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A Self-Organizing Chemical Assembly Line

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Supporting Information

ABSTRACT: Chemical syntheses generally involve a series of discrete transformations whereby a simple set of starting materials are progressively rendered more complex. In contrast, living systems accomplish their syntheses within complex chemical mixtures, wherein the self-organization of biomolecules allows them to form "assembly lines" that transform simple starting materials into more complex products. Here we demonstrate the functioning of an abiological chemical system whose simple parts self-organize into a complex system capable of directing the multistep transformation of the small molecules furan, dioxygen, and nitromethane into a more complex and information-rich product. The novel use of a self-assembling container molecule to catalytically transform a high-energy intermediate is central to the system's functioning.

Biological systems have developed the ability to efficiently shuttle high-energy chemical intermediates along specific transformational pathways, thus avoiding side reactions and interference between processes that operate in parallel,[1] and preventing these reactive intermediates from initiating damaging events.[2] Whereas eukaryotes rely upon membrane compartmentalization to separate subsystems, prokaryotes are able to direct the fates of reactive intermediates within a single space bounded by the cell membrane. Prokaryotes' biomolecular machinery thus requires functional subsystems to self-organize so as to avoid destructive interference between them.[1] Chemists have recently begun to investigate the design of systems that undergo complex self-organization[3] or self-sorting,[4] due to the orthogonality of the interactions among their various chemical components.[5] The present work brings together the concept of self-organization with the emerging area of relay multicatalysis,[6] whereby several catalysts work together to effect sequential transformations.

Here we describe a mixture of simple chemical precursors that self-organize to generate a functional "assembly line"[7] of molecular actors able to transform the simple substrate furan (**a**, Figure 1) into the more structurally complex 5-hydroxy-3-(nitromethyl)dihydrofuran-2(3*H*)-one (**c**). Key features of this system are the *in situ* self-assembly[8] of metal–organic cage[9] **1** (Figure 1) and the lack of interference between the different catalytic cycles.

The photooxidation cycle (Figure 1A) generates a high-energy intermediate endoperoxide[10] (shown in Figure 1B) that subsequently passes through cage **1** and is thus transformed into a lower-energy intermediate **b**, which is able to participate in the organocatalytic cycle (Figure 1C). Cage **1** assembles *in situ* from its "programmed" subcomponents without interference from other components of the constitutionally dynamic system.[11]

This process demonstrates not only how a high-energy intermediate may be selectively transformed by a metal–organic cage, but also how a self-organizing system based on simple building blocks can be designed to transform and functionalize a simple molecule within a complex mixture under mild conditions using water as a solvent, dioxygen as a reagent, and visible light as the energy source.

In its initial state, the aqueous reaction mixture contains the subcomponents necessary to assemble the previously described $[Fe^{II}_4L_6]^{4-}$ cage **1**[12] (i.e., 2-formylpyridine, iron(II) ions, and 4,4′-diaminobiphenyl-2,2′-disulfonic acid) together with furan, nitromethane, L-proline, methylene blue, and dioxygen. Within this chemical system, the hetero-Diels–Alder cycloaddition of furan with singlet oxygen ($^1O_2$) generated by catalytic action of the sensitizer methylene blue takes place (cycle A in Figure 1). Concurrently, cage **1** assembles *in situ* and catalyzes the subsequent transformation (cycle B), which yields fumaraldehydic acid **b**. Cycle A thus feeds into cycle B, which in turn feeds into organocatalytic cycle C to afford the final product **c** through the L-proline-catalyzed 1,4-addition of nitromethane to intermediate **b** followed by cyclization. The absence of one of the subcomponents of the cage was observed to lead to nonselective pathways, whereby the high-energy intermediate endoperoxide[10] reacted to give different products. These did not react further in cycle C to give product **c**.

The design of these one-pot relay transformations required not only understanding of each individual step, but also analysis of their combination in order to guarantee compatibility between the different catalytic cycles,[13] as discussed below.

It has long been established that the hetero-Diels–Alder cycloaddition of singlet oxygen ($^1O_2$) with furan leads to the formation of an unstable endoperoxide (Figure 1), which undergoes ring opening to yield multiple products.[10] Based upon prior studies,[14] we envisioned that the endoperoxide would be a suitable guest for host **1**, and that encapsulation might lead to selective transformation into a single product.[15] The reaction of $^1O_2$, photogenerated from $^3O_2$ by methylene blue (3.5 mol%), with furan **a** in the presence of cage **1** (0.5 mol%) in D_2O buffered to pD 4.0 at room temperature provided **b** in 60% yield (reaction I, Figure 2). This reaction performed in the absence of cage **1** gave hydroxybutenolide **d** as the major product (35% yield) along with several other oxidation products (reaction II, Figure 2). Interestingly, product **b** could also be generated from **d** following addition

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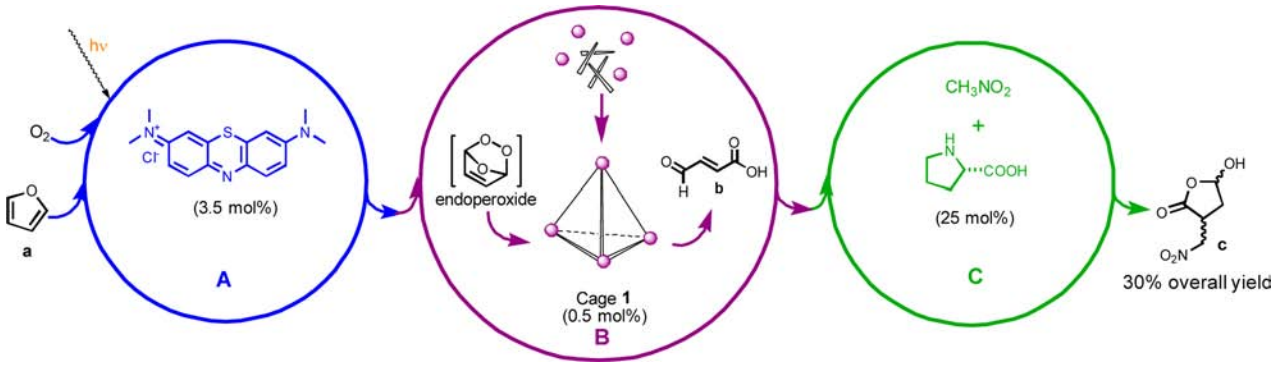

Figure 1. Relay multicatalytic system, in which all steps take place in water at room temperature at pH 4.0. In this one-pot sequential transformation, reaction of furan **a** with singlet oxygen (photogenerated by methylene blue, cycle A) gave the corresponding endoperoxide. This high-energy intermediate was transformed into fumaraldehydic acid **b** in the presence of a catalytic amount of cage **1** (cycle B) which assembled *in situ* without interference from the other components within the mixture. The L-proline-catalyzed 1,4-addition of nitromethane to **b** (cycle C) afforded the final product **c** in 30% overall yield. The derivatization of **c** allowed the determination of its ratio of enantiomers (er = 84:16).

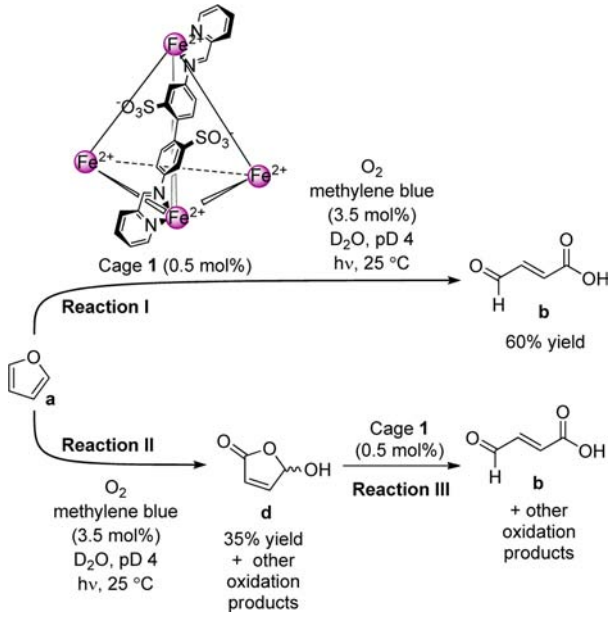

Figure 2. Reaction of furan with $^1O_2$ in the presence and absence of cage **1**. Reaction I shows the conversion of furan **a** to fumaraldehydic acid **b** in the presence of a catalytic amount of cage **1** (0.5 mol%) in D_2O (pD 4). In the absence of cage **1** (reaction II), hydroxybutenolide **d** was formed along with other oxidation products. In reaction III, product **b** was generated from **d** upon addition of cage **1** to the mixture of intermediate products. Only one of the six ligands is represented for clarity in cage **1**.

of cage **1** to the mixture of products from $^1O_2$ and **a** (reaction III, Figure 2). Although this same transformation of **d** might be operative in reaction I, the absence of photooxidation byproducts in this reaction lends weight to the inference that cage **1** is acting on a high-energy intermediate, such as the endoperoxide, thus transforming it selectively into **b** (Figure 1) before competitive pathways leading to multiple byproducts can become operative. This hypothesis is corroborated by the observation of no **d** by ^1H NMR spectroscopy whenever **1** was present. Mechanistic hypotheses for the cage-mediated production of **b** are presented in the Supporting Information (SI), section 2.

Control experiments confirmed that the presence of cage **1** was essential for the production of **b**. Conducting the photooxidation of furan under conditions similar to those employed in reaction I (Figure 2), wherein the individual subcomponents of the cage were used separately in place of the whole cage, showed **d** as the major product along with other oxidation products and no trace of product **c** (SI, section 1.6). Other experiments confirmed that cage **1** clearly acted to transform **d** into **b** over much shorter times (e.g., after 26 min, 25% of **d** was converted to **b** at pD 4 and room temperature, see Figures S16 and S17). Under otherwise identical conditions, a maximum conversion of **d** to **b** of only 5% after 1 week (see Figure S19) was obtained in the absence of cage **1** or in the presence of an incomplete subset of its subcomponents.

The use of chiral amine catalysts to accomplish asymmetric transformations has become a topic of intense development in the field of enantioselective organocatalysis.[16] Combining concepts of organocatalysis with a photoredox catalytic cycle has been shown to result in useful selective transformations.[17] This development prompted us to explore the proline-catalyzed 1,4-addition of nitromethane to **b**, envisaging its combination with the previously described cycles A and B (Figure 1). Iminium-catalyzed reactions are usually performed in the presence of acid co-catalyst.[18] Cage **1** was observed to be stable at pH >3.5; therefore, we performed our reaction at pH 4. After screening different molar ratios for the catalyst L-proline it was found that 25 mol% was required at pH 4 in order to convert **b** into **c** (71% yield) in 16 h (Figure 3). The conversion of **c** into the lactone **e** through *in situ* reduction

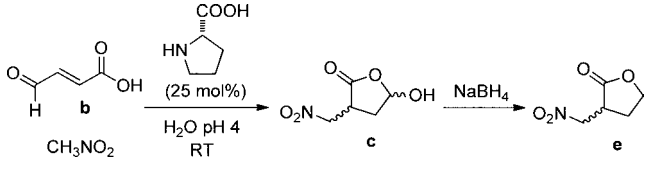

Figure 3. Proline-catalyzed conversion of aldehyde **b** to (nitromethyl)-hydroxyfuranone **c**, and further derivatization to the more stable lactone **e**. The addition of nitromethane to **b** in the presence of L-proline (25 mol%) was followed by cyclization, affording **c** in 71% yield (after isolation) and diastereomeric ratio (dr) = 1:1 (as determined by ^1H NMR). Reduction *in situ* provided lactone **e** in 46% overall yield (after isolation) and 70:30 er (determined by chiral GC using a CP-Chirasil-Dex CB column).

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using $NaBH_4$ was necessary to determine its enantiomeric ratio (er = 70:30) by chiral gas chromatography (Figure 3).

Our investigation and understanding of each individual step, described above, was crucial to the design of the one-pot conversion of **a** into **c**. Components of each of the catalytic cycles shown in Figure 1 were mixed with the subcomponents required to form cage **1** in water buffered to pH 4 (t = 0 in Figure 4). Following irradiation with a 20 W compact fluorescent bulb at room temperature for 48 h under a dioxygen atmosphere, product **c** was isolated in 30% overall yield (t = 48 h in Figure 4). The enantioselectivity of the proline-catalyzed step was determined by chiral GC after derivatization to lactone **e** using $NaBH_4$ as described above. Surprisingly, the enantiomeric ratio obtained in the one-pot transformation (Figure 4) was measured to be 84:16, showing an enhancement in enantioselectivity compared to the independently carried-out 1,4-addition to product **b** (Figure 3, er = 70:30). As cage **1** has no obvious influence on the organocatalytic cycle, we ascribe the improvement in enantioselectivity to the lower steady-state concentration of aldehyde **b** during the combined reaction (see Figure S34B,C). At a lower concentration, proportionally more of the aldehyde will be bound to proline, leading to enantioselective reaction pathways being favored.

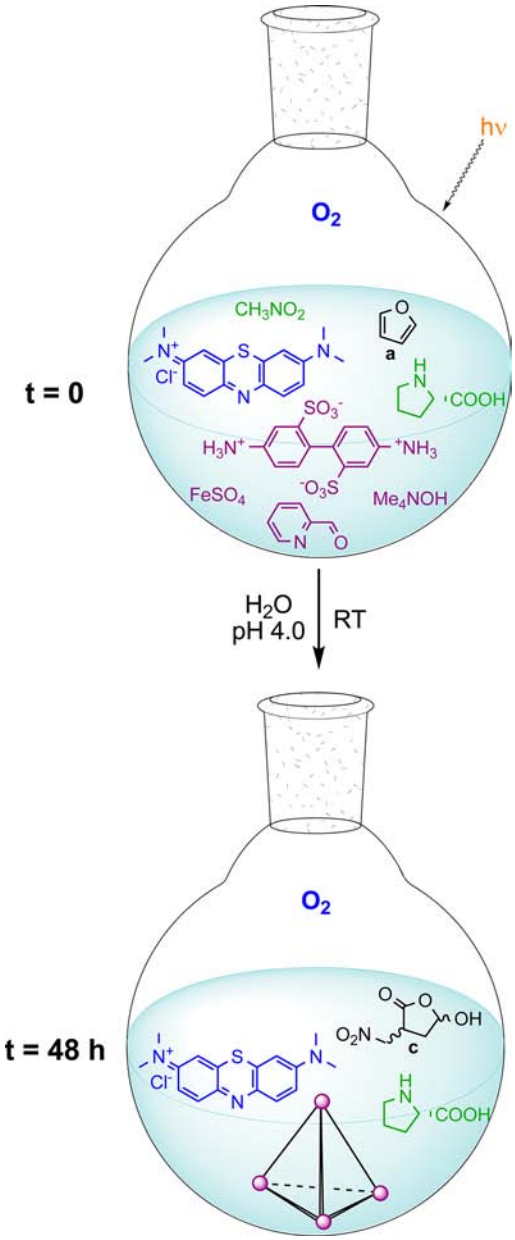

Figure 4. Relay multicatalytic system incorporating the *in situ* assembly of cage **1**. Components of each one of the catalytic cycles were mixed with the subcomponents required to form cage **1** in water (t = 0). The flask was irradiated using a 20 W compact fluorescent bulb for 48 h under an O_2 atmosphere.

The multicatalytic system described herein is easily scalable (from 0.026 to 1.4 mmol of furan, a 54-fold increase), and there is no need for column chromatography to isolate the final product **c**. In the absence of 4,4′-diaminobiphenyl-2,2′-disulfonic acid, which is one of the subcomponents of cage **1**, only the photooxidative catalytic cycle was active, giving **d** as the major product (SI, section 1.13). This outcome confirms that the self-assembly of subcomponents into cage **1** is of paramount importance to obtain **b** through the sequential transformations depicted in Figure 1. In more general terms, the removal of any one of the components from the system, i.e., the deletion of one of the instructions from the system's "program", derails its synthetic outcome.

Two levels of orthogonality can be identified within this one-pot molecular assembly line. First, the orthogonal reactivities of the catalytic cycles avoid interference between the different catalysts and reagents brought together.[13] Second, while the reactions that result in the formation of cage **1** are not strictly chemically orthogonal to the other reactions taking place in the system, their reversibility leads to *de facto* orthogonality. For example, cage **1** is able to self-assemble in the presence of proline (Figure 4) despite the ability of proline to condense with the aldehyde group of the cage subcomponent 2-formylpyridine. The iminium linkage thus formed can exchange, however, allowing an error-checking process to proceed and for cage **1** to self-assemble cleanly.

Similarly, Fe^{II} is prone to oxidation to Fe^{III} under a dioxygen atmosphere; nevertheless, the mutual stabilization[19] between imine ligands and Fe^{II} plays an essential role preventing the oxidation and allowing the formation of a stable assembly. The interplay between the two levels of orthogonality along with the compatible kinetics of the catalytic cycles was thus crucial for function to be achieved.

The functioning of this self-organizing system is thus underpinned by the robust self-assembly of cage **1** and its novel ability to catalyze the production of **b**, which could be joined to a subsequent organocatalytic step in order to allow for further transformations to occur. This one-pot process avoids intermediate purification procedures and changes in reaction conditions and is scalable 50-fold. All starting materials are commercially available, and mild experimental conditions were employed. Further investigations may allow this approach to be extended and refined, for example, to allow for the preparation of a wider array of organic molecules of interest[20] by taking advantage of other cage-mediated transformations.[21]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; control experiments; one-pot multicatalytic procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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