Graphical Abstract

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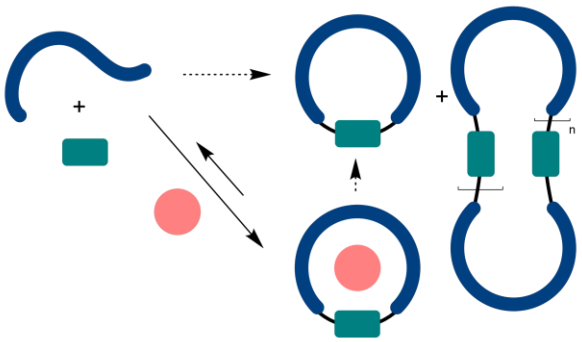

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Digest paper

Kinetic and thermodynamic concepts as synthetic tools in supramolecular chemistry for preparing macrocycles and molecular cages

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ABSTRACT

Macrocyclic and cage structures preorganize functional groups around a central cavity providing unique properties in the field of supramolecular chemistry. Their synthesis requires an appropriate design of the building blocks that will form a macrocycle through a macrocyclization reaction or a cage through a cage formation reaction. Besides the importance of the appropriate geometry of the building blocks, it is necessary to design a suitable synthetic route with special attention to the final macrocyclization or cage formation reaction pathway. The kinetic and thermodynamic aspects are crucial factors to consider for a successful reaction that will be analyzed in this digest.

1. Introduction

Macrocyclic and cage structures are key structures in supramolecular chemistry. Such structures preorganize in a convergent fashion functional elements around a central cavity resembling the active sites of biomolecules. Despite their unique properties and broad areas of application, their use can be limited as their synthesis, involving a macrocyclization step or a complex cage formation pathway, can be relatively difficult.[1] The central cavity of macrocycles and cages allows controlling the intrinsic porosity for selective guest uptake or separation.[2]

This digest will review the different synthetic approaches to prepare macrocycles and molecular cages, analyzing the synthetic advantages and drawbacks of each methodology, paying special attention to the kinetic and thermodynamic aspects. The selected examples of macrocycles are focused on pseudopeptidic systems showing the versatility to obtain different structures through different synthetic methodologies. The selected examples of molecular cages include small cage molecules formed by small organic molecules as building blocks, as well as larger cages obtained from calixarenes.

2. Synthesis of macrocycles

In the synthesis of macrocycles, a key aspect is the preorganization of the building blocks, and in particular, the preorganization of the open-chain macrocycle precursor that yields the final macrocyclic structure.[3] To achieve a high level of favorable preorganization in the open-chain macrocycle precursor it is necessary, in most cases, to perform complicated and long synthetic routes to obtain a good macrocyclization yield.

There are two main synthetic strategies depending on the type of reaction employed for the assembly of the building blocks into the final macrocyclic structure, these are irreversible reactions with macrocyclic products obtained under kinetic control, and reversible reactions with macrocyclic products obtained under thermodynamic control. Whereas classic methodologies are based on irreversible reactions that require complex synthetic routes involving numerous steps, including protection and deprotection steps, that usually result in low yields; the use of reversible bonds allows obtaining macrocyclic structures under thermodynamic control in larger yields.[3]

The conceptually simplest approach is the cyclization of a single open-chain precursor containing complementary functionalities at both ends of the chain (Figure 1). In this reaction, the macrocycle formation competes with the formation of open-chain and macrocyclic oligomers representing an important drawback lowering the yield.

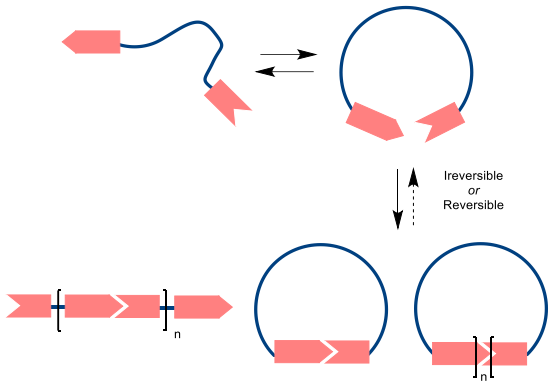

Figure 1. Macrocyclization reaction from a single open-chain precursor and competing processes taking place by an irreversible or a reversible reaction.

For the coupling of two different building blocks, the formation of the [1+1] macrocycle along other structures such as [2+2] macrocycles and higher-order open-chain and cyclic oligomers can also occur (Figure 2). In this scheme, all macrocycles are formed by a ring-closing reaction from the corresponding linear precursor, being a critical step for an efficient macrocyclization.

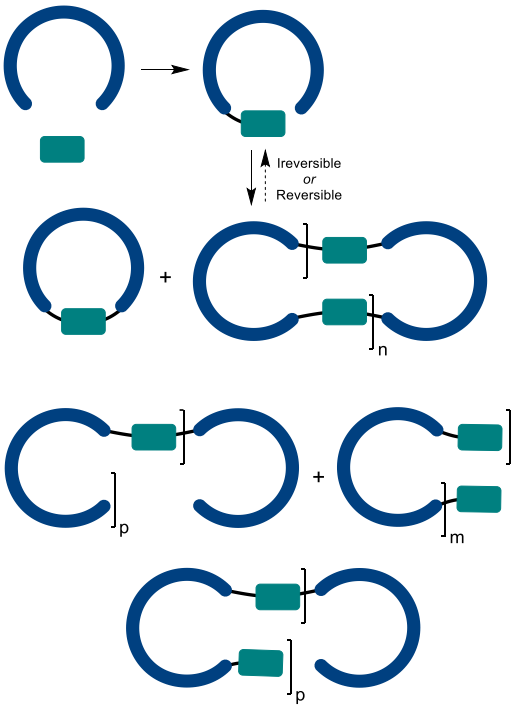

Figure 2. Macrocyclization from two components. Formation of [1+1] and [*n*+*n*] macrocyclic structures and oligomeric by-products by an irreversible or a reversible reaction.

When the structural elements of the open-chain precursors do not provide a correct preorganization to favor the macrocyclization, a template molecule can be used to change the incorrect conformation towards a favorable conformation (Figure 3), in particular, anionic templates have been widely used.[4,5] For macrocyclizations through reversible reactions, thermodynamic templates can stabilize preferentially one of the possible macrocyclic compounds that can be formed favoring its formation at equilibrium (Figure 3 top). In the case of a process involving irreversible reactions, kinetic templates can selectively stabilize the transition state leading to the macrocyclic compound (Figure 3 bottom). It is important to note that for the case of reversible reactions, the template molecule can act, simultaneously, as a kinetic and thermodynamic template. In many cases, a last synthetic step will involve decomplexation of the template to obtain the free macrocycle.

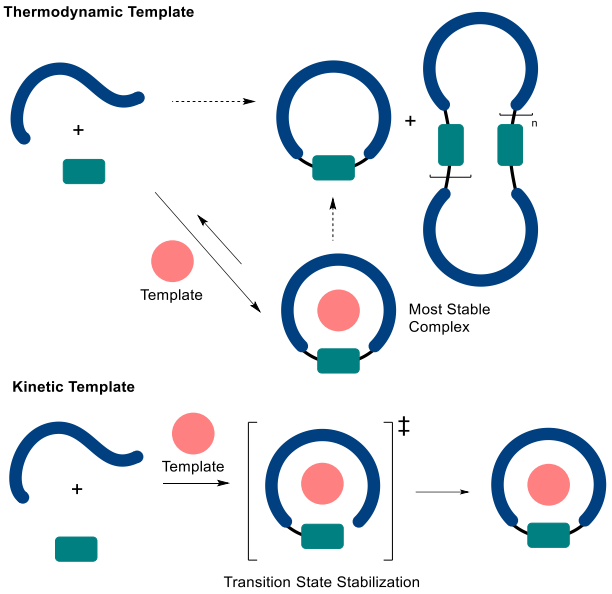

Figure 3. Schematic representation of the mechanism of action of kinetic and thermodynamic templates in macrocyclization reactions.

2.1. Synthesis of macrocycles though irreversible bonds

In the macrocyclization reactions based on irreversible bonds (S_N2 reactions, amide bonds, etc.), the fine balance between the desired macrocyclization reaction (intramolecular reaction) and the competing oligomerization reactions (intermolecular reactions) is crucial to obtain a macrocyclization good. In this regard, the effective molarity (*EM*), defined as k_{intra}/k_{inter}, has been used to identify the influence of the concentration on the efficiency of the macrocyclization.[6] The *EM* (k_{intra}/k_{inter}) represents the concentration of the reactants at which the rate of macrocyclization matches the rate of oligomerization, and therefore, favorable macrocyclization reactions have a high EM value. If the EM value for a particular reaction is low, it is possible to kinetically favor the intramolecular versus intermolecular reactions by using high-dilution conditions. In this regard, Collins and James developed the *Emac* index, defined as $Emac = \log(yield^3 \times concentration)$ to compare the efficiency of macrocyclization reactions.[7]

Considering the definition of *EM*, it can be increased by selectively favoring the intramolecular reaction using a kinetic template. Alcalde and coworkers reported the synthesis of dicationic[1_4]imidazoliophanes **4** in 42% yield in the absence of any kinetic template. In contrast, when chloride or bromide anions were used as templates in the macrocyclization reaction, the macrocyclization yields increased to 83% and 75%, respectively. In this reaction, the templating anion produces a stabilizing interaction with transition state **3** that generates the macrocyclic product through hydrogen bonding. The kinetic constants for the macrocyclization reaction step in the presence of chloride demonstrate the catalytic effect, producing a selective acceleration of the macrocyclization reaction (Figure 4).[8,9]

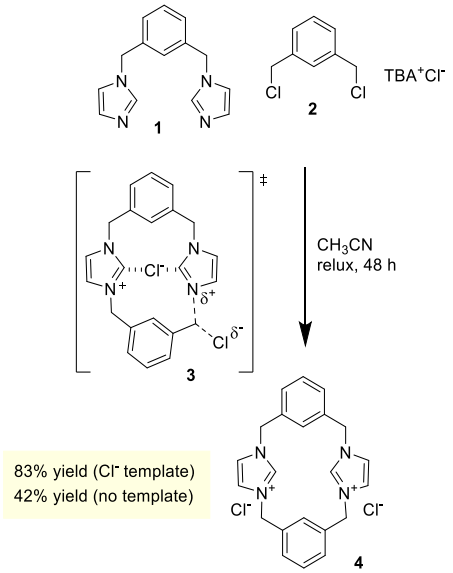

Figure 4. Chloride templated macrocyclization.

Based on this strategy, the use of kinetic templates has a key role in the outcome of the macrocyclization reaction of pseudopeptides **5** through amide bond formation and also by S_N2 reactions (Figure 5).[10,11] Whereas in the absence of any added template the macrocyclization of **5c** with **6** (at 10 mM concentration) gives a 3% of the [1+1] macrocycle **7**, in the presence of chloride anion as a kinetic template, a 38% yield is obtained, producing a 12-fold increase in the yield. A 3- 4-fold increase of yield was obtained for **5a** (also forming [2+2] macrocycle **8a**) and **5b**. Despite the more modest increase, the anion still produces a templating effect.

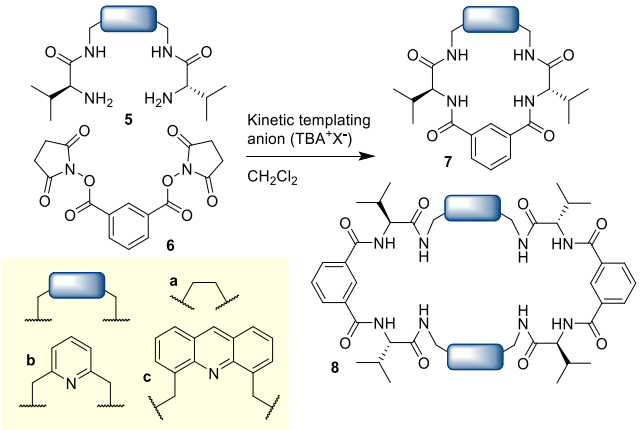

Figure 5. Anion templated synthesis of isophthalamide containing macrocyclic pseudopeptides. TBA = tetrabutyl ammonium.

2.2. Synthesis of macrocycles though reversible bonds

Dynamic covalent chemistry (DCC) allows performing synthesis under thermodynamic control, allowing obtaining a thermodynamically controlled product distribution at equilibrium.[12,13] Among the different possible reactions, dynamic covalent reactions include mainly imine, olefin, and alkyne metathesis, being imine chemistry the most used bond formation in macrocycle synthesis. The success of the macrocyclization reaction is highly affected by the conformation of the building blocks as shown in Figure 6.[14,15] The flexible pseudopeptide containing an ethylene diamine spacer **9** only yields oligomeric by-products. In contrast, the more rigid cyclohexanediamine **12** provides to the peseudopeptidic building block the appropriate and favorable preorganization yielding the expected [2+2] macrocycle **13** in 55% yield. When the stereo configuration of the amino acid is changed from S to R, the resulting geometry of **14** is not suitable for the macrocyclization, and therefore, no macrocyclic product is detected in the reaction, showing a "match/mismatch" effect of the configuration of the components of the pseudopeptide. For the cases where no product was formed due to the unfavorable preorganization of pseudopeptides **9** and **14**, the use of terephthalate **8** as a thermodynamic template allows obtaining the expected [2+2] macrocyclic products **11** and **16** in 50-65% yield, highlighting the effectiveness of thermodynamic templates to drive the formation of unfavored macrocyclic products. Making use of this strategy, it was also possible to prepare cage molecules using benzene-1,3,5-tricarboxylate as a template.[16]

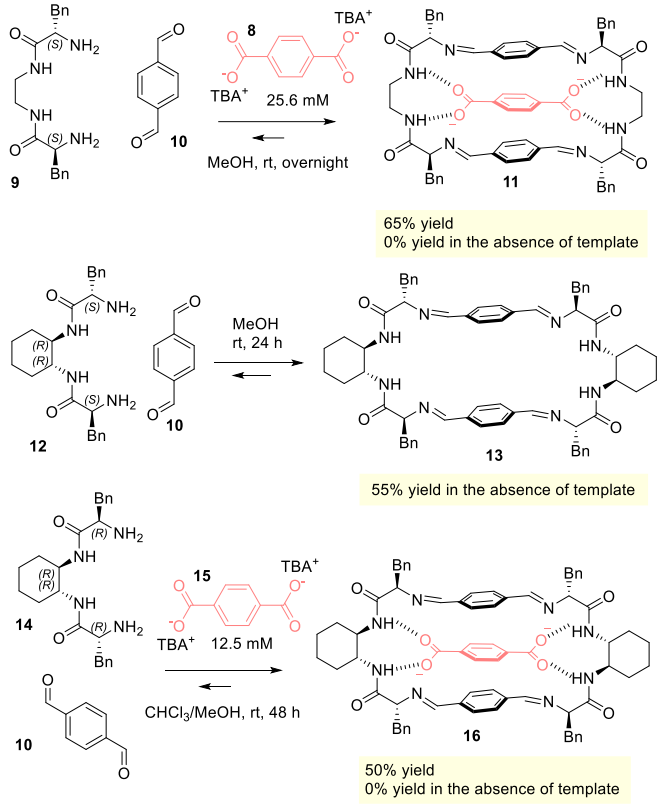

Figure 6. Configurational effects in the [2+2] macrocyclization of pseudopeptides in the absence and presence of thermodynamic anion template. Isolated yields determined after reduction with $NaBH_4$. TBA^+ = tetrabutylammonium.

3. Synthesis of molecular cages

In analogy with the synthesis of macrocycles, the synthesis of molecular cages involves the assembly of convergent building blocks, which must have an appropriate preorganization. Both macrocycles and cages have a central cavity, but the main difference between molecular cages with macrocycles is the 3D nature of their central cavity. For cage synthesis, the same two main synthetic strategies described to prepare macrocycles depending on the type of reaction employed for the assembly of the building blocks, irreversible and reversible bond formation, can also be employed to prepare cage molecules.

3.1. Synthesis of molecular cages though irreversible bonds

Although irreversible bonds were used to prepare the first examples of molecular cages back in 1969 by Lehn, Sauvage, and Dietrich in 25% overall yield,[17] irreversible bonds do not allow

self-correction of mistakes produced during the cage formation, resulting in low overall yields. The low-efficiency results in extremely low yields for more complex cage structures. In this regard, Sherman and coworkers prepared a cage compound with 6 cavitand building blocks **17** held together by irreversible bonds in four lineal reaction steps from the starting cavitand molecule. The yield of each step was 26%, 16%, 58%, and 35%, resulting in an overall cage **19** formation yield of 0.8% (Figure 7).[18]

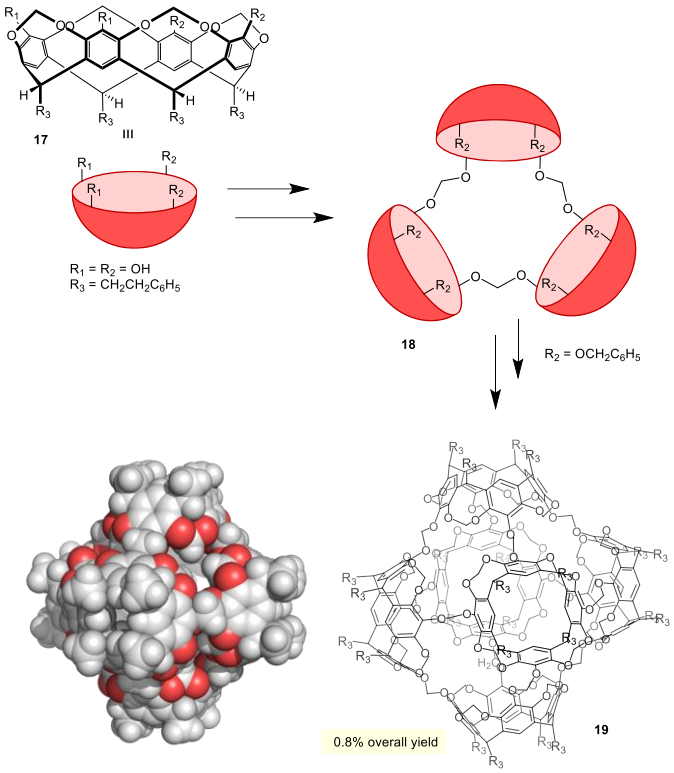

Figure 7. Synthesis of cages through irreversible bonds.

3.2. Synthesis of molecular cages though reversible bonds

DCC can also be used to prepare molecular organic cages under thermodynamic control. The use of reversible bonds allows the self-correction of mistakes produced during the self-assembly process, and therefore the reaction is driven towards the formation of the thermodynamically most stable cage. The reversible imine bond formation is the most used reaction for cage formation, allowing to easily achieve the equilibrium.[12] Mastalerz and coworkers explored the imine bond dynamics in cage formation observing that the formation process of cages **23** and **24** is solvent dependent. If products are soluble the equilibrium is reached if, in contrast, if precipitation takes place the reaction does not reach the equilibrium (Figure 8).[19]

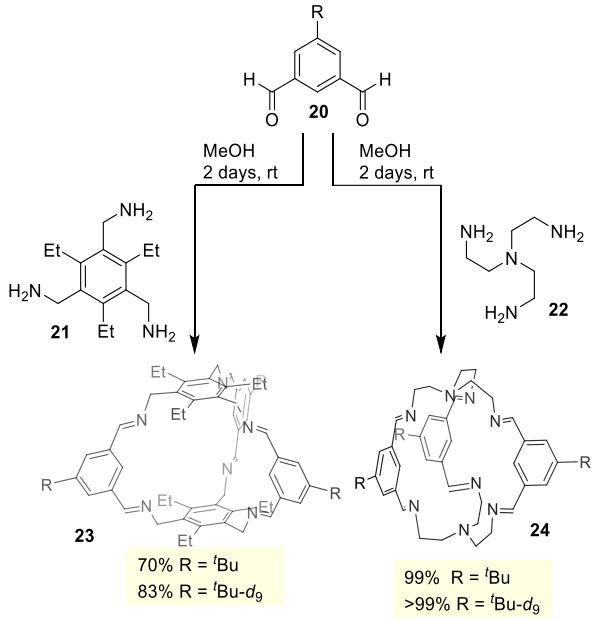

Figure 8. Synthesis of [2+3] organic cages.

This methodology has been used to prepare porous crystals with a uniform pore distribution and high surface areas, as well as good stability. In particular, the CC3 cage has been widely used as it provides excellent properties for gas separation with a Brunauer–Emmett–Teller (BET) surface area of 624 m^2/g (N_2, 77 K).[20] The cage can be obtained in one step from the condensation of 4 molecules of benzene-1,3,5-tricarbaldehyde with ethylenediamine, 1,2-diaminopropane, or (*R*,*R*)-1,2-diaminocyclohexane, yielding CC1, CC2, and CC3 cages, respectively (Figure 9). Whereas the original synthesis of CC1–CC3 cages allowed obtaining <50 mg of material as the reactions had a low yield of 18–35%, the synthetic methodology was being improved to obtain the target cage molecule in almost 100% yield with high purity in a 4-gram scale as demonstrated for CC1 cage.[21] Customization of the properties of the porous materials requires controlling not only the pore size and shape but also the connectivity of the pores that are responsible for the diffusion of the gas molecules along the material. In fact, the porosity in these materials has two components, the intrinsic cavities from the cage molecules, and the extrinsic voids produced from inefficient molecular packing. These materials can achieve excellent performance for gas storage and separation with BET surface areas up to 2796 m^2/g.[22]

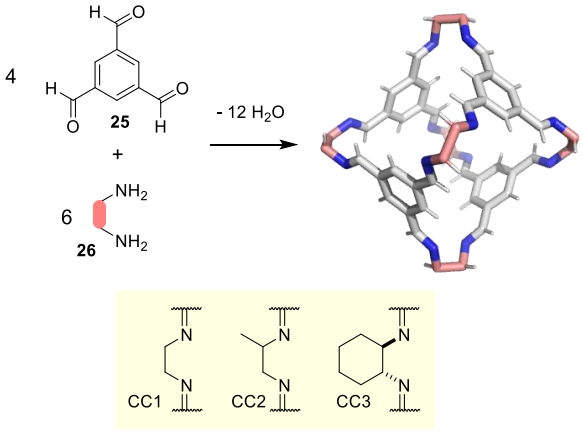

Figure 9. Synthesis of CC1–CC3 cages.

Using the same imine condensation strategy, it is possible to obtain larger cages with larger cavity volumes. Cram and coworkers showed that the reaction of tetraformylcavitand **27** with

1,3-phenylenediamine **30** yields quantitatively the hemicarcerand compound **31a** formed by two cavitand molecules that are held together with 4 diamine molecules (Figure 10).[23,24] Whereas the original synthesis produced the cage in 45% yield using dry pyridine as the solvent at 65 ºC during 4 days, performing the same reaction in $CDCl_3$ in the presence of a catalytic amount of trifluoroacetic acid allows the formation of the cage in less than 1 h in almost quantitative yield, suggesting that the reaction is thermodynamically driven. Small differences in building block size results in cage structures with different topologies, from the [2+4] cage described by Cram to the [6+12] octahedral cage observed by Warmuth and coworkers.[25] The reaction of tetraformylcavitand **27** with 1,3-diaminopropane **28** or 1,4-diaminobutane **29**, using the same trifluoroacetic acid-catalyzed condensation conditions, the corresponding hemicarcerands **31b** and **31c** in over 95% yield. The use of the catalyst allows error correction during the cage self-assembly pathway. In contrast, when the reaction is performed with ethylendiamine **28**, an analysis of the reaction mixture by ^1H NMR showed a sluggish formation of a highly symmetrical larger cage assembly product in ca. 80% yield. Further analysis showed that this new assembly was the octahedral cage **33** that is formed by the condensation of 6 molecules of tetraformylcavitand **27** and 12 molecules of ethylendiamine **32** (Figure 10). For this reaction, solvent plays a key role, yielding a tetrahedral cage in THF, a square antiprismatic cage in CH_2Cl_2, and the octahedral cage already described in $CHCl_3$.[26]

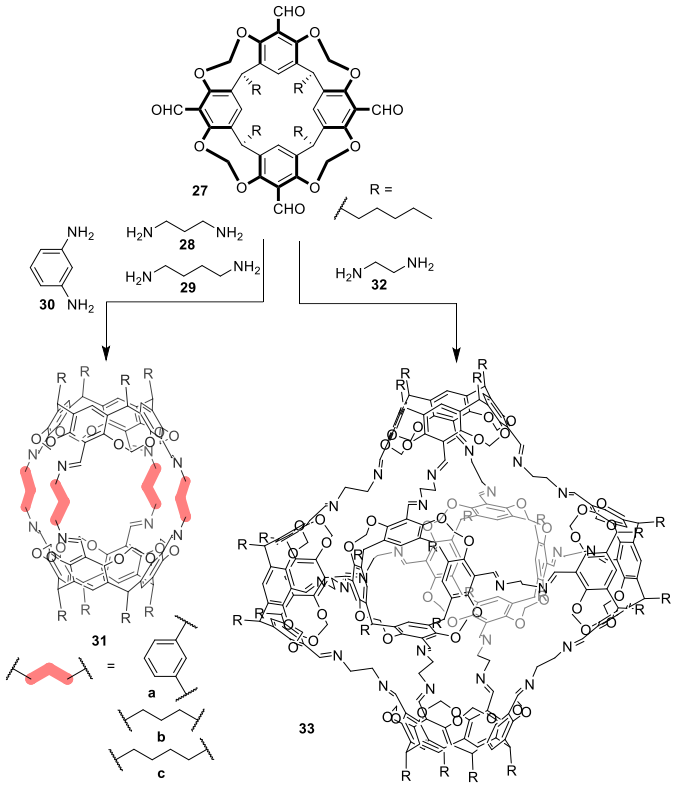

Figure 10. Synthesis of the cages based on the reaction of a tetraformylcavitand and different diamines.

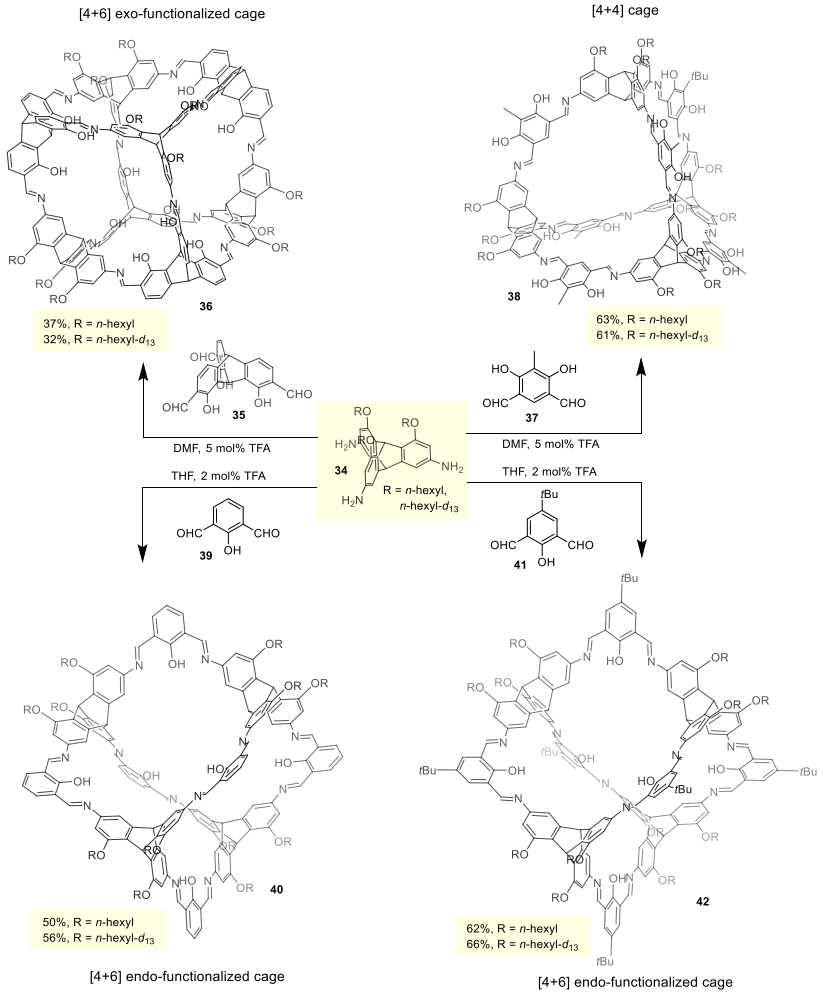

Figure 11. Synthesis of soluble cages based on triaminotriptycene functionalized with *n*-hexyloxy chains.

To obtain kinetic information of the formation of large cage assemblies, it is necessary to overcome the low solubility of the final cage systems and the corresponding reaction intermediates. Mastalerz and coworkers introduced solubilizing *n*-hexyloxy groups, that improved the solubility of the systems allowing them to study the dynamics of imine cage formation. The use of deuterated and non-deuterated groups allowed studying the dynamics of 4 different cages (Figure 11). While the [4+6] endo cages **36**, **40**, and **42** are formed quickly in approximately 1 h, the [4+4] cage **38** is formed slowly, even at 150 ºC. Monitoring of the [4+4] cage **38** formation reaction by ^{1}H NMR shows a formation of a complex mixture of oligomers and polymers, followed by their conversion to the thermodynamically stable [4+4] cage **38**. To obtain information on the thermodynamic or kinetic stability of the cages, as well as the reversibility of cage formation, a series of scrambling experiments of deuterated and non-deuterated cages were performed. The [4+4] cage **38** does not undergo exchange in any of the essayed conditions, in agreement with the observed slow kinetics of cage formation. In contrast, the [4+6] endo- and exo-functionalized cages **36**, **40**, and **42** scramble in the presence of a catalytic amount of TFA or p-toluidine.[27]

4. Other strategies for the synthesis of macrocycles and molecular cages

Macrocycles and cages can also be prepared by the self-assembly of multiple molecules of a rigid building block in just one reaction step using a condensation reaction involving a small molecule for linking the rigid building blocks. Li and coworkers reported the use of a condensation reaction as a powerful tool to prepare macrocycles and cages. Initially, they developed a modular one-pot synthetic strategy to prepare macrocycles **44**-**48** from bis(2,4-dimethoxyphenyl)arene **43** and paraformaldehyde using a high-yielding condensation reaction catalyzed by a Lewis acid (see Figure 12 top). Whereas the authors do no report data regarding the reversibility of the reaction or describing if the reactions are performed under kinetic or thermodynamic control, the effect of different Lewis acids ($BF_3{\cdot}Et_2O$, $FeCl_3$, TfOH, $AlCl_3$, TsOH) on the outcome of the reaction was tested, as well as different reaction conditions including solvent, temperature, and reaction time. All assayed Lewis produced the expected macrocyclic products, being $BF_3{\cdot}Et_2O$ the one that showed the best results, in particular using 1,2-dichloroethane as solvent at 25ºC for 30 minutes as increasing the temperature or longer reaction times increased the formation of by-products.[28] The same group used the developed one-pot methodology for the synthesis of cages from 1,3,5-tris(2,4-dimethoxyphenyl)benzene **49**, showing the versatility of the synthetic protocol. Dimeric cage **50** was prepared in 52% yield using isobutyraldehyde and tetrameric cage **23** was prepared in 46% yield using paraformaldehyde (see Figure 12 bottom).[29]

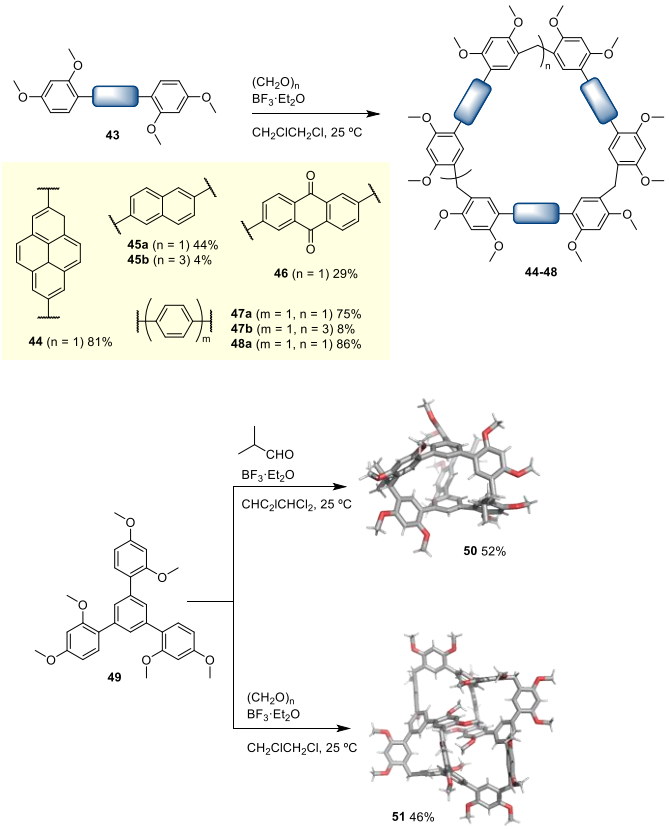

Figure 12. One-pot synthesis of macrocycles and cages.

5. Perspective

This digest summarizes the kinetic and thermodynamic strategies for the synthesis of macrocycles and molecular cages. Synthetic methods based on irreversible bonds do not allow the correction of mistakes produced during the self-assembly reaction, resulting in the formation of unwanted by-products that minimize the yield, and also make more difficult the purification steps. In contrast, methods based on reversible reactions allow correction of mistakes during the self-assembly reaction, resulting in larger yields, that in some instances can be very close to quantitative yields. The examples presented in the digest show that methods based on reversible bonds allow preparing complex cage structures in good yields. Therefore, it is straightforward to predict that the fields of macrocycles and molecular cages will continue growing making use of synthetic methods based on reversible bonds, and also for the case of macrocycles using specific irreversible reactions that give preferentially the macrocyclic product. From a synthetic point of view, this means that the discovery of new types of reversible reactions will enable the formation of novel macrocycle or cages not possible to obtain with current synthetic methods.

Acknowledgments

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