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# New dimensions in calix[4]pyrrole: the land of opportunity in supramolecular chemistry

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The quest for receptors endowed with the selective complexation and detection of negatively charged species continues to receive substantial consideration within the scientific community worldwide. This study is encouraged by the utilization of anions in nature in a plethora of biological systems such as chloride channels and proteins and as polyanions for genetic information. The molecular recognition of anionic species is greatly interesting in terms of their favourable interactions. In this comprehensive review, in addition to giving accounts of some selected syntheses, we illustrated diverse applications ranging from molecular containers to ion transporters and drug carriers of a supramolecular receptor named calix[4]pyrrole. We believe that the present review may act as a catalyst in enhancing the novel applications of calix[4]pyrrole and its congeners in the other dimensions of science and technology.

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## 1. Introduction

The past few years have witnessed a continuous evolution towards the construction of molecular architectures possessing high selectivity and affinity for specific anions in the domain of supramolecular chemistry.<sup>1–3</sup> Supramolecular chemistry being the chemistry beyond the molecular level leads to the generation of architecturally simple but effective receptors known as host molecules. These host molecules interact with diverse guests (*e.g.*, cations, anions, and neutral molecules), and these host–guest interactions play significant roles not only in the realm of host–guest chemistry but also in biological systems. To this end, the design as well as the construction of powerful receptors having exceptional applications such as sensing, recognition, and transport of anions has been considered to be of prime importance and the need of the hour by supramolecular chemists. Due to their unique conformations, structural diversity, and molecular recognition properties, calix[4]pyrroles (C4Ps) have been studied as modern generation host receptors in the arena of supramolecular chemistry.<sup>4–13</sup>

C4Ps are synthetic non-planar, non-aromatic tetrapyrrolic macrocyclic receptors capable of binding an array of anions as well as neutral substrates through N–H hydrogen bonding. From a chemical viewpoint, in recent years, C4Ps have been explored as catalysts in preparative organic chemistry<sup>14</sup> and also as vital precursors for the generation of important organic

molecules such as calixpyridines and calixpyridinopyrroles.<sup>15</sup> In addition to acting as novel solid supports to separate anion mixtures and also as anion transporters across lipid bilayer membranes,<sup>16</sup> they have found significant applications in fluorescent,<sup>17</sup> colorimetric<sup>18</sup> and electrochemical signaling devices.<sup>19</sup> In addition to this, the anion binding ability of C4Ps makes them efficient in various domains of daily life; for example, they have found applications in waste-water treatment,<sup>20</sup> composites in food packaging, storage, preservation, detection of pollutants, removal of heavy metal ions, *etc.*<sup>21–23</sup>

In the past two decades, many transformations and modifications<sup>5,24–27</sup> have been carried out to tune the binding affinity of C4Ps including *β*/*meso*-substitution(s), strapping and appending of aromatic rings at the *meso*-positions.<sup>28–32</sup> Among these, the simplest method is the incorporation of a single arm into the C4P core (2, Fig. 1). On one hand, as can be seen in Fig. 1, structures 3 and 4 are two and four-walled C4P derivatives, respectively, and 5 is a strapped system. On the other hand, the more intricate and factually difficult-to-synthesize 6 is the capped system; its synthesis still remains a challenge. To the best of our knowledge, among various modified C4P skeletons reported in the literature, strapped C4Ps are found to be the most operative in anion binding territories. The strapping of C4Ps is the mode to amend their structural behaviour, which in turn accounts for their binding performance. The selection of the strap plays a vital role in enhancing the inherent anion binding affinity of C4Ps as well as in governing the receptor anion stoichiometry. Because the degree of preorganization increases from 2 to 6, it might be expected that the thermodynamics of

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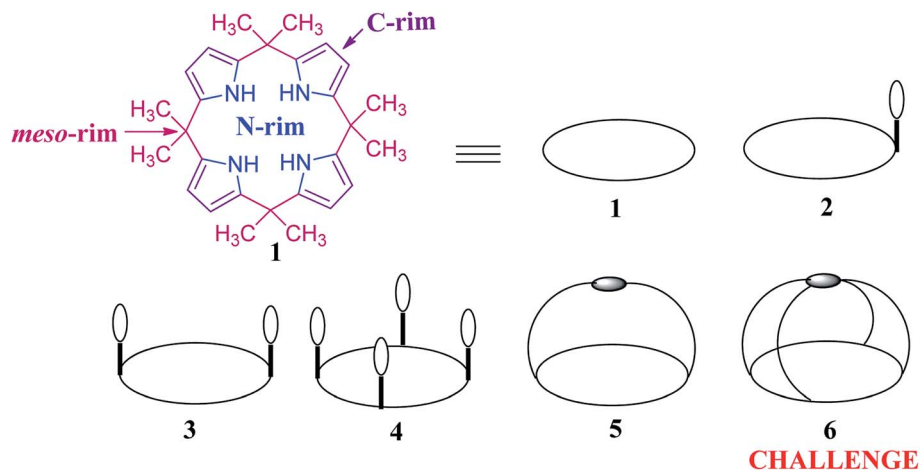
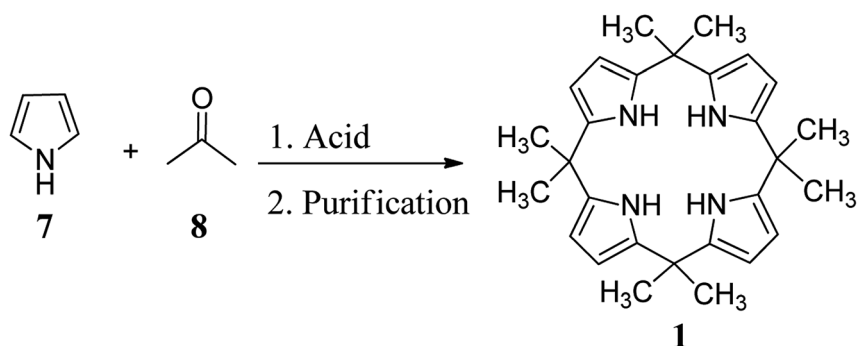


Fig. 1 Different modifications of the basic core of C4P systems.



Scheme 1 Synthesis of octamethylcalix[4]pyrrole (OMCP).

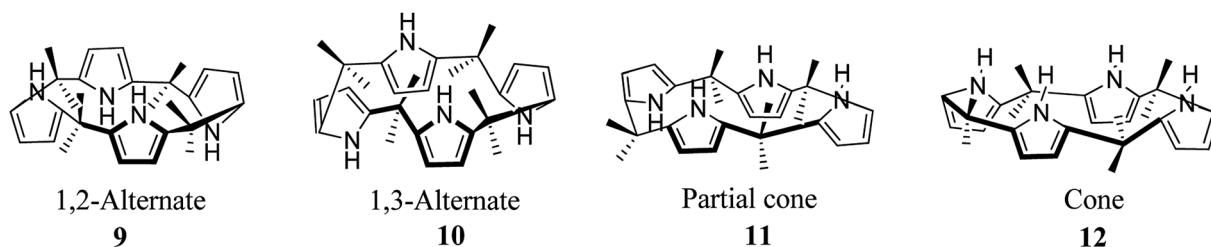


Fig. 2 Different conformations of C4P.

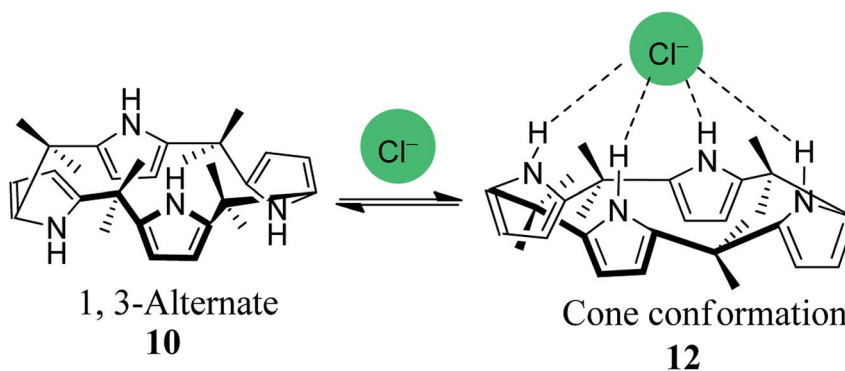
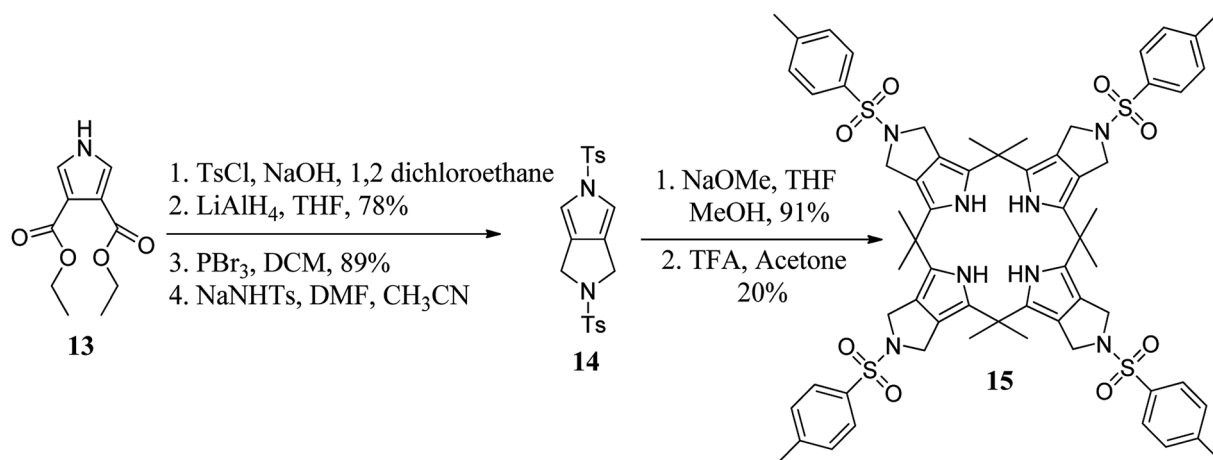
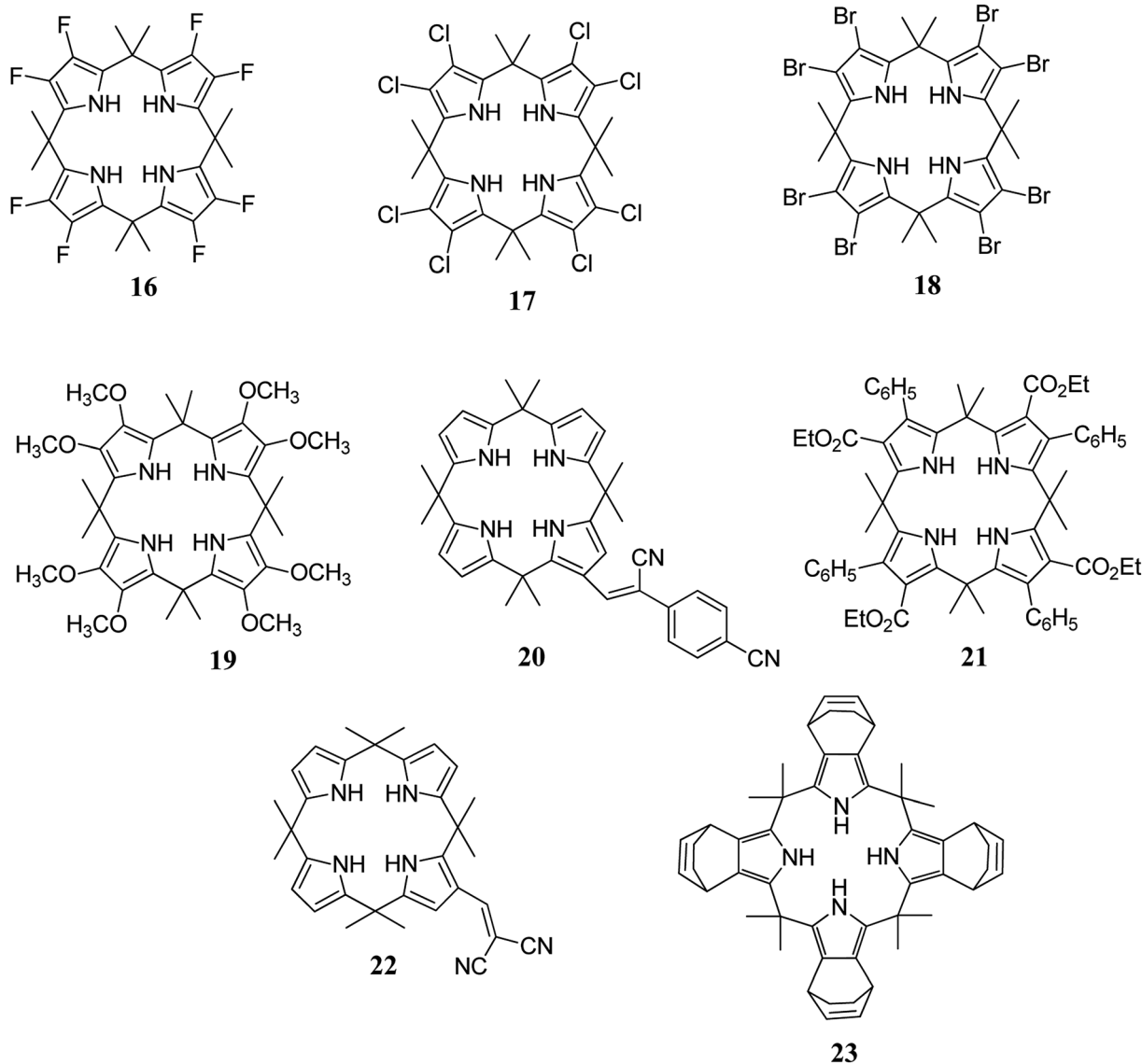
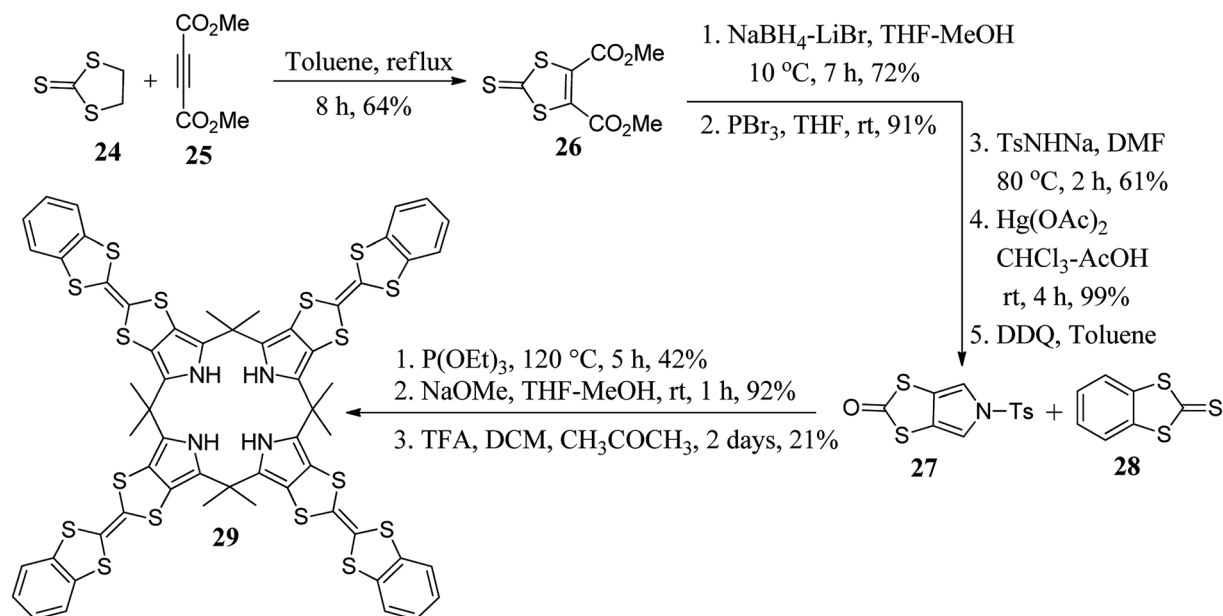


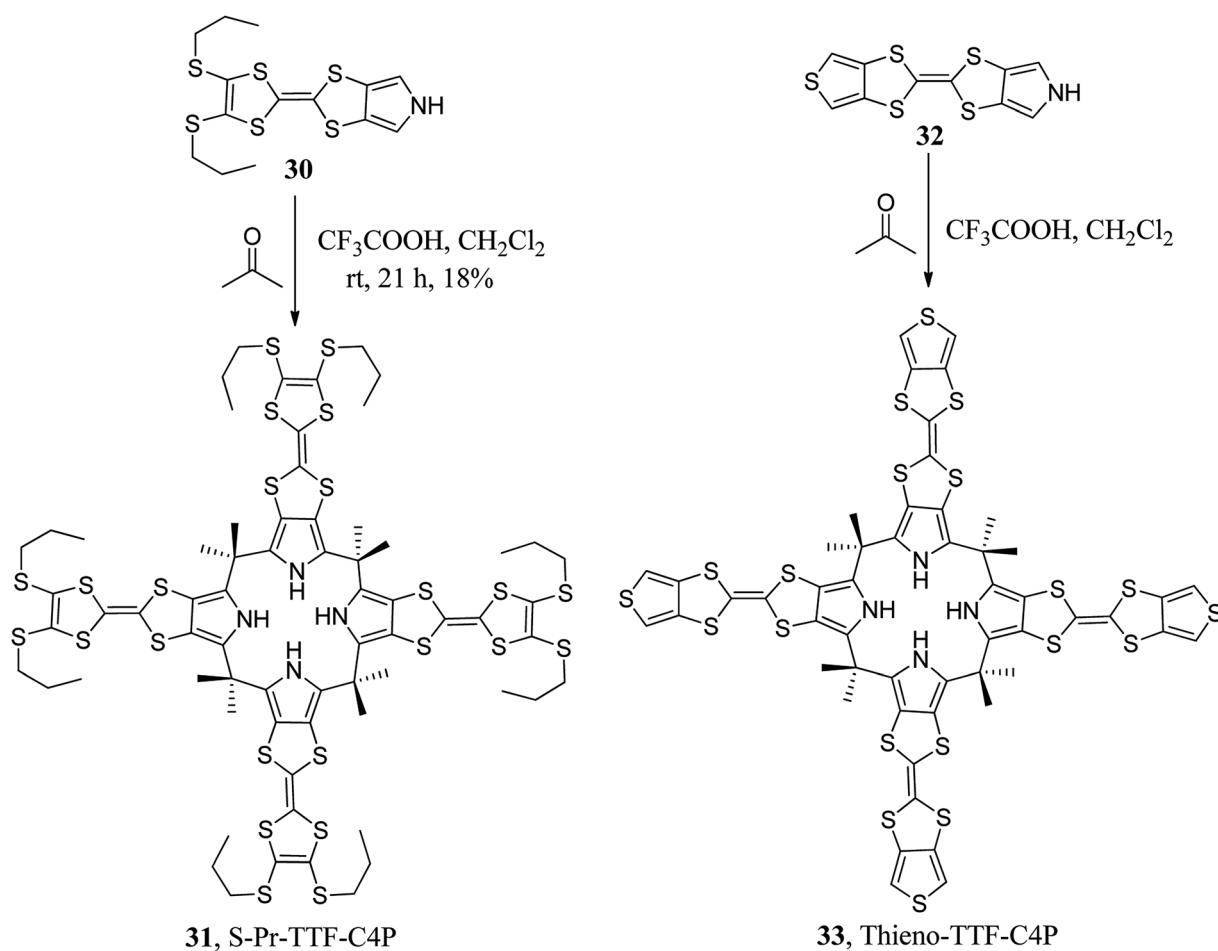
Fig. 3 Transformation of the 1,3-alternate conformation into the cone conformation via anionic species.



Scheme 2 Synthesis of  $\beta$ -substituted C4P.Fig. 4 Structures of various  $\beta$ -substituted C4Ps.

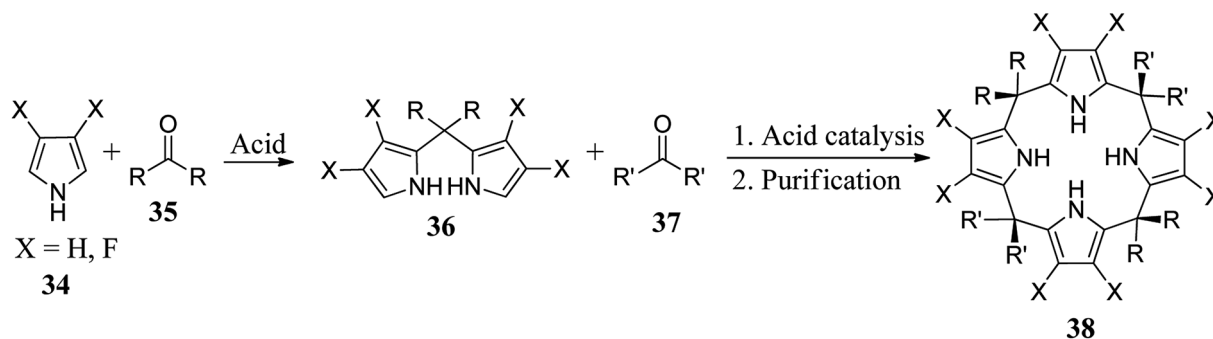


Scheme 3 Synthesis of benzo TTF-C4P.

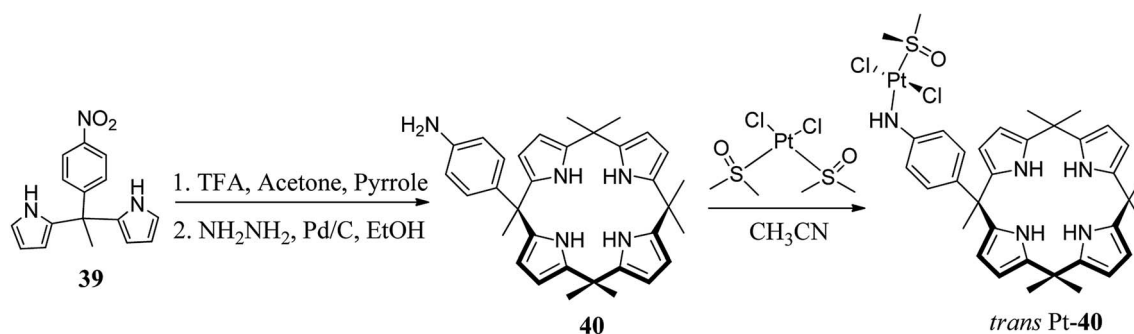


Scheme 4 Synthesis of S-Pr-TTF-C4P and thieno-TTF-C4P.





Scheme 5 Synthesis of meso-substituted C4Ps.

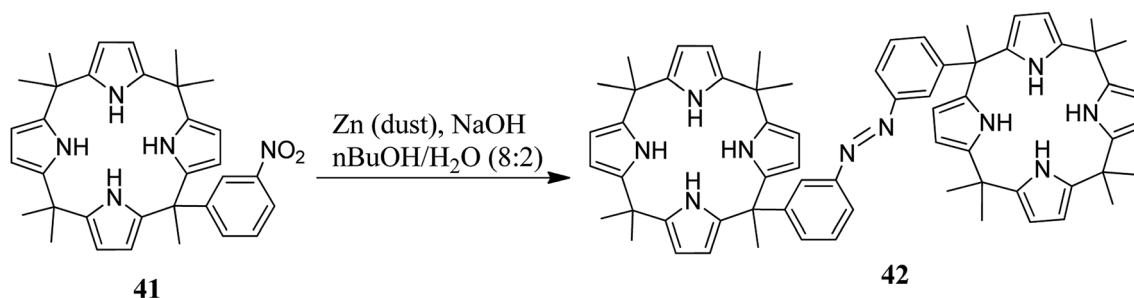


Scheme 6 Synthesis of C4P-derived meso-p-nitroaniline trans-coordinated to a Pt(II) center.

binding as well as the inherent anion selectivity for properly tailored anionic substrates would subsequently increase. It has also been observed from the literature that the strapped system 5 has inherent advantages over the deep cavity system 4.<sup>33–39</sup> We are fairly certain that once the synthesis of 6 is achieved, it will definitely provide a new dimension to the C4P chemistry.

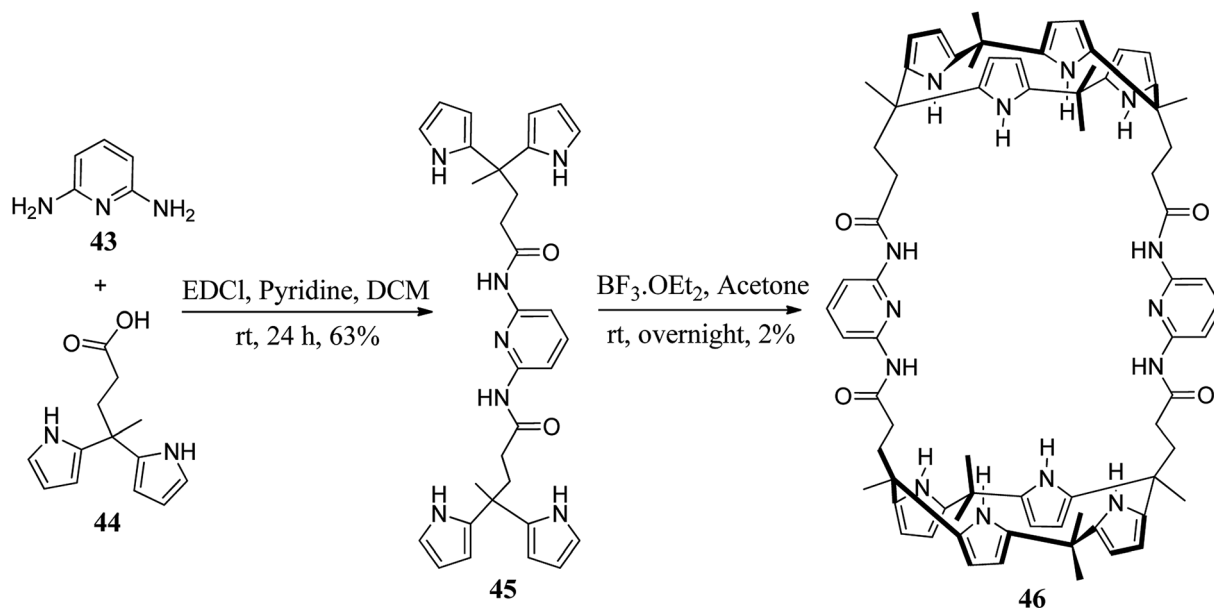
The first synthetic approach for C4P was carried out by Baeyer in 1886 in terms of hydrochloric acid-catalyzed condensation of pyrrole with acetone (Scheme 1).<sup>27</sup> Three decades later, the same reaction was repeated by Chelintzev *et al.*, and they proposed the cyclic tetrameric porphyrinogen structure.<sup>40</sup> The same synthesis was improved by Rothmund and Gage in 1955 by employing methane sulfonic acid as a catalyst.<sup>41</sup> In addition to these significant findings, C4Ps were

studied occasionally in the next 100 years after their discovery.<sup>5,42–44</sup> In 1990, Floriani and teammates commenced a widespread work on deprotonated calixpyrroles. The reconstruction and anion binding properties of C4P 1 were first determined in 1996 by J. L. Sessler and teammates at the University of Texas (Austin); they demonstrated that these macrocycles have many novel applications in diverse areas.<sup>5</sup> Since then, this area of research has been continuously growing in all directions and has resolved several problems for chemists. However, we believe that this wonderful area of research is still immature, and there is a continuous need to design and synthesize more interesting and easily fabricated C4P-based receptors with inherent binding abilities. Keeping the extensive literature on C4Ps in view, we have organized the overall



Scheme 7 Synthesis of 3,3'-bis(meso-heptamethylC4P)azobenzene 42.





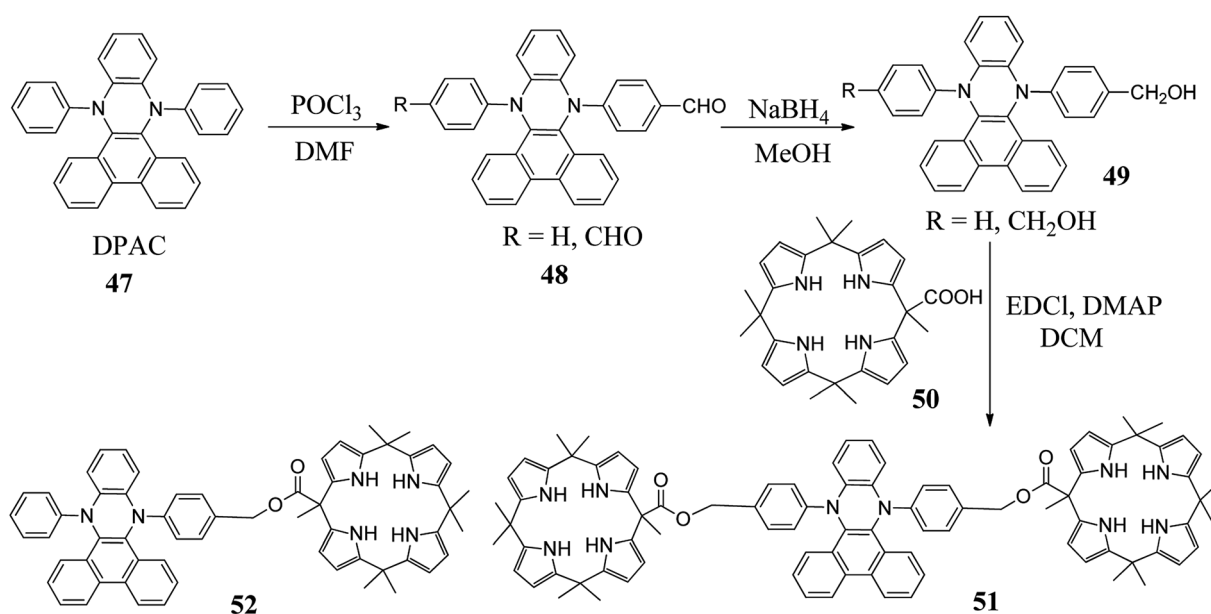
Scheme 8 Synthesis of the bis-C4P capsule starting from 2,5-diaminopyridine and dipyrromethane.

content into two major parts. The first part is devoted to some selected syntheses, and the second part is reserved for the applications of various functionalized C4Ps.

## 2. Structures and stabilities of various conformations of calix[4]pyrrole

The fundamental structure of C4P consists of four pyrrole rings and is divided into three major parts, *viz.* C-rim, N-rim, and

*meso*-rim (Fig. 1).<sup>45</sup> After extensive study, Jonathan L. Sessler and teammates concluded that unsubstituted C4Ps exist in four different conformations, analogous to calix[4]arene (Fig. 2). They also observed that the thermodynamically more stable 1,3-alternate conformation is highly favoured in the absence of anionic guests, as determined by theoretical as well as by X-ray studies. Molecular mechanics calculations also indicate that the 1,3-alternate conformation is the most stable conformation, with a torsional interaction energy about 1 to 2  $\text{kcal mol}^{-1}$  lower than that of the other conformations. In the absence of an



Scheme 9 Synthesis of DPAC-bisC4P 51 and DPAC-monoC4P 52.





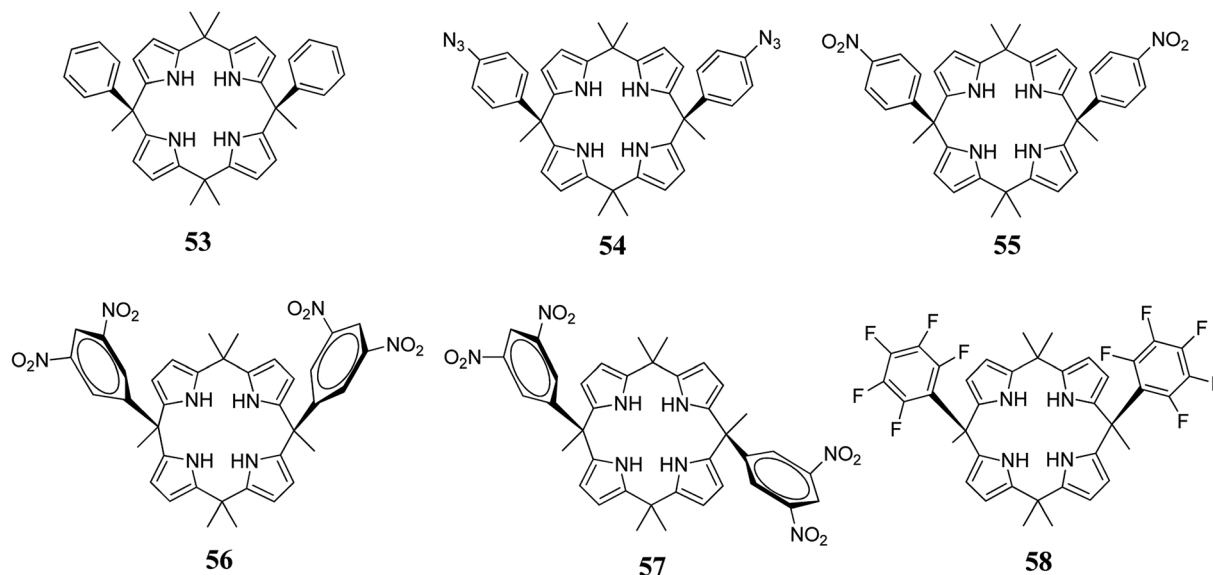


Fig. 5 Molecular structures of two-walled aryl-extended C4Ps.

anion, the predicted stability sequence of various conformers of C4Ps is 1,3-alternate > partial cone > 1,2-alternate > cone; this has been confirmed by gas phase as well as solution phase ( $\text{CH}_2\text{Cl}_2$ ) studies along with the computational support of energy optimization by BLYP/6-31G and BLYP/6-31+G\*\*. It has also been revealed in the literature that the 1,3-alternate conformation is most benefitted by electrostatic effects aided by *anti*-orientation of each adjacent pyrrole pair. On the other hand, the cone conformation mostly experiences electrostatic repulsion by virtue of the *syn*-orientation of all the pyrrole rings and has been found to be the dominant conformation in the presence of anionic guest species by virtue of hydrogen bonding interactions among the four pyrrolic NH-groups and anionic species (Fig. 3).<sup>46</sup>

### 3. Synthesis of calix[4]pyrroles

Three universal methods are commonly used for the synthesis of C4Ps. These include:

- (i) [1 + 1 + 1 + 1] condensation: direct synthesis or one-pot approach of ketones with pyrrole and its derivatives in the presence of an acid catalyst.
- (ii) [2 + 2] condensation: acid-catalyzed condensation of dipyrromethanes with ketones.
- (iii) [3 + 1] condensation: acid-catalyzed reaction of tripyrrane with pyrrole.

It is very clear from the literature that the one-pot approach is the most accepted of the aforementioned methods for the generation of a variety of C4Ps using either a Lewis acid or Brønsted acid in a catalytic amount. On the other hand, in recent years, acidic zeolites and graphite oxide have also been used as powerful catalysts for the synthesis of diverse dipyrromethanes as well as C4Ps in acceptable yields.<sup>47</sup>

#### 3.1. $\beta$ -Substituted calix[4]pyrroles

To tune the binding ability of C4Ps (hosts) with their guests (anions), researchers worldwide have designed and synthesized various  $\beta$ -substituted calix[4]pyrrole derivatives. For example, in 2011, Sessler's group synthesized  $\beta$ -octaalkyl-substituted C4P derivative 15 using *N*-tosylpyrrolidine pyrrole and acetone in satisfactory yield (Scheme 2).<sup>48</sup> On the other hand, with the aid of well-adopted synthetic procedures, scientists have also carried out the synthesis of various other  $\beta$ -substituted C4P derivatives (Fig. 4).<sup>49–51</sup>

It is clear from the literature that tetrathiafulvalene (TTF) plays a vital role in diverse areas of science and technology.<sup>52</sup> In this context, Sessler's group attached the TTF moiety at the  $\beta$ -positions of C4P to generate diverse TTF-C4Ps (29, 31, and 33), as shown in Schemes 3 and 4.<sup>53–57</sup>

#### 3.2. *Meso*-substituted calix[4]pyrroles

The simple calixpyrrole derivatives can be assembled in a single step in good yields through the condensation of appropriately chosen pyrrole derivatives with suitable ketones; however, for properly *meso*-substituted calixpyrroles, researchers working in this area generally prefer two-step methods starting from acidic condensation of pyrrole derivatives with appropriate ketones to form substituted dipyrromethanes followed by acid-catalyzed condensation with ketones to achieve the desired targets (Scheme 5).

Recently, Cafeo *et al.* synthesized functionalised C4P 40 (Scheme 6). After its reaction with *cis*-[PtCl<sub>2</sub>(DMSO)<sub>2</sub>], they obtained a crystalline compound, *trans*-Pt 40, which was used to deliver the *trans*-Pt anticancer drug to the target site.<sup>58</sup>

On the other hand, the same group reported 3,3'-bis(*meso*-heptamethylC4P)azobenzene 42 along with its host-guest chemistry with various aliphatic bis-carboxylates (Scheme 7).<sup>59</sup>



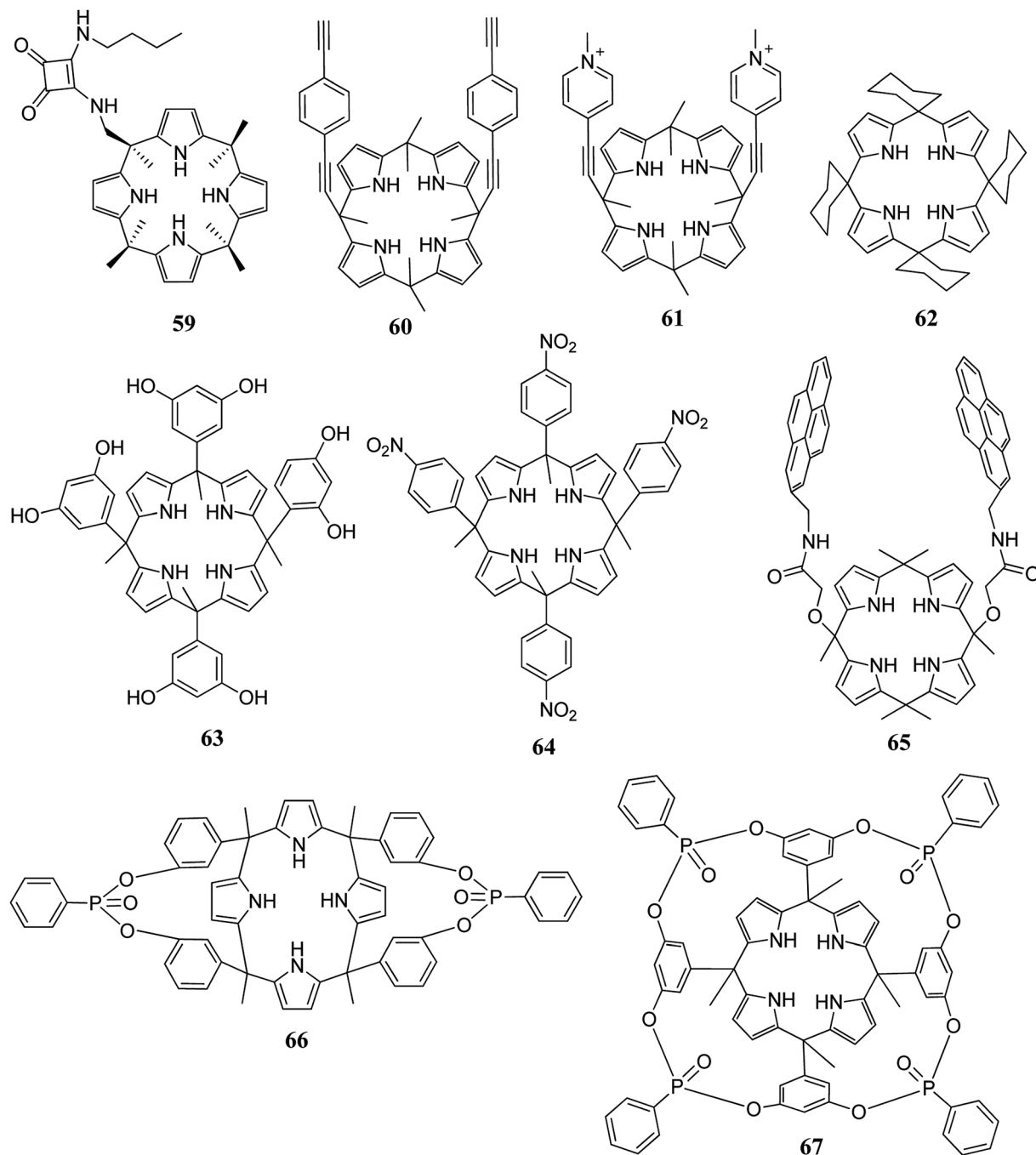


Fig. 6 Structures of various *meso*-substituted two and four-walled C<sub>4</sub>Ps.

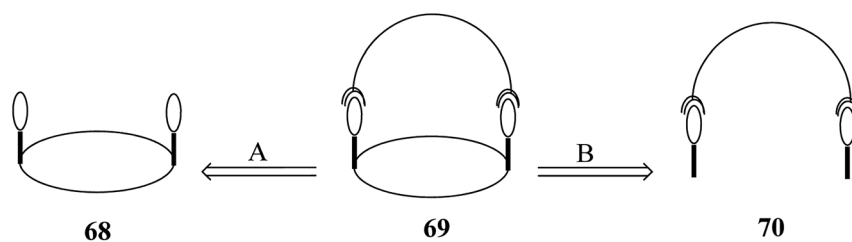
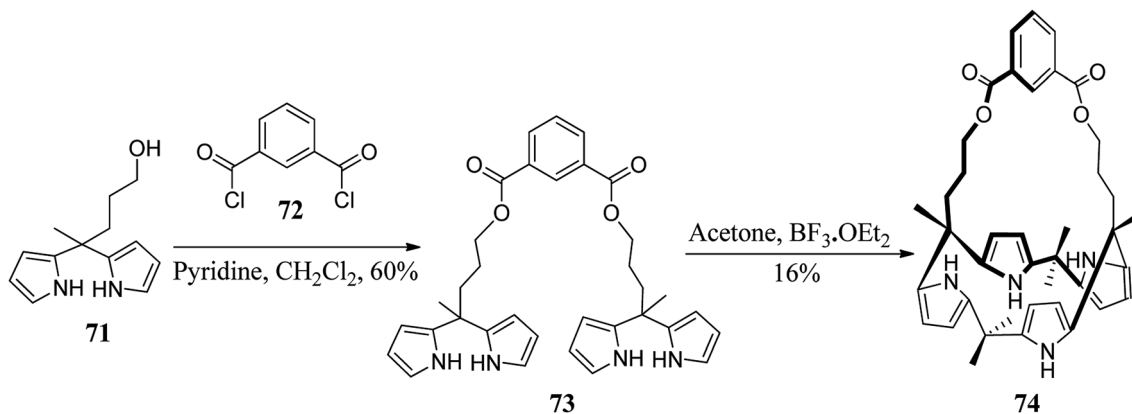


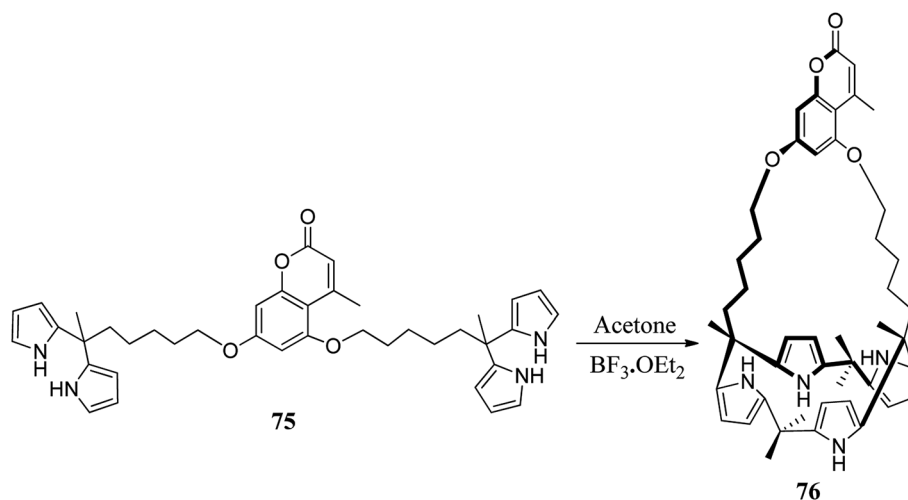
Fig. 7 Retrosynthetic analysis of strapped systems.







Scheme 10 Synthesis of strapped C4P 74.



Scheme 11 Synthesis of coumarin-strapped C4P 76.

Recently, Sessler and his teammates synthesized large, capsule-like bis-C4P **46** (Scheme 8).<sup>60</sup> The capsule **46** possesses a relatively large internal cavity which hosts various oxoanions.<sup>61–63</sup>

Quite recently, Sessler's group synthesised a fluorescent sensor (**51**) for sensing various aliphatic and aromatic dicarboxylate anions (Scheme 9). It contains the vibrationally induced active 9,14-diphenyl-9,14-dihydrodibenzo[*a,c*]phenazine (DPAC) chromophore between two C4P units.<sup>64</sup>

For the exploration of C4Ps in the domain of anion- $\pi$  interactions, in 2013, Ballester's and Matile's groups designed and synthesized *meso*-substituted two-walled aryl extended C4Ps for the binding of nitrate anion (Fig. 5), thereby highlighting the potential roles being played by different aryl- $\pi$  substituents in anion- $\pi$  contact.<sup>33,65,66</sup> Researchers worldwide

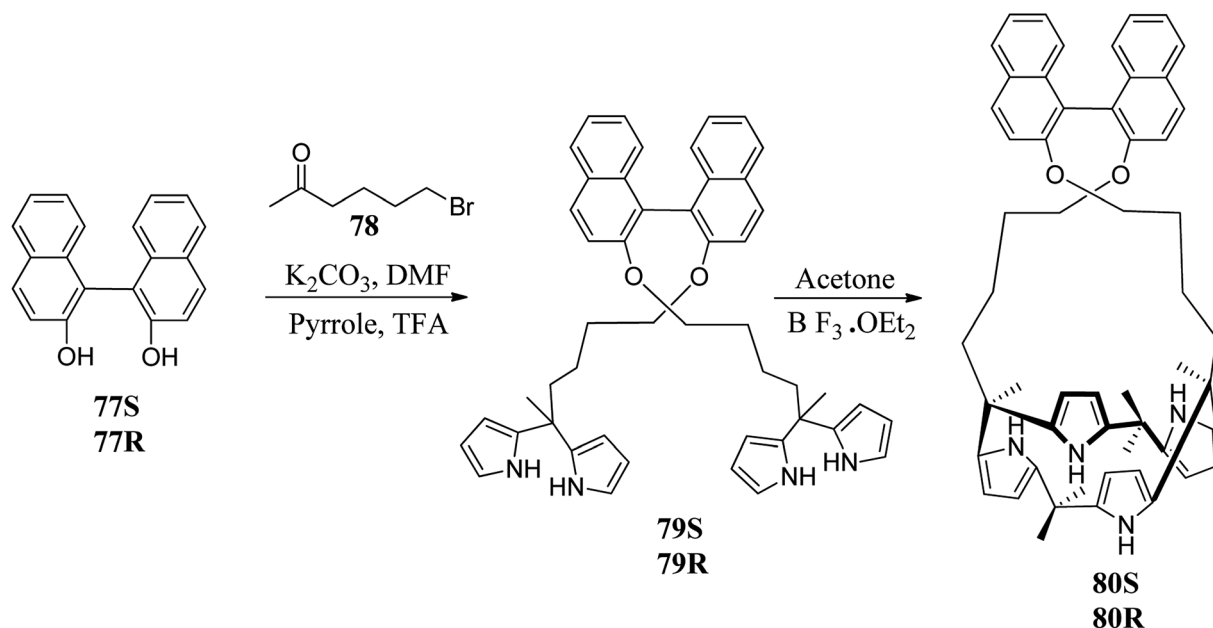
have also carried out the synthesis of various other *meso*-substituted two and four-walled C4Ps (Fig. 6).<sup>67–81</sup>

### 3.3. Strapped calix[4]pyrroles

The chemistry of strapped C4Ps has thrived in the past several years.<sup>82</sup> For the synthesis of strapped C4P-based receptors, two different pathways appear to be very suitable. These include primary construction of the C4P central loop followed by bridging with a strap (Fig. 7, path A) and initial formation of an associated precursor followed by C4P loop construction (Fig. 7, path B); however, it is the second path which has been found to be most effective and is generally adopted for the synthesis of strapped C4Ps.

In 2003, Lee *et al.* synthesized strapped C4P **74** by means of [2 + 2] condensation of dipyrromethane **71** with isophthaloyl





Scheme 12 Synthesis of chiral binol strapped C4Ps **80(R)** and **80(S)**.

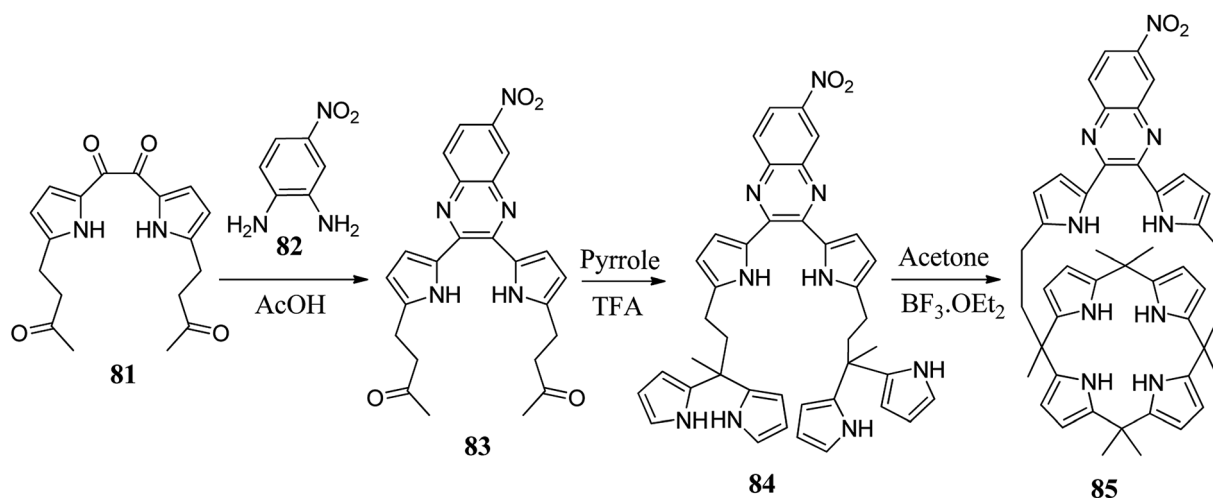
chloride (Scheme 10).<sup>83</sup> On the other hand, in 2005, Miyaji *et al.* synthesized a new fluorophore-strapped C4P (**76**) via the dipyrromethane **75** (Scheme 11).<sup>84</sup>

Sessler and coworkers synthesized a pair of chiral C4Ps, **80(R)** and **80(S)**, which may be extremely useful in the recognition and removal of a variety of anions containing enantiomeric species (Scheme 12).<sup>85</sup>

On another occasion, Jaeduk Yoo *et al.* reported the synthesis of dipyrrolylquinoxaline-strapped C4P **85** (Scheme 13).<sup>86</sup> In addition to the above strapped C4P-based receptors, researchers worldwide have carried out the synthesis of other novel strapped C4P receptors (Fig. 8).<sup>84–98</sup>

## 4. Applications of functionalized calix [4]pyrroles

Calix[4]pyrrole, since being reconstructed and studied by Sessler's group in 1996, has made significant contributions to supramolecular chemistry; its diverse applications range from sensory materials to drug delivery (Fig. 9). Considering its activities and applications in different areas of day-to-day life, C4P has earned fame not only in the supramolecular community but also in other branches of science, such as polymer chemistry and catalysis. We therefore believe that this old-yet-new member of the supramolecular family will



Scheme 13 Synthesis of dipyrrolylquinoxaline-strapped C4P **85**.



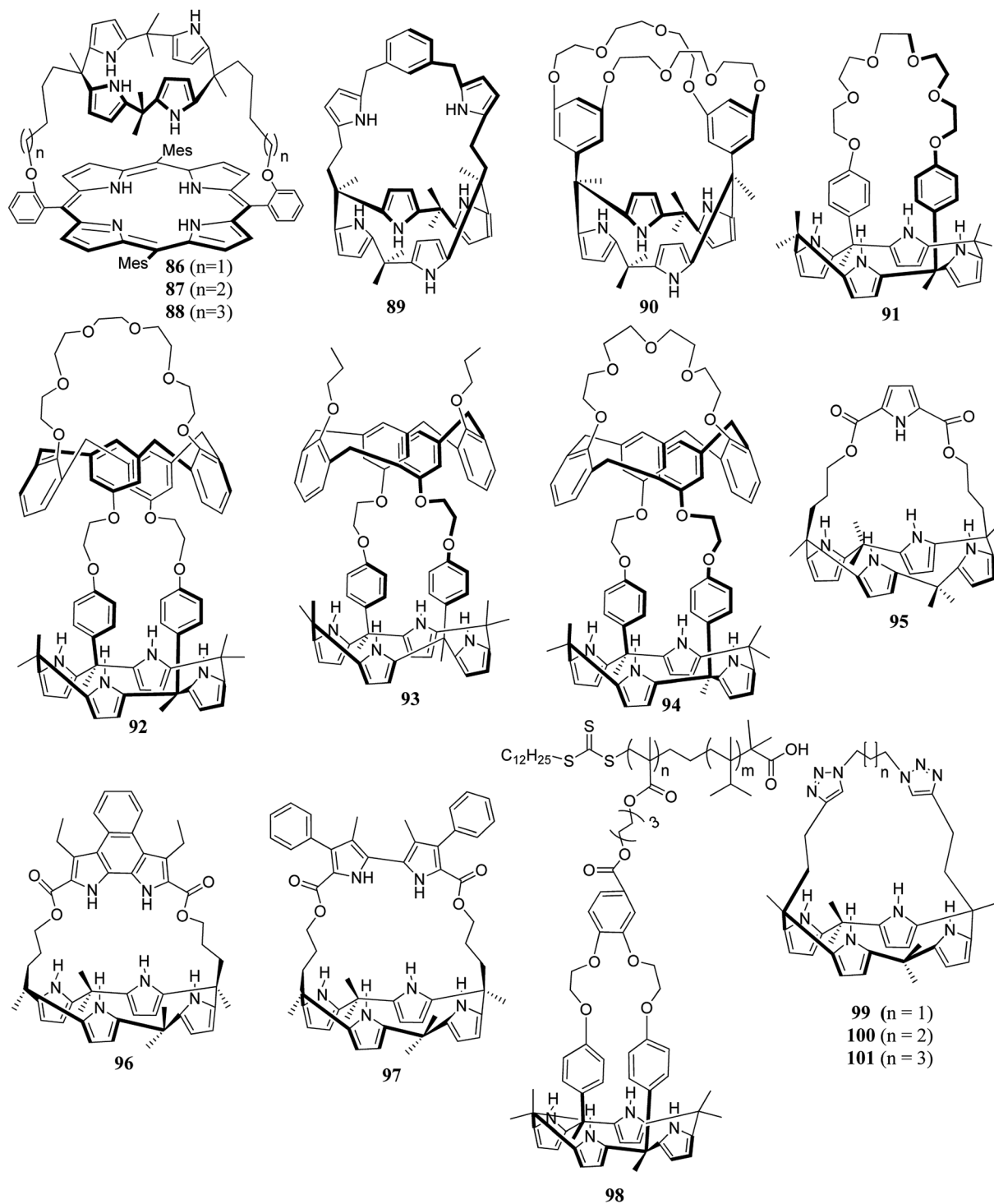


Fig. 8 Structures of various interesting strapped C4Ps.

provide a new direction to branches of science and technology. In this comprehensive review, we are highlighting the applications of this supramolecular receptor, as depicted below in Fig. 9.

#### 4.1. Role of calix[4]pyrroles in anion binding

Anions play vital roles in biological processes because they take part in 70% of all enzymatic events. Hence, in recent years, “anion complexation and recognition” has emerged as



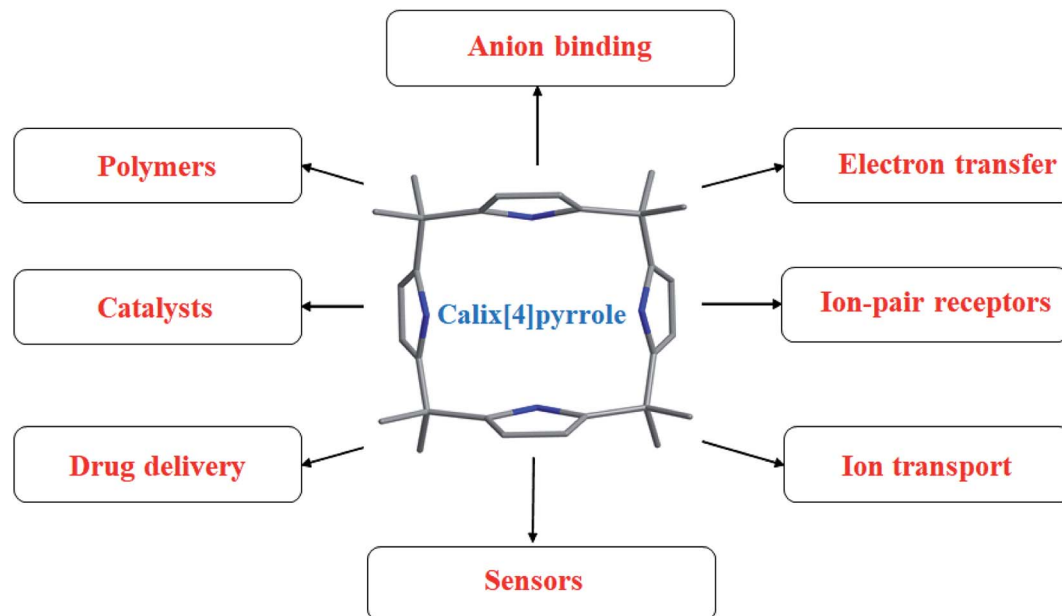


Fig. 9 Flowchart showing the applications of simple C4P and its derivatives.

a topic of leading importance in the realm of supramolecular chemistry.<sup>99,100</sup> To construct synthetic anion receptors, diverse non-covalent interactions such as halogen bonding, van der Waals forces, dipole–anion interactions, multiple hydrogen bonding, cation– $\pi$  contacts, anion– $\pi$  contacts, and hydrophobic contacts have been employed.<sup>101–103</sup> Among these, anion– $\pi$  non-covalent contacts (interaction of anionic entities with electron-deficient arene systems), reported around a decade ago, have become an actively investigated area in the heart of supramolecular chemistry<sup>104–107</sup> and have opened new opportunities for the design and synthesis of various novel sensors.<sup>108–117</sup> In this context, Ballester and coworkers observed that *cis*-3,5-dinitrophenyl functionalized C4P **56** displays selective binding of  $\text{NO}_3^-$  by means of hydrogen bonding and anion– $\pi$  interactions. X-ray crystallographic analysis elucidated that the nitrate anion in the form of tetramethylammonium nitrate (TMANO<sub>3</sub>) resides in

a perpendicular orientation to the 3,5-dinitrophenyl rings of *cis*-3,5-dinitrophenyl-functionalized C4P **56** (Fig. 10).<sup>33</sup>

Recently, Park and his teammates reported the complete solid-state analysis of *cis*-3,5-dinitrophenyl-functionalized C4P **56** with various polyatomic oxyanions along with spherical anions (halides). They also compared the anion binding affinities of the *cis*-isomer (**56**) with the *trans*-isomer (**57**) and concluded that the *cis*-isomer shows better results than the *trans*-isomer, as expected. The results obtained clearly indicate that all examined anions reside within the cavity irrespective of their size and geometry, as can be inferred from Fig. 11. All halides with 1 : 1 stoichiometry were found to be situated in the cavity *via* four concerted  $\text{NH}\cdots\text{X}^-$  hydrogen bonding interactions, while trigonal anions such as  $\text{NO}_3^-$ ,  $\text{HCO}_3^-$ , and  $\text{AcO}^-$  reside nearly parallel to the two dinitrophenyl rings; this displays a sharp contrast to Ballester's report, which showed a perpendicular orientation of TMANO<sub>3</sub>

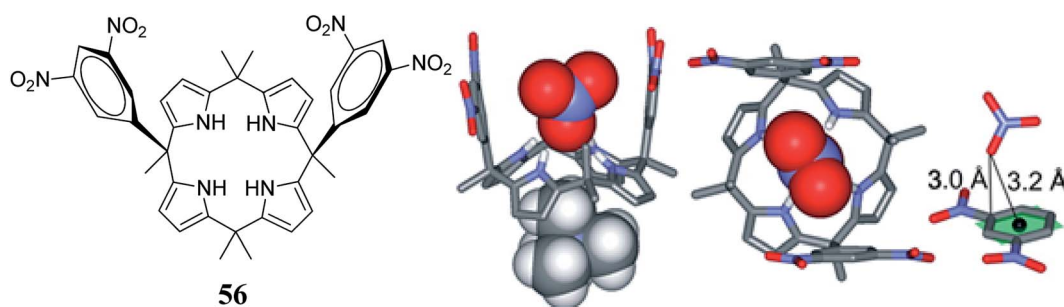


Fig. 10 Molecular structure of *cis*-3,5-dinitrophenyl functionalized C4P **56** and crystal structures of the **56**@ $\text{NO}_3^-$  complex displaying the perpendicular orientation of  $\text{NO}_3^-$  to the 3,5-dinitrophenyl rings (reproduced and adapted with permission from ref. 33. Copyright 2013 American Chemical Society).



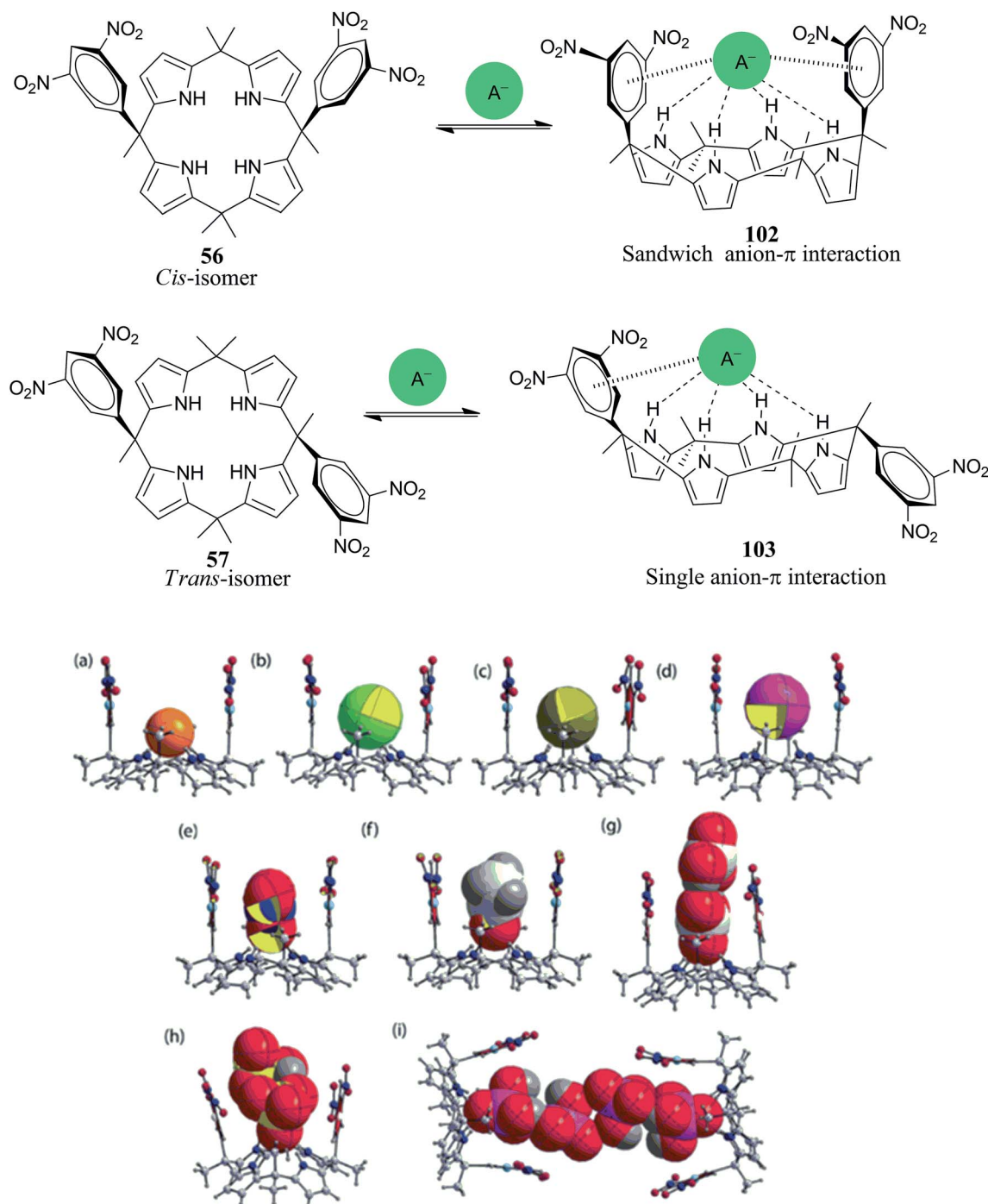


Fig. 11 Representations of hydrogen bonding and anion- $\pi$  interactions in *cis*- and *trans*-3,5-dinitrophenyl functionalized C4Ps (**56** and **57**) along with X-ray analysis of the assemblies between **56** and tetraalkylammonium anion salts: (a) **56** + TBAF, (b) **56** + TBACl, (c) **56** + TBABr, (d) **56** + TBAI, (e) **56** + TBANO<sub>3</sub>, (f) **56** + TBAOAc, (g) **56** + TEAHCO<sub>3</sub>, (h) **56** + TBAHSO<sub>4</sub> and (i) **56** + TBAH<sub>2</sub>PO<sub>4</sub>. Solvent molecules and tetraalkylammonium groups are omitted for simplicity (reproduced with permission from ref. 118. Copyright 2016 Royal Society of Chemistry).

in the *cis*-3,5-dinitrophenyl functionalized C4P (**56**). Interestingly, 1 : 2 stoichiometry was observed in the solid-state between **56** and anions such as HCO<sub>3</sub><sup>-</sup> and HSO<sub>4</sub><sup>-</sup>, and 2 : 4 stoichiometry was observed for H<sub>2</sub>PO<sub>4</sub><sup>-</sup>. Using UV-Vis photometric titrations, they also investigated the binding properties

of **56** and **57** in the solution state (Table 1). With the aid of Job plot analysis in acetonitrile solution, it was clarified that all the anions show 1 : 1 stoichiometry, where the binding constants of the *cis*-isomer (**56**) were higher than those of the *trans*-isomer (**57**); this clearly indicates favourable sandwich-





**Table 1** Binding constants (using UV-Vis titrations) of **1**, **56** and **57** for various anions

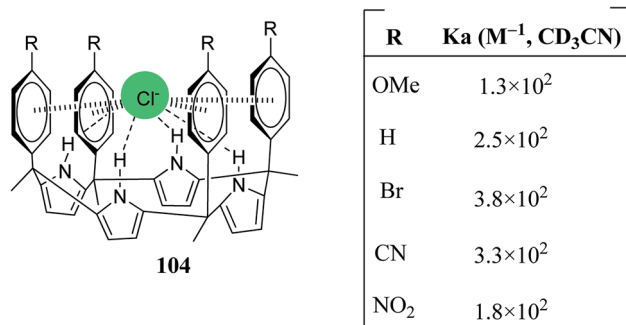
Anion	<b>1</b> ( $K_a$ , $M^{-1}$ )	<b>56</b> ( $K_{a1}$ , $M^{-1}$ )	<b>57</b> ( $K_{a2}$ , $M^{-1}$ )	$K_{a1}/K_{a2}$
F <sup>−</sup>	—	$2.1 \times 10^7$	$7.2(\pm 4.4) \times 10^6$	3
TEACl <sup>−</sup>	—	$1.8(\pm 0.09) \times 10^6$	$3.6(\pm 0.08) \times 10^4$	50
TBACl <sup>−</sup>	$1.02 \times 10^5$	$1.9(\pm 0.2) \times 10^6$	$1.1(\pm 0.05) \times 10^5$	17
THACl <sup>−</sup>	—	$2.5(\pm 0.2) \times 10^6$	$1.5(\pm 0.14) \times 10^5$	17
Br <sup>−</sup>	$1.05 \times 10^3$	$5.4(\pm 0.04) \times 10^4$	$3.0(\pm 0.04) \times 10^3$	18
I <sup>−</sup>	—	300(±1)	10(±0.1)	30
NO <sub>3</sub> <sup>−</sup>	—	1500(±6)	80(±1)	19
AcO <sup>−</sup>	$2.17 \times 10^5$	$1.4 \times 10^7$	$1.5(\pm 0.25) \times 10^6$	9
HCO <sub>3</sub> <sup>−</sup>	—	$2.1 \times 10^6$	$8.0(\pm 0.6) \times 10^4$	66
HSO <sub>4</sub> <sup>−</sup>	—	1700(±6)	20(±0.4)	85
H <sub>2</sub> PO <sub>4</sub> <sup>−</sup>	$2.65 \times 10^3$	$5.9 \times 10^6$	$1.6(0.07) \times 10^4$	369

**Table 3** Binding constants of receptor **31** with different anions using ITC in CH<sub>2</sub>ClCH<sub>2</sub>Cl

Anion	<b>31</b> ( $K_a$ $M^{-1}$ )
Cl <sup>−</sup>	$2.5 \times 10^6$
Br <sup>−</sup>	$5.8 \times 10^4$
CN <sup>−</sup>	$1.1 \times 10^6$
NO <sub>2</sub> <sup>−</sup>	$1.2 \times 10^6$
CH <sub>3</sub> CO <sub>2</sub> <sup>−</sup>	$1.3 \times 10^6$

**Table 4** Association constants ( $K_a$ ) of **76** with various anions in different solvents (3% H<sub>2</sub>O–CH<sub>3</sub>CN, NaPF<sub>6</sub>–CH<sub>3</sub>CN, and CH<sub>3</sub>CN) at 298 K

Anion source	$10^{-4}$ ( $K_a$ , $M^{-1}$ )		
	3% H <sub>2</sub> O–CH <sub>3</sub> CN	NaPF <sub>6</sub> –CH <sub>3</sub> CN	CH <sub>3</sub> CN
TBACl	190	230	360
TBABr	3.7	10	11
TBAOAc	89	130	190

**Fig. 12** Representation of hydrogen bonding and anion– $\pi$  contacts with the *meso*-tetraaryl C4P receptor and their association constants with chloride in CD<sub>3</sub>CN.

type anion– $\pi$  interactions. It was also found that the *cis*- and *trans*-isomers show visible colour changes after the addition of some anions, *viz.* fluoride anion addition produces a drastic colour change from yellow to blue, and these changes were accompanied by spectral changes. Thus, anion– $\pi$  interactions in the case of electron-deficient 3,5-dinitrophenyl-substituted C4P leads to the development of chromogenic materials.<sup>118</sup>

Ballester and coworkers also reported binding energy studies of *meso*-substituted four-walled (tetraaryl) C4P receptor **104** (Fig. 12) with chloride in the solution phase and finally quantified the chloride– $\pi$  interactions. <sup>1</sup>H-NMR and X-ray

**Table 2** Binding constants of *trans*-**42** and *cis*-**42** with bis-carboxylates (as TBA salts)

bis-Carboxylate	$K_a$ for <i>trans</i> - <b>42</b>	$K_a$ for <i>cis</i> - <b>42</b>
Succinate	$6.4 \times 10^3$	$5.3 \times 10^5$
Glutarate	$7.4 \times 10^4$	$2.2 \times 10^5$
L-Glutamate	$2.7 \times 10^3$	Not determined
Adipate	$8.6 \times 10^4$	$2.2 \times 10^4$

crystallographic analysis was employed to demonstrate the interactions between the electronically tunable cavity of the receptor and the chloride ion. The required association constants of **104** with diverse anions were calculated in the solution phase (CD<sub>3</sub>CN), as can be seen by inspection of Fig. 12.<sup>119</sup>

Cafeo *et al.* observed that the complexation of 3,3'-bis(*meso*-heptamethylC4P)azobenzene receptor **42** (Scheme 7) with diverse bis-carboxylates has considerable kinetic effects on both the thermal and photochemical *trans/cis* isomerization of the azobenzene unit. They carried out binding constant evaluations of both the *cis*- and *trans*-forms of **42** with various bis-carboxylates (Table 2).<sup>59</sup>

Regarding the anion-binding studies of  $\beta$ -substituted C4Ps, Sessler and his teammates carried out replacement of the  $\beta$ -pyrrolic protons with complex substituents.<sup>120</sup> They designed and synthesized various TTF-C4Ps and other oligopyrrolic macrocycles.<sup>55,121–126</sup> They utilized TTF-based C4P **31** (Scheme 4) and carried out anion binding studies with diverse anions such

**Table 5** Calculated  $K_a$  values of receptor **85** with diverse anions carried out in CH<sub>3</sub>CN/DMSO at 25 °C

Anion	UV-Vis ( $K_a$ , $M^{-1}$ )	ITC ( $K_a$ , $M^{-1}$ )	C4P ( $K_a$ , $M^{-1}$ )
F <sup>−</sup>	$8.97 \times 10^6$	$K_1 = 3.72 \times 10^8$ $K_2 = 5.0 \times 10^5$	Not available
Cl <sup>−</sup>	$1.09 \times 10^4$	$1.94 \times 10^4$	$1.02 \times 10^5$
Br <sup>−</sup>	$3.65 \times 10^2$	Not determined	$1.05 \times 10^3$
AcO <sup>−</sup>	$8.12 \times 10^3$	$1.89 \times 10^4$	$2.17 \times 10^5$
H <sub>2</sub> PO <sub>4</sub> <sup>−</sup>	$1.13 \times 10^3$	$1.33 \times 10^3$	$2.65 \times 10^3$





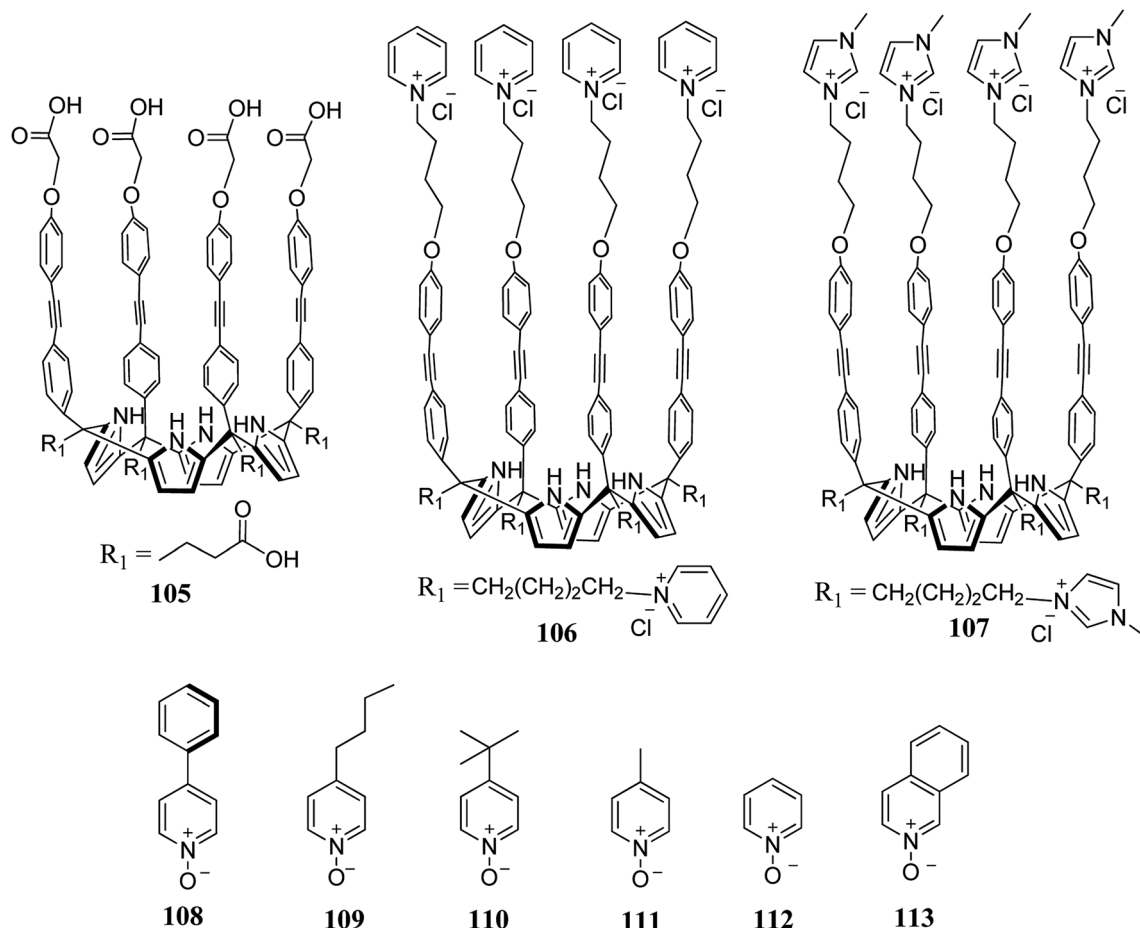


Fig. 13 Molecular structures of super aryl-extended C4P hosts (105–107) and pyridyl *N*-oxide guests (108–113).

as  $\text{Br}^-$ ,  $\text{Cl}^-$ ,  $\text{CN}^-$ ,  $\text{NO}_2^-$ , and  $\text{AcO}^-$  by means of  $^1\text{H}$ -NMR spectroscopy and isothermal titration calorimetry (ITC) techniques (Table 3).<sup>52–57</sup>

Regarding the anion binding significance of strapped C4Ps, researchers worldwide have employed various strapped C4Ps in the binding of diverse anions. In this context, Lee *et al.* carried out anion binding studies of a host, **74** (Scheme 10), and confirmed that chloride anion rests inside the cavity.<sup>83</sup> The chloride complex of **74** also reveals that the aryl CH participates in anion recognition in terms of hydrogen bonding. With the

aid of ITC calculations, they also observed that strapped C4P **74** has a higher binding constant for chloride anion ( $K_a = 1.01 \times 10^5$ ) than unstrapped C4P ( $K_a = 1.2 \times 10^3$ ). Thus, it is the shape and size of C4Ps which determine the enhanced anion selectivity of the anion receptors.<sup>84,87–94</sup>

Miyaji *et al.* determined the association constants of coumarin-strapped C4P receptor **76** (Scheme 11) with various anions by means of fluorescence and ITC titrations (Table 4).<sup>84</sup> On the other hand, Sessler and teammates revealed that chiral C4P **80(S)** (Scheme 12) exhibits high affinity to bind chiral carboxylate anions, *viz.* (*R*)-2-phenylbutyrate and (*S*)-2-phenylbutyrate, in acetonitrile. The (*S*)-guest–(*S*)-host pair possesses  $K_a$  values 10 times greater than those of the analogous (*R*)-guest–(*S*)-host pair.<sup>85</sup> On another occasion, Jaeduk Yoo *et al.* carried out anion binding studies of dipyrrolylquinoxaline-based strapped C4P **85** (Scheme 13) with  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{AcO}^-$ , and  $\text{H}_2\text{PO}_4^-$  by means of UV-Vis absorption spectra in  $\text{CH}_3\text{CN}$ /DMSO and ITC (Table 5).<sup>86</sup>

The solubility of C4Ps in aqueous media is a challenging aspect which was recently overcome by Ballester and coworkers. They reported various water-soluble super aryl-extended C4Ps

Table 6 Binding constants of **105** and **106** with polar guests (108–113) using ITC and  $^1\text{H}$ -NMR titrations

Polar guest	$K_a$ for <b>105</b>	$K_a$ for <b>106</b>
<b>108</b>	$1.2 \pm 0.5 \times 10^9$	$2.6 \pm 0.6 \times 10^9$
<b>109</b>	$1.0 \pm 0.4 \times 10^8$	$3.7 \pm 0.6 \times 10^8$
<b>110</b>	$9.1 \pm 3.0 \times 10^6$	$3.7 \pm 0.6 \times 10^7$
<b>111</b>	$2.0 \pm 0.1 \times 10^6$	$6.1 \pm 0.1 \times 10^6$
<b>112</b>	$8.6 \pm 0.5 \times 10^5$	$1.9 \pm 0.1 \times 10^6$
<b>113</b>	$2.2 \pm 0.2 \times 10^7$	$7.1 \pm 0.2 \times 10^6$



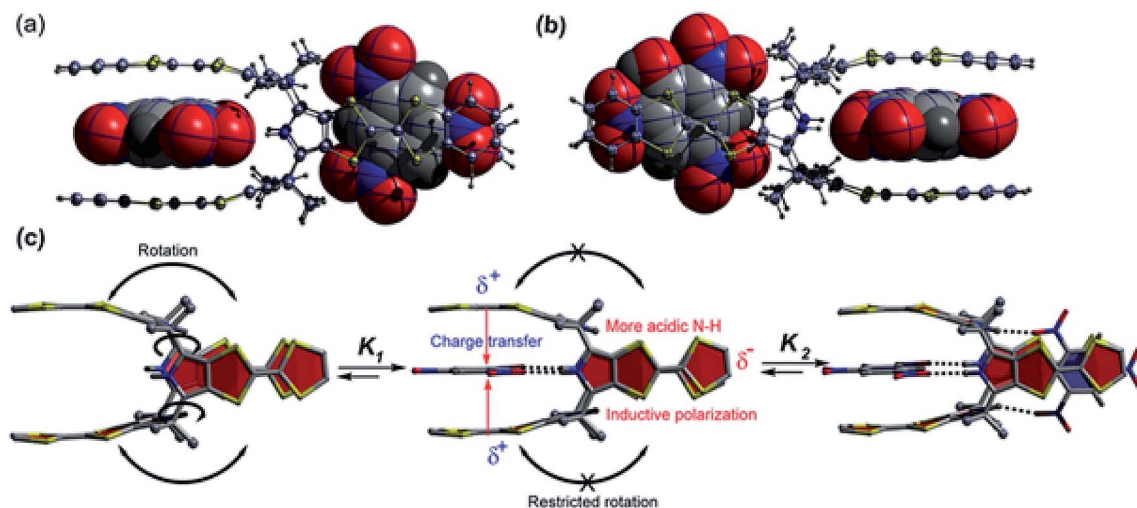


Fig. 14 X-ray studies of (a) TNB2  $\subset$  29 and (b) TNP2  $\subset$  29 and (c) illustration of positive homotropic cooperative binding (reproduced with permission from ref. 56. Copyright 2018 American Chemical Society).

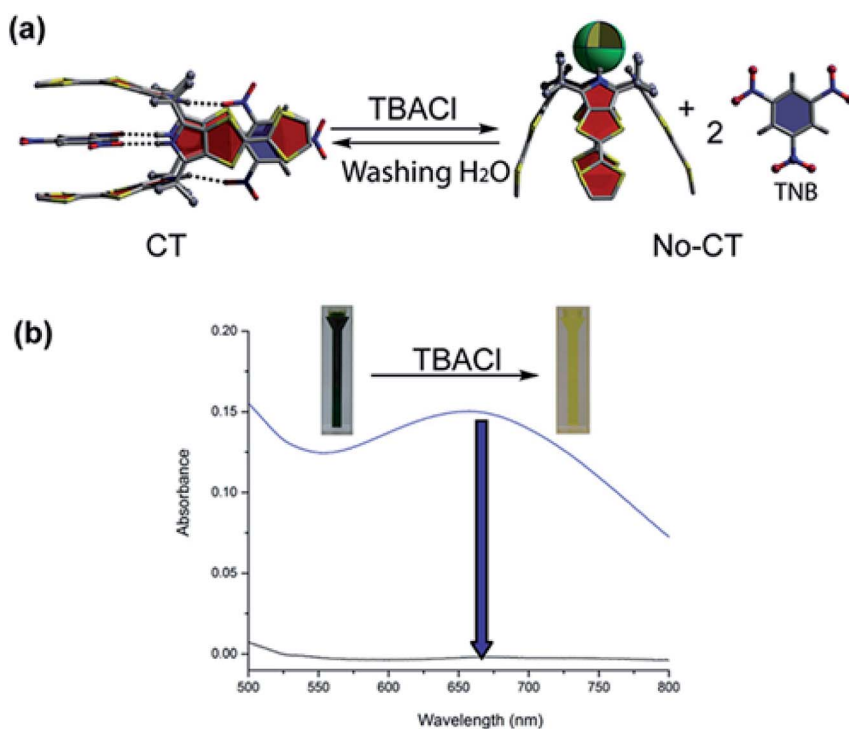


Fig. 15 Switching between TNB2  $\subset$  29 and its fundamental elements in terms of chloride. (b) Absorption spectral changes (reproduced with permission from ref. 56. Copyright 2018 American Chemical Society).

(105–107) for the binding of polar pyridyl *N*-oxides (108–113) in water (Fig. 13).<sup>127</sup> These super aryl-extended C4Ps form 1 : 1 stable complexes with polar guests in water and offer larger binding constants (Table 6). It has also been observed that the thermodynamic stability of 1 : 1 complexes is enhanced by increasing the surface area of the non-polar substituents at the

*para* positions of pyridyl *N*-oxides (Fig. 13). With the aid of these non-polar residues, they quantified the hydrophobic effects in the cavities of these systems by means of ITC and <sup>1</sup>H-NMR titrations. This effect plays a prominent role in the binding of polar guests, with assistance from dispersion and hydrogen bonding interactions.<sup>127</sup>



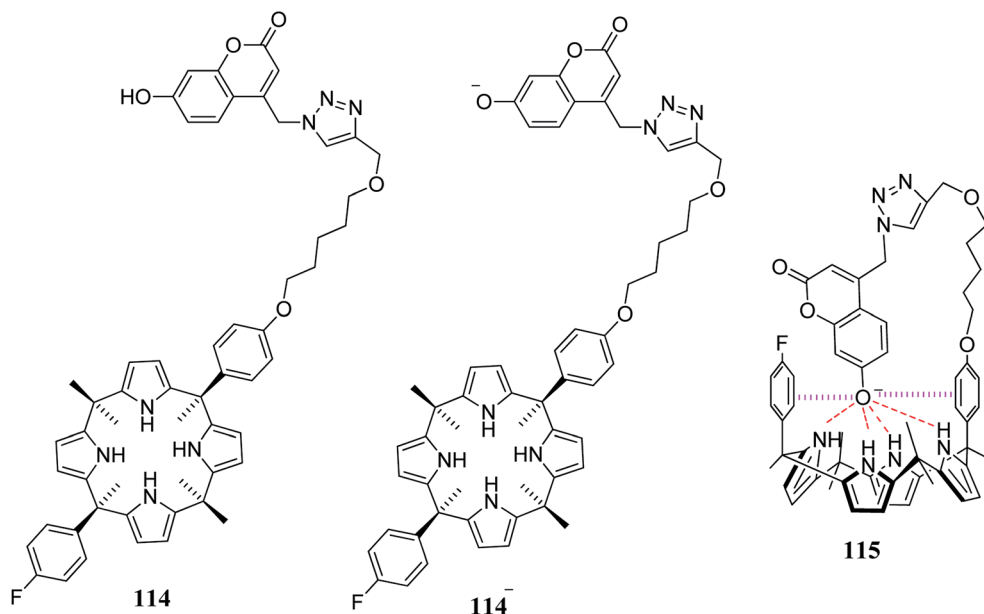


Fig. 16 Molecular structures of fluorophore-tethered C4P **114**, ionized receptor **114<sup>-</sup>** and host-guest complex **115**.

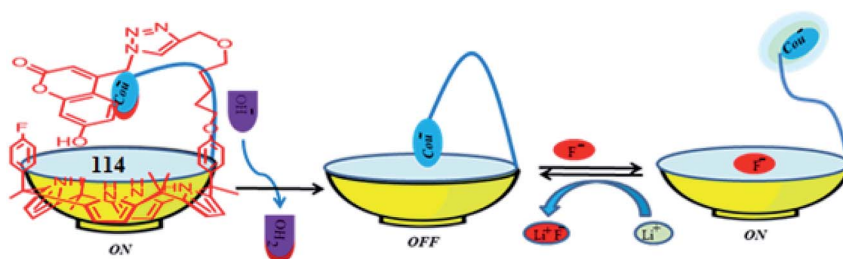


Fig. 17 Schematic illustrating the operative mechanism of fluorescence switching of the receptor **114**.

#### 4.2. Calix[4]pyrroles as sensors

The rapid search for relatively inexpensive, sensitive and intrinsically selective sensory materials to detect small amounts of nitroaromatic explosives is a significant concern for national as well as global security. To this end, the exponentially

increasing demand to enhance the protection of society and to aid the location of hidden land mines has encouraged supramolecular chemists to design novel chemosensors to detect nitroaromatic explosives. In recent years, Sessler's group has synthesized various TTF-C4P-based fluorophores to detect and discriminate diverse highly explosive nitroaromatic

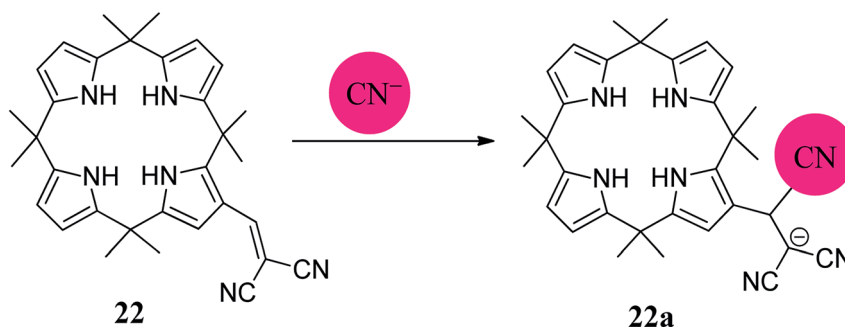


Fig. 18 Functional and ratiometric C4P-based receptor **22** for cyanide anion.



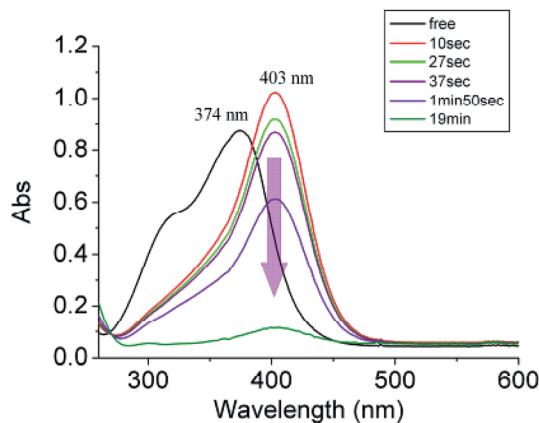


Fig. 19 UV-Vis changes of the host **22** with cyanide anion (20 equiv.) in  $\text{CH}_3\text{CN}$ –DMSO (3%) (reproduced with permission from ref. 132. Copyright 2009 Royal Society of Chemistry.).

compounds. These fluorophores exhibit positive allosteric behaviour with electron-deficient explosive guests such as 2,4,6-trinitrophenol (TNP), 2,4,6-trinitrotoluene (TNT), and 1,3,5-trinitrobenzene (TNB). By virtue of their small sizes, the guests are inserted into 1,3-alternate conformations of **29**, **31**, and **33** and display 1 : 2 stoichiometry, as confirmed by X-ray diffraction studies (Fig. 14).<sup>128</sup> The best allosteric behaviour with good agreement of overall binding constants was found in the case of thiophene-TTF-C4P **33**, followed by benzo-TTFC4P **29** and S-Pr-TTF-C4P **31**. As far as future perspectives are concerned, we hope that opportunities for supramolecular chemists and biologists will be expanded by manipulating allosteric regulators in order to control and replicate complex biological systems

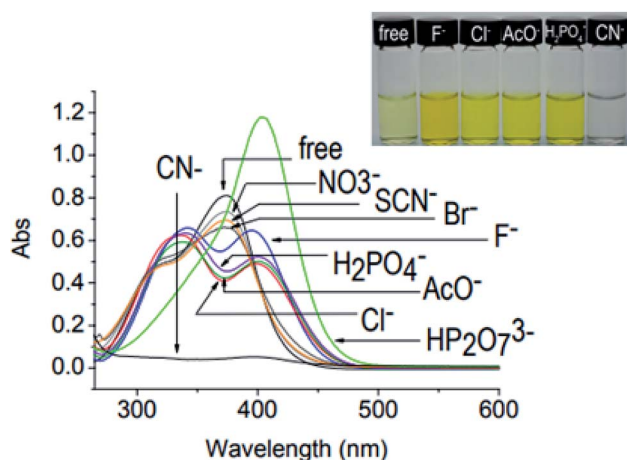


Fig. 20 UV-Vis spectral changes of free host **22** upon addition of diverse anions (20 equiv.) in  $\text{CH}_3\text{CN}$ –DMSO (3%). Color changes of **22** observed in the presence of  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{H}_2\text{PO}_4^-$ ,  $\text{AcO}^-$ , and  $\text{CN}^-$  are also displayed (reproduced with permission from ref. 132. Copyright 2009 Royal Society of Chemistry.).

in simple paradigms. Molecular-scale logic devices bearing allosteric functions are thus likely forerunners of modern supramolecular chemistry.<sup>129</sup>

Sessler's group also observed visual colour changes upon mixing TTF-C4Ps with electron-deficient substrates; these colour changes were attributed to the emergence of charge-transfer bands.<sup>130</sup> Complete vanishing of the wide charge-transfer bands was observed on adding tetrabutylammonium chloride to chloroform solutions containing nitroaromatic complexes of TTF-C4P host **29**. This occurs by virtue of switching from the 1,3-alternate conformation to the cone conformation, as can be inferred from Fig. 15.<sup>128</sup> The cone conformation, in sharp contrast to the tweezer-like 1,3-alternate conformation, contains a bowl-shaped cavity that is inappropriate for the binding of small nitroaromatic explosives; as a result, the guests are released into solution. After the salt is eliminated from this mixture by carrying out  $\text{H}_2\text{O}$ -based washing of the organic phase, the charge-transfer complexes are regenerated, as can be inferred from Fig. 15.

In 2016, Lee and coworkers devised a highly selective and sensitive single-molecular ion-mediated fluorescent switching receptor **114** which possesses an appended fluorophore in its structure (Fig. 16).<sup>79</sup> The fluorescent receptor **114** on treatment with tetrabutylammonium hydroxide (TBAH) undergoes deprotonation very easily, and the resulting solution becomes completely non-fluorescent because the ionized receptor **114**<sup>−</sup> generates a hydrogen bonding complex with a C4P moiety to form host–guest complex **115** (Fig. 16); upon treatment with LiF, the fluorescence is recovered, as displayed in Fig. 17. They also observed that the fluorescence of the system is turned off again in the presence of metal ion. This is because the hydrogen bonding is disrupted by strong coulombic interactions between the metal ion and receptor-bound anion. Thus, with the aid of external stimuli, the devised system operates efficiently in a sequential “on–off–on–off” manner (Fig. 17).<sup>79</sup>

Although anions perform essential roles in the biological as well as in the physical world, they must be treated with care because some anions are toxic to biosystems.<sup>131</sup> Thus, in order to overcome the poisonous effects of these anions, some synthetic sensors which sense these anions have been designed and synthesized; this can lead to the elimination of toxic effects. Cyanide ion is highly toxic to living animals and is released as unwanted waste from numerous industrial processes, such as gold mining and electroplating, into the environment, leading to serious problems. In this context, in 2009, Chang-Hee Lee and coworkers developed a dual functional and ratiometric sensor **22** with a dicyanovinyl group at the  $\beta$ -position for the detection of cyanide anion (Fig. 18).<sup>132</sup> They found that unlike the parent  $\beta$ -unsubstituted C4P, which is transparent in the visible region, the substituted **22** is yellow, with a  $\lambda_{\text{max}}$  of 374 nm. The receptor **22** acts as an anion-selective ratiometric sensor for cyanide anions by means of a nucleophilic addition reaction, as shown in Fig. 18. They also noted a large



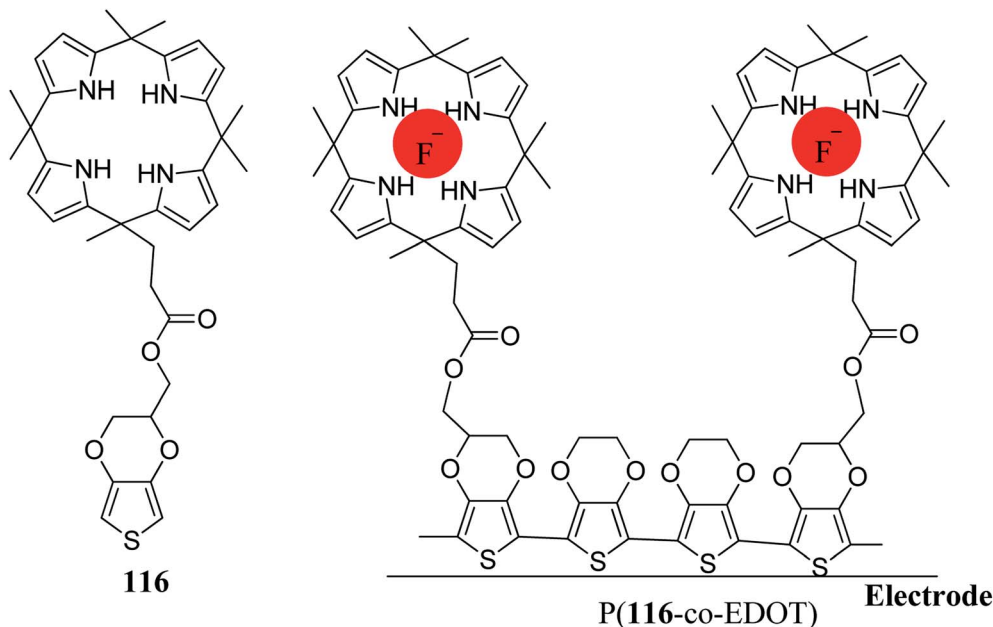


Fig. 21 Structure of **116** and the conductive copolymer **P(116-co-EDOT)** encapsulating  $F^-$ .

bathochromic shift from  $\lambda_{\max}$  374 nm to 403 nm in the presence of cyanide anion using time-dependent UV-Vis spectroscopy (Fig. 19). The selective nature of the interaction of cyanide ion with the host **22** was further evaluated by studying the absorption spectral changes in comparison to the other anions, such as  $F^-$ ,  $Cl^-$ ,  $Br^-$ ,  $NO_3^-$ ,  $SCN^-$ ,  $H_2PO_4^-$ ,  $AcO^-$  and  $HP_2O_7^-$  (Fig. 20).<sup>132</sup>

Aydogan *et al.* reported 3,4-(ethylenedioxy)thiophene (EDOT) functionalized C4P **116** along with its selective electrochemical sensing of fluoride anion in water, as shown in Fig. 21. They also carried out square wave voltammetry of **116** in order to verify the fluoride anion sensing (Fig. 22).<sup>133</sup>

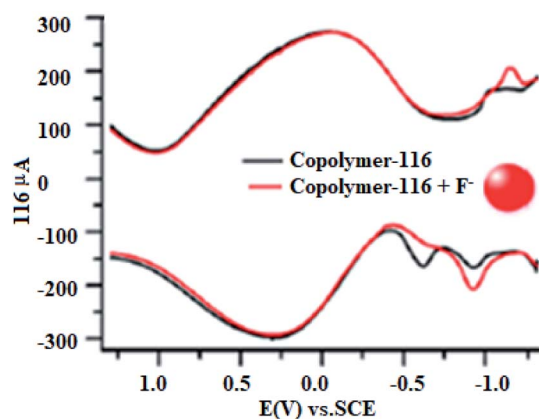


Fig. 22 Square wave voltammetry of ITO/**P(116-co-EDOT)** with increasing quantities of  $F^-$  in an  $H_2O/LiClO_4$  electrolyte system (reproduced with permission from ref. 133. Copyright 2014 American Chemical Society).

In another experiment, they developed the sensor **118** from pyrene-linked C4P **117** attached with non-covalent contacts to single-walled carbon nanotubes (SWCNT). The developed sensor was used for the selective sensing of acetone vapors on paper (concentration range 20 to 500 ppm) (Fig. 23).<sup>134</sup>

On other occasions, C4P has also been used as a chromophore. For example, Sessler and coworkers developed a novel anion sensor for sensing 4-nitrophenolate by virtue of a color change. They observed a prominent colour change in tetrabutylammonium-4-nitrophenolate from yellow to colourless upon the addition of C4P to its solution in  $CH_2Cl_2$ ; the yellow colour of 4-nitrophenolate was restored by the addition of fluoride anion, as can be inferred from Fig. 24.<sup>135</sup> Using UV-Vis spectroscopic analysis, they observed a significant decrease in intensity of the band at 432 nm upon the addition of C4P to tetrabutylammonium 4-nitrophenolate (Fig. 25), and the strongest absorbance was also observed upon the addition of  $F^-$  followed by  $Cl^-$  and phosphate ion (Table 7).<sup>135</sup>

#### 4.3. Calix[4]pyrroles as ion-pair receptors

Receptors that can bind both anionic and cationic guests are particularly interesting because they may permit modification of their recognition properties by suitable assignment of the ion binding locations within properly preorganized frameworks. The C4P scaffold has emerged as an effective supramolecular receptor for ion pairs and has the ability to bind the cation as well as the anion simultaneously, with higher selectivity compared to simple ion receptors.<sup>101,136–144</sup> The enhancement in the recognition function of C4P-based ion-pair receptors is by





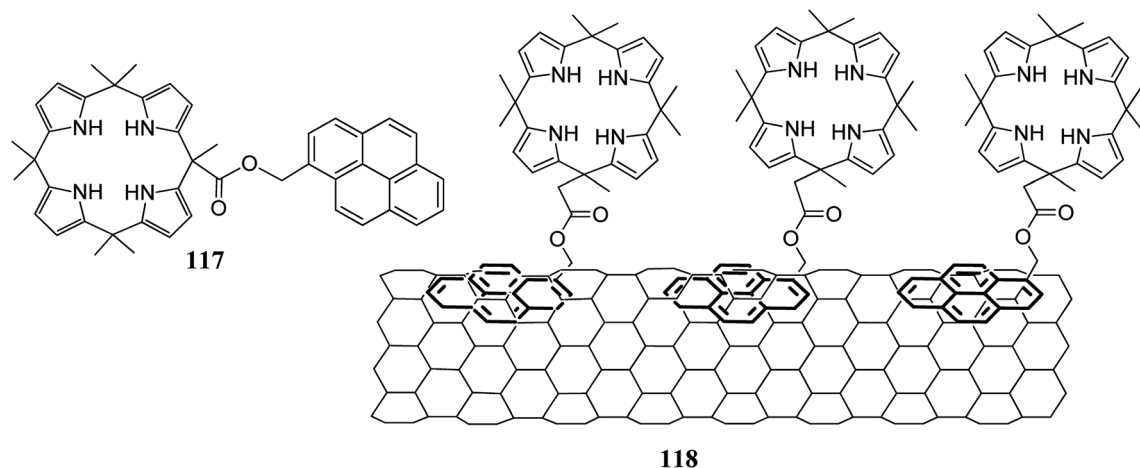


Fig. 23 Molecular structure of pyrene-functionalized C4P **117** and an illustration of C4P **117**-decorated SWCNT **118**.

virtue of both positive allosteric effects and electrostatic interactions in the ion pairs. These C4P-based ion-pair receptors are also competent to curtail the solvation effects of the counterions, which can otherwise have an undesirable effect on the interaction between the receptors and the targeted ions.<sup>140–142</sup> Here, we highlight some important C4P-based ion-pair receptors, and we will take into consideration ditopic<sup>145</sup> as well as multitopic ion-pair receptors.<sup>146–148</sup>

In order to produce advanced ion-pair receptors, many research groups have functionalized the  $\beta$ - and *meso*-carbon atoms of the C4P loop with various cation recognition sites.<sup>120</sup> Researchers have linked crown ethers of varying sizes with the *meso*-carbon atoms of the C4P skeleton, as in compounds **90** and **91**.<sup>28,96</sup> When **123** is exposed to cations such as  $\text{Li}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$  in acetonitrile, ion-pair complexation occurs. In sharp contrast to cations such as  $\text{Li}^+$  and  $\text{K}^+$  bound inside the crown

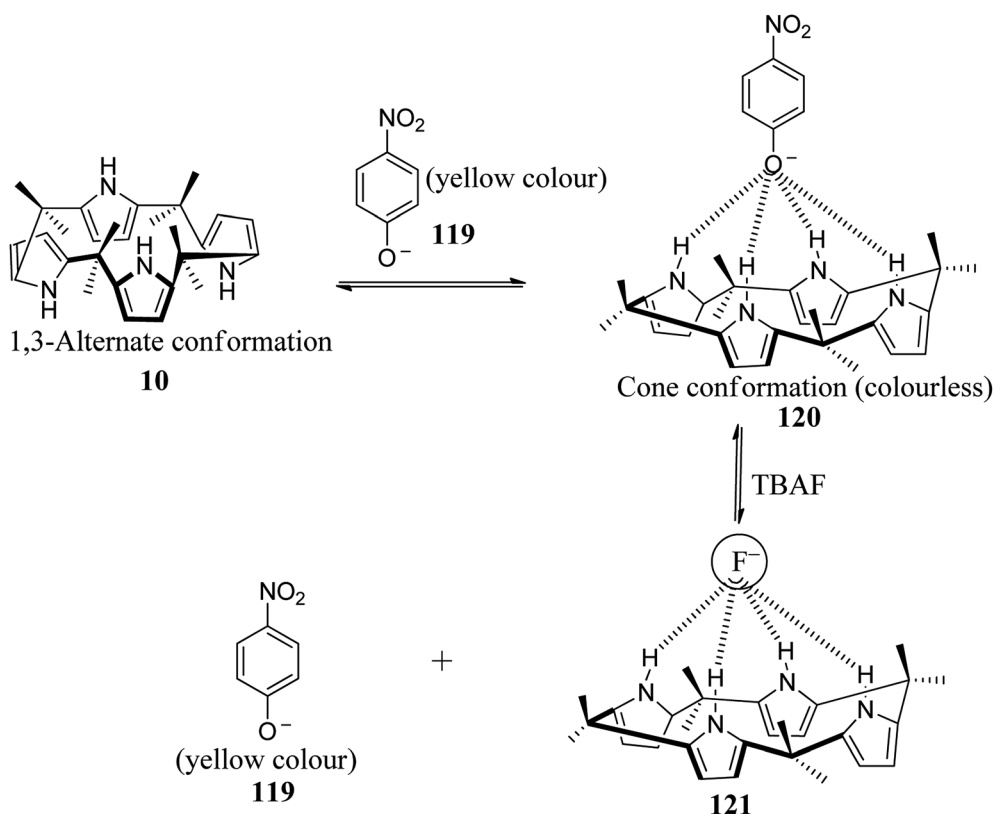


Fig. 24 C4P as an anion sensor for tetrabutylammonium-4-nitrophenolate.





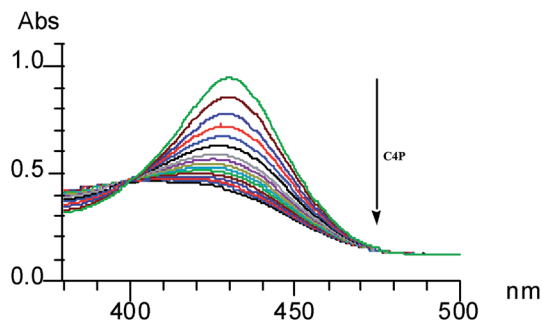


Fig. 25 Decreasing absorbance of the 4-nitrophenolate anion upon addition of C4P in  $\text{CH}_2\text{Cl}_2$  at 25 °C (reproduced with permission from ref. 135. Copyright 1999 Royal Society of Chemistry).

Table 7 Relative absorbance values of **120** with equimolar concentrations of anions

	$\text{F}^-$	$\text{Cl}^-$	$\text{H}_2\text{PO}_4^-$	$\text{Br}^-$	$\text{HSO}_4^-$
$\Delta A$	0.282	0.193	0.162	0.092	0.015
Relative absorbance	1.0	0.68	0.57	0.33	0.05

ether of **123**, the cesium cation was found to be coordinated with the cone conformation of the C4P cavity (Fig. 26). Exposure of **123** to sodium, magnesium or calcium perchlorate salts leads

to decomplexation of chloride anion, as can be inferred from Fig. 26.<sup>28</sup>

The multitopic ion-pair receptor **94** comprises one anion binding site and three cation recognition sites (Fig. 27). The 1,3-alternate conformer of **94** has an inherent partiality for  $\text{K}^+$  comparative to  $\text{Cs}^+$ . In the absence of the  $\text{K}^+$  cation, the receptor **94** likely forms the complex with  $\text{Cs}^+$  cation. Subsequently, it must be exposed to the  $\text{K}^+$  cation in order to release the  $\text{Cs}^+$  cation, as can be inferred from Fig. 27.<sup>142,146</sup>

Recently, Ballester's group reported a neutral [2]rotaxane-based C4P system **127**, which was found to be an effective heteroditopic receptor for tetraalkylammonium salts of anions ( $\text{Cl}^-$ ,  $\text{NO}_3^-$ , and  $^-\text{OCN}$ ) in chloroform solution (Fig. 28).<sup>149</sup> From  $^1\text{H-NMR}$  and ITC studies, they inferred the formation of thermodynamically as well as kinetically stable 1 : 1 ion-pair complexes for all the above mentioned anions, and they also reported selectivity for cyanate anion over chloride or nitrate ion in the case of their tetrabutylammonium (TBA) salts. In addition to this, they observed an almost three-fold increase in binding affinity in the case of the chloride ion-pair when they changed the cation from TBA to methyltriocetylammunium (MTOA). In 2012, the same group reported [2]pseudorotaxane **128**, which displays ion-pair recognition (Fig. 28).<sup>150</sup> They observed that on adding more than 1 equiv. of the TBA salt of an anion ( $\text{Cl}^-$ ,  $\text{NO}_3^-$ , and  $^-\text{OCN}$ ) to **127** and **128**, the 1 : 1 stoichiometric complexes gradually disassemble to 2 : 1 stoichiometric complexes (Fig. 29).<sup>149</sup>

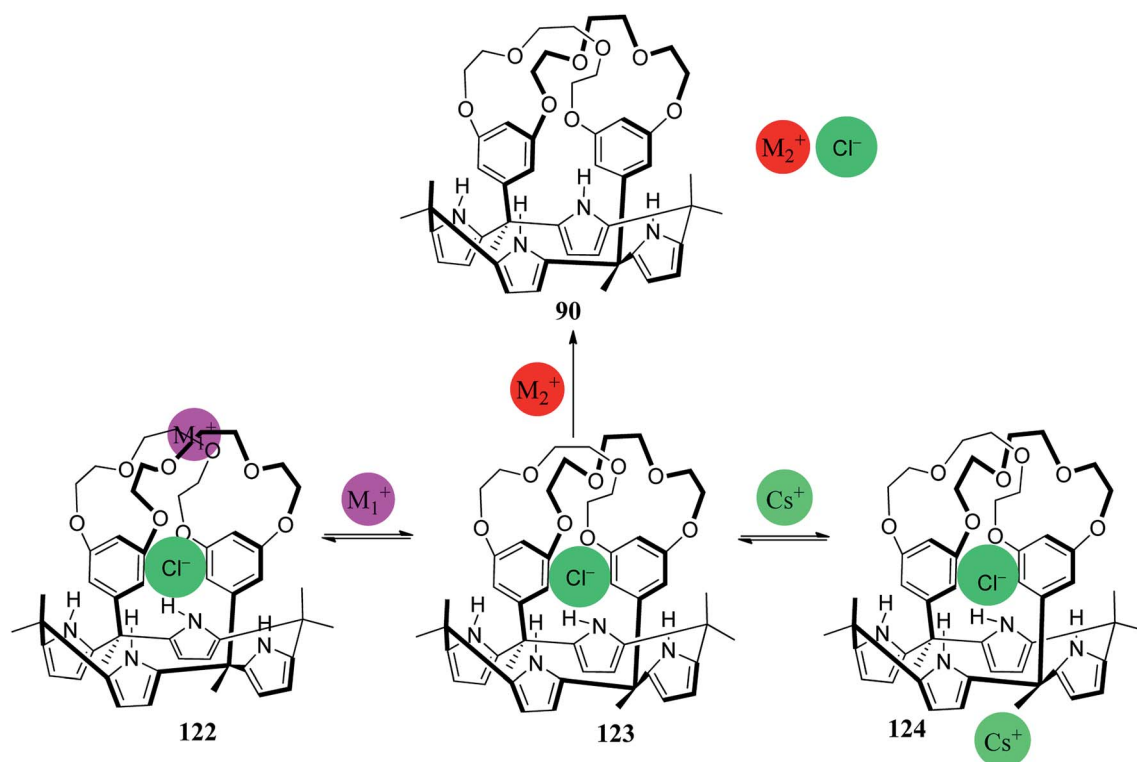


Fig. 26 Complexation behaviour observed for **123** TBA salt upon introduction to perchlorate salts of the metal cation in  $\text{CH}_3\text{CN}$  ( $\text{M}_1^+ = \text{Li}^+$  and  $\text{K}^+$ ;  $\text{M}_2^+ = \text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Na}^+$ ;  $\text{M}_2^+\text{Cl}^- = \text{CaCl}_2$ ,  $\text{MgCl}_2$ , and  $\text{NaCl}$ ).



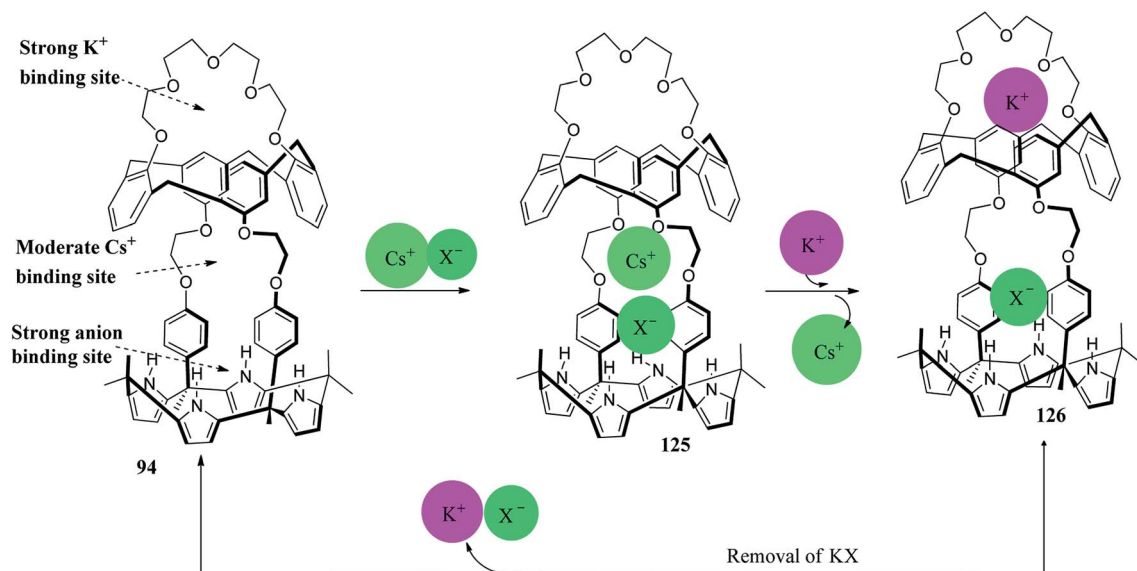


Fig. 27 Schematic view of ion-pair receptor 94.

In addition, they reported bis-C4P macrocycle **130** and its pair-wise anion binding with tetraalkylammonium salts. This pair-wise binding signifies switching between negative cooperativity and no cooperativity.<sup>151</sup> The use of TBA·Cl and TBA·OCN afforded 2 : 1 ion-pair receptor complexes. These complexes possess close-contact or cascade-like binding geometries of the incorporated ion-triplet, which does not display allosteric binding cooperativity (Fig. 30). In sharp contrast, MTOA·Cl binding displays large negative cooperativity in terms of the receptor-separated binding geometries of two bound ion-pairs (Fig. 30).<sup>151</sup>

Recently, Yeon *et al.* constructed a hybrid chromogenic calix [4]arene-calix[4]pyrrole ion-pair receptor, **131** (Fig. 31). Using

solution-phase spectroscopic analysis, it was revealed that receptor **131** is capable of binding cesium ion pairs only. It was found that this chromogenic receptor displays AND logic gate behaviour and displays a colorimetric response to cesium ion pairs under solid-liquid and liquid-liquid extraction conditions (Fig. 31).<sup>152</sup>

Lee's group also observed that the fluorescence intensity of receptor **76** was enhanced by the addition of Na<sup>+</sup> ion and decreased by the addition of Cl<sup>−</sup> ion. The sodium cations are believed to bind to the carbonyl oxygen atom of coumarin, leading to inhibition or turning off the intrinsic photoinduced electron transfer (PET) quenching process. On the other hand, anions such as Cl<sup>−</sup> are known to bind inside the C4P core and

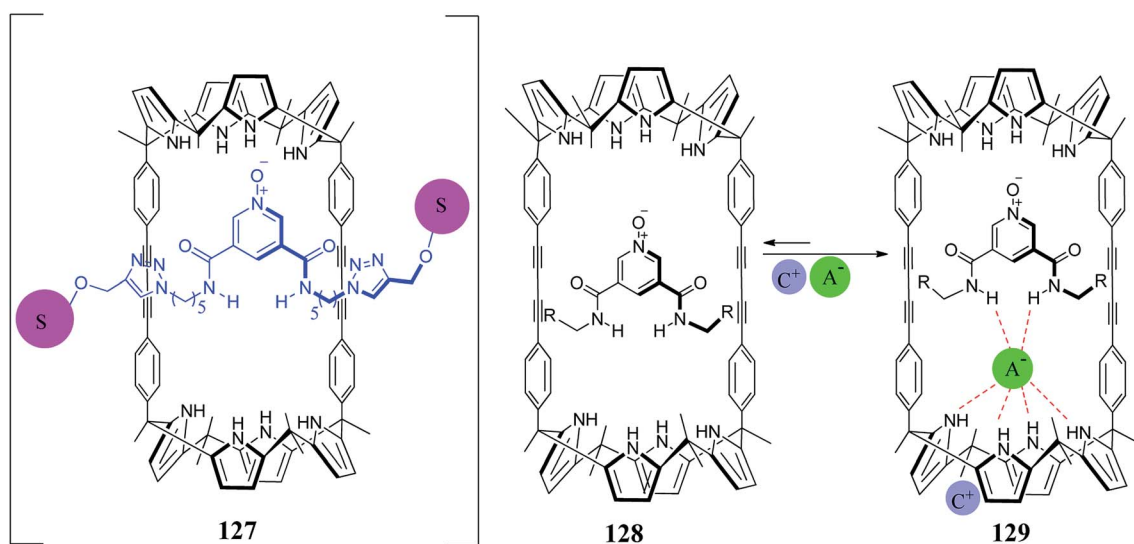


Fig. 28 Molecular structure of [2]rotaxane **127** and ion-pair recognition of [2]pseudorotaxane **128**.



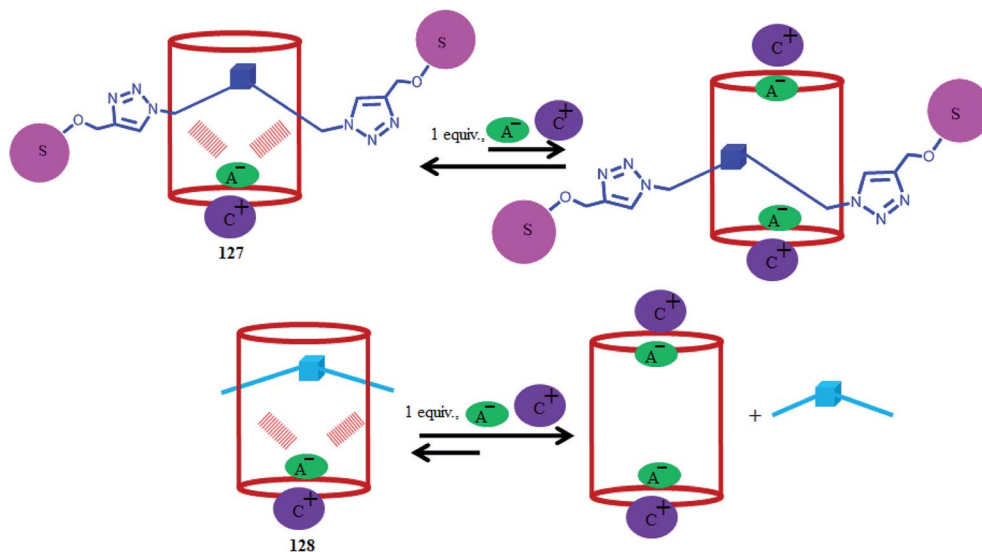


Fig. 29 Cartoon representation of the probable equilibria involved in the disassembly of 1 : 1 ion-paired complexes of [2]rotaxane **127** and [2]pseudorotaxane **128**.

help quench the fluorescence by activating a different PET mode (Fig. 32).<sup>84</sup> Thus, the receptor **76** acts as a supramolecular logic device.

#### 4.4. Calix[4]pyrroles in electron transfer processes

For many biological energy conversions, reversible electron transfer (ET) reactions are an indispensable attribute. These electron transfer reactions are operated by cofactors and ionic species; both forward and backward electron transfer are supported. In TTF-C4P, the electron-rich TTF arms are responsible

for various charge and electron transfer processes. Park *et al.* studied S-Pr-TTF-C4P **31** in concurrence with an electron-deficient bis-imidazolium quinone dication ( $\text{BIQ}^{2+}$ ) acceptor, **136**.<sup>153</sup> Electrostatic considerations support the better electron-donor nature of the anion-bound cone conformer **31**. Hence, it favours electron transfer; the “On-ET state” is achieved on binding with the electron-deficient  $\text{BIQ}^{2+}$  guest, leading to an overall 2 : 1 receptor/substrate ratio ( $[\mathbf{31}]_2 \cdot \text{BIQ}^{2+} \cdot 2\text{Cl}^-$ ), as can be observed from Fig. 33. On the other hand,  $\text{TEA}^+$  cation can also bind in the cone conformer by dislocating the  $\text{BIQ}^{2+}$  guest. Thus, it hinders the electron transfer and creates the “Off-ET

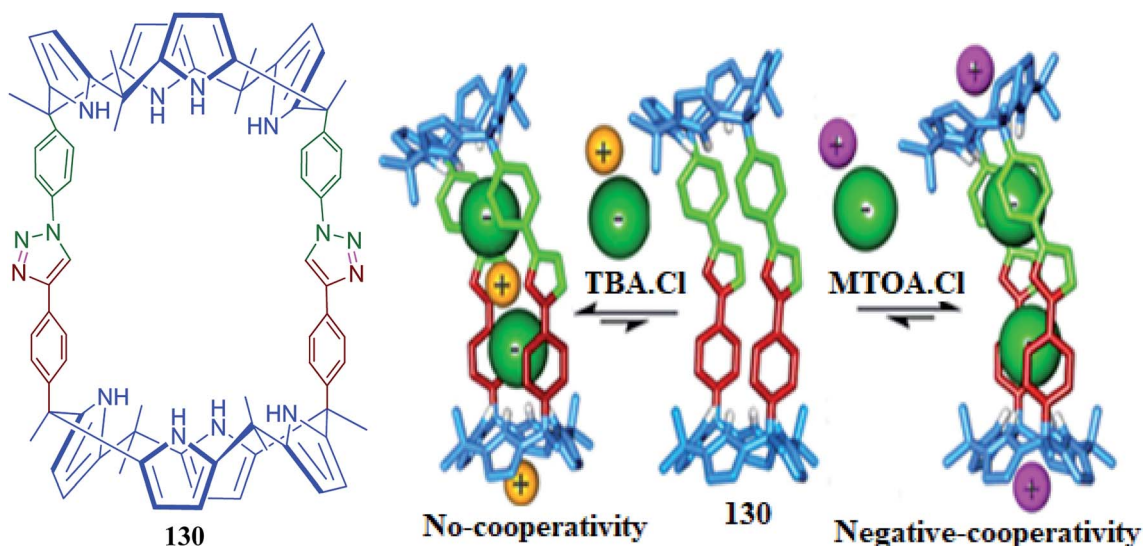


Fig. 30 Molecular structure of bis-C4P macrocycle **130** and schematic of absent and negative cooperativity after binding ion-pair dimers (reproduced with permission from ref. 151. Copyright 2018 American Chemical Society).



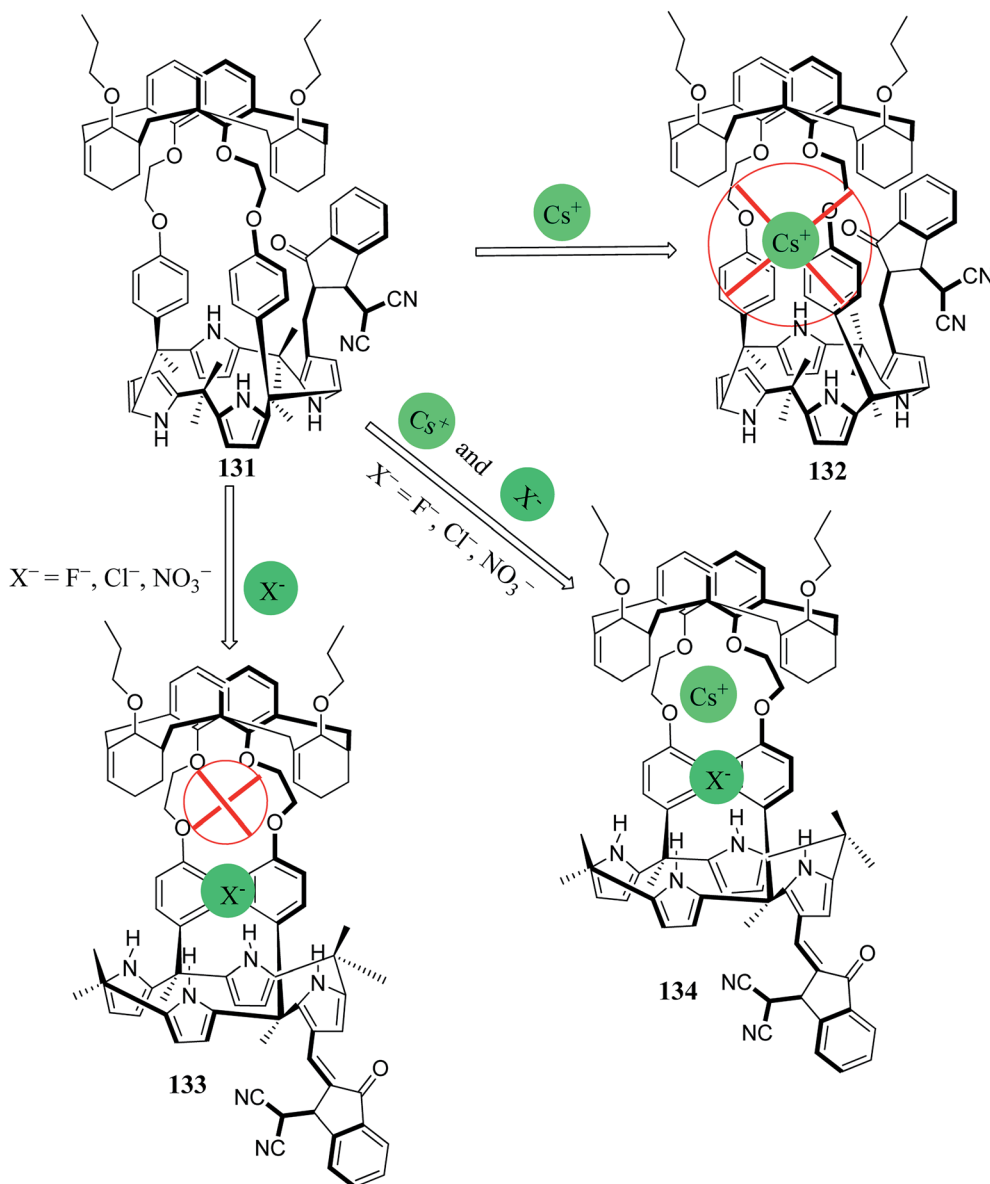


Fig. 31 AND logic gate behavior exhibited by the ion pair receptor **131** after exposure to different cesium salts in 10%  $\text{CD}_3\text{OD}-\text{CDCl}_3$ .

state,” as can be observed from inspection of Fig. 33. Thus, by employing different ionic inputs, switching between “On-ET” and “Off-ET” states could be accomplished perfectly.<sup>153</sup>

On the other hand, Sessler and his teammates described another electron transfer system involving TTF-C4Ps and the electron acceptor  $\text{Li}^+@\text{C}_{60}$ , which is significantly easier to reduce.<sup>154</sup> The presence of a suitable anion source (TBACl) leads to a ground-state electron transfer “On-ET state” of the resulting 1 : 1 receptor/substrate complex,  $[\mathbf{31}]^{\bullet+} \cdot [\text{Li}^+@\text{C}_{60}]^{\bullet-} \cdot \text{Cl}$ . On adding a small competitive cation ( $\text{TEA}^+$ ) to the ET complex, the ET process is switched off to the “Off-ET state,” as can be seen from Fig. 34.

#### 4.5. Calix[4]pyrroles as molecular nanocontainers for ion transport

In the last two decades, C4Ps have been used as molecular nanocontainers for the removal of both anions and ion-pairs. In 2008, Tong *et al.* demonstrated the transmembrane transport studies of C4P and revealed that this nanocontainer acts as a mediator for the transport of  $\text{CsCl}$  across the lipophilic membranes with greater selectivity and competence compared to other alkaline salts (Fig. 35).<sup>16,58,155</sup>

In 2011, Kim *et al.* used receptor **94** for the selective removal of  $\text{CsNO}_3$  from aqueous phase followed by complexation in the organic phase (nitrobenzene), which upon exposure to  $\text{KClO}_4$  releases  $\text{Cs}^+$  ion (Fig. 36). Finally, regeneration of receptor **94**





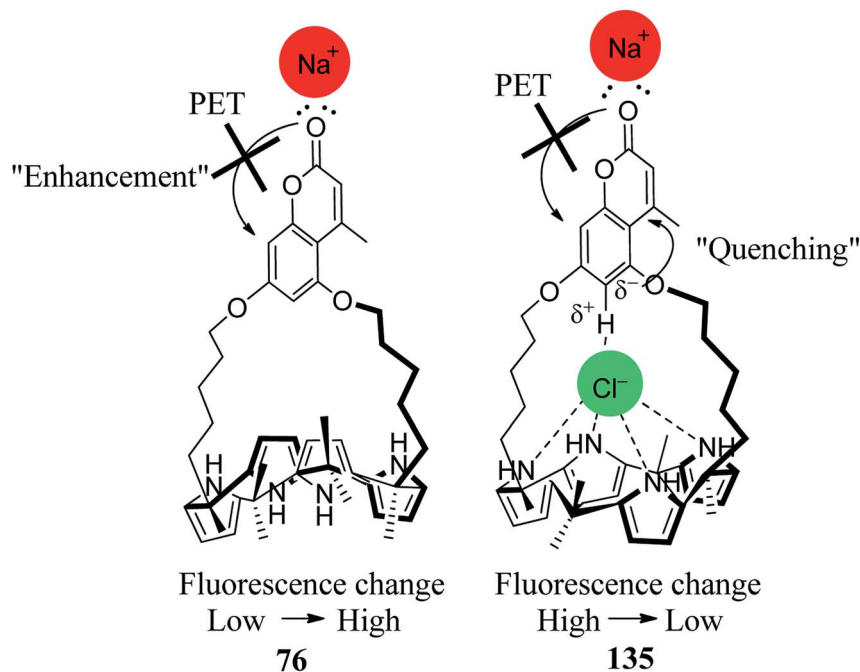


Fig. 32 Diagrammatic depiction of the anticipated interactions between 76 with sodium cation and a chloride anion.

occurs in the organic phase after the nitrobenzene layer comprising the potassium complex comes in contact with  $\text{H}_2\text{O}$  and  $\text{CHCl}_3$  (Fig. 36).<sup>142</sup> These two-phase extraction studies, therefore, highlight the importance of strapped C4Ps.<sup>146</sup>

Fluoride is a stabilizer in water and oral hygiene products;<sup>156</sup> it can be harmful to health at high levels and can lead to fluorosis, which affects both teeth and bones.<sup>157</sup> Fluoride complexation in water has become a taxing problem due to its small size, hard and basic nature and higher hydration energy. Deprotonation of anion receptors by fluoride in organic

environments<sup>158–162</sup> is also a challenging process for fluoride complexation. Thus, there is a need to develop novel fluoride receptors which can overcome the abovementioned challenges. To this end, in 2016, Gale and his teammates reported the electrogenic mechanism of selective fluoride anion transport across lipid bilayers by virtue of strapped C4P 99, as can be observed from Fig. 37.<sup>163</sup> Because anion transporters such as strapped C4P 99 can bind and assist the flip-flop of fatty acids across lipid bilayer membranes,<sup>164</sup> the interaction of 99 has

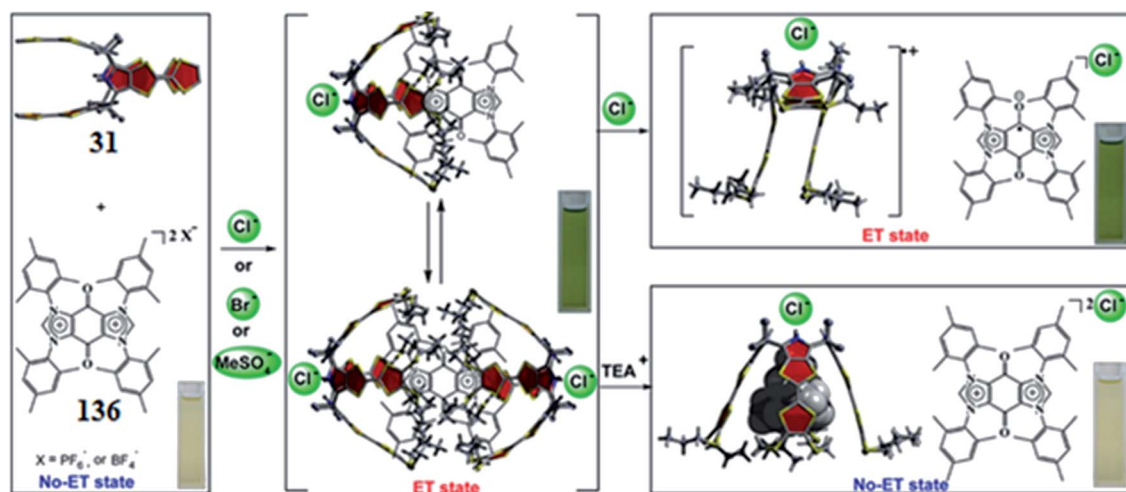


Fig. 33 Ion-intervened electron-transfer event between TTF-C4P 31 and BIQ<sup>2+</sup> acceptor 136 (reproduced and adapted with permission from ref. 153. Copyright 2010 Science).



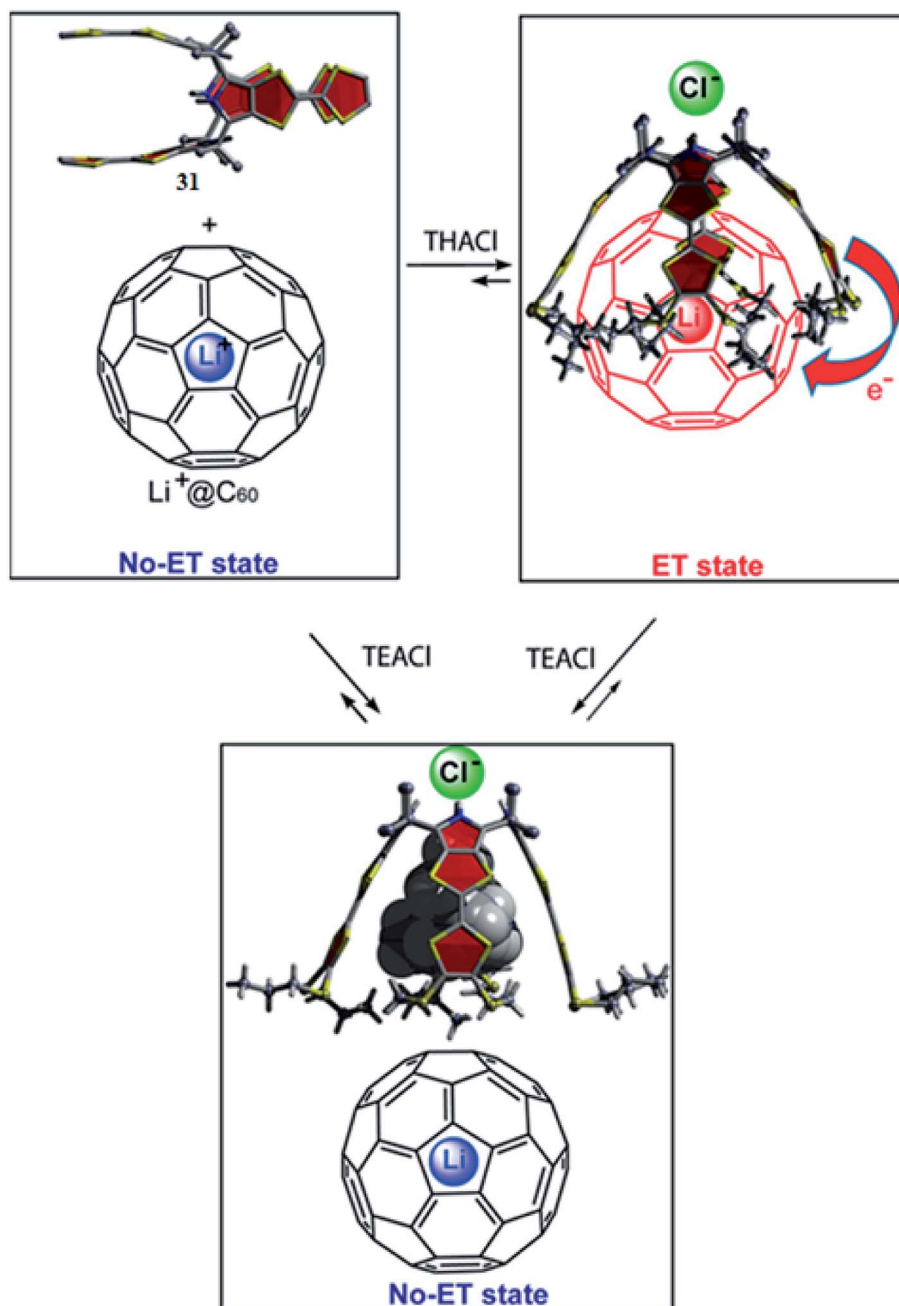


Fig. 34 Ion-intervened electron-transfer route relating TTF-C4P **31** and  $\text{Li}^+@C_{60}$  (reproduced with permission from ref. 56. Copyright 2018 American Chemical Society).

been studied with  $\text{CH}_3\text{COO}^-$  in solution and fatty acids in lipid bilayer membranes.<sup>165</sup>

#### 4.6. Calix[4]pyrroles as drug delivery and anticancer agents

Toxic side effects of drugs pose a serious threat to human life. Therefore, in order to safely achieve the desired therapeutic effect of a pharmaceutical agent (drug) in a particular body tissue without causing many side effects, it is necessary to develop approaches and create systems which enable pharmaceutical agents to reach the target site in the body and

display a desired therapeutic effect only at that target site. These systems are known as drug delivery systems. In fact, recent efforts in the domain of drug delivery are focusing on the development of targeted drug delivery, in which the drug becomes active only in the target area of the body. Based on the accomplishments of supramolecular chemistry, various novel drug-delivery approaches have also come into existence in recent years.<sup>166–169</sup> C4Ps, by virtue of their anion binding ability along with their ion-pair and neutral molecule receptor





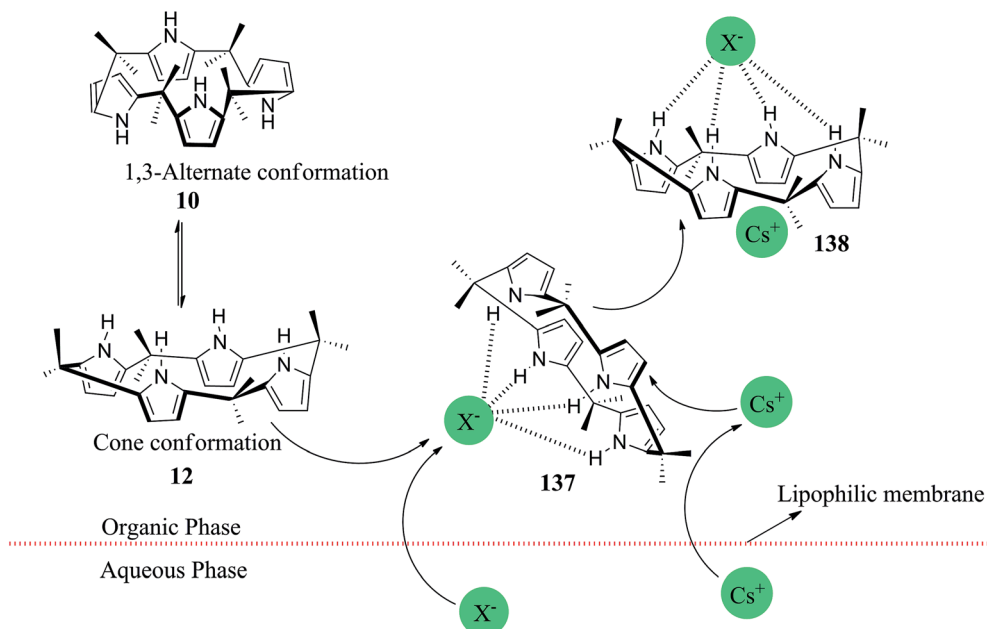


Fig. 35 Schematic illustration showing cesium halide salt extraction across a lipophilic membrane.

nature, have gained significant attention in the domain of drug delivery. Although C4Ps are not toxic themselves, the conjugates they form with various pharmaceutical agents display cytotoxicity to cell lines. Thus, these have been fruitfully used in the delivery of active pharmaceutical agents; for example, Cafeo *et al.* reported in 2013 that a C4P-*trans*-platinum(II) conjugate (*trans*-Pt **40**) could be used as a prodrug, thereby highlighting the role of C4Ps in drug delivery.<sup>58</sup> They used adenosine monophosphate (AMP) as a typical compound to assess the potential of the targeted delivery of metal to deoxyribose nucleic acid (DNA) nucleobases, as can be observed in Fig. 38. *In vitro* studies of *trans*-Pt **40** on diverse cancer cell lines signify cytotoxic activity that is categorically obtained from the co-occurrence of both the *trans*-Pt(II) portion and the C4P unit. It exhibits good antiproliferative activity compared to *trans*-[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>], in which Pt(II) is not bound to the C4P core.<sup>58</sup>

Lappano *et al.* reported that C4P (**1**) acts as a G-protein coupled estrogen receptor **1** (GPER1) antagonist in both breast tumour cells and cancer-associated fibroblasts (CAFs) obtained from breast cancer patients. C4P (**1**) exhibits inhibitory action on GPER-activated signals. Upon exposure to estrogen, it becomes highly selective for GPER without interfering with estrogen receptor-dependent responses.<sup>170–174</sup>

Sessler's group also reported that two pyridine diamide-strapped C4Ps, **142** and **143**, can induce apoptosis through facilitation of chloride anion transport into cells (Fig. 39).<sup>175</sup> Quite recently, Park *et al.* reported that the ion transporter octafluorocalix[4]pyrrole **16** (Fig. 4) also induces apoptosis by

increasing the sodium and chloride concentrations of cells.<sup>176</sup> In addition to inducing apoptosis, it has also been observed that ion transporter octafluorocalix[4]pyrrole **16** inhibits autophagy. This suppression of autophagy is due to its ability to interrupt lysosome function. Pyridine diamide-strapped C4P **143** has been observed to display enhanced cell death without interfering with autophagy.<sup>176</sup>

On the other hand, Geretto *et al.* recently reported a novel *meso*-(*p*-acetamidophenyl)-C4P, **144** (Fig. 39), which acts as a potential anticancer agent and forms genotoxic adducts with DNA.<sup>177</sup> Pharmacokinetic studies revealed that **144** is a potential drug that has the ability to cross the blood-brain-barrier and simultaneously kill both primary and metastatic brain cancer cells.

#### 4.7. Calix[4]pyrroles as catalysts

Scientists have developed novel artificial catalysts which are of considerable physical and biological importance. These catalysts mimic the action of enzymes, which are natural catalysts. bis-C4P capsule **46** (Scheme 8) acts as an artificial catalyst (mimics the action of an enzyme) and constrains two oxo-anions in close proximity, thereby acting as a structural model for understanding natural oxo-anion recognition processes.<sup>178,179</sup> In 2007, García *et al.* studied the effects of C4P on the catalytic activity of cuprous chloride (CuCl) in the aziridination of chloramine-T with styrene; they finally concluded that C4P acts as a promoter for this reaction (Scheme 14).<sup>180</sup> This finding provides a new approach to reaction enhancement, particularly when the anion receptor-like C4P activates an



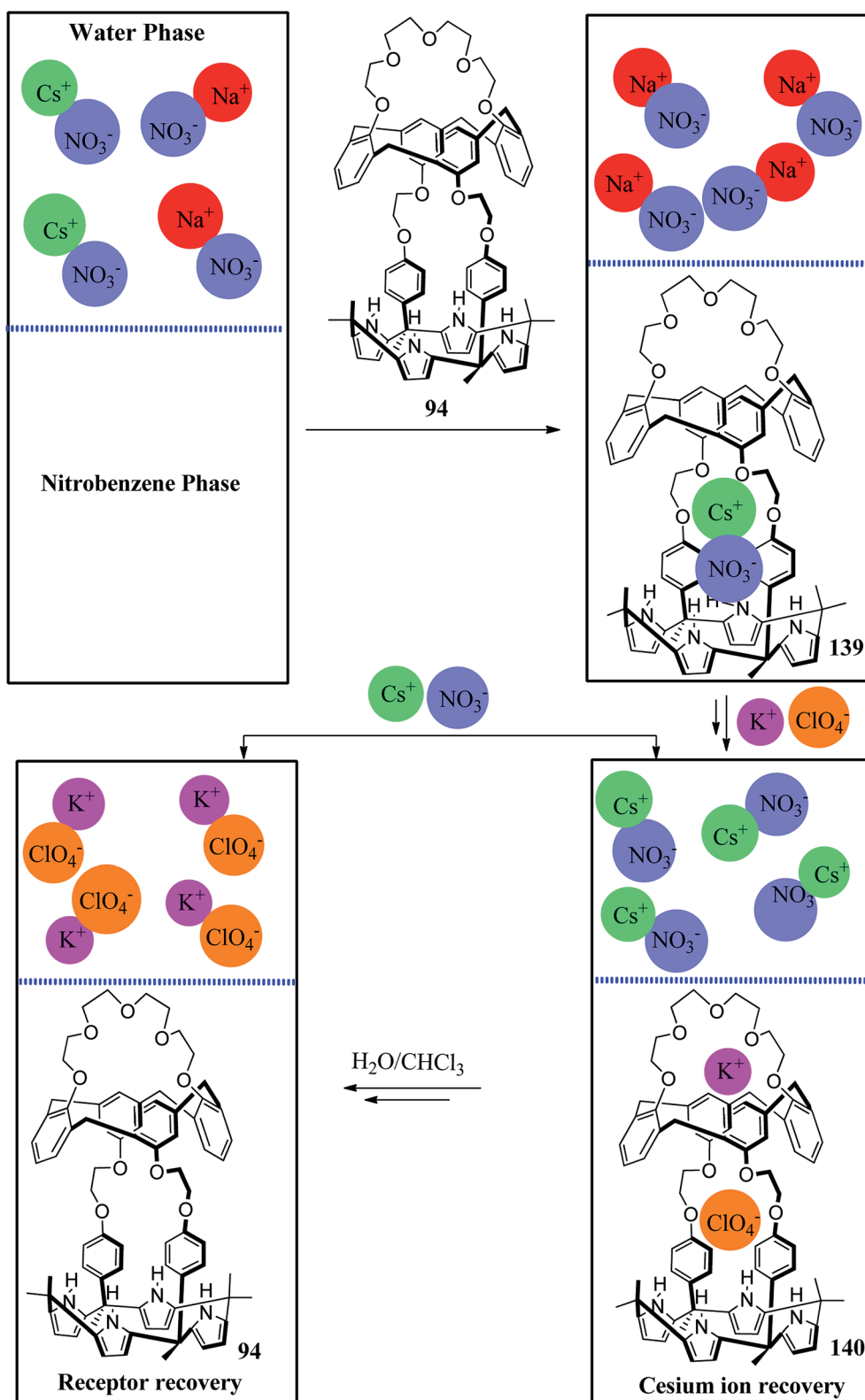


Fig. 36 Diagrammatic depiction of a two-phase  $\text{CsNO}_3$  removal and recovery process using ion-pair receptor **94**.



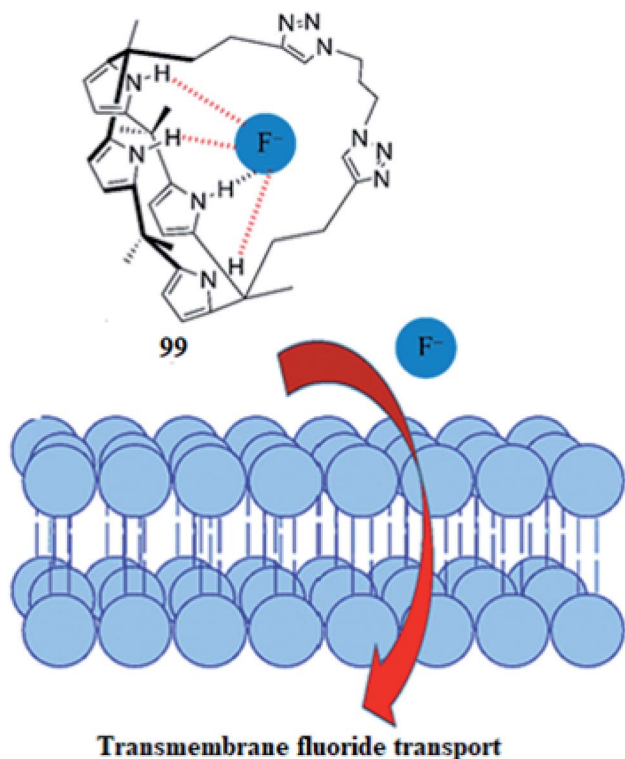


Fig. 37 Fluoride transport across biomembranes by virtue of strapped C4P 99.

incipient anion cleavage event. It was found that the presence of C4P has no effect when CuI is employed as a catalyst, showing the selectivity of CuCl towards the C4P. The yield was even lower in the case of the CuCl<sub>2</sub>-catalyzed reaction, displaying the

selective nature of the reaction. In fact, the enhancement effect provided by C4P was found to be independent of the presence of trace quantities of water.<sup>181</sup> Thus, the proper and judicious selection of reaction chemistry along with anion receptors such as C4P is likely to open a new door for synthetic organic chemistry.

Chemical transformations of CO<sub>2</sub> into beneficial compounds has received much attention because CO<sub>2</sub> is considered to be a vital raw material in organic synthesis.<sup>182,183</sup> Recently, Maeda and teammates reported that C4P 1 in association with tetrabutylammonium iodide (TBAI) catalyzes the transformation of epoxides and CO<sub>2</sub> into cyclic carbonates (Scheme 15).<sup>184</sup> Thus, C4P 1 acts as a robust and dynamic macrocyclic organocatalyst. It has been observed from DFT studies that C4P 1 organocatalyst stabilizes anionic species produced during catalysis only in the 1,3-alternate conformation. The key transition state of epoxide ring-opening involves activation of the epoxide by means of the pyrrolic NH of C4P 1 and tetrabutylammonium (TBA) cation-assisted hydrogen bonding. On the opposite side of C4P 1, another NH group directs I<sup>−</sup> anion. Being placed away from the TBA cation, the I<sup>−</sup> anion attacks the epoxide from the backside.<sup>184</sup>

On the other hand, in the same year, Sakthivel and coworkers reported the synthesis of rhodium calix[4]pyrrole 152 (Rh-C4P 152) and its catalytic applications in nitrobenzene reduction (Scheme 16).<sup>185</sup> They grafted Rh-C4P 152 on the surface of a diamino-functionalized SBA-15 molecular sieve material, which eventually showed the complete reduction of nitrobenzene to aniline as a final product. It was observed that the catalytic activity of macromolecule Rh-C4P 152 was enhanced considerably and also remained intact even after numerous catalytic runs.<sup>185</sup>

#### 4.8. Use of calix[4]pyrroles in the advancement of polymer chemistry

C4Ps by means of anion complexation have been employed to increase the ionic conductivity of solid polymer electrolytes such as C4P/LiCl/PVC (PVC = polyvinyl chloride) with great ionic mobility. Anion complexations were found between anions and C4Ps dissolved in PVC. The resulting systems have found versatile applications.<sup>186</sup> Jain *et al.* developed two novel azo-C4P amberlite XAD-2 polymeric chelating resins that were found to be important in the preconcentration and sequential removal of Zn(II), Cu(II) and Cd(II) in natural waters.<sup>187</sup> Other C4P-based novel chelating resins, used for the preferential removal of fluoride anions over other halides, were synthesized by Trochimczuk and teammates.<sup>188,189</sup> On the other hand, Trochimczuk and teammates also synthesized Langmuir-type isotherms for hybrid calixpyrroles, which were used as sorbents for noble cations such as Ag(I), Pt(IV), Pd(II), and Au(III).<sup>189,190</sup> On another occasion, Aydogan *et al.* produced copolymers containing

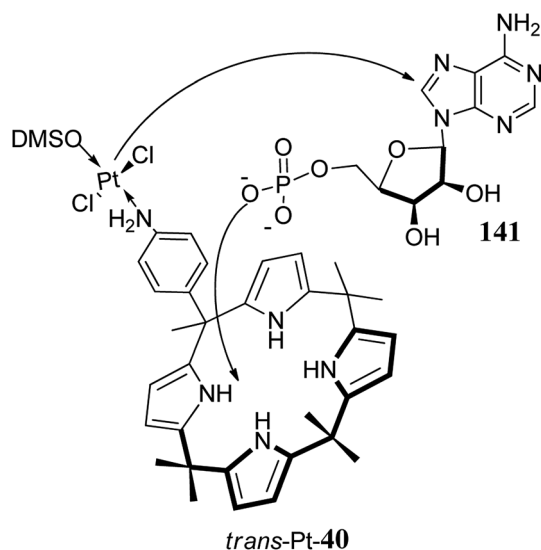


Fig. 38 Depiction of transfer of Pt metal from the C4P-trans-platinum(II) conjugate to DNA via phosphate anion-binding.



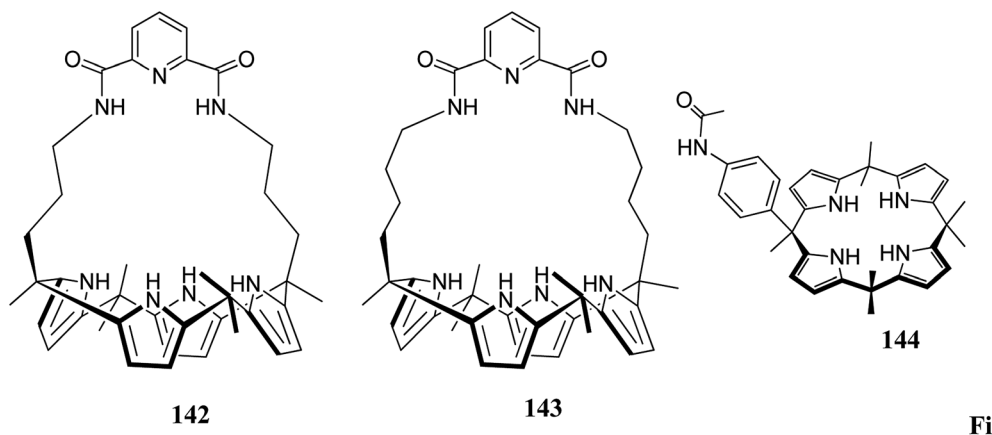
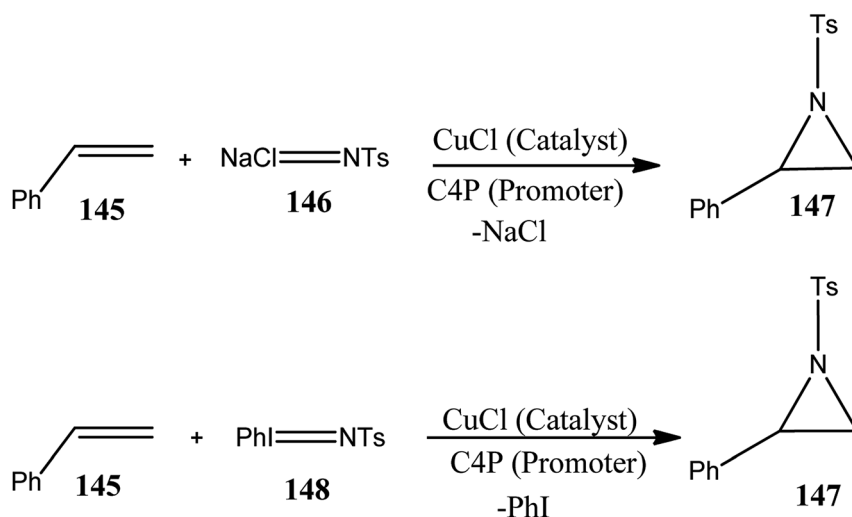
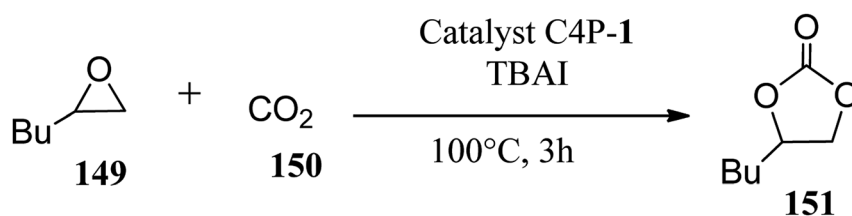


Fig. 39 Molecular structures of pyridine diamide-strapped C4Ps that induce apoptosis and *meso*-(*p*-acetamidophenyl)-C4P, which acts as a potential anticancer agent.



Scheme 14 Synthesis of aziridine products.



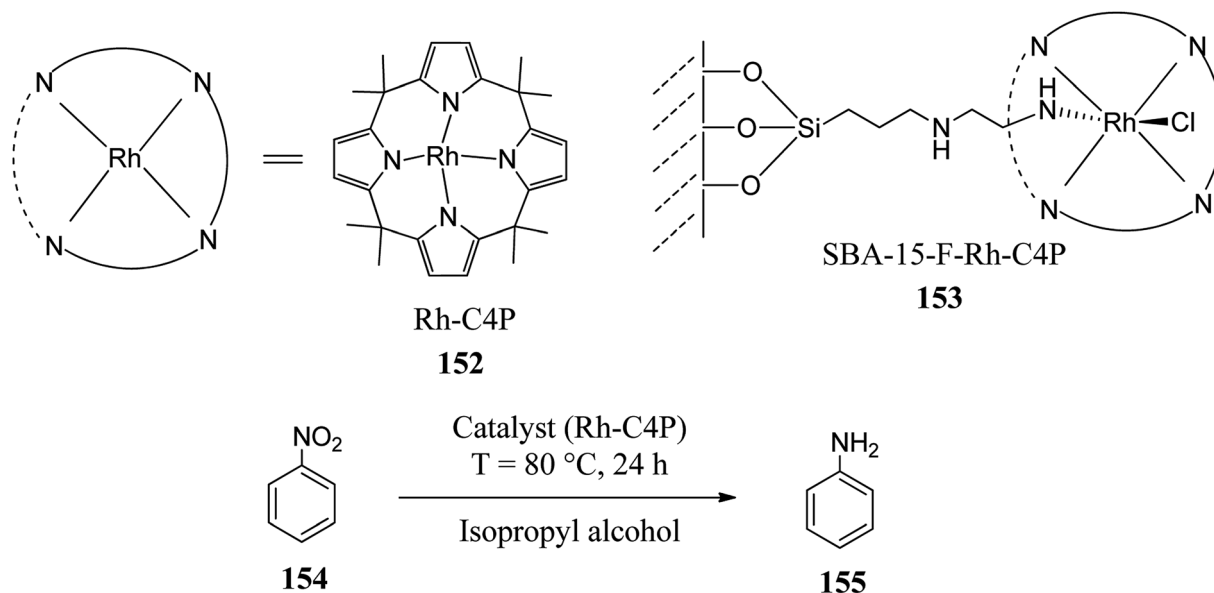
Scheme 15 Preparation of cyclic carbonates using macrocyclic C4P (1) as an organocatalyst.

C4Ps and showed that they can extract certain halide anion salts.<sup>191,192</sup>

The 1,3-alternate conformers of TTF-C4Ps 29, 31, and 33 can bind two nitroaromatics; this has led to the discovery of

stabilizing chemoresponsive supramolecular polymeric materials by means of heterocomplementary donor–acceptor interactions. For this purpose, Sessler's group chose bis(di-nitrophenyl) *meso*-substituted C4Ps which are electron-





Scheme 16 Reduction of nitrobenzene to aniline using a diamino-functionalized SBA-15 surface-grafted Rh-C4P catalyst (153).

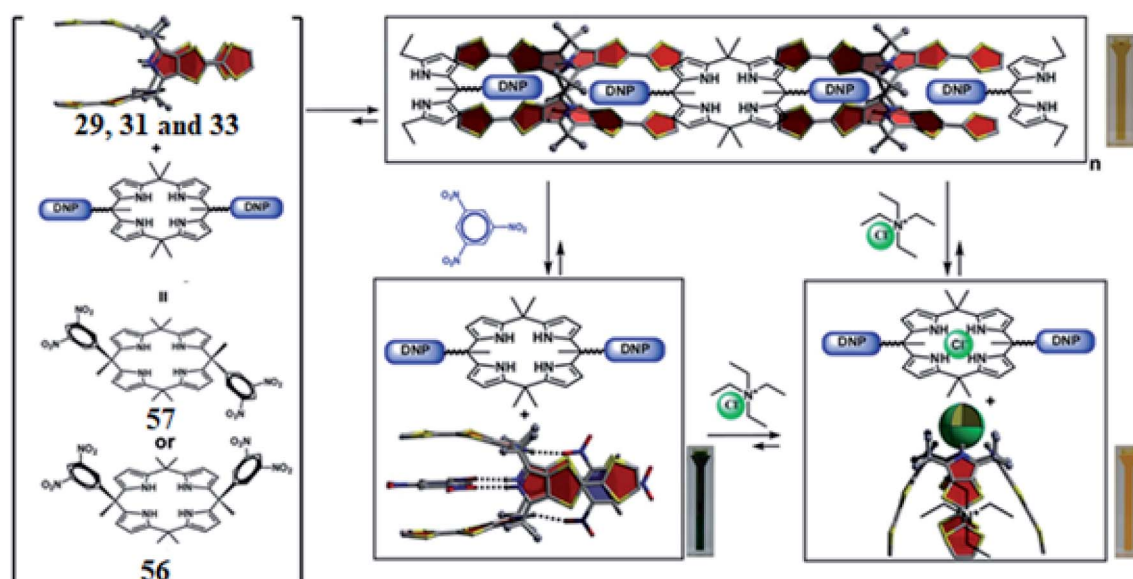


Fig. 40 Diagrammatic depiction of heterocomplementary self-association of TTF-C4Ps 29, 31, and 33 with 56 and 57 (reproduced with permission from ref. 56. Copyright 2018 American Chemical Society).

deficient in nature (Fig. 40).<sup>193</sup> When these guests were combined with TTF-C4Ps (29, 31, and 33) in halogenated solvents, oligomeric materials were generated. The observed self-assembly reflects a stabilizing grouping of  $\pi$ - $\pi$  donor-acceptor interactions and hydrogen bonding. Upon the addition of Cl<sup>-</sup> or trinitrobenzene (TNB), the self-assembled assemblies experience disaggregation to generate distinct host-guest supramolecular ensembles, as can be inferred from Fig. 40. Therefore, two different stimuli, such as Cl<sup>-</sup> and

TNB, can be employed to disrupt the supramolecular oligomers.<sup>56</sup>

In another experiment, Aydogan and coworkers synthesized a triazole-bridged bis-C4P 157 for the construction of thermoresponsive AAB-type linear supramolecular polymers (Fig. 41). This became possible in terms of the utilization of hydrogen bonding interactions among the NHs of C4P and the carboxylate components of tetrabutylammonium suberate 156.<sup>194</sup>





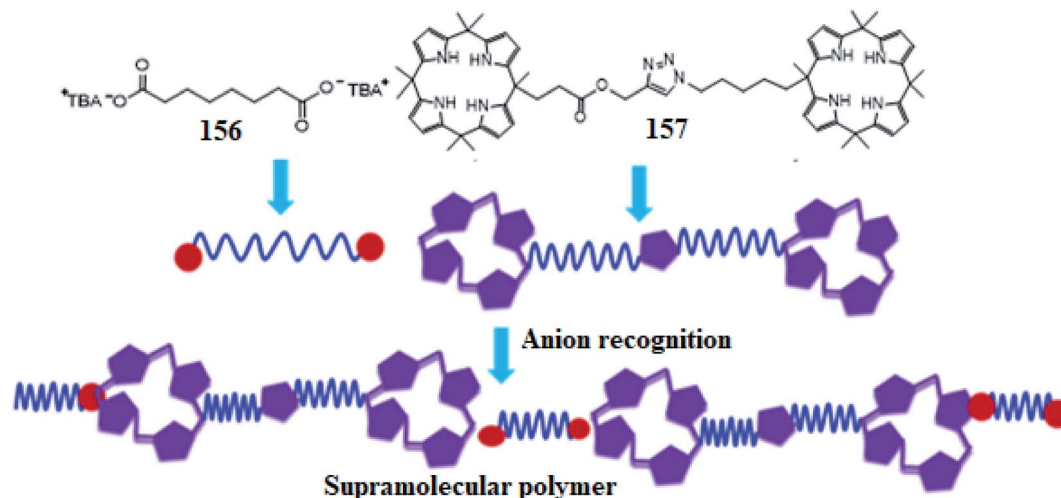


Fig. 41 Molecular structures and pictorial depictions of **156** and **157**, and an illustration of AABB-type linear supramolecular polymers.

## 5. Conclusions and outlook

In summary, C4P is a versatile and striking receptor system for many anions and ion pairs. In order to amend the intrinsic selectivity and acquire enhanced anion binding affinity of C4Ps, an array of novel and tailored calixpyrroles and their derivatives have been synthesized from simple and commercially available starting materials using simpler synthetic procedures. By means of its structural diversity, inimitable conformations, and useful molecular recognition properties, calixpyrrole is evolving as a new generation macrocyclic host molecule at the heart of supramolecular chemistry. Although several reviews of C4Ps have been reported in the literature, numerous important applications of C4Ps are missing in existing accounts. We believe that the current report definitely represents a new episode in the chemistry of C4Ps. As far as future perspectives regarding the applications of C4P derivatives are concerned, we believe that this member of the supramolecular chemistry family will be further explored in the areas of drug delivery, catalysis, molecular machines and solubility in aqueous medium.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgements

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