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# Transient Substrate-Induced Catalyst Formation in a Dynamic Molecular Network**

*Hugo Fanlo-Virgós, Andrea-Nekane R. Alba, Saleh Hamieh, Mathieu Colomb-Delsuc, and Sijbren Otto**

**Abstract:** *In biology enzyme concentrations are continuously regulated, yet for synthetic catalytic systems such regulatory mechanisms are underdeveloped. We now report how a substrate of a chemical reaction induces the formation of its own catalyst from a dynamic molecular network. After complete conversion of the substrate, the network disassembles the catalyst. These results open up new opportunities for controlling catalysis in synthetic chemical systems.*

Most chemical reactions in nature are mediated by enzymes. The concentrations of these enzymes are controlled in space and time through elaborate regulatory mechanisms, giving rise to complex functional behavior that is essential for biology.[1] Synthetic catalysts have been developed, many of which complement enzymatic catalysis with respect to types of reactions and substrate scope. Despite recent progress in supramolecular,[2] allosteric,[3] and switchable[4] catalysts, temporal control over catalyst concentrations remains underdeveloped in synthetic systems, imposing limits on the functional potential of catalysis. We reasoned that more elaborate control over synthetic catalysts may be achieved using a dynamic molecular network.[5] Such networks have been mostly used for creating dynamic combinatorial libraries (DCLs),[6] which are powerful tools for discovering synthetic receptors,[7] ligands for biomolecules,[8] self-assembling materials,[9] interlocked molecules,[10] and sensors.[11] Dynamic combinatorial approaches to catalysis are relatively underexplored.[12] In dynamic molecular networks building blocks are reacted to form an equilibrating mixture of molecules that continuously exchange their building blocks. Such networks are responsive: for example, introducing a guest molecule into a mixture of hosts tends to shift the equilibrium toward (ideally) the best binding hosts at the expense of the other compounds in the system. With the exception of applications in sensing,[11] the objective of most DCL experiments is reductionistic: the identification of a single molecule with special properties. However, their network character make DCLs potentially powerful tools for systems chemistry,[13] in which function derives from the entire network as opposed to an individual molecule. We now report a dynamic molecular network based on reversible disulfide chemistry in which the catalyst concentration is controlled by the substrate of the chemical reaction on which the catalyst operates.

A substrate may act as a template for the production of its own catalyst within a dynamic molecular network by binding to this catalyst, thereby shifting the equilibrium of the network toward catalyst formation. However, catalytic activity requires that the catalyst binds to and stabilizes the transition state of the reaction more than it stabilizes the substrate. Hence, our approach to substrate-triggered catalyst formation relies on screening a series of DCLs for their ability to produce molecules that bind both the substrate and the transition state of a chemical reaction. The potential for substrate and transition state binding may be assessed in two separate screening steps. Whereas substrate affinity may be evaluated directly by searching for library members that increase in concentration upon exposure to this substrate, the transient character of the transition state of a chemical reaction makes a similar direct assessment of transition state binding impossible. However, by using a stable molecule that resembles the structural and electronic nature of the transition state (a transition state analogue (TSA); this strategy has been extensively utilized in the field of catalytic antibodies),[14] an indirect assessment of transition state binding may still be obtained. Following the two screening steps, systems may be identified for which the substrate and the TSA amplify the same species. Such systems may show two different outcomes that are, in the absence of any further information, equally likely: the prospective catalyst binds the transition state stronger than the substrate and we see catalysis, or vice versa and there is no catalytic activity.

We set out to screen for molecular networks that are capable of catalyzing the intramolecular[15] aza-Cope rearrangement of **1** in aqueous solution (Scheme 1a).[16] This concerted reaction proceeds through a six-membered cyclic transition state **2** giving an unstable enammonium ion product **3** that reacts rapidly with water to give aldehyde **4** and dimethylamine **5**.[17] We used cyclic ammonium salt **6** as the TSA for the rate-determining aza-Cope rearrangement step.

In previous work we developed aqueous DCLs made from dithiol building blocks, which were able to respond to the presence of quaternary ammonium salts.[5] With these results in mind we decided to screen several DCLs based on disulfide chemistry for binding to substrate **1** and TSA **6** (representative examples are shown in the Supporting Information (SI),

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[*] H. Fanlo-Virgós, Dr. A.-N. R. Alba, S. Hamieh, M. Colomb-Delsuc, Prof. Dr. S. Otto
Centre for Systems Chemistry, Stratingh Institute
University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
E-mail: s.otto@rug.nl
Homepage: http://www.otto-lab.com

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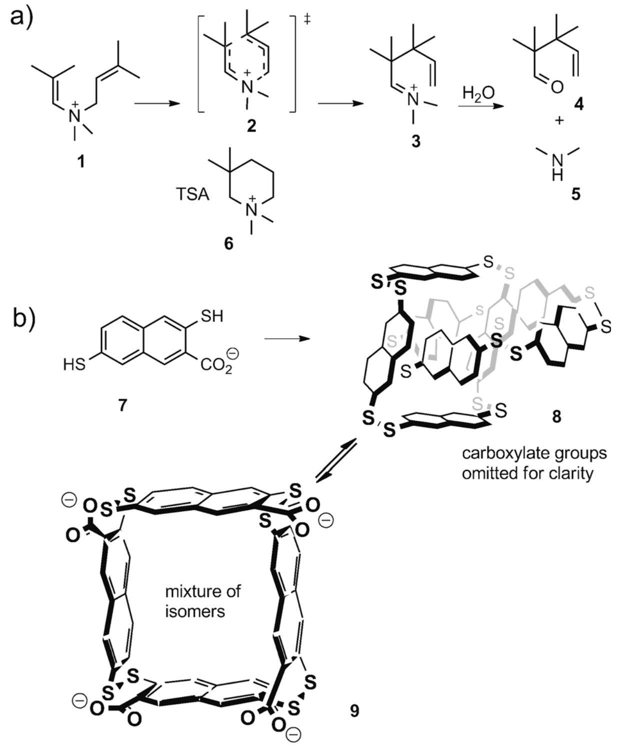

***Scheme 1.*** Catalyzed reaction and dynamic molecular network: a) Aza-Cope rearrangement and its TSA. b) Oxidation of dithiol building block **7** gives rise to a small dynamic molecular network containing catenanes **8** and macrocycles **9** as mixtures of stereoisomers.

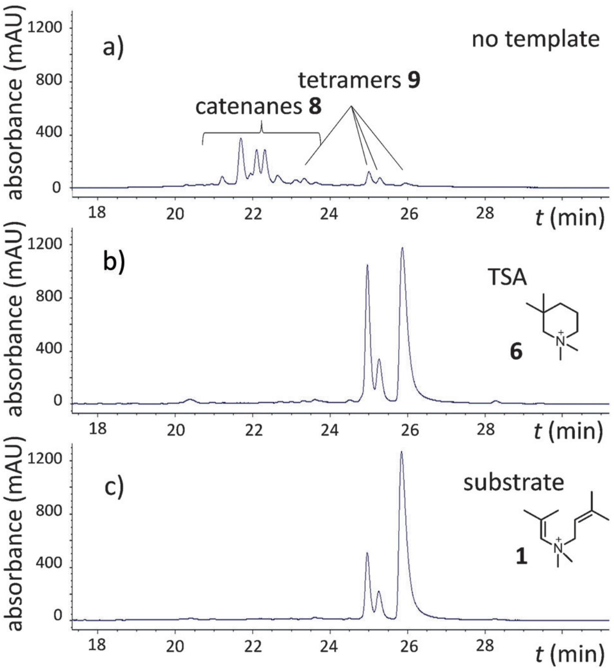

***Figure 1.*** Templating results. a) Part of the HPLC chromatogram of a small fully oxidized dynamic combinatorial library made from **7** (8.0 mM in 50 mM borate buffer, pH 8.0) in the absence of template; b) in the presence of 2.0 mM **6**, and c) in the presence of 2.0 mM **1**. Chromatograms (b) and (c) were acquired 12 h after the addition of the corresponding templates. The LC-MS analysis, performed on an analogous untemplated sample (at a lower global oxidation state and therefore also containing partially oxidized library members) is shown in Figure S5.

Figures S1 and S2). Disulfide DCLs can be generated by oxidizing thiol building blocks using oxygen from the air. The disulfide exchange is mediated by nucleophilic attack of disulfides by thiolate anions; hence, the DCLs remain dynamic as long as there are thiolate anions present in solution.[18] To guarantee the dynamic nature of the molecular networks we performed the experiments at a constant redox state, in which about two-thirds of the thiol groups had been oxidized to disulfides. Promising results were obtained for a small DCL prepared by partially oxidizing an aqueous solution of building block **7** (Scheme 1 b). In the absence of any template molecules the dynamic mixture was dominated by a set of isomeric 2-catenanes (**8**), consisting of two interlocked tetrameric macrocycles, as reported previously (Figure 1 a).[19] Only minor amounts of four isomeric tetramer macrocycles (**9**) were obtained. Exposing the dynamic molecular network to TSA **6** induced a dramatic shift in the product distribution, in favor of the tetrameric macrocycles (Figure 1 b). Exposing the network to substrate **1** gave an almost identical result (Figure 1 c), suggesting that the tetramers are capable of binding both the substrate and the transition state of the aza-Cope rearrangement, a necessary condition to obtain catalysis.

We then proceeded to study the effect of the dynamic molecular network on the kinetics of the aza-Cope rearrangement. Monitoring the appearance of the signals of the dimethylamine product by $^1$H NMR spectroscopy (Figure 2 a and Figure S14) showed that, at room temperature, the aza-Cope rearrangement in the presence of the dynamic disulfide mixture was complete after three days ($t_{1/2} = 26$ h), while the uncatalyzed reaction had only reached 50 % conversion after 360 h. Thus, the dynamic disulfide mixture was able to catalyze the aza-Cope rearrangement. We could not quantitatively monitor the disappearance of the substrate by NMR, as it gave broad signals in the presence of the catalyst. However, an analysis by HPLC showed that the rate at which the substrate disappears corresponds well to the rate at which the product appears (see Figure S3). Hence, there is no significant built-up of any intermediate, indicating that the aza-Cope rearrangement remains the rate-determining step and that the subsequent hydrolysis is still fast. Further kinetic investigations revealed that the reaction is first order in substrate as well as in catalyst **9** (see SI). We have also investigated the effect of the TSA on the rate of the catalyzed reaction. As expected, the TSA acts as a competitive inhibitor of the aza-Cope rearrangement. Figure 2 b shows how the rate of the catalyzed reaction diminishes in the presence of increasing amounts of TSA. The inhibitory effect of the TSA is relatively small—some catalysis is still taking place in the presence of ten equivalents of the TSA—suggesting that it has an unexpectedly weak affinity for the catalyst. This was further confirmed in a templating experiment in which a DCL made from **7** was exposed to a 1:1 mixture of substrate **1** and TSA **6**. We monitored the product distribution of the network immediately after adding the templates, before any **1** had reacted. This experiment resulted in the amplification of the isomeric tetramers of **7** with a ratio that matched the ratio that

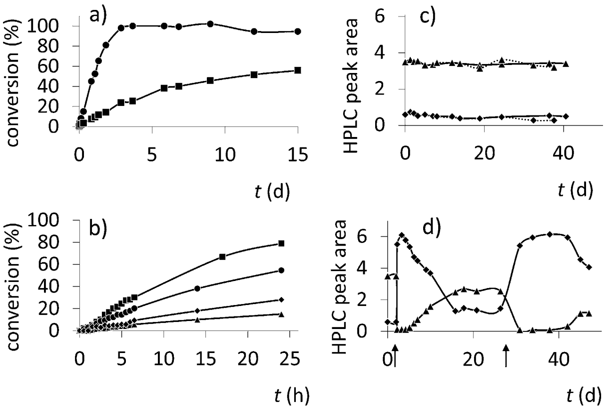

*Figure 2.* Kinetic profiles at room temperature and [**7**] = 8.0 mм. a) Appearance of product **5** in a reaction mixture starting from 2.0 mм **1** as a function of time in the absence (■) and presence (●) of a DCL made from building block **7** (8.0 mм in 100 mм phosphate buffer in $D_2O$, pD = 8.0). b) Kinetics of the aza-Cope rearrangement in the absence of catalyst **9** (▲); in the presence of 1 equiv of **9** (■); in the presence of 1.0 equiv of **9** and 1 equiv of TSA **6** (●), and in the presence of 1.0 equiv of **9** and 10 equiv of TSA (◆) as inhibitor. Conditions: 2.0 mм of substrate **1** in 50 mм borate buffer pH 8.0. c) The disulfide network in the absence of **1** (solid lines) consists of a constant concentration of catenanes **8** (▲) and tetramers **9** (◆), which is unaffected by the presence of the products of the aza-Cope reaction: dimethylamine and 2,2-dimethylpent-4-enal (dotted lines). d) Change in composition of the dynamic disulfide network over the course of the aza-Cope rearrangement, showing the rapid conversion of catenanes **8** (▲) into tetramers **9** (◆) upon addition of substrate **1** at day 2 followed by slow return back toward **8** as substrate **1** is converted into product **5**. Further **1** was added at $t = 24$ days. Arrows mark the points of addition of **1**.

was obtained when only the substrate was used as a template, but was different from the ratio obtained when using only the TSA (SI, Figure S4). Taken together, these results suggest that the substrate binds more strongly to the tetramers than to the TSA. The fact that we nevertheless obtain catalysis indicates that the TSA is not a perfect model for the real transition state.[20]

We have established that the catalyst is capable of turnover. After complete transformation of substrate **1** in the presence of a DCL made from **7**, addition of a second equivalent to the same library led to full conversion over a time scale of 150 h (see SI, Figure S6). Finally, other reaction substrates of the same family as **1** were also tested and comparable catalytic effects were obtained (see SI, Figure S7).

While the aza-Cope rearrangement is catalyzed in the small dynamic disulfide network, it also influences the product distribution of the disulfide network. We monitored the distribution of the disulfide products over the course of the reaction. In the absence of aza-Cope substrate **1** the mixture was dominated by catenanes **8** and its composition did not change in the course of 40 days (Figure 2c, solid lines). Introducing substrate **1** resulted in a rapid re-equilibration in favor of tetramers **9** as shown in Figure 2d. As **1** is consumed in the course of the aza-Cope rearrangement, the disulfide composition gradually reverts back to catenanes **8**. Immediately after **1** has reacted away, transmission electron microscopy (TEM) revealed the presence of poorly defined aggregates (TEM analysis is shown in the SI, Figure S8a). We have found that the kinetics of the return toward the original disulfide distribution is slower than the re-equilibration upon the exposure to **1** and also somewhat slower than the catalyzed aza-Cope rearrangement (as seen by comparing Figure 2a with Figure 2d). We hypothesize that the formation of the aggregates shown in Figure S8a is reversible, although it slows down to some extent the kinetics of disulfide exchange and, therefore, the return of the library to catenanes **8**.

We have also observed a different type of aggregate, which builds up at room temperature. After several cycles of addition and reaction of substrate **1** to a library formed by **7** (8.0 mм), TEM reveals the presence of fibers (SI, Figure S8b). These fibers are likely assembled as a result of the aggregation of one of the isomeric tetramers (HPLC analysis reveals that one of the isomers builds up; see SI, Figures S9 and S10). We speculate that this aggregation into fibers prevents the library from completely returning to the original composition. After a library was allowed to re-equilibrate for more than 20 days (Figure 2d), about 11% of **7** remained irreversibly trapped in the fibrous material. However, the nonaggregated part of the system (i.e. the catenanes) remains dynamic, because the introduction of more **1** after 24 days (Figure 2d) induces the re-emergence of the tetramers, and gives further conversion of **1** into aza-Cope products (SI, Figure S11). The formation of fibrous aggregates and the accompanying enrichment in one of the tetramer isomers appears to require a significant tetramer concentration. No fibrous aggregates are formed in samples that do not contain a template that amplifies the tetramers, even over a period of 40 days (Figure 2c). The assembly into fibrils reduces the catalytic activity of the tetramers substantially: Figure S6 in the SI shows that upon three subsequent additions of substrate **1** (which each time increases the amount of tetramer that becomes irreversibly trapped in the fibrils; see SI, Figure S10) the apparent rate constant of the aza-Cope rearrangement is reduced from $8.5\times10^{-6}\,s^{-1}$ to $2.7\times10^{-6}\,s^{-1}$, whereas the rate constant for the uncatalyzed reaction is $1.8\times10^{-6}\,s^{-1}$.

To minimize the aggregation into fibrils, other conditions were explored. We found that the use of higher temperatures (50 °C) and lower building block concentrations (1.0 mм of **7**) significantly reduced fibril formation. Yet, the substrate is still able to amplify the tetramers (Figure S13). As shown in Figure 3, several cycles of addition of substrate can be performed and the mixture remains dynamic and recovers to close to its initial composition (i.e., catenanes as the main constituent) once the substrate is consumed. Under these conditions no fibrous aggregates were observed and the ratio of tetramer isomers did not change significantly with time even upon repeated additions of aza-Cope substrate (see SI, Figure S9).

The data in Figures 2 and 3 suggests that the tetramers are able to catalyze the aza-Cope rearrangement. This conclusion was supported by experiments in which we used completely oxidized, and therefore no longer dynamic, disulfide mixtures that were dominated by either the catenanes **8** or the tetramers **9**, which showed that the aza-Cope rearrangement is accelerated by the latter, but not by the former (SI, Figure S12). This outcome precludes the involvement of partially oxidized library members in catalysis.

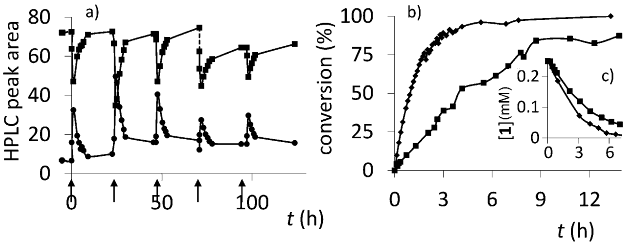

*Figure 3.* Kinetic profiles at 50 °C and [**7**] = 1.0 mM (a) or 8.0 mM (b). a) Change in composition of the dynamic disulfide network (1.0 mM of **7**, in 50 mM borate buffer in $D_2O$, pD = 8.0) over the course of the aza-Cope rearrangement, showing the rapid conversion of catenanes **8** (■) into tetramers **9** (●) upon adding substrate **1** at $t = 0$ h ([**1**] = 0.25 mM), followed by return back toward **8** as substrate **1** is converted into product **5**. Further **1** was added at $t = 24$, 46, 70, and 97 h. Arrows mark the points of addition of **1**. Before the fourth addition, the dashed line indicates a partial reduction of 10% of the disulfide bonds with tris(2-carboxyethyl)phosphine (TCEP) to offset the effect of inadvertedly introducing oxygen. b) Appearance of product **5** in a reaction mixture starting from 2.0 mM **1** as a function of time in the absence (■) and presence (◆) of a DCL made from building block **7** (8.0 mM in 50 mM borate buffer in $D_2O$, pD = 8.0 at 50 °C). c) Disappearance of substrate **1** in a reaction mixture starting from 0.25 mM **1** as a function of time in the absence (■) and presence (◆) of a DCL made from building block **7** (1.0 mM in 50 mM borate buffer in $H_2O$, pH 8.0).

The overall behavior of the system is summarized in Figure 4. Note that the products of the catalyzed reaction do not have a detectable effect on the library distribution as shown by the addition of dimethylamine and 2,2-dimethylpent-4-enal to a dynamic library made from **7** (Figure 2c, dotted lines).

In conclusion, we have demonstrated that screening DCLs using both starting material and TSA enables the identification of a dynamic molecular network that responds to the substrate of a reaction by transiently producing its catalyst. After completion of the reaction the mixture returns towards its original composition. This dynamic molecular network approach to catalysis, with in situ and on-demand formation and consumption of the catalyst, opens new possibilities for control over synthetic catalytic systems. For example, several catalytic systems could be assembled sequentially to transform a substrate into a product in separate catalytic steps.

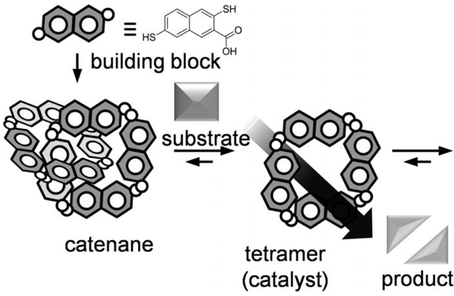

*Figure 4.* A solution of building blocks gives rise to a dynamic combinatorial library in which the dominant library member changes from the initial catenane to the catalytic tetramer upon addition of the reaction substrate. Once the substrate is consumed, the DCL shifts back toward the initial catenanes.

## Experimental Section

The following procedures were performed in a glove box to exclude oxygen. Borate buffer (50 mM pH 8.0) was used for preparing solutions and was previously deoxygenated by purging with $N_2$ for 1 h. The libraries were stirred in closed vials using magnetic stirrers. A solution of 8.0 mM of **7** was prepared in borate buffer. A controlled oxidation of **7** (monitored by HPLC) was performed by adding aliquots of a 200 mM solution of sodium perborate until two-thirds of the starting material was oxidized. Three samples of 1 mL were taken from this solution and combined with 16 μL borate buffer, 16 μL of a 125 mM solution of **6** in borate buffer, or 16 μL of a 125 mM solution of **1** in borate buffer. Aliquots of 15 μL of the templated solutions were transferred into vials that were tightly sealed before being removed from the glove box and analyzed by HPLC.

The catalytic behavior of **9** was monitored by comparing the increase of the dimethylamine $^1$H NMR signals in a sample in the presence and absence of the dynamic mixture made from **7**. For that, 1 mL of an 8.0 mM solution of **7** in borate buffer (50 mM pD 8.0, prepared with $D_2O$), was transferred to a first NMR tube. A blank was prepared in absence of **7** in a second NMR tube. An aliquot of 16 μL of a solution of 125 mM of **1** in borate buffer was added to each of the NMR tubes. Several NMR spectra were recorded during the following 15 days for both tubes and the results were plotted as change of $^1$H NMR peak area of **5** versus time.

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