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[11] All MD simulations were performed under constant-pressure periodic boundary conditions (NPT ensemble under PBC conditions) using the AMBER 5[12] suite of programs. The explicit solvent model of TIP3P[13] water was used. For each of the simulations, 46 Cl^- ions were added as counterions to neutralize the systems. We built a rectangular box of 5540 solvent molecules for **3c** and of 5991 solvent molecules for **4c** using the program XLEAP. The **3c** and **4c** systems are composed of 17398 and 20479 atoms, respectively. The SHAKE[14] procedure was employed to constrain all bonds involving hydrogen atoms. The time step of the simulations is 1 fs, with a nonbonded interaction cutoff of 8 Å. Details of the MD simulation will be reported elsewhere.

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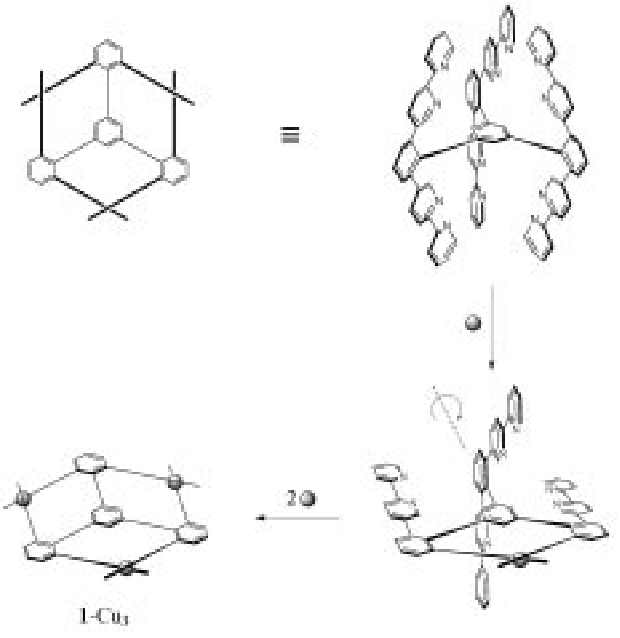
Trinuclear Copper(I)-bipyridine Triskelion: Template/Bascule Control of Coordination Complex Stereochemistry in a Trefoil Knot Precursor[**]

Craig R. Woods, Maurizio Benaglia, Shinji Toyota, Kenneth Hardcastle, and Jay S. Siegel[*]

Projection of a knotted structure in the plane can be oriented to reveal a principal core "crossing structure" and a periphery of connecting arcs. From that perspective, the retrosynthesis of molecular knots and links can be divided into problems related to the control of a) macrocyclizations and b) stereochemistry of "crossing structures". Molecular designs that capitalize on symmetry and cooperativity lead to efficient control of stereochemistry.[1, 2] In the double helicates, the regular helical structure provides cooperative reinforcement for each new metallostereocenter to be of uniform configuration.[3] The identification of the double helix motif in a representation of the trefoil knot is key to understanding the rational synthesis where stereochemical control of helicity dictates the product identity, chirality, and yield.[4–9] An alternative representation of the trefoil knot has a D_3-symmetric core embedded within.[10] This core is also common to the Borromean link motif.[11–14] As such, synthesis and stereochemical control of an appropriate D_3 triskelion would provide a new class of stereoregular polynuclear coordination complexes and set the path to high-symmetry molecular knots and links.

Templating is a tried-and-true method for regulating the juxtaposition of molecular substructures.[15–20] A bascule mechanism pivots about the midpoint of a beam and couples the motion of the two ends such that as one end raises the other lowers.[21] Combining a tripodal template with tangential bascule beams readily evokes a D_3-symmetric construct in which neighboring beam-ends can cross. If these beam-ends were bidentate ligands, their crossing points would constitute binding sites for metals with tetrahedral ligand fields. Thus, emerges a design for a trinuclear copper(I)–bipyridine triskelion (**1**) (Scheme 1). The triskelion comes from three equivalents of a crescent-shaped polyaryl (**2**) and a 1,3,5-triethynyl core.



Scheme 1. Bascule mechanism for binding three metals in a triskelion. ● = Cu^I.

Synthesis of **1** depends heavily on the application of palladium-based Suzuki,[22–24] Stille,[25] and Sonagoshira[26] type aryl couplings (Scheme 2).[27–29] Although one begins from anisyl boronic acid (**3**) and 2,6-dibromopyridine to form 6-anisyl-2-bromopyridine (**4**), the coupling strategy rapidly builds much larger products. The stannylation of **4** occurs by reaction with butyllithium at −78 °C followed by quenching with trimethylchlorostannane. This stannyl reagent reacts

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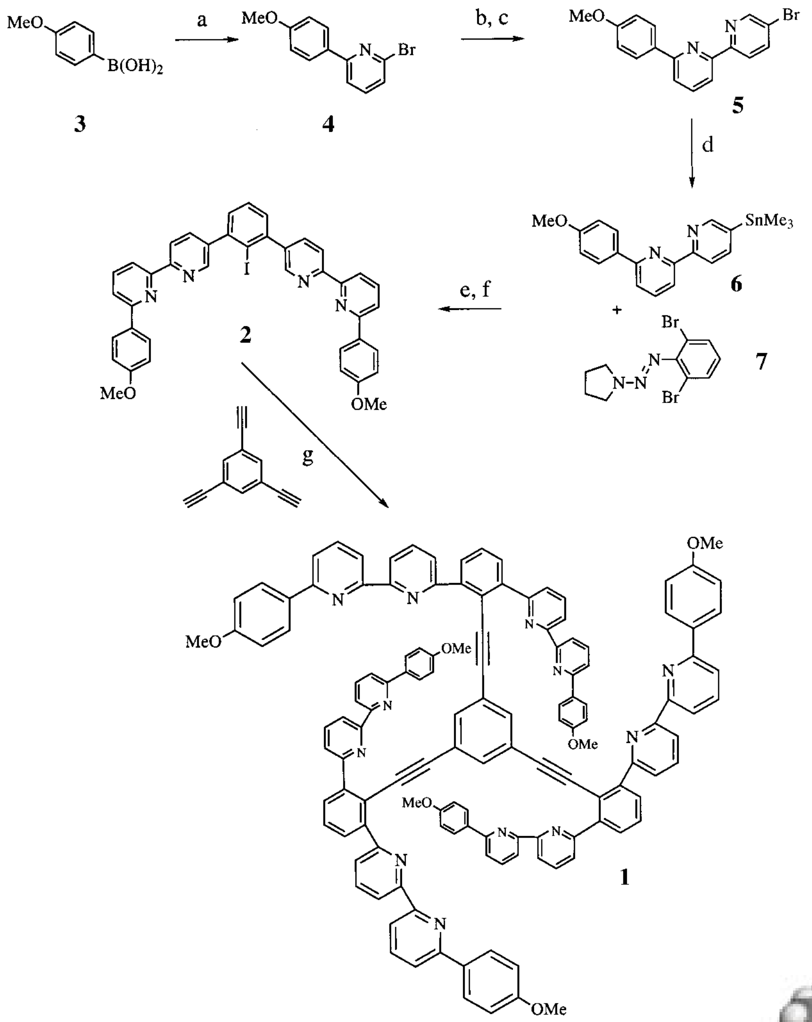

Scheme 2. Synthesis of **1**: a) 2,6-dibromopyridine, $[Pd(PPh_3)_4]$, Na_2CO_3, toluene, reflux, 74%; b) 1) BuLi, Et_2O, −78 °C, 2) Me_3SnCl, 85%; c) 2,5-dibromopyridine, $[Pd_2(dba)_3]$, $AsPh_3$, DME, reflux, 57%; d) $Me_3SnSnMe_3$, $[Pd(PPh_3)_4]$, DME, reflux, 57%; e) $[Pd(PPh_3)_4]$, DME, reflux, 66%; f) I_2, dichloroethane, reflux, 78%; g) $[PdCl_2(PPh_3)_2]$, Et_3N, THF, reflux, 51%. dba = dibenzylideneacetone.

regioselectively with the 2 position of 2,5-dibromopyridine to give 6′-anisyl-5-bromobipyridine (**5**). Problems with the stannylation of **5** led to the development of a direct stannylation procedure, which employs hexamethyldistannane and catalytic amounts of palladium in dimethoxymethane (DME).[30] The 5-stannyl derivative **6** coupled cleanly with the dibromophenyltriazene **7**, and, after conversion of the triazene functionality to the iodide with iodine in refluxing dichloroethane,[31] **2** was obtained. Sonogashira coupling of three equivalents of **2** with 1,3,5-triethynylbenzene yielded the desired D_3-symmetric ligand,[26] which readily bound copper(I) in acetonitrile solution (**1**-Cu_3).

The characteristic deep red color of **1**-Cu_3 was the first sign of successful complexation, and electrospray mass spectrometry confirmed molecular mass and composition, but neither could prove our goal: control of stereochemistry. Additional evidence came from the ^1H and ^{13}C NMR spectra that display the limited set of signals one would associate with D_3 symmetry. The X-ray crystal structure of **1**-Cu_3 complemented the solution work and showed the successful template/bascule construction (Figure 1).[32] Thus, barring anomalous crystal forces in combination with dynamic averaging in the solution NMR spectra, the idealized structure of **1**-Cu_3 is D_3-symmetric in all chemical phases, as designed.[33, 34]

Inspection of the structural details reveals that the bipyridine arms from neighboring units cross to form the envisioned tetrahedral metal binding sites. The overall structure is distorted away from D_3 symmetry; but this distortion is most likely the result of crystal packing forces. The bond lengths and bond angles are in good agreement with standard values.

The bascule mechanism ensures that the stereochemical configuration set during the binding of the first metal ion dictates the same configuration for the remaining sites. A related question is whether that initial metal binding also promotes subsequent metal bindings (positive cooperativity).[35] Titration of **1** with Cu^I ions leads to clean isosbestic behavior consistent with an intermediate-free transformation. Indeed, when observing the process by NMR spectroscopy, addition of a given fraction of the complement of three Cu^I ions leads to that fraction of **1**-Cu_3 and free **1** with no other species or intermediates (Figure 2). These two sets of data provide strong

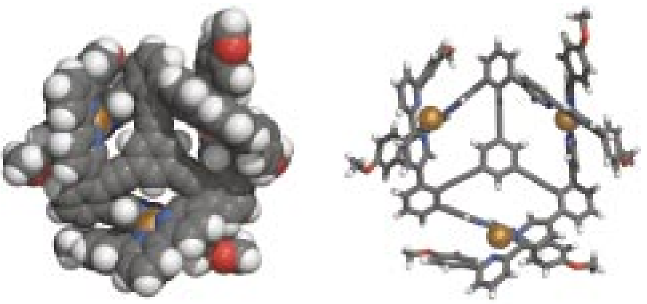

Figure 1. Space-filling (left) and framework (right) representation down the C_3 axis of the crystal structure of **1**-Cu_3.

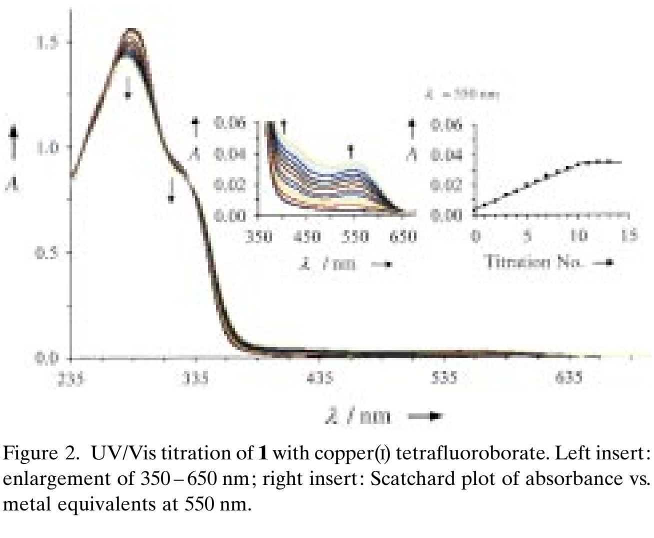

Figure 2. UV/Vis titration of **1** with copper(I) tetrafluoroborate. Left insert: enlargement of 350–650 nm; right insert: Scatchard plot of absorbance vs. metal equivalents at 550 nm.

evidence for positive cooperativity among the metal binding sites in **1**-Cu_3.

Thus, metal-binding properties of **1** and the high symmetry of **1**-Cu_3 illustrate a high degree of control over the degree and regularity of molecular entwinement. In combination with an appropriate macrocyclization method, the stage is set for the directed synthesis of complex topological stereoisomers of high symmetry, specifically, a molecular trefoil knot.[36]

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[32] Crystal structure analysis of **1**-Cu_3: Bruker CCD SMART diffractometer, sealed tube, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, Ω scans, temperature 213(2) K, cell determination with 317 reflections ($1.1 < \Theta < 19.3°$). Data collection, data reduction, Lorentz and polarization corrections using SMART and SAINT, absorption correction by SABABS, solution by direct methods, remaining non-H atoms by LS – ΔF syntheses, refinement against F^2 (SHELXL) with all H atoms included in idealized positions, all Cu, O, and F atoms refined anisotropically. Structure solution, refinements, graphics, and tables calculations performed with SHELXTL/PC. **1**: $C_{132}H_{90}B_3Cu_3F_{12}N_{12}O_6$, M_r 2391.21, monoclinic, space group $P2_1/c$ (no. 14), $a = 24.879(2)$, $b = 14.4764(12)$, $c = 37.097(3)$ Å, $\beta = 102.912(1)°$, $V = 13023(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.220\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.558\ mm^{-1}$, crystal dimensions ca. $0.15 \times 0.06 \times 0.06\ mm^3$, $2\theta_{max} = 38.6°$, 37667 reflections measured, 9851 unique reflections($R_{int} = 0.149$), 770 parameters, 3 restraints, $R_1(wR_2) = 0.1163$ (0.2624) for 5498 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-148313. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Tetranuclear Copper(I)-Biphenanthroline Gridwork: Violation of the Principle of Maximal Donor Coordination Caused by Intercalation and CH-to-N Forces**

Shinji Toyota, Craig R. Woods, Maurizio Benaglia,
Richard Haldimann, Kenneth Wärnmark,
Kenneth Hardcastle, and Jay S. Siegel*

The amelioration of "hot spots" in a molecule through specific molecular association is a general chemical principle, which has been recently highlighted as a driving force for "supramolecular" reactions.[1] The instability of unpaired radicals, uncoordinated metal ions and ligands, and unasso-

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