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Self-assembly of a family of suprametallomacrocycles: revisiting an o-carborane bisterpyridyl building block

James M. Ludlow III, Masato Tominaga, Yoshiki Chujo, Anthony Schultz, Xiaocun Lu, Tingzheng Xie, Kai Guo, Charles N. Moorefield, Chrys Wesdemiotis,* and George R. Newkome*

Reaction of an o-carborane-based, bisterpyridyl building block with a labile metal gives mixtures of the enthalpically and entropically favored ring architectures and can be driven to the entropically favored product by dilution. NMR and ESI-TWIM-MS and molecular modeling afforded insights into the parameters affecting ring formation.
Self-assembly of a family of suprametallomacrocycles: revisiting an o-carborane bisterpyridyl building block

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The self-assembly of the o-carborane-based, bisterpyridyl monomer, 1,2-bis[4'-(4-ethynylphenyl)-2,2':6',2''-terpyridine]-o-carborane, utilizing either ZnII or FeII in a precise metal:ligand ratio (1:1), generated a family of metalmacrocycles that were studied via ESI-TWIM-MS, 1H NMR, and 2D NMR (COSY, NOESY). Under kinetic control, via formation of FeII complexes, the main cyclic product was triangular, as is typical of 60°-based bisligands. Under thermodynamic control using more labile transition metal complexes, e.g. ZnII, the ratio of cyclic species was found to be concentration and temperature dependent, and under an adequate entropic driving force, the cyclic dimer was formed. This system was probed via variable temperature NMR to reveal dynamic equilibrium between the entropically favored dimer and enthalpically favored trimer.

Introduction

Carborane-containing macromolecules exhibit several properties of interest, including chemical and thermal stability, aggregation induced emission (AIE), radiation shielding coatings that enable their use in medical applications, and boron neutron capture therapy (BNCT). Consequently, carboranes have been incorporated into a variety of macromolecular structures, including polymers and dendrimers in order to instill water-solubility and enhance their properties and utility. These approaches primarily rely upon covalent bonding; however, biomolecular systems exploit a range of weaker, non-covalent inter- and intra-molecular forces, including van der Waals, hydrogen bonding, π-π stacking, electrostatic, and coordination to achieve macro-molecular structure. Notably, the incorporation of carborane into (metallo)supramolecular structures has received limited attention.

Metal-ligand self-assembly has been utilized to form various metallosupramolecular structures including coordination polymers, macrocycles, and 3D structures. The incorporation of [2,2':6',2"]terpyridine (tpy) has received increasing attention due in part to its ability to coordinate with

![Figure 1](https://example.com)
diverse transition metals permitting control of bond strengths, properties, and desired molecular architectures. Terpyridine-based materials have found various applications, including supramolecular chemistry, catalysis, nanoparticles, electroactive nanostructures, and life science applications. With metals that can form strong coordinate bonds, such as Os, Ru, and Fe, the final product is kinetically determined by creation of irreversible \( <\text{tpy-M}\text{-tpy}> \) complexes; in contrast, metals capable of more labile coordinate bonds, e.g. Zn and Cd, allow equilibration to the thermodynamic product.

Specific architectures are thus determined, in part, by building block geometry, e.g., the angle between conjoined ligands. Exploitation of the angular orientation and stoichiometric control of precursors is generally known as the directional bonding approach to supramolecular synthesis. Ortho-carboranes possess an angle of 53° between substituents attached to the two adjacent carbon atoms and are thus well-suited for macrocyclizations, as has been reported with 60°-oriented bisligands.

Chujo and Kokado recently reported the synthesis and characterization of bis(terpyridyl) o-carborane 1, which was subsequently complexed with Zn (Figure 1) to give a coordination polymer that was investigated via \(^1\)H NMR, UV-Vis, and fluorescence spectroscopies. The polymerization was also evaluated under various (metal \( \text{II} \) to ligand) ratios. However, additional product characterization was not pursued with respect to possible discrete structure formation as is standard practice for polymeric reactions. With reports detailing related 60°-based bisterpyridine ligands (e.g. 2) that give almost exclusively cyclic structures, we investigated further.

In collaboration with the Chujo group, it was subsequently confirmed that, with a 1:1 metal to ligand ratio, o-carborane 1 forms predominately (85%) macrocyclic structures, including the dimer, trimer, and tetramer along with minor polymeric and oligomeric species. To assess the self-assembly of 1 in a non-labile system, Fe was used to form stable \( <\text{tpy-Fe}\text{-tpy}> \)-based macrocycles (Scheme 1), which were easily separated by column chromatography. The ratio of trimer to dimer was ca. 8:1 with isolated yields of 30 and 4%. This indicates that the kinetic, cyclic product is a triangle, as is typical of a nominal 60° ligand, such as 1. To assess self-assembly of 1 in a labile system, Zn was used to form \( <\text{tpy-Zn}\text{-tpy}> \) complexes. Variable temperature \(^1\)H NMR and dilution studies indicated that the relative ratio of cyclic species was concentration and temperature dependent; whereas, with more dilute conditions and higher temperatures the dimer is favored. As well, sufficient dilution drove the system exclusively to the cyclic dimer, a structure more characteristic of a bis-parallel ligand 3. Furthermore, van’t Hoff analysis indicated an equilibrium between the entropically favored dimer and the enthalpically favored trimer (Scheme 2). The resultant product distributions were characterized via ESI-TWIM-MS, \(^1\)H NMR, and 2D NMR (COSY, NOESY). Molecular modeling was undertaken on the dimer, trimer, and tetramer species in order to obtain additional structural insights.

**Experimental**

**Materials, synthesis, and analytical data**

Chemicals were commercially purchased and used without further purification. Thin layer chromatography (TLC) was conducted on flexible sheets (Baker-Flex) precoated with Al\(_2\)O\(_3\) (IB2-F) or SiO\(_2\) (IB2-F) and visualized by UV light. Column chromatography was conducted using basic Al\(_2\)O\(_3\), Brockman Activity 1 (60-325 mesh) or SiO\(_2\) (60-200 mesh) from Fisher Scientific. \(^1\)H NMR spectra were recorded on a Varian 500 MHz spectrometer. Variable temperature NMR was conducted on a Varian 400 MHz NMR spectrometer; the temperature was varied from -40 to +70 °C in 10 °C increments. The temperature range was limited by the melting and boiling points of CH\(_3\)CN. Electrospray ionization (ESI) mass spectra (MS) were obtained on a Synapt HDS quadrupole/time-of-flight (Q/ToF) mass spectrometer (Waters Corp., Milford, MA). The Synapt Q/ToF instrument contains a travelling wave ion mobility (TWIM) device, in which ions drift under influence of a traveling wave field against the flow of the carrier gas (N\(_2\)). This process disperses ions based on their mass, charge, and shape. The separated ions travel through a transfer cell from which they are conveyed to an orthogonal ToF analyzer for m/z measurement. The acquired data are typically displayed in 2-D plots of m/z ratio vs. the corresponding drift time through the IM cell. TWIM MS experiments were performed under the following conditions: ESI capillary voltage, 1 kV; sample cone voltage, 8 V; extraction cone voltage, 3.2 V; desolvation gas flow, 800 L/h (N\(_2\)); trap collision energy (CE), 3 eV; transfer CE, 1 eV; trap gas flow, 1.5 mL/min (Ar); TWIM cell gas flow, 22.7 mL/min (N\(_2\)); sample flow rate, 5 µL/min; source temperature, 30 °C; desolvation temperature, 40 °C; TWIM wave height, 7.5 V; and TWIM wave velocity, 350 m/s. TWIM data analyses were conducted using the MassLynx 4.1 and DriftScope 2.1 programs provided by Waters. Modeling and energy minimization of complexes were done with Spartan (Wavefunction, Inc.).

**Bisterpyridyl o-carborane 1** was synthesized and characterized according to the literature (Figure S1).

**Complex synthesis**

\( \text{Zn}_n(\text{I}) \quad (n = 2 \cdot 4) \) (ZnC2 – ZnC4): To a stirred solution of ligand 1 (23 mg, 24 µmol) in CHCl\(_3\) (10 mL), was added a MeOH (2.4 mL) solution of Zn(OAc)\(_2\)·2H\(_2\)O (2.4 mL, 24 µmol), then stirred at 25 °C for 1 h. Excess NH\(_4\)PF\(_6\) was added to precipitate the complexes.

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**Scheme 1.** Complexation of ligand 1: Conditions for ZnC2-4: Zn(OAc)\(_2\)·2H\(_2\)O, CHCl\(_3\); MeOH (4:1 v/v); and for FeC2-4: FeCl\(_3\), CHCl\(_3\); MeOH (3:2 v/v). Representations of the cyclic dimer (MC2), trimer (MC3), and tetramer (MC4).

**Scheme 2:** Equilibrium between ZnC3 (trimer) and ZnC2 (dimer).
added and stirred. The resultant cream-colored precipitate was filtered and washed with copious amounts of MeOH to give (85 %) complex \( \text{Zn}(1)_n \): 24 mg, m.p. >30 °C; \(^1\)H NMR (CD3CN, 500 MHz): \( \delta = 8.99 \) (s), 8.93 (s), 8.73 (d, \( J = 8 \) Hz), 8.62 (d, \( J = 8 \) Hz), 8.24 (d, \( J = 9 \) Hz), 8.15 – 8.22 (m), 7.71 - 7.97 (m), 7.73 (d, \( J = 5 \) Hz), 7.68 (d, \( J = 9 \) Hz), 7.64 (d, \( J = 9 \) Hz), 7.52 (d, \( J = 9 \) Hz), 7.47 (d, \( J = 9 \) Hz), 7.41 (dd, \( J_1 = 9 \) Hz, \( J_2 = 5 \) Hz), 7.19 (dd, \( J_1 = 9 \) Hz, \( J_2 = 5 \) Hz), 7.20 – 3.00 ppm (br m, B2H2). ESI–MS analysis of a dilute solution of \( \text{Zn}(1)_n \)_3 (1:1 v/v) and \( \text{Zn}(1)_n \)_2 (2:1 v/v) were taken at each concentration and the relative proportion of cyclic dimer was assessed via integration of the two 3',5' singlets (Figure 4). Upon dilution, the singlet at 8.99 ppm diminishes relative to the singlet at 8.93 ppm indicating an equilibrium shift toward the dimer relative to the trimer. And, the \(^1\)H NMR and ESI-MS data showed the dimer \( \text{Zn}(2)_2 \) as the major product (Figures 4 and 5). 

**Effects of Concentration on the Zinc Complexes**

The \( \text{Zn}(1)_n \)_3 system showed concentration dependence; thus, a dilution study was performed in CD3CN. \(^1\)H NMR spectra were taken at each concentration and the relative proportion of cyclic species was assessed via integration of the two 3',5' singlets (Figure 4). Upon dilution, the singlet at 8.99 ppm diminishes relative to the singlet at 8.93 ppm indicating an equilibrium shift toward the dimer relative to the trimer. And, the \(^1\)H NMR and ESI-MS data showed the dimer \( \text{Zn}(2)_2 \) as the major product (Figures 4 and 5).

ESI–MS analysis of a dilute solution of \( \text{Zn}(1)_n \)_3 (20 µg/mL) supports the presence of the dimer \( \text{Zn}(2)_2 \) (Figure 5). Thus, the more shielded set of protons is exclusively from the dimer. This shift to an entropically favored species follows Le Chatelier’s Principle. As concentration is decreased, the system responds by shifting the equilibrium toward the species assembled with fewer components. The sharp, distinct peaks from each set of tpy protons indicate a rapid equilibrium between molecular architectures relative to the NMR time scale.
fractions were derived from integration of each 3',5' peaks. The assumption was made that the upfield peak represents trimer, exclusively. This assumption is safest at the higher end of the temperature range studied so the data from 10 – 70 °C was used. Assuming ideal behavior, $K_{eq}$ for the equilibrium shown in Scheme 2 can be written:

$$K_{eq} = \frac{\text{[dimer]}^3}{\text{[triangle]}^2} \quad (1)$$

The van't Hoff equation is shown in (2).

$$\ln K_{eq} = \frac{\Delta H_{eq}}{RT} + \frac{\Delta S_{eq}}{R} \quad (2)$$

A van't Hoff plot was constructed and analyzed (Figure S10). $\Delta H_{eq}$ for conversion of two triangles into three dimers was found to be positive (ca. 12 kJ/mol) indicating that dimer formation is endothermic and suggesting that the cyclic dimer is the more strained structure. $\Delta S_{eq}$ was positive (ca. 40 J/mol K) reflecting the increase in the number of macrocycles, as the equilibrium shifts to the dimeric species. These results are similar to dynamic equilibrium reported between triangles and squares in labile systems such as Pd$^0$ and Pt$^{11}$ with linear (180°) bispyridyl ligands.\textsuperscript{31-36} Equilibrium pairs between dimeric and trimeric species are uncommon but have been reported.\textsuperscript{37} This is, to the best of our knowledge, the first reported cyclic dimer-trimer equilibrium driven via <tpy-M$^3$-tpy> complexation.

### Iron Complexes

In order to isolate and study non-labile analogues of these cyclic species, I was reacted with FeCl$_2$ to generate <tpy-Fe$^{II}$-tpy> complexes, which are stable and separable via chromatography. ESI-MS of the crude reaction mixture revealed formation of a variety of cyclic species - primarily dimer, trimer, and tetramer (Figure 7). The most prominent species in the spectra is trimer, FeC$_3$, showing charge states 3+ through 6+. Larger macrocycles, such as pentamer and hexamer, were detected at trace levels.

The dimer and trimer species were isolated chromatographically on SiO$_2$ using H$_2$O/MeCN/sat'd KNO$_3$(aq) (1:30:1; v/v/v) and then converted to PF$_6^-$ salts. The trimer was the main cyclic product isolated as would be expected of a nominal 60° ligand. Both products were characterized by $^1$H NMR (Figure 8) and ESI-TWIM-MS (Figures 9 and S7).
observed difference can be attributed to the more highly shielded proton environment that results from proximity interactions of the dimer's complexes as seen in molecular models. The sharp tpy proton resonances observed in the dimer spectra also suggest correlated rotation of the complexed protons at a rate greater than the NMR timescale. Note that superposition of these spectra would match the pattern seen with the initial zinc system, i.e., two distinct sets of tpy protons and that the dimeric species is further upfield. Assignments were confirmed via COSY and NOESY (Figures S3-5 in Supplemental Information).

Figure 9 (top) shows the ESI-MS spectrum for the FeC2 species, which includes the 4+ and 3+ charge states as well as theoretical and experimental isotope patterns for the 4+ charge state. The ESI-TWIM-MS plot (bottom) shows the expected step pattern and does not indicate the presence of superimposed isomers or conformers. Similar results were observed for the FeC3 species (Figure S7).

Experimental Collision Cross Sections (CCSs)\textsuperscript{17,38,42} were calculated based on TWIM data to further characterize the different architectures (Table 1). Relative CCSs for these architectures show a clear trend with respect to mass. Energy minimized structures were generated for FeC2, FeC3, and FeC4 via simulated annealing. Theoretical CCS values were calculated via the projection approximation (PA) method using MOBCAL and found to be 443 ± 3, 720 ± 2, and 925 ± 1 Å\textsuperscript{2} for FeC2, FeC3, and FeC4, respectively, corresponding well with experimental values. The population of model structures for both FeC3 and FeC4 each included a set of folded conformations showing intramolecular π-π interactions. Their CCS values were calculated separately and found to be 580+/23 and 668+/40 Å\textsuperscript{2}, respectively.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Z} & \textbf{FeC2} & \textbf{FeC3} & \textbf{FeC4} \\
\hline
3+ & 507 & 723 & - \\
4+ & 496 & 770 & - \\
5+ & - & 805 & - \\
6+ & - & 756 & - \\
7+ & - & - & 1068 \\
\hline
\textbf{Average} & 502 & 764 & 1068 \\
\textbf{Std. Dev.} & 8 & 34 & - \\
\hline
\end{tabular}
\caption{Experimental Collision Cross Sections (CCSs) of FeC2, FeC3, and FeC4.}
\end{table}

Molecular Modeling

Molecular modeling provided insight into experimental findings, including the proton shifts relative to the trimer and ligand's ability to behave similarly to a bis parallel ligand. Figure 10 shows the cyclic dimer, the planar cyclic trimer, and the folded cyclic tetramer.

The tetramer architecture is analogous to previously reported Dondorff rings.\textsuperscript{43} The folded conformation of the tetramer reduces strain relative to a planar conformation and is typical for a nominal 60° bis-ligand. The angle between the ligand arms is essentially the same as for the trimer; thus, there is little or no enthalpic penalty to its formation. Cyclic dimer species are generally formed from bis parallel ligands such as 3. A cyclic dimer such as this has not been previously reported with 60° oriented bisterpyridyl ligands. Side-on and end-on views of the dimer are depicted in Figure 11.

The model indicates that the ligand arms must adopt a tighter, more strained angle (ca. 30°) to form the cyclic dimer. The inner 4,4" and 5,5" protons are projected into the adjacent complex unit and should be more highly shielded than in the cyclic trimer. In Figure 2, the \textsuperscript{1}H NMR of this cyclic dimer showed significant upfield shifting of...
the complexed 4,4″ and 5,5″ protons relative to the trimer as expected for a close-packed, metal-terpyridine moiety. 1H NMR also gave a very crisp, single set of tpy protons and yet the model shows that the 4,4″ and 5,5″ protons are also exposed to a non-shielded exterior of the molecule. This suggests gear-like correlated rotation of the intertwined complexes. These results match with observations seen in previous interlocked species.39,44 Both slipped parallel (π-π) and T-shaped (CH-π) stacking interactions can be envisioned. Dimensions of the model also match closely those reported33 for interacting tpy complexes formed from bispyridyl ligands. For example, the metal to metal distance in FeC2 is ca. 9Å vs. reported 3.7-3.9Å for the reported complex.

Factors contributing to the ability of this ligand to form a cyclic dimer include: 1) inherent flexibility of the alkyne moieties, 2) favorable π-π and CH-π interactions between the interacting complexes, 3) length of the arm possessing two phenyls and an alkyne spacer, and 4) 53° angle and C-C bond length of o-carborane.

Though the alkyne group is generally linear, it is flexible as exhibited in cyclooctyne and larger cycloalkynes, where the alkyne group can adopt a cisoid bend due to covalent bonding constraints. In the case of cyclodecyne, the internal strain is reported to be ca. 20 kJ/mol.35 So, while there would be an energetic penalty to adopting the more strained conformation of the dimer - it is not prohibited. Conversely, the π-π interactions upon dimer formation should be energetically favorable at a similar magnitude. Such π-π interactions are generally described as parallel, T-shaped, and slipped-parallel and their respective energies reported36 to be -6.2, -10.3, and -10.4 kJ/mol respectively. In the specific case of π stacking between bispyridine-metal complexes, evidence for its favorability is seen in Constable’s examples, where the complexes interact, even when the spacers linking bispyridines are longer and highly flexible.44 Therefore, the enthalpic penalty of forming these more strained dimers is likely offset to some degree by favorable π-π and CH-π interactions. Also, adequate arm length via two phenyl spacers removes steric obstruction to dimer formation and, though the alkyne is the most flexible part of the arm, it does provide additional structure for strain distribution. Molecular modeling also indicates slight bending of the phenyl rings in the dimer. Characteristics unique to carborane also likely play a role. Relative to the phenyl ring in a ligand such as 1, o-carborane has more narrow bite angle (53° vs. 60°) and longer C to C bond length. While the phenyl C to C bond length is ca. 1.4Å, in carborane the C to C bond is reported47 to range from 1.65 to 1.75Å in the crystal state, indicating that it is not only longer but can adopt a variety of lengths depending upon conditions.

Conclusions

The self-assembly characteristics of the recently reported5 bispyridyl o-carborane 1 were examined and it was found to undergo macrocyclizations when reacted with Zn11, Fe3, characterization was achieved by NMR, ESI- and ESI-TWIM-MS, and molecular modeling. More specifically, using a 1:1 metal-to-ligand ratio, the cyclic dimer, trimer, and tetramer were confirmed as major products. Under kinetic control, i.e. for the Fe11 complexes, the predominant cyclic product was trimeric; whereas, under thermodynamic control, i.e. for the Zn11 complexes, ligand 1 formed the dimer exclusively, given adequate entropic driving force. Molecular modeling suggests that the ligand's alkyne moieties, arm length, and favorable π-π interactions, upon complexation, play a role in enabling this unique behavior. Notably, the potential to obtain discrete products from polymeric-type reactions should be considered, as has been observed in other cases, where polydentate ligands were present.34-36

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Notes and references