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Self-sorting in dynamic disulfide assembly: New biphenyl-bridged "nanohoops" and unsymmetrical cyclophanes

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### Self-sorting in dynamic disulfide assembly: New biphenyl-bridged "nanohoops" and unsymmetrical cyclophanes

Ngoc-Minh Phan,[a] Emma P. K. L. Choy,[a] Lev N. Zakharov[b] and Darren W. Johnson*,[a]

We expand on our approach combining dynamic covalent self-assembly and sulfur extrusion to synthesize new biphenyl-linked disulfide and thioether macrocycles, which are variants of the venerable phenyl-bridged paracyclophanes. We then advance this strategy further to use two different thiols in tandem to provide new, elusive unsymmetrical disulfides which can also be trapped as unsymmetrical thioether "nanohoops". This approach enables substantial amplification of two unsymmetrical trimers out of a library of at least 21 possible macrocycles of various sizes.

Supramolecular self-assembly uses sub-components that are designed to interact through reversible, typically weak/secondary intermolecular forces to produce complex supramolecules.[1,2] This synthetic strategy has been applied to the construction of beautiful assemblies such as molecular machines (e.g., rotaxanes[3–6] and catenanes[7–10]), spectacular self-assembled cubes,[11] and dodecahedra among many other structures.[12,13] While self-assembly is a highly useful synthetic tool for preparing symmetrical macromolecules, it is not widely employed for constructing unsymmetrical, multi-component assemblies since typical self-assembled structures comprise multiple copies of a single building block. One approach to overcome this limitation involves the self-sorting[14,15] of different sets of molecules into a small number of well-defined molecular aggregates. Self-sorting behavior has demonstrated its utility in the construction of many challenging multi-component complexes (e.g. cages,[16] "meso-helicates",[17] supramolecular oligomers[18]) and in directing high fidelity homomeric association ("narcissistic self-sorting"[19]) or heteromeric aggregation ("social self-sorting"[20]).

Herein, we offer another application of self-sorting: to prepare unsymmetrical macrocycles that are challenging to synthesize *via* stepwise methods. We first report the synthesis of new biphenyl-bridged disulfide and thioether macrocycles.

We then explore social self-sorting between biphenyl- and phenyl-bridged thiols to develop a new family of unsymmetrical "nanohoops" (**Scheme 1**). We then focus on amplifying the yield of unsymmetrical trimers since these targets are challenging for traditional methods, which typically focus on symmetric products resulting from cross-coupling reactions.[21,22]
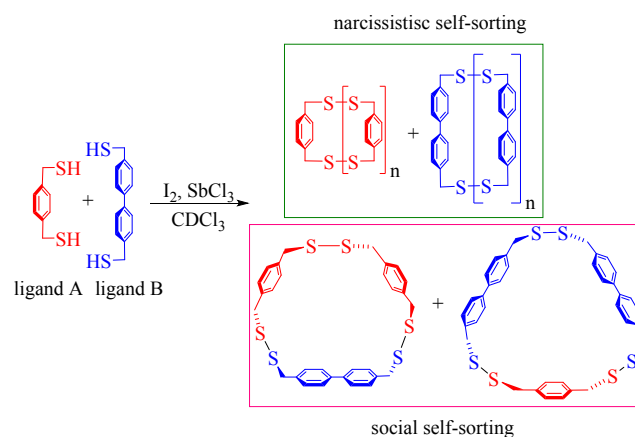
Scheme 1. Self-sorting of 2 different ligands, bis(mercaptomethyl) phenyl (A) and bis(mercaptomethyl) biphenyl (B), leads to narcissistic and social self-sorted products.

Our ability to enhance the yield of the desired unsymmetrical trimers arises from dynamic covalent chemistry (DCC),[23] the reversible making and breaking of covalent bonds to produce complex supramolecules. We have previously shown that cyclic disulfide macrocycles can be easily synthesized from thiols *via* oxidation with iodine (I_2) when activated by a pnictogen ion (As^{3+} and Sb^{3+})[24] or Cu^{2+} (Scheme 2).[25] This report expands on these DCC studies by investigating the effect of tuning multiple parameters (e.g. concentration, equivalents),[26–28] which are well-known to affect distributions of self- assembled disulfides. Once the yield of the desired disulfides is optimized, these structures are then subjected to sulfur extrusion[29] to generate thioethers (e.g. thiacyclophanes).

We first sought to show that our approach could give new biphenyl-bridged symmetrical cyclophanes (ligand B, Scheme 1). Previous studies with ligand A (Scheme 1)[24,29,30] have shown that pnictogen-assisted iodine oxidation can construct macrocyclic disulfides from thiols in a single step. Ligand B was

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chosen because it has a similar shape and coordination motif to that of ligand A, making the narcissistic and social self-sorting process competitive. Through self-assembly, macrocycles **1a**-**4a** were synthesized (Figure 1) in 99% combined yield. A mixture of all four compounds was subjected to sulfur extrusion to give the more stable thioethers (**1b**-**4b**) in 81% total yield.
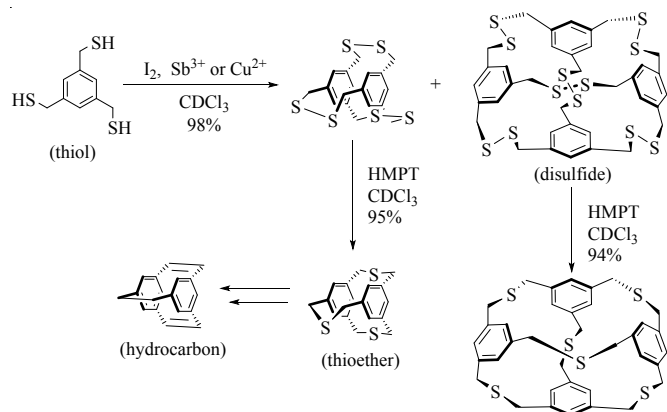
Scheme 2. Pnictogen-assisted iodine oxidation and subsequent sulfur extrusion to generate thioethers from basic thiol building blocks.

We were able to grow single crystals of thioethers **1b** and **2b** (Figure 1, right), and their resulting structures showed deviation from the typical 32° dihedral angle[31] found in unstrained biphenyls. Compound **1b** shows dihedral angles of 36.68° and 49.94°, whereas the dihedral angles in trimer **2b** are 3.40°, 6.52° and 46.90°. This data shows that the thermodynamic driving force for self-assembly of discrete structures can overcome moderate to considerable strain.

Whereas traditional cyclophane syntheses employ the "high dilution principle"[32] to prevent the aggregation of insoluble oligomers/polymers, our self-assembly approach can take place in much higher concentrations (up to 3mM instead of submicromolar). Furthermore, DCC gives us the intrinsic ability to control the product distribution with small changes in the reaction conditions. For example, the concentration of the reaction has a profound effect on the amount of dimer produced: as the concentration decreases, more dimer **1a** is produced (Table 1). We also found that the dominance of **1a** at low concentration only occurs with a stoichiometric amount of I_2 (2:1 I_2 to dithiol). With an excess of I_2, both the dimer **1a** and trimer **2a** become the prominent species (Table S1). Studying the solvent effect on the self-assembly of B, we found that the yield of the trimer **2a** can be increased from 47% to 75% just by switching solvents (Table S2), indicating a possible solvent templating effect. These results also suggest we can form virtually all possible disulfide structures in one pot and tune the energetic bias to isolate a desired product in high yield, reminiscent of other self-assembling disulfide systems that can respond to a variety of external stimuli.[33–35]

After subjecting the two ligands to pnictogen-assisted iodine oxidation, we were curious if a mixed ligand system would produce a series of unsymmetrical macrocycles, which would be challenging targets using traditional methods.[21,22] The lack of traditional methods to synthesize such unsymmetrical structures might also explain why these species remain unknown despite active cyclophane R&D in academic and industrial laboratories.[36–38] Immediately after mixing A and B, we realized that the system is self-sorted: the product distribution lies far from the expected statistical distribution of the various dimers through pentamers that can form between these two ligands (Figure S6). Since we did not observe all 21 statistical species, we sought to investigate the identities of the dominant ones and how to maximize their yields.

In unoptimized conditions (3 mM solution, 2.0 equiv. I_2, 2.0 equiv. $SbCl_3$), we observed the presence of 5 species of dimers and trimers in >90% combined yield (Figure S8). The two most
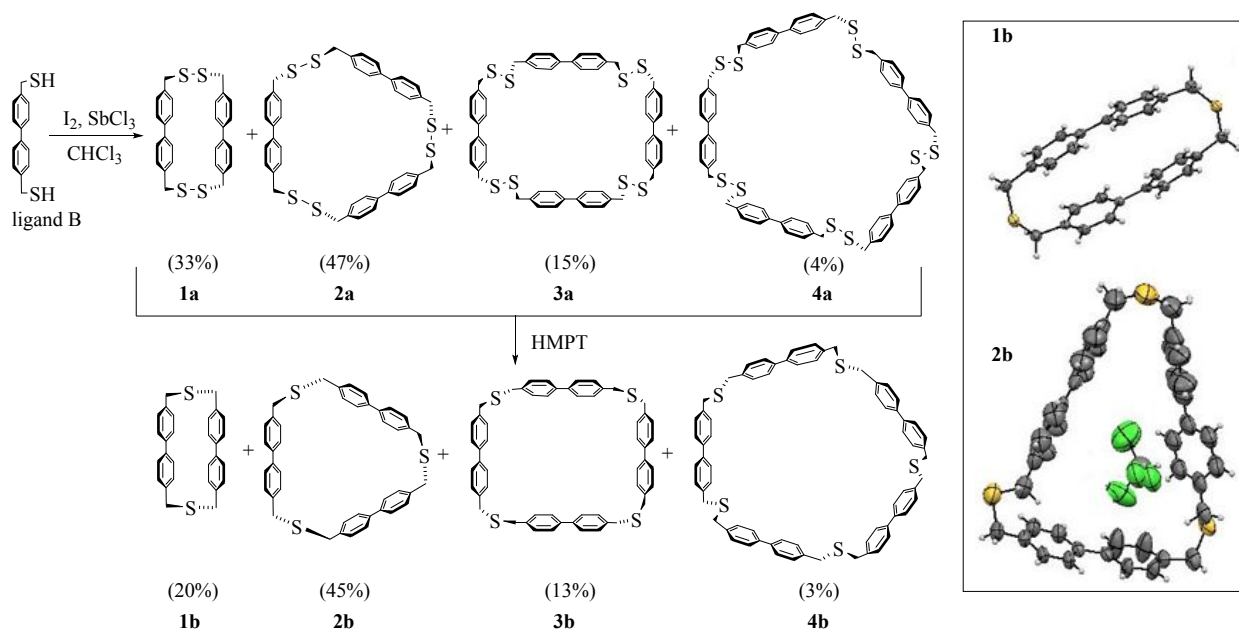

Figure 1. Self-assembly of ligand B to give biphenyl-based disulfide structures **1a**-**4a** and sulfur extrusion to give thioethers **1b**-**4b** (left). Crystal structures of **1b** and **2b** (right).

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Table 1. Effects of concentration on the product distribution of the ligand B system (chloroform as an example)

Conc. (mM)	% dimer (1a)	% trimer (2a)	% tetramer (3a)	% pentamer (4a)
3	33	47	15	4
1	51	34	10	4
0.5	60	26	9	4
0.25	72	20	7	-
0.125	82	12	5	-

abundant species in solution are the unsymmetrical trimers "AAB" and "ABB". Each compound exhibits 3 distinct methylene signals in their ^{1}H NMR spectra and so do their sulfur-extruded thioethers (Figure 2). For the "AAB" cyclophanes **5a** and **5b**, there are 4 aromatic doublets, meaning the molecule has a C_2 symmetry axis bisecting the single biphenyl group. Similarly, the "ABB" cyclophanes show 4 doublets and 1 singlet in the aromatic region, which suggests a C_2 symmetry axis, which in this case bisects the bonds bridging 2 biphenyl groups.

We were able to grow single crystals of disulfide **5a** and thioether **6b** (Figure 2, right), and the resulting structures explain why the most statistically likely species—unsymmetrical dimer AB (Figure S6)—is not observed under any reaction conditions. First, dimer disulfides are known to have strained C–S–S–C torsional angles,[24,25,29] whereas C–S–S–C torsion angles in the unsymmetrical trimer **5a** (Figure 2) do not deviate substantially from ideality (90°) as the angles are 87.62°, 88.98° and 90.18°. Thus, like the macrocycles formed from ligand B

described above, the comparative lack of strain allows trimers to be easily formed. More importantly, the significant size difference between the two ligands makes bending these rigid motifs into a single structure of dimer AB challenging.

Learning from the optimization of self-assembly conditions using ligand B described above, we focused on concentration and I$_2$ equivalents as the two most important factors in optimizing unsymmetrical trimer assembly. Tuning the ratio of ligands to 4:3 A:B, we were able to amplify the yield of the unsymmetrical trimers **5a** and **6a** to 40%, an improvement over a statistical yield of 19.1% (Figure S7). In tandem with employing an excess amount of I$_2$ using this ratio, the yield of **5a** and **6a** further increases to 65%, a >3-fold amplification from statistical distribution. Under these conditions, the only symmetrical structure formed is the trimer AAA in 15% yield, indicating the successful bias of social self-sorting in this DCC system. This is important to note since social self-sorting has traditionally been less commonly observed than narcissistic self-sorting due to the difficulty of incorporating different ligands into a single unsymmetrical complex.[16] These conditions also allowed us to isolate the unsymmetrical tetramers in 17% yield; these structures have not been previously synthesized by any other methods and will be discussed in the follow-up manuscript.

This work shows that a marriage between self-assembly and dynamic covalent chemistry can give rise to new symmetrical biphenyl-based cyclophanes. Incorporating self-sorting into this system by combining different dithiols yields unsymmetrical structures that are challenging to prepare *via*
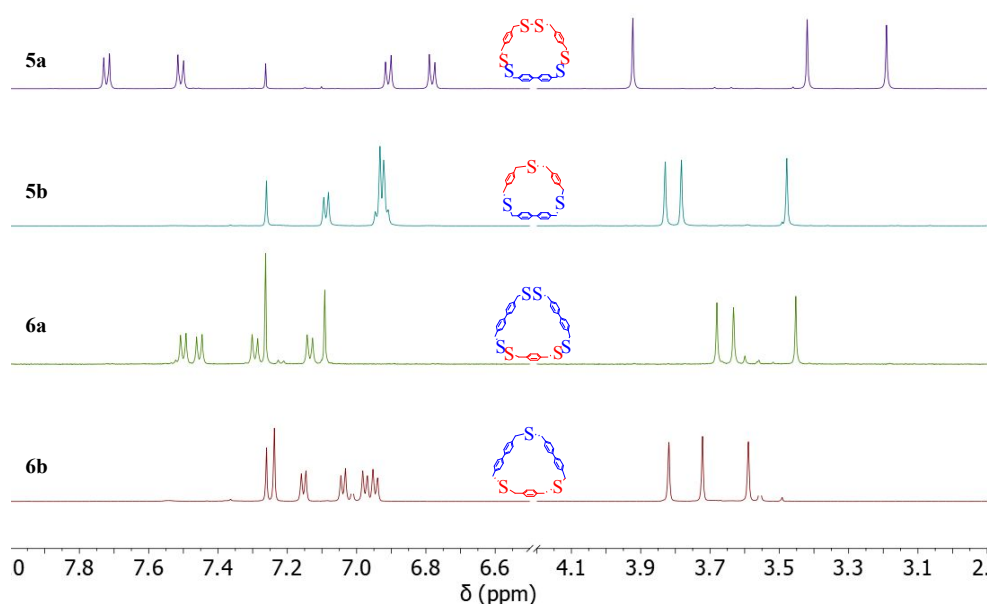

Figure 2. ^{1}H NMR spectra of compounds **5a-b** and **6a-b** (left) (CDCl$_3$ – 7.26 ppm). Crystal structures of **5a** and **6b** (right).

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traditional stepwise methods.[39] Product distribution easily changes in response to small changes in reaction conditions enabling amplification of unsymmetrical trimers. We believe this approach could advance fundamental cyclophane synthesis, giving rise to novel unsymmetrical disulfide and thioether macrocycles, and perhaps even new hydrocarbon nanohoops. Application includes the formation of new nanohoops and cages, congeners of which have contributed to separations science and molecular recognition.

Conflicts of interest

There are no conflicts to declare.

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From at least 21 possible macrocycles, self-sorting and DCC strategies provide a high-yield route to two new unsymmetrical, trimeric nanohoops.
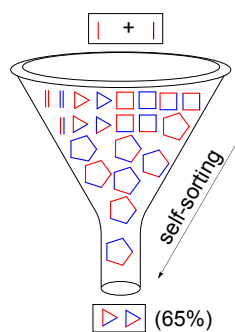
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Copper (II) Serves as a Greener Additives to Pnictogen-Directed Self-Assembly of 23 Thiacyclophanes