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Crystallization- and Metal-Driven Selection of Discrete Macrocycles/Cages and Their Metallosupramolecular Polymers from Dynamic Systemic Networks

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Abstract: Reversible imine- and metal-coordination reactions are dynamic enough to produce complex libraries of macrocycles, cages, and supramolecular polymers in solution, from which amplification effects have been identified in solution or during crystallization in response to ligand- and metal-driven selection modes. Crystallization-driven selection can lead to the amplification of unexpected metallosupramolecular architectures. The addition of Ag^+ triggered the change of the optimal components, so that the crystallization process showed different ligand preferences than in solution. The most packed constituents are amplified in the solid state, taking into account the optimal coordination of metal ions together with non-specific non-covalent interactions between the macrocycle packed in dimers or trimers in the solid state.

Keywords: supramolecular chemistry; macrocycles; cages; dynamic chemistry; crystallization

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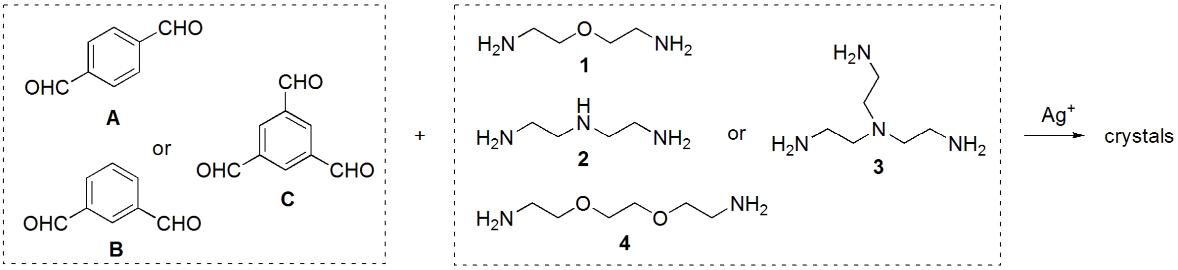
Constitutional dynamic chemistry (CDC) [1–4] has emerged as a new adaptive approach for the generation of emergent dynamic materials [2–9], molecular machines [10,11], bioactive compounds [12,13], cages [14–16], knots [17], rotaxanes [18], metallodendrimers [19], and macrocyclic [20] structures. Moreover, such dynamic systems can adapt under the influence of internal or external stimuli such as pH (Figure 2c,d), temperature [21], light [22,23], precipitation [24,25], and host enzyme [26,27] when optimal constituents can be selectively formed and amplified as the best/fittest constituents from the multicomponent dynamic library [28,29].

Among the different internal effectors, crystallization-driven selection can lead to out of phase amplification of the most stabilized constituents in solid state [30–32]. However, the out of equilibrium crystallization strategy has not been widely studied, probably due to the facility of obtaining high quality single crystals or other solid-state species that can be used for accurate structure determination.

Previously, we have reported the metal-driven single/double dynamic 3D cages from imine-connected systems [33]. The discovery of the "Ag^+-driven" selection of crystalline interlocked cages showed the artwork of unexpected topologically complex metallo-supramolecular architectures from very simple starting components. Herein, we present new results in the exploration of the crystallization-driven selection from dynamic libraries with expanded components, from the combination of single imine/carbonyl-amine and coordination bonds to dynamic covalent networks. More importantly, a comparison study of the constituent selection between solution and crystal states and between the presence and absence of metal coordination phenomena has been carried out, leading to a stimuli-induced switch of amplifications.

In order to establish dynamic systems for the purpose of crystallization-driven selection, different aldehydes **A**–**C** and amine **1**–**4** compounds (Scheme 1) were first screened for the possibility of forming single-crystals. from the solution of simple methanolic mixtures of amine-aldehyde components.



Scheme 1. Approaches to forming dynamic imine macrocycle or cage crystals from different dialdehyde **A**–**C** and amine **1**–**4** compounds with or without the presence of Ag^+ metal ions.

Terephthaldehyde (**A**), for its good reactivity and linear structural geometry, was chosen to interact with different diamine derivatives through imine formation reactions in methanol. When 2-(2-aminoethoxy)-ethylamine (**1**) was added in a ratio of 1:1 to react with **A**, a crystalline macrocycle $\mathbf{A_2{\cdot}1_2}$ was formed (Figure 1a) with the absence of a metal cation. Meanwhile, with the presence of silver triflate (AgOTf), two types of crystals were simultaneously formed: a cage $\mathbf{A_6{\cdot}1_6{\cdot}Ag_4}$ with three-layered macrocycles connected by four Ag^+ metal ions (Figure 1b) and a metal-coordinated supramolecular polymer of exo-coordinated macrocycles $(\mathbf{A_2{\cdot}1_2{\cdot}Ag_2})_n$ (Figure 1c). The unexpected formation of crystalline multi-layer and polymeric macrocyclic superstructures instead of simple metallo-macrocyclic monomeric structures can probably be attributed to the preferred four coordination numbers and to the adaptive chelating bonds for Ag^+ with no Ag^+-Ag^+ contacts within the frameworks. In particular, the rarely seen metallosupramolecular polymeric macrocycles $(\mathbf{A_2{\cdot}1_2{\cdot}Ag_2})_n$ demonstrated the high structural diversity that can be discovered and provided by dynamic covalent chemistry.

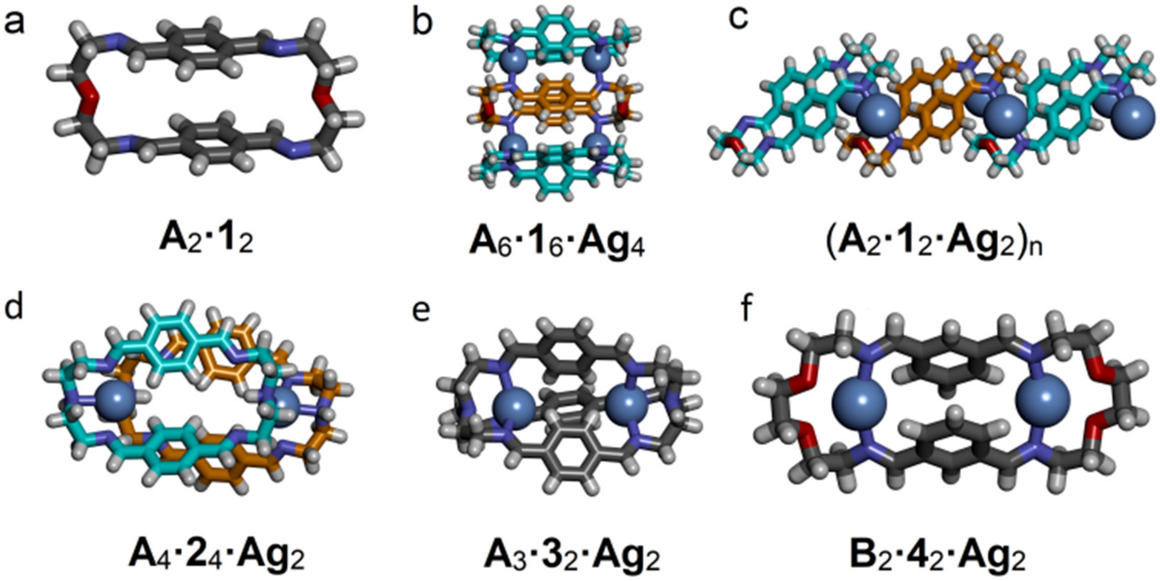


Figure 1. Crystal structures of macrocyclic (**a**) $\mathbf{A_2{\cdot}1_2}$, metallosupramolecular macrocycles and cages (**b**) $\mathbf{A_6{\cdot}1_6{\cdot}Ag_4}$, (**c**) $(\mathbf{A_2{\cdot}1_2{\cdot}Ag_2})_n$, (**d**) $\mathbf{A_4{\cdot}2_4{\cdot}Ag_2}$, (**e**) $\mathbf{A_3{\cdot}3_2{\cdot}Ag_2}$, and (**f**) $\mathbf{B_2{\cdot}4_2{\cdot}Ag_2}$.

When the compound diethylenetriamine (**2**) was mixed with dialdehyde **A** in a ratio of 1:1, no crystal was detected without the presence of the metal cation, leaving only a cyclic imine product formed in solution. With the addition of Ag^+, interestingly, the formed crystal $\mathbf{A_4{\cdot}2_4{\cdot}Ag_2}$ was a cage (Figure 1d) constructed of double-layer macrocyclic dimers instead of a polymeric-layered one. The Ag^+ metal ions are four-coordinated by diethylenetriamine arms from two neighboring macrocycles.

By expanding the structure of the amine part from 2D to 3D, tris(2-aminoethyl)-amine (TREN) **3** was chosen to react with dialdehyde **A** and AgOTf, in a ratio of 3:2:2 and the crystal structure of cryptand $\mathbf{A_3{\cdot}3_2{\cdot}Ag_2}$ was obtained (Figure 1e), with four nitrogen atoms in each TREN molecule to coordinate with Ag^+ metal ions. The narrow-shaped structure with high atom density on each end and three aromatic rings in the middle gave very little space inside the cage. As a result, this very compact monomeric structure is the only one amplified in the solid state and no other polymeric crystal packing structures with a higher degree of complexity were detected during the crystallization process.

Efforts to increase the chain length by using 2,2′-(ethylenedioxy)-bis(ethylamine) **4** as the diamine to react with dialdehyde **A** did not result in the formation of any exploitable single-crystal formation, with or without the presence of Ag^+. On the other hand, isophthalaldehyde (**B**) led to macrocycle crystals $\mathbf{B_2{\cdot}4_2{\cdot}Ag_2}$ upon interaction with diamine **4**, together with AgOTf (Figure 1f). The reason for the unique formation of the macrocycle between **B** and **4** can be attributed to the asymmetrically distributed aldehyde groups in **B**, which provided the possibility for the long-chain diamine **4** to naturally expand between the twisted two aromatic rings and the formation of two O_2N_2 macrocycles coordinating the Ag^+ metal ions on two inner coordinating sites. However, no crystals were further obtained by mixing dialdehyde **B** with amine compounds **1**, **2,** or **3**, even with the coordination possibilities with Ag^+, probably due to the steric hindrances from meta-positioned dialdehyde when mixed with short-chain amines.

So far, by one-to-one mixing of each aldehyde and amine compound, distinct crystal structures have been obtained and amplified through the out-of-phase crystallization-driven selection. Within this type of dynamic systems possessing the possibility of forming various formats of the products, including macrocycles, cages, and polymers, the obtained results have already demonstrated the high selectivity and screening efficiency of the crystallization-driven process. Furthermore, we would like to push the dynamic adaptive selection to a library scale by expanding the system with the addition of more starting components, for example, other aldehyde or amine compounds, together in one pot. However, due to the requirement for a certain degree of purity during the crystallization procedure, the size of the dynamic libraries has been limited.

Thus, we established two small dynamic libraries that were examined with or without the presence of Ag^+. The reactivity of different diamines or aldehydes in solution and the competitive crystallization ability in each dynamic library can be screened with proper references:

- **L1**: dialdehyde **A** with diamines **1** and **2**;
- **L2**: diamine **1** with aldehydes A and C.

The first library, **L1**, was generated by mixing **A**, **1**, and **2** in a molar ratio of 1:1:1. For analysis, the reaction in solution was followed by ^{1}H-NMR while the crystals were collected and compared to the parameters of each possible crystal, respectively. In the absence of Ag^+, an excess of complex $\mathbf{A{\cdot}2}$ was found in solution slowly exchanging with low-concentrated homocomplex $\mathbf{A{\cdot}1}$ and heterocomplex $\mathbf{A{\cdot}1{\cdot}2}$ (Figure 2b), while no crystal formation was detected from these mixtures. After the addition of Ag^+, complex peak patterns could be identified from the NMR spectra, reminiscent of fast and low exchange species present in solution. Interestingly, homocomplex $\mathbf{A{\cdot}1}{\cdot}Ag^+$ species could be easily identified in solution, although with a low conversion, while the $\mathbf{A_6{\cdot}1_6}{\cdot}Ag_4$ cage was selectively formed in a solid crystalline state.

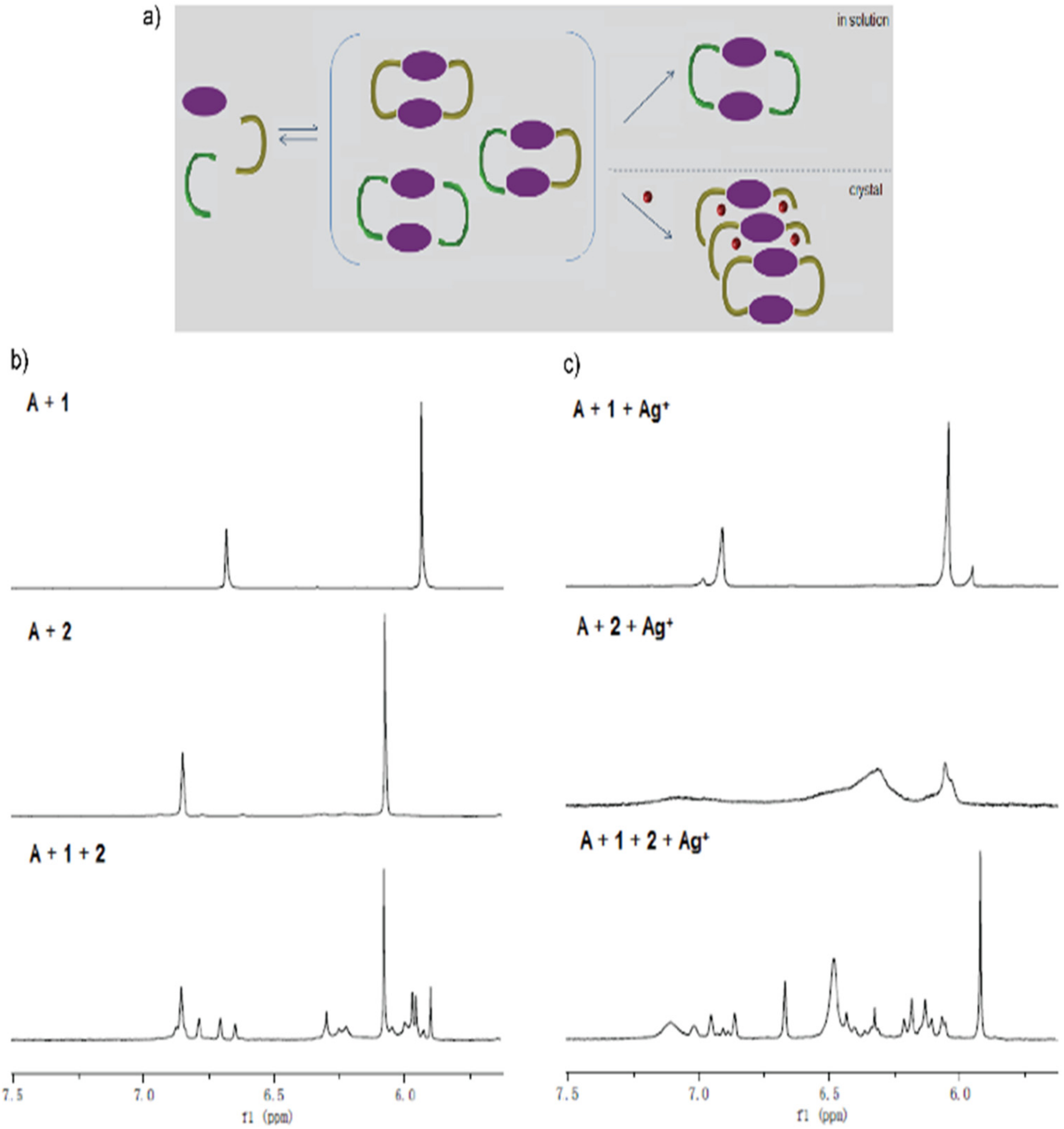


Figure 2. (**a**) Schematic presentation of a selection from the dynamic library **L1** containing dialdehyde **A** and amines **1** and **2**. ^{1}H-NMR spectra of L1 (**b**) with the absence and (**c**) with the presence of Ag^+.

Then, a second library **L2** containing dialdehyde **A**, 1,3,5-positioned trialdehyde **C**, and diamine **1**, in a ratio of 3:2:3, was established. The same analytical methods as ^{1}H-NMR and X-ray crystallography were adopted to monitor the dynamic systematic screening processes. We previously reported that trialdehyde **C** reacting with diamine **1** generates a cage of $\mathbf{C}_2{\cdot}\mathbf{1}_3$ or an interconnected cage metallosupramolecular Ag^+ polymer $(\mathbf{C}_2{\cdot}\mathbf{1}_3{\cdot}Ag_2)_n$. [16]. As a result, in the absence of Ag^+, the **A·1** complex was preferred to be formed in the mixture, with a lower amount of **C·1** shown in the ^{1}H-NMR spectra (Figure 3b); meanwhile, crystal **C·1** was detected out of solution as well. On the other hand, with the presence of Ag^+ to coordinate and stabilize the imine products, the **C·1·Ag** complex was selectively produced in solution, while only the $\mathbf{A}_6{\cdot}\mathbf{1}_6{\cdot}\mathbf{Ag}_4$ cage crystal was collected in solid state. These are very interesting results, since not only did the addition of Ag^+ trigger the change of the optimal components, but also the crystallization process showed different ligand preferences than in solution (More detailed data see in supplementary materials).

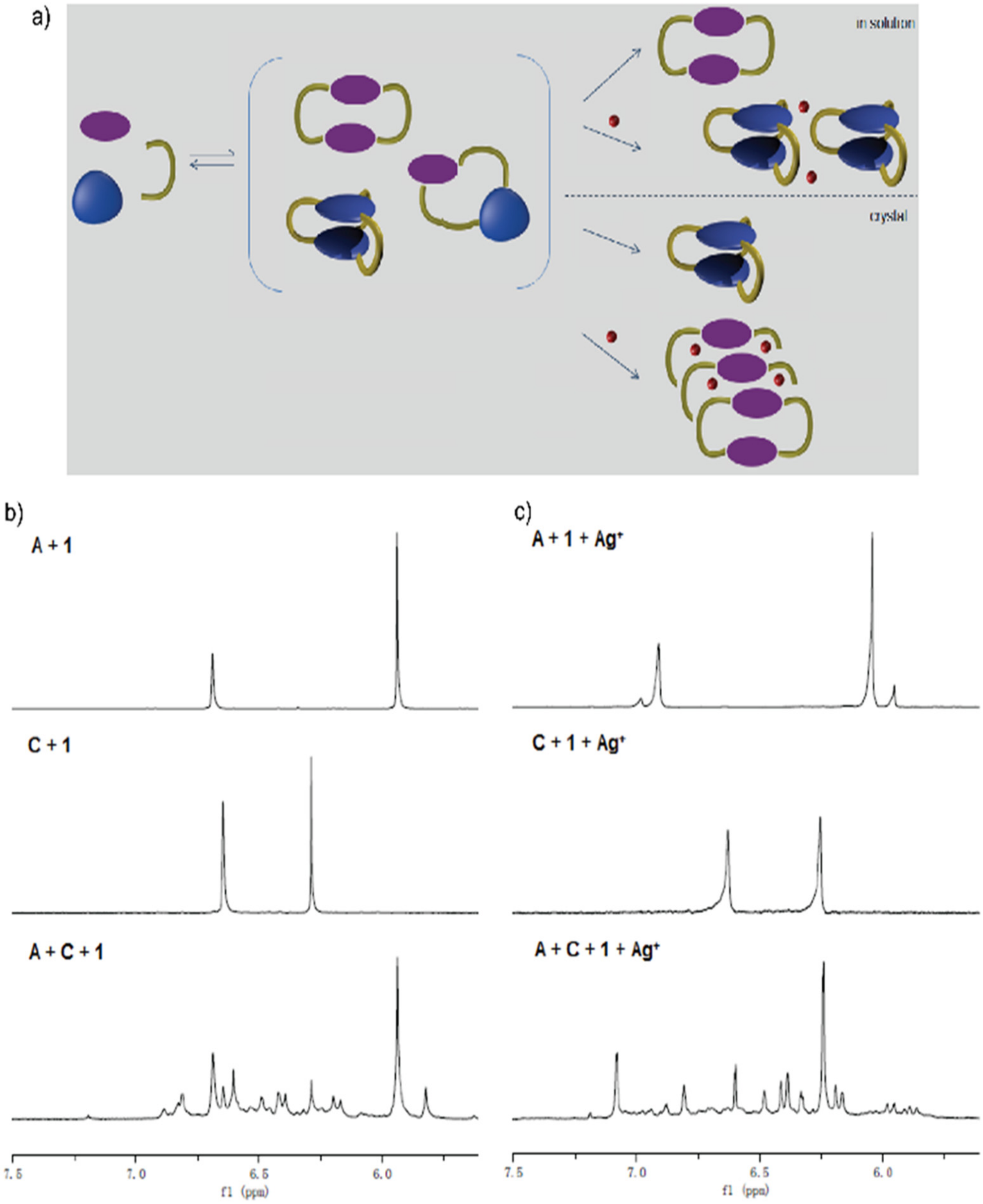


Figure 3. (**a**) Schematic presentation of selection from a dynamic library containing dialdehyde **A**, trialdehyde **C**, and amine **1**. ^{1}H-NMR spectra of L2 (**b**) with the absence and (**c**) with the presence of Ag$^+$.

In conclusion, we discovered new Ag$^+$ coordinated imine crystals from simple dialdehyde and amine compounds, which led to macrocycle crystal structures, cages of two- or three-layer macrocycles, and even supramolecular polymers. Among the various complex possibilities, the out-of-phase amplification has again proved the amplification effect of imine-connected systems. Furthermore, the dynamic libraries have been generated by mixing more than one aldehyde or amine compound in one system. The resulted change of constituent selection upon addition of Ag$^+$, or by comparing chemical distribution in solution and solid states, has fully exemplified the adaptivity of dynamic systems towards different internal structural constraints.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry4040084/s1, Figure S1: ^{1}H NMR spectrum of crystal $A_2{\cdot}1_2$. Figure S2: ^{1}H NMR spectrum of crystal $\mathbf{A_6{\cdot}1_6{\cdot}Ag_4}$. Figure S3: ^{1}H NMR spectrum of crystal $\mathbf{A_4{\cdot}2_4{\cdot}Ag_2}$. Figure S4: ^{1}H NMR spectrum of crystal $\mathbf{A_3{\cdot}3_2{\cdot}Ag_2}$. Figure S5: ^{1}H NMR spectrum of crystal $\mathbf{B_2{\cdot}4_2{\cdot}Ag_2}$. Figure S6: Full ^{1}H NMR spectra comparison for dynamic library 1, containing dialdehyde **A** and amine **1** and **2**, with or without the presence of Ag^+. Figure S7: Full ^{1}H NMR spectra comparison for dynamic library 2, containing dialdehyde **A**, trialdehyde **C**, and amine **1**, with or without the presence of Ag^+. Table S1: Crystallographic data. References [34–38] are cited in the supplementary materials

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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