Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 47 (2006) 7117–7120

Tetrahedron
Letters

A fluorocarbon nucleoamphiphile for the construction of actinide loaded microspheres

Louis Moreau,[a] Nathalie Campins,[a] Mark W. Grinstaff[b] and Philippe Barthélémy[a,*]

[a] *Inserm, U386, Bordeaux, F-33076 France; Université Victor Segalen Bordeaux 2, 146 rue Leo Saignat, F-33076, Bordeaux Cedex, France*

[b] *Departments of Biomedical Engineering and Chemistry, Metcalf Center for Science and Engineering, Boston University, Boston MA 02215, USA*

Received 25 April 2006; revised 22 June 2006; accepted 26 June 2006

Abstract—The synthesis of a novel fluorocarbon based nucleoamphiphile; 2′,3′-*O*-di-2*H*,2*H*,3*H*,3*H*-perfluoro-undecanoyl-uridine-5′-phosphocholine (DiF$_{17}$UPC) is described. DiF$_{17}$UPC self-assembles into lamellar organizations unlike 1,2-distearoyluridinophosphocholine (DSUPC) which forms DNA-like helical fibre under similar conditions. The fluorocarbon chains have a significant impact on the supramolecular assemblies formed by the nucleoamphiphiles. The SEM and TEM images collected clearly indicate the formation of microspheres when DiF$_{17}$UPC is hydrated in the presence of thorium nitrate at high temperature ($T > 90$ °C). The DiF$_{17}$UPC/Th^{4+} microspheres vary in size from 0.5 to 12 μm.

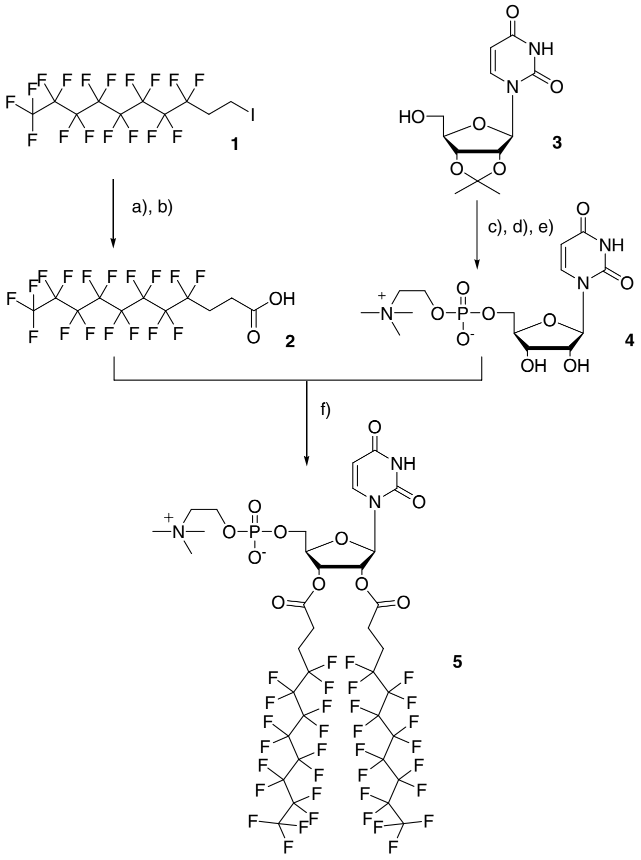
Due to their unique properties, fluorocarbon amphiphiles are being investigated in many areas including biology, chemistry and material science.[1–4] Amphiphiles possessing perfluoroalkyl chains possess high chemical–thermal stabilities, a remarkable biological inertness and an extreme hydrophobic character as well as lipophobic characteristics. These properties lend to amphiphiles which can be used to prepare nano and micro structures. Of the many self-assembled structures which can be formed, microspheres are of interest for fundamental studies as well as for applications.[5] Recently, we have reported the formation of hollow microspheres constructed from f-block elements and hydrocarbon amphiphiles. These hybrid lipid–salt supramolecular assemblies are prepared simply by mixing a nucleoside based amphiphile[6] with an aqueous solution containing either actinide or lanthanide salts.[7] We have demonstrated that the stabilization of the hybrid hollow microspheres depends on the following three stabilizing factors (a) chain–chain hydrophobic interactions; (b) base–base formation and (c) phosphate/salt binding. Owing to their remarkable properties, fluorocarbon chains constitute a useful building block for the construction of supramolecular systems such as microspheres. To this end, the combination of the self-assembly potential of nucleoside with the hydrophobic character of highly fluorinated chains represents an approach to prepare new self-assembled structures. In the present study, we report the synthesis of a zwitterionic fluorocarbon nucleoamphiphile, its self-assembly properties and the formation of microspheres in the presence of Thorium salts. The chemical structure of the new fluorocarbon amphiphile **5** derived from uridine phosphocholine is shown in Scheme 1.

The fluorocarbon amphiphile **5** was synthesized following a route as detailed in Scheme 1. First, in a two-step procedure the fluorinated acid **1** (2*H*,2*H*,3*H*,3*H*-perfluoroundecanoic acid),[8] having two methylene groups as a spacer, was synthesized from the commercially available compound **1**. Following a published procedure,[9] the uridine acetonide derivative **3** was reacted with an excess of chloro-oxo-dioxaphospholane in THF at 0 °C to afford a cyclic phosphate function grafted to the 5′-hydroxyl (Scheme 1, step c). Treatment of the resulting intermediate with trimethylamine in acetonitrile gave the phosphocholine moiety (Scheme 1, step d). Finally, the 5′-phosphocholine uridine **4** was obtained after cleavage of the isopropylydene protecting group in acidic conditions. 2*H*,2*H*,3*H*,3*H*-Perfluoroundecanoic acid was

---

* Corresponding author. Tel.: +33 5 57 57 10 14/48 53; fax: +33 5 57 57 10 15; e-mail: barthelemy@bordeaux.inserm.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.182



Scheme 1. Reagents and conditions: (a) KCN, H_2O, DMSO, heating at 70 °C, 20 h (yield = 50%); (b) H_2SO_4, CH_3COOH, H_2O, heating at 100 °C, 24 h (yield = 77%); (c) chloro-oxo-dioxaphospholane, TEA, THF, 0 °C, 15 h; (d) trimethylamine, AcCN, THF, 60 °C, 24 h (yield for c) and (d): 82%; (e) HCl in HCO_2H/H_2O (yield = 70%) and (f) $C_{10}H_4F_{17}CO_2H$, DCC, DMAP, DMF, 24 h (yield = 42%).

DCC coupled to the 2′ and 3′ secondary hydroxyls of **4** to afford the fluorinated nucleoamphiphile **5** (2′,3′-*O*-di-2*H*,2*H*,3*H*,3*H*-perfluoro-undecanoyl-uridine-5′-phosphocholine, $DiF_{17}UPC$).[10]

Given our interest in nucleoamphiphiles, one of the goals of the present study is to characterize the properties of $DiF_{17}UPC$ and compare those results with that observed for the analgous hydrocarbon nucleoamphiphiles. In order to determine the morphology of fluorocarbon nucleoamphiphile supramolecular assemblies at room temperature, an aqueous $DiF_{17}UPC$ solution (5 mg/mL) was sonicated in a Branson 3200 cleaning bath for 15 min. As shown in Figure 1, this procedure affords heterogeneous large vesicular organizations and/or lamellar systems. In such systems, the main phase transition temperature (T_m) is an important parameter that determines the permeability and the stability of the bilayers. It has been shown that fluorinated phosphocholine amphiphiles featuring a C_8F_{17} segment possess substantial higher melting temperatures than their hydrocarbon analogues.[11,12] No phase transition was detected for $DiF_{17}UPC$ dispersed in distilled water (0.5 mg/μL, in the range 3–95 °C) by modulated differential scanning calorimetry (MDSC). This result suggest a T_m value likely above 95 °C indicating a high membrane ordering likely due to the presence of the uridine moiety on the molecular structure. Surprisingly, contrary to hydrocarbon analogs, $DiF_{17}UPC$ tends to form lamellar systems below T_m. Hydrocarbon nucleoamphiphiles possessing saturated alkyl chains such as DSUPC (1,2-distearoyluridinophosphocholine), self-assemble into helical structures in the crystalline state below their T_m and bilayers above T_m.[9] The unexpected lamellar systems observed in the case of $DiF_{17}UPC$ below T_m can be partly explained by the greater stiffness and volume of the fluorocarbon chains, which prohibit the chain–chain packing needed for the stabilization of the helical structure previously observed for hydrocarbon derivatives. Indeed, the volume of CF_2 and CF_3 groups are estimated at 38 and 92 Å^3 versus 27 and 54 Å^3 for CH_2 and CH_3, respectively.[13,14] These characteristics generally tend to form aggregates possessing a small curvature and low surface energy.[15] In our case, the high volume of the $DiF_{17}UPC$ chains stabilizes a heterogeneous lamellar assembly in the crystalline state below T_m, whereas the uridine moiety increases the membrane rigidity. A drawing illustrating the different self assembled structures observed at room temperature for $DiF_{17}UPC$ (bilayer, left) and DSUPC (helical structure, right) is shown in Figure 2.

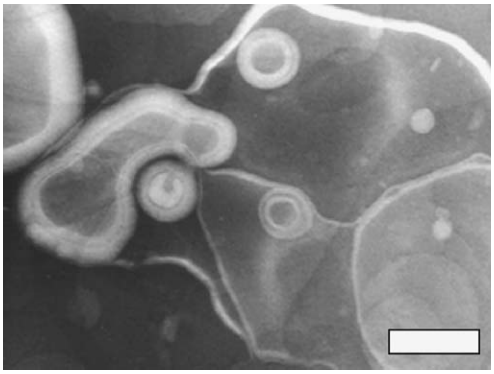


Figure 1. TEM image of lamellar systems obtained after sonication and extrusion of $DiF_{17}UPC$ (bar 250 μm).

We next focused our attention on the application of $DiF_{17}UPC$ as a building block for the construction of hybrid microspheres. We have previously demonstrated that microspheres can be obtained in the presence of highly hydrophobic nucleoamphiphiles bearing saturated chains.[7] When a natural phospholipid (such as DSPC, 1,2-distearoylphosphocholine), which lacks the nucleoside is used instead of DSUPC, no microspheres are observed. Among the various parameters important for the formation of hybrid microspheres, chain–chain hydrophobic interactions play a major role in the assembly process. We hypothesized that the use of a fluorocarbon amphiphile would allow for the stabilization of these hybrid micro-objects. For this purpose, the 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoyl chain was selected to provide a similar hydrophobicity as the palmitoyl/stearoyl hydrocarbon chains. Given that one CF_2 group corresponds to roughly 1.7 CH_2 groups in terms of hydrophobic character.[16] We estimated that the

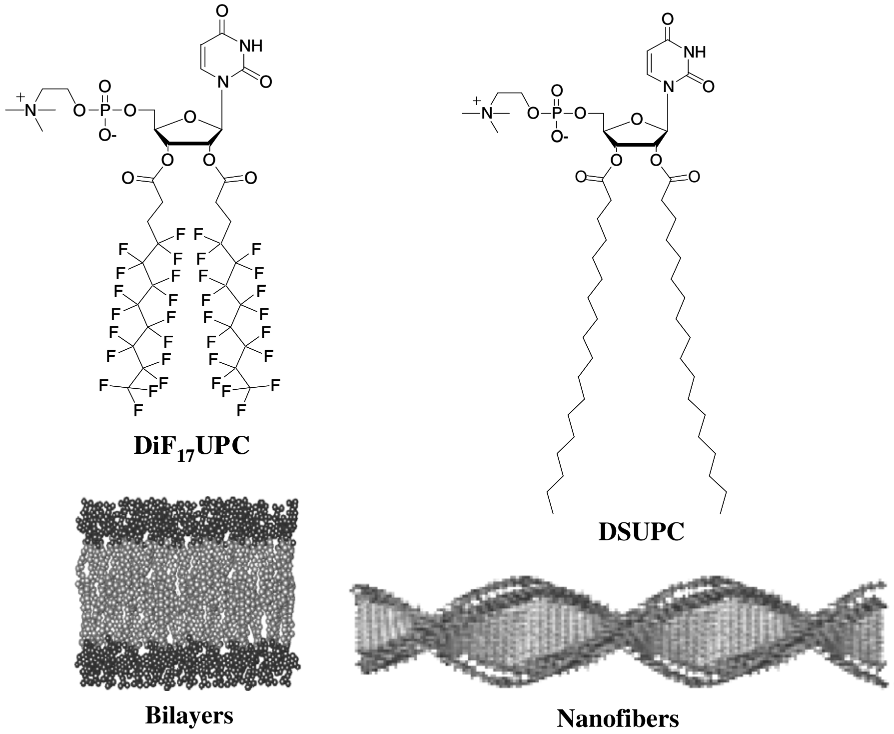


Figure 2. Illustration of the different supramolecular organizations obtained. At room temperature DiF$_{17}$UPC stabilizes a lamellar system (left), whereas helical structures are observed with DSUPC in the same conditions (right).

hydrophobic character of DiF$_{17}$UPC would be similar to DPUPC (1,2-Dipalmitoyluridinophosphocholine) and DSUPC, which are the best hydrocarbon nucleoamphiphiles for forming microspheres.

We investigated whether DiF$_{17}$UPC was capable to form microspheres in the presence of thorium or not. DiF$_{17}$UPC (20 mg) was hydrated in the presence of 0.5 mL of a thorium nitrate solution (0.16 M) at high temperature (95 °C) for 2 min. This procedure affords a white precipitate, which was characterized by Scanning Electron Microscopy (SEM). As shown in Figure 3, the precipitate exhibits numerous microspheres varying in size between 0.5 and 12 μm. The size distribution of the DiF$_{17}$UPC/Th^{4+} microspheres obtained was compared to DSUPC/Th^{4+} micro-objects previously described. The results obtained from the electron microscopic images (SEM) revealed a slightly more polydisperse population in the case of the DiF$_{17}$UPC with few large objects (diameter >5 μm), which were not observed in the case of DSUPC samples. A mean diameter of approximately 2.5 μm was observed in both cases (Fig. 3c). A TEM photograph of DSUPC/Th^{4+} microspheres is shown in Figure 3d.

In summary, we have synthesized the first example of a fluorocarbon nucleoamphiphile using a four steps synthetic route. The presence of the fluorocarbon chains on the 5′-phosphocholine nucleoside structure gives self-assembled lamellar systems in aqueous media at room temperature, whereas its hydrocarbon analogues (DPUPC, DSUPC) form helical structures under similar conditions. This different behaviour indicates the impact of the fluorocarbon chains on the organization of the

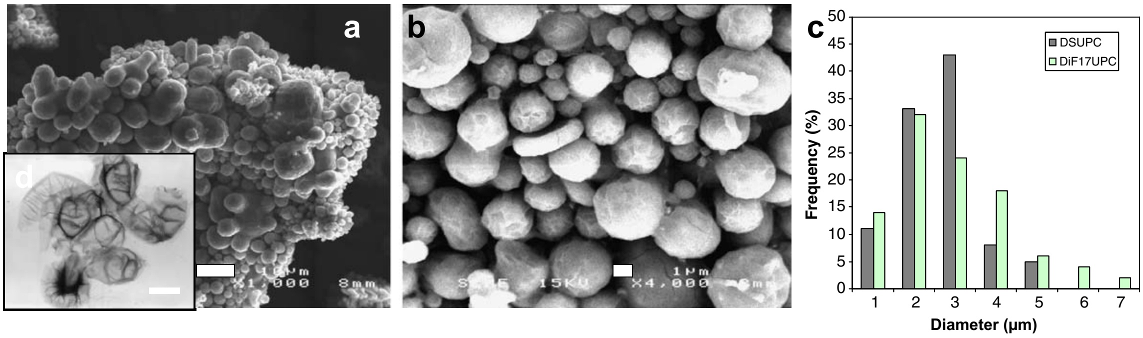


Figure 3. (a) and (b) SEM images of DiF$_{17}$UPC/Th^{4+} microspheres at different magnifications (bars: 10, 1 and 2 μm, (a), (b) and (d), respectively). (c) Microspheres populations of DiF$_{17}$UPC/Th^{4+} (grey) and DSUPC/Th^{4+} (green) systems. (d) Inset (a), TEM image showing thorium loaded microspheres.

supramolecular systems. The formation of actinide loaded microspheres illustrates that fluorocarbon nucleoamphiphiles can be used to construct hybrid supramolecular systems. Such materials are likely to be of interest for multiple applications ranging from chemistry to medicine.[17] In fine, these data show that combining fluorocarbon chains with nucleoside moieties affords interesting structures and these results broaden the scope and potential uses of nucleoamphiphiles in the field of supramolecular chemistry.

Acknowledgements

This work was supported by the Army Research Office and the 'Association pour la Recherche sur le Cancer' (ARC), which are greatly acknowledged.

References and notes

1. Riess, J. G. *Tetrahedron* **2002**, *58*, 4113.
2. Krafft, M. P. *Adv. Drug Delivery Rev.* **2001**, *47*, 209.
3. (a) Kissa, E. Fluorinated Surfactants. Synthesis. Properties. Applications. In *Surfactant Science Series*; Marcel Dekker: New York, 1994; Vol. 50; (b) Kissa, E. *Fluorinated surfactants and repellents*, 2nd ed. In Surfactant science; Marcel Dekker: New York, 2001.
4. Barthélémy, P.; Chaudier, Y.; Tomao, V.; Pucci, B. Fluorocarbon amphiphiles for supramolecular assemblies. In *Self Assembly*; Robinson, B. H., Ed.; IOS Press: Amsterdam, The Netherlands, 2003; pp 80–91.
5. (a) Shchukin, D. G.; Sukhorukov, G. B.; Möhwald, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4472; (b) McKenna, B. J.; Birkedal, H.; Barti, M. H.; Deming, T. J.; Stucky, G. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5652; (c) Thibault, R. J.; Hotchkiss, P. J.; Gray, M.; Rotello, V. M. *J. Am. Chem. Soc.* **2003**, *125*, 11249; (d) Peyratout, C. S.; Dähne, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3762; (e) Webb, A. G.; Wong, M.; Kolbeck, K. J.; Magin, R.; Suslick, K. S. *J. Magn. Reson. Imaging* **1996**, *6*, 675.
6. (a) Berti, D.; Baglioni, P.; Bonaccio, S.; Barsacchi-Bo, G.; Luisi, P. L. *J. Phys. Chem. B* **1998**, *102*, 303; (b) Onda, M.; Yoshihara, K.; Koyano, H.; Ariga, K.; Kunitake, T. *J. Am. Chem. Soc.* **1996**, *118*, 8524; (c) Baglioni, P.; Berti, D. *Curr. Opin. Colloid Interface Sci.* **2003**, *8*, 55; Moreau, L.; Grinstaff, M. W.; Barthélémy, P. *Tetrahedron Lett.* **2005**, *46*, 1593.
7. Moreau, L.; Ziarelli, F.; Grinstaff, M. W.; Barthélémy, P. *Chem. Commun.* **2006**, *15*, 1661.
8. Compound **2** showed consisting spectroscopic data according to the literature (Benno Hungerhoff, Helmut Sonnenschein and Fritz Theil, *J. Org. Chem.* **2002**, *67*, 1781).
9. Moreau, L.; Barthélémy, P.; El Maataoui, M.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2004**, *126*, 7533.
10. *Preparation of 2′,3′-O-di-2H,2H,3H,3H-perfluoro-undecanoyl-uridine-5′-phosphocholine* **5**: *2H,2H,3H,3H*-perfluoroundecanoic acid **2** (720 mg, 3 equiv, 1.47 mM), DCC (303 mg, 3 equiv, 1.47 mM) and DMAP (180 mg, 3 equiv, 1.47 mM), were added to uridine phosphocholine **4** (200 mg, 0.49 mM) in 12 mL of anhydrous DMF. After 24 h at room temperature, the DMF was evaporated and the residual solid was dissolved in 20 mL of methylene chloride–methanol 1:1. DCU was removed by filtration and solvent was removed under reduced pressure. The crude material was purified by exclusion chromatography (LH 20, DCM/MeOH 5/5). 280 mg of a white powder (product **5**) was isolated. (Yield: 42%.) rf: 0.30 (reverse phase, DCM/MeOH 5/5). ^{1}H NMR (300.13 MHz, CD_3OD) δ: 2.31 (m, 4H, $–CF_2CH_2–$), 3.64 (m, 4H, $–CO_2CH_2–$), 4.23 (s, 9H, $N(CH_3)_3$), 4.65 (m, 2H, CH_2N^+), 5.09 (m, 2H, H5′), 5.28 (m, 2H, CH_2O), 5.40 (m, 1H, H4′), 6.47 (m, 1H, H3′), 6.58 (m, 1H, H2′), 6.79 (d, $J = 8.12$ Hz, 1H, H5), 7.14 (d, $J = 6.61$ Hz, 1H, H1′), 8.90 (d, $J = 8.12$ Hz, 1H, H6). ^{13}C NMR (75.468 MHz, CD_3OD) δ: 26.03 ($–C{=}OCH_2–$), 26.99 ($–C{=}OCH_2–$), 31.91 ($–CF_2CH_2–$), 33.22 ($–CF_2CH_2–$), 54.78 $N^+(CH_3)_3$, 60.64 (CH_2O), 66.13 ($C_{5'}$), 67.58 (N^+CH_2), 73.08 ($C_{3'}$), 74.97 ($C_{2'}$), 83.12 ($C_{4'}$), 87.89 ($C_{1'}$), 103.93 (C_5), 106.25 ($–CF_{2–}$), 107.68 ($–CF_2–$), 108.05 ($–CF_2–$), 108.15 ($–CF_2–$), 111.60 ($–CF_2–$), 112.17 ($–CF_3$), 112.67 ($–CF_2–$), 116.62 ($–CF_2–$), 142.30 (C_6), 152.40 (C_2), 165.82 (C_4), 171.73 ($–C{=}O–$), 171.94 ($–C{=}O–$). ^{19}F NMR (282 MHz, CD_3OD): −82.81 (t, $J = 10.31$ Hz, 3F, CF_3), −82.94 (t, $J = 10.31$ Hz, 3F, CF_3), −116.25 (m, 4F, CF_2), −123.38 (m, 12F, CF_2), −124.22 (m, 4F, CF_2), −124.92 (m, 4F, CF_2), −127.78 (m, 4F, CF_2). ^{31}P NMR (121.495 MHz, CD_3OD): −0.557 ppm. FAB^+ MS (MH^+): 1358.
11. (a) Ravily, V.; Santaella, C.; Vierling, P.; Gulik, A. *Biochim. Biophys. Acta (BBA) – Biomembranes* **1997**, *1324*, 1; (b) Kunitake, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 6, 709.
12. Santaella, C.; Vierling, P.; Riess, J. G.; Gulik-Krzywicki, T.; Gulik, A.; Monasse, B. *Biochim. Biophys. Acta (BBA) – Biomembranes* **1994**, *1190*, 25.
13. (a) Tiddy, G. J. T. Concentrated surfactant systems. In *Modern Trends of Colloid Science in Chemistry and Biology*; Eicke, H. F., Ed.; Birkhäuser: Basel, 1985; pp 148–159; (b) Smart, B. E. Characteristics of C–F systems. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 57–88.
14. Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99.
15. Mukerjee, P. *Coll. Surf., A* **1994**, *84*, 1.
16. Ravey, J. C.; Stébé, M. *Coll. Surf., A* **1994**, *84*, 11.
17. (a) Bunzli, J.-C.; Piguet, C. *Chem. Rev.* **2002**, *102*, 1897; (b) Hainfeld, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11064; Gorden, A. E. V.; Xu, J.; Raymond, K. N.; Durbin, P. *Chem. Rev.* **2003**, *103*, 4207.