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Supramolecular Cages

Combining Imine Condensation Chemistry with [3,3] Diaza-Cope Rearrangement for One-Step Formation of Hydrolytically Stable Chiral Architectures

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Abstract: Dynamic covalent chemistry (DCC) has, in recent years, provided valuable tools to synthesize molecular architectures of increasing complexity. We have also taken advantage of imine DCC chemistry to prepare **TPMA**-based supramolecular cages for molecular recognition applications. However, the versatility of this approach has as a major drawback the intrinsic hydrolytic lability of imines, which hampers some applications. We present herein a synthetic strategy that combines the advantages of a thermodynamic-driven formation of a supramolecular structure using imine chemistry, together with the possibility to synthetize chiral hydrolytically stable structures through a [3,3]-sigmatropic rearrangement. A preliminary mechanistic analysis of this one-pot synthesis and the scope of the reaction are also discussed.

Dynamic covalent chemistry (DCC) has been widely used for the formation of elaborate supramolecular architectures from relatively simple building blocks.[1–6] Among the possible reversible bonds, imine condensation has been extensively used for the synthesis of large organic cages of defined shape and size in excellent yields.[7–9] This powerful capability arises from the dynamic nature of imine bonds that offers the building subcomponents the possibility to experience an "error-checking" process which allows the most stable thermodynamic assembly to be obtained primarily.[10–12] However, this chemical versatility has a major drawback: the intrinsic lability of the C=N bond, which limits the functional applicability of the resulting architectures. For this reason, various post-synthetic approaches have been developed. As an example, one possibility to transform imines into more chemically stable bonds is offered by the reduction to the corresponding amines using hydrides.[13–15] However, this reaction can lead to a greater degree of flexibility of the reduced architecture and this can be accompanied by a loss of the shape-persistency and porosity in the solid state.[16,17] Nevertheless, this property could be recovered by a post functionalization reaction of the resulting amine cage in order to change the functional properties (e.g. solubility, porosity, etc.).[18–20] Other possibilities to stabilize imine cages have been reported by Mastalerz, who, by using either a Pinnick oxidation[21,22] or a Povarov cyclization,[23] was able to prepare hydrolytically stable cages. However, even if the yields of the final products were usually from moderate to high, reported examples required the isolation of the imine precursors. In addition, to the best of our knowledge, examples of chemical "stabilization" regarding chiral imine architectures have not been reported.

Recently, we also exploited DCC imine chemistry for the synthesis of tris(2-pyridylmethyl)amine **TPMA**-based supramolecular cages.[24] Beside high yields offered by this approach, the dynamic nature of imine chemistry offered us the intrinsic possibility to: *i*) trigger their assembly and disassembly in solution,[25] *ii*) use them as differential sensors for dicarboxylic acids,[26] and *iii*) synthesize these structures in complex matrixes.[27,28] However, attempts to extend their applications were hampered by imine lability. In addition, attempts to use reducing agents to form more stable systems (e.g., $NaBH_4$ or $NaBH(OAc)_3$) resulted in very low conversions and, due the nature itself of the reduced compound (*viz.* a polypyridine amine system), we were not able to develop efficient reaction work-ups. In this communication, we present a synthetic strategy which combines the advantages of imine chemistry (*viz.* formation of the thermodynamic product) with a [3,3]-sigmatropic rearrangement which lead to the formation of stable C–C bonds among the "dynamic" subcomponents.

Using this combined methodology, three novel hydrolytically stable chiral architectures have been prepared in high yields in a one-pot reaction. The molecular factors influencing the rearrangement reactivity, mechanistic insights of the novel formed architecture and the crystal structure of a novel chiral cage are also presented.

In recent years we extensively employed aldehydic system **1** in combination with diamines for the preparation of different **TPMA**-based cages.[30] In the quest for the synthesis of chiral diamines subcomponents not commer-

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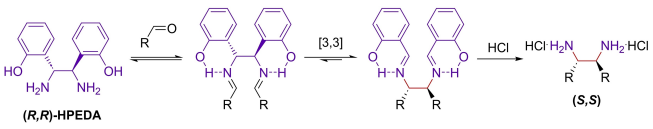
cially available,[31] we found in literature the reaction developed by Chin which offers the possibility to prepare them starting from (*R*,*R*)-1,2-bis(2-Hydroxyphenyl)ethylenediamine **(*R*,*R*)-HPEDA** and aldehydes (Scheme 1).[32] The reported procedure take advantage of an initial imine formation followed by a stereospecific [3,3]-sigmatropic Diaza-Cope rearrangement.[33] The shift of the rearrangement equilibrium toward the products is driven by the **(*R*,*R*)-HPEDA** phenols which favor the formation of strong resonance-assisted hydrogen bonds (RAHB). The desired chiral diamine is obtained by acid hydrolysis.[34,35]

Inspired by this powerful reaction, we envisioned the possibility to apply this strategy for the synthesis of novel chiral and hydrolytically stable **TPMA**-based architectures. More in detail, aldehyde zinc(II) complex **1** (1 equiv) was mixed with **(*R*,*R*)-HPEDA** (2.5 equiv) in the presence of malonic acid **C_3** acid (0.5 equiv) in CD_3CN containing 5 % of DMSO-d_6. One hour after the addition, ^{1}H NMR spectra (Figure 1) highlighted as expected the formation of cage **C_3@2**. This was confirmed by the singlet at 5.40 ppm corresponding to the CH protons of the unrearranged diamine (Figure 1—orange dots). As the reaction proceeded, this peak became broad, and barely visible after 24 hours. Along this time, ^{1}H NMR kinetic profile showed the complete disappearance of the aldehyde peak at 10.05 ppm and the appearance of the proton imine signal at 8.60 ppm (Figure 1—yellow dots). In addition, since the initial acquisitions it was possible to observe a signal at 13.03 ppm (Figure 1—red dots), which was indicative of the characteristic RAHB proton of the rearranged systems (*viz.* structures in which at least one cage arm has rearranged). After 24 hours, **C_3@3** was hydrolyzed adding 37 % HCl to the reaction mixture. The obtained bright yellow solid, filtered, and recrystallized from acetone, corresponded to the poly-pyridine ammonium salt ***S*-4** as confirmed by ^{1}H NMR and ESI-MS (overall yield 87 %, Figures S42–S46). ***S*-4** was completely soluble in water, methanol, DMSO with 5 % of water, and showed a high stability at low pH (e.g. addition of DCl to pH 1 showed a ^{1}H NMR stable for more than two weeks (Figures S61–S63), while is insoluble at pH > 7. X-ray diffraction of ***S*-4** single-crystals, obtained by slow evaporation of a water/DMSO solution, disclosed a C_3 symmetry for the architecture in the solid state in which the two **TPMA** units adopt an opposite propeller arrangement. Crystal packing revealed in addition an intrinsic porosity with a honeycomb arrangement of the cages, that is driven by salt bridges formed by the chloride anions and the cage ammonium groups (Figure 2 and Figure S22).

The synthesis was repeated with the **(*S*,*S*)-HPEDA** and, the other enantiomer of the cage was obtained as confirmed by the opposite circular dichroism spectra (Figure S1).

To gather more mechanistic information on the different steps involved in the cage **3** formation, rearrangements templated by six diacids of different lengths (**C_3**–**C_8**) were monitored via ^{1}H NMR to have quantitative kinetic information about the formed species (Figure 3 and Section S5). It should be noted that the overall reaction proceeded through a molecular contraction of the architecture and, for this reason, we expected a strong influence of the guests length on the rate and yield of the reaction.

Independently by the guests' dimensions, aldehyde system **1** was converted in 24 hours (Figure 3—black dots) and the first products to rise were the imine cages **C_n@2** (Figure 3—blue dots). After this initial stage, the formation



Scheme 1. [3,3]-sigmatropic Diaza-Cope rearrangement for the synthesis of chiral diamines.

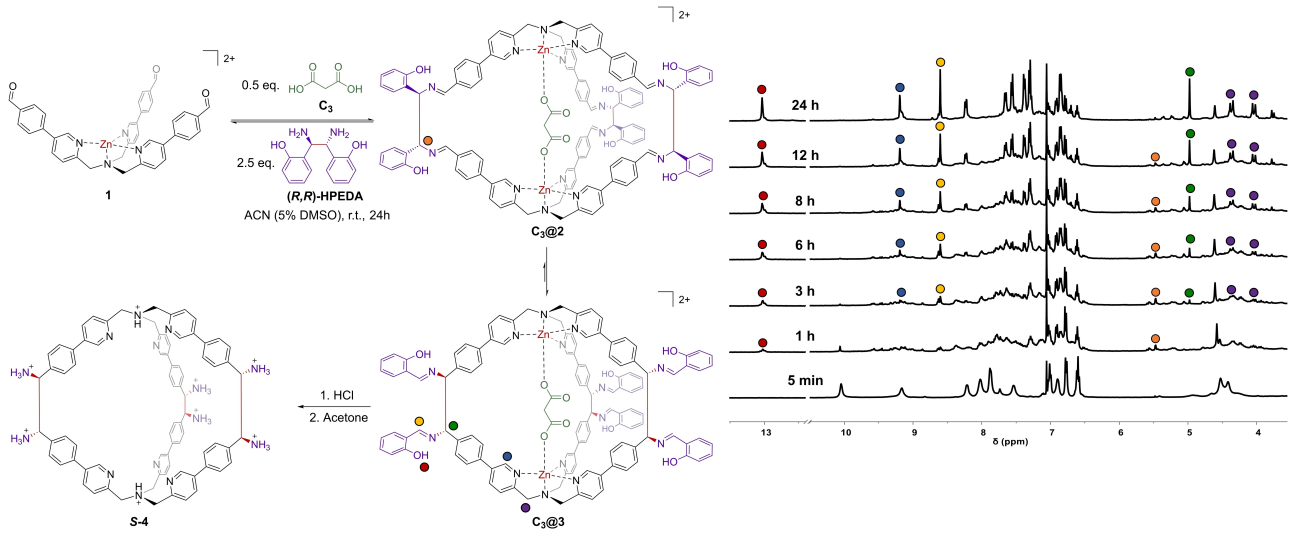


Figure 1. Reaction Scheme for the synthesis of chiral **TPMA**-based cage ***S*-4** and ^{1}H NMR (400 MHz, 301 K, CD_3CN with 5 % DMSO-d_6) spectra of complex **1** after the addition (time = 0) of 2.5 equiv of **(*R*,*R*)-HPEDA** and 0.5 equiv of **C_3**. Perchlorate, chloride, and pyridine proton counterions are removed for clarity.[29]

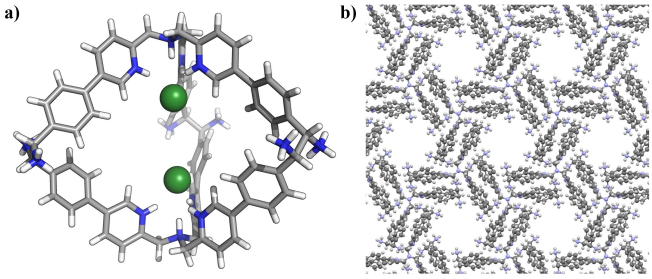


Figure 2. a) Single-crystal X-ray structure of cage ***S-4***. b) Pore system of cage ***S-4*** in the crystal structure. Chloride ions and solvent molecules are removed for clarity.[36]

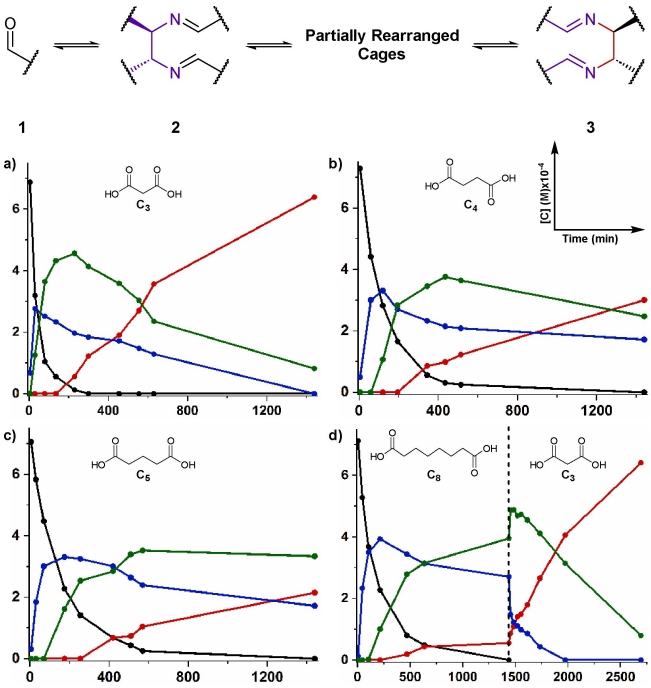


Figure 3. Kinetic profiles for the formation of the rearranged cage in the presence of a) malonic acid (**C$_3$**), b) succinic acid (**C$_4$**), c) glutaric acid (**C$_5$**), and d) suberic acid (**C$_8$**) with the addition of malonic acid (**C$_3$**) after 24 hours. Concentrations have been determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (Section S5). The reaction in the case of malonic acid has been also followed by circular dichroism, thus confirming the stereospecific character of the rearrangement (Section S6).

of partially and totally rearranged structures started to occur (Figure 3—green dots intermediate structures and red dots for totally rearranged). The formation of the totally rearranged systems **C$_n$@3** (Figure 3—red dots) is strongly influenced by the guest size. In the case of the shortest diacid **C$_3$**, partially rearranged structures are rapidly formed at the beginning of the reaction and almost completely converted into the final product in the 24 hours timescale. On the other hand, longer diacids were slowing down the rearrangement and shifted the final equilibrium distribution toward partially rearranged systems. In the case of suberic acid **C$_8$**, where after 24 hours only 8 % of rearranged **C$_8$@3** was formed (Figure 3d), subsequent addition of malonic acid **C$_3$** shifted the system to a re-equilibration toward **C$_3$@3**. This "triggered" rearrangement, which has been also performed in the absence of a templating agent (Section S5.7), beside confirming the influence of the guest lengths on the product distribution, has confirmed the dynamic character of the whole reaction. Guests size influence can be explained taking into account that a chair like transition state in which the two carbon imine bonds are in close proximity has been postulated for the [3,3]-sigmatropic Diaza-Cope rearrangement.[33] While the shorter diacid has the correct length to pre-organize all the three cage arms in the correct conformation (Section S7), longer diacids tend to favor geometries less favorable for the complete rearrangement.[31] The scope of the synthetic approach was tested with two others starting **TPMA**-based structures with one, or two, aldehyde groups with the aim to verify the versatility of the reaction and to test if a different degree of closure was influencing the course of the reaction (Figure 4 and Section S2). The reactions, templated also in this case with malonic acid **C$_3$**, proceeded to the clean formation of the rearranged products. Hydrolysis of the reaction mixtures after 24 hours furnished both the chiral architectures in high yields and purity (Figures S51–S60).

Finally, to test the complexation capabilities of the novel cage, a stoichiometric amount of zinc(II) chloride was added to a solution of ***S*-4** in water. As shown in Figure 5, the complexation occurred, as confirmed by the shift of the signals in the NMR spectrum and by the ESI-MS spectrum (Figures S47–S50). Interestingly, ***S*-Zn-4** binds chiral dicarboxylic acids (malic and tartaric) in buffered water solution (pH 6.9) furnishing different ^{1}H NMR signals for the different enantiomers (Section S9).

In conclusion, the use of DCC imine chemistry in combination with a [3,3]-sigmatropic Diaza-Cope rearrangement for the formation of chiral supramolecular architectures is herein reported for the first time. This strategy allowed the preparation of novel chiral **TPMA**-based systems which are hydrolytically stable due to the formation of C–C bonds. Among these structures, a novel C_3 symmetric cage has been prepared and it has been shown to retain its shape also in the solid state. Preliminary mechanistic studies of the reaction have shown a decisive role of

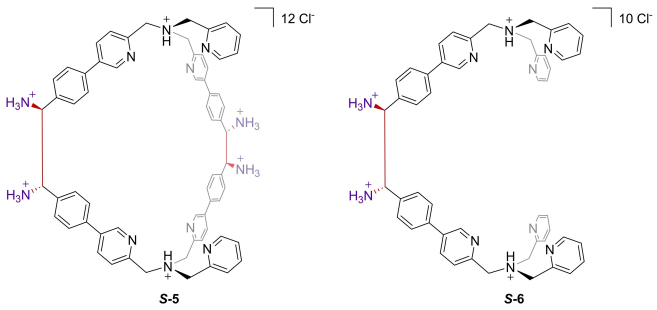


Figure 4. Novel **TPMA**-based architectures developed using Diaza-Cope rearrangement. Chloride ions and pyridine-proton counterions are removed for clarity.

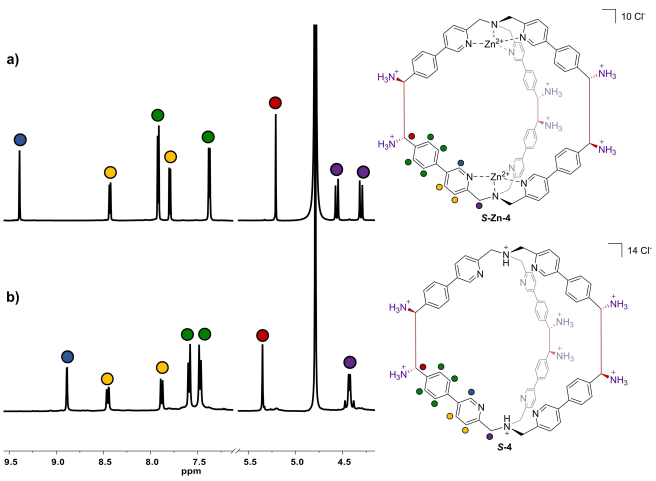


Figure 5. Partial ^{1}H NMR (400 MHz, 301 K, D_2O) spectra of a) cage ***S*-Zn-4** after complexation with $ZnCl_2$ and b) cage ***S*-4**. Chloride ions and pyridine-proton counterions are removed for clarity.

the molecular length of the templating guest in the outcome of the reaction. Moreover, the complexation of the cage ligand has been performed, thereby opening up future studies where metals can be exploited for their catalytic or recognition properties. The demonstration of the versatility of this reaction sequence, combined with the explanation of the geometrical requirements to have higher yields, can open up novel molecular architectures in contexts where DCC imine chemistry is involved.

Supporting Information

Synthetic procedures and characterization of all new compounds (NMR and ESI-MS); selected 2D NMR experiments (COSY, DOSY), crystallographic analysis and DFT calculations.[25,31,35,37–39]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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