Letter

Manipulating Replication Processes within a Dynamic Covalent Framework

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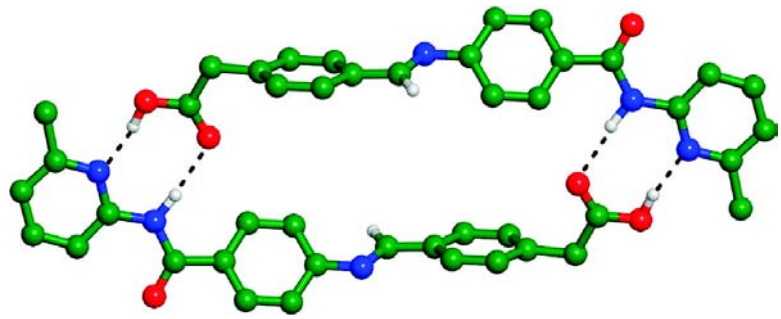

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Manipulating Replication Processes within a Dynamic Covalent Framework

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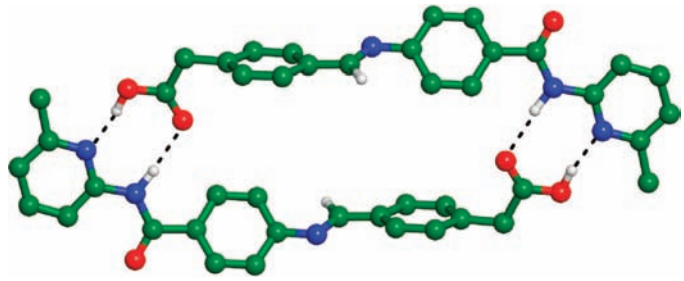
ABSTRACT



The reaction of an amine bearing an amidopyridine recognition site and an aldehyde bearing a carboxylic acid recognition site affords an imine that is capable of directing its own formation through a dynamic covalent replication cycle. Additionally, the amine, formed by reduction of the replicating imine, is a more efficient catalyst for the formation of the replicating imine than the imine is a catalyst for its own formation.

The fabrication of materials and intelligent devices that operate on the nanometer scale could be revolutionized by the development of molecular and supramolecular architectures that can direct their own formation. A fundamental understanding of the recognition-mediated processes that allow molecules to function as specific and efficient templates[1] for the formation of themselves will drive the development of protocols that establish and manage replication, organization, and evolution within synthetic supramolecular assemblies. This approach to predetermined dynamic behavior has been termed[2] "systems chemistry". In the context of our long-term goals, we have been able to exploit replication to amplify a single structure from a pool of reagents based on its ability to guide its own formation through recognition processes. The cycloadditions of maleimides with *N*-aryl nitrones or furans have been incorporated successfully[3] into modular self-replicating systems. These reactions form covalent bonds irreversibly, thus the structures amplified by virtue of recognition-meditated events are a result of kinetic selection processes operating within the reaction networks present in the replicating systems.

Motivated by our interest in the study of complex reaction networks, we became intrigued by the possibility of introducing a reversible covalent bond-forming reaction into our replicating systems, thus marrying the opportunities[4,5] of dynamic combinatorial chemistry (DCC) with those of self-replicating systems. The condensation reaction between an aniline derivative and an aromatic aldehyde to form an imine,

(1) For general reviews on replication, see: (a) Patzke, V.; von Kiedrowski, G. *Arkivoc* **2007**, 293. (b) Paul, N.; Joyce, G. F. *Curr. Opin. Chem. Biol.* **2004**, *8*, 634. (c) Li, X.; Chmielewski, J. *Org. Biomol. Chem.* **2003**, *1*, 901. (d) Robertson, A.; Sinclair, A. J.; Philp, D. *Chem. Soc. Rev.* **2000**, *29*, 141. (e) Lee, D. H.; Severin, K.; Ghadiri, M. R. *Curr. Opin. Chem. Biol.* **1997**, *1*, 491.

(2) (a) Kindermann, M.; Stahl, I.; Reimold, M.; Pankau, W. M.; von Kiedrowski, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6750. (b) Stankiewicz, J.; Eckardt, L. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 342. (c) Corbett, P. T.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8858. (d) Sarma, R. J.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 377. (e) Ludlow, R. F.; Otto, S. *Chem. Soc. Rev.* **2008**, *37*, 101. (f) Dadon, Z.; Wagner, N.; Ashkenasy, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6128.

(3) (a) Allen, V. C.; Philp, D.; Spencer, N. *Org. Lett.* **2001**, *3*, 777. (b) Quayle, J. M.; Slawin, A. M. Z.; Philp, D. *Tetrahedron Lett.* **2002**, *43*, 7229. (c) Pearson, R. J.; Kassianidis, E.; Philp, D. *Tetrahedron Lett.* **2004**, *45*, 4777. (d) Kassianidis, E.; Pearson, R. J.; Philp, D. *Org. Lett.* **2005**, *7*, 3833. (e) Pearson, R. J.; Kassianidis, E.; Slawin, A. M. Z.; Philp, D. *Chem.—Eur. J.* **2006**, *12*, 6829. (f) Kassianidis, E.; Philp, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 6334.

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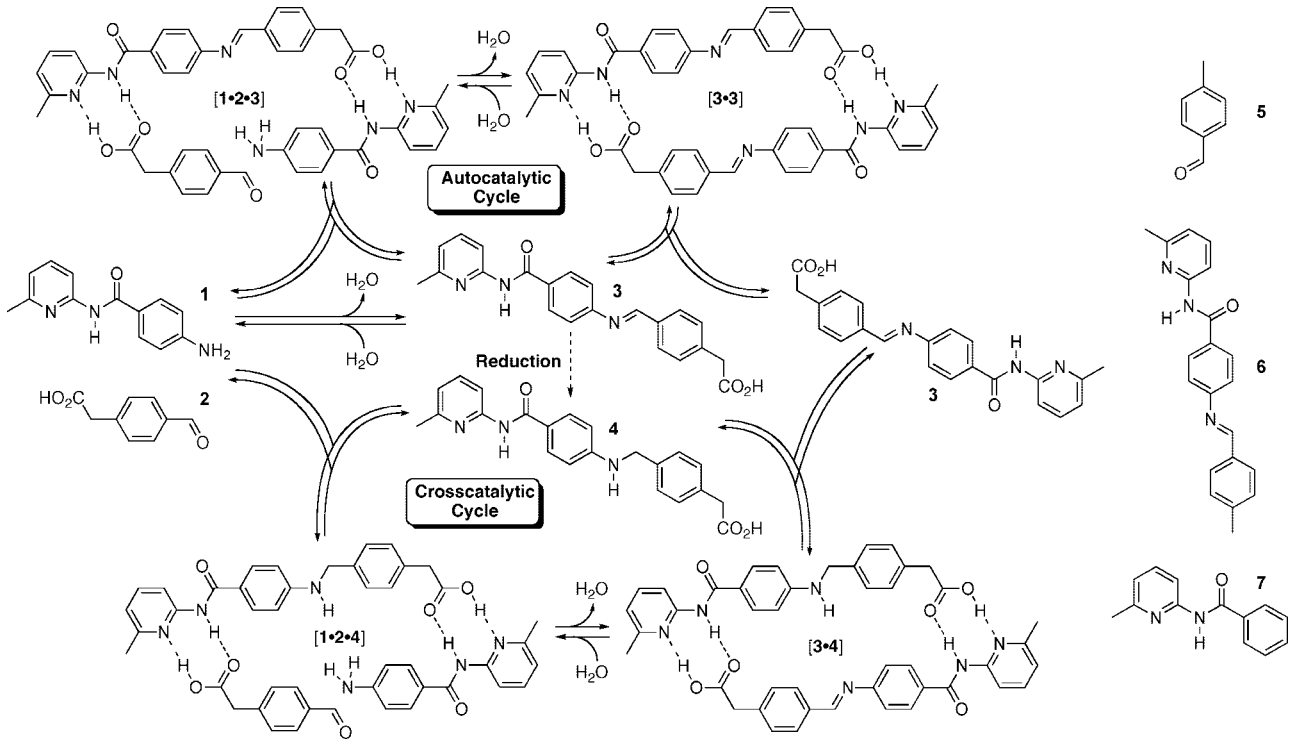
Scheme 1



a well-studied[6] reaction in the context of DCC, is central to the design (Scheme 1) of our system. Amine **1** and aldehyde **2** can react reversibly through a bimolecular mechanism to form imine **3** which can potentially act as a template for its own formation. Imine **3** is capable of recognizing and binding both **1** and **2** forming the ternary complex [**1**•**2**•**3**]. Reaction of **1** and **2** within this complex leads to an additional copy of imine **3** and the formation of the product duplex [**3**•**3**]. At this point, imine **3** has completed a formal replication cycle, and dissociation of the product duplex [**3**•**3**] completes the autocatalytic cycle. In contrast to previous work on kinetically controlled replication, this autocatalytic cycle has a number of interesting features that arise from the reversibility inherent in imine formation. The reaction between **1** and **2** to form imine **3** within the ternary complex is pseudounimolecular and, therefore, should proceed at a faster rate than the bimolecular reaction between the same reagents. However, since the reverse reaction is still bimolecular, this acceleration of the forward reaction[7] will also affect the overall stability of imine **3**. We also envisaged that amine **4** might act as a crosscatalytic template for the formation of **3** through the catalytic cycle shown in Scheme 1. Here, we demonstrate that imine **3** is capable of directing its own formation through the recognition-mediated manipulation of the dynamic equilibria shown in Scheme 1 and that amine **4** is capable of acting as a crosscatalyst for the formation of **3**.

In order to assess the effects of molecular recognition on this system, aldehyde **5**, which is incapable of recognition, was used as a model for the background bimolecular reaction between **1** and **2**. Initially, we wished to establish the position of equilibrium under the reaction conditions (dry[8] $CDCl_3$,

(4) For general reviews, see: (a) Lehn, J.-M. *Chem.—Eur. J.* **1999**, *5*, 2455. (b) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898. (c) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652. (d) Otto, S.; Severin, K. *Top. Curr. Chem.* **2007**, *277*, 267.

(5) For a set of imine-based replicating systems which operate in polar aprotic solvents, see: Terfort, A.; von Kiedrowski, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 654. For an imine-based self-duplicator, see: Xu, S.; Giuseppone, N. *J. Am. Chem. Soc.* **2008**, *130*, 1826.

(6) For some recent examples, see: (a) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913. (b) Nitschke, J. R.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 11970. (c) Godoy-Alcantar, C.; Yatsimirsky, A. K.; Lehn, J.-M. *J. Phys. Org. Chem.* **2005**, *18*, 979. (d) Nitschke, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3073. (e) Giuseppone, N.; Schmitt, J. L.; Schwartz, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5528. (f) Oh, K.; Jeong, K. S.; Moore, J. S. *Nature* **2001**, *414*, 889. (g) Zhao, D. H.; Moore, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 9996. (h) Hochgurtel, M.; Kroth, H.; Piecha, D.; Hofmann, M. W.; Nicolau, C.; Krause, S.; Schaaf, O.; Sonnenmoser, G.; Eliseev, A. V. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3382. (i) Storm, O.; Lüning, U. *Chem.—Eur. J.* **2002**, *8*, 793. (j) Bugaut, A.; Toulme, J. J.; Rayner, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3144. (k) Schultz, D.; Nitschke, J. R. *Chem.—Eur. J.* **2007**, *13*, 3660. (l) Sarma, R. J.; Otto, S.; Nitschke, J. R. *Chem.—Eur. J.* **2007**, *13*, 9542. (m) Nitschke, J. R. *Acc. Chem. Res.* **2007**, *40*, 103.

(7) The reversible formation of [**3**•**3**] from [**1**•**2**•] is associated with an equlibrium constant *K*, which is the equal to $k_{forward}/k_{reverse}$ for this transformation. The intramolecular nature of [**1**•**2**•**3**] → [**3**•**3**] will result in this process being accelerated with respect to the bimolecular pathway **1** + **2** → **3**. The reverse process [**3**•**3**] → [**1**•**2**•**3**] is still bimolecular, and thus, one would envisage that this rate is close to that for **3** → **1** + **2**. The net effect is therefore to increase *K* for the recognition-mediated process making the formation of **3** from [**1**•**2**•**3**] more favorable.

(8) $CDCl_3$ (99.8% atom D) was purchased from Aldrich as 100 g bottles. Bottles were opened under a positive pressure of Ar, and the contents were stored over preactivated 4 Å molecular sieves. The water content was determined to be 14 ppm using Karl-Fischer titration (Mettler Toledo DL32 coulometer).

25 °C) in the absence of recognition. We therefore measured[9] (Figure 1a, green diamonds) the rate of reaction between **1**

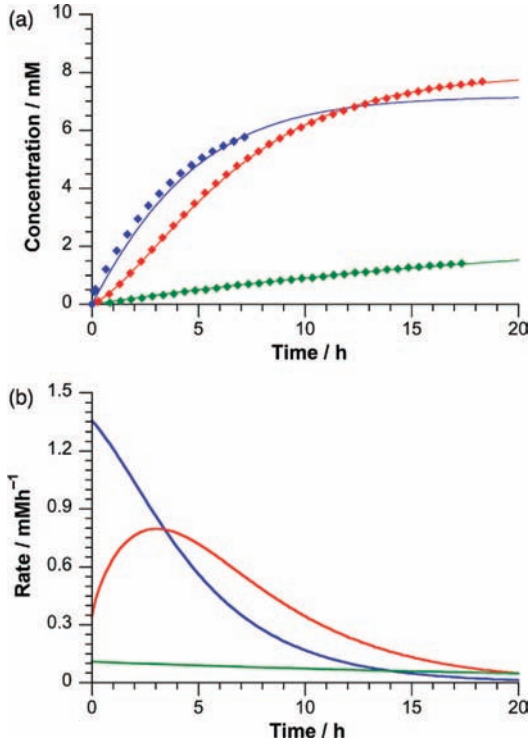


Figure 1. (a) Concentration vs time profiles for the formation of **6** from **1** and **5** (green diamonds), **3** from **1** and **2** (red diamonds), and **3** from **1** and **2** in the presence of 15 mol % **3** at the start of the experiment (blue diamonds). The data for the reaction in the presence of added **3** is corrected for the initial concentration of **3** and, thus, represents *new* imine **3** formed during the experiment. All experiments were conducted in $CDCl_3$ at 25 °C from starting concentrations of the appropriate reagents (**1** and **2** or **1** and **5**) of 15 mM. In each case, the solid line represents the best fit of the experimental data to the appropriate kinetic model (see the text and Supporting Information). (b) Rate vs time profiles derived from the concentration−time data in (a). Formation of **6** from **1** and **5** (green line), **3** from **1** and **2** (red line) and **3** from **1** and **2** in the presence of 15 mol % **3** at the start of the experiment (blue line).

and **5** in dry $CDCl_3$ at 25 °C ([**1**] = [**5**] = 15 mM, [4-bromophenylacetic acid][10] = 15 mM). After 16 h, the conversion of **1** and **5** to imine **6** was only around 9%. Next, we assessed the effect of introducing recognition into the reagents on both the reaction rate and the position of equilibrium. We therefore measured the rate of reaction between **1** and **2** in dry $CDCl_3$ at 25 °C ([**1**] = [**2**] = 15 mM). In this case, the recognition-mediated reaction (Figure 1a, red diamonds) between **1** and **2** was significantly faster, reaching more than 50% conversion after 16 h, and the concentration vs time profile for the formation of **3** is clearly sigmoidal. Additionally, the rate vs time profile (Figure 1b, red line) for the reaction between **1** and **2** shows the characteristic rate maximum for an autocatalytic reaction with the maximum rate of formation of **3** (0.79 mM h^{-1}) being achieved after 3 h. Taken together, these data suggest that imine **3** is capable of replication. In order to confirm this hypothesis, we performed two additional experiments. The role of hydrogen bonding in the formation of imine **3** was confirmed by performing the reaction between **1** and **2** in the presence of the competitive inhibitor **7**. Amide **7** disrupts the association between the carboxylic acid present in **2** and amidopyridine-bearing species present in the autocatalytic cycle (Scheme 1). Thus, reaction between **1** and **2** in the presence of **7** ([**1**] = [**2**] = 15 mM, [**7**] = 7.5 mM, dry $CDCl_3$, 25 °C) results in a significant decrease[11] in the rate of reaction. This result demonstrates that the formation of imine **3** is recognition-mediated. Critically, we were able to demonstrate that imine **3** is capable of accelerating its own formation. The addition of substoichiometric amounts of **3** at the start of the reaction between **1** and **2** should result in a significant increase in the initial rate of formation of **3**. Thus, reaction of **1** and **2** under conditions identical to those described previously, in the presence of 15 mol % of imine **3**, results (Figure 1, blue data) in a disappearance of the lag period for the formation of imine **3** and a maximum rate of 1.36 mM h^{-1} was reached at the beginning of the reaction (t = 0) as expected.

From these data, it is clear that imine **3** is capable of directing its own formation through the autocatalytic cycle presented in Scheme 1. It is also clear that the recognition-mediated reaction processes operating in this system affect both the rate of formation of **3** and the equilibrium concentration of **3**. We turned to kinetic simulation and fitting in order to gain further insight into the changes in the rate and equilibrium constants for this system engendered by molecular recognition. Fitting of the experimental concentration vs time data to a simple bimolecular model (Figure 1a, green line) affords an equilibrium constant of 0.30 for the formation of **6** from **1** and **5**. The bimolecular rate constant for the forward reaction between **1** and **2** is 4.54 × 10^{-4} M^{-1} s^{-1}. Fitting of the experimental concentration vs time data for the formation of **3** from **1** and **2** to our standard kinetic model for replicating systems[3a,d−f] gives excellent fits (Figure 1a, red and blue lines, see the Supporting Information for details). From these fits, a number of interesting thermodynamic and kinetic parameters can be extracted. The unimolecular rate constant for the formation **3** in the [**1**·**2**·**3**] ternary complex is is 8.14 × 10^{-3} s^{-1} revealing that this complex generates a kinetic effective molarity[12] of 17.9 M and a thermodynamic effective molarity of 15.0 M. The best fit association constant for the product duplex [**3**·**3**] is 65000 M^{-1}, corresponding to a connection

(9) The time course of each reaction was followed by 500 MHz ^{1}H NMR spectroscopy. The disappearance of the resonances arising from the aldehyde protons in **2** and **5** (δ = 9.95−10.05) and the simultaneous appearance of resonances arising from the imine protons in **3** and **6** (δ = 8.42−8.47) were monitored. Concentration vs time profiles were constructed by deconvolution of these resonances.

(10) 4-Bromophenylacetic acid (1 equiv) was added to the control reaction between **1** and **5** to ensure that the acid concentration was the same as in reactions involving aldehyde **2**.

(11) See the Supporting Information for the concentration vs time profile for this experiment.

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free energy (ΔG^s) of −8.08 kJ mol^{-1}. Given the single point association of carboxylic acid **2** and amidopyridine **7** has an association constant of 50 M^{-1}, this result indicates that the formation of the product duplex from two separate binding events is significantly positively cooperative. Some evidence for the stability of the [**3**•**3**] duplex comes from the fact that this species could be crystallized intact from $CDCl_3$ solution and its structure determined (Figure 2a) by single crystal X-ray diffraction. The overall equilibrium constant for the formation of **3** from **1** and **2** is now 3.59. Thus, the net effect of all of the recognition events within this system is to stabilize **3** by 6.19 kJ mol^{-1} with respect to the situation in the absence of recognition and to dramatically shorten the time taken for the system to reach equilibrium.

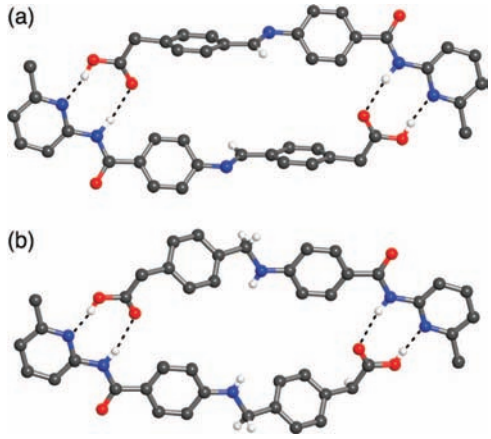

Figure 2. Ball and stick representations of the structures of (a) [**3**•**3**] and (b) [**4**•**4**] as determined by single-crystal X-ray diffraction. Carbon atoms are colored dark gray, nitrogen atoms are colored blue, oxygen atoms are colored red, and hydrogen atoms are colored light gray. Most hydrogen atoms have been omitted for clarity. Dashed lines represent hydrogen bonds.

It is clear, however, that, despite the efficient recognition-mediated processes that operate within this system, there is a fundamental limit to the formation of imine **3** that cannot be breached. We have observed[13] this phenomenon previously in small dynamic libraries, and it is manifest in the template-directed experiment performed here (blue line, Figure 1a) — the initial addition of template **3** limits the amount of new template **3** that can be formed and this amount diminishes as the amount of template added at the start of the experiment increases. It is therefore clear that in order to breach the limit imposed by the fully dynamic nature of the system, an irreversible reaction step must be incorporated within the reaction network. Reduction of imine **3** to amine **4** in situ should, in principle, drive the reversible condensation reaction between **1** and **2** toward the full consumption of starting materials. The reduction of imines to "freeze" dynamic libraries has been reported[14] widely. The methods employed for reduction make use of an excess of borane or borohydride reagents in nonprotic solvents.

The structural similarity of the [**4**•**4**] duplex, as determined by single crystal X-ray diffraction (Figure 2b), to that of the [**3**•**3**] duplex intrigued us. We reasoned that the [**1**•**2**•**4**] ternary complex should have significant stability, thus opening up the crosscatalytic cycle shown in Scheme 1. Accordingly, we performed condensation reactions between **1** and **2** in the presence of 5 mol %[15] of **4** ([**1**] = [**2**] = 15 mM, [**4**] = 0.75 mM dry $CDCl_3$, 25 °C). The maximum rate of formation of imine **3** was found to be 1.22 mM h^{-1}, indicating that **4** is a better crosscatalyst for the formation of imine **3** than imine **3** is an autocatalyst for the formation itself. Although we have investigated the condensation reaction between amine **1** and aldehyde **2** and the in situ reduction of imine **3** in $CDCl_3$ (at t = 0, [**1**] = [**2**] = 15 mM, [$NaBH(OAc)_3$] = 45 mM; 25 °C), precipitation of the reduced product **4** (presumably as its Na salt) prevented us from recording adequate kinetic data.

In summary, we have demonstrated that it is possible to design and implement an efficient replicating system based on reversible imine formation in a nonpolar solvent. The ultimate efficiency of this replicator is, however, hampered by the fully dynamic nature of the system. We have demonstrated that a simple functional group transformation (reduction) can convert the autocatalytic, but dynamic, imine into a static crosscatalyst for the formation of imine **3**, namely amine **4**. We are currently developing the use of this methodology in more complex reaction networks.

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Supporting Information Available: Synthetic procedures and characterization for compounds **1**, **2**, **3**, **4**. and **7**. Experimental details of kinetic experiments and kinetic simulation and fitting. Details of solid state structures of [**3**•**3**] and [**4**•**4**] determined by single-crystal X-ray diffraction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870. (b) Aricó; Chang, T.; Cantrill, S. J.; Khan, S. I.; Stoddart, J. F. *Chem. Eur. J.* **2005**, *11*, 4655. (c) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363. (d) Hartley, C. S.; Elliot, E. L.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 4512. (e) Liu, X.; Liu, Y.; Li, G.; Warmuth, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 901. (f) Liu, X.; Warmuth, R. *J. Am. Chem. Soc.* **2006**, *43*, 14120. (g) Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308. (h) Peters, A. J.; Chichak, K. S.; Cantrill, S. J.; Stoddart, J. F. *Chem. Commun.* **2005**, 3394. (i) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106.

(15) The limited solubility of amine **4** in $CDCl_3$ prevented the study of the system in the presence of higher loadings of **4.**