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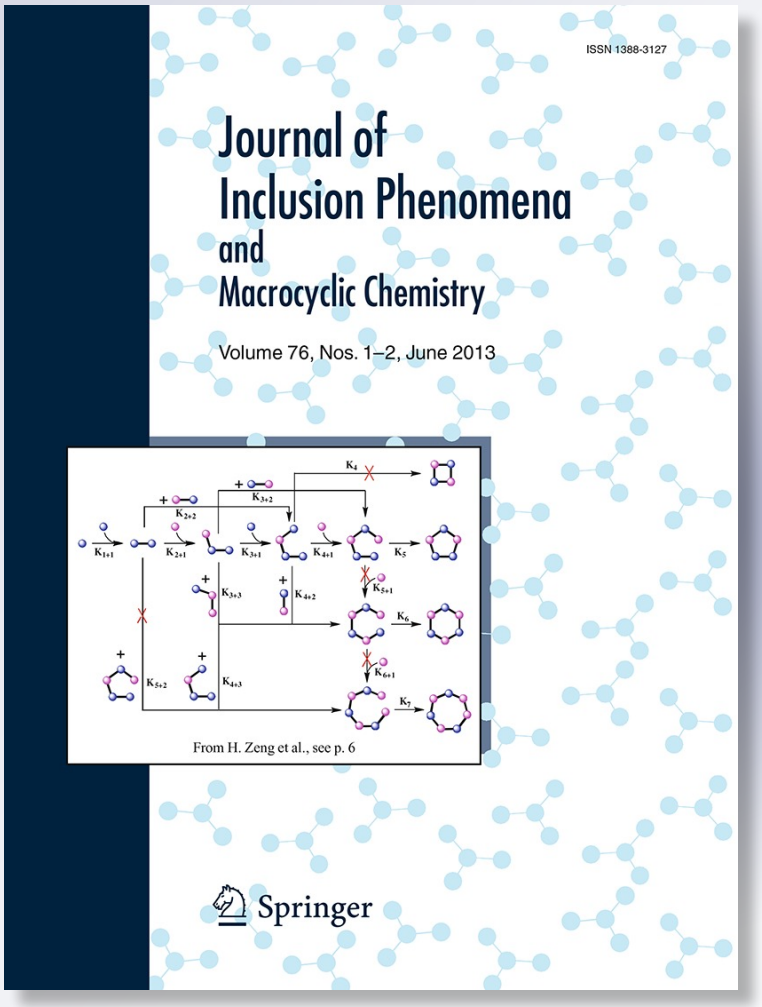


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REVIEW ARTICLE

# Rapid construction of shape-persistent H-bonded macrocycles via one-pot H-bonding-assisted macrocyclization

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**Abstract** The study of macrocycles has crossed many traditional disciplines such as chemistry, physics, biology, medicine and engineering with many research areas concentrating on specific and selective molecular recognition, self-organisation and its already demonstrated and other promising applications. Compared to traditional strategies to synthesize macrocycles with widely ranging structures using such as templated cyclization or dynamic covalent bond formation, one-pot H-bonding-assisted macrocyclization has been shown to provide a simple, fast and cost-efficient method to synthesize shape-persistent H-bonded macrocycles of varying types containing an internal cavity of as large as 2.9 nm in diameter. This review will summarize the recent works on such "greener" syntheses of H-bonded macrocycles that help to create a whole new dimension of research and to offer a new bottom-up strategy for constructing functional architectures and materials.

**Keywords** Hydrogen bonds · Macrocycles · One-pot macrocyclization · Supramolecular chemistry · Foldamers

## Introduction

Since the seminal works on macrocyclic ligands by Pedersen [1, 2], Lehn and co-workers [3, 4], and Cram and co-workers [5, 6], macrocyclic chemistry has prospered over the past four ensuring decades to become one of the most dynamic and promising frontiers of chemical research, offering specific and selective molecular recognition, self-organization and specific functions that cut across many traditional scientific boundaries among chemistry, physics, biology, medicine and engineering. Simultaneous with these innovative progresses are their enormous applications primarily involving host–guest interactions as a focal point. These apparently limitless applications can be illustrated by their current and potential uses in catalysis, sensors, ion selective electrodes, separation technology, molecular electronics/photonics, enzyme mimicry, channel replacement therapy, medical diagnostics, tumor/antivirus therapy, etc.

One salient feature of macrocyclic hosts is a degree of substantial rigidity offered by the preorganized backbone, physically conferring a particular shape onto the host–guest structure and directly contributing to the enhanced binding with the guest over their acyclic analogs. Traditionally, this effect has been termed as "macrocyclic effect" [7]. Forming preorganized macrocyclic structures, however, is entropically disfavoured with the cost typically paid from the reaction enthalpy. Such entropic penalty complicates the reactions and largely accounts for the low yield formation of the desired macrocycles along with an observation of many by-products, including linear/cyclic oligomers of various lengths [8]. To diminish this entropic cost and also to promote the effective macrocyclization, various strategies have been developed that include one-step cyclization [8, 9], templated cyclization [8, 9], intramolecular ring closure, intermolecular coupling [8] and dynamic covalent bond formation [10]. Despite these advances, most of the cyclization reactions are still carried out under conditions of high dilution [8, 11], and critical challenges still remain in the efficient construction of macrocycles with precise control over the ring sizes and the regiospecific functionalization around the periphery.

Within the context of establishing alternative protocols for improved macrocyclization efficiency, conformation-

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directed macrocyclization [12] was conceived that operates in a way akin to templated cyclization. Typically, the templated reaction relies on the auxiliary templates to bring the reactive sites into close proximity (pre-organization) such that they readily undergo efficient "intramolecular" cyclization. The newly disclosed conformation-directed macrocyclization, however, utilizes the biased backbone to purposely predispose the two reactive termini into a predictable geometry, inducing a "template effect" that accelerates the intramolecular macrocyclization reaction while minimizing the "overshooting" by-products. In the majority of reported conformation-assisted macrocyclization reactions, conformational bias is an intrinsic feature of the overall molecular backbone, rather than the repeating units, which results from an interplay of multiple forces including covalent bonds, hydrogen bonding (H-bonding), steric and electronic factors [13].

Elegant examples recently appeared in the literature, describing another type of conformation-assisted one-pot multi-molecular macrocyclization reactions for folding molecules of varying structural diversities. In these cases, the conformational preorganization is induced and stabilized by H-bonding forces [14, 15] to facilitate one-pot multi-component macrocyclization reactions. Every monomer to be incorporated into the macrocyclic backbone is characterized by its unique H-bond-enforced conformational bias that determines and parameterizes the H-bonded backbone curvature. The more monomers incorporated, the more curved the resulting backbone until it reaches a point where the terminal reactive sites are placed within reacting distances, leading to an efficient intramolecular macrocyclization reaction that prevents the chain from overgrowth. Undoubtedly, this strategy is among the newest, arguably the most efficient addition to the macrocyclization toolbox as it requires simple starting material and high yields can be possibly obtained with minimized by-products. This review will summarize the recent works, investigating the intramolecular H-bonding-assisted one-pot macrocyclization that has allowed for the "greener" synthesis of H-bonded macrocycles with different sizes and structures. Special attention is therefore given to the one-pot reactions that are multi-molecular in nature, involve readily avaiable monomers, rely on the intramolecular H-bonds for backbone rigidification and produce macrocycles consisting of more than two repeating units.

## Concept formulation

The pioneering study on H-bond-assisted macrocyclization was performed by Hunter and co-workers in 1994 [14]. In their study, the preferred *cis*-NH arrangement of 2,6-pyridyl (**1**) or the preferred *trans*-NH of *iso*-phthaloyl (**2**) diamide derivatives were used to facilitate and direct the formation of various macrocycles (Fig. 1a). By reacting different diamines (**3** and **5**) with different diacid chlorides, various cyclic dimers, tetramers or higher oligomers could be obtained in high yields of 80–90 % (Fig. 2a). The proposed non-covalent intramolecular H-bonding forces orient and preorganize the uncyclized intermediates such that the reactive sites at the two ends of the reacting partners are brought into close proximity, forming the macrocycles. It was further demonstrated that higher yields of macrocycles were obtained with the stronger H-bonding network. On the other hand, higher yield of catenanes can be obtained when the H-bonding interactions are weaker and this was usually observed in cases when the unfavourable *cis*-NH of *iso*-phthaloyl was stabilized through complexation.

## Aryl amide macrocycles

Although the work by Hunter explored the important concept of using H-bond-directed self-organization as one way for an efficient preparation of macrocycles, it has not led to good synthetic utilities until an inspiring work by the group of Gong in 2004 [15], a year of the renaissance for re-examining the pivotal role of H-bonds in macrocycle synthesis. By using a localized three-center intramolecular H-bonding system (Fig. 2a) to preorganize the in situ generated intermediate acyclic oligomers into a defined crescent-shaped conformation, Gong and co-workers succeeded in producing AB-type hexameric aryl amide macrocycles containing an internal cavity of $\sim 8$ Å and bearing different exterior side chains (**9**) in high isolated yields of 69–82 % by coupling different diacid chlorides (**7**) with 4,6-dimethoxy-1,3-phenylenediamine (**8**) via one-pot H-bonding-directed macrocyclization reactions in about one day under very mild conditions [15]. In the absence of the three-center intramolecular H-bonding network, the yield obtained for the respective cyclic hexamers was found to be extremely low even when the reaction was carried out in the presence of a template or in high dilution conditions due to the backbone flexibility of the conformationly ill-defined intermediate oligomers [16]. Apparently, the preorganized backbone of the acyclic hexamer precursors generated in situ via intramolecular H-bonds explains the highly efficient formation of **9**. A lack of significant strain in the transition state of these acyclic hexamers accounts for the fact that six-residue macrocycles were formed as the predominant products with macrocycles of other sizes remaining scarcely present in solution. This type of acyclic oligomers with H-bond-rigidified backbones has been shown crystallographically to require $\sim 6.5$ building blocks in order to form a helical turn [17].

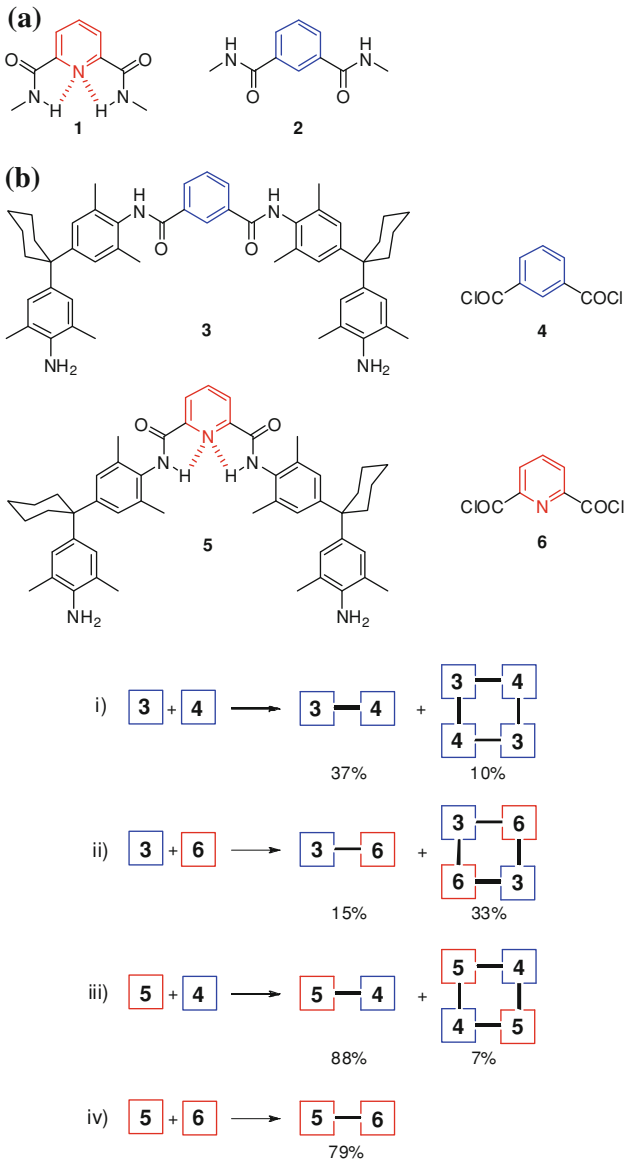


**Fig. 1** **a** Structures of 2,6-pyridyl and *iso*-phthaloyl diamide derivatives showing the preferred *cis*-NH (H-bonds in *red broken lines*) and *trans*-NH H-bonds conformations. **b** Schematic diagram showing the formation reactions of cyclic dimers and tetramers from different diacid chlorides and diamines. (Color figure online)

This suggests acyclic oligomers shorter than hexamer could not cyclize easily due to the rigidity of their backbones while the intramolecular cyclization of other helically folded oligomers with longer backbones cannot proceed readily, either, as a result of substantial amount of ring strains. Only in the case of the acyclic hexamer precursor can a folded backbone of suitable length bring the amino and acid chloride end groups into close proximity, resulting in a rapid intramolecular cyclization with minimized strains.

A detailed mechanistic investigation of the above one-pot macrocyclization reaction was then attempted by the

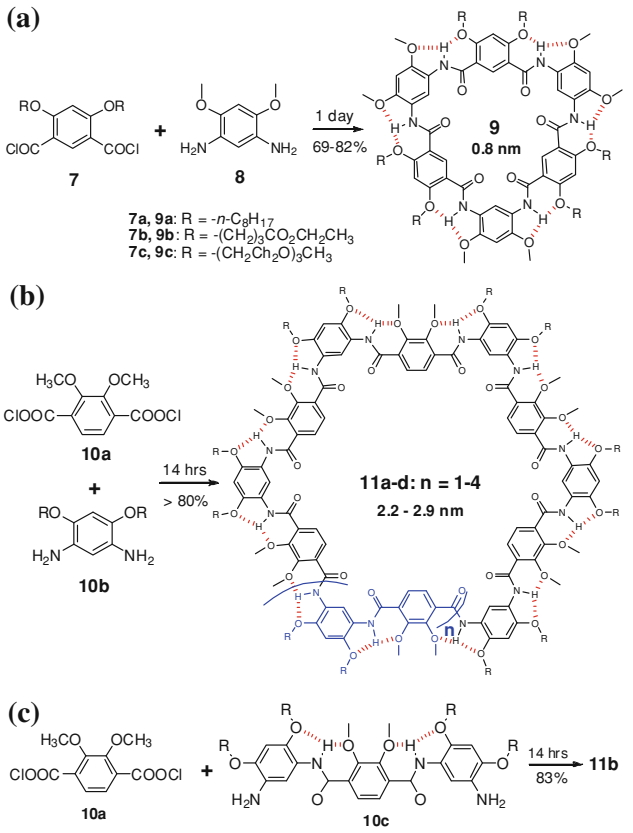


**Fig. 2** Synthesis of AB-type macrocycles composed of **a 3** and **b 7** to **10** repeating AB units using various diacid chlorides and diamines via one-pot macrocyclization. Internal diameter of as large as 2.9 nm in **11d** can be created. H-bonds are shown as *red broken lines*. (Color figure online)

same group who carried out a step-by-step synthesis approach where a series of oligoamides of varying lengths and sets of carefully designed bimolecular reactions were tested. It was found that the reaction is bimolecular in nature and largely kinetically controlled, and that it is the remote steric effect that discourages the formation of oligomers longer than six residues long [18]. The suggested mechanism was further supported by the efficient synthesis of a 16-residue macrocycle with an internal cavity of 2.5 nm across (**11b** with $n = 2$, Fig. 2b) in 81 % yield using monomeric *para*-diacid chloride **10a** and *meta*-diamines **10b** with concurrent productions of 14- and 18-residue macrocycles that enclose a respective lumen size of 2.2 and 2.9 nm. This result is also in line with further computational analyses, revealing 16-residue macrocycle to be the most stable. By alternatively performing the condensation reaction using not only monomeric reactants such as **10a** but also oligomers of suitable lengths such as trimer **10c** as exemplified by 16-residue macrocycle **11b** in Fig. 2c, selective formation of 16- and 18-residue macrocycles was demonstrated to proceed respectively in yields of 83 and 85 %. The same strategy was applied to

make "unfavored" 8-residue macrocycle, structurally similar to **9** (Fig. 2a) but having one more AB unit, by the condensation involving a pentameric diamine and a trimeric diacid chloride in yield of 75 % [19]. Further extension of the strategy using a pentameric diamine as one substrate and variable diacid chlorides from monomer up to pentamer as the other leads to the synthesis of highly strained macrocycles composed of up to 10 residues [20].

Additional tuning in reaction conditions showed that the condensation reactions using only monomeric building blocks as the starting materials are, as expected, temperature-dependant with the yield for the thermodynamically more stable six-residue macrocycle **9** (Fig. 2a) decreasing from 65–80 % at −20 °C to 40 % at 20 °C and that of less stable macrocyclic octamer increasing from trace amount at −20 °C to 23 % at 20 °C [19].

Li and co-workers [21] later assessed the abilities of H-bonding motifs of F···H–N, MeO···H–N and N···H–N to direct one one-pot macrocyclization reactions using the corresponding diamines and diacid chlorides (Fig. 3a). Depending on the types of monomer units used, macrocycles of different structures containing inwardly located F-, O- and N-atoms that lead to intramolecular H-bonding networks for backbone rigidification can be prepared in good to modest yields of up to 45 % in just one hour under mild conditions. Interestingly, by using monomers of different types such as **12a** and **12e**, 2-, 4- and 6-residue macrocycles containing 1:1 ratio of units **12a** and **12e** can be prepared with 4-residue macrocycle produced in the highest yield of 40 % (Fig. 3b).

The reports discussing one-pot macrocyclization reactions by Gong and Li invariably used symmetric bifunctional monomers (e.g., diacid chloride or diamine) to form macrocycles. Asymmetric bifunctional monomers are also suitable candidates for investigating the macrocyclization that however could be more difficult due to the presence of both acid and amine groups, needing chemistry beyond the classical conditions for acid chloride generation. By treating asymmetric monomeric 8-amino-2-quinolinecarboxylic acid (**14a**) with triphenylphosphite ($P(OPh)_3$) in polar solvent and at high temperature, a cyclic trimer (**15a**) and a highly strained cyclic tetramer (**15b**) could be obtained with about 20 % yield each (Fig. 4) [22]. In this case, the H-bonding network similarly preorganizes the acyclic trimer intermediate for the cyclization reaction, and its formation thus can be anticipated. The formation of the highly strained cyclic tetramer in 20 % is somewhat unusual as the helically folded acyclic tetramer intermediate would have extended by about 1.5 turns, making the two reactive ends of the oligomer too far apart for cyclization and in mean time introducing ring strain. Hence, the yield of cyclic tetramer is, as expected, much lower than the cyclic trimer. The X-ray crystal structure of the tetramer indeed confirms

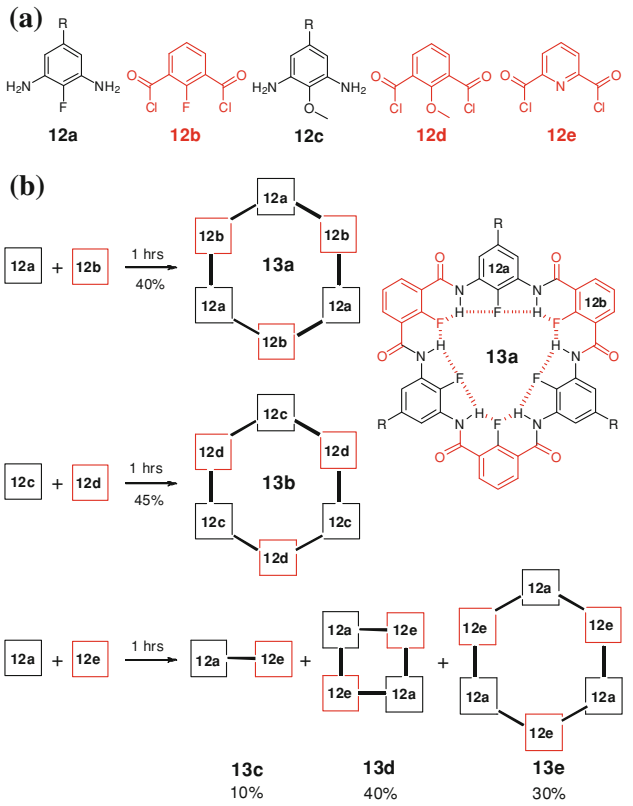


**Fig. 3** Construction of AB-type macrocycles composed of **1**–**3** repeating AB units using various diacid chlorides and diamines via one-pot macrocyclization. The H-bonds are located in the interior as opposed to those in macrocycles in Fig. 2

a strong deviation of its macrocyclic backbone from planarity, leading to a saddle shape (Fig. 4a). This saddle shape results in a loss of two intramolecular H-bonds in the inner rim, and breaks two pairs of conjugations between the aryl and their adjacent amide groups as the dihedral angle between them were found to be near 90°. The loss of the H-bonds and conjugation would lead to some strain in the cyclic tetramer. It was proposed that the use of polar solvent, high temperature and the coordination of $Li^+$ ions help the formation of the unusual cyclic tetramer as only trace amount of it was observed when a milder reaction condition was used. For comparison, 50 % of cyclic trimer was isolated under the same conditions. By using a slightly different 2-quinoline derived monomer **14b**, Jiang and co-workers [23] reported one-pot reaction mediated by dichlorotriphenylphosphorane ($PPh_3Cl_2$) to form another new class of cyclic tetramers (**15c** and **15d**, Fig. 4b).

Recently, our group described a series of methoxybenzene-based helically folded folding molecules with their aromatic backbones enforced by internally placed continuous H-bonding networks [24, 25]. With a further backbone confinement via a covalent macrocyclization, the appropriately sized pentamers can become circularly

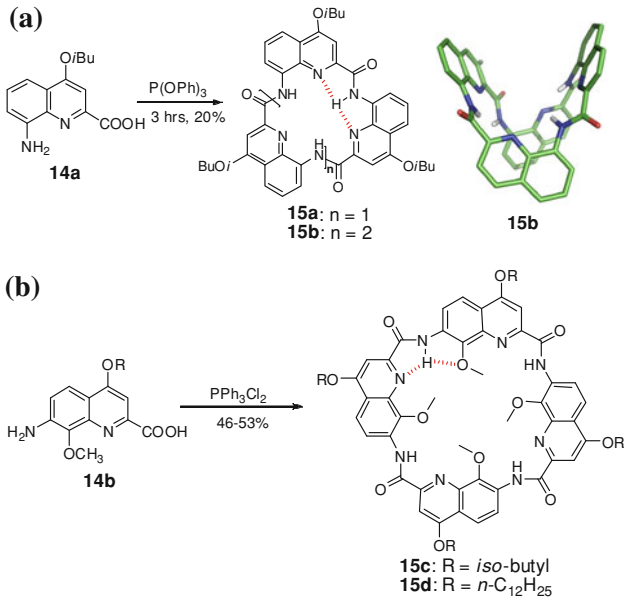


**Fig. 4** **a** $P(OPh)_3$- and **b** $PPh_3Cl_2$-mediated mediated one-pot macrocyclization with the use of asymmetric bifunctional monomers by Huc and Jiang, yielding cyclic trimer **15a**, highly strained tetramer **15b** and tetramers **15a** and **15b**. Also shown in **a** is the side view of the crystal structure of highly strained tetramer **15b**

folded to arrive at a unique pentagon shape (Fig. 5a) [26–29]. This intrinsic peculiarity requiring five identical repeating units to form a macrocycle is quite unusual and bears few precedents among synthetic foldamers. The reported stepwise construction of the macrocycles nevertheless gives a very low overall yield of ~5 % after months' efforts [26]. Therefore, it would be of high interest to see if these H-bonded organic pentagons can be made more efficiently by one-pot macrocyclization in shorter times. After testing many coupling reagents and different conditions, phosphoryl trichloride, $POCl_3$, was finally identified to be a powerful macrocyclization reagent [30]. By using $POCl_3$ as the "coupling" reagent, monomer building blocks (**16**) such as methoxy and other alkoxy based aromatic amino acid can react to form the nearly planar cyclic pentamers as the predominant product (**17**) with a yield of up to 46 % (Fig. 5a–b) at a concentration of 100 mM at room temperature in "ordinary" HPLC grade acetonitrile ($CH_3CN$) containing ≤0.01 % water. Due to the presence of ring strain imposed by interior methoxy methyl groups and H-bonding network, ~6 % of hexamer and trace amount of tetramer and heptamer were observed, an observation that is in agreement with ab initio calculation, showing the relative stability per repeating unit to increase in the order of highly strained tetramer < highly strained heptamer < strained hexamer < pentamer [31]. Although the ethyl group is bulkier than methyl groups, macrocycles containing ethoxy groups in the interior can be similarly prepared in comparable yields of 26–32 %.

By re-investigating the $POCl_3$-mediated one-pot reactions as rigorously as possible by using $CaH_2$ to remove trace amounts of water from reaction solvent $CH_3CN$, an overall yield inclusive of 5-, 6- and 7-residue macrocycles was boosted from 52 % (46 % pentamer **17a** + 6 % hexamer **17g**) in "ordinary" $CH_3CN$ to 78 % in "dry" $CH_3CN$ (40 % pentamer **17a** + 24 % hexamer **17g** + 14 % heptamer **17i**) at room temperature [31], suggesting that even trace amounts of water present in the reaction significantly impede the one-pot macrocyclization reaction possibly by inactivating the acid chloride of intermediate oligomers. A couple of interesting observations deserve mentioning here: (1) one-pot macrocycliztion is temperature-dependant with the highest yield of 91 and 64 % produced at 40 °C respectively for macrocycles containing methyl and ethyl groups in their interior. This indicates the reactivity of either acid chloride or amine groups are intrinsically low and can be much augmented at higher reaction temperatures and (2) the reaction is also concentration-dependant whose dramatic effect on the macrocyclization is somewhat unpredictable.

Mechanistic studies of these reactions by kinetic simulations suggest that the $POCl_3$-mediated macrocyclization that leads to circular pentamers occurs through a chain growth mechanism where the addition of monomer into the growing backbones is faster than other competing bimolecular reactions between two monomers or two higher oligomers (Table 1; Fig. 6) [32] while those macrocyclization reactions producing strained hexamer and highly strained hepatmers (Fig. 5d–f) proceed in a bimolecular fashion involving two higher oligomers (Fig. 6) [31].

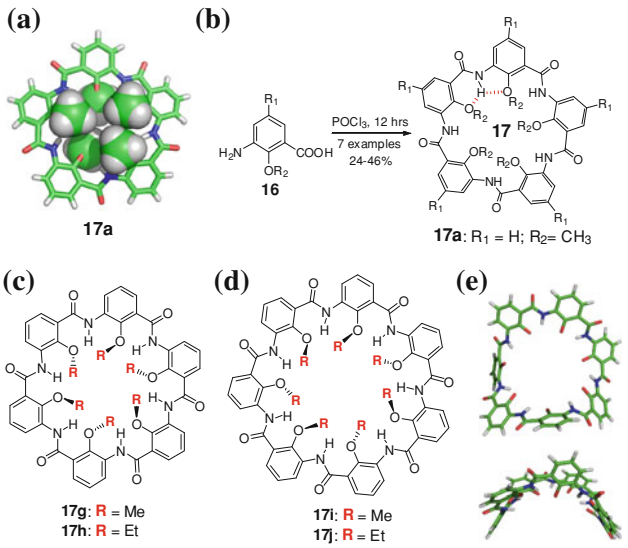


**Fig. 5** **a** crystal structure of pentagon-shaped **17a**. $POCl_3$-mediated one-pot macrocyclization yielding, **b** cyclic planar pentamers that differ by interior and exterior side chains, **c** strained macrocyclic hexamers, and **d** highly strained macrocyclic hexamers. **e** Computationally determined structure for **17j**

Mechanistic studies further show that bimolecular reactions involving only oligomers higher than monomers appear to be facilitated by high temperature at certain ranges more than the chain-growth reactions. As a result, the strained hexamers and heptamers are produced not only in higher yields at 40 °C than at room temperature but also proportionally more in regard with pentamers. It was proposed that acyclic pentamers may not constitute the ideal precursors for producing acyclic hexamers or heptamers via $K_{5+1}$, $K_{5+2}$ and $K_{6+1}$ reactions. Instead, these strained acyclic oligomers are more likely generated by bimolecular reactions of $K_{4+2}$, $K_{3+3}$ and $K_{4+3}$ types(Fig. 6) [31].

The elucidated chain-growth mechanism underlying the $POCl_3$-mediated macrocyclization highlights a possibility to regiospecifically modify the exterior surface of circular aromatic pentamers **17** (Fig. 5b). A continued exploration by our group indeed demonstrated that $POCl_3$ also selectively produces hybrid five-residue macrocycles comprising of mixed building blocks that bear exterior side chains of different types (Fig. 7) [33]. This discovery, for the very first time, enables a regiospecific functionalization around the pentameric periphery achievable via one-pot co-macrocyclization of variable repeating units.

We have also reported for the first time a BOP-mediated one-pot macrocyclization [34], allowing for pyridone-based building block (**18**) to form a new class of cyclic planar pentamer (**19**) that contains an interior cavity of ~2.83 Å convergently aligned with carbonyl O-atoms for efficient cation recognition (Fig. 8) that may promise some interesting applications [35]. The macrocyclization is also likely to proceed by a chain-growth mechanism.

By comparing the reactivities of newly discovered $POCl_3$ and BOP as macrocyclization reagents, it was noted that $POCl_3$ and BOP only allow the circular pentamers to be prepared from their monomeric methoxybenzene and pyridone building blocks, respectively. Further noted is that all the amide coupling conditions ever tried including $POCl_3$ and BOP do not yield any circular fluoropentamer or pyridine tetramer respectively built from monomeric fluorobenzene [36, 37] or pyridine [38–42] motifs. The inference thus made is that every type of monomer building block destined to form the most stable circular pentamer or tetramer may require their own unique "cognate" macrocyclization regents that ought to be "orthogonal" to each other and function well only against their own specific set of "cognate" monomer units. It therefore remains as an outstanding interest to see whether the "cognate" macrocyclization regents for fluorobenzene and pyridine motifs can be identified or not in the future.

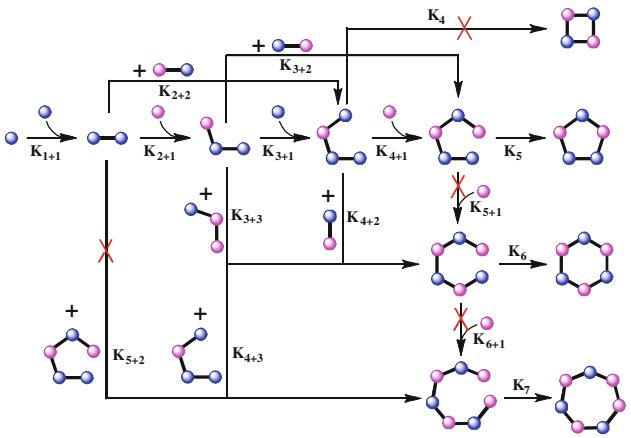


**Fig. 6** Possible reaction pathways accounting for the preferred formation of acyclic oligomeric intermediates and circular aromatic oligomers. The circular tetramers (under-shooting products) are not formed while hexamers and pentamers (over-shooting products) may be possibly formed via different pathways from the reaction. Due to the steric hindrance and a possible difference in the thermodynamic stability of various oligomers, some reactions are faster than the others, which determine the mechanistic pathways underlying the one-pot macrocyclization. The balls in *blue* or *purple* represent the repeating aromatic units. K is reaction rate constant and $K_{n+m} = K_{m+n}$. Reactions of $K_4$, $K_{5+1}$, $K_{5+2}$ and $K_{6+1}$ types are expected to be much slower than other types of reactions shown in the scheme. (Color figure online)

Very recently, we serendipitously found that tetrabutylammonium chloride or bromide salts (TBACl/Br) are capable of achieving efficient folding-promoted chemo- and regio-selective demethylations, eliminating up to two out of five methyl groups situated in similar macrocyclic chemical microenvironments as in **17a** [28, 29]. By combining with the one-pot synthesis of **17a** in 46 % yield, macrocyclic anionic pentamers can now be prepared in just two steps with an overall yield of ~45 % within a day rather than ~5–10 % yields after months' efforts. Efficient

**Table 1** Simulated kinetic rate constants for $POCl_3$-mediated one-pot macrocyclization, yielding cyclic planar pentamers, hexamers and heptamers **17** as shown in Fig. 5 that suggest a chain-growth mechanism

| Simulated kinetic rate constants ($s^{-1}$)[a] | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $K_{1+1}$ | $K_{2+1}$ | $K_{3+1}$ | $K_{4+1}$ | $K_{2+2}$ | $K_{3+2}$ | $K_{4+2}$ | $K_{3+3}$ | $K_{4+3}$ | $K_{5+1}$ | $K_{6+1}$ | $K_{5+2}$ | $K_5$ | $K_6$ | $K_7$ |
| 0.01 | 0.023 | 0.035 | 0.021 | 0.007 | 0.005 | 0.0038 | 0.004 | 0.002 | | ~0.0003 | | | >0 | |

[a] Simulation over 4,000 s that allows the respective yields to reach >99.9 % of the maximally allowed chemical yields

[b] All the simulated chemical yields fall within the experimental ranges and are deviated from experimental averaged values by ≤1 %. Addition of a monomer to either pentamer or hexamer, or a dimer into a pentamer is kinetically very slow as evidenced by their small values in their rate constants ($K_{1+5}$, $K_{1+6}$, and $K_{2+5}$) with respect to others

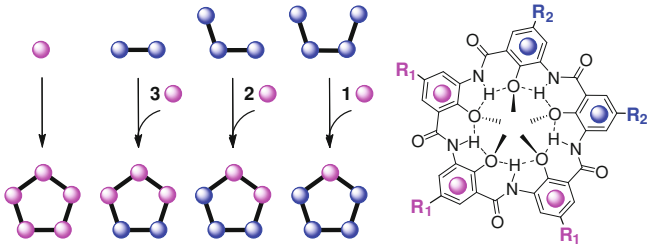


**Fig. 7** $POCl_3$-mediated regiospecific functionalization around the pentameric periphery can be achieved by reacting monomers (*purple circles*) with higher oligomers (*blue circles*) that bear different exterior side chains. The produced cyclic planar pentamers can have *purple* and *blue* repeating units in varying ratios within the same pentamer molecule. (Color figure online)

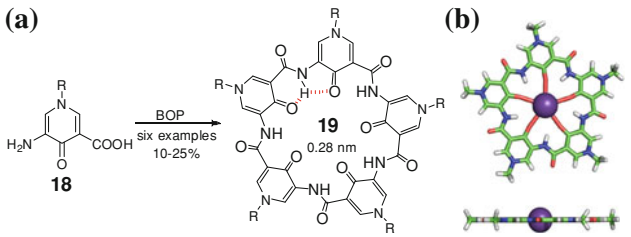


**Fig. 8** **a** BOP-mediated one-pot macrocyclization, leading to a new class of cation-binding macrocycles. **b** Computationally determined structure, revealing an interior cavity of ~2.85 Å in radius and macrocyclic planarity in the complexed

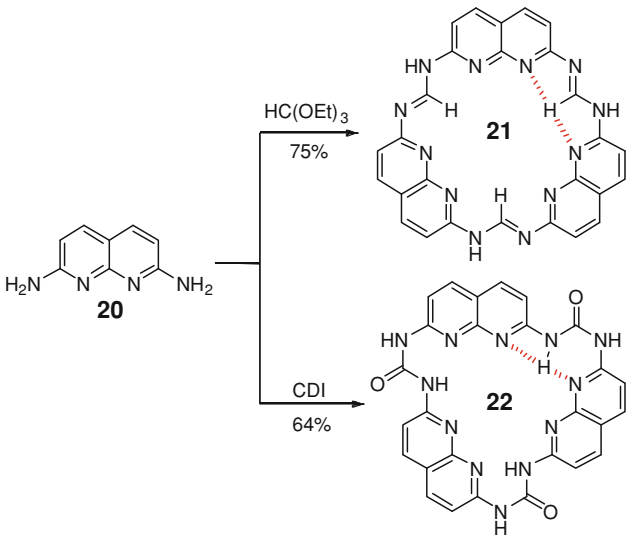


**Fig. 9** One-pot macrocyclization of naphthyridine diamine, forming macrocycles that contain urea (**21**) and formamidine (**22**) linkages

construction of circularly folded anionic pentamers is important given their recently proven abilities to differentiate between $Na^+/K^+$ and $Rb^+/Cs^+$ ions in a highly selective and tight fashion [35].

## Macrocycles containing non-amide linkages

Beside the above aryl amide macrocycles, one-pot intramolecular H-bond-directed macrocyclization reactions have also been demonstrated to work with macrocycles containing formamidine [43], urea [43–45], hydrazide [46] and Schiff-base [47, 48] linkages.

Using naphthyridine-based building blocks (**20**), Cuccia and co-workers [43] synthesized macrocycles containing formamidine- (**21**) and urea-linkages (**22**) in yields of 64 and 75 % by the condensation of building block **20** respectively with triethyl orthoformate and 1,1-carbonyldiimidazole (Fig. 9). The presence of the H-bonding network and good planarity of the synthesized macrocycle **21** was supported by the crystal structure.

Gong and co-workers [44] further studied the likelihood of producing macrocycles containing linkages other than amide bonds by employing the same one-pot macrocyclization approach. While diarylurea **23a** affords macrocyclic tetramers **24** by a bimolecular reaction, the corresponding monoaryl urea **23b** has thus far not been demonstrated to produce **24** possibly due to the highly deactivated nature of the corresponding monomeric diamines that bear two electron-withdrawing ester groups (Fig. 10a). By replacing the electron-withdrawing ester groups with electron-donating alkoxy groups, monoaryl urea **25a** pleasantly allows for the production of tetramer **26a** in high yield of 81 % by using triphosgene at very low temperature of −75 °C (Fig. 10b) [45]. At higher temperatures, complex mixture was produced, a fact pointing to possible instability of diamine **25a** or other in situ generated intermediates at elevated temperature. Surprisingly, four macrocycles of type **26b**, which lack intramolecular H-bonds, can also be prepared in high yields of 76–80 % via one-pot macrocyclization of **25b** (Fig. 10b). The hybrid tetramer consisting of 1:1 ratio of **25a**:**25b** can be similarly prepared in high yields of 77–79 %. The successful preparation of **26b** and the hybrid tetramers indicates that strong intramolecular H-bonds are not necessarily required for preorganizing the oligourea precursors for cyclization. Sufficient preorganization of the macrocyclic tetraurea backbone can be provided by (1) partial rigidification and curvature introduced by the steric

bulkiness of substituents at *meta* position, (2) trans–trans conformational preference adopted by the urea linkage and (3) weak H-bonds formed among aromatic protons and urea O-atoms (Fig. 10b). On the basis of this understanding, a wider design is anticipated that relies on the use of an interplay of multiple weak forces in producing macrocycles of varying structures and cavities.

An ease of controlling the size of the macrocyclic cavities is demonstrated by the same group [46]. In the study, hydrazine linkages were introduced into the macrocycles by using hydrazide derivative **27a** to react with pyridine-based diacid chloride **27b**, giving rise to a cyclic AB-type hexamer **28a** containing an interior cavity of ~1 nm in diameter (Fig. 11a). By simply changing the pyridine-based building block **27b** having two acyl chloride reacting groups at *meta* position into the *para*-position as shown in 2,3-dimethoxyterephthalic acid chloride **27c**, a cyclic AB-type decamer having a lumen size of >2 nm across was obtained in high yields (Fig. 11b). Computational analyses show that both macrocycles **28a** and **28b** adopt a planar geometry.

The Schiff-base macrocycles such as [2 + 2], [3 + 3] and [4 + 4] macrocycles were traditionally synthesized by the condensation of symmetric dialdehydes with diamines mostly in the presence of a template [47]. Introducing the hydroxyl group that participates in forming a strong intramolecular H-bonding network with the imine groups preorganizes the oligomeric intermediates into a crescent conformation and controls the size of the macrocycles [49]. This strategy allows for the synthesis of very large Schiff-base macrocycles (**30** and **32**) by condensing symmetric aldehydes **29a** and **31a** respectively with diamines **29b** and **31b** (Fig. 12) without the use of a template [47]. A direct condensation using monomers **29a** and **31b** produces macrocycle **30** in 2 % yield. Replacement of **31b** with trimer **29b** make one-pot macrocyclization work better and boost the yield to 25 % with a range of other undesired open-chain oligomers and, to a lesser extent, closed cycles. Mysteriously, coupling of **31a** with either **31b** or **29b** works very well and leads to **32** in 78 % yield. Both macrocycles **30** and

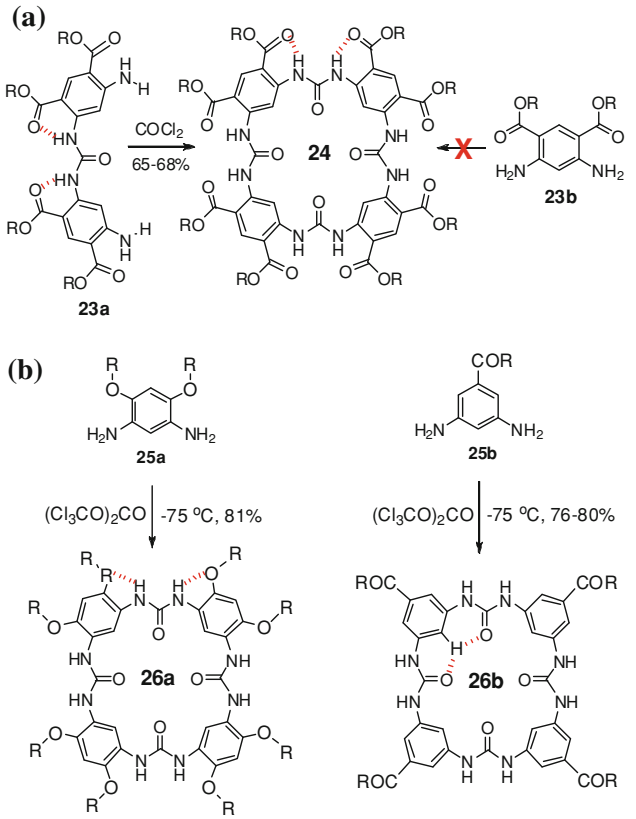


**Fig. 10** One-pot macrocyclizations that produce macrocycles containing urea or hydrazine linkages by Gong and coworkers

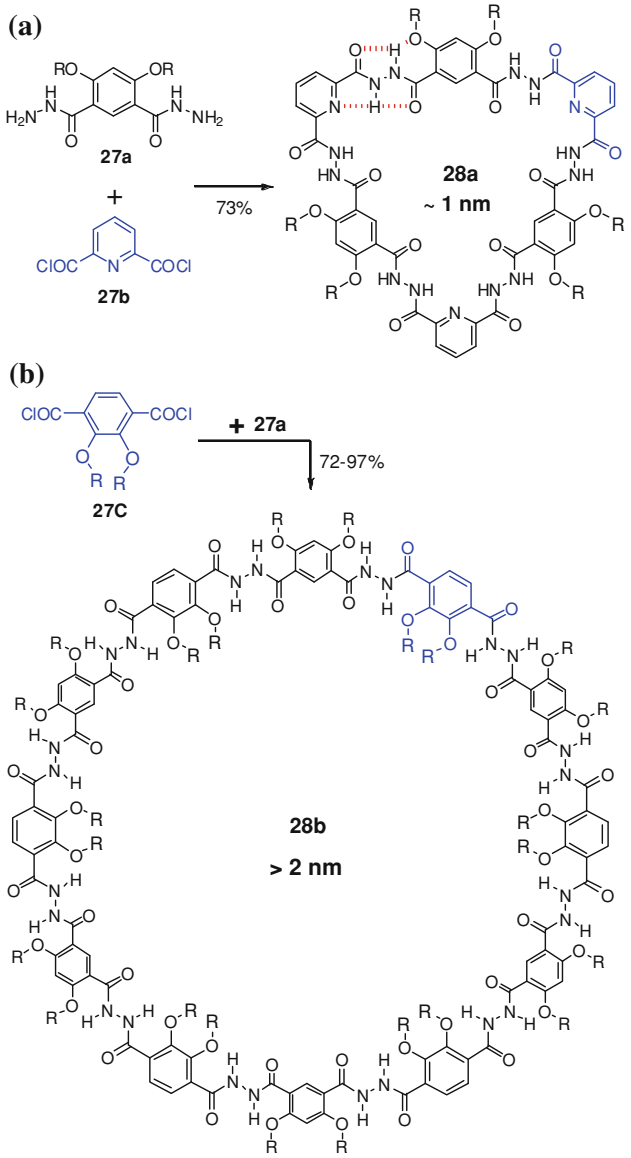


**Fig. 11** Efficient synthesis of macrocycles with easily tunable interior cavities

**32** seem to be very distorted, and metallation of them likely planarizes the macrocyclic backbones. The use of one single asymmetric precursor containing both the formyl and amino groups for the preparation of Schiff-base macrocycles have been studied previously, a few problems still remain: (1) low yield, (2) mixture of products were obtained, and (3) if a template is used, metal ions become difficult to remove. MacLachlan and co-workers [48] overcame these problems by introducing a hydroxyl group into the asymmetric bifunctional precursor (**34a** and **34b**, Fig. 12c). Using sodium dithionite, which does not reduce imines or aldehyde, as the reducing agent and starting from **34a**, fivefold symmetric macrocyclic pentamers with good planarity were obtained in high yields of 70–99 %. An alternative route using a cyclic aminal to protect formyl groups and Pd/C for reduction of nitro group produces the same macrocycles in near quantitative yields.

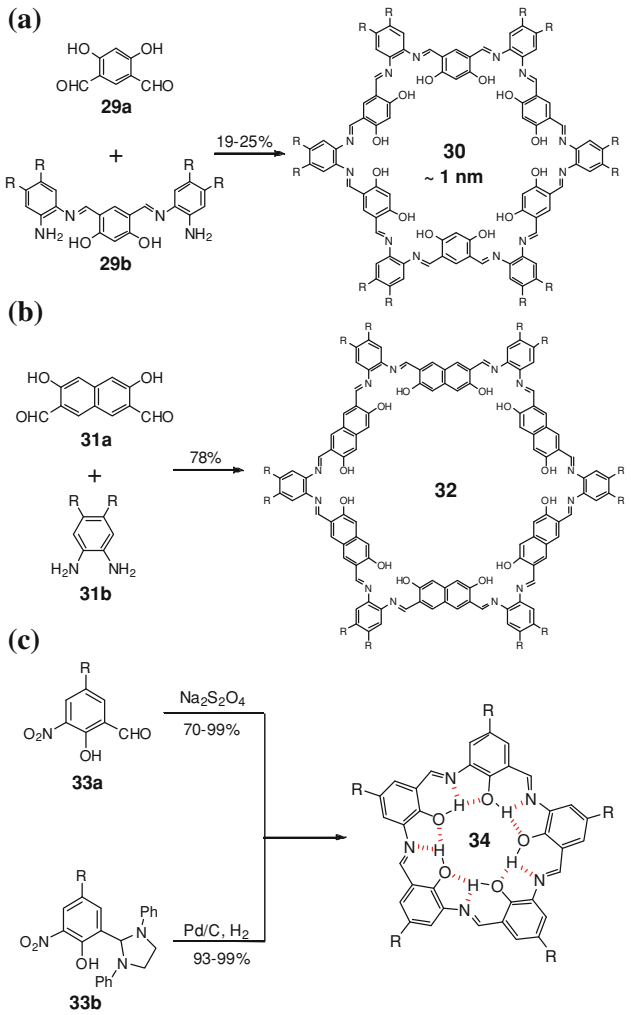


**Fig. 12** Synthesis of Schiff base macrocycles **a 30**, **b 32**, and **c 34** using one-pot macrocyclization reactions aided by hydroxyl groups that form the H-bonds with imine N-atoms and direct the macrocyclization reactions

## Conclusion

The use of intramolecular H-bonds to facilitate the one-pot macrocyclization reaction for the efficient preparation of various macrocycles from folded oligomeric intermediates and precursors have proven to be a very attractive and general approach due to its simplicity, requiring only simple starting materials, and a possibility to obtain high yields at the gram scale with minimized by-products. Since a careful structural design is critical that determines the structures and functions of the macrocycles to be obtained, this field is largely driven by chemists' intuition and imagination. In <8 years since the fabulous report by Gong in 2004 [15], many noteworthy examples illustrating rapid constructions of diverse macrocyclic structures have appeared. The developed one-pot methodologies targeting varying substrates have allowed for their noncollapsible internal cavity to be tuned from ~0.3 to 2.9 nm with systematically modifiable interior and exterior surfaces. And in some cases, the exterior surface modifications can be carried out in a regiospecific fashion by one-pot macrocyclization [33]. These unique features coupled with their now ready availability should greatly facilitate the subsequent functional studies and applications. In fact, a number of functions recently have arisen from these H-bonded macrocycles that includes tight associations with neutral molecules such as fullerenes/coronene [21] and *p*-toluenesulfonic acid [22], selective binding of and inorganic [27, 35, 50] and organic [51] cations in high affinity, stabilization of G-quadruplex structures [52] and formation of highly conducting transmembrane pores [53]. More influential functions extending into chemistry, biology, materials sciences and medicine are likely to result from the existing [54] and quickly emerging macrocycles of varied designs and structures in the future.

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