Emerging host–guest chemistry of synthetic nanotubes

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Emerging host–guest chemistry of synthetic nanotubes is reviewed, including the preparation of their encapsulation complexes, guest dynamics, exchange and potential applications.

1 Introduction

A novel type of molecular containers is quickly emerging, which are synthetic nanotubes. They have not received nearly as much attention over the last decade as the similarly shaped carbon nanotubes[1] and biologically relevant ion channels.[2]

In supramolecular chemistry, synthetic nanotubes have been overshadowed by much more popular molecular containers such as cavitands, (hemi)carcerands and self-assembling capsules.[3,4] At the same time, they possess unique topology and, as a consequence, different and interesting complexation properties. Synthetic, hollow tubular nanostructures may offer a variety of applications in chemistry, nanotechnology and biology.

In recent years, a number of general reviews appeared describing approaches towards preparation and characterization of organic nanotubes.[2,5] Instead, this feature article focuses on their *emerging host–guest chemistry*. Host–guest chemistry generally studies interactions between a "host" molecule (or receptor) and a target "guest" molecule.[6] Commonly, the host is a larger molecule or aggregate, possessing a sizeable hole or cavity. Synthetic nanotubes offer *long and narrow tubular interiors* for complexation. In this feature article, the preparation of encapsulation complexes with synthetic nanotubes will be discussed, as well as the guest dynamics and exchange. One important feature of nanotubes is the ability to align *multiple* guest species in *one dimension* (1D), which is useful for ion and molecular transport, nanowires and information flow. Other potential applications include using nanotubes as reaction vessels and molecular cylinders for separation and storage.

The research on synthetic nanotubes has been, in many ways, inspired by recent successes with ion channels from one hand and single walled carbon nanotubes (SWNTs) from the other. As valuable supplements, organic synthesis offers robust and well-defined tubular structures, with a wide variety of sizes and shapes. It also helps to control the nanotubes length and makes affordable their functionalization. Through molecular design, it is also possible to prepare stable host–guest complexes. All these features are not easy to achieve for ion channels and SWNTs.

The functions of synthetic ion channels are commonly assessed by the electrophysiological planar-bilayer voltage-clamp techniques and fluorimetric assays on liposomes. Other techniques include heteronuclear (^{23}Na, ^{7}Li, ^{35}Cl) and solid-state NMR spectroscopy. Important for SWNTs are transmission electron microscopy (TEM) and FTIR spectroscopy, which allow to study the location of molecules inside and their

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molecular vibrations, respectively, in the solid state. Solution studies with SWNTs are a great challenge because of their poor solubility. As well-defined organic structures, synthetic nanotubes overcome these difficulties. Their complexes can be prepared and handled by standard organic chemistry protocols and studied by conventional organic spectroscopies.

2 Self-assembling nanotubes

The majority of organic nanotubes known to date are formed by self-assembly.[2] Conceptually, such tubular structures are related to naturally occurring ion channels and pores. They typically include barrel-staves, hoops, rosettes, micellar pores, as well as unimolecular helical macromolecules. Self-assembly offers high synthetic convergence and efficiency, control through subunits design and built-in error correction. How ions are transported through self-assembling organic nanotubes have been documented,[2] but only recently have the first stable encapsulation complexes with organic molecules been published.

2.1 Nanotubes through coordination

Fujita and co-workers found that certain oligo(3,5-pyridine)s self-assemble into tubular structures **1** and **2** through coordination with Pd(II) cations in aqueous solution (Fig. 1).[7] Nanotubes **1** and **2** are 15 and 23 Å long, respectively. The nanotube formation, however, occurs only in the presence of a rod-like template molecule. Disodium 4,4′-biphenylenedicarboxylate **3** and biphenyls (for example, **4** on Fig. 2) were found to be effective templates. These template molecules interact strongly with the pyridine moieties through π–π interactions in water. Both ^{1}H NMR and X-ray crystallographic analysis of the nanotube–template complex shows the template molecule being tightly bound within the interior. Because of this strong binding, the template can only be removed from the nanotube assembly at high temperatures (>70 °C). However, when the template molecules are removed, the nanotube collapses into oligomers.

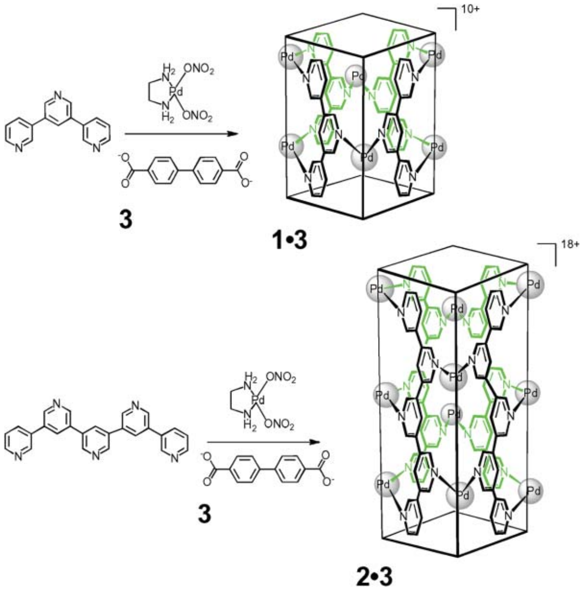


Fig. 1 Nanotubes **1** and **2** self-assemble around template molecules.

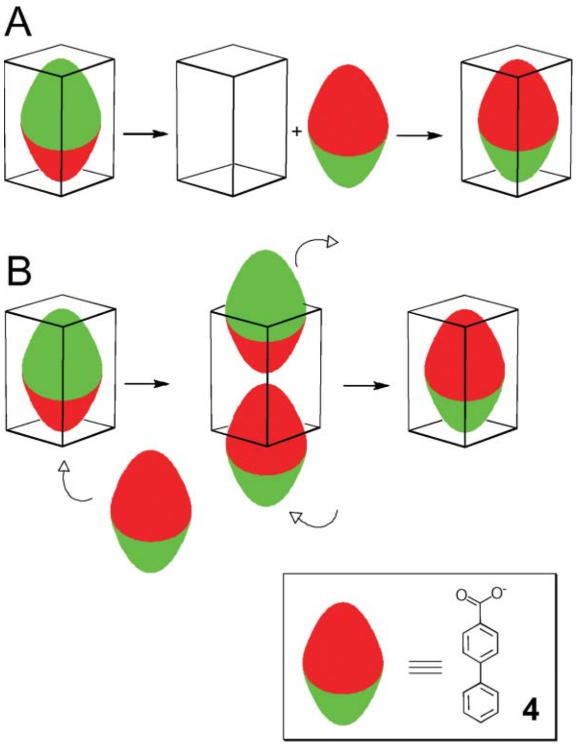


Fig. 2 Guest exchange in nanotubes.

Using unsymmetrical biphenyl derivative **4**, the authors found that the guest spins around its axis but does not flip along its axis inside the assembled nanotube at room temperature.[8] However, the guest can escape from the nanotube at high temperature.

It was also found that the coalescence temperature (T_c) decreased upon addition of an excess amount of guest. Based on this observation, two possible pathways for guest release were suggested. When the concentration of guest is less than the concentration of host, the guest molecules dissociate from the nanotube in an S_N1-type mechanism (Fig. 2(A)). On the other hand, when the concentration of guest is greater than the concentration of the host, the guest is replaced by another guest in an S_N2-type mechanism (Fig. 2(B)). The latter process is lower in energy; hence, the T_c drops significantly at high guest to host ratio.[8]

Finally, guest exchange experiments show preferential binding of anionic guests over neutral guests. This result suggests that, in addition to π–π interactions, electrostatic interactions also contribute to the nanotube–guest complexation.

A modified ligand with two units of the tris(3,5-pyridine) connected through a biphenylene spacer reacted with $enPd(NO_3)_2$ and formed a 35 Å long coordination nanotube **5** (Fig. 3).[9] The process is facilitated with 30 Å long designed templates **6** and **7**. According to X-ray crystallographic analysis, the two anthracene moieties of template **6** strongly interact with four tris(3,5-pyridine) aromatic units *via* π–π stacking and CH–π interactions.

Nanotube complex **5·7** is less stable than **5·6**. Guest **7** can be easily replaced by guest **6** within 1 h at room temperature. This

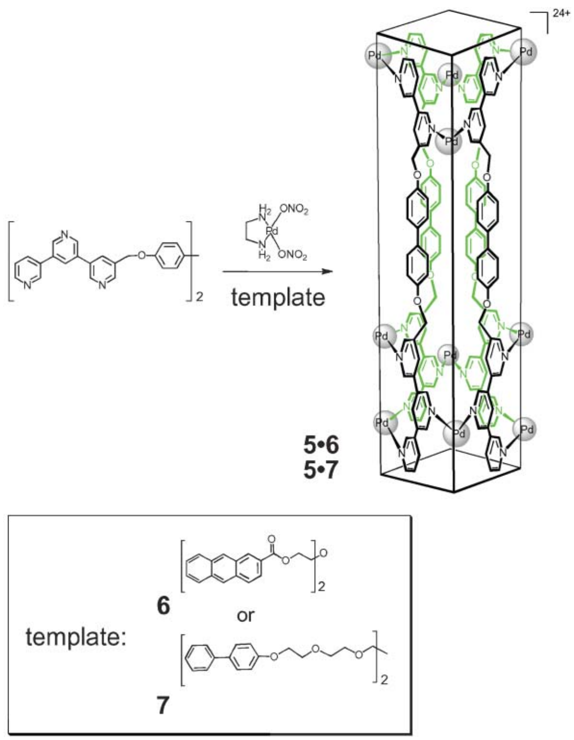


Fig. 3 Preparation of a long coordination nanotube.

is remarkable because the guest exchange requires the movement of the templates by more than 30 Å along the nanotube tunnel. The exchange, most probably, takes place by an S_N2-type mechanism (Fig. 2).

Nanotube **5** is stable even upon removal of template molecule **7**. This is in sharp contrast to shorter nanotubes **1** and **2**, which collapse when the template is removed.[7] Obviously, nanotube **5**, stitched by 24 cooperative Pd(II)–pyridine linkers, is more kinetically stable. Empty tube **5** can be filled again.

2.2 Nanotubes through hydrogen bonding

Stable complexes with fullerene were recently obtained with self-assembling nanotubes **8** (Fig. 4).[10] Infinite helical tubes **8** form in apolar $CHCl_3$ solution and in the solid state upon self-assembly of *N*,*N′*-dimethylnaphthalenediimides **9** with appended carboxylic acids (Fig. 4). The X-ray structure of **8** revealed a helix pitch of 9 Å and three aromatic units per turn. The aromatic units are attached through complementary intermolecular O–H···O hydrogen bonds between the carboxylic acids in such a way that units *i* and *i* + 3 are coplanar with each other. According to CD spectroscopy, tubes **8** exist even at micromolar concentrations.

The inner diameter of nanotubes **8** is ~12.4 Å, while fullerene C_{60} is 10 Å. The uptake of C_{60} from the solid state to $CHCl_3$ was studied by UV-vis and ^{13}C NMR spectroscopy. The fullerene concentration in solution increased up to 16-fold in the presence of nanotubes **8** relative to the solubility of C_{60} in $CHCl_3$. It was determined that approximately four to five dimethylnaphthalenediimide units are necessary to take up one fullerene molecule. In the ^{13}C NMR spectrum, an upfield shift of more than 1.4 ppm was observed for C_{60} upon complexation.

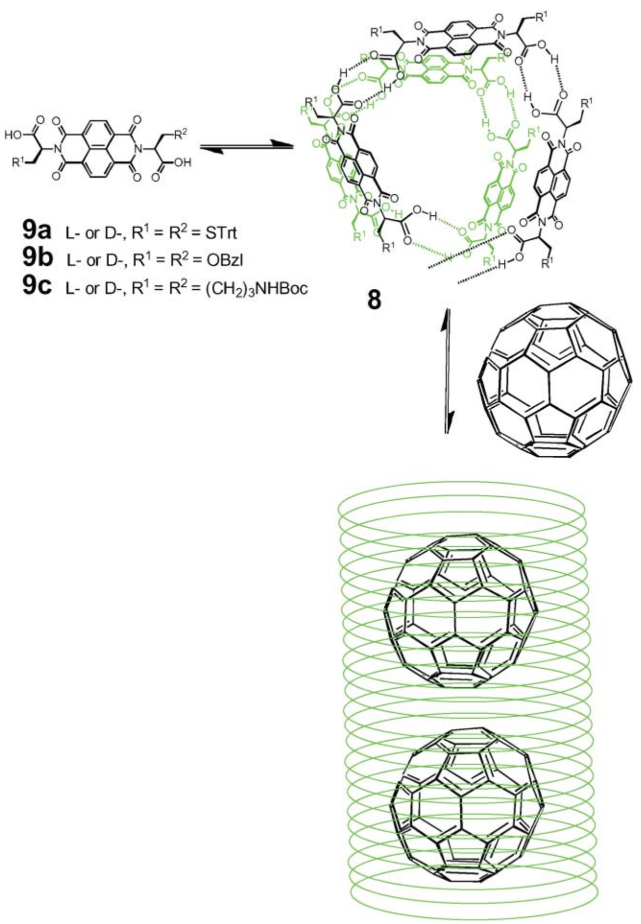


Fig. 4 Self-assembling nanotubes **8** complex fullerene.

Among the advantages of nanotubes **8** compared to other fullerene receptors, are readily available blocks that self-assemble, allowing control over solubility, optoelectronic and other properties through the amino acids synthetic derivatization, *etc*.

Among other examples, solid-state self-assembling nanotubes were recently published that are based on calixarenes.[11] While their stability and host–guest behavior in solution still remains to be investigated, it should be possible to use preorganized calixarene cavities for molecular separation and storage.

Concluding this section, it must be remembered that self-assembling nanotubes are stable only under specific, rather mild conditions. This may not be suitable for some applications. Another important but still unresolved issue is the control over their length.

3 Covalent nanotubes

In contrast to self-assembly, covalent organic synthesis offers much more robust tubular structures of various sizes and shapes. It also helps to control the nanotubes length and makes affordable their functionalization. In the recent years, more cases have been published on encapsulation complexes with covalent nanotubes.

The first covalently built synthetic nanotube **10** was introduced by Harada *et al.* in 1993 (Fig. 5).[12] They used

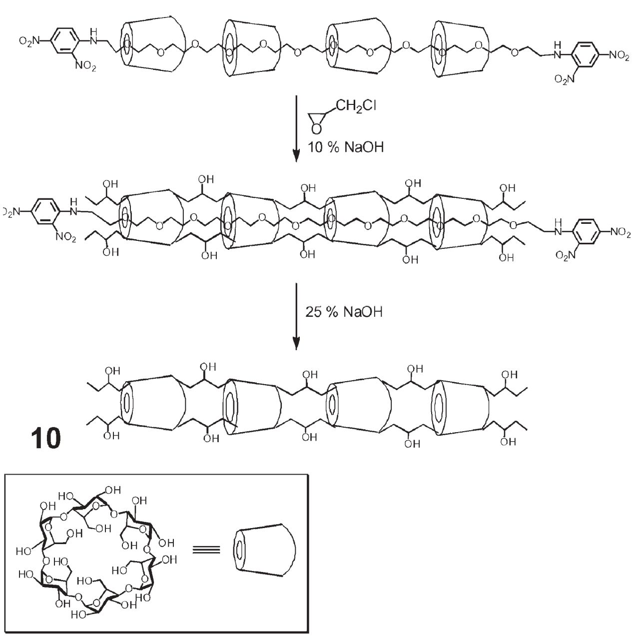


Fig. 5 Preparation of a synthetic nanotube from α-cyclodextrins.

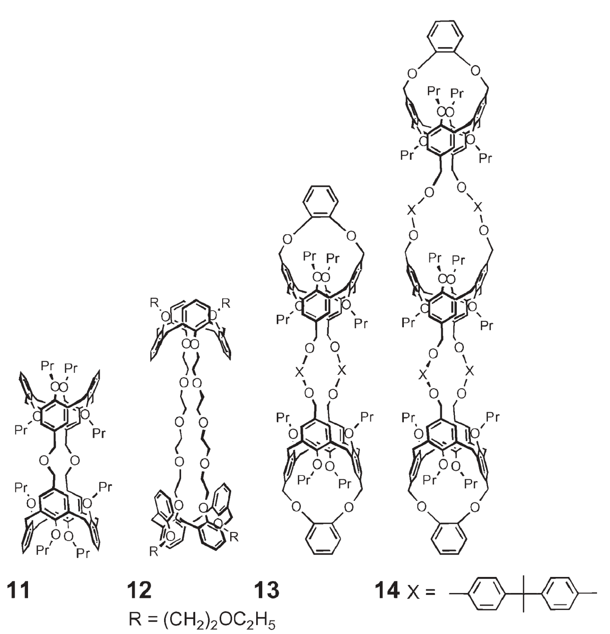


Fig. 6 Early calix[4]arene nanotubes for metal ion tunneling.

threaded α-cyclodextrins as precursors. α-Cyclodextrins are cyclic oligomers of glucose, which contain a cylindrical cavity of approximately 7 Å in depth and 4.5 Å in diameter. They were found to complex poly(ethylene glycol) very efficiently, forming a chain of threaded cyclodextrins complexes called polyrotaxanes. Bulky stoppers such as $NH(C_6H_3)(NO_2)_2$ groups were then introduced at the ends of the chain, keeping cyclodextrin molecules in close contact with each other and preventing their dissociation. Upon treatment with epichlorohydrin in aqueous base, the cyclodextrin hydroxyl groups formed covalent bonds with neighboring units (Fig. 5). Adding a large excess of the base then cleaved the stopper groups and subsequently released nanotube **10** in solution.

Nanotube **10** had a spectacular molecular weight of ~17 kDa and was reported to encapsulate I_3^- ions from a pale yellow solution of potassium iodide with iodine ($KI–I_2$), resulting in a deep-red colored solution. The color change was not observed with monomeric α-cyclodextrins nor with randomly cross-linked α-cyclodextrins, thus, possibly indicating the presence of linearly arranged I_3^- ions inside the nanotube.

The construction of early nanotubes based on calix[4]arenes was reported by Shinkai and co-workers.[13] Taking advantage of the dynamic behavior of metal cation complexes with *1,3-alternate* calix[4]arenes, they connected several such calixarenes to form nanotubes **11–14** (Fig. 6). Conceptually, nanotubes **11–14** would allow small metal cations to tunnel through its π-basic interior.

Complexation experiments with $Ag^+CF_3SO_3^-$ has revealed the presence of a 1 : 1 Ag^+ ion complex with calix[4]tube **12**. Analysis of the variable-temperature ^1H NMR spectrum of the complex suggests that the Ag^+ ion is delocalized between two calixarenes.

The authors proposed that the metal cation oscillates between metal-binding sites in calix[4]tubes in two possible modes: intracalixarene metal-tunneling and intercalixarene metal-hopping (Fig. 7). This dynamic behavior, however, was not observed in the complexation with calix[4]tube **11**. Instead, a mixture of free tube **11** and the 1 : 2 **11**·$(Ag^+)_2$ complex was found in the ^1H NMR spectra. It was suggested that the *p*-substituents used to connect the two calixarenes interfered with the cation–π interactions, thus, suppressing the metal tunneling. In this case, the Ag^+ ions were said to be localized at the edges of the tube, interacting with the calixarene rings and the propyloxy-oxygen groups through cation–π and electrostatic $O\cdots Ag^+$ interactions, respectively.

Similarly, there was no evidence of metal-tunneling in the complexation studies with calix[4]tube **13** (no report of the same experiment with **14**). A 1 : 1 mixture of **13** and $Ag^+CF_3SO_3^-$ yielded three different species: free **13**, **13**·Ag^+ and **13**·$(Ag^+)_2$ in a 1 : 2 : 1 ratio. This result implies that Ag^+ is bound to **13** according to simple probability. The lack of metal-tunneling was suspected to be the result of several structural features of **13**. These include the *p*-substitution of phenyl groups in the calixarene units, the increased distance between two calixarene units relative to other structures, and the non-ionophoric bridges connecting the calixarene units.

While Shinkai's nanotubes were only 2–4 nm long and up to 1500 Da molecular weight, it should be possible to prepare much longer structures utilizing the same calixarene

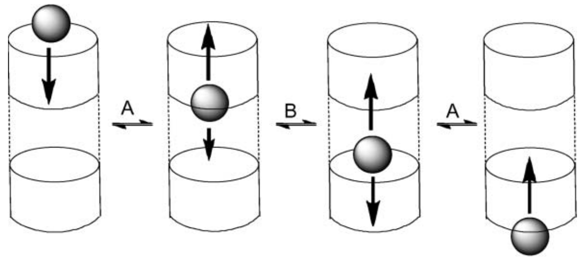


Fig. 7 Intracalixarene metal-tunneling (A) and intercalixarene metal-hopping (B).

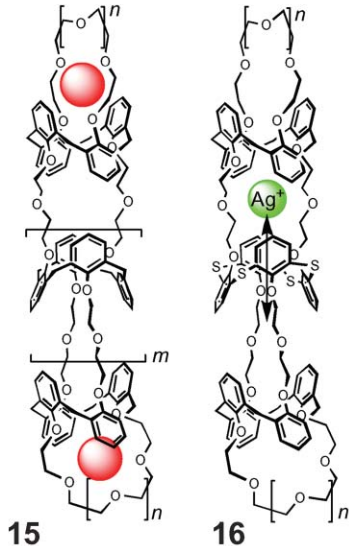
precursors. These studies, initiated in the early 1990s, also triggered quite intense research on calixarene based tubular structures for metal ion tunneling and transport.[14–16]

For example, Kim, Vicens, and co-workers reported similar multiply-connected *1,3-alternate* calix[4]arene tubes **15** (Fig. 8).[15] The terminal calixarene units were capped with crown ethers. In this design however, K^+ or Cs^+ cations were bound in tubes **15** (m = 1,2) at the end-calixcrown "stoppers" and metal shuttling was not observed. The X-ray crystal structure of the biscalix[4]crown **15** (n = 1, m = 1) with K^+ ions revealed that electrostatic interactions between the oxygen donor atoms of the crown ether ring and the metal cation plays a major role for entrapping the metal ion while the cation–π interaction plays a minor role.

The apparent problem with the early-generation calixarene nanotubes was the lack of strong cation–π interactions within the interior. Monitoring trapped cationic guests by conventional spectroscopy in these nanotubes was also difficult.

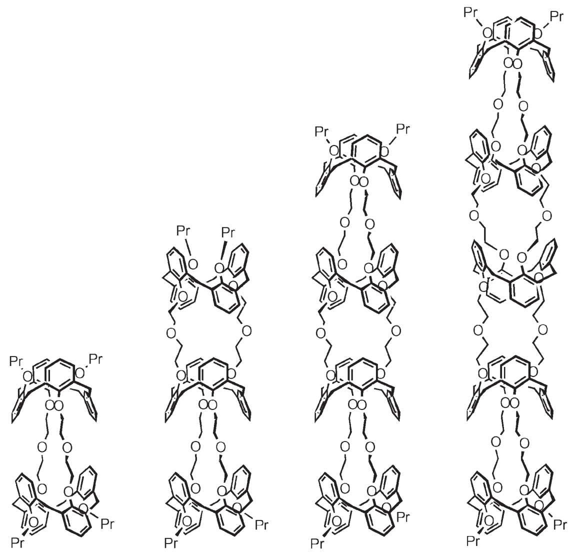
Structural analogs of nanotubes **15** was recently prepared which possesses a calixarene unit with higher affinity to metal cations. Specifically, nanotubes **16** (n = 1,2) contained thiacalix[4]arene in the middle, and the Ag^+ cation was found to be entrapped in this central unit in a 1 : 1 fashion (Fig. 8).[16] In addition to the calixarene aromatic rings, the sulfur atoms provide supplementary coordination sites for transition metal ions. Variable-temperature ^{1}H NMR spectroscopy indeed revealed that the Ag^+ oscillates through the thiacalixarene, and cation–π interactions are important in this case. With some further modifications, it should be possible to synthesize polymeric analogs of tube **16**, inside of which Ag^+ ions can freely shuttle.

Synthetic nanotubes have recently been introduced that possess even more pronounced cation–π features. These are based on reversible chemistry between calix[4]arenes and NO_2/N_2O_4 gases.[17,18] NO_2 is a paramagnetic gas, which exists in equilibrium with its dimer N_2O_4. N_2O_4 disproportionates to ionic $NO^+NO_3^-$ while interacting with simple aromatic derivatives. It was found that tetrakis-O-alkylated calix[4]arenes react with NO_2/N_2O_4 to form very stable ($K_{assoc} \gg 10^6$ M^{-1}), charge-transfer calix–nitrosonium (NO^+) complexes.[19] In these, NO^+ cations are strongly encapsulated within the π-electron rich calix[4]arene tunnel.



15 16

Fig. 8 Calixcrown nanotubes for metal ions.

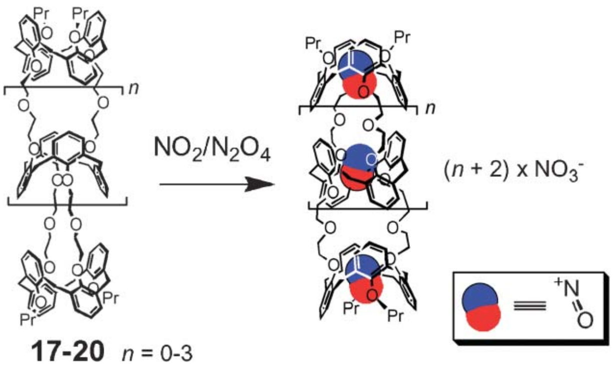


17 18 19 20

Fig. 9 Synthetic nanotubes for NO_x gases.

In nanotubes **17–20**, *1,3-alternate* calix[4]arenes were rigidly connected from both sides of their rims with pairs of diethylene glycol linkers (Fig. 9).[17] In this conformation, two pairs of phenolic oxygens are oriented in opposite directions, providing diverse means to modularly enhance the tube length. The synthesis was based on a straightforward strategy, which incorporated reliable Williamson-type alkylations and provided yields as high as 80%. The nanotubes possess defined inner tunnels of 6 Å in diameter and may entrap multiple NO^+, one per cavity. On the other hand, they can be emptied in a nondestructive manner. With lengths up to 5 nm and with up to five guests entrapped, these nanotubes are the largest nonpolymeric, synthetic molecular containers known to date.[3] For example, tubes **19** and **20** are 35 and 45 Å long and ~2.3 and 2.8 kDa in molecular weight, respectively.

Exposure of tubes **17–20** to NO_2/N_2O_4 in chlorinated solvents results in the rapid encapsulation of NO^+ cations within their interior (Fig. 10). The characteristic purple color



17-20 n = 0-3

Fig. 10 Reaction of nanotubes **17–20** with NO_2/N_2O_4 gases.

implies the charge-transfer and that the NO^+ guests are entrapped inside. The charge-transfer bands are observed at $\lambda_{max} \sim 550$ nm. The guest position inside the nanotubes can be deduced from the conventional FTIR and NMR analysis. Due to the strong binding, the NMR signals of the complexes and free hosts are seen separately. The FTIR data indicate that the NO^+ guests situated in the middle of the tube are bound more strongly than those at the tube ends.[17]

The entrapment process is reversible, and addition of water quickly regenerates the empty tubes. In a competitive complexation process, 18-crown-6 was also successfully used to remove NO^+ from nanotubes **17–20**.[17]

Among possible applications of these synthetic nanotubes are nanowires and also optical sensors for NO_x. Chemical fixation of NO_x is also of great interest. The tubes can be used for molecular storage of active nitrosonium and act as size-shape selective nitrosating reagents.[19]

In the solid state, longer nanotube units **18** pack head-to-tail, in straight rows, resulting in infinitely long cylinders (Fig. 11).[18] The neighboring nanocylinders aligned parallel to each other. In each nanocylinder, molecules **18** are twisted by 90° relative to each other, and the Ar–O–Pr propyl groups effectively occupy the voids between the adjacent molecules. In such an arrangement, the intermolecular distance between two neighboring tubes in the nanocylinder is ~6 Å. The nanocylinders are separated from each other by ~9 Å. This supramolecular order comes with the tube length and is without precedent for conventional, shorter calixarenes. The unique linear nanostructures maximize their intermolecular van der Waals interactions in the crystal through the overall shape simplification. Such a unique arrangement resembles that of bundling of SWNTs.

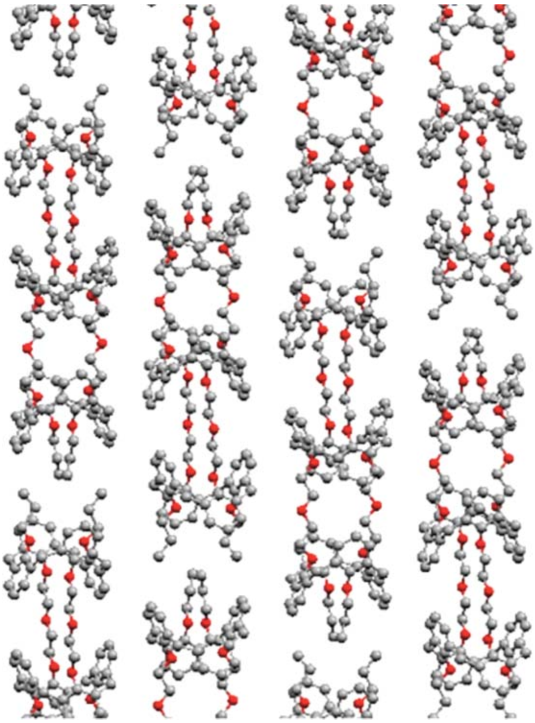


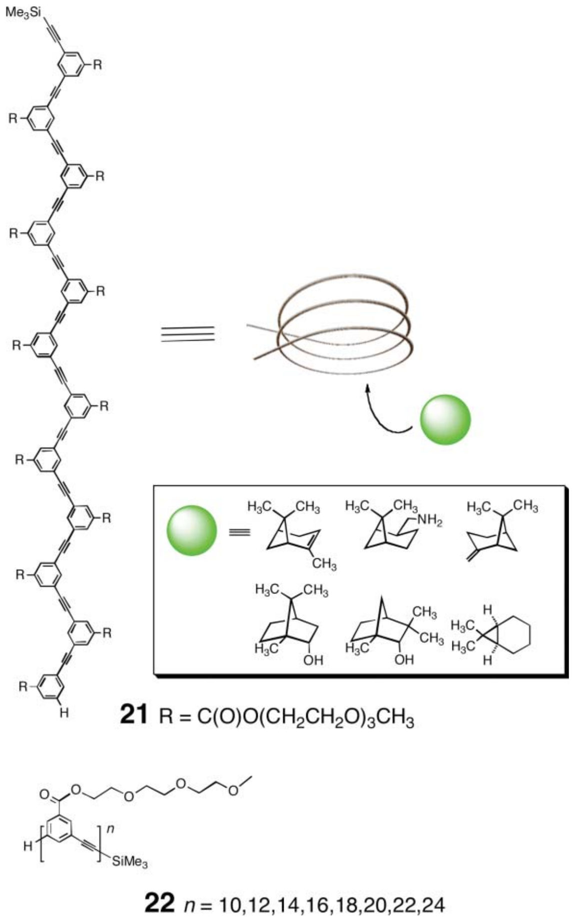
Fig. 11 Solid-state packing of calixarene nanotube **18**.

Generation of biologically important NO gas inside nanotubes **17–20** is also possible.[20] In a one-electron reduction scheme involving the calixarene–NO^+ complexes and simple hydroquinone, NO was smoothly released and free calixarenes were quantitatively regenerated. In detail, when a ~20-fold excess of hydroquinone was added to the $(CDCl_2)_2$ solutions of nitrosonium filled nanotubes **17** and **18**, the color changed from deep-purple to yellow. The ^1H NMR spectrum clearly showed the quantitative regeneration of the empty nanotubes. The NO release could be visually detected and identified by UV spectrophotometry. The use of calixarene nanotubes, capable of storing *multiple* NO^+ species, could potentially lead to interesting NO releasing materials with high gas capacity.

4 Hybrid tubular structures

A supplementary approach to synthetic nanotubes is based on combination of noncovalent forces and covalent bonding. One representative example involves so-called unimolecular foldamers.

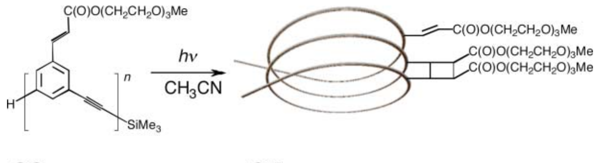
Moore and co-workers demonstrated that amphiphilic *m*-phenylene ethynylene oligomer **21** can fold from a random coil state to a compact helical conformation in polar solvent (Fig. 12).[21] Helix formation is guided by solvophobic interactions leading to exposure of the polar side chains while hiding the lipophilic aromatic backbone. So-called 6-helices



21 $R = C(O)O(CH_2CH_2O)_3CH_3$

22 $n = 10,12,14,16,18,20,22,24$

Fig. 12 Unimolecular, tubular foldamers **21** and **22**.



23 $n \sim 60$ **24**

Fig. 13 Synthesis of crosslinked amphiphilic poly(*m*-phenyleneethynylene) **24**.

that form have six repeat aromatic units per turn. Such folded structure possesses a defined tubular cavity of ~7 Å in internal diameter, which is capable of encapsulating hydrocarbon guests with a 1 : 1 stoichiometry. For example, a number of chiral monoterpenes, such as pinenes, carenes and others, were encapsulated in H_2O–MeCN solutions with binding constants K_{11} ranging from 1.8 to 6.8×10^3 M^{-1} ($-\Delta G^0$ = 4.4–5.2 kcal mol^{-1}).

A variety of shorter and longer oligo(*m*-phenylene ethynylene) helical foldamers **22** was subsequently prepared and their tubular cavities were used for binding of synthetic rodlike guests.[22] It also was presumed that longer guests should exhibit a maximum affinity to longer hosts **22**. The guests may, in principle, be used as templates for the helical chain growth and control its length.

Further exploration of this approach involved covalent post-modifications. Hecht and Kahn utilized Moore's foldamers to generate rigid organic nanotubes, with controlled dimensions and open possibilities for surface functionalization.[23] In this design, folded unimolecular helices were cross-linked through photodimerization. The synthesis starts with helically folded polymers **23** (DP ~60) that are based on amphiphilic poly(*m*-phenyleneethynylene)s bearing cinnamate groups on the periphery (Fig. 13). In polar MeCN, noncovalent forces such as π–π stacking of the aromatic units and solvophobic interactions allow the polymer strand to fold itself into a 6-helical conformation. Such conformation brings reactive cinnamates in proximity of ~3.4 Å for effective cross-linking *via* [2 + 2] photodimerization, producing rigid tubular structures **24** (Fig. 13). The helix–coil transition can be monitored using UV-vis absorption and fluorescence spectroscopies. The degree of cross-linking, however, was estimated to be only about 20–30%.

While no complexation studies with nanotubes **24** have been reported to date, post-covalent modification of noncovalently preorganized tubular structures seems to be a current trend. For example, hydrogen bonding, cyclic peptide nanotubes were recently cross-linked into distinct rod-shaped structures of 80 ± 20 nm long.[24] The bulky neighboring polymeric chains in such hybrid nanotubes somewhat overcome the hydrogen

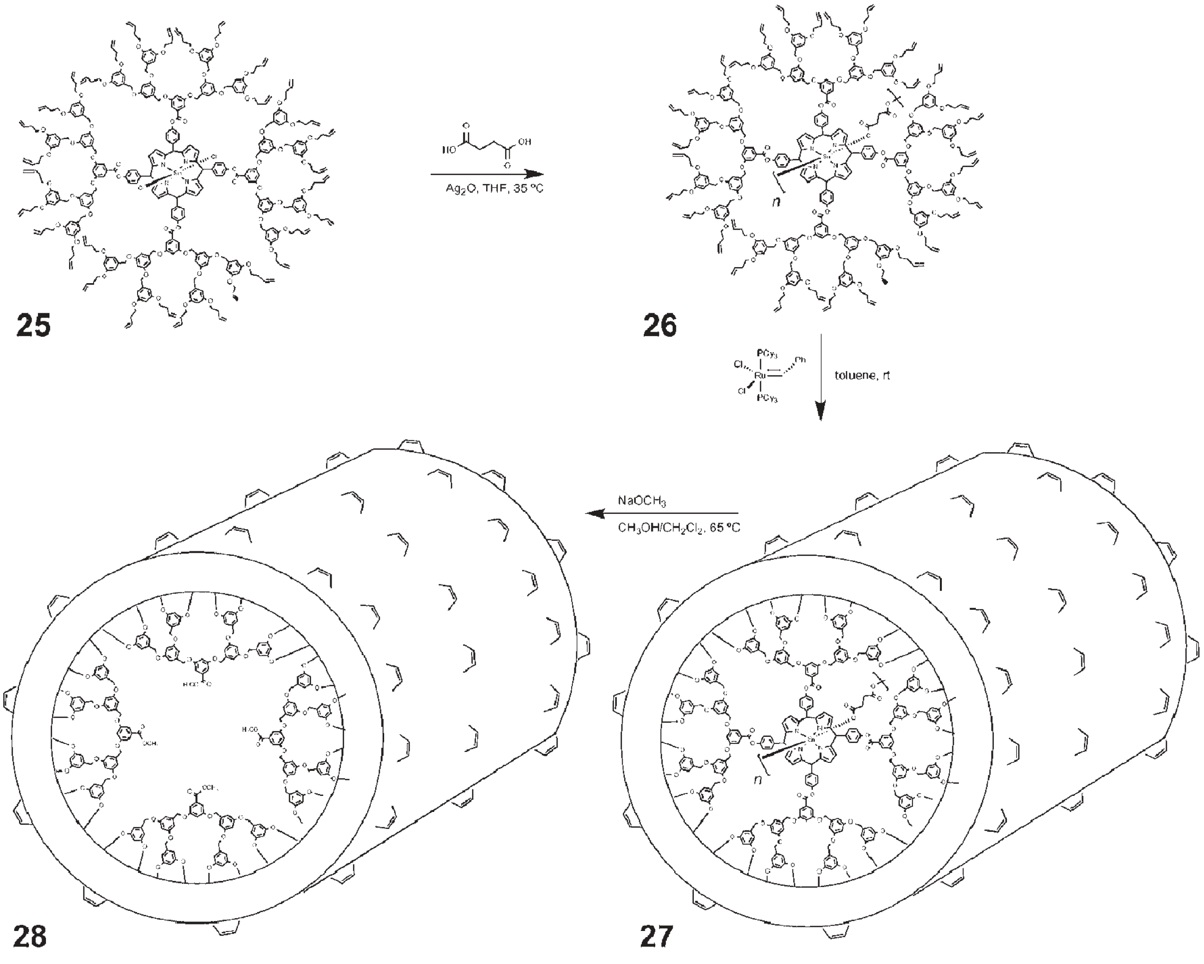


Fig. 14 Synthesis of nanotubes from porphyrin dendrimers.

bonding that hold the cyclic peptide units together. This offers a way to control the tube length.

Somewhat related design was independently introduced by Zimmerman and co-workers. This is based on metal-coordination chemistry followed by covalent cross-linking.[25] Metalloporphyrins and dendrimers were incorporated and a so-called core–shell approach was utilized. In this case, the porphyrin assembly served as a core–shell for molding dendrimers around it (Fig. 14). Porphyrin dendrimers **25** containing multiple alkene end groups were first synthesized then complexed with tin(IV). The metalloporphyrin dendrimers were bridged together with succinic acid as a bidentate ligand, forming stacks of the dendrimers **26**. The peripheral alkene groups were then subjected to ring-closing metathesis to generate the tubular structures **27**.

Finally, in order to form hollow structures, the porphyrins were removed at the dendron–porphyrin linkages by transesterification reaction. After separation through size-exclusion chromatography, a molecular weight for nanotube **28** of ~35 kDa was obtained, which corresponded to a heptamer.

With this strategy, the thickness of the tube wall can be determined by the generation of the dendron, and the inner diameter can be controlled by an appropriately sized core. Functionality of the outer and inner surfaces of the tube can also be introduced by linking desired reactive groups. However, there is no significant control over the length of the tube. Also, more information is required to determine whether the hollow structure collapses or remains open upon removal of the porphyrin core.

Conclusions and outlook

Synthetic nanotubes are now available as promising molecular containers. Their geometrical features and actual nanodimensions clearly place them in a unique position compared to conventional molecular containers.[4] Synthetic nanotubes encapsulate nanosize guests and/or simultaneously entrap multiple guests in a 1D fashion. The guest exchange mechanism is different as well, since nanotubes are open from both ends and do not require dissociation.[26] This leads to the interesting host–guest dynamics and opens the door to such applications as 1D ion mobility for transport and nanowires, inner-space reactions with the subsequent product release, and also high capacity porous materials for molecular separation and storage. This also establishes an internal order that cannot be achieved for conventional encapsulation complexes and even may influence the binding strength.

In contrast to SWNTs and ion channels, conventional organic spectroscopy can be used to study the complexation processes and monitor guest behavior within the interior.

Among the future goals will be the synthesis of even more sophisticated nanotubes. There is a need to achieve higher kinetic and thermodynamic stabilities of the encapsulation complexes. It also remains to be seen how the encapsulated guests interact and/or react with each other and the nanotube walls and whether their properties in confined environment are different from those in the bulk. These and other developments will be investigated in the near future.

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