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Template-Directed One-Step Synthesis of Cyclic Trimers by ADMET

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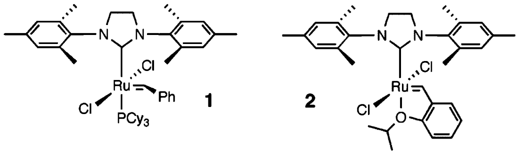
Biopolymers such as DNA, RNA, and proteins, are comprised of monomers of defined sequences and lengths. Minor perturbations in these parameters can alter drastically their biological functions and activities. In order to ensure faithful reproductions of these biopolymers within a dauntingly complex environment, nature utilizes[1] a variety of noncovalent interactions to template the formation of covalent bonds between monomer units. Achieving this high level of regioselectivity is challenging under the conventional chemical laboratory conditions as a result of interference involving multiple components at low concentrations. To overcome these obstacles, synthetic chemists need appropriate templates that recognize and transport the matching reactants into close proximity with each other, such as to achieve effective molarities that promote "intermolecular" reactions.

In the course of learning about and mimicking biological systems, synthetic chemists have developed numerous recognition motifs. Recent developments in supramolecular chemistry[2] have led to the construction of exotic molecular architectures and machines[3] based on different recognition motifs, e.g., dibenzo[24]crown-8 (DB24C8)/dialkylammonium ion binding,[4] DNA base pairing,[5] and metal−ligand coordination.[6] These noncovalent interactions are also being used as templates in directing chemical synthesis.[7] With recognition motifs readily available, another factor that has to be sought in template-directed synthesis is a methodology which is capable of linking building blocks with high efficiencies. The ruthenium−alkylidene complexes **1** and **2** have been shown (Figure 1) to be powerful functional-group tolerant catalysts[8] for new C−C bond formations employing olefin metathesis operating under thermodynamic control. This protocol has been demonstrated to be a versatile tool in the construction of mechanically interlocked compounds,[9] peptides,[10] artificial polymers,[11] and natural products.[12]

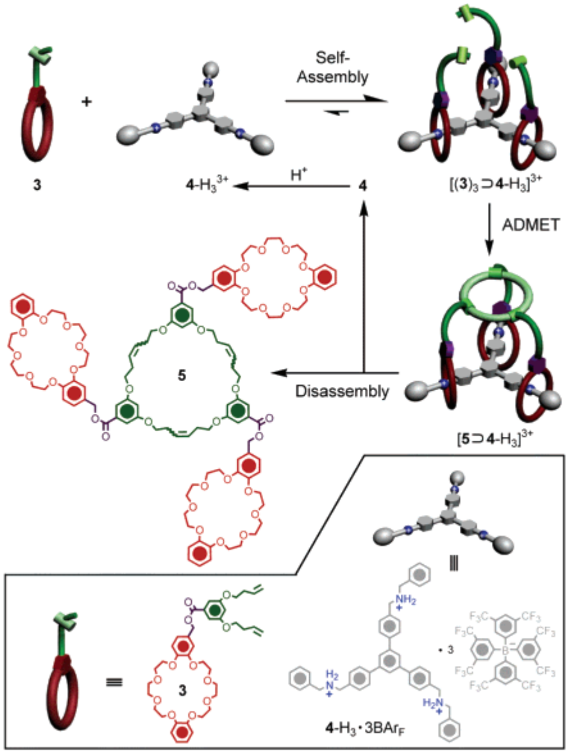


1

2

Figure 1. Ruthenium−alkylidene complexes **1** and **2**.

Scheme 1. One-Step, Catalytic Template-Directed Synthesis of Cyclic Tri-DB24C8 **5** from DB24C8 Acyclic Diene **3** and Trifurcate Template **4**-H_3^{3+} by ADMET



Recently, we have demonstrated[13] that a series of olefin cross metathesis reactions of olefin-bearing DB24C8 derivatives can be induced by a template containing two secondary dialkylammonium recognition sites. The cross metathesis reactions occur after the threading of the DB24C8 derivatives onto the template. The resulting dimer formation is greatly enhanced in the presence of the template. In order to extend the concept of catalytic, thermodynamically controlled, template-directed synthesis of oligomers with defined molecular structures, we have investigated (Scheme 1) acyclic diene metathesis (ADMET) based on (i) the complex formation in a 3:1 molar ratio of the DB24C8 derivative **3** bearing two olefinic sidearms and the trifurcated trisammonium template **4**-H_3^{3+} (as its $3BAr_F^-$ salt) and (ii) the formation of the macrocyclic tris-DB24C8 derivative **5** in one pot as a result of triple ADMET reactions, catalyzed by ruthenium−alkylidene complexes at relatively low concentrations.

The template **4**-H_3^{3+} contains three $-CH_2NH_2^+CH_2-$ centers. It has been demonstrated,[14] by isothermal titration calorimetry (ITC), that each of these three centers can thread and bind noncooperatively[15] to the DB24C8 derivative **3** with a single-site binding constant, commonly higher than 10^8 M^{-1} in CH_2Cl_2. The penetration of the crown ether rings in **3** by the trifurcated template **4**-H_3^{3+} has been verified (Figure 2b) by the ^1H NMR spectrum recorded only 5 min after mixing the two components in a 3:1 ratio (10 mM, CD_2Cl_2, 298 K). The characteristic signal, located at δ = 4.6−4.7 ppm, arises from the resonance for the CH_2 protons adjacent to the NH_2^+ (H_d and H_e) groups encircled by DB24C8 moieties. Following the formation of $[(\mathbf{3})_3 \supset \mathbf{4}\text{-}H_3]^{3+}$ in CH_2Cl_2, catalysts **1** or **2** were added to the solution which was then heated at 40 °C for 4 h. Trimerization, corresponding to 55% conversion by HPLC

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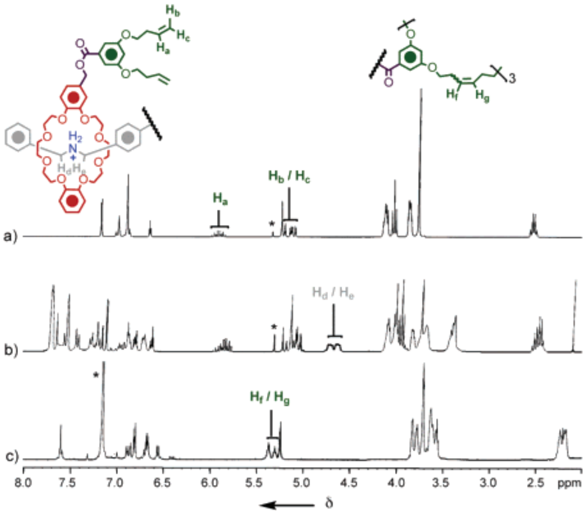

Figure 2. ^{1}H NMR spectra (300 MHz, 298 K) of (a) DB24C8 olefin monomer **3** in CD_2Cl_2, (b) the 3:1 threaded complex $[(\mathbf{3})_3\supset\mathbf{4}]^{3+}$ in CD_2Cl_2 (10 mM), and (c) the cyclic trimer **5** in C_6D_6. Asterisk = residual solvent.

(Table 1), was observed. The cyclic trimer **5** was purified further and isolated by preparative HPLC, prior to characterization by ^{1}H NMR spectroscopy and high-resolution mass spectrometry (HRMS). The template **4**-H_3^{3+} can also be recovered (Scheme 1) after preparative HPLC. The resonances observed in the olefinic proton region in the ^{1}H NMR spectrum (Figure 2c) indicate the presence of both the (*E*) and (*Z*) isomers of **5**. The MALDI-TOF-MS revealed (Figure 3) a signal corresponding to the molecular ion peak at $[\mathbf{5} + Na]^+$ of the isolated cyclic trimer **5**.

Table 1. HPLC Results for the Trimerization[a] of **3** in CH_2Cl_2

entry	component	catalyst	yield of dimer (%)	yield of trimer (%)
1	**3**	20 mol % **1**	56	0
2	**3**	20 mol % **2**	58	0
3	$[\mathbf{3}\supset\mathbf{DBA}]^+$	20 mol % **2**	17	0
4	$[(\mathbf{3})_3\supset\mathbf{4}\text{-}H_3]^{3+}$	20 mol % **1**	69	22
5	$[(\mathbf{3})_3\supset\mathbf{4}\text{-}H_3]^{3+}$	20 mol % **2**	39	55

[a] Concentration of crown ether = 1 mM.

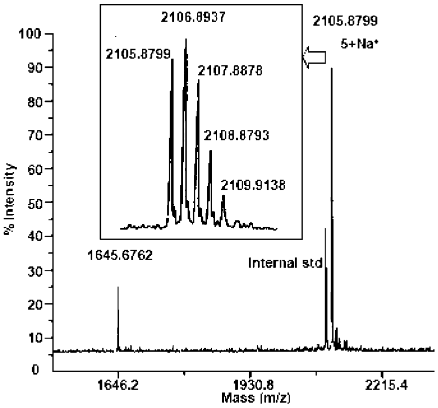

Figure 3. MALDI-TOF-MS Analysis of the cyclic trimer **5**.

Control reactions were carried out in the absence of the template under the same reaction conditions. No trimer formation was detected by HPLC (Table 1, entries 1 and 2). However, significant amounts of the dimer were formed, even at relatively low concentrations (1 mM), presumably as a result of crown ether aggregation. In an attempt to suppress this aggregation, a control experiment with the single-site complexation dibenzylammonium salt **DBA**·BAr_F was also performed. Substitution of the trifurcated template **4**-H_3^{3+} with $\mathbf{DBA}^+$ carrying three and one charge(s), respectively, resulted in reduced dimer formation and, once again, no formation of the trimer **5** (Table 1, entry 3). These results demonstrate the crucial role played by the trifurcated template **4**-H_3^{3+} in the one-step, triple ADMET reactions. The template brings the olefin units in $[(\mathbf{3})_3\supset\mathbf{4}\text{-}H_3]^{3+}$ into close proximity, thus achieving a high enough effective molarity for the reactions to occur.

In conclusion, a cyclic trimer **5**, based on a DB24C8 acyclic diene **3**, was produced at low concentrations in the presence of the trifurcated template **4**-H_3^{3+} containing three $RCH_2NH_2^+CH_2R$ recognition sites. The threading of the monomers onto the template is demonstrated to be vital for cyclic trimer formation. It is heartening to realize that a monomer, a template, and a catalyst can be brought together, such that a thermodynamically determined molecular structure[16] of some magnitude and complexity can be produced in a reasonably efficient manner.

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Supporting Information Available: Synthetic and template-directed catalytic procedures, in addition to spectroscopic and thermodynamic data. This material is available free of charge via the Internet at http://pubs.acs.org

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