

Controllable Self-Assembly of Pills and Cages via Imine **Condensation for Silver Cation Detection**

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Supporting Information

ABSTRACT: By condensing a trisamino linker with one of the two analogous bisaldehyde ligands, pills and tetrahedrons could be self-assembled. The self-assembled preference could be controlled by tuning the reaction conditions, including the size of side chain, concentration, and temperature. Coordination of silver cation quenches the fluorescence of the fluorene moieties on the pill, opening up opportunities for Ag⁺ cation detection.

R, R 0 1a : R = Me TREN 1b : R = Bu 3a : R = Me 2a : R = Me 3h · R = Bu 2h · R = Bu

 \mathbf{C} elf-assembly¹ is a more-advanced approach in synthesizing • molecules with complex architecture and topology, compared to the stepwise syntheses relying on irreversible bond formation.²⁻⁴ Dynamic bonds, including metal-ligand coordinative bonds⁵⁻¹¹ and supramolecular bonding interactions, 12-14 as well as reversible covalent linkages, 15-27 are employed to connect the building blocks for self-assembly of the target complex molecules. These dynamic bonds form in a reversible forming/cleaving manner, allowing the selfassembled products to search for their thermodynamic minimum. The implication is that a target molecule could be produced in high yields-in some cases, even to a quantitative yield-when the compound represents the most thermodynamically favored product.^{28,29} This could be accomplished by sophisticatedly designing the self-assembly precursors or controlling the reaction conditions. Therefore, it would be of importance to unravel the relationship between the selfassembly preference and the reaction factors, such as geometries of the building blocks,³⁰ solvent,³¹ reaction temperature,^{32,33} concentration,³⁴ usage of guest template,³⁴ etc. Herein, we demonstrate (Figure 1) that condensation of one of the two pseudo-linear bisaldehyde ligands bearing a fluorene group and a trisamino linkage leads to the formation of a mixture of a pill-shaped and a tetrahedral cage, which are self-assembled in the manner of $\begin{bmatrix} 2 + 3 \end{bmatrix}$ and $\begin{bmatrix} 4 + 6 \end{bmatrix}$, respectively. The self-assembly pathway could be influenced by both intrinsic and extrinsic reaction effects, including (i) more bulky side chains on the bisaldehydes favor the formation of tetrahedral product; (ii) higher precursor concentration favors the tetrahedrons; (iii) higher reaction temperature favors the molecular pills; and (iv) addition of metal cations shifts the equilibrium to the side of the pills almost exclusively. Interestingly, after coordination of a silver cation, the



Figure 1. Structural formulas of the capsules 2a and 2b, as well as the tetrahedral cages 3a and 3b, by condensing the corresponding bisaldehyde precursors 1a or 1b with the trisamino linker TREN in CDCl₂.

fluorescence of a pill is almost fully quenched, implying that the self-assembled pill product represents a promising platform for silver detection.

Two pseudo-linear bisaldehyde ligands-namely, 1a and 1b—were synthesized via a Sonogashira coupling reaction.³⁵ The two bisaldehyde compounds both containing a fluorene central moiety have similar geometry, except that they have

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different side chains, which are methyl and butyl on 1a and 1b, respectively. Ligand 1b bearing butyl side chains is significantly more soluble in CDCl₃. We first combined 1a (0.27 mg, 1 mM) and tris(2-aminoethyl)amine (TREN) (0.07 mg, 0.83 mM) in CDCl₃ (0.6 mL). The TREN/1a ratio is slightly higher than 2:3, to guarantee the full conversion of the aldehyde precursor, given that the error often occurs in weighing a small amount of substances. The mixture solution was kept at 25 °C for 12 h, and its ¹H NMR spectrum was recorded (see Figure 2A). A set of relatively sharp resonances



Figure 2. Partial ¹H NMR spectra (500 MHz, CDCl₃, 298 K) of the self-assembled products by combining 1a (1 mM) and TREN (0.83 mM) (spectrum (A)), combining 1b (1 mM) and TREN (0.83 mM) (spectrum (B)), and combining 1b (6 mM) and TREN (5 mM) in $CDCl_3$ (spectrum (A)). In spectra (A)–(C), the resonances of tetrahedral cages 3a and 3b were labeled with blue arrows, even though, in spectrum (A), 3a is barely observable, because of its low yield. In spectra (B) and (C), the resonances of the pill 2b were labeled with red arrows. Slow diffusion of diisopropylether into the solution analyzed in spectrum (C) yielded several single crystals corresponding to 3b, which were dissolved in CDCl_3 , and the corresponding ¹H NMR spectrum was recorded and shown in spectrum (D). A solution of AgBF₄ (15.9 mM) in CD₃OD (62.7 μ L) was added into the solution (CDCl₃/0.6 mL) of the self-assemled products combining 1b (2 mM) and TREN (1.67 mM) containing both 2b and 3b, which resulted in a remarkable change in the ¹H NMR spectrum, as shown in spectrum (E). All the spectra were recorded a substantial amount of time after mixing the corresponding starting materials, in order to allow the systems to reach the equilibrium.

were observed in the ¹H NMR spectrum, indicating that a pillshaped capsule **2a** with relatively high symmetry was produced as the predominant product. The ¹H NMR yield of **2a** was calculated to be 82%, by using ethyl acetate as an internal standard in the NMR sample. The ¹H NMR spectrum (Figure 2A) of **2a** differs from that of the precursor **1a**. For example, the resonance of proton *c* on the fluorene moiety of **2a** underwent a remarkably upfield shift ($\delta \approx 6.2$ ppm, $\Delta \delta \approx 1.5$ ppm), indicating the occurrence of the CH- π interactions between one of the protons *c* with an adjacent fluorene moiety. Proton *c* therefore experiences a shielded magnetic environment within the pill framework. The structures of **2a** was further confirmed by two-dimensional (2D) NMR spectroscopy (see Figures S13 and S14 in the Supporting Information) and mass spectrometry (Figure S15 in the Supporting Information). Another set of resonances are barely observed and labeled with blue arrows in Figure 2A. These resonances correspond to a tetrahedron 3a as a minor product, whose NMR yield was determined to be <5%. The trials to increase the yield of 3a by either increasing concentration or lowering temperature were proven to be unsuccessful (see Figure S32 and Table S2 in the Supporting Information), indicating that 2a is significantly thermodynamically favored compared to 3a.

When 1b (0.32 mg, 1 mM) was combined with tris(2aminoethyl)amine (TREN) (0.07 mg, 0.83 mM) in CDCl₃ (0.6 mL) at 25 °C, two sets of resonances were observed in the ¹H NMR spectrum (Figure 2B). This observation indicates that two major products were obtained, including a pill 2b and a tetrahedron 3b, which were self-assembled in the manner of [2 + 3] and [4 + 6], respectively. Pill 2b is an analogue of 2a, which also has a characteristic upshifted proton resonance due to the CH- π interactions. The yields of 2b and 3b are 46% and 33%, respectively, determined by using an internal standard. The peaks corresponding to both 2b and 3b are observed in the mass spectra (see Figures S19 and S20 in the Supporting Information).

Increasing the precursor concentration gradually shifted the equilibrium to the tetrahedron side. For example, condensing 1b (4 mM) and TREN (3.33 mM) in CDCl₃ (0.6 mL) at 25 °C produced a mixture of 2b (21%) and 3b (51%), respectively. When the concentrations of 1b and TREN further increased to 6 mM and 5 mM, the self-assembly mixture at equilibrium (Figure 2C) contained 2b and 3b, in yields of 19% and 65%, respectively. The higher yield of 3b at higher condensation concentration is consistent with Le Chatelier's principle. i.e., raising concentration shifts the equilibrium to the direction that could help to decrease the compound molarities. Therefore, tetrahedron 3b, which could be considered as a dimer of 2b, is more favored at higher concentrations. The self-assembly of both 2b and 3b is under thermodynamic control. This proposition could be proven by the observation that the self-assembled system containing 2b and 3b underwent re-equilibration by changing the concentration.

The yield of **3b** could be further increased by lowering the temperature. For example, by condensing 1b (4 mM) and TREN (3.33 mM) in CDCl₃ (0.6 mL) at 0 $^{\circ}$ C, the yields of **2b** and 3b became 20% and 71%, respectively. This is because 3b, which is composed of more building blocks than 2b, is less stable, in terms of entropy. Therefore, at lower temperature, when the entropic effect is attenuated, the formation of 3b could be more favored. Relatively pure solid-state 3b was obtained by means of crystallization. This was done by slow diffusion of diisopropylether into the aforementioned solution of a 2b/3b (20%/71%) mixture at a lower temperature, namely 0 °C. Sadly, the quality of these single crystals is not good enough for X-ray diffraction. The crystals were redissolved for solution-state characterization. Once dissolved, 3b underwent re-equilibration and decayed into a 2b/3b mixture over the course of one or two days. Luckily, this tetrahedral compound was kinetically stable for a few hours, during which its structure was confirmed by both ¹H NMR (Figure 2D) and twodimensional NMR spectroscopy (Figures S24 and S25 in the Supporting Information). A ¹H NMR diffusion-ordered spectroscopy (DOSY) experiment (see Figures S16, S21, and S26, as well as Table S1 in the Supporting Information)

demonstrates that **3b** has a smaller diffusion coefficient than that of **2b** in CDCl₃. The hydrodynamic radii (r_c) of **2b** and **3b** were calculated to be 0.84 and 1.21 nm, respectively, an observation which further confirms our argument that **3b** contains more building blocks and has a larger size, compared to **2b**.

Diffraction-grade single crystals of **2a** (Figure 3A) and **2b** (Figure 3B) were obtained by slow vapor diffusion of isopropyl



Figure 3. Side view of the core structure of (A) **2a** and (B) **2b** obtained from single-crystal X-ray diffraction experiments. [Legend: white, hydrogen atoms; gray, carbon; blue, nitrogen.] The disordered solvent molecules, as well as hydrogen atoms that are not involved in the CH $-\pi$ interaction, are omitted for the sake of clarity.

ether into the corresponding CDCl₃ solutions of the selfassembled mixtures, which provided unambiguous evidence for the formation of these two pills. In the solid-state structures of 2a and 2b, the corresponding H-centroid distances between one of the fluorene protons and an adjacent fluorene moiety are \sim 2.8 Å, which is an observation confirming the occurrence of CH $-\pi$ interactions. These observations were also consistent with the aforementioned observation that, in the ¹H NMR spectrum (Figure 2A), proton c undergoes a remarkable upfield shift. In 2a, the six methyl side chains are located in relatively remote positions, with respect to each other. As a comparison, in the case of 2b, the six more bulky butyl side chains introduce relatively larger steric hindrance occurring in the manner of either chain-chain or chain-fluorene. For example, the closest contact between a methylene proton in one butyl chain and an adjacent fluorene proton is only 2.4 Å. This steric hindrance decreases the thermodynamic favoritism of 2b and shifts the equilibrium to tetrahedral cage 3b, whose structure has larger interchain distances.

It is well-reported that TREN residues represent a type of ideal tetradentate ligand to coordinate to metal cations.^{36,37} Therefore, we investigated the possibility^{38,39} of using metal cations to control the self-assembly preference of the 3b/2b mixture. A variety of metal cations, including Zn²⁺, Ag⁺, Co²⁺, Ni^{2+} , Cu^+ , Fe^{2+} , were added to the mixture solution of 3b/2b. The corresponding ¹H NMR spectra indicate that addition of these cations converted the 3b/2b mixture into $2b\cdot 2$ M (M = Zn^{2+} , Ag^+ , Co^{2+} , Ni^{2+} , Cu^+ , Fe^{2+}) almost exclusively (see Figures S37-S42 in the Supporting Information). We reasonably hypothesize that the TREN residues in 2b might have a more convergent conformation than that in 3b. The former pill thus represents a better tetradentate ligand to coordinate to the metal cations, forming more-stable metal complexes. We also obtained a few single crystals of these complexes. However, their quality did not seem good enough for single-crystal X-ray diffraction (XRD) studies. The

formation of $2b \cdot 2Ag^+$ was confirmed by matrix-assisted laser desorption ionization—time of flight (MALDI-TOF) mass spectrometry (see Figure S30 in the Supporting Information). Upon cation coordination, $2b \cdot 2$ M undergoes a fluorescence change (Figure 4A), compared to the 3b/2b mixture. Zn^{2+} ,



Figure 4. (A) Fluorescence spectra of a mixture of 2b/3b obtained by condensing 1b (1.2×10^{-2} mM) and TREN (1×10^{-2} mM) in the mixture solvent of CHCl₃ and CH₃OH (v/v = 15:1), after addition different amount of Ag⁺ cation in the mixture solvent of CHCl₃ and CH₃OH (v/v = 15:1). (B) Fluorescence spectra of a mixture of 2b/3b obtained by condensing 1b (1.2×10^{-2} mM) and TREN (1×10^{-2} mM) in the mixture solvent of CHCl₃ and CH₃OH (v/v = 15:1). (B) Fluorescence spectra of a mixture of 2b/3b obtained by condensing 1b (1.2×10^{-2} mM) and TREN (1×10^{-2} mM) in the mixture solvent of CHCl₃ and CH₃OH (v/v = 15:1), after addition 1 equiv (i.e., relative to the precursor TREN) of different cation solutions in the mixture solvent of CHCl₃ and CH₃OH (v/v = 15:1). (C) Fluorescence intensity at the λ_{max} of the spectra in panel (B). (D) Photograph of the solutions used for panel (B), demonstrating the relative fluorescence intensity of the 2b/3b mixture upon coordination with various metal cations. It was observed that Ag⁺ can almost fully quench the fluorescence of the self-assembled products.

Co²⁺, Ni²⁺, and Fe²⁺ were observed to enhance the fluorescence of the self-assembled 3b/2b mixture (Figure 4B). As a comparison, Ag^+ or Cu^+ are able to quench the fluorescence to some extent (Figures 4A,B). It is noteworthy that addition of 1 equiv of Ag⁺ relative to the TREN precursor could quench the fluorescence close to completely (Figure 4C and 4D), i.e., the luminescence intensity at λ_{max} is only 6%, compared to the solution before the addition of Ag⁺. This quenching behavior might potentially be employed to detect a silver cation, although this detection might be disturbed by the presence of Cu⁺. The trials to investigate the sensing ability of **2a** toward metal cations such as Ag⁺ or Cu⁺ were unsuccessful. This is because the poor solubility of 2a in polar solvents such as MeOD, i.e., adding the solution of the metal cations in MeOD into a CDCl₃ solution of 3a/2a mixture, led to precipitation of the cage products. Addition of the same amount of MeOD without the corresponding Ag⁺ solute into the solution of 3b/2b mixture barely influenced the fluorescence intensity (see Figure S43 in the Supporting Information). This experiment ruled out the hypothesis that the fluorescence quenching of 3b/2b mixture might also result from the addition of MeOD.

In summary, pills and tetrahedrons could be self-assembled by condensing pseudo-linear bisaldehyde compounds with a triamino linkers via imine condensation in relatively high yields. The self-assembly preference could be tuned by changing the temperature and concentration, as well as the addition of metal cations. The side chains on the pseudo-linear compounds introduce steric hindrance during the formation of pills, thus favoring the formation of tetrahedron. The addition of the silver cation could remarkably quench the fluorescence of the fluorene unit in the pill, which opens up opportunities for developing silver cation sensors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b03174.

Details of experimental procedure and characterization data (PDF)

Accession Codes

CCDC 1852721 and 1852722 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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