Communication

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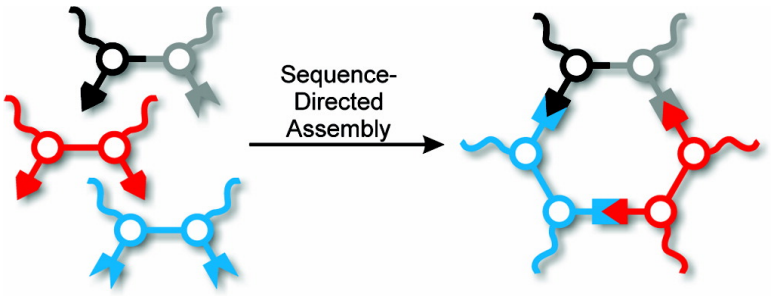

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Programmed Dynamic Covalent Assembly of Unsymmetrical Macrocycles

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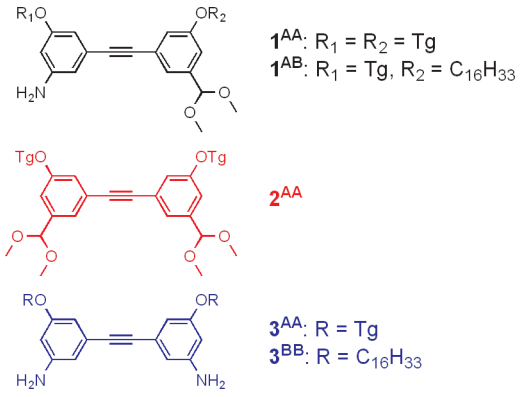
Shape-persistent macrocycles are now well-established as an important class of rigid supramolecular building blocks for organic materials,[1] in part owing to their propensity to self-assemble into π-stacked structures.[2] Both kinetically and thermodynamically controlled macrocyclization strategies have been used to access this class of compounds.[1a] Kinetic approaches offer precise control over monomer composition (potentially yielding complex, nonsymmetrical products), although the syntheses are generally long with relatively low overall yields. In contrast, thermodynamic approaches (using dynamic covalent chemistry, DCC)[3] offer high yields and short syntheses, although the products tend to be symmetrical and uniformly functionalized. Here we demonstrate a sequence-directed, dynamic covalent approach to unsymmetrical macrocycles using imine formation and exchange. Specifically, diphenylacetylene monomers (**1**−**3**) in various combinations undergo a three component macrocyclization. This self-assembly of the monomers is programmed by their sequence of N-donor and C-donor groups and by the thermodynamic driving force toward the smallest possible ring size (trimers) in which all groups react. Thus, each monomer segment can be individually addressed allowing a high level of control over, for example, side-chain functionalization. To illustrate the potential of this approach, macrocycles exhibiting a selection of useful side-chain patterns have been prepared. To our knowledge, this represents the first example of sequence-directed dynamic covalent chemistry and offers a thermodynamically controlled route to unsymmetrical shape-persistent macrocycles as well as basic tools for the self-assembly of complex organic nanostructures.



We designed monomers **1**−**3** as part of a larger project on the construction of two-dimensional molecular grids using DCC.[4] Inspired by the use of the information encoded into the hydrogen bond donor/acceptor sequence to direct the association of complementary DNA strands, we decided to explore the possibility of building fully *covalent* structures using imines to cross-link synthetic oligomers. In a trivial sense, all imine forming reactions are sequence-directed; by definition, the directionality of the imine bond requires the combination of two unique components (i.e., sequences of a single "bit"). Monomers **1**−**3** represent binary sequences of imine-forming groups which are uniquely identified by their N-donor/C-donor pattern (CN, CC, NN, for **1**, **2**, and **3**, respectively). We wished to explore whether this encoded information could be used to direct their self-assembly into larger structures (macrocycles).

Since molecules containing both aldehyde and amino groups would be difficult to manipulate (because of undesired imine formation prior to the self-assembly step), we first needed to establish conditions for one-pot imine formation from a protected aldehyde. In our earlier work,[4] we had used scandium(III) triflate for self-assembly as it is an effective transimination catalyst.[5] It has also been used to effect imine formation directly from anilines and dimethyl acetals, at elevated temperatures (refluxing toluene) and with azeotropic byproduct removal.[6] Formation of macrocycle $\mathbf{A_6}$ (Scheme 1) was carried out by treating $\mathbf{1^{AA}}$ with $Sc(OTf)_3$ in 1,2,4-trichlorobenzene (1,2,4-TCB) at 75 °C for 3 h, followed by stirring under reduced pressure (1 mmHg) at room temperature for 5 h (to drive the reaction to completion). The imines were then reduced to facilitate handling of the product. Analysis by gel permeation chromatography (GPC) suggests that $\mathbf{A_6}$ was produced in high yield (77% by deconvolution of the chromatogram[7]). The macrocycle was isolated by preparatory GPC (59%), in good purity (88% based on GPC), and was characterized by ^{1}H and ^{13}C NMR, MALDI mass spectrometry, and GPC.[7] The MALDI spectrum suggests that the major impurity in the isolated product was the tetrameric macrocycle (i.e., $4\times\mathbf{1^{AA}}$).

While the synthesis of $\mathbf{A_6}$ is effective, it is also representative of the limitations inherent to a strategy based on thermodynamic control. Thus, although macrocycle $(\mathbf{AB})_3$ was obtained in similar yield and purity from $\mathbf{1^{AB}}$ (Scheme 1 and Table 1), it is impossible to obtain more complicated substitution patterns without additional control over the self-assembly (short of separating a complicated mixture of products). Despite this problem, more sophisticated side-chain patterns are important as an external means to direct the intermolecular organization of the functional macrocyclic cores. Amphiphilic patterns, for example, have been shown to organize shape-persistent discs (including macrocycles) into complex supramolecular structures.[8]

A synthetic approach that achieves a balance between the efficiency of thermodynamic-control and the product complexity of kinetic-control would enable a broad range of new shape-persistent macrocycles to be prepared and studied. We reasoned that **1**, **2**, and **3** (equimolar) would self-assemble into a macrocyclic product dictated by their imine sequences (Scheme 2). This macrocycle is favored in the equilibrium distribution as it is again the smallest possible ring which satisfies all reactive groups on the monomers; other products either have dangling reactive sites (e.g., linear oligomers), or, by violating the initial 1:1:1 stoichiometry,

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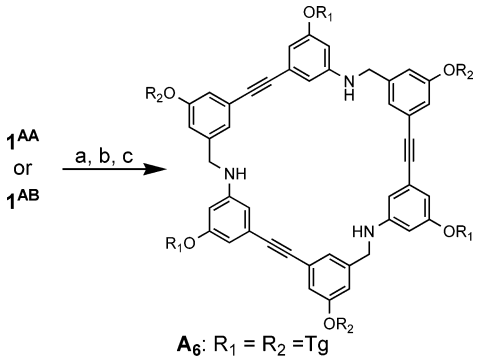
Scheme 1 [a]



A_6: $R_1 = R_2 = Tg$
$(AB)_3$: $R_1 = Tg$, $R_2 = C_{16}H_{33}$

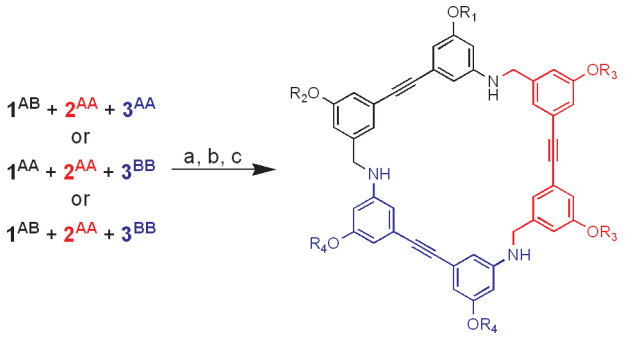
[a] (a) $Sc(OTf)_3$, 1,2,4-TCB, 75 °C, 3 h; (b) 25 °C, 1 mmHg, 5 h; (c) $NaBH(OAc)_3$.

Table 1. Macrocycle Yields (Crude and Isolated)

macrocycle	crude yield[a]	isolated yield (purity[a])
A_6	77%	59% (88%)
$(AB)_3$	72%	69% (90%)
A_5B	46%	44% (83%)
A_4B_2	64%	56% (88%)
A_3B_3	69%	58% (90%)

[a] Based on the deconvolution of GPC traces.[7]

Scheme 2 [a]



A_5B: $R_1 = R_3 = R_4 = Tg$; $R_2 = C_{16}H_{33}$
A_4B_2: $R_1 = R_2 = R_3 = Tg$; $R_4 = C_{16}H_{33}$
A_3B_3: $R_1 = R_3 = Tg$; $R_2 = R_4 = C_{16}H_{33}$

[a] (a) $Sc(OTf)_3$, 1,2,4-TCB, 75 °C, 3 h; (b) 25 °C, 1 mmHg, 5 h; (c) $NaBH(OAc)_3$.

cause the formation of other byproducts with dangling reactive sites.[9] Owing to the symmetry of monomers **2** and **3**, it is not possible to produce macrocycles with completely arbitrary control over the side-chain substitution. However, we have demonstrated a variety of useful patterns, including amphiphilic "Janus" structures (**A_3B_3**), and mono- and difunctionalized macrocycles (**A_4B_2** and **A_5B**). These latter patterns could be used to incorporate tether points for attachment to other macromolecules or surfaces.[10]

It is noteworthy that despite many potential byproducts, the crude yields, isolated yields, and purity of these more complex macrocycles were similar to those of **A_6** (Table 1). A comparison of the crude yields and GPC traces[7] of **A_6** and **A_3B_3** suggests that there was only a slight increase in the formation of higher molecular weight byproducts in the three component case. In all examples, NMR confirms the reduced symmetry of the macrocyclic core, and the desired products dominate the MALDI mass spectra. The MALDI spectra also suggest that only a small (but observable) amount of the undesired macrocycles resulting from trimerization of **1** (**A_6** or **$(AB)_3$**) was present in the final products.[7]

We believe the dynamic nature of this chemistry is critical to the success of these reactions. Under kinetic control, 3-fold intermolecular macrocyclizations proceed in only low yield (20−25%).[11] The error-correcting aspects of DCC are likely of particular importance to the self-assembly of macrocycles **A_5B**, **A_4B_2**, and **A_3B_3** as the system must presumably reclaim a variety of unwanted oligomeric byproducts resulting from initial mismatching of **1**−**3**. To demonstrate that this system is dynamic, macrocycles **A_6** and **$(AB)_3$** (unreduced imine forms) were prepared in separate flasks, then mixed. After it was stirred at room temperature (8 h), the reaction mixture was reduced as before.[7] Analysis by MALDI mass spectrometry (Figures S1 and S2, Supporting Information) indicates that the final mixture incorporated all possible macrocycles containing **1^{AA}** and **1^{AB}**, and was qualitatively in agreement with the expected 1:3:3:1 equilibrium ratio for $3\times\mathbf{1^{AA}}$ (**A_6**), $2\times\mathbf{1^{AA}}+\mathbf{1^{AB}}$, $\mathbf{1^{AA}}+2\times\mathbf{1^{AB}}$, and $3\times\mathbf{1^{AB}}$ (**$(AB)_3$**), respectively. This interchange of monomers under the reaction conditions confirms the dynamic nature of this system.

To summarize, we have demonstrated the self-assembly of diphenylacetylene monomers into complex, unsymmetrical shape-persistent macrocycles. A series of potentially useful side-chain patterns, including monofunctionalized and Janus-type structures, has been demonstrated. We believe this is the first nontrivial example of the directionality of a dynamic covalent bond being used to program the construction of an organic nanostructure. We are currently exploring methods to exploit this process in more complex, polyfunctional oligomer self-assembly.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-0642413 and DMI-0328162).

Supporting Information Available: Experimental procedures for monomer synthesis and macrocycle self-assembly, details of the **A_6**/**$(AB)_3$** scrambling experiment, and full characterization data for all macrocycles. This material is available free of charge via the Internet at http://pubs.acs.org.

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