Kinetic Self-Sorting of Dynamic Covalent Catalysts with Systemic Feedback Regulation

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Ⓢ *Supporting Information*

ABSTRACT: Constructing small molecule systems that mimic the functionality exhibited in biological reaction networks is a key objective of systems chemistry. Herein, we report the development of a dynamic catalytic system where the catalyst activity is modulated through a dynamic covalent bond. By connecting a thermodynamically controlled rearrangement process to resolution under kinetic control, the catalyst system underwent kinetic self-sorting, resulting in amplification of a more reactive catalyst while establishing a catalytic feedback mechanism. The dynamic catalyst system furthermore responded to catalytic events by self-perturbation to regulate its own activity, which in the case of upregulation gave rise to systemic autocatalytic behavior.

The design, realization, and evaluation of complex reaction networks constitute important parts of systems chemistry and biology.[1−3] Detailed understanding of reaction networks is, for example, essential for exploring emergent functionality and connectivity in chemical and biological systems, and for delineating complexity evolution related to the origin of life.[4−6] In this context, reaction control is a major challenge, and programming of complex chemical networks has been attempted to introduce function by design. For example, chemical systems capable of self-organization,[7−10] self-replication,[11−13] self-resolution,[14−16] compartmentalization,[17,18] allosteric regulation,[19] and constituent selection via secondary interactions[20−24] have been developed, providing chemical models for advanced biological functions. However, an area with limited progress is catalytic feedback and self-regulation. While this is an ubiquitous feature in nature due to its importance in homeostasis and metabolism, few examples of catalytic procedures capable of dynamic self-adaptive behavior have been reported.[25−28]

In conjunction to supramolecular interactions, dynamic covalent bonds are significant as design elements for systems chemistry, their labile nature ensuring reversibility and entailing error-correcting potential into complex networks.[29,30] Based on this chemistry, we recently developed dynamic covalent organocatalysts, where a reversible imine bond was integrated in the catalyst structure.[31] This led to the hypothesis that such an adaptable catalyst could display self-sorting or self-regulation behavior when introduced into larger systems, leading to dynamic catalytic systems able to modulate their own overall activity.

Catalysts that are able to adapt in response to their surroundings have been pursued, and examples of switchable

or self-replicating organocatalysts have been developed.[32−37] However, there are no reports of a catalyst that is able to modify its own molecular architecture in response to the catalytic event in which it partakes. This has been addressed in the present study, where dynamic catalysts for the Morita−Baylis−Hillman (MBH) reaction have been constructed and shown to undergo systemic changes by feedback up- or down-regulation of the overall systemic activity (Figure 1a).[38]
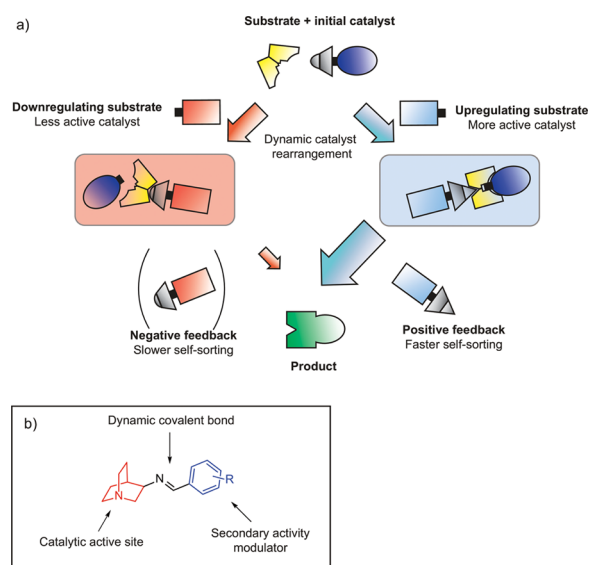

Figure 1. (a) Schematic illustration of reaction network; (b) dynamic covalent organocatalyst used.

The nucleophilic catalyst structure was composed of a catalytically active quinuclidine unit that activates the acrylate via nucleophilic attack of the tertiary nitrogen, a secondary activity modulator of the catalytic activity through noncovalent interactions (such as H-bonding or $\pi-\pi$ interactions), and a dynamic imine bond connecting the two parts (Figure 1b). The MBH reaction of aromatic aldehydes with acrylates was chosen as model reaction due to its well-known sensitivity to changes in catalyst structure, as well as its comparatively slow kinetics. The low rate allowed the imines to undergo exchange in parallel to the MBH reaction, which operated under kinetic control under the present conditions (cf. Supporting Information) and removed the reacting aldehydes from the dynamic system.

The dynamic catalysts **C1**−**C9** were synthesized from 3-aminoquinuclidine and the corresponding aldehydes, and their activities evaluated in a model reaction between *p*-nitrobenzaldehyde and methyl acrylate in MeCN (Table 1). All

Table 1. Catalyst Evaluation with Model Reaction[a]

catalyst	R	k_{rel}[b]
C1	4-NO$_2$	1.00
C2	2,4-NO$_2$	0.48
C3	H	2.24
C4	2-OMe	2.01
C5	4-OMe	2.21
C6	2,4-OMe	2.76
C7	2-OH	0.45
C8	4-OH	0.43
C9	2-OH, 3-OMe	N/A

[a]Conditions: aldehyde **1**, (0.1 mmol), methyl acrylate (0.3 mmol), catalyst (0.02 mmol), MeCN (0.5 mL), rt, N$_2$. [b]Relative initial rate over first 7 h with catalyst **C1** as reference; estimated by ^{1}H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard.

reactions proceeded readily, with no traces of byproducts detected, and revealed a trend in catalyst performance with respect to aldehyde substitution pattern. The more electron-rich catalysts **C3**−**C6** performed significantly better than the electron-poor catalysts **C1**−**C2**, indicating a correlation between activity and electron density. It was furthermore reasoned that introduction of a hydrogen-bonding phenolic moiety could potentially facilitate the reaction through stabilization of the zwitterionic reaction intermediate.[39] However, the three hydroxyl-containing catalysts **C7**−**C9** all performed poorly, with catalyst **C9** failing to provide more than trace amounts of product even after extended reaction times.

When a dynamic system is subjected to pressure from a substrate-selective[40] resolving reaction, kinetic self-sorting can be observed.[15,41−45] It was hypothesized that this effect could be implemented in the dynamic catalyst system since MBH reaction rates are often strongly dependent on aldehyde electrophilicity, with orders of magnitude rate differences between fast-reacting electron-poor and slow-reacting electron-rich aldehydes.[46,47] Thus, connecting a kinetic self-sorting protocol to an equilibrating system of dynamic covalent catalysts conceivably gives rise to a scenario in which the total catalytic activity in the system changes continuously during the reaction in response to the substrate-selective transformation. The overall catalytic activity of the catalyst mixture thus changes along with the degree of self-sorting, giving rise to indirect feedback loops and systemic self-regulation.

To evaluate the self-resolving properties of the MBH catalysts, dynamic systems were constructed in which catalyst **C1** was mixed with equivalent amounts of aldehyde. Exchange with aldehydes **3**, **5**, and **6** produced ^{1}H NMR spectra with overlapping peaks, whereas the combination of catalyst **C1** and aldehyde **4** enabled selective quantitation of each system component (Figure 2a). The imine exchange between compound **C1** and aldehyde **4** to yield aldehyde **1** and new imine catalyst **C4** was next studied in detail (cf. Table S4). Under acid catalysis with added H$_2$O to facilitate imine exchange, an
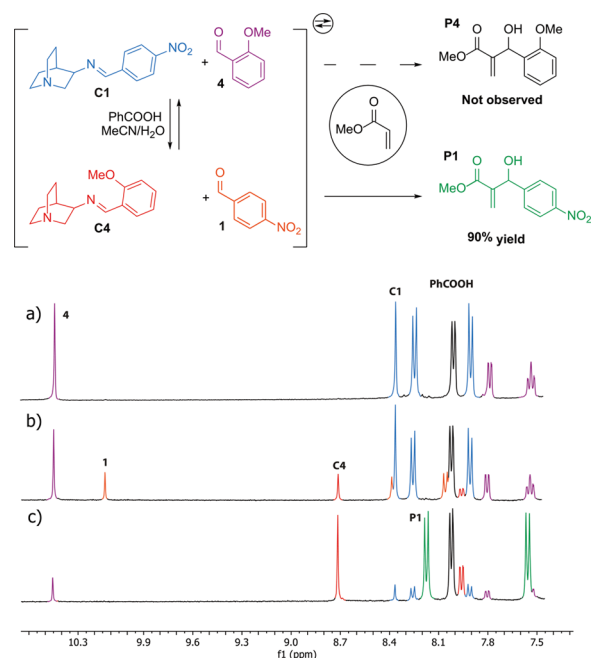

Figure 2. Top: Dynamic systemic rearrangement. Bottom: ^{1}H NMR spectra of catalytic system at (a) $t = 0$ and (b) equilibrium in the absence of methyl acrylate; (c) $t = 5$ d in the presence of methyl acrylate. Conditions: catalyst **C1** (0.04 mmol), aldehyde **4**, (0.04 mmol), PhCOOH (0.04 mmol), methyl acrylate (0.4 mmol), MeCN/H$_2$O (99:1, 0.2 mL), r.t., N$_2$.

equilibrium of 1:0.3 between catalysts **C1** and **C4** was established within 24 h (Figure 2b).

Next, kinetic self-sorting was evaluated in systems based on aldehyde **4**, methyl acrylate, and catalyst **C1** (Figure 2c). Although a mixture of MBH adducts **P1** and **P4** was expected since aldehyde **1** is more reactive but aldehyde **4** was initially present in higher concentration, product **P1** was the only observable MBH adduct, together with the rearranged imine catalyst **C4**. Furthermore, the reaction proceeded in 90% yield after 5 days, with no side product formation (Table S5).

As long as the reactivities of the different substrates are sufficiently different, clear self-sorting behavior can be observed. The obtained result indicates that the selectivity for this particular catalyst/substrate combination is indeed remarkably high, as trace quantities of product **P4** could only be observed after more than 1 week of reaction time. Furthermore, utilizing catalyst **C4** and aldehyde **1** as starting components, under otherwise identical conditions, produced the same reaction outcome (87% yield of product **P1**, 48 h), demonstrating a high level of robustness in the system.

The dynamic catalyst **C1** was thus capable of self-correcting an unfavorable reactivity situation and underwent a systemic rearrangement with continuous self-resolution. To investigate the underlying mechanisms behind the rearrangement, a series of control experiments was conducted (cf. Supporting Information). Performing the experiment under dry conditions completely inhibited the reaction, as did omitting the benzoic acid necessary for imine rearrangement. These results suggest an imine hydrolysis/condensation exchange mechanism, where benzoic acid acts as both imine exchange facilitator and cocatalyst for the MBH reaction. However, increasing the amount of acid beyond one equivalent led to retardation of the reaction rate,

likely due to partial protonation of the reactive zwitterion intermediate.[48]

The system kinetics was next investigated using ^{1}H NMR spectroscopy. As can be seen in Figure 3, the initial imine
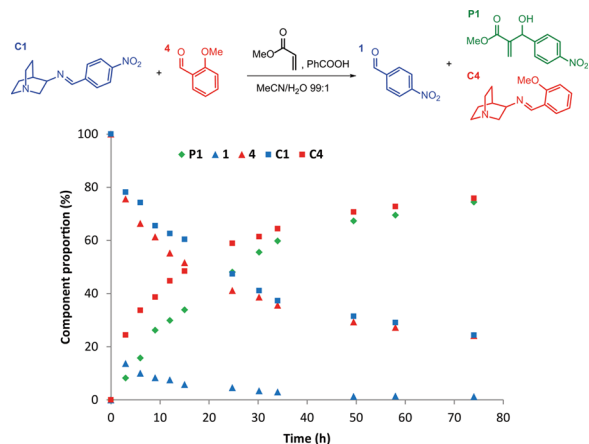

Figure 3. Kinetic analysis of systemic rearrangement with catalyst **C1** and aldehyde **4**. Component proportion based on aldehyde; estimated by ^{1}H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard.

exchange proceeded considerably faster than the subsequent MBH reaction. After 3 h, the imine system had already rearranged to a significant extent, while only small amounts of product **P1** had been formed. In the connected network, the MBH reaction thus acted as the rate-determining reaction, which controlled the kinetics of the entire set. The decrease in concentration of catalyst **C1** and increase of catalyst **C4** were closely mirrored within the experimental accuracy of ^{1}H NMR measurements ($\pm$5%). Also, the formation of new compounds **P1** and **C4** were connected, indicating that the dynamic imine system adapted to the consumption of aldehyde **1** by dissociation of catalyst **C1** to form more of compound **1** and eventually more of catalyst **C4**. Interestingly, the local imine exchange equilibrium did not have time to settle under these conditions, due to the constant perturbation induced by the MBH reaction. The system thus operated in the out-of-equilibrium regime, where methyl acrylate acted as the energy source that consistently drove the system away from the equilibrium state.[49]

The systemic rearrangement observed, turning a less active catalyst into a more active species, led to the hypothesis that this change in activity space could result in systemic autocatalysis. Thus, the formation rate of product **P1** was conceived to be dependent not only on the imine exchange rate to release aldehyde **1**, but also on the catalytic activity of the entire catalyst system. In contrast to direct autocatalysis[50] of compound **P1** formation, the *product set* of adduct **P1** and catalyst **C4** are then involved in a positive feedback loop, leading to autocatalytic behavior of the set as a whole. Product **1** on its own is not a catalyst, but production of the MBH adduct is always accompanied by an increase in catalyst **C4**. A synergetic relationship between the compounds of the set is then expected since compound **C4** is more adept at forming adduct **P1** than the initial catalyst **C1**, and formation of product **P1** is accompanied by a perturbation of the dynamic imine system to yield more compound **C4**.

Importantly, for such a scenario to be valid, the individual catalysts must display independent behavior during the reaction.

Thus, different ratios of **C1** and **C4** were used as catalysts in a model reaction (Figure S1). No indication of any indirect cooperativity could be found, and the catalyst mixtures behaved as linear combinations of the individual catalysts. A closer investigation of the rate profile of **P1** formation was also conducted (Figure S2). A sigmoidal reaction profile was recorded, with the initial lag phase likely due to rate limiting imine exchange during the first part of the reaction. As expected, it was not evident from the data if generation of **C4** affected the rate of **P1** formation. Considering the relatively low difference in activity between **C1** and **C4**, such effects are likely negligible in comparison to other factors.

Instead, the systemic feedback regulation was evaluated by relative comparisons. This was based on the fact that the change in composition during the self-resolution of catalyst **C1** and aldehyde **4** led to upregulation of the systemic catalytic activity, thus presumably leading to the decreased formation rate of product **P1** when a less active catalyst is created from **C1** (Figure 4). Thus, confirmation of the systemic feedback regulation can be
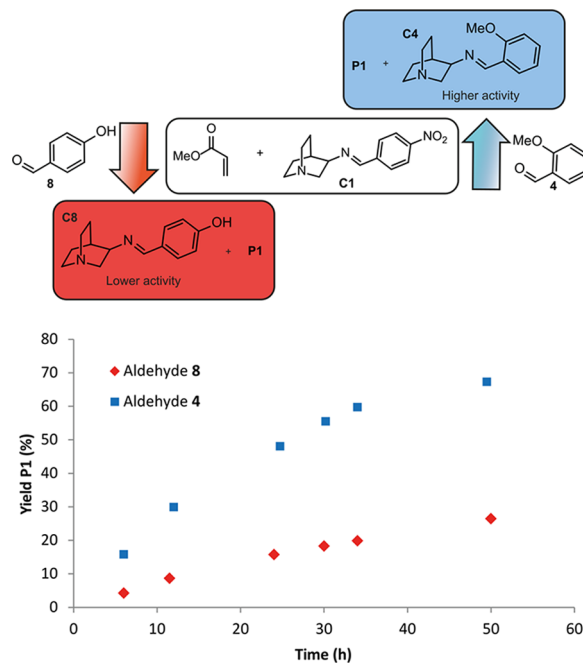

Figure 4. Self-regulation of error-correcting systems; addition of modulator leading to a more/less active catalyst leads to faster/slower system rearrangement. Conditions: catalyst **C1** (0.06 mmol), aldehydes **4** or **8** (0.06 mmol), PhCOOH (0.06 mmol), methyl acrylate (0.6 mmol), MeCN/H$_2$O (99:1, 0.3 mL), r.t., N$_2$.

obtained by comparison of the self-resolution efficiency at any given point for an up- and downregulating system, respectively.

To test this hypothesis, aldehydes **2** and **7**−**9** were added to the system instead of aldehyde **4** under otherwise identical conditions. Substrate selectivity for aldehydes **2**, **7**, and **9** was intermediate, and mixtures of MBH adducts were obtained. However, for aldehyde **8**, the systemic rearrangement progressed smoothly with full selectivity for nitro-substituted adduct **P1**. The system perturbation progressed significantly slower than with the "upregulating" aldehyde **4**, despite the imine exchange reactions proceeding with comparable rates. After 48 h, the yield of product **P1** was 26% for the "downregulated" reaction versus 68% for the "upregulated" counterpart. Extending the reaction time beyond 72 h for the system with aldehyde **8** led to formation

of a heterogeneous reaction mixture, obstructing further analysis. Nevertheless, this finding provides validation that systemic activity is continuously changing during self-sorting, leading to catalytic feedback regulation.

In conclusion, this study has demonstrated how small-molecule catalytic networks can be programmed to incorporate activity feedback regulation, and how substrate selectivity and differential catalytic activity work in concert to provide kinetic self-sorting of a catalyst–substrate pair. It has also been shown that the rearrangement rate is dependent on the modulating agent of the system, which leads to temporal resolution where more effective catalyst systems evolve faster. This behavior could in principle act as a blueprint for creating molecular "Darwinism" in the far-from-equilibrium regime, especially when coupled with a compartmentalization procedure. The approach toward complexity evolution should furthermore hold significant interest for origin-of-life research. The successful self-sorting observed, based on high catalytic substrate selectivity, dynamic catalyst scaffolds, and a resolving reaction that acts on components in the dynamic covalent connection, also lends itself to be generalized to more biologically relevant entities, such as peptides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04250.

> Experimental procedures, control experiments, and characterization data (PDF)

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Notes
The authors declare no competing financial interest.

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