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Directed flexibility: self–assembly of a supramolecular tetrahedron

James M. Ludlow III, Tingzheng Xie, Zaihong Guo, Kai Guo, Mary Jane Saunders, Charles N. Moorefield, Chrys Wesdemiotis, and George R. Newkome

Self-assembly of a tribenzo-27-crown-9 ether functionalized with six terpyridines generated (85%) an expanded tetrahedral structure comprised of four independent triangular surfaces interlinked by crown ether vertices.

Metal–ligand self-assembly has been utilized to form various metallosupramolecular structures including coordination polymers,1 macrocycles,2,3 and 3D structures.4,5 The N-heteroaromatic ligand [2,2′,6′,2″]terpyridine (tpy) has received increasing attention due in part to its ability to coordinate diverse transition metals permitting control of bond strengths, properties, and desired molecular architectures.6,7 With metals that can form strong coordinative bonds, e.g. OsO4, RuO4, and FeO4, the final product is kinetically determined by creating irreversible <tpy-MOtpy> linkages; in contrast, metals capable of more labile coordinative bonds, e.g. ZnO2 and CdO2, give access to the thermodynamic products.

Specific architectures are determined, in part, by the geometry of the building blocks, i.e. angle(s) of the conjoined ligands with respect to one another. Exploiting the angular orientation and stoichiometric control of precursors is generally known as a directional bonding approach to supramolecular synthesis.8 As shown in Scheme 1, ligands with 60° angles have been used to form triangular structures.9,10 The structural and kinetic favorability of triangular-based systems has been harnessed, through use of multitopic 60°-based ligands to create large and intricate architectures, such as a spiked wheel11 and the Sierpiński triangle.12 A synthetic improvement via replacement of a 120° angle with two 60° angles has also been demonstrated.13 These triangle-based architectures are planar and utilize 60° ligands, e.g. ortho-aryl, and can introduce a rigid framework into the resultant end product. Likewise, in biomolecular systems, directionality and positioning of non-covalent interactions are critical to molecular recognition and supramolecular structure formation, for example hydrogen bonding in protein structures and base pairing in DNA. Also, flexibility plays a key role in such systems to allow the folding and winding necessary to achieve the required structure and function. Using a similar strategy of balanced directionality and flexibility, Scheme 1 depicts the quantitative construction of a rigid triangular component9 that can be used to align other highly flexible components, such as the tribenzo-27-crown-9 ethereal vertices (Schemes 2 and 3). Flexible linkages, such as crown ethers, have been used in conjunction with multitopic terpyridine ligands;14 however, these examples did not incorporate angular directionality and isolation of cyclic species required use of non-labile metals and purification via chromatography. Flexibility can also be incorporated into cage forming N-donor ligands via methylene bridges15,16.

Herein, we describe the design and synthesis (Scheme 2) of a novel hexa[terpyridine] ligand containing three 60° juxtaposed bisligands connected by a flexible crown ether vertex (5) and demonstrate its self-assembly with ZnO2 to generate an expanded tetrahedral structure under thermodynamic control (Scheme 3). The flexible vertex allows an extension into a 3D structure, which was studied via ESI-TWIM-MS, TEM, 1D and 2D NMR, as well as molecular modeling. The NMR studies and molecular modeling indicate the presence of parallel (π-π) and T-shaped (CH-π) interactions of stacked tpy complexes, which would be forbidden by more traditional, rigid architectures. A model ‘free triangle’ (2) is synthesized for comparison (Scheme 1) to demonstrate the influence of the tetrahedral structure.

Scheme 1. Synthesis of the simplest ‘free triangle’ 2.

Scheme 2. Synthesis of the vertex reagent 5.
NMR confirmed proton assignments (Figures S5-8 in the Supplemental Information).

thereby supporting the bisterpyridine Zn²⁺ complexation; no uncomplexed terpyridine was observed. Both COSY and NOESY ¹H NMR confirmed proton assignments (Figures S5-8 in the Supplemental Information).

Figure 1. 500 MHz ¹H NMR spectra – aromatic region at 20 °C. Bottom: neat ligand 5 (CDCl₃) at 10 mg/mL and top: L⁴M₁₂ in CD₃CN/DMF-d₅ (5:1) at 0.6 mg/mL. *-DMF.

Figure 2 compares the aromatic regions of 2 and L⁴M₁₂. Since the ‘free triangle’ 2 is, essentially, chemically identical to the interlinked triangles of L⁴M₁₂, any differences observed in chemical shift must arise from the L⁴M₁₂’s supramolecular structure. A single set of terpyridines is observed for each, with the sole exception of the aryl singlets, all of the resonances of L⁴M₁₂ is observed for each, with the sole exception of the aryl singlets. ESI-MS coupled with travelling wave ion mobility²² (TWIM) was used to further support the tetrahedral structure (Figure 4). L⁴M₁₂ shows the expected step pattern of charge states. Each charge state has a narrow drift time distribution indicative of an absence of superimposed isomers or conformers. Experimental collision cross-sections were calculated using the TWIM data and are shown in Table 1. ESI-MS coupled with travelling wave ion mobility²² (TWIM) was used to further support the proposed structure: Gradient tandem mass spectrometry²² (gMS²) was used to probe the stability of L⁴M₁₂ by subjecting the 10⁺, 8⁺, and 6⁺ charge states to collisionally activated dissociation (with Ar gas) prior to ion mobility separation (Figure S11). Collision energies of 45, 60, and 80 eV, respectively, were required to fully dissociate the complex. These translate into center-of-mass collision energies (Ecm) of 1.0184, 1.0614, and 1.0376 eV.

Variable temperature (VT) ¹H NMR experiments were conducted on both L⁴M₁₂ and 2. As the temperature was lowered, the chemical shift attributed to the L⁴M₁₂ shows that the 5,5” peaks are shifted upfield. Conversely, the chemical shifts of the protons in 2 were insensitive to temperature variations (Figure S9). Similar chemical shift changes with temperature were also observed with stacked <tpy-M²⁺-tpy> complexes.⁵,²⁰ This result implies that, as molecular motion is decreased, the shielding effect from the tetrahedral structure is enhanced. Conversely, the environment of the aromatic protons of 2, where intramolecular stacking cannot occur, has been shown to be insensitive to the degree-of-molecular motion. Previous reports⁵ indicate that the proton signals of cyclic <tpy-M²⁺-tpy> trimers, such as 2, show negligible chemical shift changes when the temperature is varied.

L⁴M₁₂ was characterized by ESI-MS (Figure 3). The series of peaks match with charge states 5⁺ through 10⁺ for the combination of 4 ligands, 12 metals (Zn²⁺), and the corresponding number of PF²⁻ anions. ESI-MS coupled with travelling wave ion mobility²² (TWIM) was used to further support the tetrahedral structure (Figure 4). L⁴M₁₂ shows the expected step pattern of charge states. Each charge state has a narrow drift time distribution indicative of an absence of superimposed isomers or conformers. Experimental collision cross-sections were calculated using the TWIM data and are shown in Table 1. ESI-MS coupled with travelling wave ion mobility²² (TWIM) was used to further support the proposed structure: Gradient tandem mass spectrometry²² (gMS²) was used to probe the stability of L⁴M₁₂ by subjecting the 10⁺, 8⁺, and 6⁺ charge states to collisionally activated dissociation (with Ar gas) prior to ion mobility separation (Figure S11). Collision energies of 45, 60, and 80 eV, respectively, were required to fully dissociate the complex. These translate into center-of-mass collision energies (Ecm) of 1.0184, 1.0614, and 1.0376 eV.

Figure 3. ESI-MS of L⁴M₁₂ showing a series of peaks corresponding to charge states 5⁺ thru 10⁺ and (inset) theoretical and experimental isotope patterns for the 10⁺ charge state; 0.6 mg/mL in MeCN/DMF (5:1).

Figure 4. ESI-TWIM-MS plot of L⁴M₁₂ (m/z vs. drift time). 0.6 mg/mL in MeCN/DMF (5:1).
A dilute solution of L4M12 (ca. 10^-5 M, MeCN/DMF, 5/1) was cast onto Cu grids and observed via transmission electron microscopy (TEM). Dimensions of the observed, discrete nanostructures (Figure 5) correspond well with measured molecular model dimensions. The calculated edge length for the tetrahedron is ca. 3.5 nm, which closely matches the ca. 4 nm observed in the TEM. Molecular modeling of L4M12 (Figure 5) also indicates close proximity of adjacent complexes. The <tpy-M^2-tpy> protons are projected into the adjacent complex unit and should, therefore, be more highly shielded than in a non-stacked complex, such as the free triangle as is demonstrated in Figure 2. These results match with observations seen in previously reported stacked <tpy-M^2-tpy> species. The presence of the slipped parallel (σ-σ) and T-shaped (CH-π) stacking interactions are shown; these π-π interactions are generally regarded as energetically favorable, and are reported to be -6.2 and -10.3 kJ·mol^(-1), respectively, in model systems. Such cooperative interactions could stabilize the tetrahedral structure and/or promote its formation relative to other structures in which such intramolecular interactions do not occur. Metal-to-metal distances in the model closely match those reported for stacked tpy complexes formed from parallel bis-ligands. For example, the metal-to-metal distances in L4M12 ranged from ca. 9.2 to 9.5 Å vs. 8.8 Å in the reported complex. Stacked tpy complexes have been confirmed in a variety of solid-state structures.

The internal volume of L4M12 is estimated to be ca. 2400 Å^3, making it an excellent candidate for guest-host chemistry. 19F NMR was used to probe anion encapsulation properties of L4M12 in solution. The 19F spectra of L4M12 with PF6^- counterions (volume 62Å^3) only showed one peak. Previous studies of cage-like structures using PF6^- have reported that this occurs with rapid endo-exo anion exchange relative to the NMR timescale. 13,14 To reduce the exchange rate, the larger and tetrahedral anion, tetrakis(perfluorophenyl)borate (BARF) (volume 446 Å^3), was used to precipitate L4M12. The 19F NMR of L4M12 with BARF counterions showed the presence of additional, smaller peaks at -151.6, -182.7, and -183.8 ppm (Figure 6) suggesting the presence of a dynamic equilibrium of one or more BARF counterions within the cavity. As expected, these endo peaks were not detected with 2 using BARF as the counterions.

![Figure 5](image51x192to300x423)  
**Figure 5.** TEM with magnified inset and space filling model cutaways of L4M12 showing stacked <tpy-M^2-tpy> complexes. Color scheme: H: white; C: grey; N: purple; O: red; Zn: green. The 4,4” and 5,5” protons are noted (right). Regions of T2-shaped (CH2-π) and parallel (π-π) interactions are noted (left).

![Figure 6](image470MHz19FNMRL4M12topand2(middle)bothinCD3CN/DMF-d5(5:1)at20°C,1mg/mLwithBARFcounterions.BottomspectrumshowsnearK-tetra(perfluorophenyl)borate.)

**Figure 6.** The 470MHz 19F NMR of L4M12 (top) and 2 (middle) both in CD3CN/DMF-d5(5:1) at 20 °C, 1 mg/mL with BARF counterions. Bottom spectra shows near K-tetra(perfluorophenyl)borate.

Finally, using a strategy of balanced directionality and flexibility, we describe the design and synthesis of a novel hexakisterpyridine ligand containing a trio of 60°-directed bisligands connected by crown ether vertices and its self-assembly into a tetrahedral structure under thermodynamic control. The flexible vertex allows a controlled extension into new 3D structures facilitated by intramolecular π-σ interactions. Molecular modeling supports the NMR data suggesting the presence of parallel (σ-σ) and T-shaped (CH-π) interactions in the close-packed tpy complexes. VT NMR experiments support this model in which 19F NMR experiments are indicative of the presence of BARF within the cavity. The crown ether groups can serve as "pores" or ports for molecular guests and/or anchoring sites for further supramolecular interactions; work in this direction is ongoing.

**Acknowledgments**

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**Notes and references**


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**Table 1.** Experimental and theoretical CCS values for L4M12. Standard deviations are in parenthesis.
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Self-assembly of 4 terpyridine-modified, flexible crown ether ligands with 12 Zn$^{2+}$ ions results in high yield tetrahedron construction.