$). LC–MS: MS(+ESI) *m*/*z* (relative intensity): 806 ([M+Na]$^+$ 100) actual $C_{25}H_{19}BrF_{15}NO_3$ MW 784.30.

3.5. 1-[3-(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluoro-dodecyloxycarbonyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridin-2-ylmethyl]-pyridinium bromide (4)

0.30 g (0.38 mmol) of the above compound **3** was dissolved in 0.5 mL dry acetone and while stirring magnetically (0.40 mmol) 0.032 g of dry pyridine were added and the flask was stoppered. The reaction mixture was left stirring overnight, filtered and the solid was washed with diethyl ether to provide 0.26 g of a white powder in 79% yield, mp 145–151 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ = 10.56 (br s, 1H, NH), 9.51 (d, $^3J_{HH}$ = 5.6 Hz, 2H, o-Py), 8.42 (t, $^3J_{HH}$ = 7.6 Hz, 1H, p-Py), 8.12 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.6 Hz, 2H, m-Py), 7.25 (t, $^3J_{HH}$ = 7.6 Hz, 1H, m-Ph), 7.21 (t, $^3J_{HH}$ = 7.6 Hz, 1H, p-Ph), 7.14 (d, $^3J_{HH}$ = 7.6 Hz, 2H, o-Ph), 6.39 and 6.25 (two d, $^2J_{HH}$ = 13.5 Hz, 2H, AB-syst, CH_2Py), 4.18 (dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, C_4H), 4.06 and 4.02 (two dt, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.4 Hz, 2H, AB-syst, OCH_2), 3.16 (dd, $^2J_{HH}$ = 16.1 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, CH_ACOO), 2.57 (d, $^2J_{HH}$ = 16.1 Hz, 1H, CH_BCOO), 1.94 (m, 2H, CH_2CF_2), 1.54 (m, 2H, CH_2CH_2O), 1.37 (m, 2H, $CH_2CH_2CF_2$). ^{13}C NMR, 100.6 MHz ($CDCl_3$): δ = 169.29 (C_6), 166.47 (COO), 145.97 (p-Py), 145.40 (o-Py), 141.74 (C_2), 141.14 (i-Ph), 129.0.5 (m-Ph), 128.56 (m-Py), 127.39 (p-Ph), 126.53 (o-Ph), 120–108 (six br m, 8CF's), 112.78 (C_3), 64.33 (OCH_2), 57.42 (C_2CH_2), 38.59 (C_4), 38.29 (C_5), 30.28 (t, $^2J_{CF}$ = 22.3 Hz, CH_2CF_2), 27.87 (OCH_2CH_2), 16.83 ($CH_2CH_2CF_2$). ^{19}F NMR, 376.2 MHz ($CDCl_3$): δ = −80.78 (t, $^3J_{FF}$ = 9.3 Hz, 3F, CF_3), −114.32 (m, 2F, CH_2CF_2), 121.73 (m, 2F, $CH_2CF_2CF_2$), −121.91 (m, 4F, CF_2C2F_5 and $CH_2C_2F_4CF_2$), −122.71 (m, 2F, CF_3CF_2), −123.51 (m, 2F, $C_3F_7CF_2$), −126.11 (m, 2F, $C_4F_9CF_2$). LC–MS: MS(+ESI) *m*/*z* (relative intensity): 784 ([M−Br]$^+$ 100) actual $C_{30}H_{24}BrF_{17}N_2O_3$ MW 863.40.

3.6. 1-[3-(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Heptadecafluoro-dodecyloxycarbonyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridin-2-ylmethyl]-triphenylphosphonium bromide (5)

0.50 g (0.64 mmol) of compound **3** and 0.17 g (0.64 mmol) triphenylphosphine were dissolved in 5 mL of dry acetonitrile. The yellow solution was stirred magnetically at 40 °C for 2 h and then cooled in the fridge. The precipitated product filtered and washed with diethyl ether to give 0.55 g (82%) of a yellowish powder mp 162–167 °C. ^{1}H NMR 400 MHz($CDCl_3$): δ = 10.06 (br s, 1H, NH), 7.85 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HP}$ = 13.5 Hz, 6H, o-Ph), 7.76 (td, $^3J_{HH}$ = 7.6 Hz, $^5J_{HP}$ = 1.7 Hz, 3H, p-Ph), 7.63 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HP}$ = 3.7 Hz, 6H, m-Ph), 7.20 (t, $^3J_{HH}$ = 7.6 Hz, 2H, m-Ph), 7.16 (t, $^3J_{HH}$ = 7.6 Hz, 1H, p-Ph), 7.04 (d, $^3J_{HH}$ = 7.6 Hz, 2H, o-Ph) 5.86 and 5.66 (two dt, $^2J_{HH}$ = 14.9 Hz, $^2J_{HP}$ = 14.7 Hz, 2H, AB-syst., C_2CH_2), 3.90 (m, 1H, C_4H), 3.75 and 3.52 (two dt, $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 6.2 Hz, 2H, OCH_2), 2.70 (dd, $^2J_{HH}$ = 16 Hz, $^3J_{HH}$ = 8.7 Hz, 1H, C_5H_A), 2.42 (dd, $^2J_{HH}$ = 16 Hz, $^2J_{HH}$ = 1.9 Hz, 1H, C_5H_B), 1.87 (m, 2H, CH_2CF_2), 1.35 (m, 2H, OCH_2CH_2), 1.27 (m, 2H, $CH_2CH_2CF_2$). ^{13}C NMR 100.6 MHz ($CDCl_3$): δ = 167.92 (C_6), 165.96 (d, $^3J_{CP}$ = 3 Hz, COO), 141.21 (d, $^5J_{CP}$ = 3.9 Hz, i-Ph), 140.96 (d, $^2J_{CP}$ = 11.3 Hz, C_2), 135.24 (d, $^4J_{CP}$ = 3.3 Hz, 3 C, p-Ph) 134.62 (d, $^2J_{CP}$ = 10.4 Hz, 6 C, o-Ph), 130.01 (d, $^3J_{CP}$ = 13.2 Hz, 6 C, m-Ph), 128.9 (m-Ph), 127.26 (p-Ph), 126.62 (o-Ph), 117.43 (d, $^1J_{CP}$ = 86.6 Hz, 3 C, i-Ph), 111.41 (d, $^3J_{CP}$ = 9.3 Hz, C_3), 120–108 (six br m, 8CF's), 63.57 (OCH_2), 38.33 (d, $^4J_{CP}$ = 2.4 Hz, C_4), 38.04 (C_5), 30.21 (t, $^2J_{CF}$ = 23.2 Hz, CH_2CF_2), 27.73 (OCH_2CH_2), 27.32 (d, $^1J_{CP}$ = 48.9 Hz, CH_2Br), 16.78 ($CH_2CH_2CF_2$). ^{19}F NMR 376.2 MHz ($CDCl_3$): δ = −80.79 (t, $^3J_{FF}$ = 9.74 Hz, 3F, CF_3), −114.32 (m, 2F, CH_2CF_2), −121.72 (m, 2F, $CH_2CF_2CF_2$), −121.92 (m, 4F, $CF_2C_2F_5$ and $CH_2C_2F_4CF_2$), −122.71 (m, 2F, CF_3CF_2), −123.52 (m, 2F, $C_3F_7CF_2$), −126.11 (m, 2F, $C_4F_9CF_2$). ^{31}P NMR 161.86 MHz ($CDCl_3$) δ = 24.77 ppm. LC–MS: MS(+ESI) *m*/*z* (relative intensity): 966 ([M−Br]$^+$ 100) actual $C_{43}H_{34}BrF_{17}NO_3P$ MW 1046.59.

3.7. Sample preparation for AFM and DLS observations

Compound **4a**, **4b**, or **5** was dispersed in an aqueous solution at a concentration of 0.3 mg/mL by sonication using a probe type sonicator, Cole Palmer ultrasonic processor CPX 130 (W), amplitude 30%, pulse 15 s on, 15 s off, 5 min. – compound **4a** and **4b** and 25 min. – compound **5**. Freshly cleaved mica plates were dipped into the solutions and kept for 30 s to allow the nanoaggregates to stick to the negatively charged surface. The mica samples were dried at room temperature and observed by AFM in tapping mode. The DLS measurements on the same aqueous samples were recorded on a Zetasizer Nano S90 instrument.

4. Conclusion

A fluorous 3,4-dihydro-2(1*H*)-pyridone-5-carboxylate has been synthesized and further elaborated to yield two cationic amphiphiles with either a pyridinium bromide or triphenylphosphonium bromide polar head group. These amphiphiles self-assembled in aqueous solution and as observed by AFM formed nanoaggregates. The hydrodynamic diameters ranging from 90 to 395 nm were determined by DLS measurements. NPs with a diameter range 100–200 nm are good candidates for cellular transport applications, and further studies to this end are continuing in our lab.

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References

[1] M.F. Strozhev, I.E. Lielbriedis, O.Ya. Neiland, Chem. Heterocycl. Compd. 26 (1990) 655–657.
[2] A. Morales, E. Ochoa, M. Suárez, Y. Verdecia, L. Gonzalez, J. Heterocycl. Chem. 33 (1996) 103–107.
[3] E. Ruiz, H. Rodríguez, J. Coro, E. Salfrán, M. Suárez, R. Martínez-Alvarez, N. Martín, J. Ultsonch. 18 (2011) 32–36.
[4] E. De Clercq, Farmaco 54 (1999) 26–45.
[5] R.L.T. Parreira, O. Abrahao, S.E. Galembeck, Tetrahedron 57 (2001) 3243–3253.
[6] G. Pastelin, R. Mendez, E. Kabela, A. Farah, Life Sci. 33 (1983) 1787–1796.

[7] W.K. Anderson, D.C. Dean, T. Endo, J. Med. Chem. 33 (1990) 1667–1675.
[8] S.B. US Patent 5,962,478 (1999).
[9] Q. Li, L.A. Mitscher, L.L. Shen, Med. Res. Rev. 20 (2000) 231–293.
[10] P.S. Dragovich, T.J. Prins, R. Zhou, E.L. Brown, F.C. Maldonado, S.A. Fuhrman, L.S. Zalman, T. Tuntland, C.A. Lee, A.K. Patick, D.A. Matthews, T.S. Hendrickson, M.B. Kosa, B. Liu, M.R. Batugo, J.P.R. Gleeson, S.K. Sakata, L. Chen, M.C. Guzman, J.W. Meador III, R.A. Ferre, S.T. Worland, J. Med. Chem. 45 (2002) 1607–1623.
[11] P.S. Dragovich, T.J. Prins, R. Zhou, T.O. Johnson, E.L. Brown, F.C. Maldonado, S.A. Fuhrman, L.S. Zalman, A.K. Patick, D.A. Matthews, X. Hou, J.W. Meador, R.A. Ferre, S.T. Worland, Bioorg. Med. Chem. Lett. 12 (2002) 733–738.
[12] S.J. Patankar, P.C. Jurs, J. Chem. Inf. Comput. Sci. 42 (2002) 1053–1068.
[13] Z. Hyvonen, A. Plotniece, I. Reine, B. Chekavichus, G. Duburs, A. Urtti, Biochim. Biophys. Acta, Biomembranes 1509 (2000) 451–466.
[14] M.P. Krafft, F. Giulieri, J.G. Riess, Angew. Chem. Int. Ed. Engl. 32 (1993) 741–743.
[15] M.P. Krafft, J. Polym. Sci. Part A: Polym. Chem. 44 (2006) 4251–4258.
[16] L.J. Alvey, R. Meier, T. Soós, P. Bernatis, J.A. Gladysz, Eur. J. Inorg. Chem. (2000) 1975–1983.
[17] E. Ochoa, M. Suarez, Y. Verdecia, B. Pita, N. Martin, M. Quiteiro, C. Seoane, J.L. Soto, J. Duque, R. Pomes, Tetrahedron 54 (1998) 12409–12420.
[18] Z.A. Kalme, R.A. Zhalubovskis, A. Shmidlers, J. Celmins, G. Duburs, Chem. Heterocycl. Compd. 40 (2004) 862–868.
[19] J. Sitterberg, A. Ozcetin, C. Ehrhardt, U. Bakowsky, Eur. J. Pharm. Biopharm. 74 (2010) 2–13.
[20] E.I. Goksu, J.M. Vanegas, C.D. Blanchette, W.C. Lin, M.L. Longo, Biochim. Biophys. Acta 1788 (2009) 254–266.
[21] T.H.V. Ngo, C. Damas, R. Naejus, R. Coudert, J. Fluorine Chem. 131 (2010) 704–708.
[22] S.K. Brar, M. Verma, Trends Anal. Chem. 30 (2011) 4–17.