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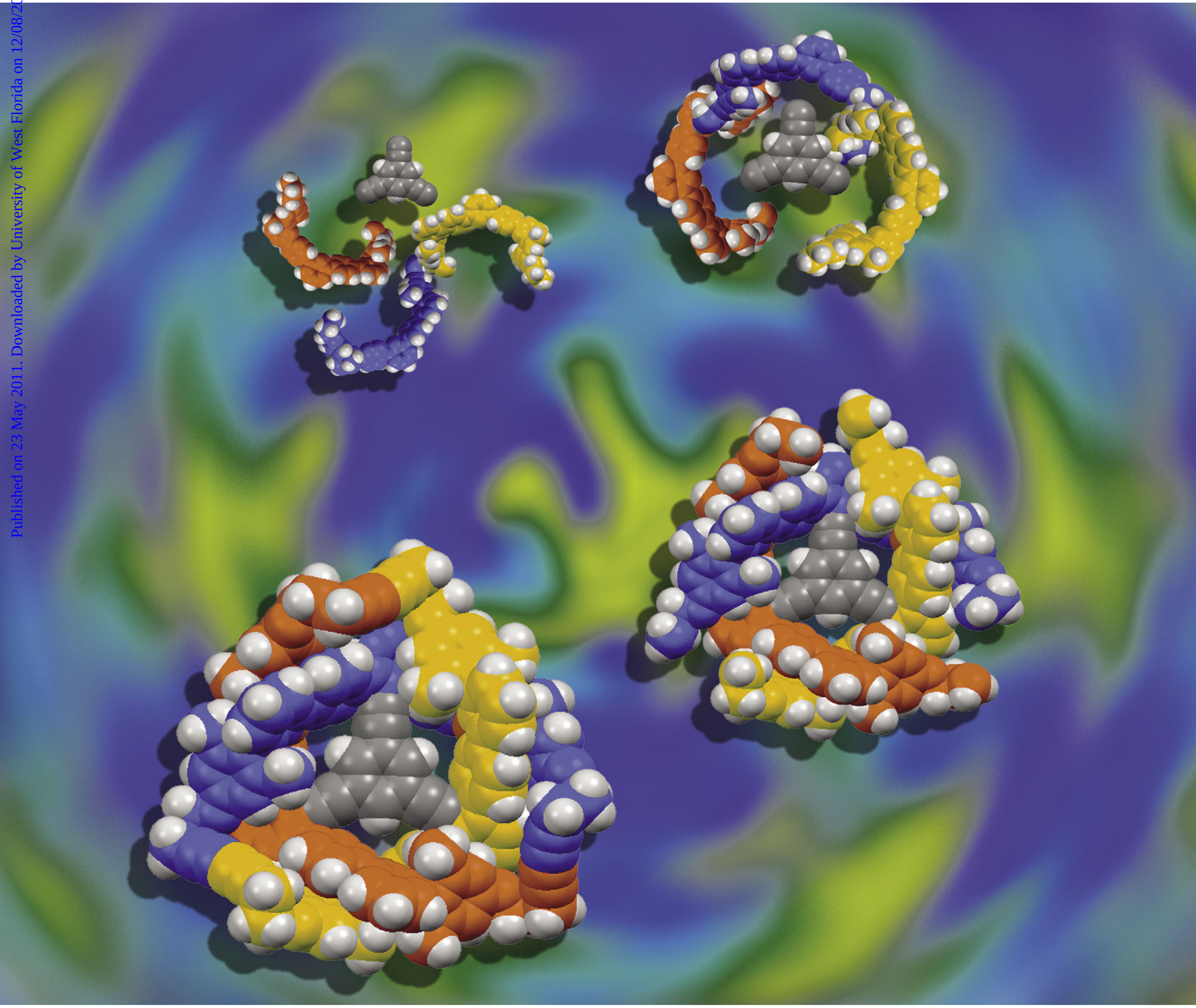

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COMMUNICATION

Synthesis of a D_3-symmetric "trefoil" knotted cyclophane†

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A D_3-symmetric knotted cyclophane, with a subgraph of trefoil topology, was synthesized by cyclization of a D_3-symmetric scaffold. Control of configuration at the three metal-based stereocenters arises from a bascule/pivot mechanism.

Complex topologies sophisticate life's macromolecules, provoke molecular architects and challenge stereochemical theory.[1,2] From Byzantine biopolymers[3] to concatenated coordination complexes,[4] these purely mathematical constructs find empircial expression as effigies of valence-bond-encoded molecular graphs. The taxonomy of topological stereochemistry focuses on three fundamental classes: links, knots and "non-planar" graphs.[5] Each structure requires an entwinement wherein entropy disfavors a stochastic selection. The most successful synthetic strategies toward topological targets employ templating effects like metal coordination,[6,7] charge-transfer stacking,[8] and hydrogen-bonding templates,[9] each of which has led to trefoil knotted molecules of various symmetries. A metal-directed approach *via* a D_3-symmetrical scaffold offers a strategy to a D_3-symmetrical knotted cyclophane with high stereoselectivity.

The retrosynthesis of the knotted cyclophane is easily visualized (Fig. 1). Key challenges include: (a) configurational (over–under) control of the metal-based stereocenters, (b) construction of the crescent-shaped pivot arms, and (c) installation of the peripheral linkers capable of closing the circuit and completing the knotted architecture. To control the configuration of the metal-coordinating stereocenters, a template was designed comprising three bis-bipyridylphenyl pivot arms centrally connected *via* alkyne spacers to a rigid benzene core.

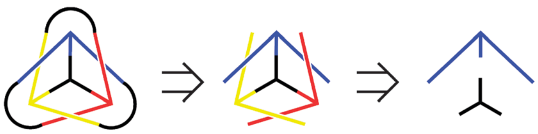
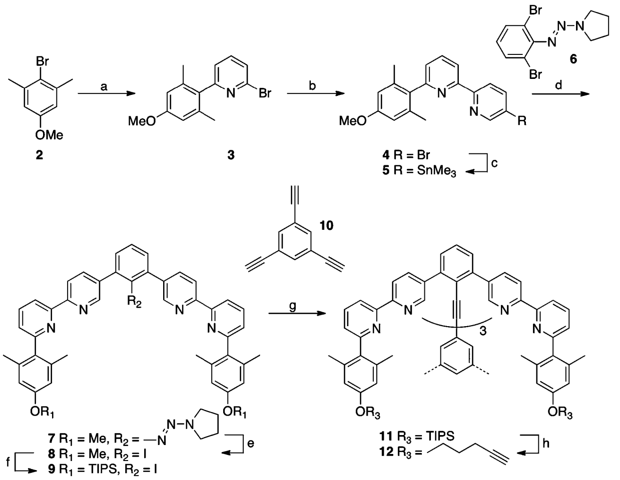


Fig. 1 Schematic retrosynthesis of a D_3-symmetrical knotted cyclophane.

Initial coordination of a metal ion, like Cu^I, by ligands of neighboring pivot arms sets the configuration about the metal-centered stereocenter and then a cantilever mechanism dictates the overall configuration at the remaining metal-based stereocenters; when one side of the pivot arm moves down to coordinate to a metal, the other moves up. The result is the formation of a D_3-symmetric complex.[10]

Synthesis of **12** results from a manifold use of palladium-catalyzed cross-coupling reactions (Scheme 1). Bipyridine **4** comes *via* two successive Negishi couplings.[11] Palladium catalyzed conversion of **4** to stannane **5** proceeds in excellent yield, albeit with stoichiometric amounts of hexamethylditin.[12] Two equivalents of **5** couple well to dibromophenyltriazine **6** under optimized Stille conditions, to form **7**, which precipitates out of



Scheme 1 Synthesis of **12**: (a) 1. *n*BuLi/THF, −78 °C, 40 min, 2. $ZnCl_2$/THF, −78–0 °C, 1 h, 3. 1 equiv. 2,6-dibromopyridine, 1.5 mol% $Pd(PPh_3)_4$/THF, reflux, 18 h [83%]; (b) 1. *n*BuLi/THF, −78 °C, 40 min, 2. $ZnCl_2$/THF, −78–0 °C, 1 h, 3. 1 equiv. 2,5-dibromopyridine, 1.5 mol% $Pd(PPh_3)_4$/THF, reflux, 18 h [48%]; (c) $(SnMe_3)_2$, 2 mol% $Pd(PPh_3)_4$/DME, reflux, 5.5 h [92%]; (d) 0.5 equiv. **6**, 10 mol% $Pd(PPh_3)_4$/toluene, reflux, 18 h [83%]; (e) 2 equiv. $I_2/ClCH_2CH_2Cl$, reflux, 48 h [96%]; (f) 47% HI (aq.), reflux, 16 h, // 3 equiv. TIPSOTf/CH_2Cl_2, NEt_3, −78–0 °C, 14 h [88%]; (g) 0.3 equiv. **10**, 10 mol% $Pd(PPh_3)_4$/1 : 1 NEt_3 : toluene, reflux, 18 h [70%]; (h) 1. 6.6 equiv. TBAF/THF, −78 °C—RT, 4 h, 2. 6.6 equiv. pent-4-ynyl toluenesulfonate, 20 equiv. Cs_2CO_3/DMF, 85 °C, 18 h [95%].

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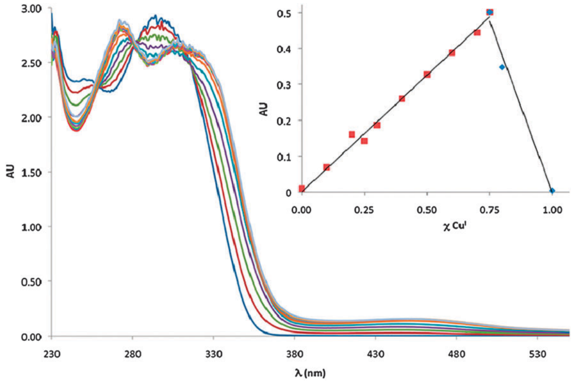


Fig. 2 UV/Vis spectral titration of Cu^I(MeCN)$_4$PF$_6$ with **12** in CH$_2$Cl$_2$. Inset: Job Plot for Cu^I(MeCN)$_4$PF$_6$ *vs.* **12** at 450 nm in CH$_2$Cl$_2$.

solution.[13] After filtration, crescent **7** is converted to the corresponding iodo-crescent (**8**) with iodine in refluxing 1,2-dichloroethane.[14]

Manisyl groups improved the solubility compared to anisyl groups, making it easier to work with **8–12**.[15] Deprotection of **8** in refluxing 47% HI (aq) and subsequent reprotection as the triisopropylsilyl (TIPS) ether formed **9** (two steps). Copper-free Sonogashira coupling of **9** with **10** (3 equiv.) afforded **11**,[16] and *in situ* desilylation/alkylation of **11** crafted **12** [9 steps, 17% yield].[17]

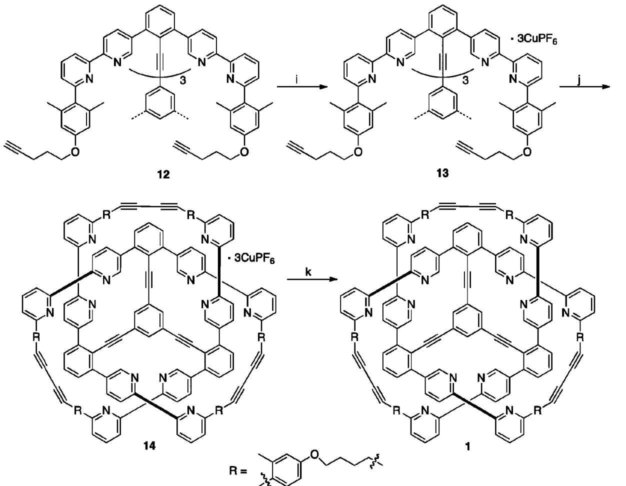
A Job plot of mole fraction **12** *vs.* Cu^I(MeCN)$_4$PF$_6$ at 450 nm displays a sharp maximum at a Cu^I : **12** molar ratio of 3 : 1, supporting one Cu^I per site (Fig. 2). Such a sharp maximum suggests strong binding in favor of the 3 : 1 complex; however, titration of **12** with Cu^I(MeCN)$_4$PF$_6$ does not show clean isosbestic behavior. With the addition of up to 1.5 equiv. of Cu^I to **12**, the absorption curves share isosbestic points at 260, 281, and 315 nm. From 2 to 2.5 equiv. of Cu^I, the absorption curves share isosbestic points at 256, 277, 300, and 359 nm. Beyond 3 equiv. of Cu^I, the curves are constant. This behavior suggests the presence of at least two intermediate bound states in solution.[18] The values of the stability and formation constants of the tri Cu^I complex were determined from the UV/Vis spectra (Table 1),[19] and indicate that the formation of **13** from Cu^I and **12** is at best weakly cooperative.

Treatment of **13** with excess Cu^{II}(OAc)$_2$·H$_2$O in refluxing CH$_3$CN[20] results in the formation of knotted cyclophane **14** in excellent yield (Scheme 2). Formation of the desired product was deduced from ESIMS data, plus the loss of the terminal alkyne signals in both the IR and ^{1}H NMR spectra. (Fig. 3).

Table 1 Stability constants of CuI(MeCN)$_4$PF$_6$ into **12**

log K_1	log K_2	log K_3	log β_2	log β_3
6.54(0)	4.33(9)	5.50(0)	10.88(0)	16.38(2)

Calculated using ReactLab Equilibria from UV/Vis spectra in CH$_2$Cl$_2$.



Scheme 2 Synthesis of **1**. (i) 3 equiv. Cu^I(MeCN)$_4$PF$_6$/1 : 1 NEt$_3$: CH$_2$Cl$_2$, RT, 2 h [95%]; (j) 36 equiv. Cu^{II}(OAc)$_2$·H$_2$O/CH$_3$CN, reflux, 16 h [85%]; (k) 20% KCN (aq.)/CH$_2$Cl$_2$, RT, 2 h [91%].

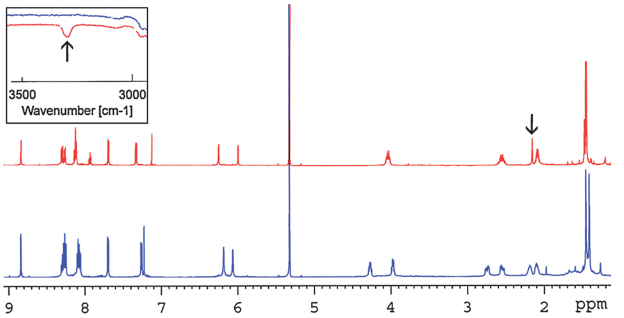


Fig. 3 600 MHz ^{1}H NMR of **13** (red) and **14** (blue) in CD$_2$Cl$_2$. (ref. 5.32 ppm from CHDCl$_2$). Inset: IR of **13** (red) and **14** (blue). Black arrows indicate the terminal alkyne signal in **13**.

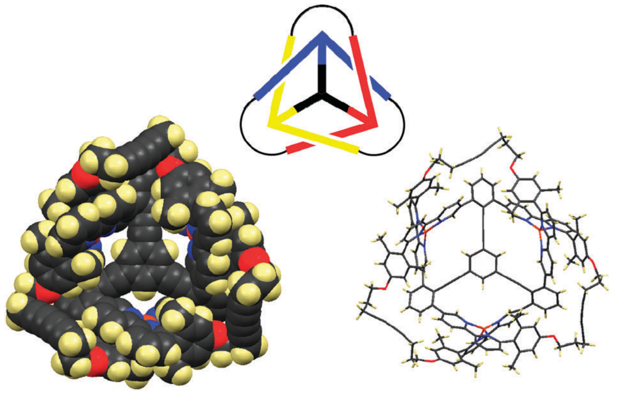


Fig. 4 Crystal structure of **14**: (left) spacefilling; (right) capped-stick.

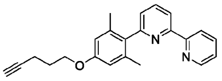
Dark red crystals were grown from vapor diffusion of ether into a nitromethane solution of the hexafluorophosphate salt of **14**; crystal structure determination unequivocally confirmed the formation of the desired knotted structure, which possesses the correct topology and connectivity (Fig. 4).[21] The formally D_3 knotted cyclophane **14** packs with crystallographic C_3 symmetry. It displays three Cu^I centers at the vertices of an equilateral triangle of edge length *ca.* 10.9 Å. Further analysis of the crystal structure reveals that the knotted copper-complexed cyclophane crystallizes as a racemate within a cubic crystal system (space group: $P_{\bar{4}3n}$). Synthesis of knotted metal-free cyclophane **1** was achieved by the removal of the copper with an aqueous solution of KCN (*c.f.* Scheme 2).

Table 2 Absorption and emission maxima, molar absorptivity values (log ε), quantum yields (ϕ_f), and lifetimes (τ_f)

	UV/Vis[a]		Fluorescence[ab]		
	λ_{abs}/nm	log ε/cm^{-1} mol^{-1} L	λ_{em}/nm	ϕ_f	τ_f/ns
15	283	4.19	370	0.04	1.63
16	310	4.73	372	0.08	2.58
12	297	5.15	375	0.31	2.79
1	293	5.03	373	0.20	3.02

[a] All values measured in CH_2Cl_2. [b] PPO in cyclohexane (ϕ_f = 0.94) was the standard;[22] the emission maxima values were obtained at 75% height.

The photophysical properties of reference compounds **15**, **16** and **12** showed an increase in the molar absorptivity, quantum yield, and lifetime in CH_2Cl_2 across the series. The behavior of **12** most closely matches that of **1** (Table 2).



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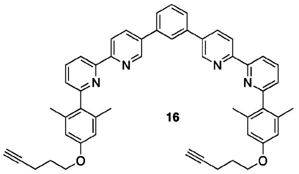

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Synthesis of a D_3-symmetric knotted cyclophane was achieved by the cyclization of the alkynyl-capped intermediate **12** using the Eglinton protocol. The desired over–under arrangement is controlled by means of a cantilever mechanism to complex Cu^{I} ions to the crossed polypyridine arm in **12** → **13**. Completion of the trefoil knot synthesis still requires the cleavage of the central triethynylbenzene scaffold.

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