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Tomáš Bříza[a]; Robert Kaplánek[b]; Martin Havlík[a]; Bohumil Dolenský[a]; Zdeněk Kejík[a]; Pavel Martásek[b]; Vladimír Král[a]
[a] Department of Analytical Chemistry, Institute of Chemical Technology in Prague, Prague 6, Czech Republic [b] First Faculty of Medicine, Charles University in Prague, Prague 2, Czech Republic

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Synthesis of Highly Functionalized Fluorinated Porphyrins

TOMÁŠ BŘÍZA[a,b,*], ROBERT KAPLÁNEK[a,b,*], MARTIN HAVLÍK[a], BOHUMIL DOLENSKÝ[a], ZDENĚK KEJÍK[a], PAVEL MARTÁSEK[b] and VLADIMÍR KRÁL[a]

[a]*Department of Analytical Chemistry, Institute of Chemical Technology in Prague, Technická 5, Prague 6 16628, Czech Republic;* [b]*First Faculty of Medicine, Charles University in Prague, Katerinská 32, Prague 2 12108, Czech Republic*

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Highly functionalized fluorinated porphyrins were synthesized by a convergent strategy. Nucleophilic substitution using fluorinated branched unit and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin afforded highly functionalized fluorinated porphyrin 8 containing 24 fluorinated chains in the peripheral region.

Keywords: Fluorinated dendritic structure; Polyfluoroalkylated porphyrin; Fluorous; Porphyrin core

INTRODUCTION

Fluorinated highly branched structures are a specific class of highly functionalized compounds possessing remarkable properties. Several fluorinated dendrimers have been synthesized to date [1]. These fluorinated macromolecules can be utilized, for example, as surfactants in biphasic systems [2], phase transfer catalysts [3], and nanoreactors [4]. In the field of material science they have been used as electron transport materials for organic light-emitting diodes [5], materials for non-linear optic [6] and, in the field of biomedicinal chemistry, as drug delivery systems [7]. Known fluorinated highly branched structures reported previously contain a core such as aryls [8], alkylsilanes [9], aminoalkylmethanes [2], azacrowns [10], thiophosphates [11], fluorophenyls [12], cations of transition metals [13], etc. To the best of the author's knowledge, there are only a few polyfluoralkylated porphyrins.

In 1997 Pozzi *et al.* prepared highly fluorinated porphyrin [14]. It containined eight polyfluorinated chains and was used as a ligand for fluorous biphasic catalysis [14]. In 2002 a porphyrin substituted with four polyfluorinated chains was prepared which showed complexation ability for fluorinated aromatic compounds [15]. Thus, the aim is to develop synthetic routes for the preparation of highly functionalized fluorinated porphyrins which could serve in novel investigations.

RESULTS AND DISCUSSION

The strategy for preparation of highly functionalized fluorinated porphyrins is based on, analogous to syntheses of dendrimers, convergent approach. Suitable dendrons are synthesized and then connected to the porphyrin skeleton. The design utilizes highly functionalized benzene derivatives.

Initially, a suitable building block for the construction of the branched fluorinated unit was looked for. Methyl gallate was chosen because it enables the connection of three fluorinated units via hydroxyl groups. Moreover, it bears an ester moiety, which can be employed after another transformation (reduction) as a focal site for monomer connectivity.

As a model dendritic unit a gallate substituted with three 3-(perfluorohexyl)propyl chains was chosen. Similar gallates with three fluorinated chains were already prepared [16–18], but the fluorinated chains were separated from the gallate group by a four carbon spacer. The method used enables one to prepare dendrons whereby perfluoralkylated chains are insulated by three carbon spacers only. As a fluoroalkylating agent 3-(perfluorohexyl)propyl triflate was used prepared under similar conditions to those of 2-(perfluorohexyl)ethyl triflate [19–21]. The triflate was reacted with the trisodium salt of gallate and the reaction afforded corresponding

*Corresponding author. E-mail: ftor@seznam.cz; Fax: +420 224 310 352. E-mail: robert.kaplanek@vscht.cz

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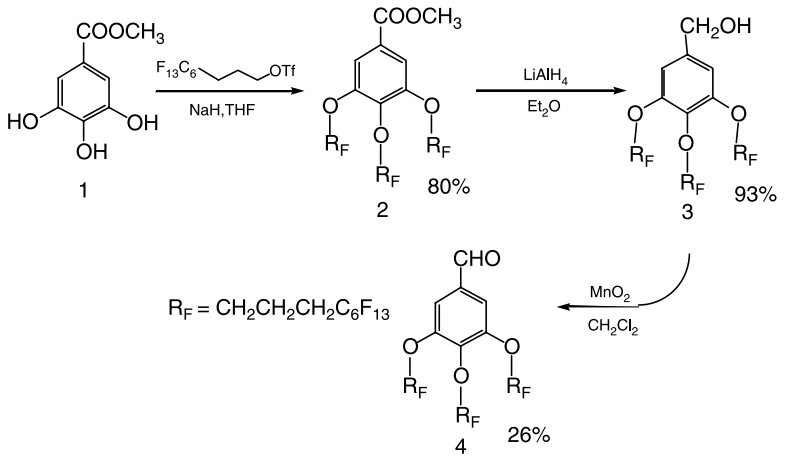

FIGURE 1 Synthesis of model dendritic units.

polyfluorinated gallate **2**. The gallate ester **2** was reduced to alcohol **3** by $LiAlH_4$. The alcohol **3** was oxidized by mangan (IV) oxide to aldehyde **4** (Fig. 1).

For final synthesis to attain dendritic fluorinated pophyrins two synthetic approaches were chosen. In the first approach the common method for the construction of porphyrins from an aldehyde and pyrrole [22] was chosen. Thus aldehyde **4** was reacted with pyrrole under conditions for preparation of the porphyrins [22]. Unfortunately, the reaction afforded only a complex and intractable mixture of unidentified compounds.

Therefore a second approach was tried, based on the nucleophilic substitution of 5,10,15,20-tetrakis (pentafluorophenyl)porphyrin by fluorinated alcohol **3**. Alcohol **3** was converted to its corresponding sodium salt with NaH and reacted with the porphyrin in DMF. The reaction afforded polyfluorinated porphyrin **5** with 12 perfluorohexyl chains in the peripheral region (Fig. 2).

Because the model synthesis of fluorinated porphyrin **5** was successful this approach was used for the construction of larger fluorinated dendritic porphyrins with double the number of fluorinated chains. Initially, it was necessary to prepare a suitable dendron with the required number of fluorinated chains. At this point the authors were able to use, to great advantage, their recently published branched fluorinated triflate [23]. According to the published results a corresponding fluorinated gallate **6** was prepared with six fluorinated chains from gallate **1** and branched triflate. The ester group was reduced with $LiAlH_4$ to alcohol **7**. Alcohol **7** was used according to the model reaction with compound **3** described above, for the construction of a fluorinated porphyrin **5**. Compound **7** was transformed to the sodium salt with NaH and reacted with 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. The reaction afforded highly functionalized fluorinated porphyrin **8** with 24 fluorinated chains in the peripheral region (Fig. 3).

The solubility of both porphyrins **5** and **8** is dramatically different. The porphyrin **5** is soluble in such common organic solvents as dichloromethane, chloroform, diethyl ether, acetone, etc. On the other hand, porphyrin **8** with a two-fold number of fluorinated chains dramatically decreased its solubility in common organic solvents with the exception of diethyl ether in which it is surprisingly well soluble. The solubility of pophyrin **8** can be enhanced by adding freon CCl_3F (F 113) to common solvents. Thus, NMR spectra were successfully obtained in a mixture of $CDCl_3$ and F 113.

The detailed structure of porphyrin **8** is shown below (Fig. 4).

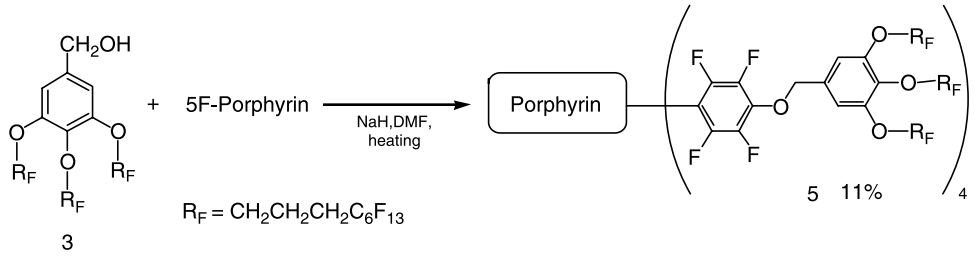

FIGURE 2 Synthesis of porphyrin **5**.

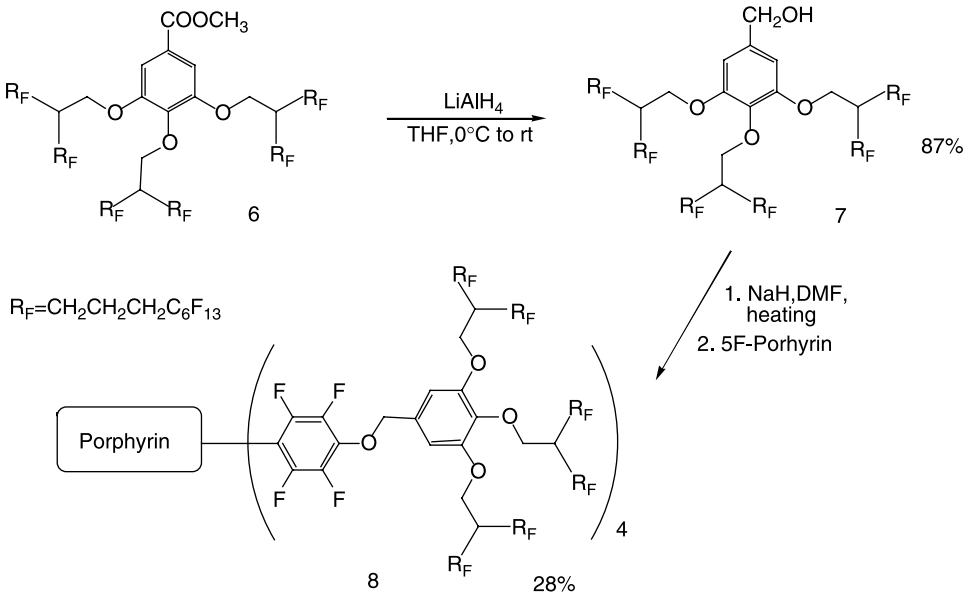

FIGURE 3 Synthesis of porphyrin **8**.

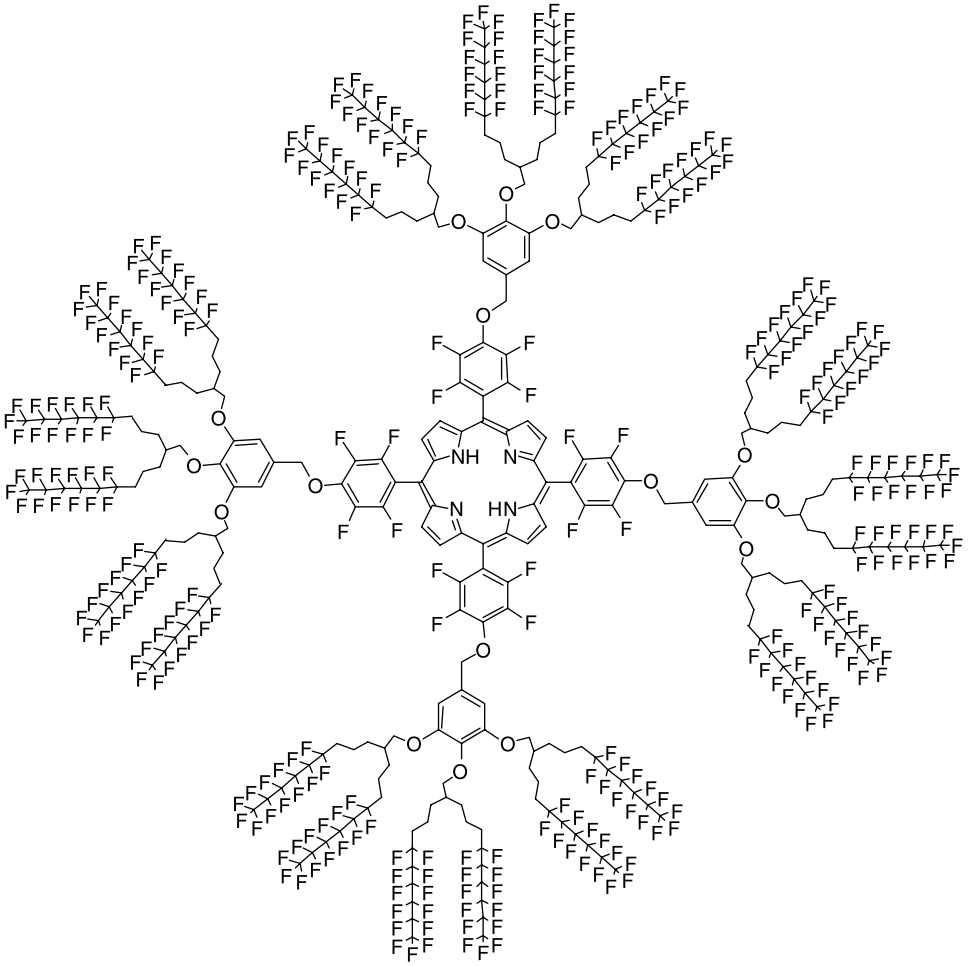

FIGURE 4 Porphyrin **8** ($C_{321}H_{206}F_{328}N_4O_{16}$).

CONCLUSION

Fluorinated highly functionalized porphyrins **5** and **8** were synthesized by a convergent synthesis. The synthesis was based on a nucleophilic substitution between dendritic units **3**, **7** and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. Porphyrins **5** and **8** will be studied as a potential ligands, drug delivery systems, and as a possible shuttle for the transport of gases.

EXPERIMENTAL

Measurements and Materials

All chemicals were purchased from Aldrich and used without further purification. All reactions required anhydrous conditions and were performed using dried solvents and under argon atmosphere. NMR spectra were recorded on a Varian Gemini 300 HC (FT, ^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 281 MHz) instrument using TMS and $CFCl_3$ as the internal standards. Chemical shifts are quoted in ppm (δ-scale; s-singlet, bs-broad singlet, d-doublet, t-triplet, q-quadruplet, m-multiplet), coupling constants *J* in Hz, solvents $CDCl_3$. IR spectrometry analyses were performed on a Bruker IFS 66v/S instrument. Mass spectrometry analyses were performed on a Hewlett–Packard GC HP5890 instrument.

Compound 2

A flask was charged with sodium hydride (60% suspension in mineral oil, 160 mg, 3.96 mmol) and THF (3 mL). The mixture was cooled to 0°C and a solution of methyl gallate **1** (220 mg, 1.19 mmol) in THF (5 mL) was slowly added. When addition was complete a portion of THF (30 mL) was added to the mixture. Then the cooling bath was removed and the mixture was stirred at laboratory temperature for 30 min. After this time a solution of [3-(perfluorohexyl)propyl] triflate (2.00 g, 3.92 mmol) in THF (12 mL) was dropped in to the reaction mixture. When addition was complete, the mixture was refluxed for 1 h. After this time, the mixture was diluted with water (10 mL) and brine (50 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The organic phase was dried over $MgSO_4$. The drying agent was removed by filtration and solvent was evaporated by means of vacuum rotary evaporator. The product was separated by column chromatography on silica (2.5 × 25 cm, eluent—dichloromethane). The product **2** was obtained as yellowish viscous oil (1.210 g, 80%).

^{1}H NMR ($CDCl_3$) δ = 2.01 (m, 2H), 2.14 (m, 4H), 2.38 (m, 6H), 3.89 (s, 3H), 4.59 (t, 2H, $^3J_{HH}$ = 5.6), 4.12 (t, 4H, $^3J_{HH}$ = 5.9), 7.29 (s, 2H); ^{13}C NMR ($CDCl_3$) δ = 20.6 (s, 2C), 21.5 (s, 1C), 27.8 (t, 3C, $^2J_{CF}$ = 22), 52.0 (s, 1C), 67.2 (s, 2C), 71.9 (s, 1C), 108.2 (s, 2C), 107.0–120.0 (m, 18C), 125.7 (s, 1C), 141.6 (s, 1C), 152.3 (s, 2C), 166.4 (s, 1C); ^{19}F NMR ($CDCl_3$) δ = −81.3 (m, 9 F), −115.2 (m, 6F), −122.5 (m, 6F), −123.5 (m, 6F), −124.4 (m, 6F), −126.8 (m, 6F). Anal. Calcd for $C_{35}H_{23}F_{39}O_5$: C, 33.25; H, 1.83; Found: C, 33.74; H, 2.34.

Compound 3

A flask was charged with gallate **2** (100 mg, 79 μmol) and diethyl ether (5 mL). The mixture was cooled to −78°C and $LiAlH_4$ (1 M solution in diethyl ether, 9 mg, 237 μmol) was slowly added. Then, the cooling bath was removed and the mixture was stirred at laboratory temperature for 1 h. The reaction was quenched with MeOH (2 mL), diluted with water (50 mL) and mixture was extracted with diethyl ether (3 × 50 mL). The organic phase was dried over $MgSO_4$. Drying agent was removed by filtration and solvent was evaporated by means of vacuum rotary evaporator. The product was separated by column chromatography on silica (2.5 × 20 cm, eluent—diethyl ether). The product **3** was obtained as yellowish viscous oil (91 mg, 93%).

^{1}H NMR ($CDCl_3$) δ = 2.00 (m,2H), 2.12 (m,4H), 2.35 (m, 6H), 3.95 (t, 2H), 4.08 (t, 4H), 4.62 (s, 2H), 6.60 (s, 2H); ^{13}C NMR ($CDCl_3$) δ = (s, 2C), 21.3 (s, 1C), 27.8 (t, 2C, $^2J_{CF}$ = 22), 27.9 (t, 1C, $^2J_{CF}$ = 22), 65.1 (s, 1C), 67.5 (s, 2C), 71.8 (s, 1C), 105.3 (s, 2C), 107.0–122.0 (m, 18C), 136.7 (s, 1C), 137.1 (s, 2C), 152.6 (s, 1C); ^{19}F NMR ($CDCl_3$) δ = −81.4 (m, 9 F), −114.9 (m, 6F), −122.5 (m, 6F), −123.4 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F). Anal. Calcd for $C_{34}H_{23}F_{39}O_4$: C, 33.03; H, 1.87; Found: C, 33.54; H, 2.49.

Compound 4

A flask was charged with gallate **3** (1.01 g, 0.82 mmol), dichloromethane (20 mL) and mangan (IV) oxide (248 mg, 2.85 mmol). The mixture was stirred under reflux for 4 h and then next portion of mangan (IV) oxide (250 mg, 2.88 mmol) was added, heating bath was removed and the mixture was stirred at laboratory temperature overnight. Then the mixture was evaporated to dryness, diluted with diethyl ether and filtered. The product was separated by column chromatography (2.5 × 25 cm, eluent—dichloromethane). The isolation afforded product **4** as viscous colorless oil (260 mg, 26%) and starting alcohol (430 mg).

^{1}H NMR ($CDCl_3$) δ = 2.03 (m,2H), 2.15 (m,4H), 2.35 (m, 6H), 4.11 (t, 2H, $^3J_{HH}$ = 5.8), 4.14 (t, 4H, $^3J_{HH}$ = 5.8), 7.16 (s, 2H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ = 20.6 (s, 2C), 21.5 (s, 1C), 27.8 (t, 2C, $^2J_{CF}$ = 22), 67.7 (s, 2C), 72.0 (s, 1C), 108.1 (s, 2C), 107.5–121.7 (m, 18C), 132.1 (s, 2C), 143.0 (s, 1C), 153.0 (s, 1C), 190.7 (s, 1C); ^{19}F NMR

($CDCl_3$) δ = −81.58 (t, 6F, $^3J_{FF}$ = 10), −81.64 (t, 3F, $^3J_{FF}$ = 10) −115.0 (m, 6F), −122.5 (m, 6F), −123.5 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F). Anal. Calcd for $C_{34}H_{21}F_{39}O_4$: C, 33.08; H, 1.71; Found: C, 33.31; H, 1.92.

Porphyrin 5

A flask was charged with compound **3** (50 mg, 40 μmol), anhydrous DMF (2 mL) and sodium hydride (60% suspension in mineral oil, 2 mg, 84 μmol). The mixture was stirred at laboratory temperature for 20 min. The 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin was added and the mixture was heated to 90°C overnight. Then the mixture was evaporated to dryness and product was separated by column chromatography on silica (2 × 20 cm, eluent—dichloromethane/petroleum ether 1:1). The product **5** was obtained as dark red wax (7 mg, 11%).

^{1}H NMR ($CDCl_3$) δ = −2.91 (2H, s), 2.08 (8H, m), 2.19 (16H, m), 2.3–2.5 (24H, m), 4.10 (8H, m), 4.19 (12H, t, $^3J_{HH}$ = 5.5 Hz), 5.51 (8H, s), 6.88 (8H, s), 8.85 (8H, s); ^{19}F NMR ($CDCl_3$) δ = −81.4 (9F, t, J_{FF} = 10 Hz), −115.0 (6F, m), −122.5 (6F, m), −123.4 (6F, m), −124.1 (6F, m), −126.7 (6F, m), −139.0 (2F, dd, J_{FF} = 7 Hz, J_{FF} = 22 Hz), −156.3 (2F, dd, J_{FF} = 7 Hz, J_{FF} = 22 Hz); MS (MALDI): for $C_{180}H_{98}F_{172}N_4O_{16}$ Calculated: 5840.5; Found: 5839.5.

Compound 7

A flask was charged with compound **6** (880 mg, 0.36 mmol) and THF (40 mL). The mixture was cooled to 0 °C and $LiAlH_4$ (1 M solution in diethyl ether, 20 mg, 0.53 mmol) was slowly dropped under vigorous stirring. Then the mixture was stirred for 30 minutes at this temperature and then was slowly warmed to laboratory temperature within 15 min. The reaction was quenched with MeOH (3 mL), diluted with water (50 mL) and mixture was extracted with diethyl ether (3 × 50 mL). The organic phase was dried over $MgSO_4$. Drying agent was removed by filtration and solvent was evaporated by means of vacuum rotary evaporator. The product was separated by column chromatography on silica (2.0 × 20 cm, eluent—hexane/dichloromethane—1:1). The product **7** was obtained as yellowish viscous oil (760 mg, 87%).

^{1}H NMR ($CDCl_3$) δ 1.50–1.74 (m, 24H), 1.82–1.90 (m, 3H), 1.98–2.14 (m, 12H), 3.83 (d, 1H, $^3J_{HH}$ = 5.49), 3.92 (d, 2H, $^3J_{HH}$ = 4.94), 4.63 (s, 2H), 6.59 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 17.7 (s, 12C), 30.9 (t, 6C, $^2J_{CF}$ = 26), 38.2 (s, 2C), 38.9 (s, 1C), 65.4 (s, 1C), 70.6 (s, 2C), 75.2 (s, 1C), 104.9 (s, 2C), 107.4–121.7 (m, 36C), 136.7 (s, 2C), 136.9 (s, 1C), 152.9 (s, 1C).

^{19}F NMR ($CDCl_3$) δ −81.6 (m, 18F), −115.1 (m, 12F), −122.6 (m, 12F), −123.6 (m, 12F), −124.3 (m, 12F), −126.9 (m, 12F). MS (LRMS): for $C_{67}H_{50}F_{78}O_4$ Calculated: 2401; Found: 2400.

Porphyrin 8

A flask was charged with compound **7** (270 mg, 0.11 mmol), anhydrous DMF (10 mL) and sodium hydride (60% suspension in mineral oil, 10 mg, 0.25 mmol). The mixture was stirred at laboratory temperature for 20 min. The 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (10 mg, 0.01 mmol) was added and the mixture was heated to 90°C overnight. The mixture was diluted with water (10 mL) and was extracted with trifluoromethyl toluene (2 × 10 ml). The organic phase was dried over $MgSO_4$. Drying agent was removed by filtration and solvent was evaporated by means of vacuum rotary evaporator. The product was separated by column chromatography on silica (2.5 × 20 cm, eluent—petroleum ether/dichloromethane 1:1). The product was obtained in a form of dark red semisolid wax (45 mg). The second purification was accomplished by preparative TLC on silica (20 × 20 cm, 2000 microns, eluent—petroleum ether/dichloromethane 3:1). The pure product **8** was obtained as red dark wax (30 mg, 28%).

^{1}H NMR ($CDCl_3$/CCl_3F) δ −2.82 (s, 2H), 1.50–2.20 (m, 156H), 3.98 (d, 8H, $^3J_{HH}$ = 5.23), 4.07 (d, 16H, $^3J_{HH}$ = 4.95), 5.52 (s, 8H), 6.90 (s, 8H), 8.87 (s, 8H); ^{19}F NMR ($CDCl_3$/CCl_3F) δ −81.6 (t, 72F, $^3J_{FF}$ = 10), −115.1 (m, 48F), −122.6 (m, 48F), −123.6 (m, 48F), −124.3 (m, 48F), −126.9 (m, 48F), −138.9 (8F, dd, $^3J_{FF}$ = 7.3, $^4J_{FF}$ = 22.0), −156.9 (8F, dd, $^3J_{FF}$ = 7.3, $^4J_{FF}$ = 22.0); IR (KBr) cm^{-1} 2924, 1499, 1368, 1241, 1206, 1145, 1121. MS (MALDI): for $C_{321}H_{206}F_{328}N_4O_{16}$ Calculated: 10498.61; Found: 10499.52.

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