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Novel binding mode for fluorinated porphyrins: synthesis and fluorophilic affinity of stable atropoisomers of 5,10,15,20-tetrakis[2-(perfluoroacyl)aminophenyl]-21*H*,23*H*-porphyrins

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Abstract—The synthesis and binding properties of 5,10,15,20-tetrakis[2-(perfluoroacyl)aminophenyl]-21*H*,23*H*-porphyrins as new types of fluorophilic receptors for potential application as optical sensors are reported. The observed remarkable binding affinity for fluorinated substrates monitored by vis spectroscopy represents a novel binding mode in porphyrin chemistry.

1. Introduction

The development of chemical sensors relies on novel specific receptors with high sensitivity and selectivity connected with a proper transduction mechanism. For the development of optical sensors, porphyrin derivatives are advantageous owing to excellent photophysical properties. The binding mode of these macrocyclic compounds usually relies on hydrophobic interactions, π–π stacking, H-bonding, or axial ligation in the case of metalloporphyrins.[1] High specificity for a given substrate is usually introduced only by means of designed periphery substitution, otherwise there is no inherent high selectivity for a substrate with the macrocycle itself. In our search for new receptors for chemical sensor development[2–6] we have directed our research towards derivatives of porphyrins possessing perfluoroalkyls in order to obtain a selective tool for the detection of medicinally and environmentally important polyfluorinated compounds. It is known that substituents attached to the porphyrin system can dramatically influence the general properties of this tetrapyrrolic macrocycle in terms of spectroscopic, binding and transport properties.[1] Some of the properties can also be deeply influenced by the conformations of the side chains.[7,8] Among substitutents, perfluoroalkyls introduce into molecules, inter alia, the property of fluorophilicity, i.e. the ability of energetically favourable molecular interactions with perfluoralkylated parts of other molecules. This phenomenon has been applied to introduce long-term stabilisation of multi-component microemulsions for blood substitutes and vesicular drug delivery systems,[9–11] fluorous biphase chemistry including catalyst or reagent recovery or immobilisation,[12,13] and also catalysis in supercritical carbon dioxide[14] as a clean and environmentally friendly alternative to conventional organic solvents.

Fluorophilic properties of porphyrin derivatives possessing perfluorinated chains have not yet been studied. In order to understand how porphyrin complexation properties are influenced by the introduction of perfluoroacyl groups on the periphery of the macrocycle,[15] and how the spatial arrangement will influence the binding behaviour of these macrocycles, stable atropoisomers of *N*-perfluoroacylated 5,10,15,20-tetrakis(2-aminophenyl)porphyrins **1**–**3** were designed, prepared and preliminary binding affinities were studied. The data obtained were compared with the non-fluorinated analogue, viz. 5,10,15,20-tetrakis[2-(octanoylamino)phenyl]porphyrin **4**, for which spectroscopic properties and metalation reactivity have been reported.[16,17]

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2. Results and discussion

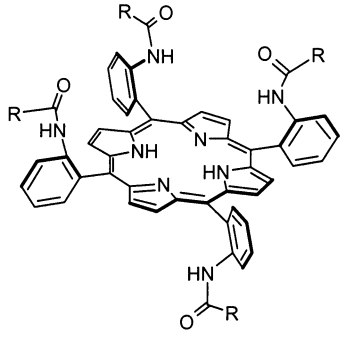
Four *meso*-tetrakis[2-(acylamino)phenyl]porphyrins **1**–**4** were synthesized and studied (Scheme 1): compounds **1**, **2** and **4** were prepared with the stable α,α,α,β-conformation, while atropoisomer **3** had the stable α,α,β,β-conformation. Acylations of the starting 5,10,15,20-tetrakis-(2-aminophenyl)porphyrin were performed[18–20] with preparative yields of ca. 95% for the new compounds **1**–**3** and for the known **4**.[16]

In studying fluorophilic and associative properties of the porphyrins **1**–**4**, association constants with a series of associants were measured. The results are summarised in Table 1. The selected porphyrin derivatives **1**–**4** in this preliminary study were used to compare: (1) the effects of two kinds of perfluorinated chains (compounds **1** and **2**); (2) the effects of perfluorinated and non-fluorinated chains of the same length (compounds **1** and **4**), and (3) the effect of conformation on the selectivity of association (compounds **1** and **3**). In Fig. 1, typical UV–vis absorption changes of fluorinated porphyrin (receptor **1**) after the addition of polyfluorinated substrate (as a dependence on the concentration of decafluorobiphenyl) are shown. Significant spectroscopic changes revealed strong binding and, in addition, a clear isosbestic point indicated 1:1 stoichiometry in the complex formation, which was proven by a Job plot UV–vis titration.

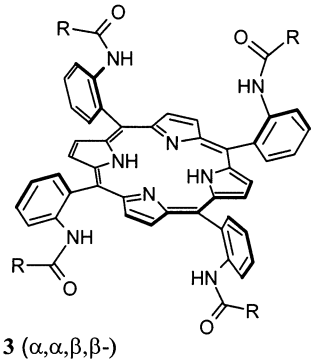
We have found a remarkable fluorophilic selectivity for perfluoroacylated derivative **1** possessing the α,α,α,β-conformation: as illustrated by entries 3–7 (Table 1), association constants are several orders higher than those for the non-fluorinated analogue **4**, but also approximately one order higher than those for the atropoisomer **3** (entries 3–7) or for the same atropoisomer **2** having branched perfluorinated polyether chains (entries 3–7). Exclusive associants with **1** are different classes of organic compounds, but all have an aromatic ring in their structure: perfluorinated biphenyl (entry 3), fluoroalkoxylated tetrafluorobiphenyl (entry 4), perfluoroacylated aniline (entry 5) or perfluoro-*p*-benzoquinone (entry 7). On the other hand, the fluorophilic selectivity of **1** relative to **4** was insignificant for (perfluorohexyl)benzene, biphenyl (entry 1), or pentafluorobiphenyl (entry 2).

The association activity of **1** in comparison with its α,α,β,β-atropoisomer **3** was usually one order higher with the exception of non-fluorinated associants (entry 1) or the partially fluorinated biphenyl (entry 2). Generally, compound **3** displayed complexation properties much closer to the non-fluorinated porphyrin derivative **4** than to the atropoisomeric compound **1**.

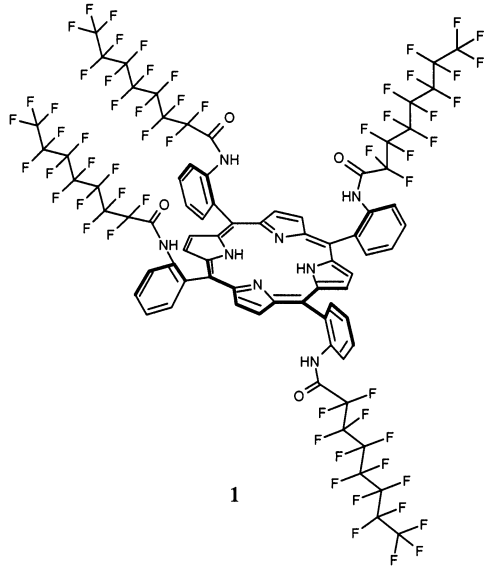
A structural analogue of **1**, i.e. the porphyrin derivative **2** possessing branched perfluorinated polyether chains, generally displayed lower fluorophilic properties closer to that of the conformationally different **3**. This study of the detailed mechanism of the new fluorophilic association phenomenon is being continued.



1,2,4 (α,α,α,β-)



3 (α,α,β,β-)



1

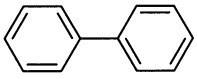
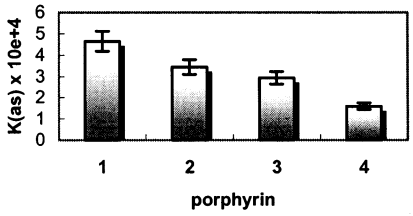
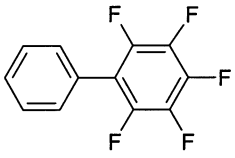
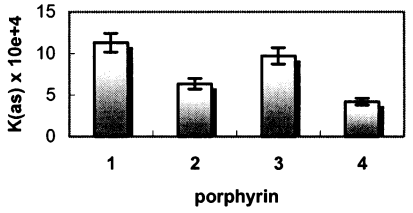
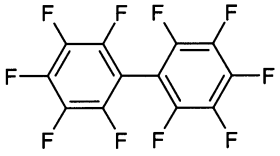
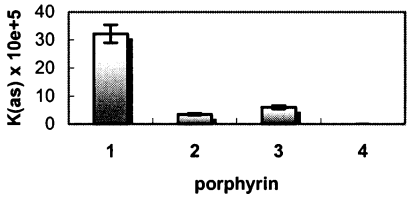
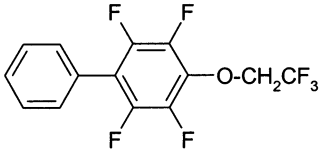
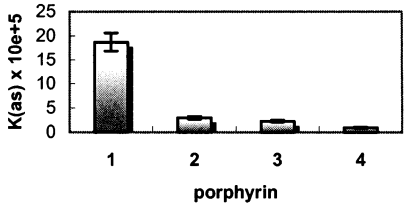
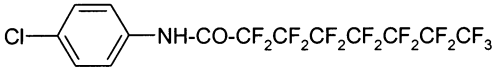
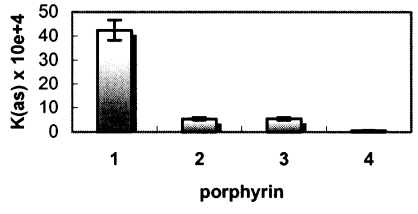
1, **3**, R = —CF_2–[CF_2]$_5$–CF_3

2, R = —CF(–O–CF_2–CF(CF_3)–O–CF_2–CF_2–CF_3)–CF_3

4, R = —CH_2–[CH_2]$_5$–CH_3

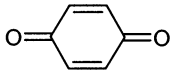
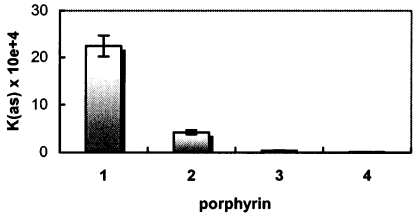
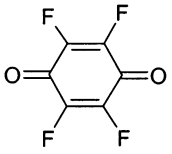
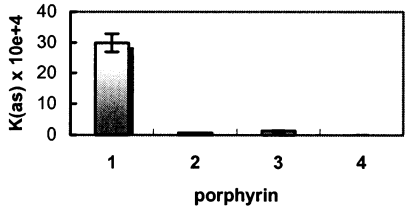
Scheme 1.

Table 1. Associants and the corresponding association constants for porphyrins **1–4**

Entry	Associant	Association constants
1		
2		
3		
4		
5		

In conclusion, we have shown that remarkable selectivity for fluorinated compounds can be introduced to the porphyrin core by substitution with perfluoroacyl substituents and can easily be monitored by UV–vis titration. The binding affinity is significantly influenced by the number of polyfluorinated chains located on the porphyrin periphery, which can cooperate on analyte binding and is consistent with the concept of

Table 1. *Continued*

Entry	Associant	Association constants
6		
7		

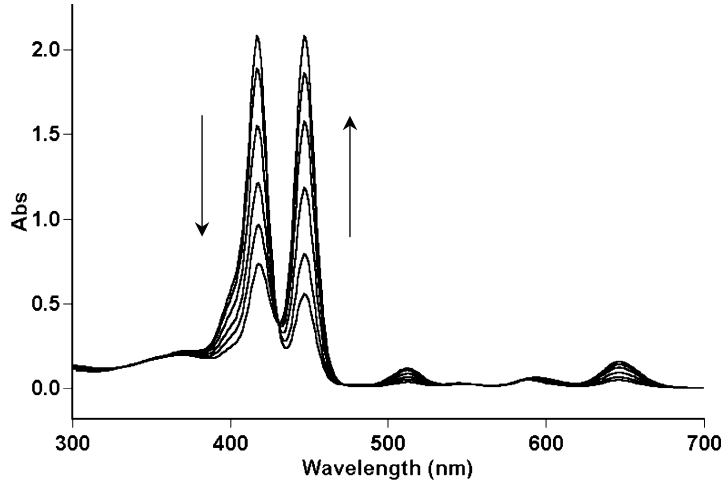


Figure 1. UV–vis absorption spectra of receptor **1** after addition of decafluorobiphenyl solution (dichloromethane, constant 2×10^{6} concentration of porphyrin, concentration of perfluorobiphenyl in the range of 3×10^{-7} to 1.06×10^{-4}).

fluorophilicity,[12,13] i.e. the ability of energetically favourable molecular interactions with perfluoralkylated parts of other molecules. The application of novel receptors for sensor development is in progress.

Acknowledgements

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20. Typical procedures:

5α,10α,15β,20β - Tetrakis[2 - (2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoylamino) - phenyl] - 21*H*,23*H* - porphyrin (1):

A heated flask (oven) with a septum was cooled under nitrogen to rt and charged with 5α,10α,15β,20β-tetrakis(2-aminophenyl)-21*H*,23*H*-porphyrin (30 mg, 44.46 μmol), triethylamine (36 mg, 0.356 mmol), dry Et_2O (5 mL) and dry CH_2Cl_2 (5 mL). The mixture was immersed in an ice bath while stirring (magnetic spinbar) and a solution of perfluorooctanoyl chloride (154 mg; 0.356 mmol) in solvent mixture (Et_2O/CH_2Cl_2, 5/5 mL) was added dropwise through the septum. The reaction mixture was stirred at 0°C for 1 h and at rt for a further hour, when the conversion of the starting tetrakis(2-aminophenyl)porphyrin was complete (checked by TLC, CH_2Cl_2). The solvents were then removed in vacuum (rotary evaporator, 40°C, 400 mmHg) and the residue was dissolved in Et_2O (15 mL). The ethereal solution was washed with a concentrated water solution of $NaHCO_3$ (3×25 mL) and saturated water solution of NaCl (3×25 mL) and then dried over $MgSO_4$. The solvent was removed in vacuum (rotary evaporator) and the crude product was purified by column chromatography (silica gel 20 g, petroleum ether/acetone/CH_2Cl_2, 15:1:1) to obtain product **1** as violet crystals, yield 96 mg (95%), mp 80–82°C.

^{1}H NMR ($CDCl_3$): δ 8.80; 8.78 (2s, 8H, β-H); 8.64 (m, 4H); 8.02 (d, 4H, $^3J_{HH}$ = 6.6 Hz); 7.93 (m, 4H); 7.82 (s, 4H, NH); 7.65 (m, 4H); −2.71 (s, 2H, NH).

^{19}F NMR ($CDCl_3$): δ −81.3; −81.6; −81.7 (3t, 1:2:1, 12F, 4×CF_3, $^3J_{FF}$ = 9.2 Hz); −120.8 (t, 2F, CF_2C=O, $^3J_{FF}$ = 12 Hz); −121.5 (m, 2F, CF_2C=O); −120.8; −121.6; (dm, 4F, 2×CF_A, F_BC=O, $^2J_{FF}$ = 264 Hz); −122.5 to −124.0 (m, 32F, 16×CF_2); −126.8; −127.0; −127.2 (3m, 1:2:1, 8F, 4×CF_2).

^{13}C NMR ($CDCl_3$): δ 155.3 (m, 4C, C=O); 136.1; 135.9; 135.84 (3s, 1:1:2, 4C Ar); 135.4; 135.0; 134.9 (3s, 2:1:1, 4C-H Ar); 132.0; 131.9 (2s, 4C Ar); 130.5 (s, 4C-H Ar); 125.2 (s, 4C-H Ar); 121.7; 121.4 (2s, 4C-H Ar); 113.9; 113.7 (2s, 4C-*meso*); 113.2 to 107.1 (m, 28C, 24 CF_2, 4 CF_3).

MS (MALDI): for $C_{76}H_{30}F_{60}N_8O_4$, calcd 2261.06; found 2259.

5α,10α,15α,20β - Tetrakis{2 - [2,4,4,5,7,7,8,8,9,9,9 - undecafluoro-2,5-bis(trifluoromethyl)-3,6-dioxanonanoylamino]-phenyl}-21*H*,23*H*-porphyrin (2):

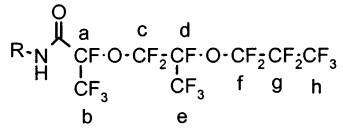
2,4,4,5,7,7,8,8,9,9,9 - Undecafluoro - 2,5 - bis(trifluoromethyl)-3,6-dioxanonanoyl fluoride (295 mg; 0.593 mmol) in solvent mixture (Et_2O/CH_2Cl_2, 5/5 mL) was reacted according to the above procedure. Product **2** as violet crystals, yield 180 mg (94%), mp 56–58°C.

^{1}H NMR ($CDCl_3$): δ 8.78 (m, 8H, β-H); 8.61 (m, 4H); 7.98 (m, 4H); 7.93 (t, 4H, $^3J_{HH}$ = 7.7 Hz); 7.77 (s, 4H, NH); 7.65 (m, 4H); −2.72 (s, 2H, NH).

^{19}F NMR ($CDCl_3$): δ −80.8 to −84.7 (m, 52F_{bcefh}); −130.4 to −130.7 (m, 8F_g); −133.5 to −134.8 (m, 4F_a); −145.9 to −146.4 (m, 4F_d).

^{13}C NMR ($CDCl_3$): δ 155.5 (t, 4C, $^2J_{CF}$ = 7.7 Hz, C=O); 136.0; 135.79 (2s, 4C Ar); 135.1; 134.6 (2s, 4C-H Ar); 132.8; 132.4 (2s, 4C Ar); 130.4 (s, 4C-H Ar); 125.4 (m, 4C-H Ar); 124.9 (m, 4C-H Ar); 102 to 120 (m, 32 C, 8 CF, 12 CF_2, 12 CF_3).

MS (MALDI): for $C_{80}H_{30}F_{68}N_8O_{12}$, calcd 2587.07; found 2588.7 (M^++1).



5α,10α,15β,20β - Tetrakis[2 - (2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoylamino)phenyl]-21*H*,23*H*-porphyrin (3):

Product **3** as violet crystals, yield 94 mg (94%), mp 185–188°C. ^{1}H NMR ($CDCl_3$): δ 8.79; 8.78 (2s, 8H, β-H); 8.66 (d, 4H, $^3J_{HH}$ = 8.24 Hz); 8.00 (d, 4H, $^3J_{HH}$ = 7.14 Hz); 7.94 (t, 4H, $^3J_{HH}$ = 7.14 Hz); 7.65 (t, 4H, $^3J_{HH}$ = 7.7 Hz); 7.61 (s, 4H, NH); −2.70 (s, 2H, NH).

^{19}F NMR ($CDCl_3$): δ −81.5 (t, 12F, 4×CF_3, $^3J_{FF}$ = 9.2 Hz); −120.9; 121.6 (dm, 8F, 4×CF_A, FBC=O, $^2J_{FF}$ = 264 Hz); −122.8; −123.1; −123.8; −123.9 (4qs, 32F, 16×CF_2); −127.0 (qs, 8F, 4×CF_2).

^{13}C NMR ($CDCl_3$): δ 155.0 (t, 4C, C=O, $^3J_{HH}$ = 27 Hz); 135.9 (s, 4C Ar); 134.9 (s, 4C-H Ar); 132.0 (s, 4C Ar); 130.4 (s, 4C-H Ar); 125.2 (s, 4C-H Ar); 121.5 (s, 4C-H Ar); 113.7 (s, 4C-*meso*); 112.4 to 107.5 (m, 28C, 24 CF_2, 4 CF_3).

MS (FAB): for $C_{76}H_{30}F_{60}N_8O_4$, calcd 2261.06; found 2261.68.