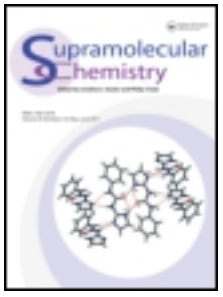

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Design of differently P-substituted *4i* PO fluorescent tetraphosphonate cavitands

Bastien Mettra[a], Yann Bretonnière[a], Jean-Christophe Mulatier[a], Brigitte Bibal[a,b], Bernard Tinant[c], Christophe Aronica[a] and Jean-Pierre Dutasta[a]*

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Experimental approaches to tetraphosphonate cavitands bearing fluorenyl-phosphonate bridges are reported. Different routes are described depending on the substitution on the cavitand structure. Tetra-, tri- and di-bridged phosphonate cavitands have been prepared as precursors of fluorescent hosts, for which the stereochemistry is highly dependent on the substitution at the wide rim of the resorcin[4]arene scaffold. The conformational change in 3*io* tetraphosphonate cavitands has been characterised by X-ray diffraction. These new molecular receptors have been used for the recognition of acetylcholine.

Keywords: host–guest chemistry; molecular recognition; phosphonate cavitand; acetylcholine; fluorescence

1. Introduction

Organic cage compounds are widely used as specific sensors for a large variety of guest molecules of interest. A particular attention is thus given to the design of molecular hosts with structure and binding sites ideally suited for the recognition of the target guests. The phosphonate cavitands represent an original class of molecular receptors, which have been actively studied over the last decade (*1–6*). The most important feature, which characterises these compounds, is the presence of an aromatic cavity delineated at its wide rim by hard donor phosphonate groups. This characteristic gives to these molecules a strong capability to complex various guests through cooperative interactions, including strong dipolar interactions and H-bonding with the PO groups, and Van der Waals interactions with the aromatic cavity. The phosphonate cavitands can exist under several configurations depending on the orientation of the substituents at the phosphorus atoms. Obviously, the inward (*i*) orientation of the P═O groups is a prerequisite to optimise the complexation properties. This has been demonstrated in the past with tetra-bridged compounds bearing four inwards-oriented P═O bonds (*iiii* or 4*i* isomer), and also with partially bridged derivatives (Figure 1). For instance, complexes with charged guests such as metal ions and ammonium derivatives and neutral species such as alcohol derivatives have been widely investigated. Most of these studies are related to the so-called 4*i* derivatives that possess four phosphonate bridges with the P═O bonds oriented towards the molecular cavity giving them strong binding capabilities (Figure 1). Nevertheless, partially bridged compounds present interesting properties due to the presence of free OH phenol groups that can be used to introduce various bridging units. For instance, they have been used for the design of supramolecular capsules (*7*) and chiral molecular containers (*8*, *9*).

In this article, we demonstrated the versatility of the synthesis of differently substituted phosphonate cavitands, and we focused on fluorophoric derivatives that can be useful to characterise the complexation of guests by means of fluorescence spectroscopy (*10*). In the first approach, we investigated the formation of tri-bridged 3*i* (*iii*) molecules and discussed the different strategies that were used for their syntheses. Similarly, di-bridged compounds (AB*ii* and AC*ii* structures in Figure 1) were prepared following known procedures. In the second step, the introduction of the fluorenyl moiety in the structure of the cavitands gave rise to new mono-, di- and tetra-fluorenyl 4*i* PO cavitand hosts that are adequately suited for the recognition of natural ammonium. This property is exemplified with acetylcholine (ACh^+) as guest by using fluorescence spectroscopy.

2. Results and discussion

2.1 Formation of tetraphosphonate 3io derivatives

Owing to the potential offered by the partially bridged phosphonate cavitands, we have investigated different

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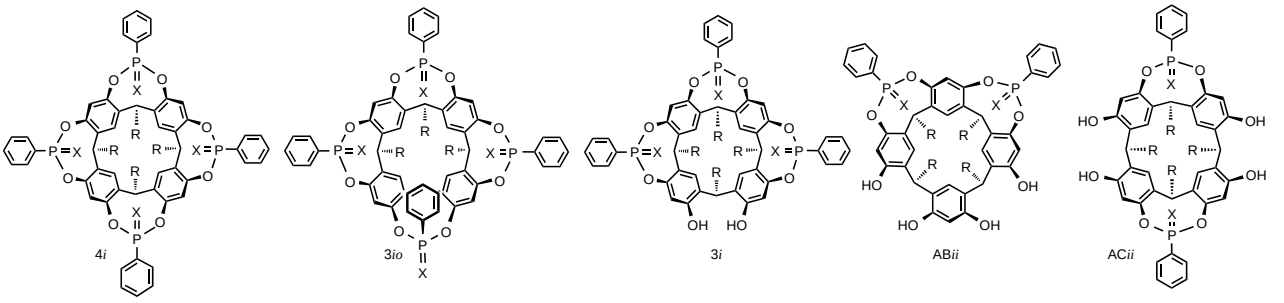
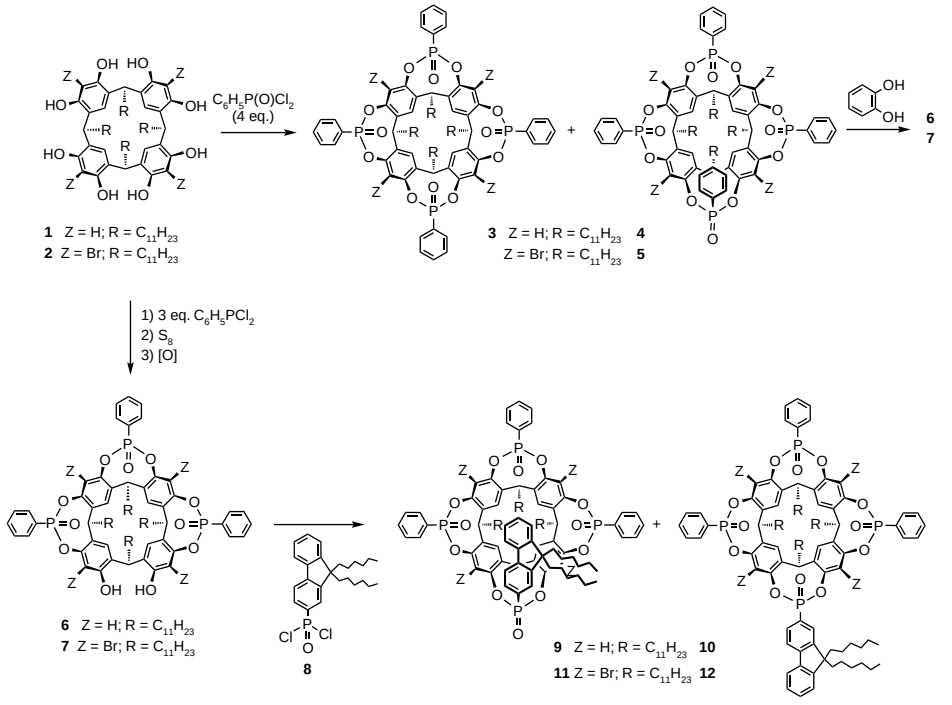


Figure 1. Structures of the tetra-, tri- and di-bridged phosphonate cavitands (R = alkyl chain; X = S, O).

routes to access to these molecules, in particular starting from derivatives with the 3*io* configuration. During the synthesis of the phosphorylated cavitands, different stereoisomers can be formed, due to the possible inwards or outwards orientations of the P═O bonds. It has been shown that the *4i* stereoisomer, which is best suited for intra-cavity complexation, is the main compound isolated from the template-directed synthesis initially developed in our laboratory (*2*, *11*). For instance, the reaction of resorcin [4]arene **1** with 4 equiv. of $PhP(O)Cl_2$ mainly gave rise to the 4*i* derivative **3** together with small quantities of the 3*io* isomer **4** (6% yield) (Scheme 1). Starting from the terabromo-resorcin[4]arene **2**, the reaction with 4 equiv. of $PhP(O)Cl_2$ only afforded the 3*io* molecule **5** as the main isolated product (52%). This result strongly differs from the previous case without bromine atoms on the resorcin[4] arene structure. However, the role of the bromine at the wide rim of the cavitand in the stereoselectivity of the ring closure reaction is not yet fully elucidated.

The solid-state structure of **4** was solved by single crystal X-ray diffraction and shows the inward orientation of one P-phenyl group that partially fills the molecular cavity (Figure 2). It is interesting to note that the four 8-membered rings formed during the ring closure reaction with $PhP(O)Cl_2$ adopt the boat-chair conformation that places the inward-oriented group on the phosphorus atom in axial position and the outward-oriented group in equatorial position. At room temperature (r.t.), the ^1H NMR spectrum of **4** in $CDCl_3$ solution shows characteristic high-field shifted resonances for the protons of the phenyl group oriented towards the cavity (Figure 3).



Scheme 1. Syntheses of 3*i*, 4*i* and 3*io* phosphonate cavitands **3**–**7** from **1** (*13*) or **2** (*14*), and of the mono-fluorenyl-tetra-phosphonate cavitands **9**–**12**.

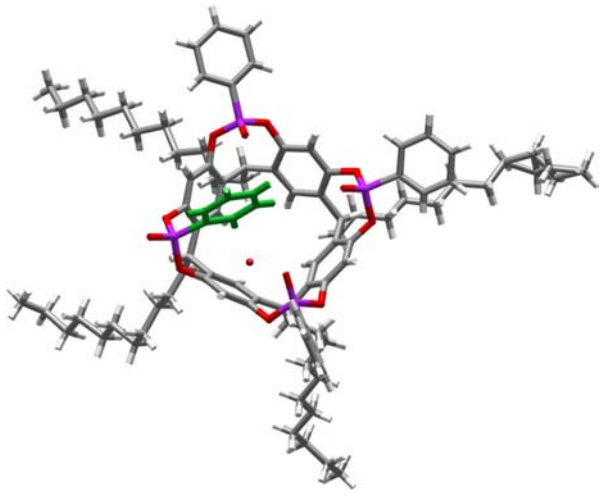


Figure 2. (Colour online) X-ray molecular structure of cavitand 3*io* **4** (the inward-oriented phenyl group is green coloured).

2.2 Syntheses of the partially bridged phosphonatocavitands

The versatility of the bridging reactions encouraged us to develop strategies for the synthesis of partially bridged compounds because they open new possibilities to introduce different bridging units for various applications. To develop the synthesis of fluorescent-sensitive cavitands, a 3*i* isomer with three phosphorylated bridges and two free OH groups has been prepared. The first route consists in the reaction of 3 equiv. of phosphorus reagent $PhPCl_2$ with 1 equiv. of resorcin[4]arene **1** followed by a sulphidation step, to give the trithiophosphonate 3*i* isomer in moderate yields (25%), which is allowed to react with *m*-chloro peroxybenzoic acid (*m*-MCPBA) or H_2O_2 to afford the 3*i* compound **6** (74%) (Scheme 1) (*12*). It should be noted that the step via the thiophosphonate derivatives is often preferred to the direct oxidation because they are more easily purified and the transformation to the oxide is straightforward.

In the second approach, the *3i* triphosphonate cavitands were synthesised by reacting the corresponding 3*io* precursor with 1 equiv. of 1,2-dihydroxybenzene (Scheme 1). This reaction scheme has been first proposed by Castro et al. for the synthesis of tri- and di-quinoxaline cavitands (*15*). Its efficient application to 4*i* tetraphosphonate cavitands bearing ethyl R groups instead of undecyl chains has been reported by Cantadori al. (*16*), who obtained the 3*i* derivative in good yields (65%). Starting from the 3*io* tetraphosphonate cavitand **4**, the *3i* derivative **6** was only obtained in low yield. Surprisingly, following this procedure with the 3*io* tetrabromo cavitand **5**, the corresponding 3*i* derivative **7** was obtained quantitatively. Therefore, the reaction is stereoselective and the outward PO group in **5** is preferentially cleaved. Compound **7** is thus obtained in two steps in 35–40% overall yield from the resorcin[4]arene **2** and $PhP(O)Cl_2$. This has to be compared with the 19% overall yield obtained previously for the related compound **6** in the reaction of **1** with 3 equiv. of $PhPCl_2$ followed by the addition of sulphur and the subsequent oxidation with MCPBA (*12*).

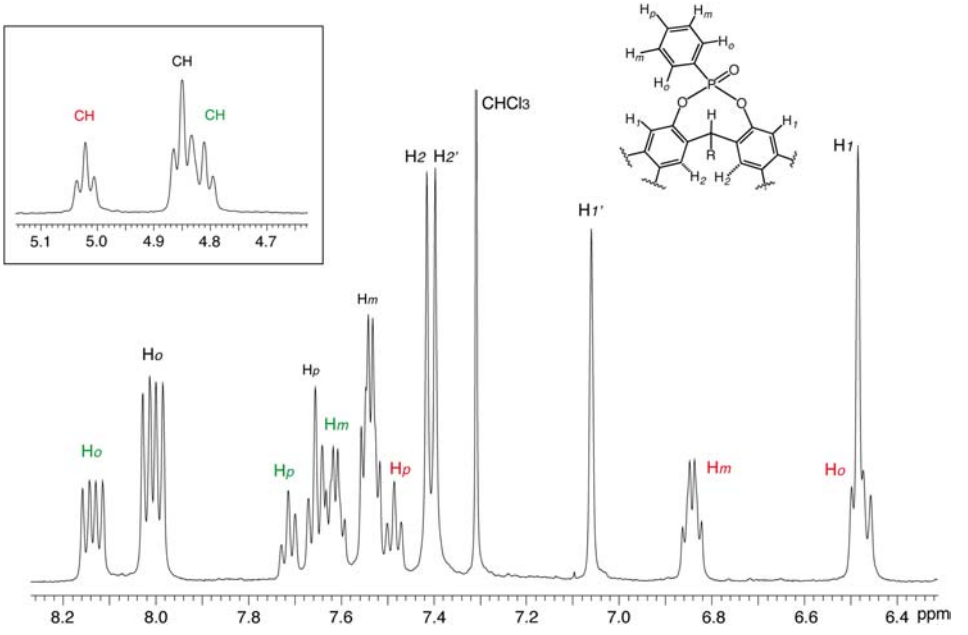
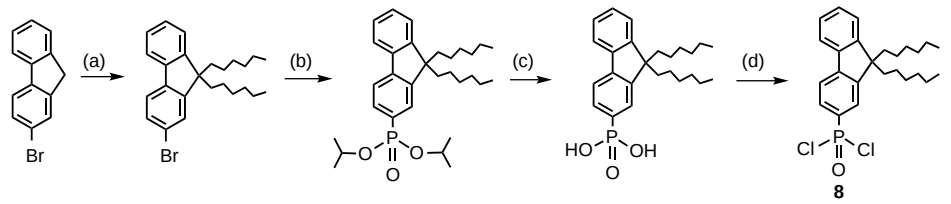


Figure 3. (Colour online) ^{1}H NMR spectrum (500.1 MHz; $CDCl_3$; 298 K) of cavitand 3*io* **4** (aromatic protons: red, inward; green and black, outward-oriented phenyl groups. Insert: methyne CH protons).



Scheme 2. Synthesis of fluorenyl-phosphonic dichloride **8**: (a) *n*-BuN(Et)$_3^+$Cl$^-$, aq NaOH, *n*-C_6H_{13}Br, dimethylsulfoxide (DMSO), 86% (*17*); (b) P(O-*i*-Pr)$_3$, $NiBr_2$, *o*-xylene, 98%; (c) HCl, 83% and (d) $SOCl_2$, DMF, 100%.

2.3 Synthesis of the mono-fluorenyl derivatives 9–12

The fluorescent probes based on the 3*i* cavitand structure were obtained by reaction with the phosphorus reagent **8** that was synthesised from P(OR)$_3$ (R = C_2H_5, *i*-C_3H_7) and 2-bromo-fluorene (Scheme 2). By this way, we thus expected the formation of the 4*i* tetraphosphorylated cavitands that are known to form strong association with cationic species. The reaction of 3*i* cavitand **6** with **8** gave rise to the 3*io* and 4*i* isomers **9** and **10**, in 9% and 69% isolated yields, respectively (Table 1). Following the procedure that produced **9** and **10** from **6**, the reaction of **7** with **8** afforded the P-fluorene tetrabromo cavitand **11** (70% yield), where the fluorenyl group is oriented inwards giving rise to a 3*io* structure (Scheme 1). This result was unexpected according to the hindrance induced by the fluorene moiety that would have directed the bulky group outwards and thus favour the 4*i* isomer **12**, which was only recovered in small amounts and characterised by mass spectrometry. However, this result is in accord with the observation reported above about the brominated and non-brominated derivatives, where the reaction of the tetrabromo-resorcin[4]arene **2** with 4 equiv. of $PhP(O)Cl_2$ afforded only the 3*io* isomer **5**.

The structure of the mono-fluorenyl derivative **11** was confirmed by an X-ray crystal structure determination showing the outwards orientation of the P═O bond attached to the fluorenyl group. As a consequence, a distorted boat conformation of the appended eight-membered ring maintains the fluorenyl group outside the cavity, allowing the inclusion of an ethanol molecule (Figure 4). This conformational change, compared with the regular boat-chair conformation observed in the other less constrained eight-membered rings in **11** (Figure 5), as well as in other structures of phosphorylated cavitands such as **4** described above, demonstrates the unexpected flexibility of the cavitand structure under strong steric hindrance.

2.4 Synthesis of poly-fluorenyl derivatives

The all inward-oriented PO groups of the tetraphosphonate cavitands are a prerequisite for the efficient recognition of guest substrates. Thus, we have been essentially interested in the preparation of 4*i* isomers, and the following will concern the non-brominated compounds. The AB*ii* PO (*8*) and AC*ii* PO derivatives (Figure 1) can be synthesised in good yields and are particularly attractive for the synthesis of di-fluorenyl cavitands (Scheme 3). For instance, the reaction of 2.5 equiv. of **8** with AB*ii* PO **13** allowed the formation of the AB*ii*CD*ii* bis-fluorene derivative **14** in 36% yield. Small amount (~12%) of the AB*ii*CD*io* bis-fluorene compound **15** was also isolated. The same procedure applied to the AC*ii* derivative **16** afforded the AC*ii* BD*ii* bis-fluorene **17** in 22% yield and the AC*ii* BD*io* bis-fluorene **18** in 34% yield.

The strategy for the synthesis of the tetra-fluorenyl cavitand is quite straightforward and follows the sequence presented in Scheme 3 using 4 equiv. of the

Table 1. Yields and ^{31}P NMR chemical shifts obtained for the mono-, di- and tetra-fluorenyl-phosphonate cavitands.

Cavitand	Isomer	H/Br[a]	No. fluo[b]	Yield (%)	$\delta\,^{31}$P (ppm)[c]
9	3*io*	H	1	9	9.54 (2P); 9.47 (1P); 8.04 (1P)
10	4*i*	H	1	69	8.91 (1P); 7.39 (2P); 7.35 (1P)
11	3*io*	Br	1	70	9.05 (1P); 7.83 (1P); 7.65 (2P)
14	AB*ii*CD*ii*	H	2	36	9.32 (2P); 7.77 (2P)
15	AB*ii*CD*io*	H	2	12	9.85 (1P); 9.15 (1P); 8.66 (1P); 8.59 (1P)
17	AC*ii* BD*ii*	H	2	22	8.53 (2P); 6.85 (2P)
18	AC*ii* BD*io*	H	2	34	10.31 (1P); 9.28 (2P); 8.37 (1P)
19	4*i*	H	4	35	8.78 (4P)
20	3*io*	H	4	9	9.86 (3P); 9.50 (1P)

[a] The substituent H or Br at the large rim.
[b] Number of fluorenyl groups.
[c] $CDCl_3$; 300 K.

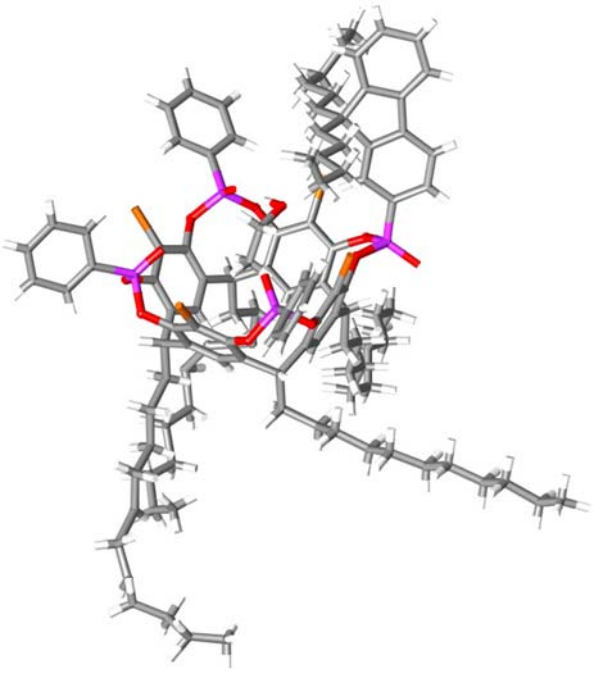


Figure 4. (Colour online) X-ray molecular structure of the mono-fluorenyl tetraphosphonate cavitand **11**.

fluorenyl-P(O)Cl_2 derivative **8**. Stereoisomers 4*i* **19** and 3*io* **20** have been isolated in 35% and 9% yields, respectively. Table 1 sums up the different cavitands bearing fluorenyl-phosphonate groups obtained in this work.

2.5 Recognition of ACh^+ guest

Due to the presence of the fluorene core, the four compounds **10**, **14**, **17** and **19** display an intense fluorescence upon excitation in the main absorption band (at 290 nm) characterised by a structured band with a maximum at 327 nm. Fluorescence quantum yields were determined and are reported in Table 2. A decrease in the quantum yield from 0.62 to 0.26 was observed when the number of fluorenyl groups increases from one to four. This may be explained by the close proximity of the fluorophores at the wide rim of the cavitands, which facilitates self-quenching and re-absorption of the emission.

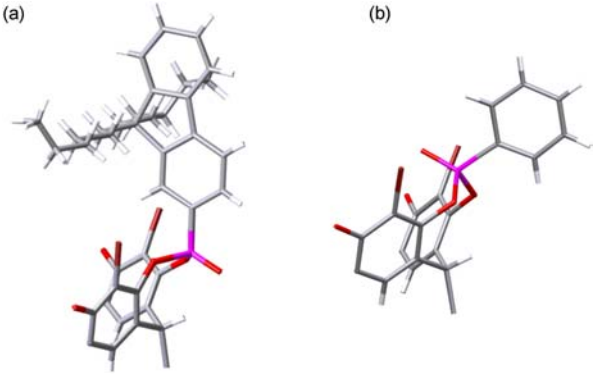
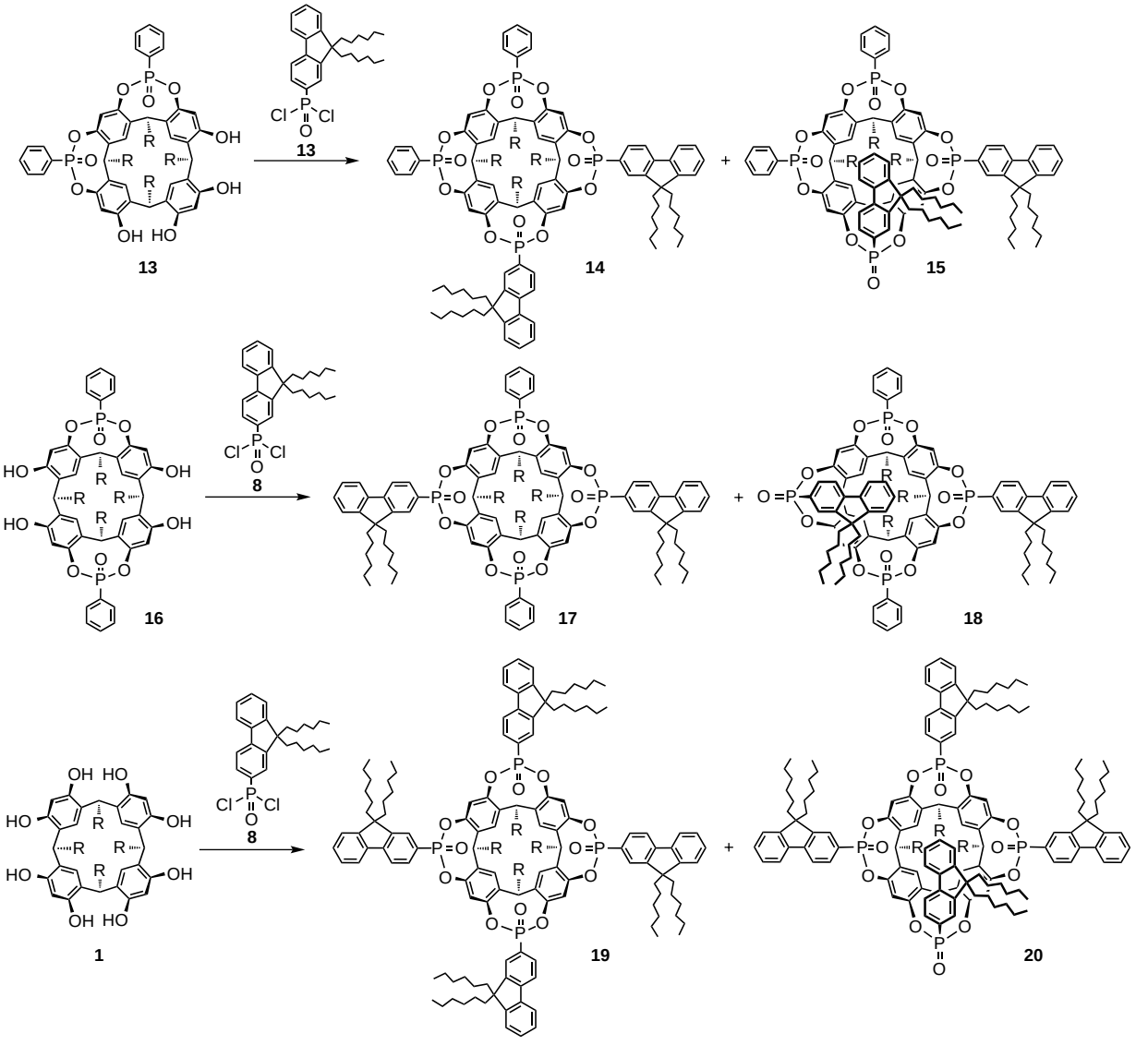


Figure 5. (Colour online) Part of the X-ray molecular structure of **11** showing the two conformations adopted by the eight-membered rings that delineate the aromatic cavity: (a) distorted boat conformation and (b) boat-chair conformation.

To check the recognition properties of the new fluorophoric cavitands, we used ACh^+, which revealed to be a suitable guest for the phosphonate cavitands due to its cationic character and the favourable CHπ interactions between the methyl groups and the aromatic cavity. We focused on the affinity of ACh^+ for the *4i* PO derivatives **10**, **14**, **17** and **19**. Upon the addition of Ach^+, the fluorescence of the host was dramatically quenched. The quantum yields Φ for **10**, **14**, **17** and **19** obtained in the presence of ACh^+ guest were identical to those of the free hosts and, compound **10** being chosen as an example, the fluorescence lifetime τ before and after the addition of guest remained constant. These features are characteristic of a static quenching due to the formation of a non-fluorescent host–guest complex in the ground state. Job plots obtained by measuring the fluorescence indicate the formation of 1:1 complexes for all compounds (Figure 6). Then, titration experiments were conducted in $CHCl_3$ with measurement of the fluorescence of the cavitands upon the addition of increasing quantity of guest (Figure 7). By plotting the change in the emission intensity I at 317 nm over the quantity of ACh^+([ACh^+]) added, a decrease was observed varying from 30% for compound **17** to 40% for compounds **10**, **14** and **19**. The data were then fitted by nonlinear regression analysis and least squares fitting according to Equation (1) (*18*):

$$I = \left(\frac{I_F - 100}{2K_a[ACh^+]}\right) \times \left[(K_a[host][ACh^+] + 1) - \sqrt{(K_a[host] + K_a[ACh^+] + 1)^2 - 4K_a^2[host][ACh^+]}\right] + 100 \quad (1)$$

where [host] and [ACh^+] are, respectively, the cavitand host and ACh^+ guest concentrations, K_a is the binding constant and I_F is the limiting value below which the fluorescence will not decrease due to the addition of ACh^+. Equation (1) was solved with I_F and K_a as unknown parameters. The values of the binding constants K_a determined are reported in Table 2 and are of the same order of magnitude ranging from 1.07×10^6 for compound **19** to 9.28×10^6 for compound **14**. We can notice that the K_a values are in the expected range for ammonium guests and do not depend on the substitution of the phosphorus atoms.



Scheme 3. Synthesis of the di- and tetra-fluorenyl-phosphonate cavitands.

3. Conclusions

Fluorescent tetraphosphonate cavitands have been synthesised from readily accessible partially bridged precursors. The brominated cavitands described herein behave differently from the non-brominated compounds. In particular, the 3*io* isomer was the main compound isolated, and it has been possible to obtain the 3*i* derivative in almost quantitative yield by excision of the outward-oriented PO group using 1,2-dihydroxy-benzene under basic conditions. Fluorescence spectroscopy was used to characterise the complexation of ACh^+, a biological relevant neurotransmitter. This highlights the potentiality of these host molecules and opens new opportunities for the development of original sensors. More interestingly, this approach demonstrates the great versatility of these molecules that can be differently designed according to substituents and functions that can be devoted to various specific guests and targeted spectroscopic techniques.

Table 2. Fluorescence quantum yields Φ for hosts **10**, **14**, **17** and **19** and K_a values for the ACh^+ complexes.

Host[a]	Φ (τ/ns)[a]	K_a (M^{-1})
10	0.62 (1.09)	1.82×10^6
14	0.46	9.28×10^6
17	0.56	1.55×10^6
19	0.26	1.07×10^6

[a] In $CHCl_3$, using tryptophan in water ($\Phi = 0.14$) as reference, $\lambda_{exc} = 290$ nm.

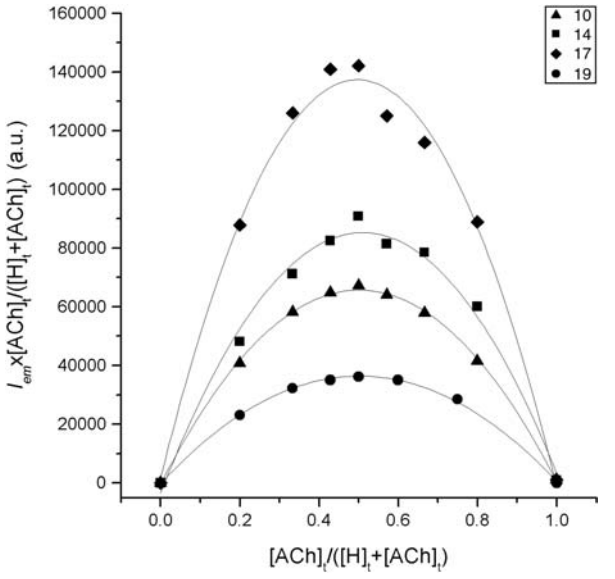


Figure 6. Job plots for the complexation of ACh^+ by cavitands **10**, **14**, **17** and **19**.

4. Experimental

4.1 Materials and instrumentation

Solvents were of commercial grade or dried on GT S100 *Dry Station* columns; $CDCl_3$ was stored over molecular sieves. ^1H, ^{13}C and ^{31}P NMR spectra were recorded at 298 K on a Bruker DPX 200 or Bruker Avance 500 spectrometers. NMR chemical shifts δ are reported in ppm referenced to the solvent signal (^1H; ^{13}C) or to external 85% H_3PO_4 (^{31}P). Resorcin[4]arenes **1** and **2** were synthesised according to the previously reported procedures (*13*, *14*). 2-Bromo-9,9-di-*n*-hexyl-9*H*-fluorene was prepared following the published procedure (*17*).

4.2 Fluorescence

UV–vis absorption measurements were recorded on a JASCO V670 spectrometer. Fluorescence spectra were measured using a Horiba-Jobin Yvon Fluorolog-3 spectrofluorometer, equipped with a red-sensitive Hamamatsu R928 photomultiplier tube. Spectra were reference corrected for both the excitation source light intensity variation (lamp and grating) and the emission spectral response (detector and grating). The fluorescence quantum yields were determined in chloroform relative to tryptophan in water ($\Phi = 0.14$) using Equation (2), where S is the slope obtained by plotting the integrated area under the fluorescence emission spectrum versus the absorbance at λ_{exc}. Superscript ref and s correspond to the reference and the sample, respectively. For each experiment, five points were recorded, all corresponding to an absorbance at λ_{exc} below 0.1.

$$\Phi^s = \Phi^{ref} \times \frac{S^s}{S^{ref}} \times \left(\frac{n_d}{n_d^{ref}}\right)^2. \quad (2)$$

Luminescence excited state lifetimes were recorded using a Jobin Yvon IBH FluoroCube photon-counting spectrometer as the detection unit. The system was equipped with a TBX-04 picosecond photon detection module for detection in the UV–vis region (300–800 nm). A 290-nm Nano-LED was used as excitation source.

4.3 Syntheses

Diisopropyl (9,9-di-n-hexyl-9H-fluoren-2-yl)phosphonate

Tri-isopropyl phosphite (7.5 ml, 30.4 mmol) was added dropwise to a solution of 2-bromo-9,9-di-*n*-hexylfluorene (3 g, 6.52 mmol) and $NiBr_2$ (0.32 g, 1.45 mmol) in *o*-xylene (100 ml). The solution was stirred overnight at 150°C under argon. The solvent was evaporated under vacuum, and the resulting oil was purified on a silica column chromatography (CC) (CH_2Cl_2–AcOEt: 10:0 to 9:1) to give the desired product as a yellow oil (3.19 g, 98% yield). ESI-MS *m/z* 521.3161 $[M + Na]^+$ (calcd 521.3161). ^1H NMR (11.7 T, 300 K, $CDCl_3$) δ 7.81–7.68

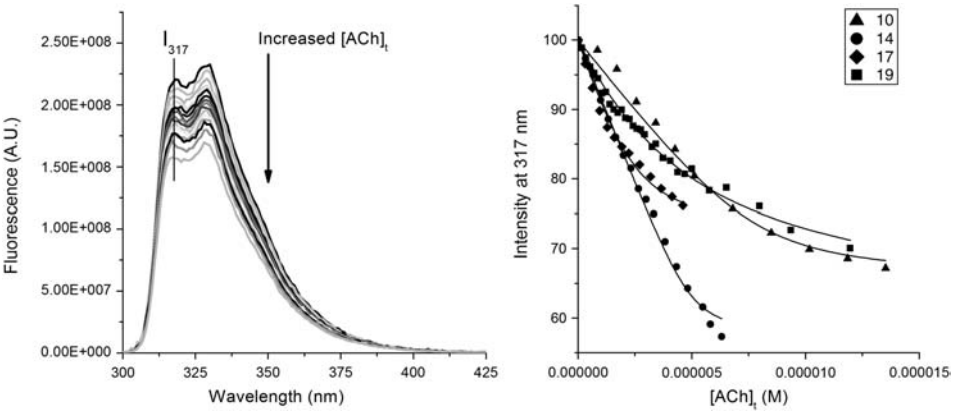


Figure 7. Fluorescence quenching by increased $[Ach]_t$: overall fluorescence decrease for **19** (left), and fluorescence quenching curves (intensity at 317 nm normalised to 100 for $[Ach]_t = 0$ M) for **10**, **14**, **17** and **19** (right). Lines are fitted curves according to Equation (1).

(m, 4H); 7.32 (m, 3H); 4.61 (m, 2H); 1.97 (m, 4H); 1.35 (d, 6H); 1.17 (d, 6H); 1.10–0.98 (m, 12H); 0.71 (m, 6H); 0.52 (m, 4H). ^{13}C NMR (11.7 T, 300 K, $CDCl_3$) δ 151.44, 150.74, 145.14, 130.94, 127.12, 126.34, 123.03, 120.55, 119.61, 70.62, 55.43, 53.52, 40.35, 31.57, 29.65, 24.21, 23.81, 22.56, 14.05. ^{31}P NMR (4.7 T, 300 K, $CDCl_3$) δ 17.85 (s, 1P).

(9,9-Di-n-hexyl-9H-fluoren-2-yl)phosphonic acid

A mixture of di-isopropyl-9,9-di-*n*-hexylfluorene phosphonate (1.057 g, 2.12 mmol) in 37% HCl solution (10 ml) was heated at reflux temperature overnight. The waxy residue was washed with water and dissolved in CH_2Cl_2. The organic solution was first washed with water until neutrality, then with a saturated solution of NaCl and then dried over Na_2SO_4. Evaporation of the solvent afforded the phosphonic acid as a white powder (725 mg, 83% yield). ESI-MS *m/z* 415.24 $[M + H]^+$ (calcd 415.52). ^{1}H NMR (11.7 T, 300 K, $CDCl_3$) δ 10.07 (s, 2H); 7.92–7.74 (m, 4H); 7.36 (m, 3H); 1.98 (m, 4H); 1.02 (m, 12H); 0.72 (m, 6H); 0.58 (m, 4H). ^{13}C NMR (11.7 T, 300 K, $CDCl_3$) δ 151.64, 150.63, 144.38, 140.31, 130.38, 128.10, 126.90, 125.53, 123.21, 120.62, 119.81, 55.51, 40.24, 31.51, 29.76, 23.93, 22.64, 14.08. ^{31}P NMR (4.7 T, 300 K, $CDCl_3$) δ 24.63 (s, 1P).

*(9,9-Di-n-hexyl-9H-fluoren-2-yl)phosphonic dichloride **8***

$SOCl_2$ (4 ml) and dimethylformamide (DMF) (0.2 ml) were added to (9,9-di-*n*-hexyl-9*H*-fluoren-2-yl)phosphonic acid (310 mg, 0.75 mmol) and heated at reflux temperature overnight. After evaporation under vacuum, **8** was obtained as a brown oil (335 mg, 0.74 mmol, 100 %) and immediately engaged in the next reaction without further purification. ^{1}H NMR (11.7 T, 300 K, $CDCl_3$) δ 7.79 (m, 1H); 7.70–7.60 (m, 3H); 7.32 (m, 2H); 7.09 (s, 1H); 1.84 (m, 4H); 0.87 (m, 12H); 0.58 (m, 6H); 0.41 (m, 4H). ^{31}P NMR (4.7 T, 300 K, $CDCl_3$) δ 37.57 (s, 1P).

*Cavitand 3i **7** (from **5**)*

Catechol (15 mg, 0.14 mmol) and K_2CO_3 (32 mg, 0.28 mmol) were added to a solution of cavitand **5** (265 mg, 0.14 mmol) in dry DMF (10 ml). The reaction mixture was heated at 80°C for 2 h. After cooling to r.t., water and few drops of aqueous 12N HCl and CH_2Cl_2 were added, and the mixture was stirred for half an hour. The organic layer was extracted and washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by CC on silica gel (CH_2Cl_2–acetone 8:2, then 1:1) to give cavitand 3*i* **7** as a beige solid (233 mg, 0.13 mmol, 94%). ESI-MS 1807.4449 $[M + Na]^+$ (calcd 1807.4424). ^{31}P NMR ($CDCl_3$, 81.02 MHz, 300 K) 7.99 (s, 2P); 7.05 (s, 1P). ^{1}H NMR ($CDCl_3$, 200.13 MHz, 300 K) 8.35–8.21 (m, 6H); 7.98 (s, 2H); 7.70–7.50 (m, 9H); 7.14 (s, 2H); 4.79–4.72 (m, 3H); 4.52 (t, 1H); 2.26 (m, 8H); 1.37–1.25 (m, 72H); 0.87 (m, 12H).

*Cavitand ACiiPO **16***

To a chloroform solution of the parent thiophosphonate cavitand AC*ii*PS as previously described (*8*) (220 mg, 0.145 mmol), *m*-MCPBA (182 mg, 1.06 mmol, 7 equiv.) was added. After stirring at r.t. overnight, the solvent was evaporated and the residue was purified by silica gel CC (CH_2Cl_2–THF, 1:0 to 4:1) to afford pure AC*ii*PO compound **16** as a white solid (210 mg, 0.14 mmol, 96%). ESI-MS 1371.8098 $[M + Na]^+$ (calcd 1371.8092). ^{31}P NMR ($CDCl_3$, 81.02 MHz, 300 K) 6.25 (s, 2P); 7.05 (s, 1P). ^{1}H NMR ($CDCl_3$, 500.1 MHz, 300 K) 9.49 (s, 4H); 8.08 (dd, 4H); 7.58 (m, 6H); 7.30 (m, 2H); 7.07 (s, 3H); 6.66 (s, 3H); 4.73 (t, 2H); 4.22 (t, 2H); 2.34 (m, 4H); 2.01 (m, 4H); 1.25 (m, 72H); 0.87 (s, 12H).

General procedure for the synthesis of the fluorenylphosphonate cavitands

The precursors **1**, **6** (*12*), **7**, **13** (*8*) and **16** were dissolved in dry toluene and azeotropically distilled under argon to eliminate traces of water. A solution of an excess of *N*-methylpyrrolidine and (9,9-di-*n*-hexyl-9*H*-fluoren-2-yl) phosphonic dichloride **8** in dry toluene was added. The mixture was heated under reflux for 5–12 h. After evaporation of the solvent, the residue was purified by CC on silica gel to give the expected phosphonate cavitand. A typical procedure was described for compounds **9** and **10**.

*Mono-fluorenyl tetraphosphonatocavitands **9** and **10***

Azeotropic distillation by means of a Dean-Stark apparatus of **6** (295 mg, 0.20 mmol) in toluene (30 ml) was performed overnight under dry argon to remove traces of water. After cooling to r.t., *N*-methylpyrrolidine (three drops) and (9,9-di-*n*-hexyl-9*H*-fluoren-2-yl)phosphonic dichloride **8** (170 mg, 0.38 mmol) were added to the toluene solution. The resultant mixture was heated at reflux temperature for 5.5 h and then evaporated under vacuum. The crude product was purified by silica gel chromatography (CH_2Cl_2–THF 9:1, 7:1 and then 5:1) to give successively the 3*io* derivative **9** (33 mg, 0.02 mmol, 9%) and the 4*i* derivative **10** (257 mg, 0.14 mmol, 69%). **9**: ESI-MS 1872.0139 $[M + Na]^+$ (calcd 1872.0132). ^{1}H NMR ($CDCl_3$, 200.13 MHz, 300 K) 8.14–7.79 (m, 8H); 7.69–7.30 (m, 17 H); 6.98 (s, 2H); 6.45 (s, 2H); 6.37 (m, 1H); 5.22 (t, 1H); 4.75 (m, 3H); 2.35 (m, 8H); 1.93 (m, 4H); 1.44–1.27 (m, 72H); 1.01–0.84 (m, 24H); 0.64

(m, 6H); 0.52 (m, 4H). ^{31}P NMR ($CDCl_3$, 81.02 MHz, 300 K) 9.54 (s, 2P); 9.47 (s, 1P); 8.04 (s, 1P). **10**: ESI-MS 1872.0119 $[M + Na]^+$ (calcd 1872.0132). ^{1}H NMR ($CDCl_3$, 200.13 MHz, 300 K) 8.10–7.94 (m, 8H); 7.83–7.72 (m, 2 H); 7.65–7.45 (m, 9 H); 7.36 (m, 3H); 7.26 (m, 4H); 7.02 (d, 4H); 4.82 (m, 4H); 2.35 (m, 8H); 1.99 (m, 4H); 1.45–1.27 (m, 72H); 1.08–1.01 (m, 12H); 0.71 (m, 12H); 0.71 (m, 6H); 0.57 (m, 4H). ^{31}P NMR ($CDCl_3$, 81.02 MHz, 300 K) 8.91 (s, 1P); 7.39 (s, 2P); 7.35 (s, 1P).

*3ioPO(Br) monofluorene (**11**)*

ESI-MS 2163.6750 $[M + H]^+$ (calcd 2163.6722). ^{1}H NMR ($CDCl_3$, 200.13 MHz, 300 K) 8.36–7.93 (m, 8H); 7.70–7.45 (m, 10 H); 7.34–7.15 (m + $CHCl_3$); 6.37 (m, 1H); 5.84 (m, 1H); 4.82 (m, 3H); 2.32 (m, 8H); 1.89 (m, 4H); 1.48–1.28 (m, 72H); 1.08–0.76 (m, 24H); 0.64 (br m, 6H); 0.47 (m, 4H). ^{31}P NMR ($CDCl_3$, 81.02 MHz, 300 K) 9.05 (s, 1P); 7.83 (s, 1P); 7.65 (s, 2P).

*4iPO(Br) monofluorene (**12**)*

Not pure. ESI-MS 2163.6730 $[M + H]^+$ (calcd 2163.6722); 2185.6580 $[M + Na]^+$ (calcd 2185.6542).

*ABiiPOCDiiPO difluorene (**14**)*

ESI-MS 2106.2593 $[M]^+$ (calcd 2106.2498). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.00 (m, 7H); 7.84 (d, 2H); 7.78 (d, 2H); 7.64 (m, 2H); 7.54 (m, 4H); 7.39 (m, 6H); 7.33 (m, 4H); 7.07 (m, 7H); 4.91 (m, 2H); 4.86 (m, 2H); 2.40 (m, 8H); 2.04 (m, 8H); 1.76 (m, 8H); 1.52–1.37 (m, 66H); 1.06 (m, 22H); 0.90 (m, 12H); 0.74 (m, 12H); 0.60 (m, 8H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 9.32 (s, 2P); 7.77 (s, 2P).

*ABiiPOCDioPO difluorene (**15**)*

ESI-MS 2106.2433 $[M + H]^+$ (calcd 2106.2498). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.69–8.24 (m, 4H); 8.03 (m, 4H); 7.72 (m, 2H); 7.42 (m, 4H); 7.32; 6.95; 6.72; 6.53; 5.38 (t, 1H); 4.80 (t, 3H); 2.33 (m, 8H); 1.84 (m, 8H); 1.43 (m, 8H); 0.95 (m, 72H); 0.84 (m, 38H); 0.69–0.53 (m, 20H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 9.85 (s, 1P); 9.15 (s, 1P); 8.66 (s, 1P); 8.59 (s, 1P).

*ACiiPOBDiiPO difluorene (**17**)*

ESI-MS 2106.2583 $[M]^+$ (calcd 2106.2498). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.09 (m, 4H); 7.91 (m, 5H); 7.88 (m, 2H); 7.57 (m, 3H); 7.44 (m, 7H); 7.36 (m, 6H); 7.06 (d, 2H); 6.51 (d, 3H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 8.53 (s, 2P); 6.85 (s, 2P).

*ACiiPOBDioPO difluorene (**18**)*

ESI-MS 2106.2407 $[M]^+$ (calcd 2106.2498). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.00 (m, 4H); 7.88 (m, 4H); 8.03 (m, 4H); 7.82 (m, 1H); 7.75 (m, 1H); 7.55 (t, 2H); 7.45 (br m, 1H); 7.42 (m, 4H); 7.36 (s, 2H); 7.35 (m, 1H); 7.30 (br m, 5H); 7.27 (s, 2H); 7.00 (s, 2H); 6.65 (m, 1H); 6.54 (s, 2H); 5.32 (t, 1H); 4.86 (t, 1H); 4.77 (t, 2H); 2.35 (m, 8H); 2.09–1.85 (m, 8H); 1.55–1.37 (m, 12H); 1.37–1.20 (br m, 60H); 1.10–0.90 (m, 24H); 0.86 (t, 12H); 0.71 (t, 6H); 0.65 (t, 6H); 0.65–0.45 (br m, 8H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 10.31 (s, 1P); 9.28 (s, 2P); 8.37 (s, 1P).

*4iPO tetrafluorene (**19**)*

ESI-MS 2618.6972 $[M]^+$ (calcd 2618.6880). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.02 (m, 8H); 7.80 (m, 4H); 7.75 (m, 4H); 7.37 (m, 10H); 7.30 (m, 6H); 7.09 (s, 4H); 4.91 (t, 4H); 2.39 (m, 8H); 2.00 (m, 16H); 1.61 (s, 8H); 1.50 (m, 8H); 1.29 (m, 56H); 1.03 (m, 48H); 0.88

Table 3. Crystallographic data for **4** and **11**.

	[**4**·CH_2Cl_2·H_2O]	[**11**·2C_2H_5OH]
Formula	$C_{97}H_{126}Cl_2O_{13}P_4$	$C_{119}H_{160}Br_4O_{14}P_4$
FW (g mol^{-1})	1694.76	2258.08
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P-1$
Size (mm)	0.2 × 0.18 × 0.18	0.1 × 0.1 × 0.1
a (Å)	14.857(6)	14.812(5)
b (Å)	36.277(12)	19.791(5)
c (Å)	17.309(7)	21.228(5)
α (°)	90.00	109.64(5)
β (°)	104.55(3)	96.56(5)
γ (°)	90.00	99.33(4)
V (Å^3)	9030(6)	5687(3)
Z	4	2
ρ_{calcd} (g cm^{-3})	1.247	1.319
μ (mm^{-1})	0.204	1.532
$F(0\,0\,0)$	3624	2016
$\lambda_{Mo\ K\alpha}$ (Å)	0.7107	0.7107
T (K)	293	293
h	0 → 14	0 → 19
k	0 → 36	−25 → 25
l	−17 → 16	0 → 27
θ_{max} (°)	20.81	27.98
Reflections collected	30468	25,184
Reflections independent	9135	22,927
Reflections with $I > 2\sigma(I)$	7103	9764
No. parameters	1066	1270
No. restraints	736	303
R_{int}	0.079	0.053
$R_1[I > 2\sigma(I)]$	0.0885	0.0972
$wR_2[I > 2\sigma(I)]$	0.2593	0.1059
R_1 (all data)	0.1057	0.2056
wR_2 (all data)	0.2724	0.1827
Goodness of fit	1.066	1.156
$\Delta\rho_{min}$ /$\Delta\rho_{max}$ (e Å^{-1})	−1.047/0.530	−1.07/1.65

(m, 12H); 0.71 (m, 12H); 0.59 (m, 16H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 8.78 (s, 4P).

*3ioPO tetrafluorene (**20**)*

ESI-MS 2640.6574 $[M + Na]^+$ (calcd 2640.6700). ^{1}H NMR (500.1 MHz, 300 K, $CDCl_3$) 8.1 (m, 2H); 8.0 (m, 2H); 7.9 (m, 4H); 7.7 (m, 1H); 7.6 (m, 4H); 7.5 (m, 4H); 7.4 (m, 8H); 7.3 (m, 1H); 7.2 (m, 10H); 7.0 (m, 2H); 6.5 (m, 2H); 5.3 (t, 1H); 4.6 (t, 3H); 2.4 (m, 8H); 2.0 (m, 8H); 1.5 (8,H); 1.4 (8,H); 1.3 (m, 64H); 1.1 (m, 8H); 0.9 (m, 12H); 0.8 (m, 12H); 0.5 (m, 8H). ^{31}P NMR (81.02 MHz, 300 K, $CDCl_3$) 9.86 (s, 3P); 9.50 (s, 1P).

4.4 X-ray crystallographic analysis

Crystal data and details of structure refinement are summarised in Table 3. The CCDC deposition numbers are 937218 (**4**) and 937222 (**11**).

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