# Recent developments in pillar[5]arene chemistry

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**Abstract**

The class of pillar[n]arene macrocycles has existed since 2008 when the synthesis and structure of the cyclopentamer, 1,4-dimethoxypillar[5]arene, was first reported. In subsequent years, members of the pillar[n]arene family have shown great potential in fields as diverse as polymer science, sensor technology and medical diagnostics. Over 350 papers have now been published on the pillar[n]arenes; this review focuses on advances made in the synthesis and applications of the pillar[5]arenes.

Keywords: pillar[5]arene; macrocycle; supramolecular; host-guest

## 1 Introduction

In the four years since the first reviews on pillar[5]arenes appeared [1-6] many advances have been made in the field, notably in the synthesis of novel derivatives, and there has been a significant expansion of their applications. A number of other reviews have been published focused on specific aspects of pillar[n]arene chemistry such as synthesis [7], post-synthesis functionalization [8], host-guest chemistry [9-13], supramolecular assembly formation [14-16], nanoparticle functionalization [17], channel formation [18] and sensor applications [19]. Tomoki Ogoshi, whose group first reported the synthesis and crystal structure of 1,4-dimethoxypillar[5]arene (**1a**) as well as initial binding data, has recently written a monograph devoted to the pillar[n]arenes [20] and an extensive review [21]. The scope here will be limited to the pillar[5]arenes which still represent the largest subclass of pillar[n]arenes in the literature.

## 2 Synthesis

The early literature on pillar[n]arenes largely revolved around routes to successful cyclization of 1,4-disubstituted hydroquinones and the inclusion behavior of those macrocycles. Initially the poor solubility of **1a** restricted interest from researchers in macrocyclic and supramolecular chemistry but improved synthetic routes led to easier product isolation. The discovery that *O*-alkylation of pillar[5]arene (**2**) yielded only *pR* or *pS* symmetric products and not a large number of stereoisomers meant that derivatization became a valuable route to introduce functionality into the pillar[5]arenes. The Ogoshi group demonstrated an affinity between **1a** and di(methyl)viologen (the herbicide, paraquat) which was soon followed by the observation that linear alkyl amines and diamines could also thread through the macrocycle. This led to a large number of papers on pillar[5]arene-based rotaxanes. The final area of interest was in the preparation of asymmetric pillar[5]arenes, where each aromatic ring had two different *O*-substituents, and co-pillar[5]arenes, where the substituents on one or more of the rings were different to the others.

### 2.1 Symmetric pillar[5]arenes

Macrocycle **1a** was originally prepared by Ogoshi's group which reported the synthesis and X-ray crystal structure in 2008 (Figure 1) [22]. The same group reported an improved yield in 2010 but still relied on the use of dry 1,2-dichloroethane (DCE) as the solvent for the reaction [23]. The main drawbacks to the synthesis were the small scale of the reaction and the poor solubility profile of the

product. Alternative syntheses by the groups of Huang [24], Cao and Meier [25] and Zhang and Yang [26] provided routes to the more soluble di(alkoxy) analogues **1b**-**1l** while Boinski and Szumna developed a method to prepare **1a** which dispensed with dry solvents [27]. The latter method has been shown by the Cragg group to be scalable so that analytically pure **1a** can now be produced on a 10 g scale from inexpensive starting materials in two days [28]. The Ogoshi group showed that its synthetic route could also be used for pillar[5]arenes with bulky linear substituents by cyclizing 1,4-bis(ethoxy)-, 1,4-bis(propoxy)-, 1,4-bis(butoxy)-, 1,4-bis(pentyloxy)-, 1,4-bis(hexyloxy)- and 1,4-bis(dodecanoxy)benzene to form their corresponding pillar[5]arene analogs **1b**-**1g** [29]. The extended pillar[5]arene, 1,4-bis(bromoethoxy)pillar[5]arene (**1k**), was synthesized by Huang's group under Ogoshi's conditions and has since become a valuable precursor to a number of functionalized pillar[5]arenes [30]. The Nierengarten group investigated the Friedel-Crafts reaction of equimolar 2,5-bis(bromomethyl)-1,4-di(ethoxy)benzene with 1,4-di(ethoxy)benzene in the presence of Lewis acids ($AlCl_3$, $FeCl_3$ or $ZnCl_2$) and found **1b** as the sole product [31]. The same result occurred for the cyclization of 2,5-diethoxybenzyl bromide under the same conditions. With the success of $FeCl_3$-catalyzed methods, the Zhang group attempted the cyclization of 1,4-di(ethoxy)benzene and paraformaldehyde in $CH_2Cl_2$ with catalytic amounts of the deep eutectic solvent formed from $FeCl_3$ and choline chloride [32]. The method was successful although it resulted in roughly equal quantities of pillar[5]-and [6]arenes.

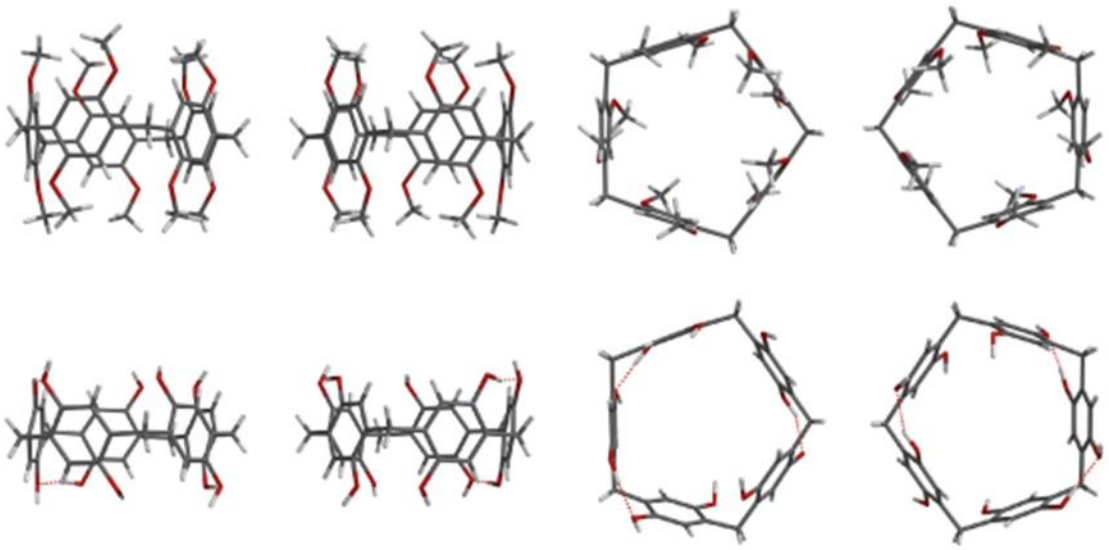
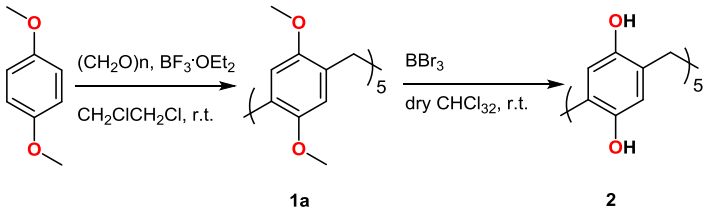
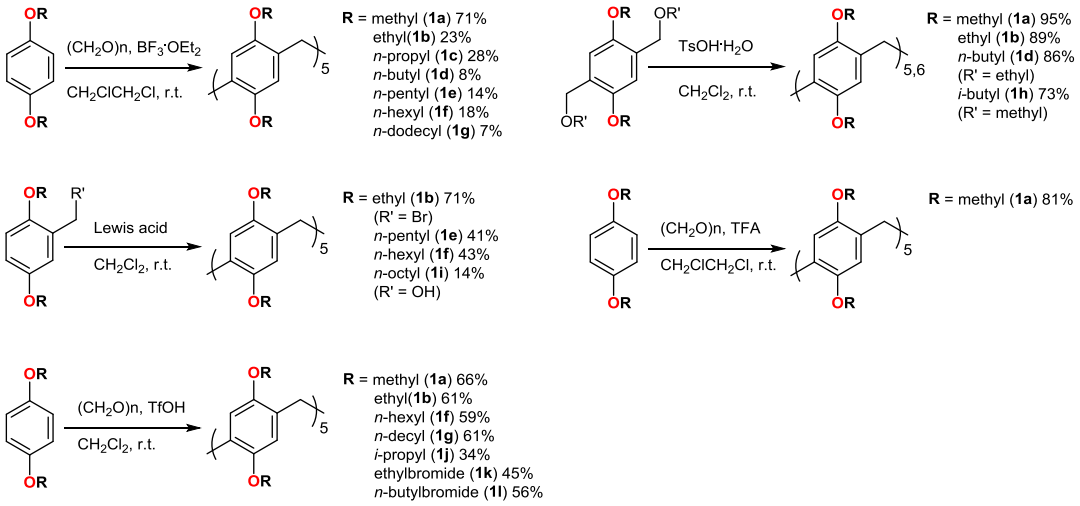


**Figure 1.** X-Ray structures of pillar[5]arenes: (top) **1a** showing *pS* and *pR* forms and (bottom) **2** showing hydrogen bonding (in red). Solvent molecules removed for clarity.




**Scheme 1.** Synthesis of 1,4-dimethoxypillar[5]arene (**1a**) and pillar[5]arene (**2**).

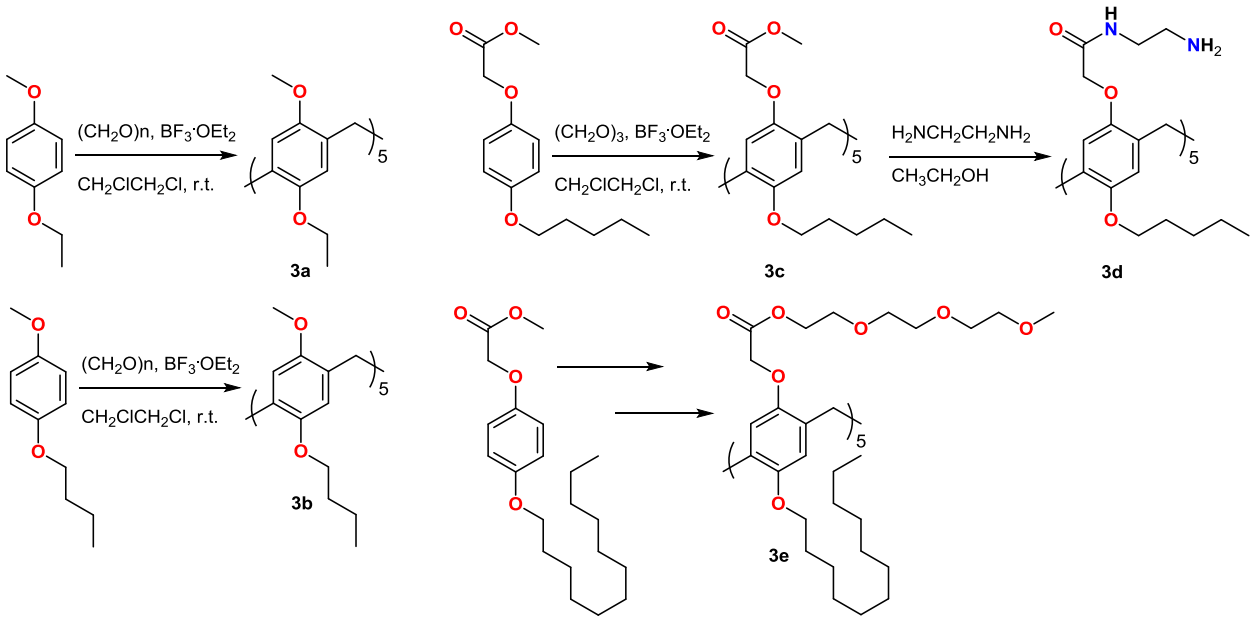



**Scheme 2.** Routes to symmetric pillar[5]arenes **1a** to **1l**.

### 2.2 Asymmetric pillar[5]arenes

Initial work on pillar[5]arenes was confined to symmetric macrocycles prepared from commercially available 1,4-dimethoxybenzene or monomeric 1,4-dialkoxybenzene precursors easily synthesized from hydroquinone. These pillar[5]arenes all have the same *pR* or *pS* $D_{5h}$ symmetry but the use of asymmetric dialkoxybenzene monomers introduced the possibility of isomers which could not be interconverted through rotation. In 2010 the groups of Ogoshi and Nakamoto reported the first asymmetric pillar[5]arene prepared from 1-ethoxy-4-methoxybenzene and, based on 2D ROESY spectra, found that each rim was decorated with either ethoxy or methoxy groups (**3a**) [33]. In the same year the Cao group prepared asymmetric pillar[5]arenes from 1-butoxy-4-methoxy-2,5-bis(methoxymethyl)benzene and obtained crystal structures of all four regioisomers of **3b** which had been separated by column chromatography [34]. While their manuscript was under review, Huang also reported the synthesis and crystal structures of **3b** [35]. In the latter case the macrocycle was prepared from 1-butoxy-4-methoxybenzene and the binding affinities for *n*-octyltrimethyl ammonium hexafluorophosphate determined. The $K_a$ values in $CDCl_3$ were 3.6 x $10^3$ $M^{-1}$ for the *cone*,

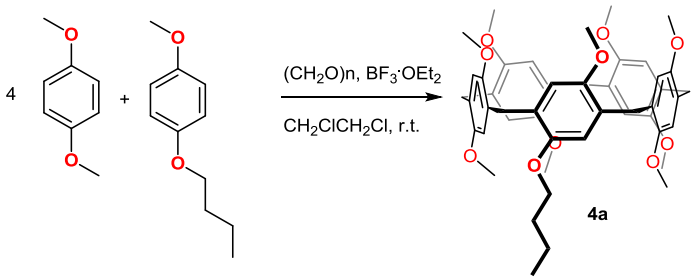
4.2 x $10^3$ $M^{-1}$ for the *partial cone*, 5.2 x $10^3$ $M^{-1}$ for the *1,2-alternate*, and 6.3 x $10^3$ $M^{-1}$ for the *1,3-alternate* isomer indicating that the more symmetric the pillar[5]arene, the higher the association constant.




**Scheme 3.** Routes to asymmetric pillar[5]arenes **3a** to **3e**.

### 2.3 Co-pillar[5]arenes

The term co-pillar[5]arene refers to those derivatives incorporating two or more different subunits. In practice a majority employ two 1,4-di(alkoxy)benzene subunits in a 4:1 ratio to give co-pillar[4+1]arenes which have only one possible isomer. However, when different units cyclize in a 3:2 ratio, the co-pillar[3+2]arenes, then the possibility of two regioisomers exists. Two identical groups could be adjacent, to give an AB arrangement, or separated by one different unit to give an AC arrangement.




**Scheme 4.** Typical route to a co-pillar[4+1]arene.

The first example was reported in 2010 by the Huang group through the reaction 1,4-dimethoxybenzene and 1,4-dibutoxybenzene in a 4:1 ratio with five equivalents of paraformaldehyde and of $BF_3{\cdot}O(C_2H_5)_2$ in DCE [36]. Column chromatography gave the desired co-pillar[4+1]arene, **4a**, in 16% yield, lower than the 22% yield of **1a** under identical conditions. Mass spectrometry of the reaction mixture contained peaks corresponding to **1a** and co-pillar[3+2]arene **4a** containing two 1,4-dibutoxybenzene units. The same reaction in which 1,4-di(butoxy)benzene was replaced by 1,4-di(octyloxy)benzene gave the analogous co-pillar[4+1]arene, **4b**, in 27% yield. Reversing the ratios of 1,4-dimethoxybenzene and 1,4-dibutoxybenzene gave the expected co-pillar[4+1]arene **4c** with four 1,4-dibutoxybenzene units, albeit in only 9% yield. In further experiments incorporating one unit of either 1-(10-bromodecyloxy)-4-methoxybenzene or 1-(10-decyloxy)-4-methoxybenzene to give the corresponding co-pillar[4+1]arenes **4d** and **4e**[37]. Crystal structures of the two compounds showed that linear polymers formed when each *n*-decyl substituent entered the cavity of an adjacent co-pillar[4+1]arene. The analog in which the substituent terminated in a bromine atom crystallized as dimers with interpenetrating substituents. Furthermore, each dimer contained one *pR* and one *pS* isomer. The same group then took the co-cyclization concept in an interesting direction by reacting 1,6-bis(4-butoxyphenoxy)hexane and 1,4-dimethoxybenzene in a 1:8 ratio [38]. The result was double co-pillar[4+1]arene **5a**, isolated in 8% yield, in which both macrocycles were linked by a hexyl bridge.

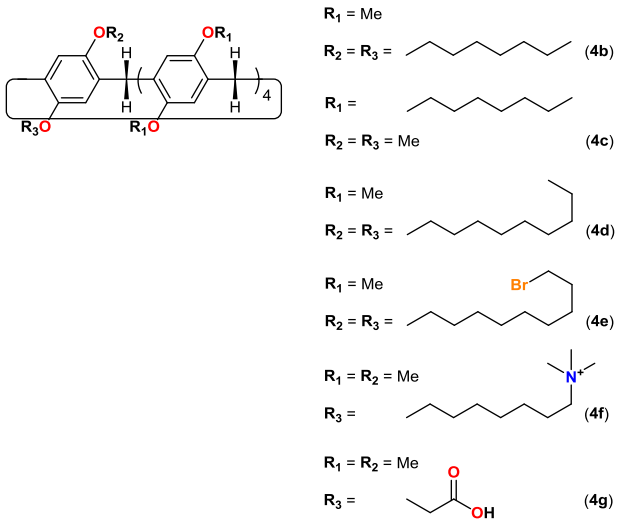



**Figure 2.** Co-pillar[4+1]arenes **4b** to **4g**.

An alternative approach to co-pillar[m+n]arene synthesis is to selectively deprotect one or more of the methoxy groups of **1a** as reported by the Ogoshi group [39]. Reaction of **1a** with 20 equivalents of $BBr_3$ leads to complete demethylation but if this is reduced to 0.9 equivalents then

monodeprotection can be achieved. Reaction with *N*-(8-bromooctyl)-trimethylammonium hexafluorophosphate gave the *N*-(octyloxy)trimethylammonium co-pillar[4+1]arene **4f**. The group also demonstrated that two methyl groups from adjacent rings could be removed selectively by $BF_3{\cdot}O(C_2H_5)_2$ [40].

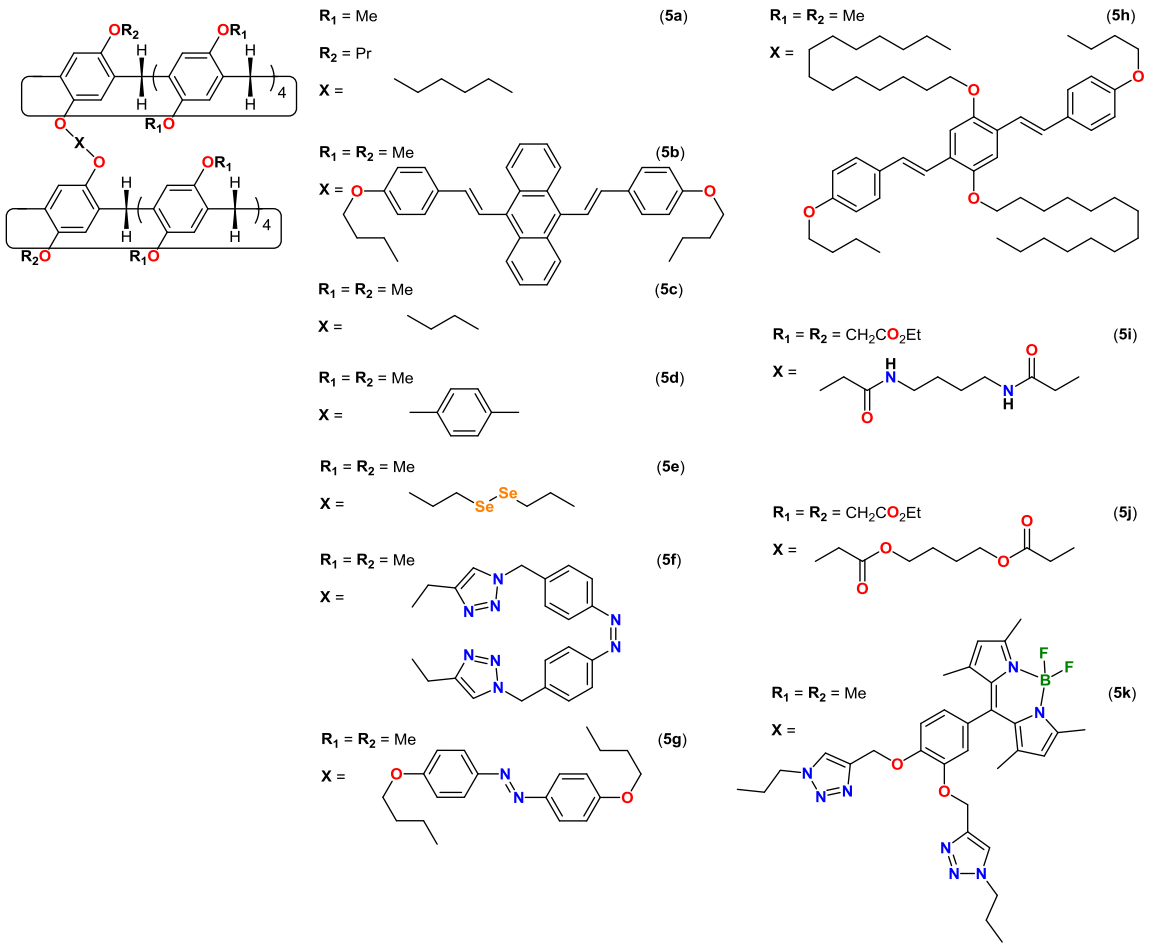
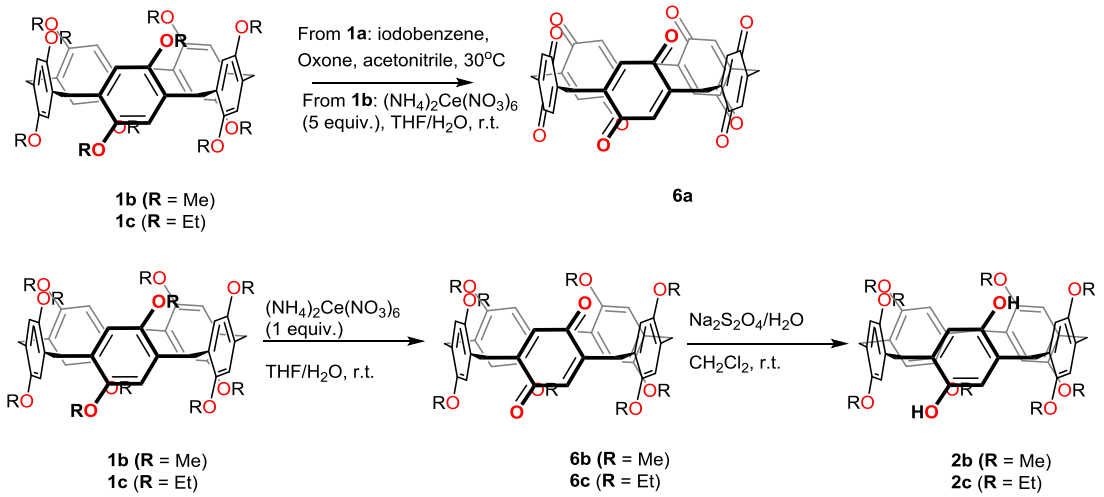



**Figure 3.** Dipillar[4+1]arenes **5a** to **5k**.

The relatively lower yield obtained for co-pillar[m+n]arenes compared to the pillar[5]arenes led the Meier group to explore alternative catalysts [41]. The use of $FeCl_3$ in $CH_2Cl_2$ proved more successful for a range of symmetric and asymmetric 1,4-di(alkoxy)benzene derivatives combined with 1,4-dimethoxybenzene and paraformaldehyde giving the corresponding co-pillar[4+1]arenes in 50-85% yield. Key to the success of this method was the ratio of 1,4-di(alkoxy)benzene derivative to 1,4-dimethoxybenzene. Unfortunately each reaction required separate optimization. Nevertheless, this remains the best approach to co-pillar[m+n]arene synthesis.




**Scheme 5.** Formation of pillar[5]hydroquinones **2a** and **2b** and pillar[5]quinone **6a**.

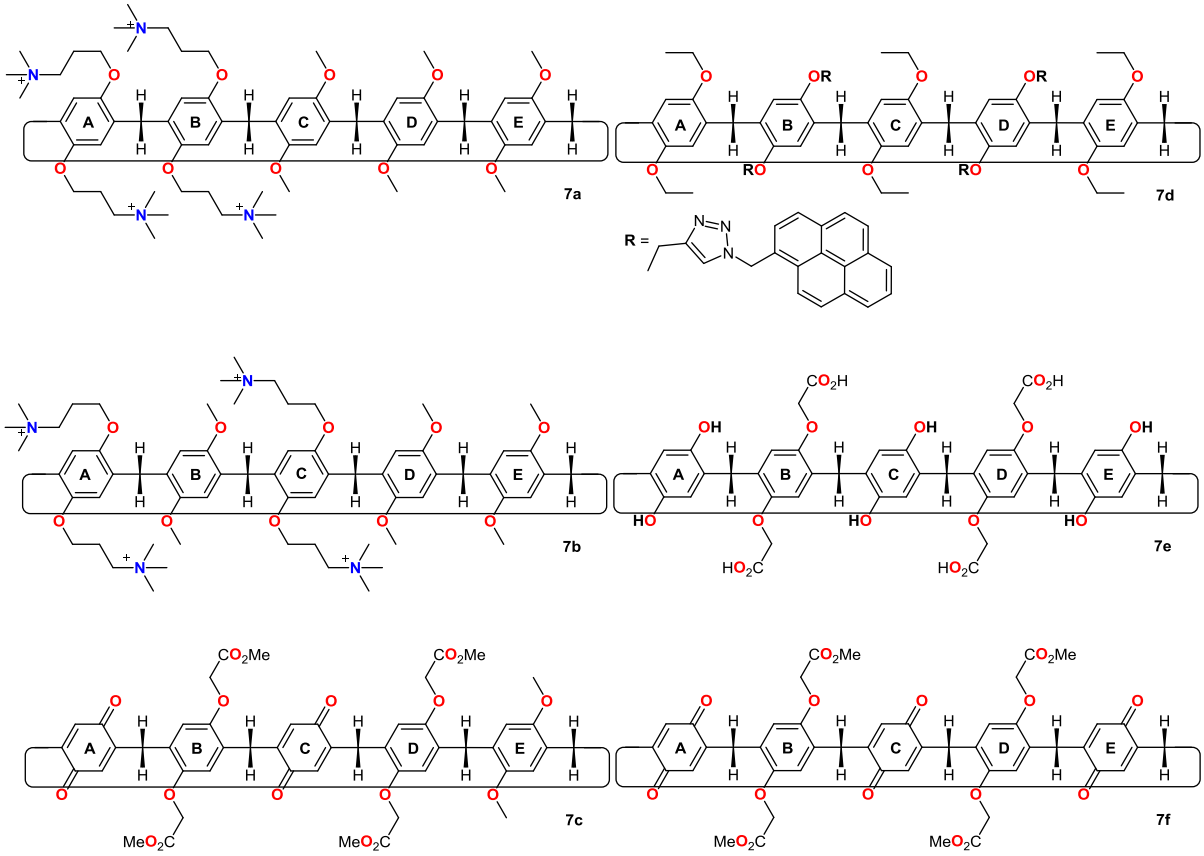



**Figure 4.** Co-pillar[3+2]arenes **7a** to **7f**.

Huang's group introduced another approach to co-pillar[4+1]arene synthesis through partial oxidation of **1a** by cerium ammonium nitrate to give the corresponding pillar[4]arene[1]quinone, **6a**

[42]. Subsequent reduction with sodium dithionate gives the hydroquinone, **2b**, which can then undergo standard *O*-alkylation. Cao and Meier's groups used the Ogoshi method [37] to prepare the precursor for monoester co-pillar[4+1]arenes which, in the case of the acetate **4g**, had the ability to self-include within the macrocyclic cavity which would suggest the possibility of [1]catenane formation [43]. Using the more traditional co-cyclization of two monomers in a 4:1 ratio, Huang's group prepared a co-pillar[3+2]arene incorporating two 1,4-bis(4-bromobutoxy)benzene units and three 1,4-dimethoxybenzene units in both AB and AC regioisomers [44]. Treatment with trimethylamine gave the water-soluble trimethylammonium bromide salts **7a** and **7b** which had different affinities for dicarboxylic acids. Having established routes to co-pillar[4+1]arenes and co-pillar[3+2]arene, it became possible to consider routes to more complex systems. Using a double quinone derivative the Xue group was able to demonstrate that three different repeating units could be incorporated in co-pillar[2+2+1]arenes such as **7c** [45].

**2.4 Derivatization**

The ability to remove all the methyl groups from **1a** immediately suggested the possibility of *O*-alkylation, however, the first pillar[5]arene derivative to be prepared was the Ogoshi group's π-delocalized alkyne-linked example [46]. Pillar[5]arene, **2**, was reacted with triflic anhydride to give the pertriflate. This was isolated and treated with ethynylbenzene under Sonogashira coupling conditions to afford the fluorescent 1,4-di(phenylethynyl)pillar[5]arene **1m**. The ability to couple substituents to pillar[5]arenes was an important step as it was unclear if steric effects would reduce the probability of substitution at all hydroquinone sites. Furthermore, while 1,4-disubstituted pillar[5]arenes exhibited $D_{5h}$ symmetry, the crystal structure of **2** showed it to be in the *1,3-alternate* conformer. Subsequent *O*-alkylation would be expected to generate the same conformer or, potentially, all four conformers in an unknown ratio. Add to this the possibility of partially successful alkylation, leaving some hydroquinone sites untouched, and the number of products would seem to be immense. Fortunately it appears that once the first substituent has been added it reorients the pillar[5]arene into the $D_{5h}$-symmetric *pS* or *pR* conformer. As more substituents add this geometry is reinforced until complete substitution has occurred.

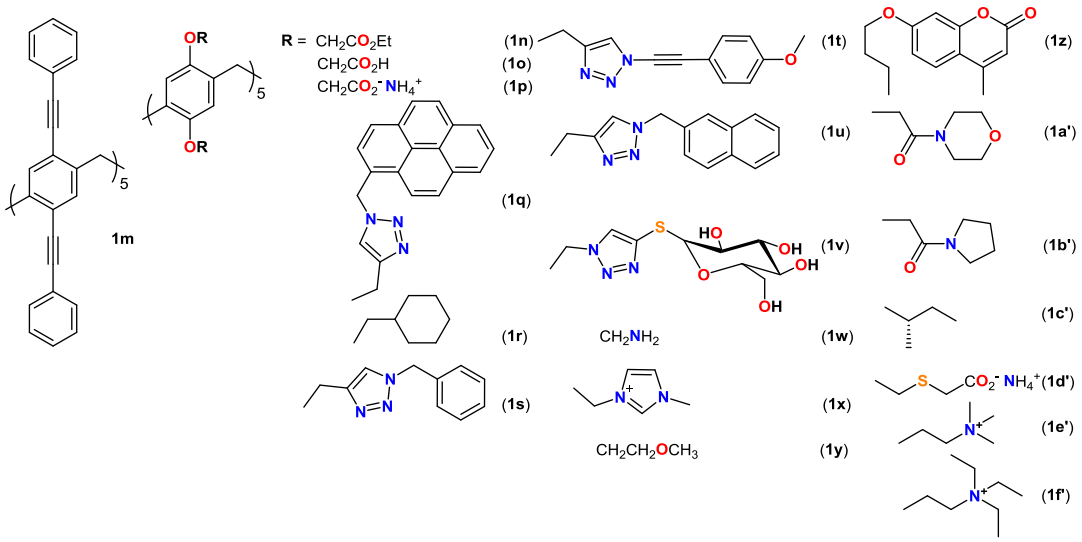



**Figure 5.** Symmetric pillar[5]arenes **1m** to **1f'**.

*O*-Alkylation was exploited by the Ogoshi group to prepare the first ester, **1n**, acid, **1o**, and water-soluble derivative, **1p**, [47], derivatives prepared from 1,4-(*O*-propargyl)pillar[5]arene by copper(I) catalyzed Huisgen-type azide-alkyne cycloaddition ("click" chemistry) such as pyrene derivative **1q** [48] and a planar chiral cyclohexylmethyl derivative, **1r**, which could be separated into its enantiomers by HPLC [49]. Click chemistry was also employed by the Stoddart group to prepare mono-azobenzene-functionalized pillar[5]arene **4i** [50]. The macrocycle self-assembled into hollow spherical vesicles which could be controlled by UV light as assemblies formed from co-pillar[4+1]arenes with *cis* and *trans* diazobenzene linkages exhibited different morphologies. Other examples of substituent extension by click chemistry include Jia and Li's group's phenyl-terminated pillar[5]arene, **1s**, which bound linear dimines [51], the Ogoshi group's di- and tetrasubstituted derivatives, e.g. **7d**, formed from mono-and diquinone intermediates [52], a liquid crystalline derivative (**1t**) reported by the groups of Nierengarten and Deschenaux [53], the Huang group's naphthyl terminated derivative (**1u**) [54], Li's supramolecular polymer-forming co-pillar[4+1]arene (**4j**) [55] and the sugar terminated derivative, **1v**, reported by Chen and Han [56].

The groups of Yu and Hou took carboxylic ester **1n** [47] and, through $LiAlH_4$ reduction, bromination with $CBr_4$, transformation into the decaazide and subsequent reduction with $Pd/H_2$, formed decaamine **1w** [57]. As anticipated, the derivative bound dicarboxylic acids with eight, nine or 20 carbon spacers effectively to form *pseudo*[2]rotaxanes. This discovery contributed to the extensive investigations into pillar[5]arene-based rotaxanes (*q.v.*).

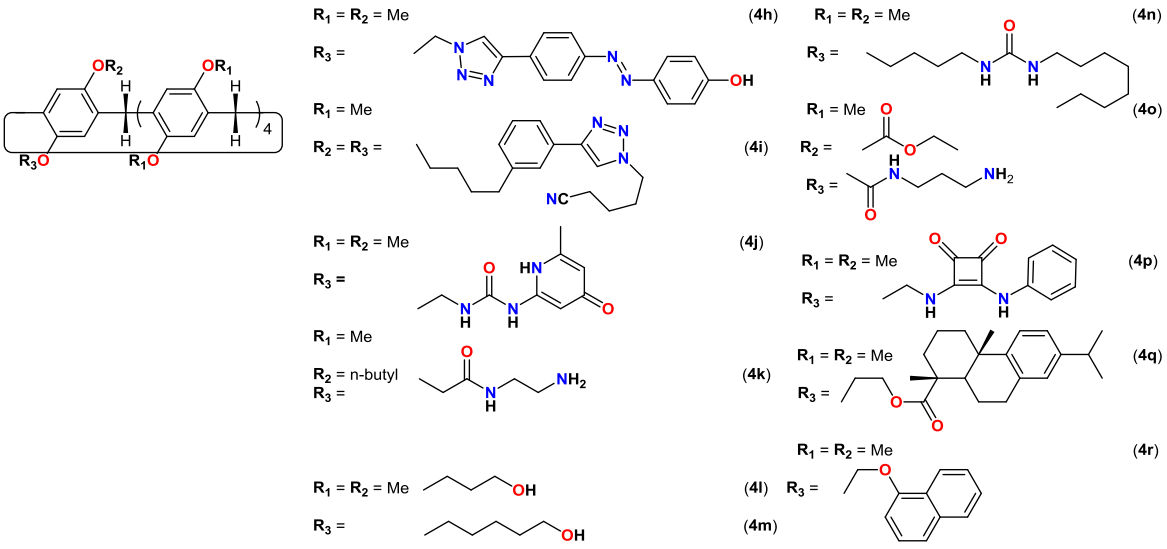



**Figure 6.** Co-pillar[4+1]arenes **4h** to **4r**.

As an alternative to the Ogoshi group's water-soluble carboxylate pillar[5]arene salts of **1n**, the Huang group developed cationic pillar[5]arenes [30] including an imidazolium-terminated pillar[5]arene, **1x**, which was used as a capping agent in the preparation of AuNPs (*q.v.*) [58]. The grous of Li and Jia linked two monodemethylated pillar[5]arenes with an array of spacers to give double co-pillar[4+1]arenes similar to those prepared by Huang's group [34] but in significantly higher yields [59]. The derivatives acted as molecular tweezers and had a high affinity for linear α,ω-dibromoalkanes. Wang's group introduced ureidopyrimidinone functionalized pillar[5]arene through the reaction of 2-(1-Imidazolylcarbonylamino)-6-methyl-4(1H)-pyrimidinone with a co-pillar[4+1]arene with a single ethoxyamine substituent (**4k**) [60]. Addition of a *n*-decane-linked di(viologen) generated a supramolecular polymer at high through host-guest and multiple hydrogen-bonding interactions.

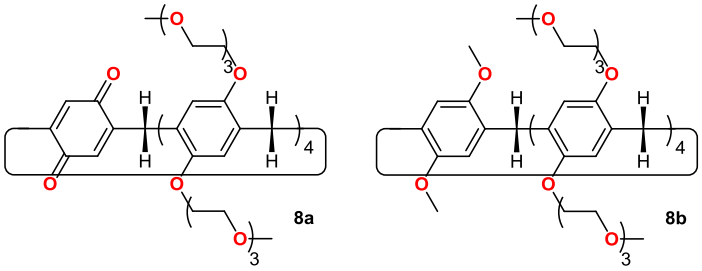



**Figure 7.** Co-pillar[4+1]arene derivatives **8a** and **8b**.

Amphiphilic pillar[5]arenes have been prepared, generally through the introduction of polyether groups to one or both rims, so that aggregation and guest binding can be investigated. Examples of these systems include those of Huang's group for controlled release of calcein and long term sequestration of TNT, **3d**, [61] and di(methyl)viologen detection through a redox response, **1y**, [62]. Ogoshi's group used a redox-tunable co-pillar[4+1]arene with a single quinone unit, **8a**, to disaggregate in response to di(decyl)viologen bromide [63].

In 2009 the Cao group prepared pillar[5]quinone **6a** as part of its investigation of synthetic routes to pillar[n]arenes [25], although no further publications concerning the synthesis of the derivative were forthcoming. An improved route was published by Shivakumar and Sanjayan [64] and further control over the degree of reduction and subsequent oxidation of 1,4-dimethoxypillar[5]arene was demonstrated by Pan and Xue who reported the crystal structures of the tri- and tetraquinones as well as that of the trihydroquinone [65]. A comprehensive investigation of conditions necessary to prepare a range of quinones was published by Huo and colleagues in 2015 [66].

Monosubstituted pillar[5]arenes allow the influence of a single functional group to be assessed. The Cao group investigated linear self-assembly through the introduction of a single 4-hydroxybutyl (**4l**) or 6-hydroxyhexyl substituent (**4m**) [67], the groups of Hu and Jiang observed self-inclusion of an alkylated monourea derivative (**4n**) in solution but dimerization in the solid state [68] and the Hou group found that similar self-inclusion occurs for **1n** when one group had been converted to an alkylamide (**4o**) [69]. Single substituents are also useful as detectors of small molecules with complementary electrostatics or other properties. The Lin group was able to demonstrate the presence of *n*-alkyl phosphonic or carboxylic acids by mono-squaramide-functionalised pillar[5]arenes such as **4p** [70], the Tian group developed a coumarin-pillar[5]arene as a fluorescent probe for the pesticide methyl-parathion (**1z**) [71] and the groups of Liu and Duan incorporated dehydroabietic acid (**4q**) [72] and naphthyl moieties (**4r**) [73] in order to assess their impact on guest binding.

Combining a macrocycle with substituents that have affinities for particular chemical species is a well-known feature of macrocyclic chemistry. Phosphorus, as either phosphine or phosphate, is able to bind to a number of substrates and can be introduced into pillar[5]arenes through selective functionalization. The groups of Feng and Yuan developed pillar[5]arene-based phosphine oxide derivatives to separate f-block elements from acidic media [74,75]. Using the Huang group's 1,4-(bromoethoxy)pillar[5]arene [30] they introduced diphenylphosphine groups through an Arbusov reaction with *iso*-propoxydiphenylphosphine. The macrocycle (**9a**) was able to extract thorium(IV) and uranyl(VI) cations far better than non-cyclic analogs. The phenyl(*iso*-propyl)phosphine derivative

(**9b**) was also an able extractant of uranyl(VI) but not to the di(*iso*-propyl)phosphine analog (**9c**) [76]. The same group also showed that a diphenylphosphine analog with a butyl spacer was an effective extractant of $Hg^{2+}$ (**9d**) [77]. The groups of Cao and Meier treated partially hydroxylated **1a** with $POCl_3$ to give the mono- and diphosphorylated pillar[5]arenes (**9e**, **9f**) which bound butanol in $CHCl_3$ [78] and alkylammonium ions and alkyl halides in water [79], respectively.

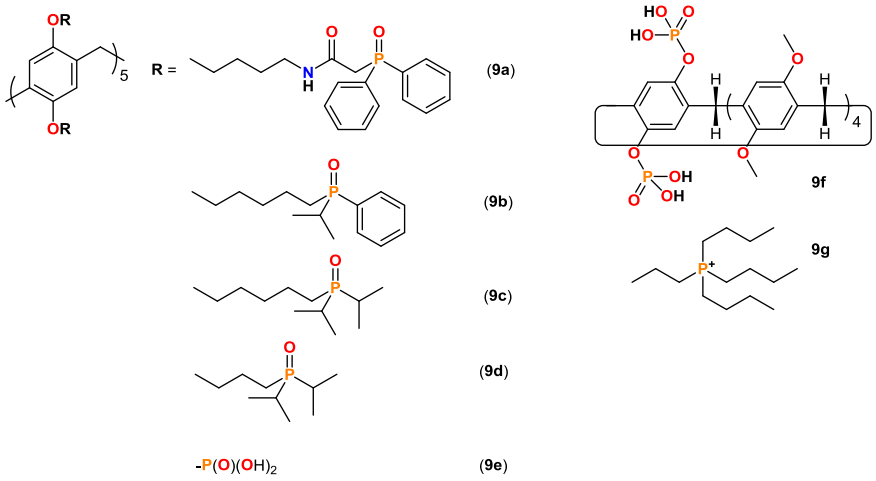



**Figure 8.** Phosphorus-containing pillar[5]arenes **9a** to **9g**.

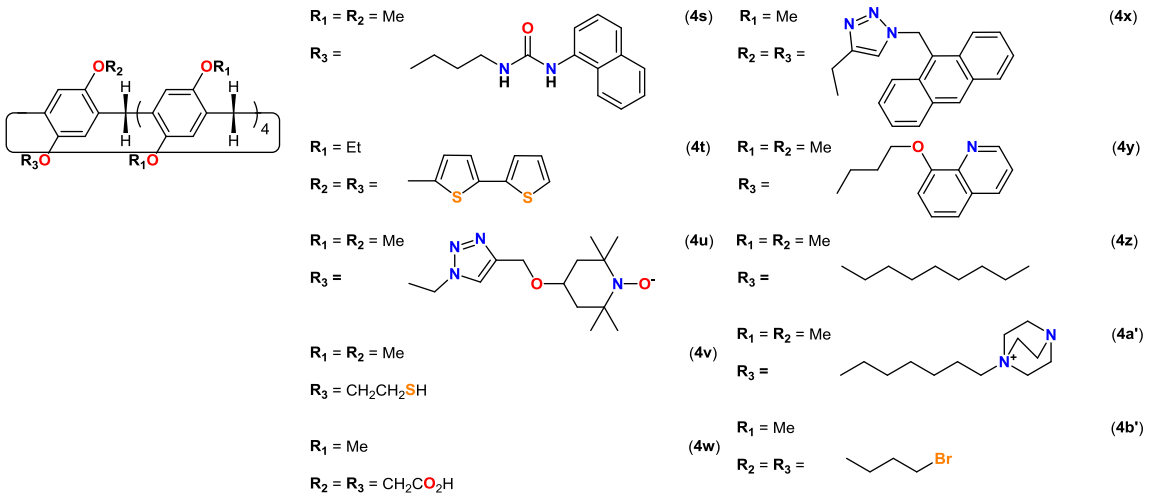



**Figure 9.** Co-pillar[4+1]arenes **4s** to **4b'**.

Other guest species have been targeted by pillar[5]arene derivatives. The Huang group incorporated a single naphthylurea moiety, via a bromobutoxy substituent which was treated with potassium phthalimide, hydrazine and isocyanatonaphthalene, to yield **4s** which bound *n*-octyltriethylammonium salts [80], the groups of Feng and Yuan developed pillar[5]arene-based

diglycolamides which were highly efficient in separating americium(III) and europium(III) [81, 82], the Stoikov group demonstrated that pillar[5]arenes with morpholide (**1a'**) and pyrrolidide (**1b'**) substituents formed complexes with alkali metal ions and had a preference for $Li^+$ [83] and Pan and Xue reported a hydroxylated co-pillar[3+2]arene with ethyl esters on the A and C rings (**7e**) which had an affinity for bis(imidazolium) salts [84].

Chiral aspects of pillar[5]arene chemistry can be investigated through derivatisation. The Ogoshi group treated 1,4-diethylpillar[5]arene with triflic anhydride followed by (5-bithienyl)boronic acid to yield a co-pillar[4+1]arene with an extended bis(thiophene) motif (**4t**) [85]. Both planar chiral isomers could be observed by circular dichroism (CD) and inclusion of achiral 1,4-dicyanobutane induced a change in the CD signal. The Stoddart group prepared a co-pillar[4+1]arene via a hydroquinone intermediate in which two hydrogens on the hydroquinone ring were exchanged for bromide [86]. The product, **10a**, was a useful probe for pillar[5]arene through-the-annulus rotation. The same group took the system a step further by replacing the bromines with amines and oxidation to the quinone with a goal of preparing materials suitable for nanotube formation (**10b**) [87]. Another approach to investigating the effects of pillar[5]arene stereochemistry on complexation is to generate the four conformers of asymmetric derivatives with binding sites incorporated on each ring. This was achieved by Huang's group with a pillar[5]arene comprised of 2-(4-pentoxyphenoxy)acetate units (**3c**) which exhibited differential binding affinities towards di(methyl)viologen [88].

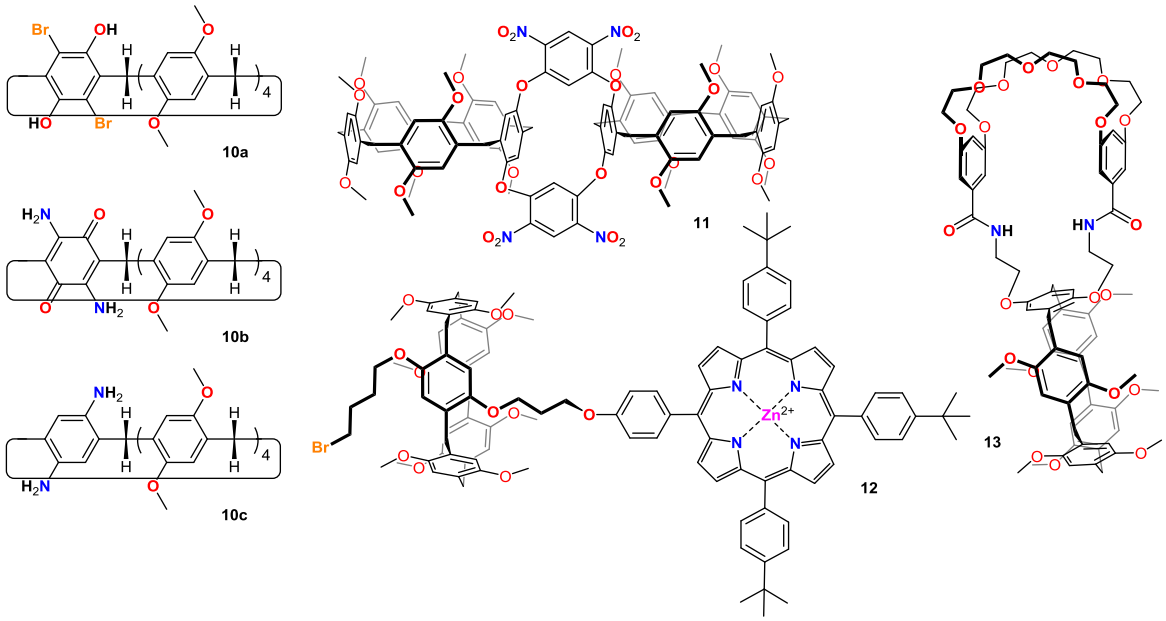



**Figure 10.** Pillar[5]arene derivatives **10a** to **13**.

Introducing substituents allows the dynamics of pillar[5]arenes to be investigated. The Ogoshi group prepared chiral derivatives from 1,4-bis[2(S)-methylbutoxy]benzene and paraformaldehyde to give a racemic mixture of *pR* and *pS* enantiomers (**1c'**) which could be differentiated by chiral HPLC [89]. Variable temperature NMR studies showed that repeated interconversion between the two was possible by switching temperatures between 0 °C and 40 °C. Pan and Xue prepared a derivative with two 1,4-di(methoxycarbonyl)benzene units and three hydroquinones (**7f**) which exhibited ring flipping during hydroquinone formation [90]. Mezzina, Lucarini and colleagues probed pillar[5]arene-guest dynamics through the introduction of a single spin-label by a click reaction between a monoazide and 4-propargyl-TEMPO (**4u**) which allowed guest binding to be followed by EPR [91].

The ability to link pillar[5]arenes is an essential starting point for any type of polymerization incorporating these macrocycles (*q.v.*). One way to avoid the potential library of products afforded through irreversible covalent bond formation is to employ a reversible linker such as a disulfide. The Yang group took a co-pillar[5]arene with a single ethoxybromide substituent and formed the monothiol with the addition of thiourea followed by base [92]. As expected the macrocycle (**4u**) formed disulfide bridges. Addition of a diimidazole generated a supramolecular polymer which formed nanospheres in aqueous solution. Another pillar[5]arene (**1d'**) that incorporates sulfur, as mercaptoacetic acid termini, was shown by the Li group to form channels in lipid bilayers which conduct $K^+$ unless $Hg^{2+}$ is present which blocks the channel [93].

One further area of interest is that of combining macrocycles to exploit the recognition properties of both species. The groups of Xue and Liu reacted a co-pillar[4+1]hydroquinone with 1,5-difuoro-2,4-dinitrobenzene as a precursor to a proposed three ringed macrocycle (**11**) [94]. The addition of potassium carbonate allowed a fluoride substituent to exchange with hydroxide giving a derivative which crystallized to give a 1D channel. More successful attempts to fuse a second class of macrocycle with a pillar[5]arene have come from the Jiang group, which prepared a porphyrin-pillar[5]arene hybrid ditopic receptor (**12**) [95] and linked one pillar[5]arene ring to a diazacrown ether thus forming a cryptand-pillar[5]arene hybrid (**13**) [96, 97].

**3 Complexation**

From the start of piilar[5]arene chemistry, with the crystal structure of the **1a**·$CH_3CN$ inclusion complex [22], it was clear that the novel macrocycle had significant potential as a macrocyclic host. Initial explorations of guest inclusion were limited to neutral linear molecules such as *n*-alkanes [98],

bis(imidazoles) [99], dinitriles [100], dihaloalkanes [101, 102], unsaturated aliphatic hydrocarbons [103] and 5-bromovaleronitrile [104]. Ogoshi also demonstrated that viologen derivatives were bound within the pillar[5]arene cavity which led to other investigations involving ammonium species [105-109].

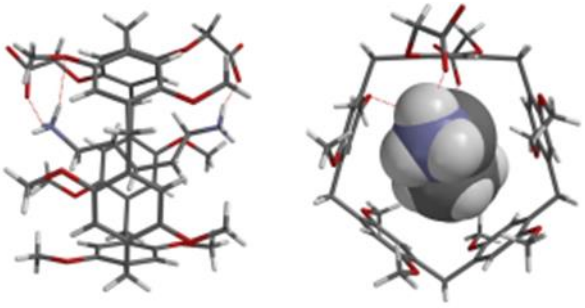


**Figure 11.** An X-ray structure illustrating diamine binding by dicarboxylate **4w**: (left) showing hydrogen bonding (in red) and (right) as a space-filling view.

Charged pillar[5]arenes have the clear potential to bind electrostatically complementary species as seen in the work of the Yu group on a co-pillar[4+1]arene dicarboxylic acid (**4w**) which bound a range of alkyldiamines from 1,5-pentanediamine to 1,10-decanediamine to form 1:1 [2]*pseudo*rotaxanes (Figure 11) [110]. NMR and X-ray crystallography gave conclusive proof of the threaded nature of these complexes but the association constants showed little variation despite the large difference in alkyl chain lengths (Figure 11). The same group later showed that the association constant of **4w** in $CHCl_3$/MeOH was an order of magnitude higher for neutral 1,9-diaminononane than for its quaternarized dication [111]. Carboxylatopillar[5]arene salt **1p** was shown to bind amino acids in $D_2O$ with arginine bound significantly better than histidine or lysine with association constants of 5.9 x $10^3$ $M^{-1}$, 1.5 x $10^3$ $M^{-1}$ and 1.8 x $10^3$ $M^{-1}$, respectively, where seven other amino acids failed to bind [112]. To underline the affinity for arginine, the tripeptide Ala-Arg-Ala had a binding constant of 4.2 x $10^3$ $M^{-1}$ and Ala-Lys-Ala, 7.5 x $10^2$ $M^{-1}$. Cadaverine (1,5-diaminopentane) was bound most strongly of all the biogenic molecules tested with an association constant of 5.6 x $10^4$ $M^{-1}$. Crystallographic analysis by the Danylyuk and Sashuk groups showed that the parent acid of **1p**, **1o,** bound the anesthetic drug tetracaine efficiently [113] and the Dong and Schalley groups demonstrated that it could transport β-carboline, a bioactive alkaloid with extensive medicinal potential, into human kidney, liver and monocyte cells with lower levels of toxicity than were observed in the absence of the pillar[5]arene [114]. The Bitter group used the same pillar[5]arene to bind a range of stilbene-based dyes resulting in a 28-fold enhancement of fluorescence enhancement, with an accompanying yellow to pink color change in the case of 4-dimethylaminostyryl-N-methylpyridinium iodide (DAST)

[115]. Upon the addition of di(methyl)viologen, DAST was displaced leading to fluorescence quenching. Ji's group used **1p** as a controlled release vector to deliver a methylpyridinium-based probe for cysteine as pH is reduced from 7.4 to 4 that mimics the partition between healthy tissues and tumors [116]. The same group also bound the probe within a pillar[5]arene with triethylene glycol monomethyl ether substituents, **8b**, and demonstrated its thermal release [117].

Cationic pillar[5]arenes also have potential to bind small molecules within an aqueous environment. Pillar[5]arenes with trimethylammonium termini (**1e'**) can bind an array of linear alcohols, with a strong correlation between chain length and association constant [118], tosylate [119], linear acids and diacids [120] and have had their binding affinities compared to those of calix[4]arenes with similar substituents [121]. The triethylammonium analog, **1f',** has been found to be an effective binding agent for methyl orange [122].

Neutral perethylated pillar[5]arene **1b** has a better solubility profile than its methyl analog and forms complexes with linear aliphatic ester, aldehyde and ketone guests [123] and *n*-alkanes [124]. A 9,10-distyrylanthracene-bridged pillar[5]arene dimer **5b** reported by the Yang group formed supramolecular linear polymers when bound to a neutral guest possessing two triazole binding sites [125]. Li and colleagues replaced the methoxy groups on one 1,4-dimethoxypillar[5]arene ring with amines (**10c**) to control binding by pH [126]. The attachment of anthracene groups allows co-pillar[4+1]arene **4x** to slide onto imidazolium groups bound, via an alkyl tether, to a gold surface [127]. Heating releases the macrocycles while cooling allows them to reassemble on the surface. A co-pillar[4+1]arene linked to 8-hydroxyquinoline, **4y**, responded to cyanide binding through enhanced fluorescence at 456 nm and was unaffected by other anions [128] and, in a reversal of the pillar[5]arene complexation discussed above, pentagonal templates have been synthesized to capture pillar[5]arene derivatives [129].

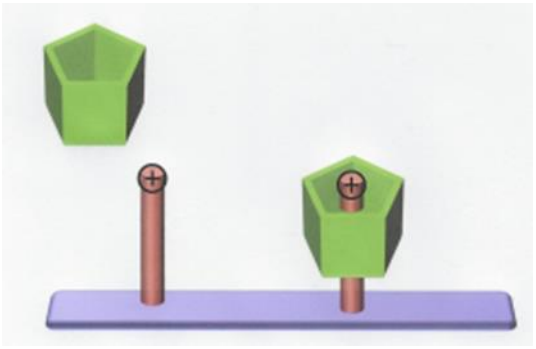


**Figure 12.** Surface functionalization facilitated by electrostatic complementarity and reversed by heating.

## 4 Polymerization and self-assembly

The ability to functionalize pillar[5]arenes allows for the introduction of reactive groups which then polymerize under the appropriate conditions. Substituents can also be introduced which are self-complementary, such as acids, or which are complementary to the pillar[5]arenes' central cavities, such as alkyl chains, that initiate the formation of supramolecular 'daisy chain' polymers. On the simplest scale, these complementary host-guest interactions lead to rotaxane formation but they can also extend in one dimension to give nanotubes.

### 4.1 Polymers

To date few covalently linked pillar[5]arene-incorporating polymers have been reported. The Stoddart group extended its diamino co-pillar[4+1]arene, **10b**, by crosslinking with terephthalaldehyde to prepare oligomers from n = 2 – 9 [87], however, the only true linear polymers reported so far come from the groups of Hu and Wang [130] and Müllen [131]. The former prepared a pillar[5]arene modified poly(phenylene-ethynylene-butadiynylene) copolymer by first preparing a dimer from co-pillar[4+1]arenes with single ethoxybromide substituents. These were linked by 2,5-diiodo-1,4-dihydroxybenzene which was extended through reaction with *p*-(trimethylsilylethynyl)phenylacetylene. Hydrolysis of the silyl groups was followed by a Cu-catalyzed homocoupling to give a pillar[5]arene-decorated conjugated polymer (**14a**). The Müllen group adopted a similar approach by crosslinking alkyne-terminated co-pillar[4+1]arenes with 1,4-diiodi-2,5-bis(octyloxy)benzene under Sonogashira conditions (**14b**). The Hu and Wang groups also linked four pillar[5]arenes to tetraphenylethene by click chemistry (**14c**) which aggregated in the presence of a linear guest, 1,4-bis((1-(4-bromobutyl)-1H-1,2,3-triazol-4-yl)methoxy)benzene, to give a luminescent response [132]. Addition of competing adiponitrile turned the fluorescence off. Similar behavior was observed by the Yang group for the same tetrapilla[5]arene derivative with linear guests terminating in cyano groups [133].

The 'daisy chain' motif provides a simple method by which pilar[5]arene derivatives can form a linear supramolecular polymer, driven by CH···π interactions, as seen in the crystal structure of the Huang group's co-pillar[4+1]arene with a single octyl substituent (**4z**)that crystallizes in linear structures where the alkyl group from one macrocycle inserts into the cavity of the next to give an A-A-A structure[134]. Ogoshi's group reported a supramolecular polymer by appending a single *n*-hexyl substituent terminating in pyridinium on the co-pillar[5+1]arene and 1,4-diazabicyclo[2.2.2]octane (DABCO) on the co-pillar[4+1]arene (**4a'**) [135]. Inclusion of pyradinium within co-pillar[4+1]arene

and DABCO within co-pillar[5+1]arene programs the binary mixture to alternate between pillar[n]arenes. The Jia and Li groups combined a di(co-pillar[4+1]arene) with a *p*-xylyl spacer (**5d**) and a co-pillar[4+1]arene with two dibromobutane substituents (**4b'**) to give an A-B-A-B motif [136]. Pairs of bromoalkyl-substituted macrocycles formed, through mutual inclusion of their substituents, and then formed *pseudo*rotaxanes with one of the two linked co-pillar[4+1]arenes leading to an A-A-B-A-A-B supramolecular polymer. A co-pillar[4+1]arene with a single methylviologen substituent (**4c'**), introduced by click chemistry, was predicted by the Stoddart group to form a self-inclusion complex in dilute solutions but to form a daisy chain polymer at higher concentrations (Figure 14) [137]. The Yang group reported a photoresponsive co-pillar[4+1]arene with an alkyl substituent incorporating a stilbene moiety and terminating in an imidazole group (**4d'**) [138]. The *Z* form of the stilbene gave a self-included *pseudo*rotaxene whereas the *E* form forms a daisy chain polymer upon protonation of the imidazole.

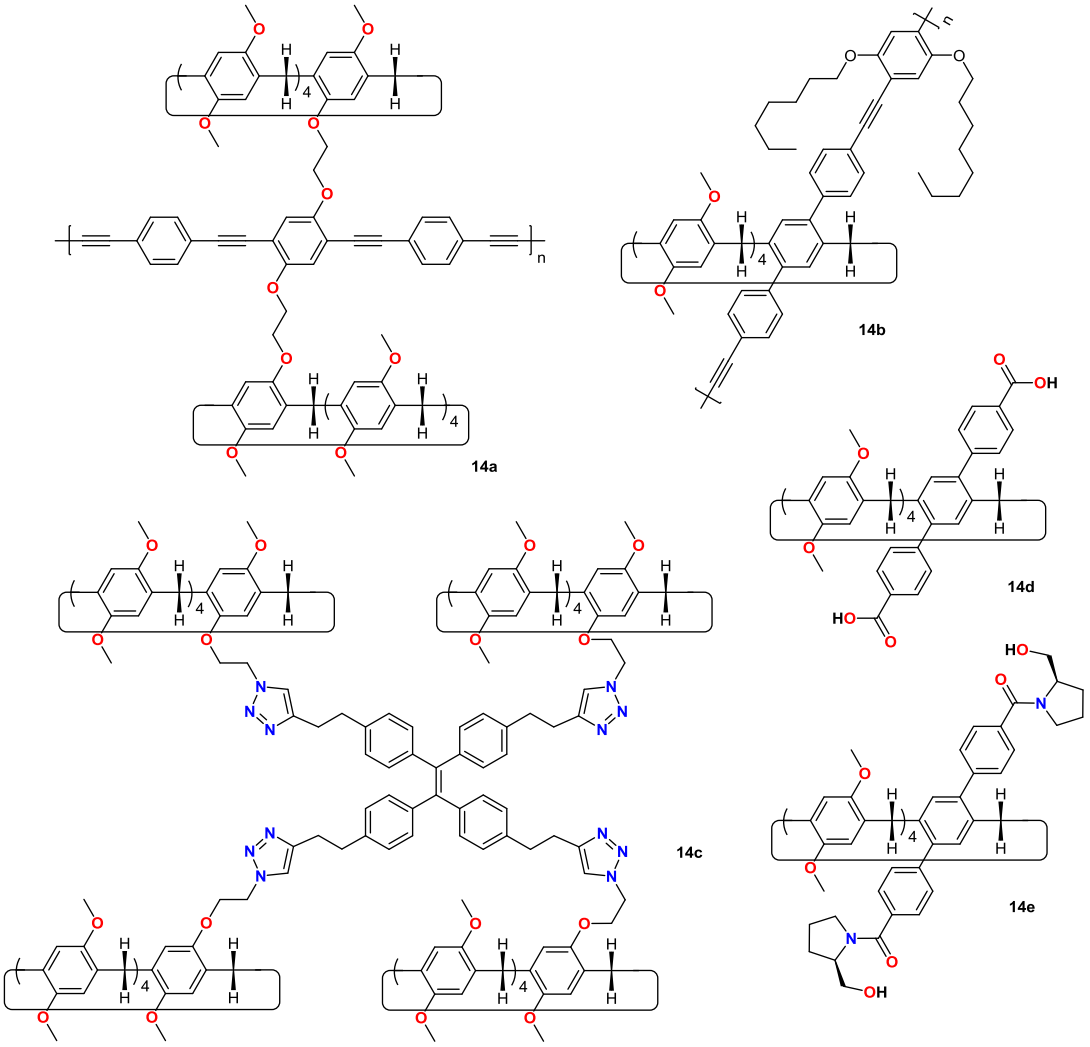



**Figure 13.** Polymeric co-pillar[4+1]arenes **14a** to **14e**.

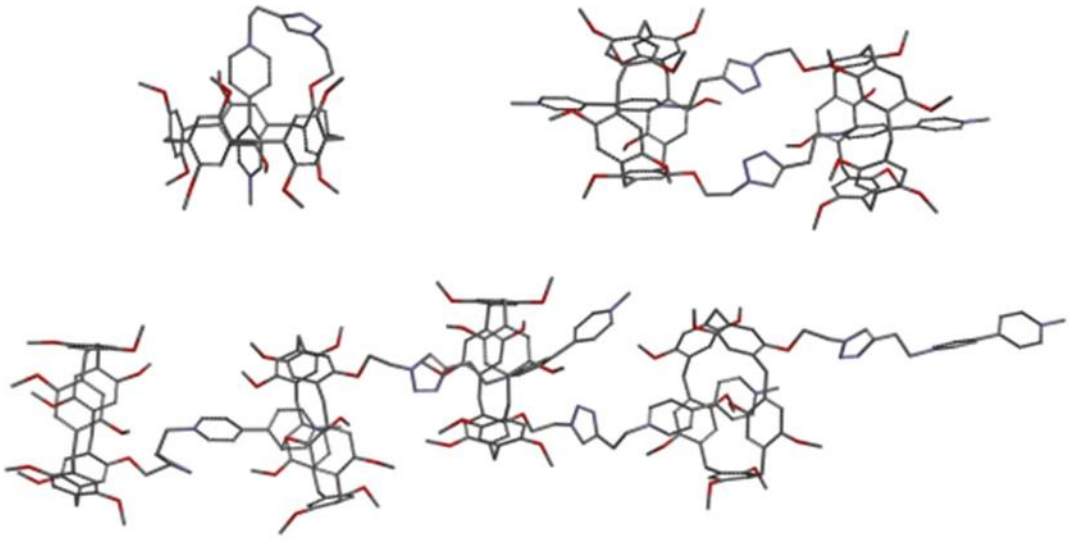


**Figure 14.** Co-pillar[5]arene binding motifs for **4c'**: (clockwise from top left) self-inclusion, dimerization and daisy chain polymerization.

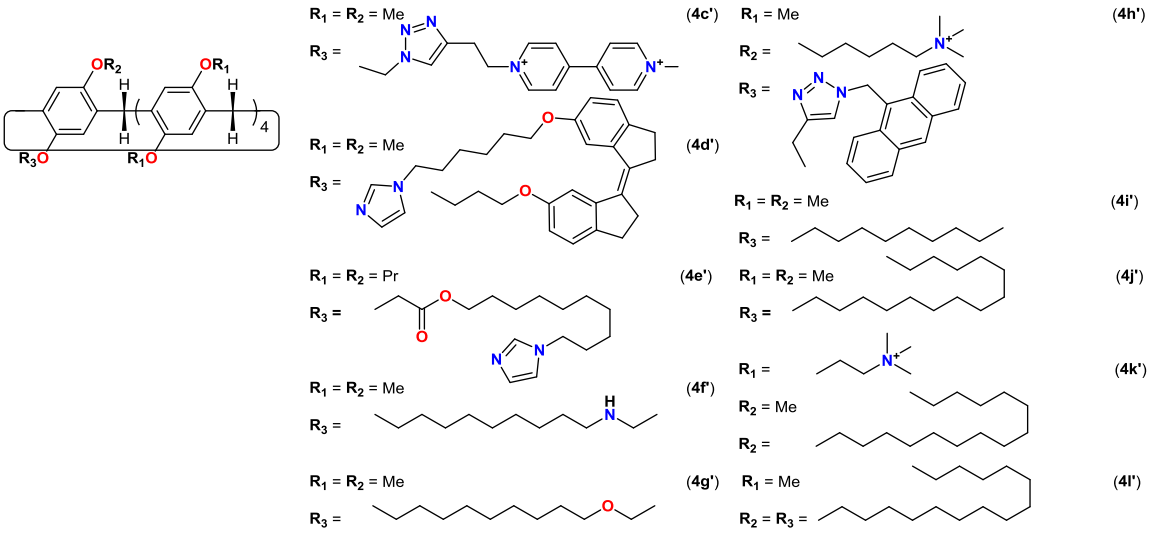



**Figure 15.** Co-pillar[4+1]arenes **4c'** to **4l'**.

The Huang group reacted a monoethyl ester co-pillar[4+1]arene with 1-hydroxydecylimidazole to give **4e'** which, when protonated, self-included at low concentration but formed a linear A-A-A daisy chain supramolecular polymer [139]. The degree of polymerization could be controlled by pH: addition of increasing amounts of triethylamine led to lower viscosity, as the neutral imidazole groups had less affinity for the macrocyclic cavities, which could be reversed through the addition of trifluoroacetic acid. The Xue group achieved a similar result with a co-pillar[4+1]arene incorporating a single *N*-ethyl-10-oxydecan-1-amine substituent (**4f'**) [140]. When protonated, an A-A-A supramolecular polymer formed through N-H···π and C-H···π interactions with a second macrocycle.

Again, the system was pH responsive as the addition of chloride destroyed the polymer. The groups of Dong and Xue showed that the oxygen-containing analog of this compound, **4g'**, also formed concentration dependent A-A-A daisy chain polymers using viscosity measurements and were successful in obtaining a crystal structure to support their assumptions about the polymeric structure [141]. The Zhang and Wang groups synthesized an asymmetric co-pillar[4+1]arene incorporating an anthracene fluorophore and a quaternarized ammonium moiety (**4h'**) [142]. The macrocycles formed fluorescent interlocking dimers which decomplexed in the presence of chloride or 1,8-diazabicyclo[5.4.0]undec-7-ene to quench fluorescence. The fluorescent intensity was also found to be temperature sensitive with weaker emission upon heating, as might be expected, but a return to fluorescence upon cooling. Multicomponent systems have been prepared so that the binding preferences of each recognition element can be harnessed. The Stoddart group reported a zinc-porphyrin complex linked to a pillar[5]arene and a viologen which formed the expected daisy chain structure (**12**) [143]. The A-A-A polymer formed fibers and was proposed to have applications in the field of light harvesting. Even simple systems give rise to emergent properties. The Wei group formed self-healing supramolecular gels from co-pillar[4+1]arenes that incorporated single dodecyl (**4i'**) or hexadecyl (**4j'**) substituents and underwent temperature-controlled reversible sol-gel phase transitions [144]. The Yao group also incorporated a hexadecyl substituent into a co-pillar[4+1]arene, via a 1-methoxy-4-cetylbenzene unit, but the remaining units terminated in water-soluble trimethylammonium groups (**4k'**) [145]. Supramolecular polymers formed from aqueous solution through a concentration and temperature dependent sol-gel process. The Wei and Zhang groups also employed hexadecyl substituents in the formation of supramolecular gels [146]. One unit of the co-pillar[4+1]arene has two hexadecyl substituents (**4l'**) which allows interpenetration of macrocycles to occur. Initially this appears to be a 2D grid but eventually a strongly fluorescent laminar structure forms as a gel. Addition of the competitive surfactant hexadecylpyridinium chloride leads to fluorescence quenching in the gel phase. The groups of Gong and Ning prepared a di(co-pillar[4+1]arene) with an oligo(p-phenylenevinylene) bridge that incorporated two *n*-dodecyl chains (**5h**) which was able to crosslink and form grids through orthogonal interactions between macrocyclic cavities and alkyl groups [147]. Sol-gel behavior was observed and gave rise to pH-controllable fluorescence. The Huang group reported a co-pillar[4+1]arene with a substituent which incorporate a urea moiety and a terpyridyl terminus (**4m'**) [148]. Pairs of molecules are connected as their substituents interpenetrate each other's macrocyclic cavities with the terpyridine groups acting as stoppers to stop de-threading from occurring. The macrocycles can shuttle towards the urea groups to shorten the dimer or away to lengthen it. Addition of iron(II) chloride links the terpyridine groups of two dimers to form an A-B-A-B metallopolymer for which extension and contraction can

be controlled by solvent (Figure 16). The polymer therefore functions as a mimic for the muscle protein, titin. The Xiao and Jiang groups combined a di(co-pillar[4+1]arene) with an ethylene spacer (**5c**) and a tetra(butoxyimidazole)porphyrin to prepare an A-B-A-B polymeric grid which can be dispersed by the addition of adiponitrile which competes with imidazole for the di(co-pillar[4+1]arene) cavity [149].

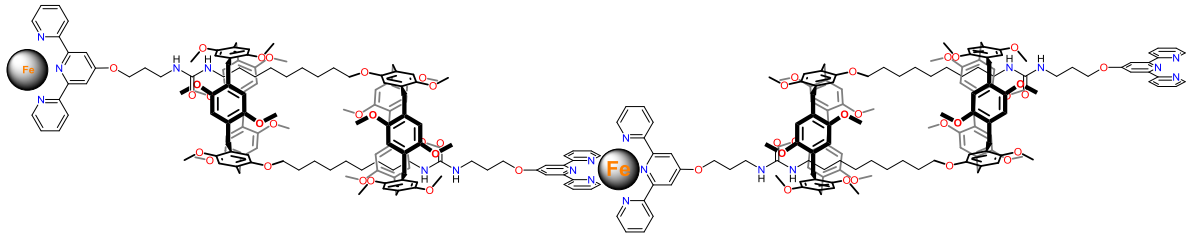


**Figure 16.** A co-polymer formed through chelation of iron(II).

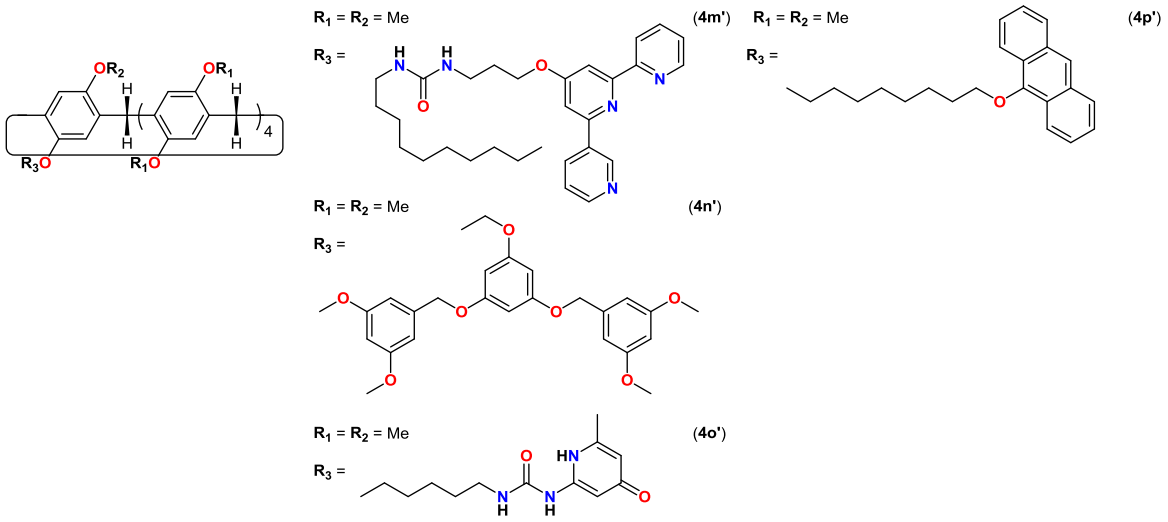



**Figure 17.** Co-pillar[4+1]arenes **4m'** to **4p'**.

Supramolecular polymers can also be prepared as AB co-polymer systems in which one component is a pillar[5]arene and the other is a ditopic guest molecule which binds to two macrocycles. Examples of these include the Li and Jia groups' combination of a tripodal molecule incorporating triazole groups linked to butanenitrile termini with a di(pillar[4+1]arene) (**5d**) to give a $A_2B_3$ copolymer [150]. The Jia group also prepared a dendritic co-pillar[4+1]arene through the reaction of monodeprotonated **1a** with 3,5-bis(3,5-dimethoxybenzyloxy)benzyl bromide (**4n'**) [151]. A second generation dendrimer with seven aromatic groups was prepared and combined with the group's tripodal spacer to give an $AB_3$ copolymer which could be destroyed with adiponitrile. Chen and

colleagues formed a ternary polymer from **1d**, *N*,*N*'-bis(n-butyl)pyromellitic diimide and a linear polyether with triazole groups linked to pentanitrile termini [152]. The pillar[5]arenes formed an *exo* complex with the diimide and an *endo* complex with the linear component. The Yao group used the same linear component to bind di(pillar[4+1]arene) **5e** linked through n-butyl selenide substituents [153]. The supramolecular A-B-A-B polymer could be fragmented by γ-rays which broke the diselenide bonds leaving pairs of macrocycles held together by the dinitrile guests. The Paek group reported an interesting example of co-pillar[4+1]arenes held together by four complementary hydrogen bond donor-acceptor groups from pyramidine-urea termini (**4o'**) [154]. The Liu group used 4,4'-dibutyl-(1,1'-biphenyl)-3,3'-disulfonate to link water-soluble pillar[5]arenes with trimethylammonium termini (**1e'**) [155].

Finally there are polymers which form through photochemical reactions of pillar[5]arene substituents such as the Yang group's co-pillar[4]arene with anthracene substituents (**4p'**) which can undergo a reversible photo[4 + 4]cycloaddition to form a covalently linked polymer [156]. Both Ogoshi's [157] and Yu's groups [158] have used azobenzene groups to link pillar[5]arenes (**5f**, **5g**) which then isomerize in response to light and heat leading to different polymer densities.

### 4.2 Pillar[5]arene rotaxanes and catenanes

Ogoshi's initial observation that **1a** bound di(methyl)viologen led his group, as well as others, to investigate the possibilities of exploiting the affinities for charged viologens and pillar[5]arenes to form rotaxanes [159-176] and *pseudo*rotaxanes (Figure18) [177-202]. Although widely encountered in daisy chain polymers, imidazole termini are only rarely encountered in rotaxanes [203] or *pseudo*rotaxanes [204]. Catenanes can also be formed using the threading principle behind rotaxanes [205,206].

Of these numerous reports several stand out as exemplars. The Ogoshi group prepared planar chiral [2]- and [3]rotaxanes from stoppered axles that incorporated pyridinium and diazo linkers along which **1b** could shuttle [161]. The planar chiral nature of the macrocycle resulted in diaselective rotaxane formation in which the aromatic units were either all-*pS* or all-*pR*. The Wang group reported a *pseudo*rotaxane from a pillar[5]arene with two aryl urea subtituents (**4q'**) [164]. Addition of linear dicarboxylic acids linked by up to 20 carbon atoms led to the formation of *pseudo*rotaxanes where the threading process was stabilized by complementary hydrogen bonding.

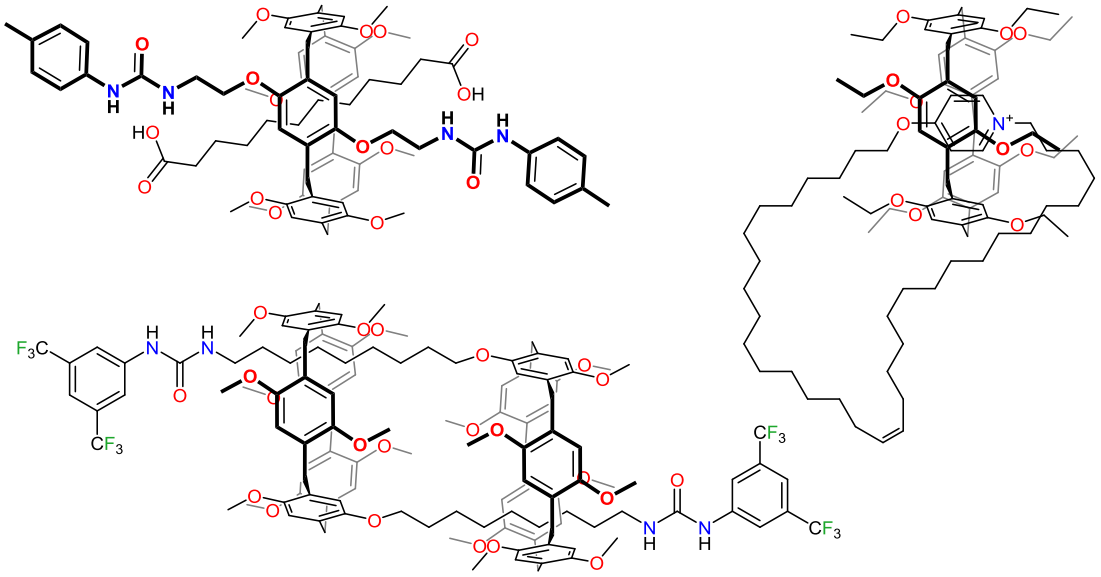


**Figure 18.** Interpenetrating structures: (clockwise from top left) Wang's *pseudo*rotaxane, Ogoshi's catenane and Huang's 'molecular spring' rotaxane.

The groups of Hu, Ma and Wang prepared a co-pillar[4+1]arene with the ability to self-include its BOC-protected terminal amine (**4r'**) and, in the process, form a *pseudo*[1]rotaxane [191]. In a very elegant example of [1]rotaxane synthesis, Xia and Xue first threaded an alkylamine with a bulky stopper through a co-pillar[4+1]arene with a single acid substituent before initiating formation of the amide [170]. The Huang group incorporated an imidizolium group in a stoppered linear alcohol, which induced threading by **1b**, which formed a [2]rotaxane upon reaction with 1-isocyanato-3,5-dimethylbenzene [203] and a similar approach was used by the groups of Li and Jia to prepare a *pseudo*rotaxane from 1,4-bis[*N*-(*N*'-hydroimidazolium)]butane derivatives and 2 [204]. The Huang group interlocked two co-pillar[4+1]arene units through mutual inclusion of linear alkyl urea groups followed by the addition of 1-isocyanato-3,5-dimethylbenzene to form stoppers [160]. The ability of the system to shorten or lengthen the distance between macrocycles led to its description as a "molecular spring". Catenanes can be formed by extending Xia and Xue's *pseudo*rotaxene synthesis to two co-pillar[4+1]arenes, as in the Liu group's mechanically self-locked catenanes [205] and the Ogoshi group's *pseudo*rotaxane which is cyclized using Grubbs' catalyst [206]. One final example, from the Huang group, demonstrates the application of pillar[5]arene-based rotaxanes [176]. The [2]rotaxanes with tetraphenylethene and triphenylphosphonium stoppers exhibited aggregation-induced emission and target mitochondria. Incorporation of DOX into the [2]rotaxane creates a prodrug capable of releasing the anticancer compound by hydrolysis in the endosomes or lysosomes.

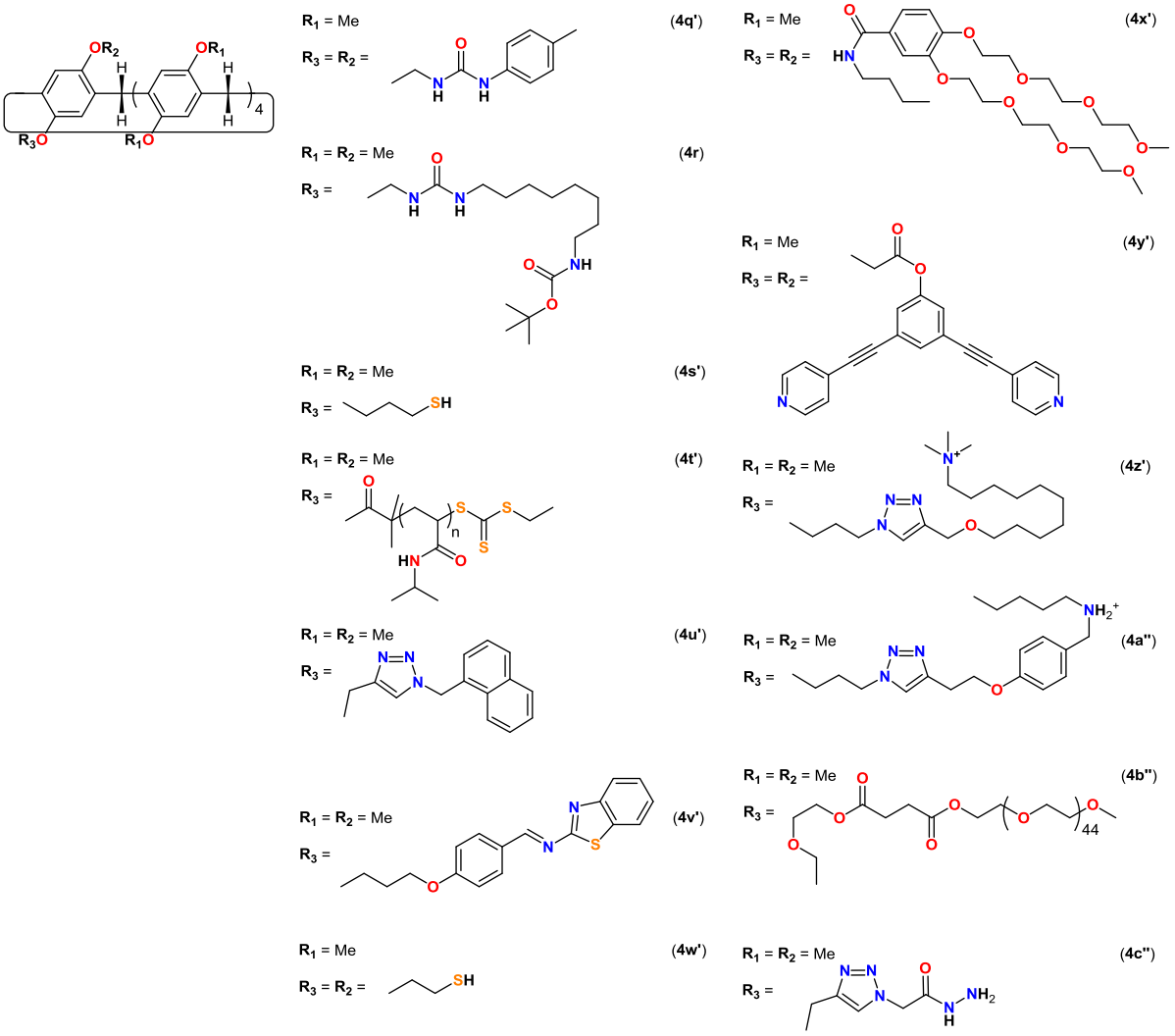



**Figure 19.** Co-pillar[4+1]arenes **4q'** to **4c''**.

### 4.3 Linear self-assembly and nanotube formation

The symmetric tubular structure of pillar[5]arenes, particularly those extended through *O*-alkylation, lends itself to linear self-aggregation and the formation of nanotubes. The first observation of this phenomenon was made by the groups of Hou and Chen [207] whose crystal structure of **1n** was shown to form end-to-end nanotubes which stacked in layers. Of greater interest was the inclusion of water molecules throughout the entire length of these tubes despite the crystals having been grown from $CHCl_3$. The crystal structure of **2** showed that tubes formed through hydrogen bonding when the compound was crystallized from $CH_2Cl_2$/DMSO, however, no solvent was included in the tubes. In separate experiments where solvents were varied and a viologen derivative added, nanotubes only formed in acetone/$CHCl_3$ in the absence of a guest [208].

When added to planar lipid bilayers, which were subjected to a potential difference of +40, 0 or -40 mV, symmetric channels formed which conducted protons in the pH range of 4.0 to 5.5 of 44 pS. Dimers formed by linking two esterified pillar[5]arenes through a single alkyl diamide (**5i**) or diester (**5j**) showed similar magnitudes of conductance [209]. Extending the pillar[5]arene channel though hydrazine-linked aromatic groups gave derivatives such as **1g'** which facilitated water passing into vesicles containing 0.3% of these derivatives [210]. Noting how the 'water wire' appeared to mimic an insulated metal wire but with protons rather than electrons being shunted from one end to the other, the Cragg group demonstrated that **1n** functioned as a proton-selective electrode when incorporated with PVC [28]. The change in conductance was non-Nernstian and gave good resolution below pH 3. The time taken for the electrodes to respond to changes in pH were independent of the proton concentration indicating that the rate determining step was the time it took for protons to attack the terminal water molecules in the electrode.

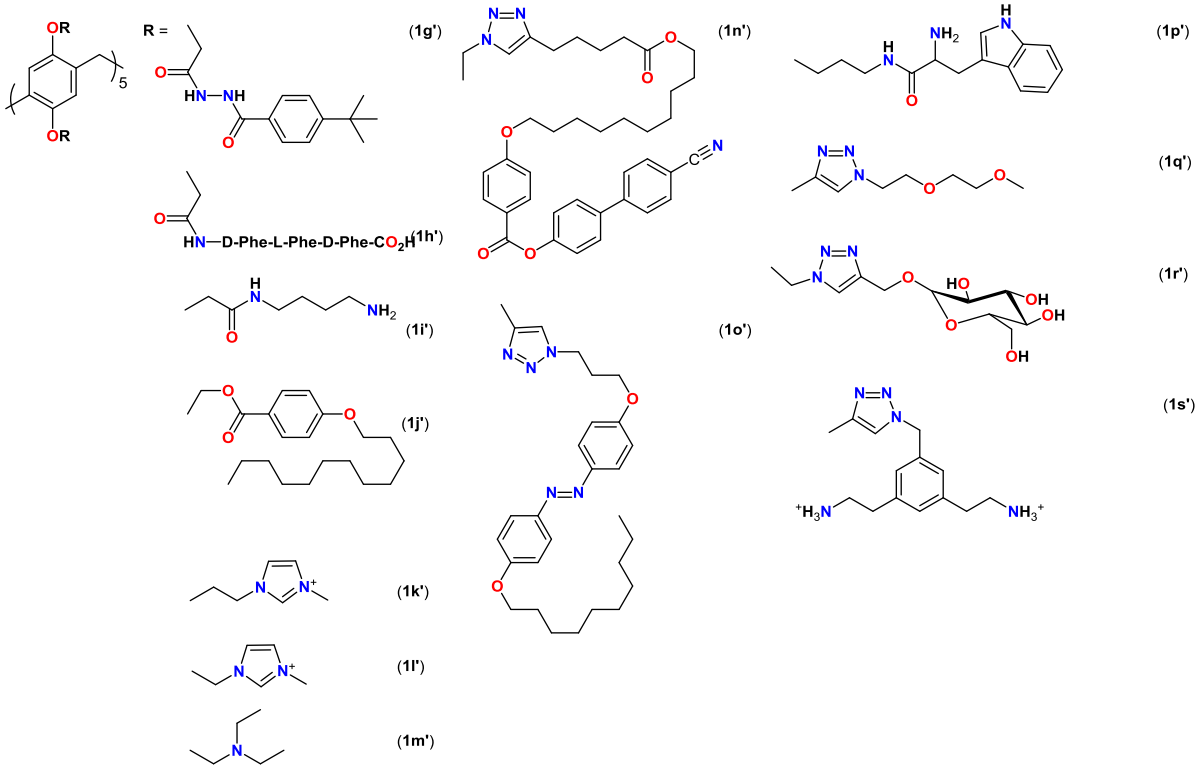



**Figure 20.** Symmetric pillar[5]arenes **1g'** to **1s'**.

Hou's group also prepared pillar[5]arene derivatives with tripeptide substituents comprising three phenylalanine moieties with varying chiralities and terminating in either an acid or ethyl ester group e.g. **1h'** [211]. These inserted into large unilamellar vesicles containing single amino acids and were found to allow glycine to pass through at about twice the rate of *L*-alanine. Transport of other amino

acids was detected but the activity was far lower. The Kumar group later showed that these pillar[5]arenes can self-assemble into 2D arrays which suggested that they could find use in gas and liquid separations [212]. The same group also prepared analogs in which one phenylalanine had been replaced with an arginine and demonstrated transmembrane transport of $K^+$ [213]. The derivative with *L*-Phe-*L*-Arg-*L*-Phe-$CO_2$Et substituents was also found to have an antimicrobial activity against the Gram-positive *Bacillus subtilis* comparable with the natural channel-forming peptide alamethicin.

Tubes and other morphologies can be controlled by guest molecules as in the Zhao group's trimeric pillar[5]arene, **15**, which binds a diviologen with a hexyl spacer [214]. Spheres, nanotubes or 3D arrays form dependent upon guest concentration. Tuning the termini of pillar[5]arenes can also generate self-assembling nanostructures. The groups of Zhou and Jin demonstrated that reaction of pillar[5]arene methyl ester with butanediamine produced **1i'** which formed micelles, vesicles or nanotubes depending upon solvent and pH. Furthermore, the nanotubes could be decorated with gold nanoparticles and used to reduce 4-nitrophenol to 4-aminophenol [215]. Nierengarten and colleagues reacted ethylbromide and ethylazide substituted pillar[5]arene with a number of benzoate derivatives, e.g. **1j'**, some of which assembled into nanotubes and then into hexagonal lattices of columnar liquid crystals [216].

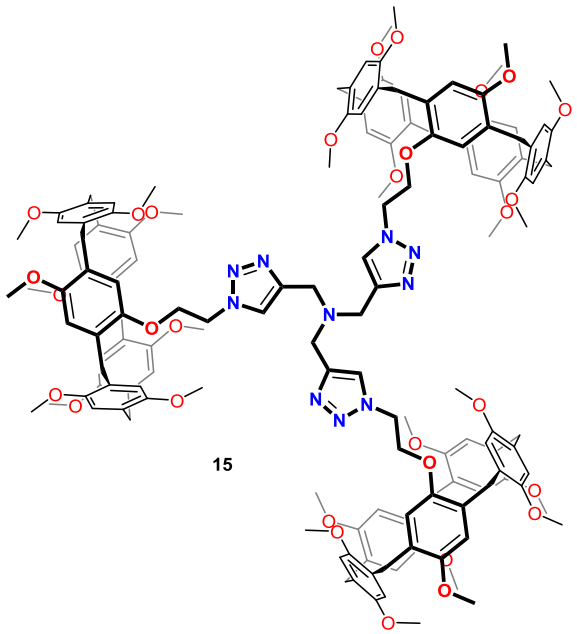



**Figure 21.** Trimeric pillar[4+1]arene **15**.

**5 Catalysis**

Given that pillar[5]arenes have excellent complexation properties and can be modified to give hydrophobic or water-soluble cationic and anionic derivatives it would seem reasonable that they have great potential as phase transfer catalysts in a range of liquid media. Surprisingly, only two examples have been reported to date. The Ogoshi group reacted tributylphosphine with 1,4-di(bromopropoxy)pillar[5]arene to give decaphosphonium derivative **9g** [217]. Linear 1-hexene was oxidized to hexanal in 99% yield by $KMnO_4$ in a $D_2O/CDCl_3$ two phase system whereas oxidation of branched 4-methyl-1-hexene to 3-methyl-1-pentanal occurred in only 31%. The monomeric analog also facilitated the oxidation of 1-hexene but only in 35% yield. The groups of Garcia-Rio and Nome used cationic **1e'** to catalyze dinitrophenylphosphate monoester hydrolysis and showed a six fold increase above pH6 over the uncatalyzed reaction [218].

## 6 Ionic liquid systems

Ionic liquids (ILs) are liquid organic salts with melting points generally in excess of 100 °C and concomitant low volatility. As salts, they have high conductivities and are electrochemically stable yet may reactions that normally require 'classical' solvents will also work in ILs. The Ogoshi group was the first to demonstrate that ILs could solubilize pillar[5]arenes when **2** was dissolved in 1-hexyl-3-imidazolium bromide and tetrafluoroborate [219]. Dissolution was facilitated by two 1-hexyl-3-imidazolium cations being complexed within the macrocyclic cavity. Complexation was also observed by the groups of Yuan and Huang which noted that a lower critical solution temperature phase change occurred when **1c** was added to 1,3-dimethylimidazolium iodide [220] and other ILs [221]. The same groups took an IL comprised of the cationic polymer 3-cyanomethyl-1-vinylimidazolium and bis(trifuoromethanesulfonyl)imide counterions and added **1o** to form a porous material which selectively absorbed alkyldiols [222].

Many IL components feature an imidazolium group which can also be introduced to pillar[5]arenes through reaction of imidazole with bromine terminated substituents. This was achieved by the Ogoshi group which produced a high molecular weight IL from **1k'** and a range of counterions [223].

## 7 Nanoparticle synthesis and decoration

Functionalized nanoparticles made from gold (AuNPs) have been prepared by using pillar[5]arenes to cap the growing particles and hence control their size. The Huang group first reported the preparation of pillar[5]arene-capped AuNPs using an imidazolium pillar[5]arene derivative, **1l'**, and

AuNPs formed from $HAuCl_4$ in aqueous solution reduced by $NaBH_4$ [224]. The AuNP sizes were controlled by the concentration of pillar[5]arene added. The Yang and Weiss groups used **1p** to prepare AuNPs and proposed that strong carboxylate-gold binding interactions stabilized the AuNPs and that, additionally, growth of the AuNPs during the reduction step was suppressed [225]. Later the Xue group reported that **1o** could be used to control AgNP size [226]. In all these methods, a basic principle is that the pillar[5]arene attaches to the metal surface via one of its functionalized rims so that the resultant NPs become covered in macrocyclic receptors (Figure 22). As classical AuNP syntheses use sodium citrate for this purpose, it is not surprising that carboxylated pillar[5]arenes have been chosen as capping agents.

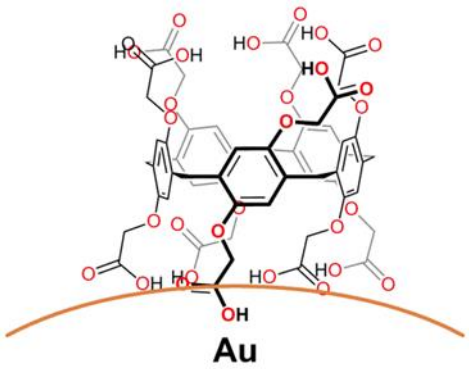



**Figure 22.** Capping AuNPs with **1o**.

Park and colleagues prepared AuNPs 17 nm in diameter from this derivative and suggested that the combination of the gold core and pilar[5]arene receptors on the surface could have enzyme-like activities [227]. The groups of Pérez-Juste and Pastoriza-Santos used **1e'** to expand 20 nm seed AuNPs to 34, 77 or 95 nm functionalized nanoparticles depending on the ratio of pillar[5]arene to AuNP [228]. Carboxylatopillar[5]arenes have been used in composites with graphene oxide by the Yang group which covalently linked them to hydroxyl sites on the graphene surface so that the nanosheets could be dispersed in water [229]. Addition of these nanosheets to solutions of rhodamine and neutral red dyes resulted in fluorescence quenching as the dye molecules were taken up by the surface-attached macrocycles. The Diao group linked asymmetric pillar[5]arene **3d** to a graphene oxide surface in a reaction initiated by hydrazine hydrate before the functionalized nanosheets were added to AuNPs [230]. The composites were adsorbed onto the surface of glassy carbon electrodes and used to detect dopamine. The derivative had previously been shown by the Huang group to form NPs and nanoribbons [231]. The same group also prepared NPs directly from **1o** and a cyanostilbene derivative which combined through the latter's inclusion in the former to

generate near-IR aggregation-induced emissive NPs [232]. Zhou and colleagues attached co-pillar[5]arenes to AuNPs through single butanethiol linkers, **4s'**, and added anthracene with an alkylammonium substituent [233]. The alkyl chains were drawn into the pillar[5]rene cavity allowing the anthracene groups which emerged from the cavity to be photodimerized which in turn crosslinked the AuNPs turning the solution from pink to blue. Heating or use of light over 300 nm reversed the aggregation. Liao and colleagues prepared a poly(*N*-isopropylacrylamide) derivative of monohydroxylated pillar[5]arene (**4t'**), via a thio(carbonothioyl)thiol linker, which was used to treat citrate-capped AuNPs [234]. Following exchange, the pillar[5]arene-capped AuNPs formed a loosely linked material which responded to the presence of n-octylpyrazinium cations by forming micelles and vesicles. Other nanoparticles can be stabilized by pillar[5]arenes. The Yang group prepared CdTe quantum dots functionalized with **1o** and demonstrated aggregation in the presence of *n*-butyl-bridged di(viologens) [235]. The same group decorated $Fe_3O_4$ NPs and used them to pre-concentrate pesticides prior to HPLC analysis [236]. The method was quite successful in reporting accurate concentrations of six pesticides in five wine and five fruit juice samples when spiked at a concentration of 0.5 mg $ml^{-1}$.

**8 Computational investigations**

Many macrocycles with the potential to act as molecular hosts for small guest molecules have been studied by computational methods yet little work of this nature has been undertaken for pillar[5]arenes. Lao and Ku modeled pillar[5]quinone **6a** as a potential anion binding agent yet it is clear that the experimental affinity is low [237]. Peerannawar and Geijii investigated the interactions between **1a** and bis(pyridinium) derivatives to better understand the strong binding of the latter species [238,239]. The Cragg group demonstrated, using molecular mechanics, that the cyclopentamer was the least strained small pillar[*n*]arene cyclooligomer [1]. The alkali metal binding preferences of **1a** were suggested by molecular mechanics and the experimental high affinities for $Na^+$ and $K^+$ were predicted by semi-empirical calculations [240]. More recently, Bhattacharyya used DFT to predict the adsorption spectra of the conformers of **2** and to probe the molecule's reactivity and aromaticity [241] and the Cai group used molecular dynamics to investigate the shuttling of pillar[5]arene rotaxanes [242].

## 9 Practical applications

As with all new compounds it is important to demonstrate that pillar[5]arene derivatives have some practical value. While the potential exists for applications in catalysis, ionic liquid formation and nanoparticle synthesis, it is the molecular recognition capabilities which hold the most promise for the pillar[5]arenes to be usefully exploited and, as a consequence, their practical applications are most likely to be linked to chemical sensors.

### 9.1 Sensors

There is an extensive literature surrounding sensors based on macrocycles. In most cases these involve the detection of small molecule guests for which the macrocyclic host has a high affinity. Unless the macrocycle is naturally electrochemically, colorimetrically or fluorescently active it is usual to attach or incorporate a chemical group which will signal the binding event through some form of response. Assuming that the guest's high affinity for the host arises through complementary fit, electrostatics or other forces then it is important not to perturb these as a consequence of functionalizing the pillar[5]arene. This was noted by the Stoddart group which introduced a single pyrene fluorophore to give **1q** [243]. The parent macrocycle, **1a**, had affinity for linear alkylamines and polyamines which was reflected in the fluorescent response of the group's derivative. Interestingly, the association constants determined for polyamines appear to be related to the length of the shortest spacer between adjacent nitrogen atoms which suggests that the guests are drawn into the host cavity just far enough to bind the first two amine groups [19]. Other sensors employing changes in fluorescence as a signaling mechanism include the Huang group's fluoride sensor, **4u'**, where naphthyl groups were appended by click chemistry and the triazoles formed in the reaction bound fluoride to significantly reduce fluorescence compared to other halides [244]. The same group showed that the highly fluorescent complex which formed between two molecules of **1p** and an alkyl imidazolium functionalized *p*-pentaphenyl guest could be disrupted by di(methyl)viologen resulting in fluorescence quenching [245]. The Xue group used the same principle to detect di(methyl)viologen and cyanide in water using a complex between **1p** and 10-methylacridinium iodide [246]. In the presence of di(methyl)viologen the weakly fluorescent complex dissociated to liberate the strongly fluorescent green dye whereas its cyanide adduct showed a reduction in green fluorescence at 490 nm and an increase in blue fluorescence at 430 nm. The groups of Wei and Zhang prepared a co-pillar[4+1]arene with a single 2-aminobenzothiazole terminus, **4v'**, with strong blue fluorescence at 432 nm in DMSO/$H_2O$ [247]. In the presence of

iron(III) the fluorescence was quenched but was restored in the presence of fluoride. Test strips incorporating the co-pillar[4+1]arene could also be used to detect both ions. The Yu group reported a triple-component supra-amphiphile consisting of a guest composed of a phenylboronic acid group and cationic trimethylamine and **1p** [248]. This ternary complex formed fluorescent nanoparticles in aqueous solution and responded to the presence of diols through fluorescence quenching.

### 9.2 Electrochemical behavior

The use of macrocycles as analyte-specific recognition elements in electrochemical sensors has a long history so it is not surprising that pillar[5]arenes have been used in this manner. Based on computer predictions which suggested a preference for sodium and potassium cations, the Cragg group incorporated **1a** in carbon paste electrodes [249]. Cyclic voltammetry showed that sodium could be detected between 40 and 200 mM, a clinically useful range, while the limit of detection for potassium was around 2 mM, well above the physiologically relevant range. The same group also found that **1n** could be incorporated in a PVC membrane and act as a low pH proton selective electrode [250]. Using a different approach the group attached a dithiol co-pillar[4+1]arene, **4w'**, to gold electrodes and discovered a selectivity for lithium over other alkali metal cations [251], confirming an observation made by the Stoikov group whose pyrrolidine (**1a'**) and morpholine (**1b'**) pillar[5]arene derivatives bound lithium more strongly than sodium, potassium or caesium cations [83]. The Evtugyn group also showed that **2** could be deposited onto a glassy carbon electrode and used to detect silver(I) in the presence of copper(I) [252] and that a potentiometric screen-printed carbon electrode covered with electropolymerized polyaniline and **2** could detect silver(I), iron(III) and copper(II) by different mechanisms [253]. The group also developed a biosensor for pesticides based on acetylcholinesterase which was linked to a glassy carbon electrode by **2** [254] and another, based on an aptomer for cytochrome c linked to glassy carbon by **1o**, which detected cytochrome c [255]. Electrochemical methods have been used by Cheng and Kaifer to probe the stepwise formation of **6a** [256], by the Shen and Deshusses groups to investigate proton flow in membranes incorporating **1n** for methanol fuel cells [257] and by the groups of Liao and He as part of a sensing platform to detect the breast cancer susceptibility gene [258].

## 10 Pillar[5]arenes at the materials interface

Pillar[5]arenes have been shown to function as surface modifiers for sensors so it might be expected that their derivatives have been used more broadly in materials science. Surprisingly there are few

examples where the molecular recognition properties of pillar[5]arenes have been applied to the solid state. The Stoddart group showed that porous mechanized silica nanoparticles could be modified with alkyl pyridinium groups which form a *pseudo*rotaxane with the sodium salt of **1o** [259]. Capture of the carboylatopilar[5]arenes was pH sensitive so that, when the nanoparticles had been filled with rhodamine B or calcein dyes, the macrocycles could be removed to release the nanoparticles' cargos in a controlled manner. The Yang group used a slightly different approach to pillar[5]arene attachment to silica [260]. The surface was first activated with $SiCl_4$ before **2** was added and linked through –O-Si-O- bridges to yield a modified silica surface which absorbed di(methyl)viologen as determined by batch adsorption techniques. The same group also demonstrated acetylcholine-triggered release of cargos from porous silica nanoparticles decorated with similar pillar[5]arene 'nanovalves' [261]. Other analytical methods usually employed for solid state materials can also be valuable tools. The groups of Harris and Sanjayan used powder X-ray diffraction to show that **6a** can be assembled into tubes at the molecular scale which aggregate to form rods on the microscale but only from 1,1,2,2-tetrachloroethane [262].

In recent years there has been a great deal of interest in metal-organic frameworks (MOFs) prepared from rigid organic components and metals with well-understood coordination geometries. The Stoddart group prepared the first example of a pillar[5]arene-incorporating MOF by selectively demethylating one aromatic unit and introducing two benzoic acid groups (**14d**) [263]. The resulting co-pillar[4+1]arene thus combined the pillar[5]arene cavity with a rigid terphenyl dicarboxylic acid spacer. A MOF was prepared, through reaction with $Zn(NO_3)_2{\cdot}6H_2O$ in DMF at 100 °C over 24 h, which had a high affinity for di(alkyl)viologens (Figure 23). Although the MOF was crystalline and transparent, stereochemical inversion prevented the solution of its X-ray structure. To solve this problem the group prepared an analog of the compound as the di(pinacol) ester, **14e**, which could be resolved into its enantiomers by non-chiral HPLC and crystallized [264]. Reaction with $Zn(NO_3)_2{\cdot}6H_2O$ gave the *pS*- and *pR*-MOFs although single crystal studies were again unsuccessful at determining their structures due to disorder which was presumed to be due to the rotational freedom of individual aromatic rings. The Yang group incorporated **1o** into a MOF using the latter's affinity for alkylamines [265]. A MOF incorporating 2-amino-1,4-benzenedicarboxylate and 1,3,5-benzene-tri-*p*-benzoate structural units linked by zinc(II) with a surface covering of amine groups was prepared and loaded with di(methyl)viologen, other quaternarized pyridine species, rhodamine dye the anticancer drug doxorubicin hydrochloride (DOX). The carboyxlatopillar[5]arene was added to cap the MOF nanoparticles and to offer a pH-sensitive release mechanism, much as has been seen elsewhere [259, 260].

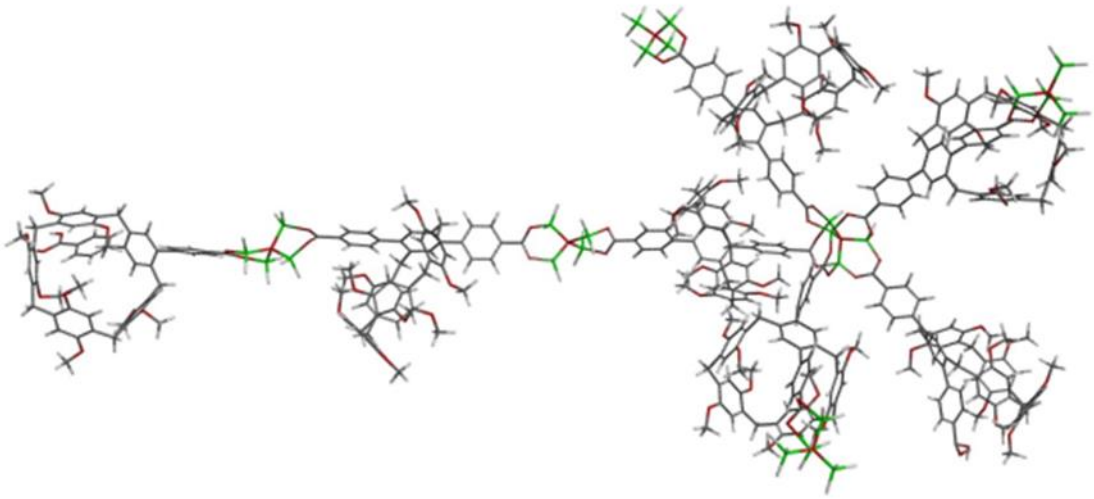


**Figure 23.** Generalized stricture of a metal-organic-framework composed of $Zn_4O$ clusters linking units of **14d** showing linear and three dimensional motifs.

One target for capture and controlled release that has emerged in recent years is $CO_2$ due to its effects, in particular, on acidification of seawater. The Huang group prepared a pillar[5]arene with diethylamine termini, **1m'**, which can readily be protonated [266]. Addition of sodium dodecylsulfate leads to the formation of micelles which can capture $CO_2$ through a process that can be reversed with $N_2$ or the presence of other competitive guests. The group also demonstrated $CO_2$ uptake when the diethylammonium termini of one ring were replaced with a decyloxynaphthalene substituent [267]. Solid state applications also involve the ability to place functionalized pillar[5]arenes in desired locations. The Yamamoto and Kudo groups used **1a** and a derivative with adamantyl ester substituents to spin coat silicon wafers, however, the resulting sensitivities of the surfaces coated with pillar[5]arenes were inferior to surfaces coated with other macrocycles [268].

Perhaps the most important area of materials science to be affected by developments in pillar[5]arene chemistry is that of soft matter, specifically functional gels, liquid crystals and micellar systems. The Huang group has reported a co-pillar[4+1]arene incorporating a single bolaamphiphile, **4x'**, which facilitated the formation of reverse multilamellar giant vesicles 2 to 8 μm in diameter in $CHCl_3$ but a gel in $H_2O$/THF [269]. The vesicles were stable for weeks, but could be disrupted through the addition of $[K{\cdot}18\text{-crown-}6]^+$, and the gel underwent sol-gel transformations in response to temperature changes or the addition of $K^+$. The group also reported that the sodium salt of **1o** was able to influence the lower critical solution temperature behavior of a thermoresponsive polymer

with methylpyridinium and propylamide repeat units [270]. The Yang group introduced a single 3,5-bis(4-ethynlpyridinyl)benzene group through esterification of the corresponding phenol and co-pillar[4+1]arene monoacid to yield a derivative, **4y'**, that could coordinate to bimetallic palladium(II) complexes with a bridging arylene or diarylene group [271]. The resulting hexameric rosettes could assemble into gels with increasing concentrations of linear dinitrile guests. Zhou, Chen and Diao reported that asymmetric pillar[5]arenes with dodecyl and triethylene glycol ester substituents, **3e**, formed vesicles which could be used to house oleic-acid-stabilized magnetic iron oxide NPs to make them magnetically responsive [272]. The Yao group also reported a metallopillar[5]arene system, a metallohydrogel prepared from a flexible copper-chelating bifunctional ligand with terpyridyl and diethylammonium termini which form fibrous gels [273]. Addition of **1p**, into which the diethylammonium group can insert, causes the metamorphosis of gels into micelles. Even simple derivatives, such as **4d**, can undergo temperature dependent sol-gel transformations as demonstrated by the Wei group [274]. Thin transparent sheets of the macrocycle also had a useful acid stability suggesting that it could be used to form acid-resistant coatings. Barberá, Deschenaux, Nierengarten and colleagues prepared a pillar[5]arene with substituents linking cyanobiphenyl termini the macrocycle by click chemistry (**1n'**) [275]. The conformationally mobile cyclopentamer displayed classic liquid crystalline behavior with much greater stability than that of the monomeric units. The Pan group also reported a liquid crystalline pillar[5]arene with diazobenzene group linked to the macrocycle through a triazole unit as in Nierengarten's example (**1o'**) [276]. The compound could be photoaligned and, when sprayed onto quartz, could render the surface opaque through control of *cis*/*trans* isomerism.

The Zhang and Yang groups prepared a co-pillar[4+1]arene with a single oxy-*N*,*N*-dimethyldecan-1-ammonium substituent linked to the macrocycle by a triazole ring, **4z'**, which formed a daisy chain polymer as might be expected [277]. The compound was amenable to electrospinning which allowed nanofibers to be prepared with linear structures which were responsive to pH, counter ion and solvent composition. Inclusion of a di(methylimidazolium)-terminated linear pentaphenyl derivative in **1p** was shown by the Xue group to form fluorescent vesicles or, when silver(I) oxide was present, 'nanosunflowers' [278]. The groups of Fan and Tian made a composite supramolecular polymer comprised of a benzo-21-crown-7 with a butanitrile sidechain and a co-pillar[5]arene with the same group as a substituent (**4a''**) [279]. A range of morphologies could be induced to form from 0D spherical aggregates through to 3D 'ordered glue'.

Control over micelle formation and, more importantly, controlled cargo release has been reported by several groups, from the thermo-responsive fluorescent vesicles of the Zhao group [280], the

asymmetric lysine-terminated pillar[5]arenes of the Sakurai group [281], the magnetic-responsive supramolecular vesicles of Zhou, Chen and Diao [282] or the biocompatible supramolecular micelles and vesicles from the Cao group [283].

## 11 Pillar[5]arenes at the biological interface

As with many macrocycles, the pillar[5]arenes' cavity is suggestive of the hydrophobic active site found at the core of many enzymes. It also has recognition properties essential to a vast array of biochemical processes from antibody-antigen interactions to the targeted transport of ions through cell membranes. Once the fundamental synthetic and molecular recognition aspects of pillar[5]arenes had been explored for a few years, their broader applications at the biological interface started to be investigated. Two areas where pillar[5]arene research has had an impact are in mimicking biological structures and as potential diagnostic or therapeutic agents.

### 11.1 Biomimicry

Natural photosystems, complex membrane-bound protein ensembles responsible for translating sunlight into useful forms of energy, are of interest to those wishing to understand how to prepare simpler systems to harness the free energy from the sun. Such systems typically have antennae to collect the light which absorb over a broad range, a reaction center where solar energy is transformed into electrical energy and an efficient linker between the two. The Wang group reported a supramolecular polymer comprising a boron-dipyrromethene (BODIPY)-bridged pillar[5]arene dimer, which acted as the antenna, and BODIPY derivatives with styryl substituents (**5k**) that could form complexes with the pillar[5]arene derivative [284]. Two systems were prepared which absorbed light of 470 nm or 490 nm and reemitted it at 595 nm or 699 nm, respectively through Förster resonance energy transfer (FRET). In doing so they successfully mimicked the photosynthetic light-harvesting system at greater than 50% efficiency.

Another area of biomimetic interest is in the construction of cell-like structures through the generation of anmphiphilic molecules or complexes which self-assemble into spherical micelles or vesicles. The Zhang group prepared an ethyl-substituted viologen as a terminus to a short polystyrene moiety and a polyethylene glycol-substituted co-pillar[4+1]arene **4b''** which, when combined in water, form vesicles [285]. The vesicles average 440 nm in diameter, with a range of 150 and 1500 nm, and a membrane thickness of about 20 nm. The addition of sodium thiosulfate disrupts the vesicles, leading to structures of 240 nm average diameter. When loaded with the fluorescent dye calcein, thiosulfate liberates the dye from the vesicle. The groups of Pei and Pei

prepared a pillar[5]arene terminating in tryptophan groups (**1p'**) [286]. These self-assembled into vesicles when their free amine groups were quaternarized and polyethers with galactose and pyridinium termini were introduced as guests. The vesicles were observed by electron microscopy and inferred from the Tyndall effect they elicited. The vesicles could be loaded with the anticancer drug DOX, the release of which could be controlled by pH, or with DNA. The DOX-loaded vesicles were able to deliver their payload to hepatoma cells with enhanced effect over direct administration of the drug due to the affinity of the pillar[5]arenes for DNA. The ability to mimic natural structures, such as cells of viral capsids, which release their contents in response to external stimuli has led to increasing interest in pillar[5]arene-related diagnostics and therapeutics.

### 11.2 Diagnostics and therapeutics

Enhanced imaging is in constant demand as clinical assays become more sophisticated and increased precision is required. The Zhao group reported a family of symmetric and asymmetric pillar[5]arene amphiphiles incorporating polyethylene glycols attached by click chemistry, e.g. **1q'** [287]. The macrocycles self-assemble into micelles where, in the case of asymmetric pillar[5]arenes, the glycol termini are arranged on the internal and external surfaces and alkyl substituents interdigitate to form a hydrophobic bilayer of the macrocycles. When micelles form in the presence of rhodamine or fluorescein isothiocyanate the dyes are encapsulated thus allowing the micelles to act as dual imaging agents. The micelles can also be filled with DOX for anticancer drug delivery.

The potential for imaging using $^{129}$Xe NMR was demonstrated by Cohen who trapped xenon within **1p** along with *n*-hexane [288]. The 1:1:1 complex was soluble in water and the presence of the alkane resulted in a 15 ppm shift in the $^{129}$Xe NMR signal compared to the 1:1 xenon : pillar[5]arene complex.

An alternative to micelle formation is to attach the pillar[5]arenes to a substrate. The Li group attached an asymmetric pillar[5]arene **4c''** onto graphene through terminal hydrazine groups on one rim of the macrocycle [289]. Methoxy groups on the opposite rim made the cavity accessible to safranine T, a dye which ordinarily gives red fluorescence but is quenched when bound to the pillar[5]arene. The decorated graphene fragments were taken up by HeLa cells, which remained viable according to an MTT assay, and the dye was released in response to competition from viologen derivatives. The release of dye can also be observed in whole animal studies allowing it to function as a marker for toxic viologens such as paraquat. Micelles comprised of pillar[5]arenes also have the potential to act as delivery vectors for drugs, as can be illustrated by examples from the

work of Jin and Ji [290] and Hu and Wang [291]. The former authors tethered DOX to methyl viologen and formed a *pseudo*rotaxane with **1p** which formed micelles under acidic conditions. Experiments with human hepatocellular carcinoma cells showed a 60% reduction in viability at concentrations of 0.5 mg $ml^{-1}$ where the group's cucurbit[8]uril analog showed only a 15% reduction. The Hu and Wang groups prepared vesicles from the same pillar[5]arene and an alkylated lysine derivative incorporating a disulfide bond. The vesicles were loaded with the anticancer drug mitoxantrone which was released in a controlled manner in the presence of glutathione. Treatment of hepatocellular cancer cells showed a 90% reduction of viability compared with a 74% reduction observed for the drug alone.

The Yu group demonstrated that anionic co-pillar[4+1]arene **4g** formed stable complexes with the 1-ethylphenylpyridine cation [292]. Complexation avoided the quenching that this fluorescent dye undergoes in aqueous media and injection of an acetone solution of the complex from water precipitated nanoparticles in a narrow size range centered on 43 nm. An MTT cytotoxicity assay found that 80% of HeLa cells were viable following incubation with the nanoparticles for 4 or 24 hours.

The biological importance of molecular recognition through sugar-binding sites has been recognized for some time. In particular, the effect of multivalency, through the application of glycoclusters, has been identified as having potential antibacterial applications. The ability to functionalize pillar[5]arenes with substituents terminating in sugar moieties has been exploited by several groups wishing to apply the macrocycles in a biological context. Nierengarten used mannosylated pillar[5]arene **1r'**, in which 10 mannose groups were introduced through click chemistry, to inhibit the hemagglutination of a uropathogenic strain of *Escherichia coli* [293]. Huang demonstrated that the opposite effect could be achieved by pillar[5]arenes decorated on one rim with galactose [294]. The pillar[5]arenes formed nanotubes with galactose substituents on the outer faces which attracted bacteria through their galactose receptors and caused *E. coli* to agglutinate. The nanotubes had low toxicity towards both cancer and normal cell lines with the implication that they could be used in vivo to remove pathogenic bacteria. Taking a similar approach to Nierengarten, the groups of Imberty and Vidal prepared decasubstituted pillar[5]arenes by click chemistry which contained galactose or fucose termini [295]. These were found to bind to lectins from *Pseudomonas aeruginosa* and *Burkholderia ambifaria* and thus inhibit cell adhesion which is essential for the spread of bacterial infections. The Nierengarten group has also experimented with a pillar[5]arene rotaxane with fucose stoppers where the macrocycle was decorated with fucose, galactose or glycine groups having varying affinities for sugar-binding lectins [296, 297]. The same group also

investigated interactions between polyvalent cationic pillar[5]arenes, e.g. **1s'**, and DNA [298]. The cationic dendritic pillar[5]arenes successfully condensed anionic plasmid DNA suggesting that these derivatives may have applications as therapeutic DNA delivery vectors. The Xue group also investigated DNA binding but employed asymmetric pillar[5]arenes with amidoethylamine substituents on one face and alkyl chains of varying length on the other such as **3d** [299]. The pillar[5]arenes self-assembled into nanotubes and captured negatively charged DNA upon acidification.

The Yu group noted the strong affinity that **1p** had for acetylcholine and exploited this to demonstrate that the macrocycle could protect against acetylcholine esterase (AChE) hydrolysis [300, 301]. In one case choline was attached to an alkyl pyrene which then inserted into the pillar[5]arene cavity and in another acetylcholine was used. In the presence of AChE, hydrolysis was slower in the presence of the pillar[5]arene.

Other examples of potential therapeutic applications for pillar[5]arenes include the Tang and Huang group's hollow mesoporous nanoparticles which were covered in DOX and then protected by **1p** [302]. This gave a drug delivery system which released its payload under the low pH conditions found in solid tumors but decomposed into biocompatible water-soluble components for excretion. At the interface between biology and materials, the Li group developed a 'protein switch' where pillar[5]arene **1d** bound to a silica surface covered with adipic acid [303]. Bovine serum albumin could be bound to the surface when the pillar[5]arenes were removed, in response to a drop in pH, and the process could be reversed when the pH rose to 11. Zhang mixed poly(ethylene glycol)-functionalized pillar[5]arene **4z** with a pyridinium-terminated porphyrin derivative which formed micelles [304]. Under the acidic conditions often encountered in tumors the low toxicity micelles released their porphyrin components with enhanced phototoxicity when irradiated.

## 12 Conclusions and Outlook

In the few years since the pillar[5]arenes first appeared as difficult to synthesize and highly insoluble macrocycles with no obvious applications, interest in them has increased dramatically. Alongside improvements in synthetic methods, the chemistry of new derivatives, such as the co-pillar[5]arenes, has been explored with elegant click chemistry providing a significantly important route into new compounds. Alongside synthetic advances have come applications driven by the molecules' inclusion properties. These range from the recognition of small molecules, which can be detected when the pillar[5]arenes are incorporated into sensors, to 'smart' polymers and responsive

surfaces. In the few years since pillar[5]arenes were hailed as “fascinating cyclophanes with a bright future” [1] it is clear that they will continue to amaze chemists for many years to come.

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