Intra- and intermolecular self-assembly of a 20 nm-wide supramolecular hexagonal grid

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For the past three decades, the coordination-driven self-assembly of 3D structures has have witnessed a rapid growth. Parallel efforts however to create large discrete 2D architectures, as opposed to polymers, have met with limited success. Indeed, the synthesis of metallosupramolecular systems with well-defined shapes and sizes in the range of 10–100 nm remains challenging. Here, we report the construction of a series of giant supramolecular hexagonal grids, with diameters on the order of 20 nm and molecular weights greater than 65 kDa, through a combination of intra- and intermolecular metal-mediated self-assembly steps. Hexagonal intermediates and the resulting self-assembled grid architectures were imaged at sub-molecular resolution by scanning tunneling microscopy. Characterization including by scanning tunneling spectroscopy enabled the unambiguous atomic-scale determination of fourteen hexagonal grid isomers.

The spontaneous self-assembly of multiple distinct building blocks is ubiquitous in nature and underlies the biosynthesis of numerous functional proteins and protein complexes[1,2]. Inspired, perhaps, by the precision of nature, in recent years supramolecular chemists have exploited the highly directional and predictable features of metal coordination to construct an impressive variety of metallosupramolecular structures[3-18]. We note however that these bottoms-up approaches have mainly given rise to either discrete assemblies smaller than 10 nm[8,9,19,20] or infinite coordination-based polymers[21,22]. Meso-sized (10-100 nm) discrete architectures with specific sizes and shapes are rare[13,23,24], likely due to the challenges associated with the fact that they are difficult to design and reliably synthesize, the intricate self-assembly processes required for their synthesis, and difficulties in their characterization. Here, we describe 2D ensembles in the 20 nm-size domain that have been produced by coordination-driven self-assembly.

In an effort to address the challenge of constructing large synthetic systems with well-defined sizes and shapes, we have combined intra- and intermolecular self-assembly, to prepare a 20-nm-wide metallosupramolecular hexagonal grid **5** with 8 isomers based on different substructure orientations (Fig. 1). The initial intramolecular self-assembly process which is reminiscent of the folding process of peptides or proteins[25,26] occurs on complexation with Fe^{2+} metal ions. Subsequent intermolecular self-assembly, also governed by complexation with Fe^{2+} ions, leads to the formation of 2D grids. As detailed below, the underlying intra- and intermolecular self-assembly processes were studied using several characterization techniques including high-resolution, ultrahigh-vacuum, low-temperature scanning tunneling microscopy

(UHV-LT-STM)[13,27] and tunneling spectroscopy. This has allowed us to characterize and identify these synthetic isomeric constructs at the atomic level.

Results and Discussion

Synthesis of supramolecular hexagonal grid. We first prepared the building block **3** in a stepwise manner combining capping strategy[6,13] and Suzuki coupling[20,28,29] with a metal-free terpyridine (tpy) (Supplementary Figs 4-6). It is the presence of open coordination sites in **3** that permits the Fe(II)-mediated intra- then intermolecular self-assembly steps to occur in a programmable manner. For instance, the addition of the first equivalent of Fe(II) favors metal-mediated intramolecular self-assembly and formation of **4** in almost quantitative yield. The relatively rigid nature of **4**then permits further self-assembly in the presence of two equivalents of Fe(II). This was found to produce the targeted meso-scale 2D construct **5** containing 13 hexagons as well as 18 Fe(II) and 36 Ru(II) metal centers, as well as 108 counterions.

As illustrated schematically in Fig. 1, **5** can flip over during self-assembly, leading to different arrangements of the Ru(II) and Fe(II) centers within **6** and thus lead to the unpredictable order of Ru(II) and Fe(II) within the outer rims. This limited programmable ambiguity is reminiscent of so-called fuzzy protein complexes in nature that are likewise characterized by a level of structural ambiguity or multiplicity[30,31]. In theory, 8 isomers (Fig. 1) could exist in solution. As a result, we faced significant challenges in characterization and were unable to identify each isomer in a mixture using conventional solution-phase approaches such as NMR spectroscopy and mass spectrometry. However, as detailed below this system proved amenable to characterization when placed on a solid support.

Characterization in solution. Electrospray ionization-mass spectrometry (ESI-MS), traveling wave ion mobility-mass spectrometry (TWIM-MS)[32], as well as NMR spectroscopy, were used to characterize the intra- and intermolecular and self-assembly processes leading to **5**. After exposure of **3** to one equivalent of Fe(II), complex **4** was obtained in almost quantitative yield without the need for purification. A downfield shift was seen for the tpy$H^{3',5'}$ resonance, while an upfield shift was seen for the tpy$H^{6,6''}$ signal in the ^{1}H NMR spectrum (Supplementary Fig. 9). Such findings provide support for the suggestion that the first equivalent of Fe(II) is selectively coordinated as would be expected for the formation of **4**; ESI-MS and TWIM-MS spectra (Fig. 2, a to d) further confirmed the molecular composition. On the basis of these combined findings, it was concluded that no other assemblies were formed at detectable levels during the intermolecular complexation process leading to **4**.

As noted above, treatment of **4** with an additional two equivalents of Fe(II) led to grid **5**. This construct, with a calculated molecular weight of 65,790 Da, is to our knowledge one of the largest 2D discrete metallo-supramolecules prepared to date[13,23,24]. ESI-MS analysis revealed a series of peaks from 29+ to 66+ (Fig. 2e), each of which agreed with the calculated mass-to-charge ratio for the corresponding charge state. A TWIM-MS analysis of **5** gave one set of signals, as would be expected for such a highly rigid system (Fig. 2f). Presumably, as the result of structural isomerism, the ^{1}H NMR spectrum of **5** was characterized by the presence of broad signals, allowing only coordination between the tpy and a complexed Fe(II) ion to be inferred from the downfield shift in the tpy$H^{3',5'}$ signals relative to **4**. A Diffusion Ordered Spectroscopy (DOSY)[33] study of **5** revealed one single band with log D = -10.15 (Supplementary Figs. 71 and 72). Such a finding is consistent with the formation of a single

discrete species and rules out the presence of substantial quantities of random coordinated polymers[34].

Characterization on surface. UHV-LT-STM was then used in an effort to further characterize grid **5**. The goal was to obtain insights into this class of supramolecular grids on two levels: i) imaging the constituent intra- and intermolecular self-assembled structures and ii) ascertaining the presence of isomers. It was expected that the low temperature (5 K), used in these UHV-LT-STM studies, would reduce thermal motion and permit high resolution imaging. In the first study, the flexible ligand **3** was dissolved in MeCN and drop cast on an Ag(111) surface. Due to the octahedral coordination structure and higher electron density around the metal ions, the <tpy-Ru(II)-tpy> units gave rise to a relatively strong signal in the form of a bright lobe when compared to the organic portions (Fig. 3). It is also possible for **3** to generate conformations on the surface due to the free rotation about the C-C single bonds. Indeed, these conformations could be detected in STM images (Fig. 3a). In all conformers, the triangle pattern made up of three <tpy-Ru(II)-tpy> linkages that define the branching point in **3** could be easily identified. In sharp contrast to **3**, only one conformation was observed for the hexagon ring **4** (Fig. 3b), which was formed by adding one equivalent of Fe(II) into a solution of **3**. In the case of **5**, each <tpy-metal(II)-tpy> was observed as a bright lobe with a pistachio-shaped morphology in the STM images (Fig. 3c to 3e). Importantly, 13 uniform hexagonal rings were seen as expected on the basis of our design (Fig. 3d). Moreover, the entire construct was found to have a diameter of ~20 nm and a height of ~6 Å (Fig. 3e to 3g); these values agree well with those expected on the basis of theoretical modeling (Supplementary Fig. 8).

Isomer identification. The presence of isomers with **5** was then studied by means of dI/dV-V tunneling spectroscopy[35,36]. This is a technique that probes the local density of states (LDOS), and thus is a method that may be used to identify the Fe(II) and Ru(II) ions, particularly in disordered domains. Tunneling spectra were measured by positioning the STM tip above each lobe of a complex of **5** on Ag (111) surface at a fixed height with a bias range of ±2V. From *dI/dV-V* the energy gap between the HOMO and LUMO can be directly obtained[37]. Thus, from the tunneling spectroscopic measurements of each <tpy-metal(II)-tpy> unit, we were able to differentiate the Fe(II) and Ru(II) centers, which provide different energy gaps.

Initial studies were conducted using **4**, which has only one coordinated Fe(II) ion. Due to symmetry breaking on the surface, complex **4** forms two separate isomers on the Ag(111) surface that are characterized by different Fe(II) locations (Fig. 4b and 4c). Among the seven sites, one site in each isomer (cf. Fig. 4b and 4c) gives a HOMO-LUMO gap of 2.5 eV (Fig. 4d) while the remaining six sites in each isomer provide a gap value of 2.8 eV (Fig. 4e). Thus, we could assign the site with a smaller gap, 2.5 eV, as Fe (II) and that of the larger gap, 2.8 eV, as the Ru (II) site. This assignment was further confirmed by density theory (DFT) calculations, which revealed that the projected density of states (PDOS) for the Fe(II) and Ru(II) centers match the experimental results (Supplementary Fig. 74). The band gap for Fe(II) is 2.4 eV, while that for Ru (II) is 2.8 eV. In addition, a Kondo effect was also detected for several Fe(II) centers (Supplementary Fig. 75). A Kondo effect is originated from many body interactions between the magnetic moment of Fe (II) and free electrons from the substrate[38]. Because Fe (II) typically has a higher magnetic moment as compared to Ru (II), a stronger Kondo effect is expected for the Fe(II) centers present in **4** for further differentiation (Fig. 4b to 4e).

Based on the above predicative studies involving **4**, an effort was made to characterize the disordered domain within grid **5**. 14 limiting isomers are possible for this supramolecular construct on the surface (Fig. 4a). Being able to distinguish the Fe(II) and Ru(II) centers was considered to be the key in identifying these isomers. Tunneling spectroscopy measurements were performed on metal sites in the disordered domain of **5**; this was done by collecting multiple tunneling spectra and then comparing the results to the averaged values obtained in **4**. Among the twelve data points obtained in this way, half of them provided a bandgap of 2.9 eV, while another six sites were characterized by a lower bandgap of 2.4 eV. Therefore, the metal centers with the higher energy gap are assigned as Ru(II) and the ones with the lower energy gap are assigned to Fe(II). This particular complex is one specific isomer (cf. Fig. 4i). Using a similar procedure, atomic scale tunneling spectroscopy analyses were carried out on a total of 63 molecules allowing us to collect data for all 14 isomers (Supplementary Figs. 76 to 89). A statistical analysis of the results allowed us to confirm that the probability of occurrence for each isomer matches well what would be predicted based on theory (Supplementary Figs 90 to 93). This concordance leads us to suggest that self-assembly of each intramolecular self-assembled building block constitutes an independent event, and that the orientation of Fe(II) in the intramolecular intermediate does not affect the formation of the final product.

In the above study, we observed slight differences in the energy gaps for the same type of metal ions in **4** and **5** [*i.e.*, 2.8 eV vs. 2.9 eV and 2.5 eV vs. 2.4 eV for Ru(II) and Fe(II), respectively]. Such a small difference in energy is attributed to the differences in the chemical environment produced as the result of self-assembly. Moreover, a given metal cation within the hexagonal grid **5** might be characterized by different electronic density of states (EDOS).

Based on the chemical environment, the entire grid **5** could be categorized into seven domains with color coding as shown in the Supporting Information (Supplementary Fig. 94). Among the four domains with Ru(II), the innermost one exhibits a distinct difference with a smaller band gap, possibly due to the close distance to the inner Fe(II) domain, while the other three are found to be similar (Supplementary Figs. 95 and 96). Among the three domains of Fe(II), the innermost domain is characterized by the smallest energy gap.

In order to visualize this, the color codes were constructed using the averaged *dI/dV* curves of each coordination site and overlaid on the STM image of Fig. 4f (cf. Figs. 4j and 4k, uncolored original version could be found in Supplementary Fig. 73). The color bar is defined in terms of the changes in the *dI/dV* signal at 1.65 eV and -1.6 eV (Supplementary Figs. 95 and 96). At +1.65 eV, all <tpy-Fe(II)-tpy> units except the innermost Fe(II) domain exhibited higher DOS values (displayed with red). Meanwhile, all <tpy-Ru(II)-tpy> units are characterized by lower DOS values (shown in yellow). At -1.6 eV, all of the Ru(II) domains produce a lower DOS values and are colored purple; also, the Fe(II) centers within the disordered domain and the middle domain give higher DOS values and are shown in blue. In contrast, the innermost Fe(II) domain show the lowest DOS values at +1.65 eV, but the highest DOS values at -1.6 eV; both of which are colored in green.

Conclusions

Compared to the self-assembly of metallo-supramolecules characterized by a single well-defined structure, our design strategy led to the construction of many structural isomers both in solution and on a supporting metal surface. Sub-molecular resolution is achieved using

UHV-LT-STM along with atomic scale tunneling spectroscopy characterization. We hope that by introducing other metal ions, such as Co(II) instead of Fe(II), it should prove possible to produce hexagonal grids that can act a single molecule information storage devices through, *e.g.*, manipulation of the underlying spin states[39]. More broadly, we believe that the present demonstration of the bottom-up preparation of 20 nm-sized molecules with precisely controlled shapes and structures will advance our understanding of the design principles governing the preparation of 2D self-assembled constructs and allow access to meso-sized materials with as-yet unprecedented functions and properties.

Methods

TWIM-MS. The TWIM-MS experiments were performed under the following conditions: ESI capillary voltage, 3 kV; sample cone voltage, 30 V; extraction cone voltage, 3.5 V; source temperature 100 ºC; desolvation temperature, 100 ºC; cone gas flow, 10 L/ h; desolvation gas flow, 700 L/h (N_2); source gas control, 0 mL/min; trap gas control, 2 mL/min; helium cell gas control, 100 mL/min; ion mobility (IM) cell gas control, 30 mL/min; sample flow rate, 5 μL/min; IM traveling wave height, 25 V; and IM traveling wave velocity, 1000 m/s.

Molecular modeling. Energy minimization of the supramolecular hexagon grids was conducted with Materials Studio version 4.3, using the Anneal and Geometry Optimization tasks in the Forcite module (Accelrys Software, Inc.). The effects of the counterions (if any) were omitted in the modeling. Geometry optimization was conducted using a universal force field with atom-based summation and cubic spline truncation for both the electrostatic and van der Waals parameters.

Density Functional Theory Calculation. Spin-polarized density functional theory (DFT) calculations were performed using the Vienna ab initio simulation package (VASP) code[40,41,42], and the core electrons are described by the projected augmented wave method[43]. Exchange-correlation was treated in the Generalized Gradient Approximation, as implemented by Perdew et al.[44] The plane wave basis was expanded to a cutoff of 600 eV and the Brillouin zone was sampled using Γ point only. Because of the giant size of Hexagonal Grid molecule, which is composed of repeated 13 hexagonal rings, calculations were performed on a single ring composed of 540 atoms.

STM. UHV-LT-STM experiments were performed at 5 K using a Createc GmbH type STM scanner. The Ag(111) sample was cleaned by repeated cycles of sputtering and annealing up to 1000 K. An electrochemically etched polycrystalline tungsten wire was used for the STM tip. The tip apex was prepared by using a controlled tip-crash procedure. The fuzzy hexagon grid was deposited onto the cleaned Ag(111) surface at 25 °C, and then cooled to 5 K inside the STM system.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions:

X.L. and Y.L. conceived and designed the experiments. Z.Z. and Y.L. completed the synthesis. Y.L., B.S., Y.Z., S. W. H and R.T performed STM. Z.Z., X.J. and M.W. conducted NMR. Z.Z. performed MS characterization. T.R. and A.T.N performed DFT calculations. Y.L., B.S., Z.Z., Y.Z., S.W.H, J. L.S., G.R.N. and X.L. analyzed the data and wrote the manuscript. All the authors discussed the results and commented on and proofread the manuscript.

Competing interests:

The authors declare no competing financial interests.

Data and materials availability:

All data are available in the manuscript or the supplementary materials.

Supplementary Materials:

Supplementary Schemes 1-6

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Fig. 1 Synthetic strategy of ligand followed by intra- and intermolecular self-assembly of supramolecular hexagonal grids with Fe(II). a. Synthesis and chemical structure of building block **3**. b. Intra- and intermolecular self-assembly process and schematic representation of 8 isomers generated from the unpredictable orientation of the terpyridine-metal(II)-terpyridine (<tpy-metal(II)-tpy>) junction during the intermolecular self-assembly process. All the detailed isomeric structures could be found in Supplementary Scheme 3.

Fig. 2 Mass spectrometry for characterization of the folding and self-assembly processes leading to 5. (**a**, **c** and **e**) Electrospray ionization-mass spectra (ESI-MS) of **3, 4** and **5**. The peaks with continuous charge states were achieved by losing different numbers of counterions (Cl^- for **3** and PF_6^- for **4** & **5**, respectively), which confirms the molecular weight of 3, 4 and 5 with single chemical composition. (**b**, **d** and **f**) Travelling wave ion mobility-mass spectra (TWIM-MS) plot (*m/z* vs. drift time) of **3, 4** and **5**. Each charge state signal showed one single band with narrow drift time distribution, which excluded formation of conformers during the intra- and intermolecular complexation process.

Fig. 3 STM imaging of the intra- and intermolecular self-assembled structures on Ag (111) surface. (**a**) Schematic representation and STM images of different conformations of building block **3**, scale bar 2 nm [Imaging parameters: V_t = 2 V, and I_t = 120 pA]. (**b**) Complex **4** produced by the addition of one equivalent of Fe(II) to **3**, scale bar 2 nm [Imaging parameters: V_t = 2 V, and I_t = 120 pA]. The bright lobes represent each <tpy-metal(II)-tpy> junction. (**c**) Magnified image of a single supramolecular hexagon grid **5** produced by adding two equivalents of Fe(II) to **4**, scale bar 5 nm, the <tpy-metal(II)-tpy> junction were observed as bright lobes with pistachio-shaped morphology; (**d**) A large area STM image of **5** showing the presence of multiple hexagon grids, scale bar 20 nm [Imaging parameters: V_t = 2 V, and I_t = 110 pA]. (**e**) STM image of the supramolecular grid **5** with molecular modeling overlay [Imaging parameters: V_t = 3 V, and I_t = 38 pA]. (**f** and **g**) STM line profile measurements made along the green and blue dashed lines shown in (e) revealed the height and the size of the supramolecule **5**.

Fig. 4 Isomeric forms of 5 on substrate and their characterization by scanning tunneling spectroscopic (STS) (**a**) Schematic representation of the 14 possible isomers that were considered likely to be present on Ag (111) surface. (**b** and **c**) UHV-LT-STM images of **4** in two different orientations on the supporting Ag(111) surface [Imaging parameters: V_t = 2 V, and I_t = 120 pA]. dI/dV-V tunneling spectroscopy data of (**d**) Fe(II) (blue) and (**e**) Ru(II) (red) correspond to different electronic features in **4**. (**f**) STM image of the supramolecular grid **5** showing 12 metal ions subject to analysis [Imaging parameters: V_t = 2 V, and I_t = 110 pA]. (**g** and **h**) dI/dV-V tunneling spectroscopy analyses of Fe(II) (blue) and Ru(II) (red) corresponding to the hexagonal grid shown in (f). (**i**) Model of the hexagonal grid shown in (f). The intensities of single point STS data measured over each lobe in (f) at +1650 meV and -1600 meV are shown with colour codes in (**j**) and (**k**), respectively: The six Fe(II) centers within the inner ring are in green colour while the STS intensities of Fe(II) and Ru(II) ions at the outer rings at +1650 meV are in red and yellow (**j**), and at -1600 meV are in blue and purple in (**k**).