

Triggering Assembly and Disassembly of a Supramolecular Cage

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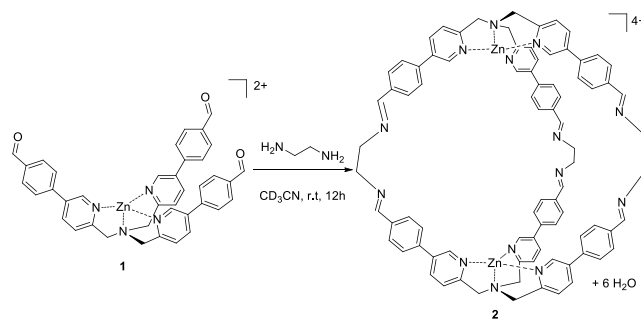
ABSTRACT: A novel supramolecular cage built from the self-assembly of tris(2-pyridylmethyl)amine TPMA zinc complexes through imine condensation chemistry is reported. The cage recognition properties over a variety of structurally related guests, together with the kinetic study of the template assembly and disassembly, have been investigated in detail. This knowledge has been used to selectively modulate the rate of both assembly and disassembly processes. In particular, a novel disassembly method induced by strain release of the guest has been developed.

INTRODUCTION

Self-assembly of small molecules in complex architectures is becoming the leading strategy for the formation of novel functional systems and materials.¹ Among the different bond-formation synthetic strategies, imine-condensation chemistry combined with coordination chemistry has been extensively used to obtain a large variety of molecular architectures ranging from supramolecular cages to topological structures.² Nowadays, the challenge for self-assembled systems is to "time control" their functions and properties. The possibility to time molecular functions (*e.g.* delivery,³ structural reorganization,⁴ stimuli programmed molecular events,^{5...}) strongly relies on thermodynamic and kinetic parameters of both assembly and disassembly processes. However, while the thermodynamic of recognition processes is currently well interpreted, the kinetic aspects of self-assembled molecular architectures remain still unexplored. In this communication, we present a novel molecular cage resulting from the self-assembly of two tris(2-pyridylmethyl)amine (TPMA) zinc complexes. The molecular recognition properties of the formed cage, together with the experimental kinetic data of assembly and disassembly, reveal interesting and unexpected properties. In particular, a novel method to trigger the disassembly of a supramolecular structure has been devised.

RESULTS AND DISCUSSION

Synthesis. Taking advantage of dynamic covalent chemistry,^{6,7} we synthesized a polyimine self-assembled cage based on the opportunely designed TPMA zinc complex **1**. The reaction of **1** with ethylenediamine **en** in acetonitrile results in the selective formation of the bimetallic molecular cage **2** in 12 hours (Scheme 1). Within this time, the aldehyde protons signal at 10.03 ppm disappears and the formation of the imine signal at 8.82 ppm is observed. ¹H NMR reflects the *D*₃ symmetry of the cage with only two signals in the aliphatic region and six signals in the aromatic region (Supporting Information, Figure S14).



Scheme 1. Synthesis of cage **2** formation from complex **1** and ethylenediamine **en**. [**1**]₀ = 1.50 mM (1.0 eq.), [**en**]₀ = 3.75 mM (2.5 eq.). Perchlorate counter anions and embedded **en** have been removed for clarity.

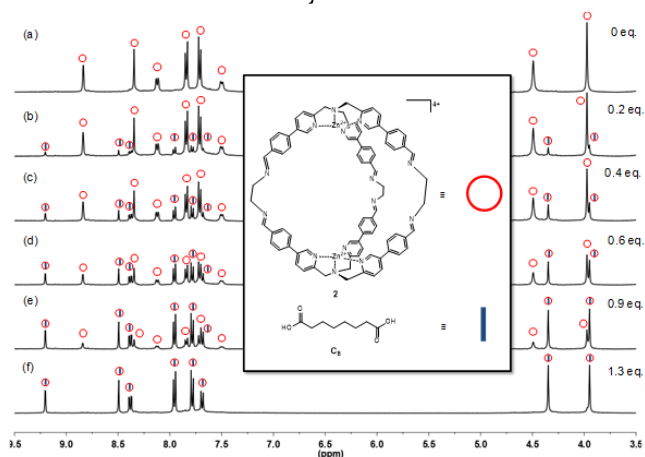


Figure 1. ¹H NMR inclusion experiments. Addition of suberic acid **C**₈ to cage **2** in CD₃CN. (a) Preformed cage **2** (0.001 M cage). The number of peaks is related to the *D*₃ symmetry of the system. (b)-(e) Addition of sub-stoichiometric amounts (0.2-0.9 equiv) of **C**₈ results in the formation of a new species that maintains the original symmetry. (f) Addition of 1.3 equiv of suberic acid totally shift the system to the new species **C**₈@**2**. Counter anions are perchlorates.

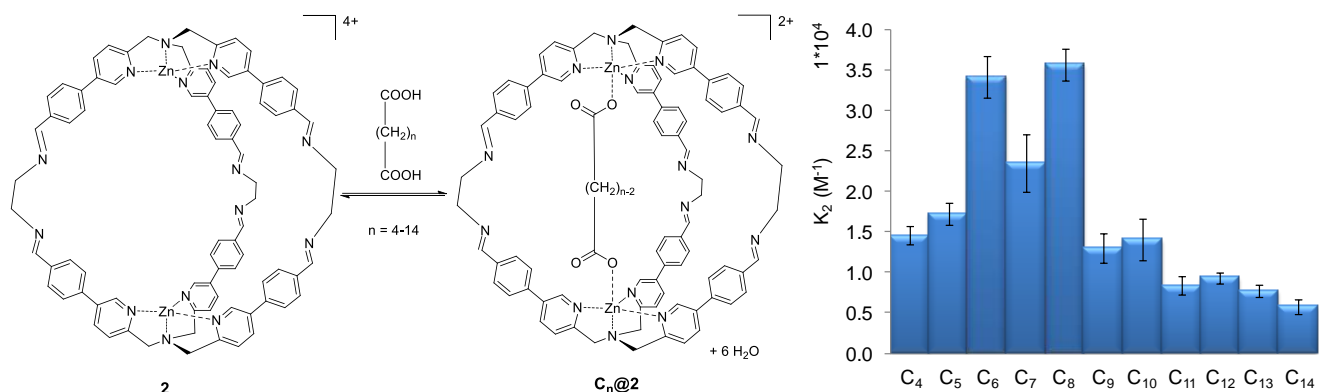


Figure 2. ¹H NMR binding constants (K_2) for the inclusion of diacids C_4 - C_{14} within cage **2** (embedded **en** and perchlorate counter anions are removed for clarity)

²D-NMR and ESI-MS experiments confirm the presence of a single species in solution (Supporting Information, Figure S15-17). Along the improvement of the synthetic method, it has been noticed that in order to obtain high conversion of the cage the reaction needs to be performed in high dilution conditions and employing an excess, up to two equivalents, of ethylenediamine. The diamine, as revealed by DOSY experiments, is embedded within the cage (Supporting Information, Figure S16).

Recognition properties of cage 2. TPMA metal complexes have already shown their capability to perform molecular recognition.^{8,9} For this reason, dicarboxylic acids inclusion in cage **2** has been explored. Addition of suberic acid **C₈** in acetonitrile in sub-stoichiometric amount

(from 0.2 to 0.9 equiv.) leads to the formation of a new set of signals that we assigned to the cage filled with the diacid, viz. **C₈@2**. An excess of **C₈** (1.3 equiv.) results in a complete conversion to the filled cage (Figure 1). These data allow to establish a 1:1 stoichiometry with a binding constant (K_2) for the association process of $3.6 \times 10^4 \text{ M}^{-1}$. The formation of the inclusion complex **C₈@2** is confirmed by two-dimensional NMR spectroscopy (ROESY, DOSY) and ESI-MS experiments (Supporting Information, Fig. S18-22). As revealed by NMR experiments, addition of diacid results in the protonation of the embedded ethylenediamine and binding of the dicarboxylate anion (Supporting Information, Fig. S4-5).

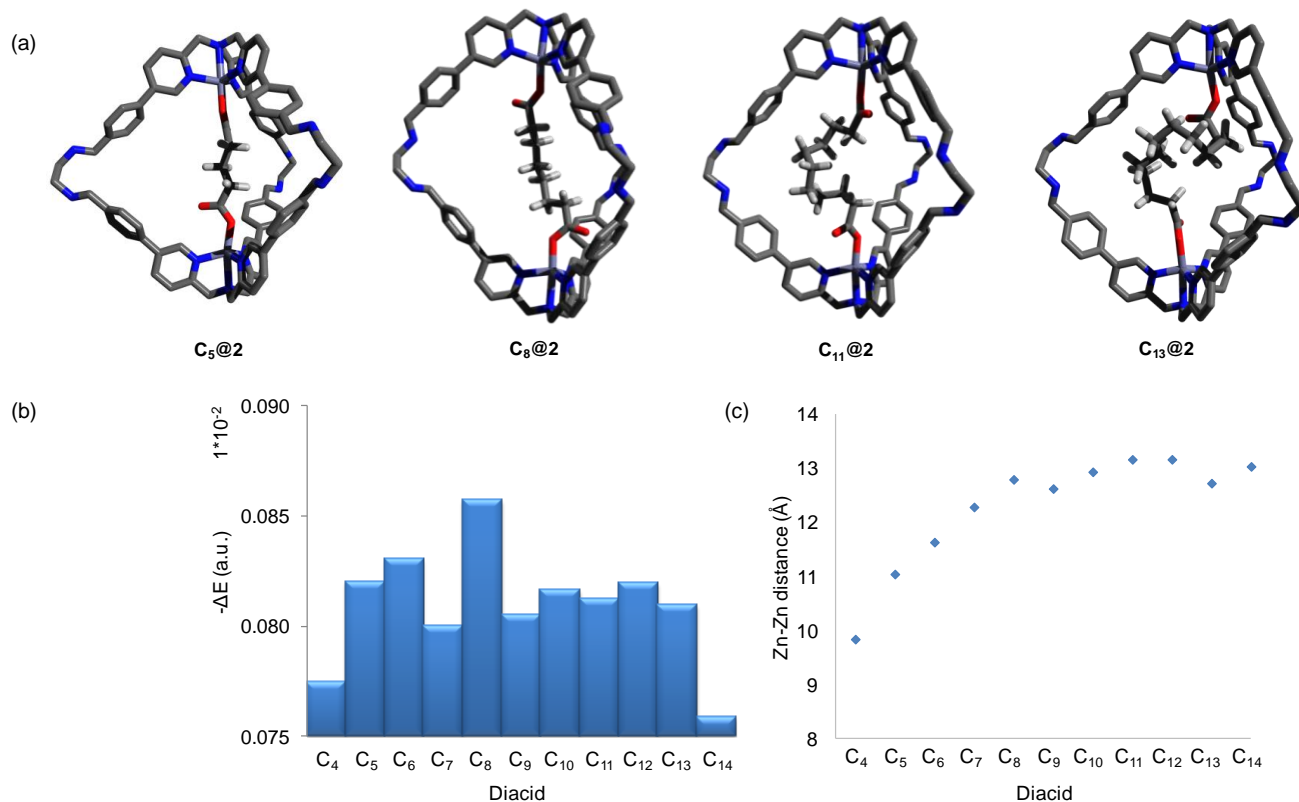


Figure 3. (a) Stick representation of the PM6 minimized structures **C₅@2**, **C₈@2**, **C₁₁@2** and **C₁₃@2**. The whole series ranging from **C₄@2** to **C₁₄@2** is in Supplementary Figure S6. (b) PM6 calculated binding energies (a.u.) and (c) zinc-zinc distances for the **C_n@2** series.

The successful binding of suberic acid C_8 by cage **2** encouraged us to study the complexation of the diacids ranging from succinic acid C_4 to tetradecandioic acid C_{14} in order to find out the dependence of the free energy of complexation from the aliphatic guest chain length. In other words, the experiment is not designed to find the best binder, but to understand how minimal structural variations affect the encapsulation phenomena.¹⁰ Binding constants for the whole series of diacids have been determined and they are reported in Figure 2. Interestingly, it is possible to highlight a pseudo-Gaussian profile, typical for processes occurring in confined spaces,¹¹ centered on suberic acid C_8 . Longer C_{9-14} and shorter C_{4-7} diacids own the geometrical features to bind both metal sites, but to a change of the aliphatic chain length, corresponds a higher thermodynamic cost for the conformational rearrangement of the host and the guest. In order to gather more information on the formed structures and to explain the cage selectivity, semiempirical PM6 calculations for the inclusion complexes for the whole C_{4-14} inclusion series have been performed.¹² As shown in Figure 3a (for the full series see Supporting Figure S8), the guests are binding at both ends inducing deformation in the cage. This deformation is more evident for shorter diacids as shown by the calculated Zn-Zn distance (Figure 3c). After diacid C_8 the distance among the two metals is not varying, independently by the guest (Figure 3c) and the dicarboxylic acid tends to coil within the cage. It is worth to notice

that PM6 calculations are somehow able to reproduce the experimental binding energy profile (Figure 3b).

Assembly and disassembly in the presence of diacids. After the analysis of the binding, rates of cage **2** formation (assembly) and hydrolysis (disassembly) have been measured in the presence of the different diacids. Initial rates for both processes have been determined using ^1H NMR without guest and with every single diacid of the C_{4-14} series. In Figure 4a the initial relative rates have been reported in order to better highlight the effect of the different diacids in the cage formation. As example, synthesis templated by diacid C_8 speeds up cage **2** formation twelve times in comparison with the untemplated process ($v_{C_8}/v_{\text{blank}} = 12$).¹³ On the other hand, initial rate of cage **2** hydrolysis in the presence of C_8 diacid is comparable to the empty cage ($v'_{C_8}/v'_{\text{blank}} = 1.0$ Figure 4b). In the whole C_4 - C_{14} series (Figure 4a), initial relative rates for this templated synthesis highlight a trend which somehow reminds of the binding constant capabilities of cage **2** (Figure 2). This observation suggests that the molecular origin of the rate enhancement can be qualitatively interpreted, besides the capability of the diacids to pre-organize the two TPMA complexes **1**, similarly to the abovementioned recognition properties of formed cage **2**. In other words, while it is not possible to compare binding energies with transition state energies, we can hypothesize that the stabilization of the diacids toward the cage formation has a molecular origin which remind those of the formed cage.

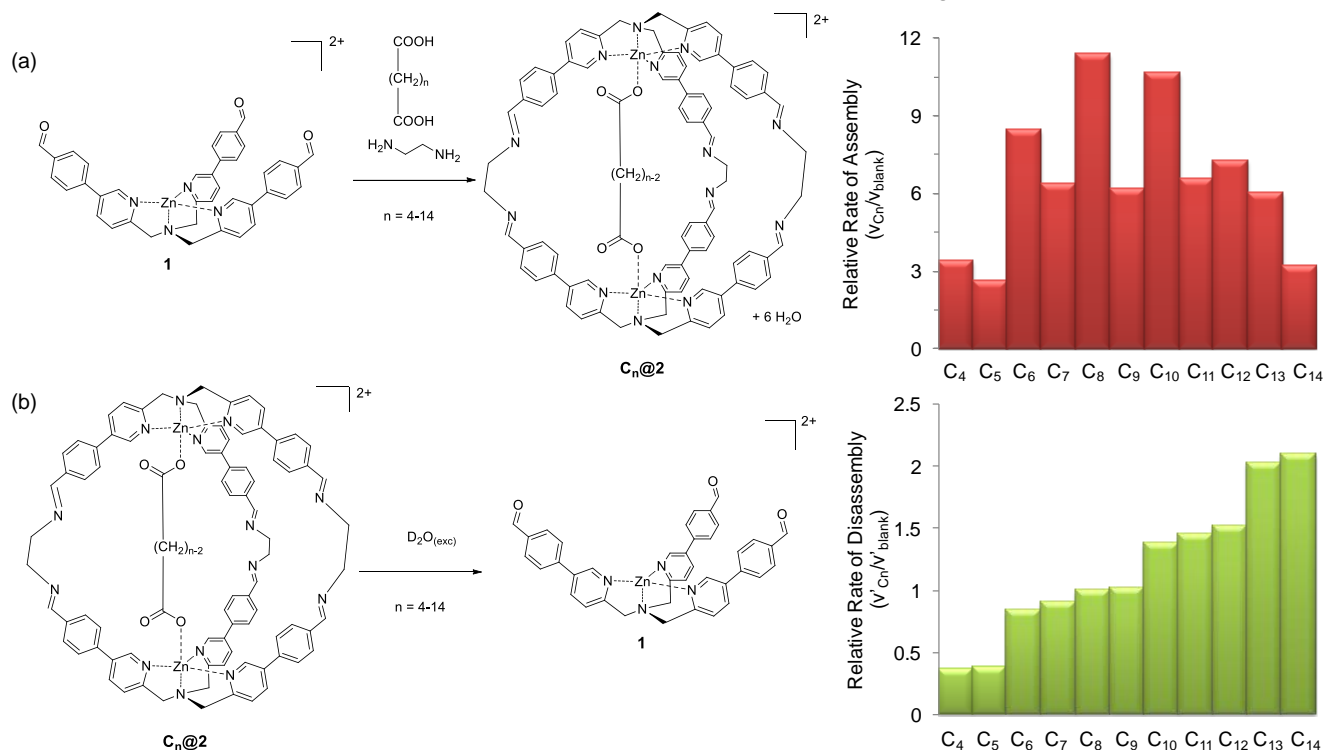


Figure 4. Initial relative rates of assembly (a) and disassembly (b) of cage **2** in the presence of diacids C_4 - C_{14} . Initial rates for the formation and hydrolysis of the cages have been measured using ^1H NMR and they have been compared with the rates of the empty cage **2**. Initial conditions for: (a) assembly $[\mathbf{1}]_0 = 1.50$ mM (1.0 eq.), [ethylenediamine] $_0 = 2.25$ mM (1.5 eq.), $[C_n] = 0.75$ mM (0.5 eq.) and (b) disassembly $[C_n@2]_0 = 0.30$ mM, $[D_2O]_0 = 16$ M. In the case of a monocarboxylic acid (hexanoic acid), the rate of formation is 2.5 times faster than the case of the empty cage while the initial relative rate of hydrolysis is 0.7 time slower than the case of the empty cage. In all the structures, the counter anions are perchlorates

On the other hand, an unexpected profile is observed for the initial relative rates of cage hydrolysis (disassembly). In this case, no relationships with the previously measured profiles is present (Figure 4b). The initial relative rate of hydrolysis constantly increases with the diacids length. Diacids from C_4 to C_6 show hydrolysis rates lower than the empty cage, in particular up to five times slower for the shortest diacid ($v'_{C_4}/v'_{\text{blank}} = 0.4$). Opposite considerations can be made for shorter diacids which tend to keep the two TPMA Zn complex units together. In this case, the opening of the cage is associated to a strain gain to keep the interaction of the carboxylates with both metal centers. In between, C_7 and C_9 have an influence towards the hydrolytic process which reminds those of the solvent molecules within the empty cage ($v'_{C_8}/v'_{\text{blank}} = 1$).¹⁴ On the opposite side of the profile, the presence of longer diacids C_{10} - C_{14} within the cage is speeding up the hydrolysis, up to almost two times faster for the longest C_{14} ($v'_{C_{14}}/v'_{\text{free}} = 2.0$).

A plausible explanation of the diacids active role in the rate of cage hydrolysis can be found in the conformation adopted within the cage by the alkyl chains, which behave as a spring.¹⁵ Therefore, longer diacids are expected to push toward both TPMA Zn complex units of the cage in virtue of their coiled conformation. The energy coming from the acids strain release is responsible for the observed acceleration (*viz.* to an opening of the structure a better binding of the longer diacids is expected).

Triggering the assembly and disassembly of cage 2

As proof of principle, an experiment in which the addition of a diacid triggers the assembly of the cage has been devised. The reaction between aldehyde **1** and ethylenediamine results in the slow formation of cage **2** (Figure 5a). However, after the addition of the diacid C_8 (red arrow) an increase of the rate of cage formation is observed leading to a total conversion of the reagents. While this experiment reminds many examples of template synthesis, novel is the triggering method designed for the disassembly. When an excess of water is added to a solution of **2** in which C_5 is present, only 7% of the cage is hydrolyzed after 40 minutes (Figure 5b). Noteworthy, the addition of diacid C_{13} gives a sharp enhancement of the disassembly rate and allows complete disassembly within 2 hours.¹⁶ In order to exclude general acid catalysis, in the same conditions a monocarboxylic acid, hexanoic acid, has been added instead of a dicarboxylic acid. The addition of hexanoic acid does not result in a change in the rate of hydrolysis. (Supporting Information S11).

It has to be noticed that despite C_5 and C_{13} diacids have a similar binding constant for **2**, they have an opposite behavior in the hydrolysis process. These guests tune the kinetic activity in virtue of their push/pull effects (*viz.* strain gain/release or pressure/vacuum generation within the cage) within the host.

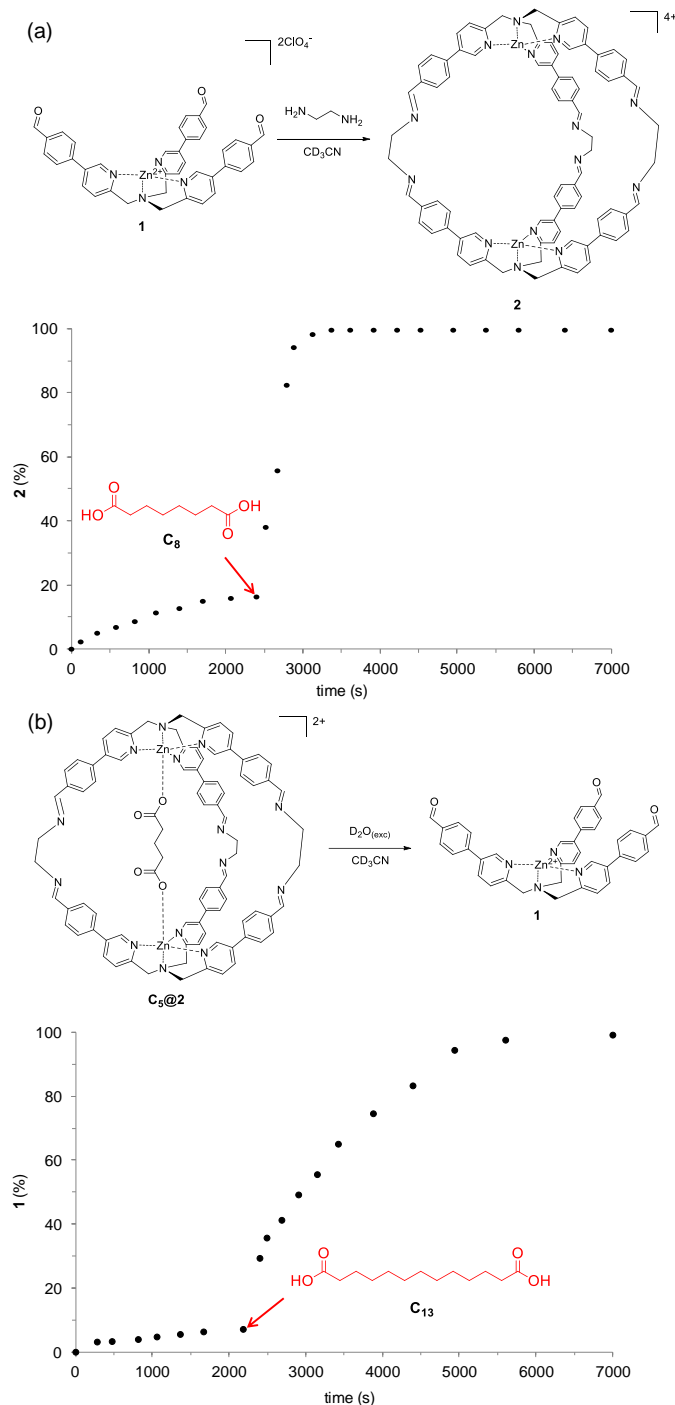


Figure 5. (a) Kinetic profile for the formation of cage **2**. Addition of C_8 increases the assembly rate. (b) Kinetic profile for the hydrolysis of cage **2** in the presence of C_5 . The addition of C_{13} increases the disassembly rate. $[C_5@2]_0 = 0.30$ mM, $[D_2O]_0 = 16$ M, $[C_{13}] = 0.30$ mM

Thermodynamic considerations over the observed effects.

In order to complete the thermodynamic framework for the cage formation/disassembly, the binding constants for the entire dicarboxylic acid series toward **1** (K_1) have been measured (Supporting Information, Figure S6). As expected, all the association constant K_1 are similar.

CONCLUSIONS

In conclusion, we have reported the synthesis of a novel self-assembled imine-based supramolecular cage. The detailed study of the kinetic and thermodynamic parameters guiding the assembly/disassembly processes reveals interesting patterns related to the size of the guest. The possibility to use guests of increasing molecular length has highlighted the link between the thermodynamic of the process formation and the kinetic of the assembly/disassembly. Moreover, two experiments in which the assembly/disassembly is triggered by the presence of a guest have been set up. In particular, the disassembly experiment represents the first example of rate enhancement exerted by strain release of the guest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Experimental details and characterization of all new compounds; selected 2D-NMR experiments (DOSY, ROESY, COSY).

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(16) While the rate of exchange between empty to filled cage is slow in the ¹H NMR timescale, a fast exchange is observed in the inclusion of two different carboxylic acids in solution.

