Self-Assembly via Condensation of Imine or Its N-Substituted Derivatives

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CONSPECTUS: Compared to traditionally used irreversible chemical reactions, dynamic covalent chemistry (DCC) including imine formation represents a more advanced technique in the preparation of molecules with complex structures and topologies, whose syntheses require the formation of many bonds. By allowing the occurrence of error checking and self-correcting, it is likely that the target molecules with high enough thermodynamic stability could be self-assembled in high or even quantitative yield. Two questions are raised herein. First, it becomes a central problem in self-assembly that how to endow a target product with high enough thermodynamic stability so that it can be produced as the major or the only product within the self-assembly library. Second, the reversible nature of dynamic bonds jeopardizes the intrinsic stability of the products. More specifically, the imine bond which represents the mostly used dynamic covalent bond, is apt to undergo hydrolysis in the presence of water. Developing new approaches to make imine more robust and compatible with water is thus of importance. In this account, we summarized the progress made in our group in the field of self-assembly based on C=N bond formation. In organic solvent where an imine bond is relatively robust, we focus on studying how to enhance the thermodynamic stability of a target molecule by introducing intramolecular forces. These noncovalent interactions either release enthalpy to favor the formation of the target molecule or preorganize the building blocks into specific conformations that mimic the product, so that the entropy loss of the formation of the latter is thus suppressed. In water, which often leads to imine hydrolysis, we developed two strategies to enhance the water-compatibility. By taking advantage of multivalency, namely, multiple bonds are often more robust than a single bond, self-assembly via condensation of imine was performed successfully in water, a solvent that is considered as forbidden zone of imine. Another approach is to replace typical imine with its more robust and water compatible derivatives, namely, either hydrazone or oxime, whose C=N bonds are generally less electrophilic compared to typical imine. With the water-compatible dynamic bonds in hand, a variety topological nontrivial molecules such as catenanes and knots was self-assembled successfully in aqueous media, driven by hydrophobic effect. When the self-assembled molecules in the form of rings and cages were designed for supramolecular purposes, water-compatibility endows a merit that allows the hosts to take advantage of hydrophobic effect to drive host−guest recognition, enabling various tasks to be accomplished, such as separation of guest isomers with similar physical properties, recognition of highly hydrated anions, as well as stabilization of guest dimers.
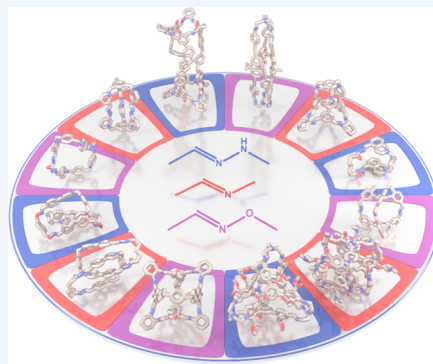
■ KEY REFERENCES

- Chen, Y.; Wu, G.; Chen, B.; Qu, H.; Jiao, T.; Li, Y.; Ge, C.; Zhang, C.; Liang, L.; Zeng, X.; Cao, X.; Wang, Q.; Li, H. Self-Assembly of a Purely Covalent Cage with Homochirality by Imine Formation in Water. *Angew. Chem., Int. Ed.* 2021, 60, 18815−18820.[1] This work shows a water compatible imine cage could be self-assembled by multivalence.

- Wu, Y.; Zhang, C.; Fang, S.; Zhu, D.; Chen, Y.; Ge, C.; Tang, H.; Li, H. A Self-Assembled Cage Binding Iodide Anions over Other Halide Ions in Water. *Angew. Chem., Int. Ed.* 2022, 61, e202209078.[2] Anion recognizing based on hydrazones.

- Li, H.; Zhang, H.; Lammer, A. D.; Wang, M.; Li, X.; Lynch, V. M.; Sessler, J. L. Quantitative self-assembly of a purely organic three-dimensional catenane in water. *Nat. Chem.* 2015, 7, 1003−1008.[3] This is the first purely covalent three-dimensional catenane based on acylhydrazone in water.

- Shen, L.; Cao, N.; Tong, L.; Zhang, X.; Wu, G.; Jiao, T.; Yin, Q.; Zhu, J.; Pan, Y.; Li, H. Dynamic Covalent Self-Assembly Based on Oxime Condensation. *Angew. Chem.,*
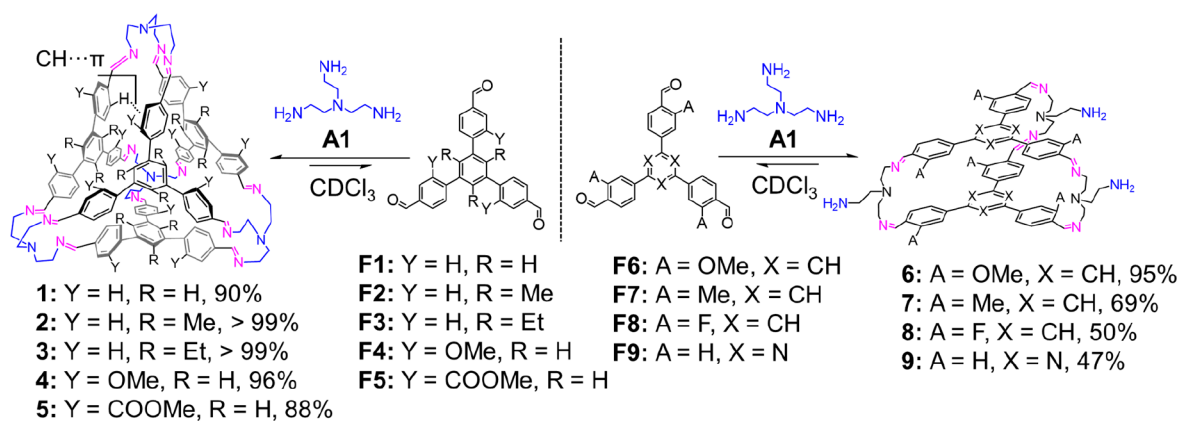
Figure 1. Structural formulas of tetrahedrons **1**−**5**, as well as triangular prisms **6**−**9** self-assembled via condensing a trisamine, namely, tris(2-aminoethyl)amine (TREN, **A1**) and each of the triformyl precursors **F1**−**F9** in CDCl₃.

Int. Ed. **2018**, *57*, 16486−16490.[4] The pioneer uses oximes as building blocks for catenane in water.

INTRODUCTION

Self-assembly relying on dynamic bond represents a more advanced technique, compared to traditional synthesis based on irreversible reactions.[5,6] The reversible nature of dynamic bond allows the occurrence of error-checking and self-correction.[3,7−14] Many external considerations, including solvent, concentration, pH and temperature can influence the equilibrium. The molecules, which represent the most thermodynamically stable state among the self-assembly libraries, could be produced in high or quantitative yield in a one-pot manner, without the need of either tedious stepwise synthetic procedures or byproduct removal.[15] This advantage is of more importance in the syntheses of molecules with complex three-dimensional architectures and topologies, which involve the formation of multiple bonds. With the reversibility in mind, the central question of self-assembly becomes how to sophisticatedly design a target molecule that is thermodynamically favored enough.

Imine is considered one of the most often used dynamic bonds.[16−26] The imines have applications in catalysis, gas storage, molecular separations, drug delivery and so on. Its advantageous features include (i) its two parent precursors namely amine and aldehyde are both synthetically accessible; (ii) imine formation can be accomplished without the need of either sophisticatedly designed catalyst, or anaerobic experimental operation; (iii) self-assembly based on imine formation leads to purely covalent molecules, which helps to rule out the usage of transition metals that might be toxic for biological concerns; (iv) water is the only byproduct that accompanies imine formation, making the latter a rather neat reaction. The last feature, however, is a double-edged sword. According to Le Chatelier's principle, addition of water shifts the equilibrium to the side of imine hydrolysis, making imine bonds rather labile in water. This disadvantage is non-negligible. First, water is the medium of life. The labile nature of imine in water makes the imine-containing molecules unlikely or impossible to realize their biological functions. Second, a molecule that is incompatible with water cannot take advantage of hydrophobic effect as the driving force for host−guest recognition. As a consequence, the functions of a self-assembled molecule designed for supramolecular purposes are jeopardized.

In this review, we summarized the recent research progress achieved in our group, in the field of self-assembly of structurally complex molecules via C=N bond formation. First, we discuss the approaches that are used in our group to enhance the thermodynamic stability of a specific target molecule, by slightly modulating the constitutions of the building blocks. The target products can thus be synthesized precisely, during which the formation of byproducts is efficiently suppressed or avoided. Second, in order to address the drawback that the self-assembled molecules containing imine is not amenable to use in water, two major strategies based on either multivalency or N-substitution, were developed. A number of molecules with complex three-dimensioned structures containing either imine bonds, or the N-substituted derivatives namely either hydrazone or oxime, were self-assembled in aqueous media, where hydrophobic effect is present for host−guest complexation. These supramolecular events enable a variety of tasks to be accomplished, including resolving isomers including enantiomers, determining the ee values of chiral guests, stabilizing guest dimers or complexes that might be not stable in bulk solution.

CHARACTERIZATION OF THE SELF-ASSEMBLED PRODUCTS

The self-assembled target products are fully characterized by NMR spectroscopy and Mass spectrometry in solution, as well as X-ray crystallography in solid state. ¹H NMR titration, UV−vis titration or isothermal titration calorimetry (ITC) experiments are used to quantify the host−guest binding affinity.

Precise Construction of a Target Molecule via Imine Condensation in Organic Media

As mentioned before, thanks to the reversible nature of imine, the most thermodynamically favored products could be self-assembled in high or quantitative yield without generating other unwanted byproducts in substantial amount. How to sophisticatedly design a target molecule with an enough low Gibbs free energy thus becomes one of the major focuses in this field. Unfortunately, self-assembly of a molecule with a well-defined structure selectively among a library of many possible products is an entropically disfavored process. The entropy loss is even more remarkable in the case that the building blocks of self-assembly are flexible. This is indeed the case for imine-based system, in whose conformation the precursors are often rather less preorganized.

One of the commonly used approaches to favor a specific product is to introduce intramolecular forces. These non-covalent interactions either release enough enthalpy that compensates entropy loss or preorganize the precursors into
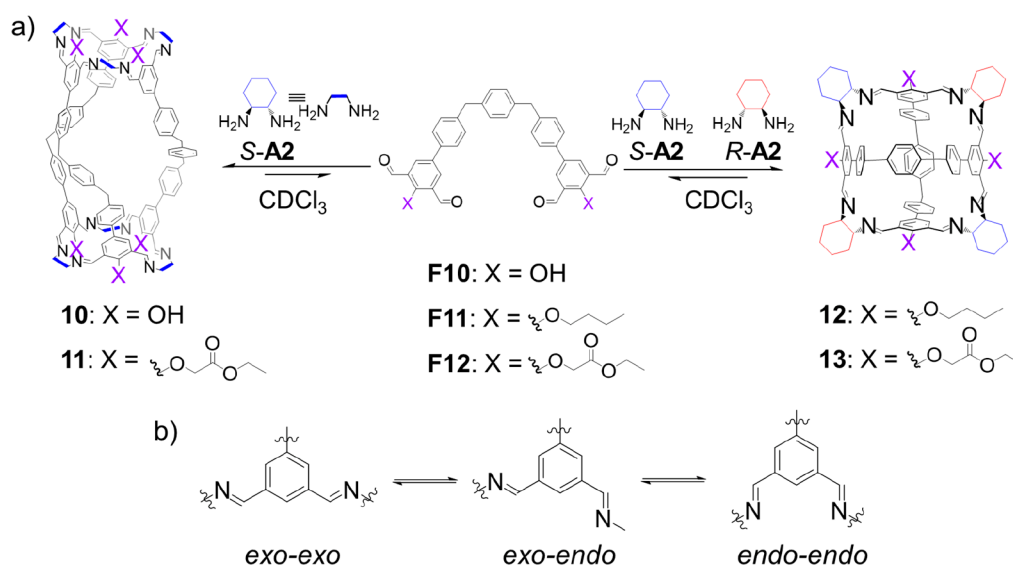
Figure 2. (a) Left: the structural formulas of two chiral capsule products (**10** or **11**) by condensing a chiral bisamine namely *tran*-diaminocyclohexane (*S*-**A2**) and a tetraformyl precursor either **F10** or **F12** respectively. Right: the structural formulas of two achiral cages (**12** or **13**), by condensing racemic *trans*-diaminocyclohexane (*S*-**A2** and *R*-**A2**) and a tetraformyl precursor either **F11** or **F12**, respectively. b) The possible conformations of an imine adduct of isophthalaldehyde.

some conformations that mimic the corresponding products; the entropy loss of whose formation is thus reduced. These noncovalent forces include van der Waals interactions (0−5 kJ/mol),[27] hydrogen bonding interactions (10−35 kJ/mol),[28,29] various π electron interactions (1−50 kJ/mol),[30] as well as steric hindrance that favors some specific conformations. Hydrophobic effect present in water also plays an important role in determining the self-assembly outcomes.[31] It will be covered in the later sections where we discuss how to stabilize C=N bonds in water.

One of the evidence convincing that intramolecular forces play important roles in self-assembly is that, when a trisformyl precursor including **F1**−**F9** (Figure 1) and a trisamine namely tris(2-aminoethyl)amine (TREN, **A1**) were combined, slightly switching the positions of the substituents in the former led to dramatic variation of the self-assembly products.[1,32,33] Combining each of **F1**−**F5** and **A1** in a 1:1 ratio produced the corresponding tetrahedral cages **1**−**5** in high or even quantitative yield. One of the major driving forces favoring the formation of these tetrahedrons is the CH···π interactions between each of the 12 phenyl protons in the ortho position with respect to each imine bond, and the corresponding adjacent phenyl π moiety. The importance of CH···π interactions was convinced by theoretical calculations, as well as a few control experiments. First, combining each of **F6**−**F8** and **A1** did not produce the putative tetrahedrons, even though the geometries of all these three precursors are not different from **F1**−**F5**. In contrast, a series of triangular prisms namely **6**−**8** were self-assembled. This is because in the case of **F6**−**F8**, one of the two ortho protons in each phenyl unit bearing imine is replaced with a substituent, namely OMe, Me or F, respectively. The other ortho proton in each phenyl of these three precursors, on the other hand, form a CH···N hydrogen bond with the corresponding imine nitrogen atom, not available for CH···π interaction either. The driving force favoring the formation of tetrahedron was thus jeopardized in the case of **F6**−**F8**. Second, the occurrence of CH···π interactions requires the trisformyl precursor to adopt a twisted conformation, so that the ortho protons are able to locate close enough to the corresponding π

moieties. This proposition was supported by the higher yields (>99%) of **2** and **3**, compared to that of **1** (90%), given that the former two cages have more twisted precursors. The trisformyl precursor **F9** contains a triazine unit, affording a planar conformation that disfavors the occurrence of CH···π interactions. As a consequence, combining **F9** and **A1** yielded a prism product **9**, instead of the putative tetrahedral product, even although both of its ortho protons are available. The driving forces to favor the formation of triangular prisms **6**−**9** include the intramolecular π···π interactions between the two triangular platforms, which are clearly observed in the solid-state structure of **9** obtained by crystallography.

More recently, we demonstrated that the self-assembly outcomes of condensing a series of ostensibly analogous tetraformyl precursors **F10**−**F12** (Figure 2) and trans-diaminocyclohexane (**A2**) underwent sharp variation by modulating the substituents in the former precursors.[34] These substituents are able to dictate the conformations of the formyl/imine bonds on both sides, by forming hydrogen bonds with different modes. For example, in the case of **F10** bearing two OH substituents, the two aldehyde/imine units were preorganized in an exo−endo conformation. This conformation mimics a chiral capsule product **10** composed of three equivalents of **F10** and six equivalents of enantiomerically pure trans-diaminocyclohexane, which was thus self-assembled as the predominant product. When the substituent was switched to O−*n*-Bu unit containing no acidic proton, the formyl/imine bonds in the **F11** residues were preorganized in an exo−exo conformation. This conformation is similar as that in an achiral cage **12**, composed of two equivalents of **F11** and four equivalents of racemic trans-diaminocyclohexane.

The latter product was thus self-assembled as the only observable products. In the case of **F12** bearing two OCH₂COOC₂H₅ unit whose protons in ester methylene unit have modest acidity, both exo−endo and exo−exo conformations are thermodynamically stable conformations. The products were thus determined by the chirality of trans-diaminocyclohexane. That is, the enantiomerically pure trans-diaminocyclohexane yielded the [3 + 6] chiral capsule **11**, while
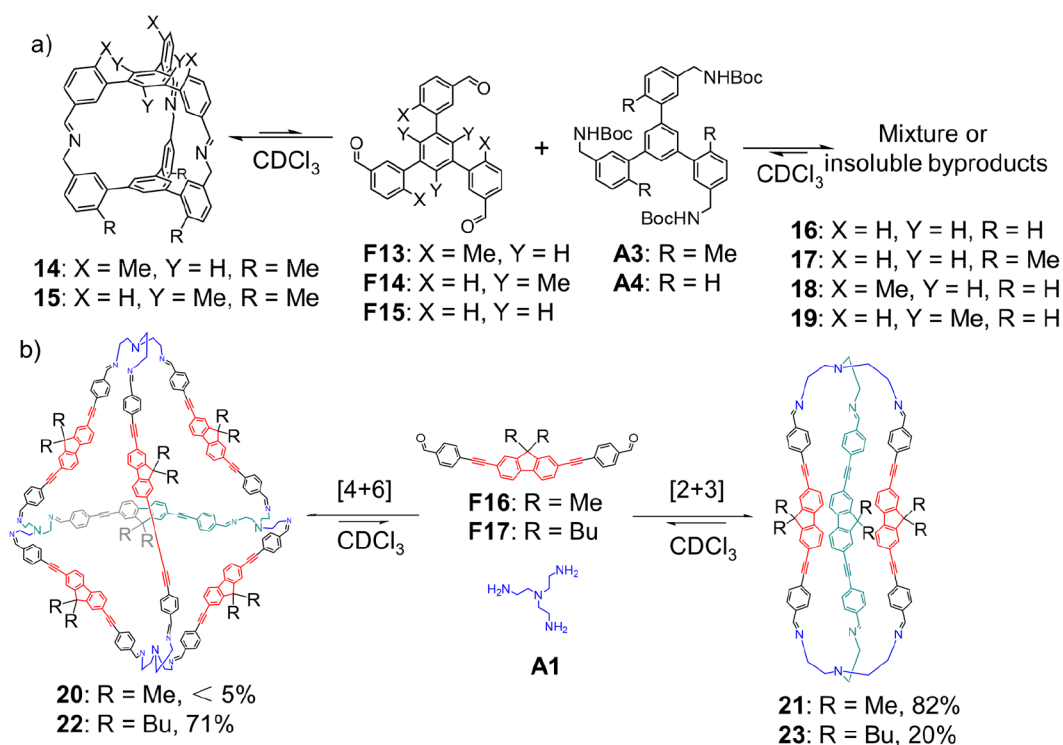
Figure 3. (a) The structural formulas of the triangular prismatic cages **14** and **15**, by condensing the boc-protected trisamino precursors **A3** and each of two trisformyl compounds, namely, either **F13** or **F14**. Switching **A3** to **A4**, or switching **F13**/**F14** to **F15**, only yielded to the formation of intractable mixtures **16**-**19**. b) Structural formulas of the capsules **21** and **23**, as well as the tetrahedral cages **20** and **22**, by condensing one of the bisaldehyde precursors namely either **F16** or **F17** and **A1**.

the racemic trans-diaminocyclohexane yielded [2 + 4] achiral cage **13**. Theoretical calculations indicated that the self-assembly preference resulted from that the system attempted to keep all the imine protons the syn conformation with respect to the adjacent methine protons, so that the steric hindrance could be efficiently avoided or decreased.

Another often used approach to precisely construct the self-assembly products is to use steric hindrance to preorganize a precursor into a specific conformation. When this conformation mimics that of a specific product, it implies that the self-assembly of the latter leads to less entropy loss and thus becomes more thermodynamically favored. The importance of steric hindrance induced preorganization is remarkable in the self-assembly of a set of triangular prisms.[35] In the triangular prismatic products, namely, **14** and **15** (Figure 3a), the three pillars orientate perpendicularly with respect to the two platforms. It is therefore not surprising that the trisformyl and trisamino precursors are forced to adopt twisted conformations that each peripheral phenyl "arm" orientate perpendicularly with respect to the central phenyl. In the trisformyl precursors, namely, **F13** and **F14**, as well as the trisamine **A3**, such conformations have already been preorganized by the steric hindrance resulting from the methyl units. Removal of methyl units in either trisformyl **F13**, **F14**, or trisamino precursors **A3** results in more planar conformations, disfavoring the formation of prismatic cages and thus generating a library of oligomeric or polymeric mixtures (**16**−**19**). Steric hindrance is also taken advantage of in realizing selective formation of a tetrahedral cage and a triangular capsule.[36] The two bisformyl precursors **F16** and **F17** (Figure 3b) have similar frameworks, bearing methyl and *n*-butyl side chains, respectively. Combining **A1** and each of these bisformyl precursors, namely, either **F16** or **F17** led to the formation of a

library of mixture containing a tetrahedron and a capsule as the major products. ^{1}H NMR spectroscopic results clearly indicated that the bulkier *n*-butyl units in **F17** shifted the equilibrium to the side of tetrahedron, whose cavity is larger relative to the capsule and thus helps to avoid steric hindrance to some extent.

Self-Assembly Based on Imine Derivatives in Water

Making C=N Bond More Robust in Water. An imine bond forms by condensing the corresponding parent aldehyde and amine, after which a water molecule is released as the byproduct. Addition of water shifts the equilibrium to the direction of imine hydrolysis. In fact, chemists often employ anhydrous solvent and dehydrating agents such as molecular sieves to remove water and drive imine formation. It is thus not surprising that water is often considered as the worst solvent for imine formation. The drawback that imine is not compatible with water leads to a few problems. First, when the imine-containing molecules are dissolved in organic solvent, hydrophobic effect is not available to drive host−guest recognition. The consequence is that, the functions of the self-assembled molecules designed for supramolecular purposes are often jeopardized.[37−39] In addition, without hydrophobic effect, a variety of topologically complex molecules such as catenanes and knots are difficult to synthesize, given that the formation of these structures are rather entropically disfavored. Second, because water is the life medium, the opportunities of using these imine-containing molecules in biological systems are also ruined. The traditional method to solidify imine bond is reduction.[40] However, the approach relying on reduction also suffers from a few disadvantages. First, reduction of imine requires the use of stoichiometric amount of reductants, which is still against the purpose of green chemistry and atom economics. Second, the reduction products contain multiple amino bonds,
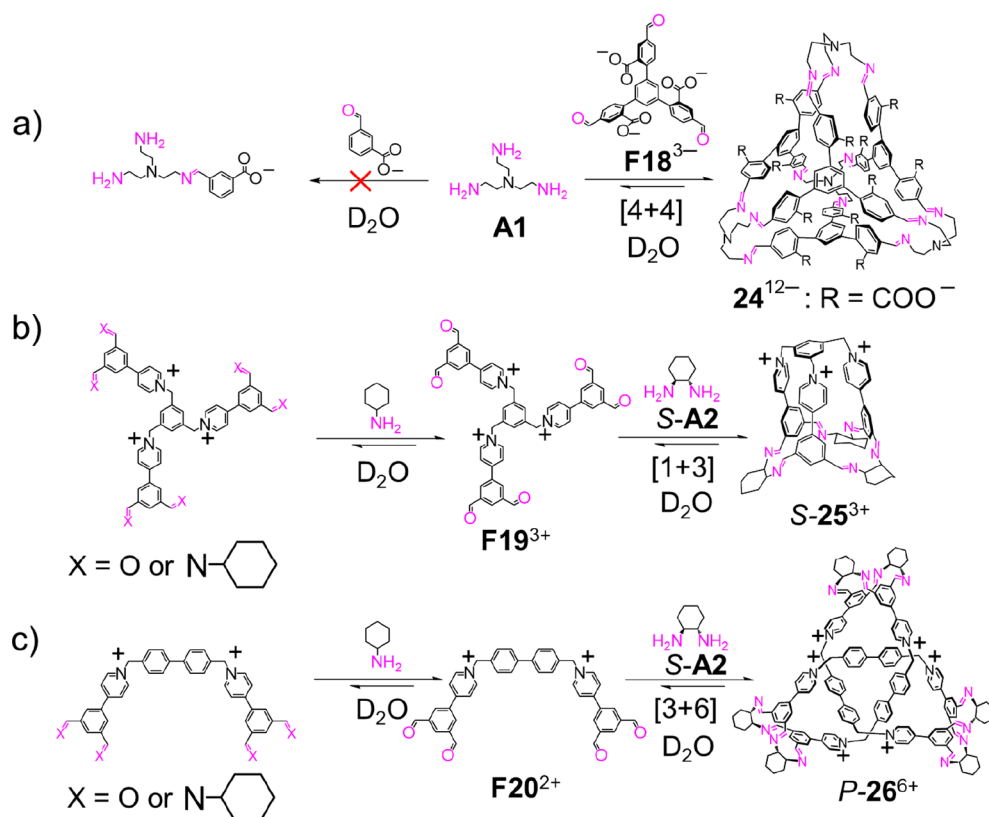
Figure 4. Structural formulas of (a) 24^{12-}, (b) S-25^{3+}, and (c) P-26^{6+} by condensing each of the corresponding amino precursors namely and either of the corresponding formyl precursors in water. The water-compatibility of these three molecules results from multivalence, as indicated by the unsuccessful formation of imine compounds when one of their precursors contains only one amino or formyl unit. Counterions are omitted for the sake of clarity.

whose purification via chromatographic methods proved rather difficult. Third, the frameworks of the amino-containing products are often much more flexible, compared to the imine molecules before reduction. The former molecules often undergo collapse and lose their intrinsic pockets or cavities for guest recognition. Last but not least, some of the self-assembled molecules were designed for developing smart materials which generate reversible responses to external stimuli. However, these functions might be jeopardized upon reduction of imine into amine. Enhancing the robustness of imine-containing molecules without reduction thus needs exploited.

Multivalency Strategy. Multivalency is a ubiquitously observed phenomenon,[41,42] which was used to refer to that cleavage of multiple bonds is thermodynamically or kinetically more difficult than breaking a single bond. For example, Nature creates double-strand DNAs by forming multiple hydrogen bonds between many complementary nucleotide base pairs, even though each single hydrogen bond is rather weak in water. Chelate effect in coordinative systems is another example of multivalency.

In order to better understand the essence of multivalency, we can assume a molecule containing two imine bonds, which is self-assembled by condensing a bisamine and a bisaldehyde. When one of the two imine bonds is cleaved via hydrolysis, the second imine bond helps to hold bisamino and bisaldehyde components together, thus favoring the recovery of the first imine bond in an intramolecular manner.
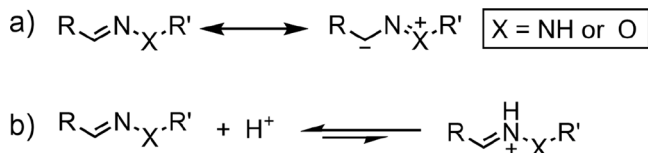
Our group thus envision that a molecule containing multiple imine bonds might be more robust compared to those counterparts containing only one or fewer bonds.[1,43,44] The

enhanced stability of imine via multivalency might allow us to perform self-assembly in aqueous media. Charged precursors, either cationic or anionic, were used to enhance water solubility, allowing self-assembly to occur in a homogeneous manner. This feature is of importance, otherwise some kinetic byproducts might be trapped due to precipitation. A variety of water-soluble multiformyl precursors were thus synthesized, including $F18^{3-}$ (Figure 4a, counterions are omitted for the sake of clarity, the same after.) bearing three anionic carboxylates, as well as $F19^{3+}$ and $F20^{2+}$ containing three or two cationic pyridinium, respectively. The impact of multivalency on enhancing the stability of imine systems is quite remarkable. For example, when A1 and 3-carboxybenzaldehyde, $F19^{3+}$ (Figure 4b) and cyclohexylamine, as well as $F20^{2+}$ (Figure 4c) and cyclohexylamine, were combined in water, imine formation either failed or only occurred partially. As comparison, in the same concentration and acidity condition, condensing A1 and $F18^{3-}$, $F19^{3+}$, and (S,S)-diaminocyclohexane ((S,S)-CHDA, S-A2), as well as $F20^{2+}$ and S-A2 in water, yielded a tetrahedral cage 24^{12-}, a cup-shaped molecule S-25^{3+}, and a trefoil knot t P-26^{6+} in water, whose counterions were omitted for the sake of clarity. Considering the formyl units in the precursor $F18^{3-}$ and the amino groups in (S,S)-CHDA have comparable reactivity relative to the monofunctional precursors namely either 3-carboxybenzaldehyde or cyclohexylamine, the successful self-assembly of 24^{12-}, S-25^{3+}, and P-26^{6+} has to be attributed to multivalency. In water, 24^{12-} and S-25^{3+} can used hydrophobic effect to encapsulate guests with complementary sizes. Both cage S-25^{3+} and the trefoil knot P-26^{6+} contain chiral building blocks, namely (S,S)-CHDA. The point chirality of (S,S)-CHDA was

amplified during self-assembly, which precisely controlled the inherent chirality of the products. When the chiral amino precursor was switched to (R,R)-CHDA, the enantiomers of products namely R-25[3+] and M-26[6+] were generated exclusively. The cage S-25[3+] or R-25[3+] can thus use its chiral cavity to resolve a pair of guest enantiomers. The formation of the trefoil knot P-26[6+] was favored or driven by hydrophobic effect, which compensated entropy loss of building blocks undergoing entwining.

N-Substituted Imine Derivative. Multivalency enhances significantly the robustness of a molecules whose components are connected via multiple imine bonds. However, the approaches to enhance the strength of a single imine bond still need to be developed. On the one hand, considering the resonance structure of an imine namely $C=N \leftrightarrow C^+-N^-$, it is easy to affirm that the carbon atom is rather electrophilic. On the other hand, the imine nitrogen taking partially negative charge is rather basic, which is apt to undergo protonation, forming a more electrophilic iminium cation namely $C=NH^+$. Both two effects make imine apt to undergo electrophilic addition by nucleophiles such as water.

The implication is that, we can stabilize a $C=N$ bond, by either diminishing the electrophilicity of the carbon, and/or decreasing the basicity of the nitrogen. In fact, both of these two effects could be realized via N-substitution of a typical imine with heteroatoms such as N or O in hydrazone ($C=N-N$) and oxime ($C=N-O$) respectively.[45−47] On the one hand, one of the lone electron pair of the heteroatom X undergoes delocalization onto the $C=N$ bond, forming a $C^−-N=X^+$ (Figure 5a) resonance structure. The negative charge on carbon

compared to the carbon atom in a typical imine, providing electron withdrawing inductive effect. The basicity of nitrogen atom in $C=N-X$ is thus decreased. The formation of the imimium cation $C=NH^+-X$ thus becomes thermodynamically more difficult (Figure 5b), making $C=N$ bond hydrolysis more unlikely to occur, given that the iminium cation $C=NH^+-X$ represents one of the key intermediates in imine hydrolysis. The enhanced stability of hydrazone and oxime compared to typical imine makes the former two bonds water compatible, even in acidic water.[48] It is noteworthy that O is more electronegative than N, and therefore the second stabilization effect is more remarkable in oxime compared to hydrazone.[49] In neutral or weakly acidic aqueous media, the dynamic nature of oxime can even be turned off on the time scale of days, acting as an irreversible chemical bond.

Catenanes. Our first trial to use hydrazone as a water-compatible dynamic covalent bond for self-assembling structurally complex molecules was performed under the direction of Sessler. A [2]catenane 27[6+] (Figure 6) composed of two mechanically interlocked cages was self-assembled, by combining two precursors including a trisformyl F21[3+] and a trisacylhydrazine A5 in water.[3] The [2]catenane 27[6+] was produced as the only observable product, as inferred from the NMR spectroscopic and HPLC results. Its structure was unambiguously confirmed via mass spectrometry, and single crystal X-ray diffraction. HPLC analysis indicated that the [2]catenane 27[6+] was the only product with an observable yield. Hydrophobic effect is one of the major driving forces, as indicated by the observation that the [2]catenane 27[6+] underwent disassembly in organic solvent such as DMSO or MeCN. Replacing the triazine unit in F21[3+] with a benzene unit namely F22[3+] led to failure of the [2]catenane formation. This observation indicates that the donor−acceptor interaction between the central triazine unit in F21[3+] and the central phenyl in A5 represents another critical driving force that favors the [2]catenane 27[6+] formation.

We also synthesized a water-soluble bisformyl precursor F23[2+] (Figure 7) contains two cationic pyridinium units.[50] Self-assembly was performed by combining F23[2+] and bisacylhydrazide A6−A10 whose two acylhydrazide are connected via an oligo-methylene chain. It was discovered that the number of methylene units in the chain had a great impact on the self-assembly outcomes, namely that a so-called even−odd rule was observed. When the bisacylhydrazide contains an odd number of methylene units, namely five or seven, [2]catenane 30[4+] and
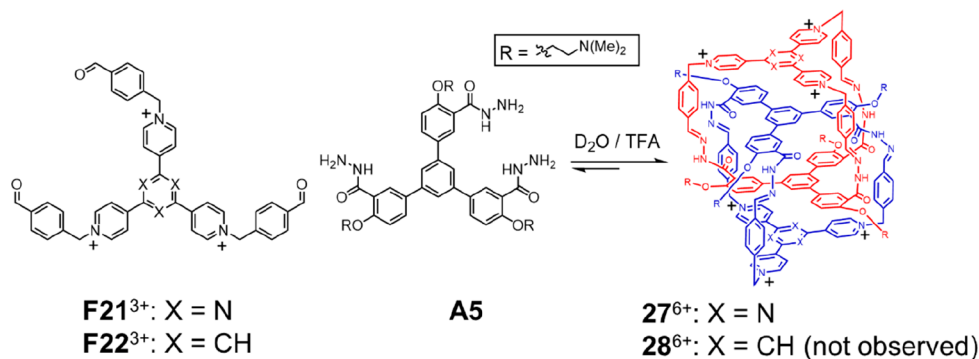

Figure 5. (a) The resonance structures of either hydrazone (X=NH) or oxime (X=O), indicating that the $C=N$ carbon atom bears a partially negative charge, on account of the conjugation effect from the α-atoms. (b) Protonation of the $C=N$ nitrogen atom in either hydrazone or oxime. This process is less favored due to the decreased basicity compared to typical imine.

F21[3+]: X = N
F22[3+]: X = CH

A5

27[6+]: X = N
28[6+]: X = CH (not observed)

Figure 6. Structural formulas of a three-dimensional catenane 27[6+] by condensing a trisformyl F21[3+] and a trisacylhydrazide A5 in acidic water. When the central triazine unit in F21[3+] was replaced by a benzene unit, namely, F22[3+], the self-assembly of a putative [2]catenane 28[6+] failed. Counterions are omitted for the sake of clarity.
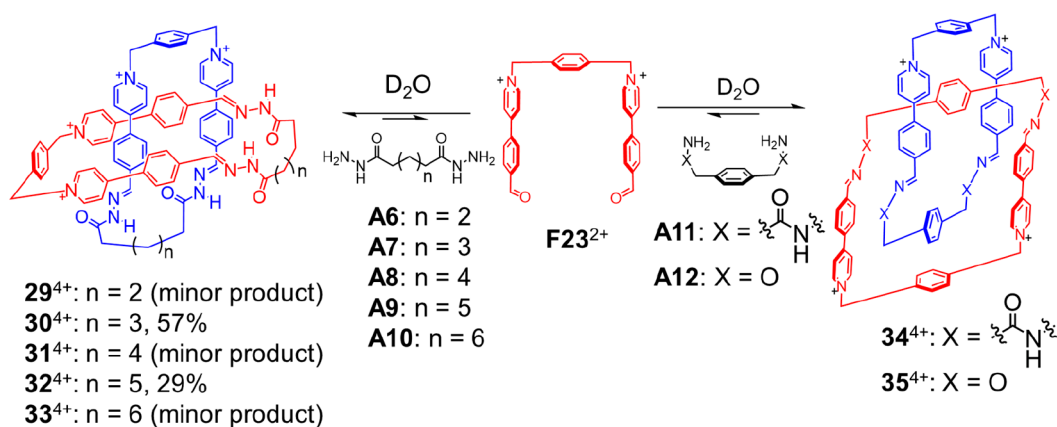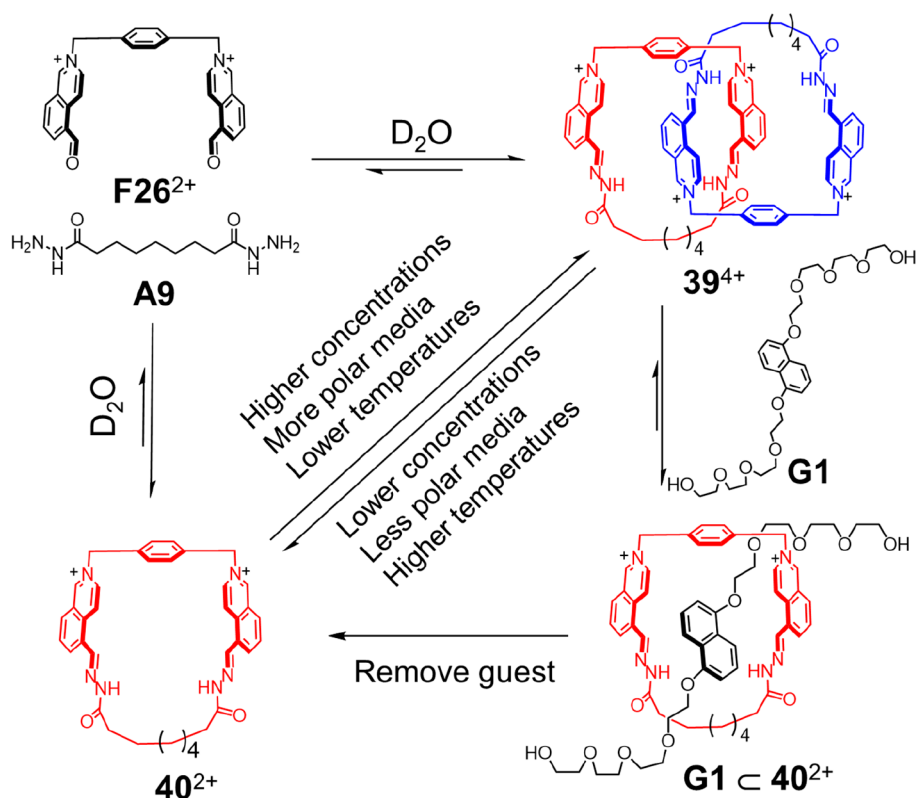
Figure 7. Structural formulas of the [2]catenanes 29^{4+}−35^{4+}, by condensing a dicationic bisaldehyde $F23^{2+}$ and each of the corresponding bisamino precursors including the bisacylhydrazine $A6$−$A11$ and a bishydroxylamino $A12$. The yields of 29^{4+}, 31^{4+}, and 33^{4+} are remarkably low and cannot be determined via NMR spectroscopic results. Counterions are omitted for the sake of clarity.
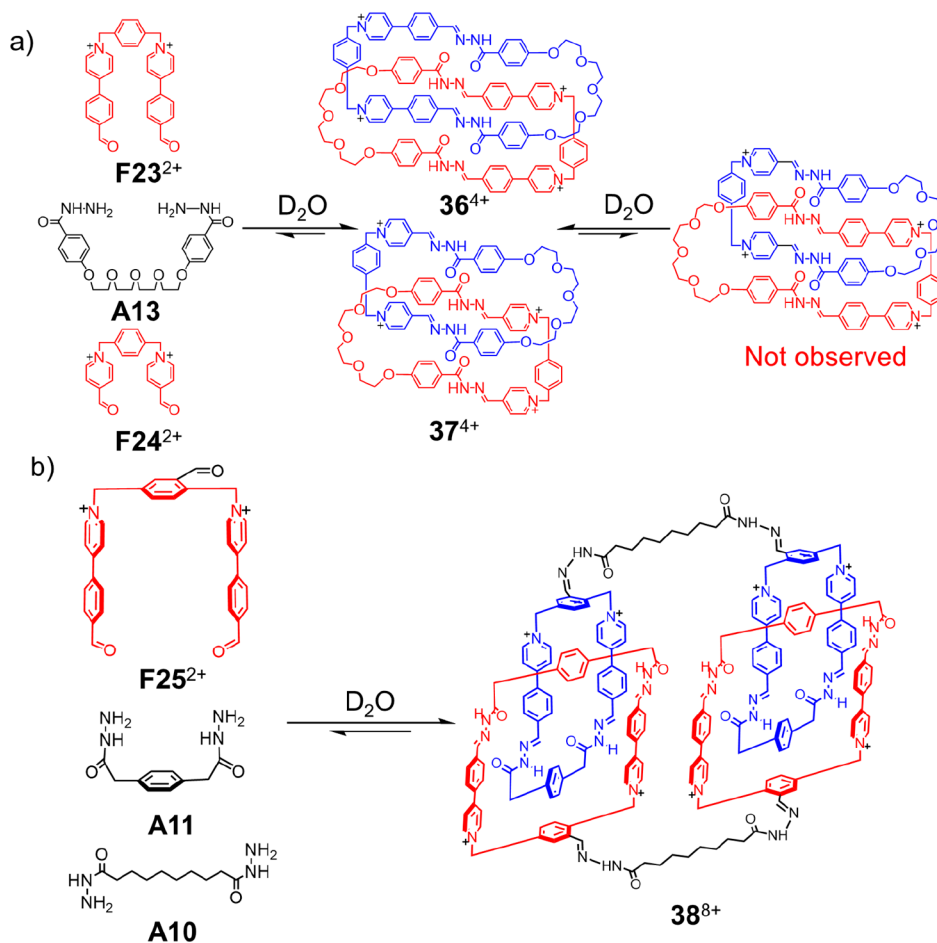

Figure 8. (a) The structural formulas of two homocatenanes 36^{4+} and 37^{4+} each bearing two identical macrocycles by condensing two formyl precursors $F23^{2+}$, $F24^{2+}$ and a hydrazide precursor $A13$ in a one-pot manner. A putative heterocatenane whose two macrocycles are different was not generated. (b) The structural formulas of a catenane dimer 38^{8+} by condensing the trisaldehyde precursor $F25^{2+}$ and two bishydrazide $A10$ and $A11$ in a one-pot manner in water. Counterions are omitted for the sake of clarity.

32^{4+} were self-assembled in 57% and 29% yield, respectively. As a comparison, when the amount of methylene units is an even number including four, six or eight, self-assembly only yielded a library of oligomeric or polymeric mixtures. The observation results from the fact that, in a methylene chain with odd number, the two terminal methylene units orientate in a syn manner, which favors both macrocyclization and catenation. Combining

$F23^{2+}$ and a bisacylhydrazide $A11$ containing a p-xylyl spacer in acidic water yielded a [2]catenane 34^{4+} in close to quantitative yield. The more successful self-assembly of 34^{4+} compared to 30^{4+} and 32^{4+} results from the p-xylyl unit providing larger hydrophobic effect. Again, hydrophobic effect plays the role of driving force to favor catenation, as inferred from the observation that these [2]catenanes underwent disassembly

Figure 9. Structural formulas of a macrocycle 40^{2+} and its dimer, namely, a tetracationic [2]catenanes 39^{4+}, by condensing a dicationic bisaldehyde $F26^{2+}$ and a bishydrazide linkers $A9$ in water. Addition of a guest $G1$ shifted the equilibrium to the complex $G1 \subset 40^{2+}$. The guest could be removed via precipitation and counterion exchange, yielding 40^{2+}. Counterions are omitted for the sake of clarity.
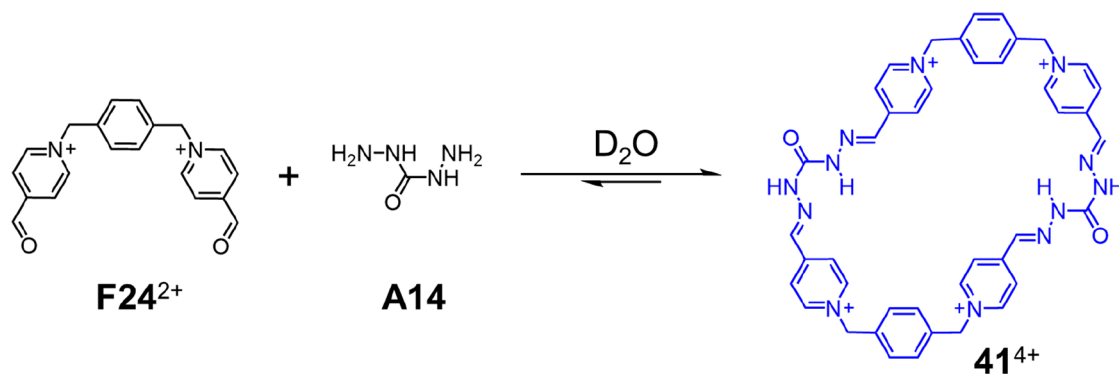
Figure 10. Structural formula of a ring 41^{4+} by condensing a bisformyl $F24^{2+}$ and a bishydrazide $A14$ in acidic water in a [2 + 2] manner. Counterions are omitted for the sake of clarity.

upon addition of organic solvent. The [2]catenane 35^{4+} is a counterpart of 34^{4+}, by condensing $F23^{2+}$ and $A12$ in a water with concentrated HCl, i.e., pH = 0.[4] After removal of the acid, the [2]catenane 35^{4+} containing oxime bonds was observed rather inert, i.e., heating its solution in MeCN at 80 °C for no less than 8 h did not lead to observable decomposition. This observation indicating that the dynamic nature of oxime could be turned OFF when the acid is absent.

The dynamic nature of hydrazone also facilitates the occurrence of self-sorting. For example, when two formyl precursors $F23^{2+}$, $F24^{2+}$ (Figure 8a) and a hydrazide precursor $A13$ were combined in water, only the homocatenanes 36^{4+} and 37^{4+} were self-assembled, without generating the heterocatenane bearing two different macrocycles.[51] The occurrence of narcissistic self-sorting resulted from the fact that, when two

identical rings were mechanically interlocked, both of their cavities could be almost completely occupied so that the hydrophobic driving force was maximized.

When a trisformyl precursor $F25^{2+}$ (Figure 8b) and two bishydrazides namely $A11$ and $A10$ were combined in water, a catenane dimer 38^{8+} was self-assembled as the only observable product.[52] The bishydrazides $A10$ and $A11$ reacted with the formyl in the central phenyl and peripheral phenyls, respectively. This selectivity results from the system attempting to form two fragments of [2]catenane 34^{4+} and maximizing the hydrophobic effect.

Macrocycles. A macrocycle can be self-assembled by condensing the corresponding bishydrazide and a bisformyl in acidic water. In most case, the smallest possible macrocyclic [1 + 1] product, namely one equivalent of hydrazide and one
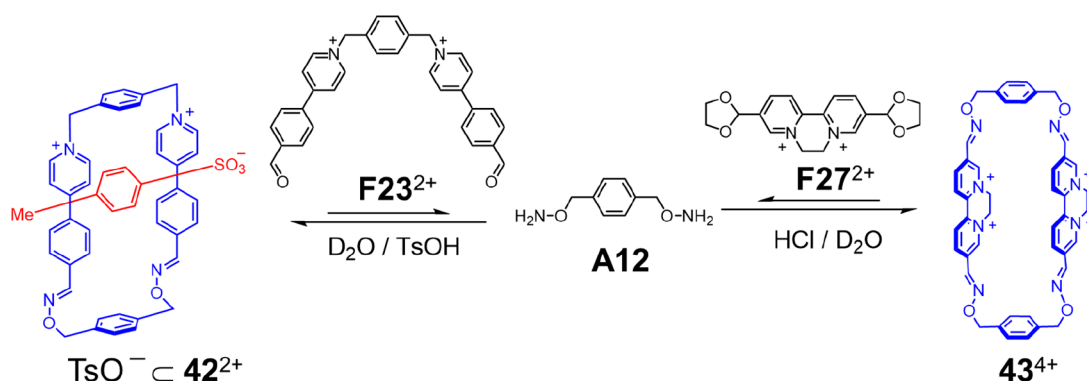
Figure 11. Structural formulas of two macrocycles 42^{2+} and 43^{4+}, by condensing a bisoxylamino **A12** and either $F23^{2+}$ or $F27^{2+}$, respectively, in acidic water. In the formation of 42^{2+}, TsO^- acted as the template. Counterions are omitted for the sake of clarity.
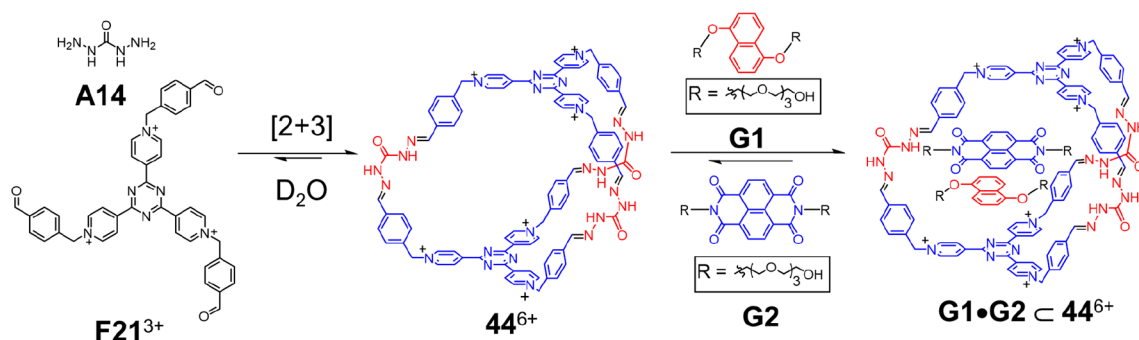
Figure 12. Structural formula of the cage 44^{6+} by mixing $F21^{3+}$ and **A14** in water. The cage was able to accommodate two guests, namely, **G1** and **G2**, driving by hydrophobic effect. Counterions are omitted for the sake of clarity.

equivalent of formyl. This [1 + 1] product represents the one containing the smallest amount of building blocks, which is often thermodynamically favored in terms of entropy.

For example, combining $F26^{2+}$ (Figure 9) and **A9** in water yielded a mixture of a macrocycle 40^{2+} and its dimer, namely, a [2]catenane 39^{4+} as the major products.[53] Increasing the concentrations of the precursors, addition of salt such as NaCl that enhanced hydrophobic effect or lowing temperature shifted the equilibrium to the side of [2]catenane 39^{4+}. In comparison, changing the opposite conditions shifted the equilibrium toward the macrocycle 40^{2+}. Addition of a hydrophobic guest **G1** shifted the equilibrium to the side of $G1 \subset 40^{2+}$ completely. A pure sample of macrocycle 40^{2+} whose counterion is Cl^- was obtained in close to quantitative yield via counterion exchange, during which the guest was removed. The macrocycle was able to recognize phenanthrene selectively over its isomer namely anthracene in water driven by hydrophobic effect. These two isomers with similar physical properties could be separated in a supramolecular manner, without relying on distillation that is rather energy consuming. This binding preference might result from the fact that phenanthrene has a more complementary geometry to the macrocycle cavity compared to anthracene.

When the bis-hydrazide and bis-formyl precursors have the mismatched sizes that disfavor the formation of [1 + 1] products, [2 + 2] or other larger macrocycles could be produced selectively. Condensing the bishydrazide **A14** (Figure 10) and bisformyl $F24^{2+}$ in acidic water yielded a [2 + 2] ring 41^{4+} as a major product in 59% yield.[54] The ring was observed rather kinetically inert at room temperature after removing the acid.

Oxime was also employed to synthesize macrocycle. This bond is dynamic in strong acidic water such as pH = 0. However, its dynamic nature could be turned OFF via removal of acid,

making the products kinetically inert. For example, a bisoxylamino linker **A12** (Figure 11) and a water-soluble bisaldehyde $F23^{2+}$ in water containing TsOH (1 M) yielded a [1 + 1] macrocycle in 85% yield.[4] TsOH here acted as both the catalyst that turned ON the dynamic nature of oxime, and a guest template that favored the macrocyclization and prevented catenation. The ring 42^{2+} has a preorganized cavity, in which a variety of π-electron rich guests were observed to be accommodated. Similarly, combining the **A12** and a bisacetal $F27^{2+}$ bearing a 2,2′-bipyridinium moiety in water containing HCl (1 M) yielded a [2 + 2] ring as the only observable product in the ^{1}H NMR spectrum.[55] HCl was used to catalyze oxime exchange, and deprotect the acetals to form formyls. The pure solid-state sample of 43^{4+} was isolated in 60% yield via counterion exchange. The two 2,2′-bipyridinium units in the framework of 43^{4+} bears a few acidic CH protons pointing inside the ring cavity. The ring can thus take advantage of a combination of hydrogen bond, electron static interactions as well as anion−π interactions to encapsulate anions including HCO_3^- and HPO_4^{2-} in water where these anions are highly hydrated.

Cages. Cages are considered three-dimensional counterparts of macrocycles, whose formation requires at least one of the two precursors containing more than two reacting sites. Heating a mixture of $F21^{3+}$ and **A14** in water at 80 °C yielded a cage 44^{6+} (Figure 12) as the only observable product in the corresponding ^{1}H NMR spectrum.[56] It seems that the elevated temperature, namely, 80 °C was of importance for the high-yielding formation of the cage 44^{6+}. This is because compared to the oligomeric or polymeric byproducts, 44^{6+} contains the minimum number of components. The latter product is thus thermodynamically more favored in terms of entropy. This proposition was
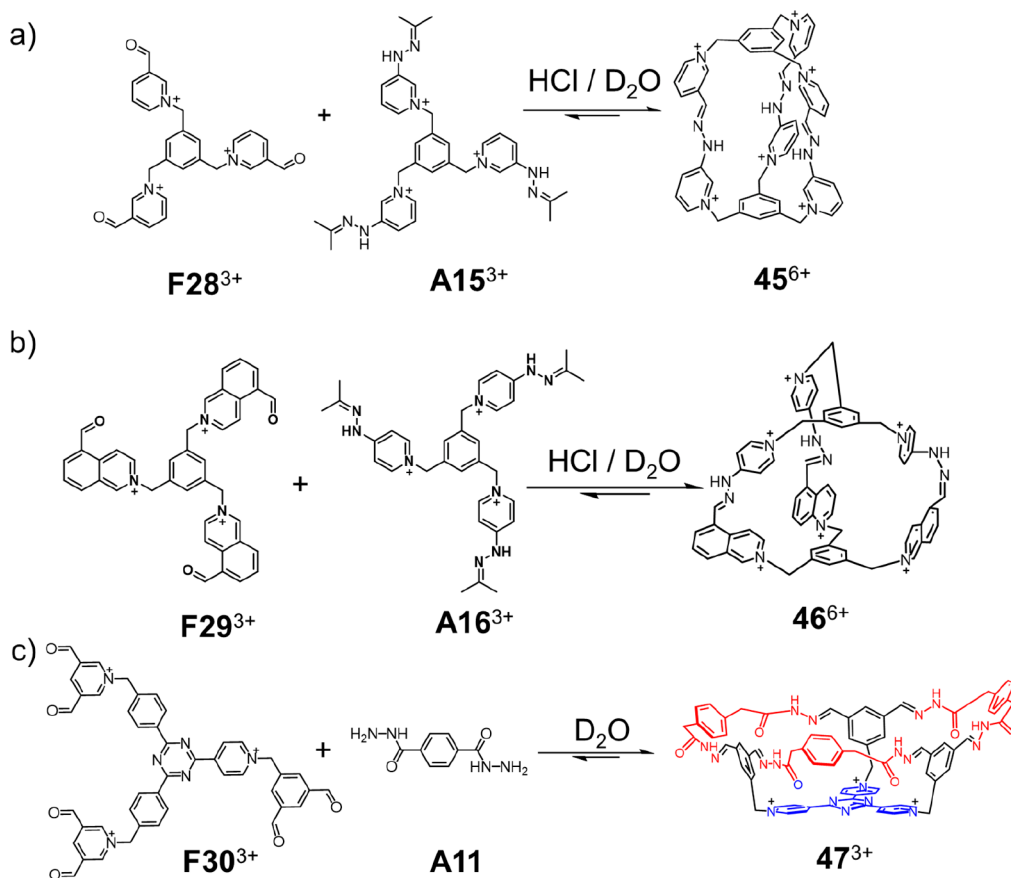
Figure 13. Structural formulas of (a) **45**$^{6+}$ by condensing **F28**$^{3+}$ and **A15**$^{3+}$ in acidic water; (b) **46**$^{6+}$ by condensing **F29**$^{3+}$ and **A16**$^{3+}$ in acidic water; (c) a bowl-shape cage **47**$^{3+}$ by condensing **F30**$^{3+}$ and **A11** in water.

convinced by a control experiment that lowering reaction temperature led to byproduct formation. By taking advantage of hydrophobic driving force, the cage was able to accommodate two guests, namely, **G1** and **G2**. Within the cage cavity, the donor−acceptor interactions between the two guests were enhanced significantly, a behavior reminiscent of enzyme in nature.

Condensing trisformyl **F28**$^{3+}$ (Figure 13a) and trishydrazone **A15**$^{3+}$ in acidic water yielded a [1 + 1] cage **45**$^{6+}$ as the major product.[57] The usage of strong acid (i.e., 1 M HCl) was of importance here, which both removed the acetone protecting group of the precursor **A15**$^{3+}$ and catalyze hydrazone exchange. The cationic cage **45**$^{6+}$ has 12 relatively acidic CH or NH protons pointing inward. This host was able to thus take advantage of a combination of electrostatic forces and hydrogen bonds to recognize anions. ^{1}H NMR spectroscopic and single-crystal X-ray diffraction results indicated that two anions, such as Cl^-, Br^-, and NO_3^-, were accommodated simultaneously. When a stoichiometric amount of two different anions were encapsulated, Cl^- preferred to bind the cage in the location where Cl^- could form hydrogen bonds with the NH protons. Such binding preference led to the formation of a hetero anion dimer as the major product, instead of a mixture of two different homo anion dimers. A little later, another cationic cage **46**$^{6+}$ (Figure 13b) was also self-assembled in a similar method.[2] This cage is a wider counterpart of **45**$^{6+}$. It can recognize I^- selectively in water over other halides including F^-, Cl^-, Br^-. The selectivity might result from the more complementary size of I^-, as well as its hydrophobic nature. A bowl-shape cage **47**$^{3+}$ (Figure 13c)

was obtained by combining a hexaformyl **F30**$^{3+}$ and a bisacylhydrazide **A11** in water.[58] Again, hydrophobic effect affords this molecular bowl the ability to accommodate a hydrophobic guest in water.

■ CONCLUSION AND OUTLOOK

The dynamic nature of C=N bond and its N-substituted derivatives allows the self-assembly systems to perform error checking and self-correcting. However, the freedom of a self-assembly system to search for its thermodynamic minimum does not necessarily guarantee that the target product will be obtained selectively. Quantitative or high-yielding syntheses only occur when some driving forces are sophisticatedly introduced, which endow thermodynamic stability of the target molecules. These driving forces include (i) the formation of the self-assembled products is accompanied by the formation of some intramolecular noncovalent bonds that release enthalpy, (ii) some intramolecular bonds or steric hindrance preorganize the precursors into some specific conformations that mimic the products, the entropy loss in whose formation would thus be suppressed.

The dynamic nature, however, jeopardizes the stability of the molecules via imine condensation. Our group thus developed two major strategies to enhance the robustness of C=N bonds, relying on multivalency and N-substitution. Multivalency enhances the stability of molecules whose components are connected via multiple imine bonds. As a consequence, self-assembly via imine formation can thus be able to be performed in aqueous media. This Account thus helps to overturn, at least

to some extent, a commonly accepted precept that water is the "forbidden zone" of using imine for synthesis of molecules in homogeneous solutions.

N-substituted imine derivatives, including hydrazone and oxime, demonstrate remarkably enhanced stability compared to typical imine, due to their decreased electrophilicity. The enhanced robustness renders these two bonds apt to use as water-compatible dynamic bonds in aqueous environment including biological media. In the case of oxime, its dynamic nature could be turned OFF when acid is absent, which acts as an irreversible bond. A variety of host molecules including macrocycles and cages were thus self-assembled in water, where hydrophobic effect was available to drive host−guest recognition. These hosts were used for application in some challenging areas such as separation of guest isomers including enantiomers, or mimicking enzymes that accommodate multiple guests and enhance their supramolecular forces. Hydrophobic effect also facilitates the syntheses of various topologically complex molecules, such as catenanes and knots, whose formation could be otherwise rather difficult considering their complex three-dimensional architectures. The water-compatibility of these self-assembled molecules allows targeting biological substrates in living systems, such as sugars or proteins. In addition, because the dynamic nature of hydrazone and oxime could be turned ON/OFF by modulating the acidity, developing pH-responsive materials becomes another direction. For example, drug delivery materials containing hydrazone bonds can accommodate drug guest molecules. These materials remain intact in neutral aqueous solution that avoids drug leakage, while they undergo disassembly in more acidic media such as tumor tissue and release the corresponding drug guests for targeted therapy. The weaker stability of typical imine relative to its N-substituted derivatives, namely, hydrazone and oxime can also be taken advantage of in developing complex systems containing mixed bonds. For example, a cage molecule containing both oxime and typical imine bonds is capable of controlling guest accommodation/release in a more reversible manner, by taking advantage of the labile nature of imine. The enhanced kinetic inertness of oxime endows the cage with better robustness, compared to the counterparts containing only typical imine bonds.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Chen, Y.; Wu, G.; Chen, B.; Qu, H.; Jiao, T.; Li, Y.; Ge, C.; Zhang, C.; Liang, L.; Zeng, X.; Cao, X.; Wang, Q.; Li, H. Self-Assembly of a Purely Covalent Cage with Homochirality by Imine Formation in Water. *Angew. Chem., Int. Ed.* **2021**, *60*, 18815−18820.

(2) Wu, Y.; Zhang, C.; Fang, S.; Zhu, D.; Chen, Y.; Ge, C.; Tang, H.; Li, H. A Self-Assembled Cage Binding Iodide Anions over Other Halide Ions in Water. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202209078.

(3) Li, H.; Zhang, H.; Lammer, A. D.; Wang, M.; Li, X.; Lynch, V. M.; Sessler, J. L. Quantitative self-assembly of a purely organic three-dimensional catenane in water. *Nat. Chem.* **2015**, *7*, 1003−1008.

(4) Shen, L.; Cao, N.; Tong, L.; Zhang, X.; Wu, G.; Jiao, T.; Yin, Q.; Zhu, J.; Pan, Y.; Li, H. Dynamic Covalent Self-Assembly Based on Oxime Condensation. *Angew. Chem., Int. Ed.* **2018**, *57*, 16486−16490.

(5) Pedersen, C. J. Cyclic Polyethers and Their Complexes with Metal Salts. *J. Am. Chem. Soc.* **1967**, *89*, 2495−2496.

(6) Odell, B.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. Cyclobis(paraquat-p-phenylene). A

Tetracationic Multipurpose Receptor. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1547−1550.

(7) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. Dynamic Covalent Chemistry. *Angew. Chem., Int. Ed.* **2002**, *41*, 898−952.

(8) Jin, Y.; Yu, C.; Denman, R. J.; Zhang, W. Recent Advances in Dynamic Covalent Chemistry. *Chem. Soc. Rev.* **2013**, *42*, 6634−6654.

(9) Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. Multiple Catenanes Derived from Calix[4]arenes. *Science* **2004**, *304*, 1312−1314.

(10) Zhang, G.; Presly, O.; White, F.; Oppel, I. M.; Mastalerz, M. A Permanent Mesoporous Organic Cage with an Exceptionally High Surface Area. *Angew. Chem., Int. Ed.* **2014**, *53*, 1516−1520.

(11) Klotzbach, S.; Beuerle, F. Shape-Controlled Synthesis and Self-Sorting of Covalent Organic Cage Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 10356−10360.

(12) Wang, Q.; Yu, C.; Zhang, C.; Long, H.; Azarnoush, S.; Jin, Y.; Zhang, W. Dynamic Covalent Synthesis of Aryleneethynylene Cages through Alkyne Metathesis: Dimer, Tetramer, or Interlocked Complex? *Chem. Sci.* **2016**, *7*, 3370−3376.

(13) Wang, Q.; Yu, C.; Long, H.; Du, Y.; Jin, Y.; Zhang, W. Solution-Phase Dynamic Assembly of Permanently Interlocked Aryleneethynylene Cages through Alkyne Metathesis. *Angew. Chem., Int. Ed.* **2015**, *54*, 7550−7554.

(14) Lee, S.; Yang, A.; Moneypenny, T. P., II; Moore, J. S. Kinetically Trapped Tetrahedral Cages via Alkyne Metathesis. *J. Am. Chem. Soc.* **2016**, *138*, 2182−2185.

(15) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. Template-Directed Synthesis Employing Reversible Imine Bond Formation. *Chem. Soc. Rev.* **2007**, *36*, 1705−1723.

(16) Quan, M. L. C.; Cram, D. J. Constrictive Binding of Large Guests by a Hemicarcerand Containing Four Portals. *J. Am. Chem. Soc.* **1991**, *113*, 2754−2755.

(17) Liu, X.; Liu, Y.; Li, G.; Warmuth, R. One-Pot, 18-Component Synthesis of an Octahedral Nanocontainer Molecule. *Angew. Chem., Int. Ed.* **2006**, *45*, 901−904.

(18) Xu, D.; Warmuth, R. Edge-Directed Dynamic Covalent Synthesis of a Chiral Nanocube. *J. Am. Chem. Soc.* **2008**, *130*, 7520−7521.

(19) Mastalerz, M. One-Pot Synthesis of a Shape-Persistent Endo-Functionalised Nano-Sized Adamantoid Compound. *Chem. Commun.* **2008**, 4756−4758.

(20) Tozawa, T.; Jones, J. T. A.; Swamy, S. I.; Jiang, S.; Adams, D. J.; Shakespeare, S.; Clowes, R.; Bradshaw, D.; Hasell, T.; Chong, S. Y.; Tang, C.; Thompson, S.; Parker, J.; Trewin, A.; Bacsa, J.; Slawin, A. M. Z.; Steiner, A.; Cooper, A. I. Porous Organic Cages. *Nat. Mater.* **2009**, *8*, 973−978.

(21) Hasell, T.; Wu, X.; Jones, J. T. A.; Bacsa, J.; Steiner, A.; Mitra, T.; Trewin, A.; Adams, D. J.; Cooper, A. I. Triply interlocked covalent organic cages. *Nat. Chem.* **2010**, *2*, 750−755.

(22) Jin, Y.; Voss, B. A.; Noble, R. D.; Zhang, W. A Shape-Persistent Organic Molecular Cage with High Selectivity for the Adsorption of CO2 over N2. *Angew. Chem., Int. Ed.* **2010**, *49*, 6348−6351.

(23) Mastalerz, M.; Schneider, M. W.; Oppel, I. M.; Presly, O. A Salicylbisimine Cage Compound with High Surface Area and Selective CO2/CH4 Adsorption. *Angew. Chem., Int. Ed.* **2011**, *50*, 1046−1051.

(24) Schneider, M. W.; Oppel, I. M.; Ott, H.; Lechner, L. G.; Hauswald, H.-J. S.; Stoll, R.; Mastalerz, M. Periphery-Substituted [4 + 6] Salicylbisimine Cage Compounds with Exceptionally High Surface Areas: Influence of the Molecular Structure on Nitrogen Sorption Properties. *Chem. Eur. J.* **2012**, *18*, 836−847.

(25) Hong, S.; Rohman, M. R.; Jia, J.; Kim, Y.; Moon, D.; Kim, Y.; Ko, Y. H.; Lee, E.; Kim, K. Porphyrin Boxes: Rationally Designed Porous Organic Cages. *Angew. Chem., Int. Ed.* **2015**, *54*, 13241−13244.

(26) Wang, Y.; Fang, H.; Zhang, W.; Zhuang, Y.; Tian, Z.; Cao, X. Interconversion of Molecular Face-Rotating Polyhedra through Turning Inside Out. *Chem. Commun.* **2017**, *53*, 8956−8959.

(27) Gobre, V. V.; Tkatchenko, A. Scaling laws for van der Waals interactions in nanostructured materials. *Nat. Commun.* **2013**, *4*, 2341.

(28) Emamian, S.; Lu, T.; Kruse, H.; Emamian, H. Exploring Nature and Predicting Strength of Hydrogen Bonds: A Correlation Analysis Between Atoms-in-Molecules Descriptors, Binding Energies, and Energy Components of Symmetry-Adapted Perturbation Theory. *J. Comput. Chem.* **2019**, *40*, 2868−2881.

(29) Riel, A. M. S.; Rowe, R. K.; Ho, E. N.; Carlsson, A.-C. C.; Rappé, A. K.; Berryman, O. B.; Ho, P. S. Hydrogen Bond Enhanced Halogen Bonds: A Synergistic Interaction in Chemistry and Biochemistry. *Acc. Chem. Res.* **2019**, *52*, 2870−2880.

(30) Zhou, H.-X.; Pang, X. Electrostatic Interactions in Protein Structure, Folding, Binding, and Condensation. *Chem. Rev.* **2018**, *118*, 1691−1741.

(31) Hummer, G. Under water's influence. *Nat. Chem.* **2010**, *2*, 906−907.

(32) Jiao, T.; Chen, L.; Yang, D.; Li, X.; Wu, G.; Zeng, P.; Zhou, A.; Yin, Q.; Pan, Y.; Wu, B.; Hong, X.; Kong, X.; Lynch, V. M.; Sessler, J. L.; Li, H. Trapping White Phosphorus within a Purely Organic Molecular Container Produced by Imine Condensation. *Angew. Chem., Int. Ed.* **2017**, *56*, 14545−14550.

(33) Jiao, T.; Wu, G.; Chen, L.; Wang, C.-Y.; Li, H. Precursor Control over the Self-Assembly of Organic Cages via Imine Condensation. *J. Org. Chem.* **2018**, *83*, 12404−12410.

(34) Chen, Q.; Li, Z.; Lei, Y.; Chen, Y.; Tang, H.; Wu, G.; Sun, B.; Wei, Y.; Jiao, T.; Zhang, S.; Huang, F.; Wang, L.; Li, H. The Sharp Structural Switch of Covalent Cages Mediated by Subtle Variation of Directing Groups. *Nat. Commun.* **2023**, *14*, 4627.

(35) Zhang, C.; Jiao, T.; Tong, L.; Wang, H.; Pan, Y.; Li, H. High Yielding Self-Assembly Favored by Preorganization. *Chem. Commun.* **2020**, *56*, 3903−3906.

(36) Cao, N.; Wang, Y.; Zheng, X.; Jiao, T.; Li, H. Controllable Self-Assembly of Pills and Cages via Imine Condensation for Silver Cation Detection. *Org. Lett.* **2018**, *20*, 7447−7450.

(37) Givelet, C.; Sun, J.; Xu, D.; Emge, T. J.; Dhokte, A.; Warmuth, R. Templated Dynamic Cryptophane Formation in Water. *Chem. Commun.* **2011**, *47*, 4511−4513.

(38) Lin, Z.; Sun, J.; Efremovska, B.; Warmuth, R. Assembly of Water-Soluble, Dynamic, Covalent Container Molecules and Their Application in the Room-Temperature Stabilization of Protoadamantene. *Chem. Eur. J.* **2012**, *18*, 12864−12872.

(39) Caprice, K.; Pupier, M.; Kruve, A.; Schalley, C. A.; Cougnon, F. B. L. Imine-Based [2]Catenanes in Water. *Chem. Sci.* **2018**, *9*, 1317−1322.

(40) Liu, M.; Little, M. A.; Jelfs, K. E.; Jones, J. T. A.; Schmidtmann, M.; Chong, S. Y.; Hasell, T.; Cooper, A. I. Acid- and Base-Stable Porous Organic Cages: Shape Persistence and pH Stability via Post-synthetic "Tying" of a Flexible Amine Cage. *J. Am. Chem. Soc.* **2014**, *136*, 7583−7586.

(41) Badjić, J. D.; Cantrill, S. J.; Grubbs, R. H.; Guidry, E. N.; Orenes, R.; Stoddart, J. F. The Exclusivity of Multivalency in Dynamic Covalent Processes. *Angew. Chem., Int. Ed.* **2004**, *43*, 3273−3278.

(42) Badjić, J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. Multivalency and Cooperativity in Supramolecular Chemistry. *Acc. Chem. Res.* **2005**, *38*, 723−732.

(43) Lei, Y.; Chen, Q.; Liu, P.; Wang, L.; Wang, H.; Li, B.; Lu, X.; Chen, Z.; Pan, Y.; Huang, F.; Li, H. Molecular Cages Self-Assembled by Imine Condensation in Water. *Angew. Chem., Int. Ed.* **2021**, *60*, 4705−4711.

(44) Lei, Y.; Li, Z.; Wu, G.; Zhang, L.; Tong, L.; Tong, T.; Chen, Q.; Wang, L.; Ge, C.; Wei, Y.; Pan, Y.; Sue, A. C. H.; Wang, L.; Huang, F.; Li, H. A trefoil knot self-templated through imination in water. *Nat. Commun.* **2022**, *13*, No. 3557.

(45) Kalia, J.; Raines, R. T. Hydrolytic Stability of Hydrazones and Oximes. *Angew. Chem., Int. Ed.* **2008**, *47*, 7523−7526.

(46) Kölmel, D. K.; Kool, E. T. Oximes and Hydrazones in Bioconjugation: Mechanism and Catalysis. *Chem. Rev.* **2017**, *117*, 10358−10376.

(47) Rodriguez-Docampo, Z.; Otto, S. Orthogonal or Simultaneous Use of Disulfide and Hydrazone Exchange in Dynamic Covalent Chemistry in Aqueous Solution. *Chem. Commun.* **2008**, 5301−5303.

(48) Cougnon, F. B. L.; Caprice, K.; Pupier, M.; Bauzá, A.; Frontera, A. A Strategy to Synthesize Molecular Knots and Links Using the Hydrophobic Effect. *J. Am. Chem. Soc.* **2018**, *140*, 12442−12450.

(49) Kulchat, S.; Chaur, M. N.; Lehn, J.-M. Kinetic Selectivity and Thermodynamic Features of Competitive Imine Formation in Dynamic Covalent Chemistry. *Chem. Eur. J.* **2017**, *23*, 11108−11118.

(50) Wang, C.-Y.; Wu, G.; Jiao, T.; Shen, L.; Ma, G.; Pan, Y.; Li, H. Precursor Control over the Self-Assembly of [2]Catenanes via Hydrazone Condensation in Water. *Chem. Commun.* **2018**, *54*, 5106−5109.

(51) Chen, Q.; Lei, Y.; Wang, H.; Wu, G.; Xu, W.; Jiao, T.; Pan, Y.; Zhang, Q.; Zhang, Y. M.; Liu, Y.; Li, H. Narcissistic Self-Sorting and Enhanced Luminescence via Catenation in Water. *Mater. Today Chem.* **2022**, *23*, No. 100679.

(52) Chen, Q.; Chen, L.; Wang, C.-Y.; Jiao, T.; Pan, Y.; Li, H. Ultramacrocyclization via Selective Catenation in Water. *Chem. Commun.* **2019**, *55*, 13108−13111.

(53) Wu, G.; Wang, C.-Y.; Jiao, T.; Zhu, H.; Huang, F.; Li, H. Controllable Self-Assembly of Macrocycles in Water for Isolating Aromatic Hydrocarbon Isomers. *J. Am. Chem. Soc.* **2018**, *140*, 5955−5961.

(54) Zhang, Y.; Zheng, X.; Cao, N.; Yang, C.; Li, H. A Kinetically Stable Macrocycle Self-Assembled in Water. *Org. Lett.* **2018**, *20*, 2356−2359.

(55) Lei, Y.; Shen, L.; Liu, J.-R.; Jiao, T.; Zhang, Y.; Zhang, C.; Tong, L.; Hong, X.; Pan, Y.; Li, H. A Diquat-Containing Macrocyclic Anion Acceptor in Pure Water. *Chem. Commun.* **2019**, *55*, 8297−8300.

(56) Zheng, X.; Zhang, Y.; Wu, G.; Liu, J.-R.; Cao, N.; Wang, L.; Wang, Y.; Li, X.; Hong, X.; Yang, C.; Li, H. Temperature-Dependent Self-Assembly of a Purely Organic Cage in Water. *Chem. Commun.* **2018**, *54*, 3138−3141.

(57) Wang, H.; Fang, S.; Wu, G.; Lei, Y.; Chen, Q.; Wang, H.; Wu, Y.; Lin, C.; Hong, X.; Kim, S. K.; Sessler, J. L.; Li, H. Constraining Homo- and Heteroanion Dimers in Ultraclose Proximity within a Self-Assembled Hexacationic Cage. *J. Am. Chem. Soc.* **2020**, *142*, 20182−20190.

(58) Wu, G.; Jiao, T.; Li, H. Self-Assembly of a Purely Organic Bowl in Water via Acylhydrazone Formation. *Molecules* **2023**, *28*, 976.