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**Effector Regulated Catalytic Cyclization of Alkynoic Acids Using Pt$_4$L$_4$ Cages**

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**Abstract:** Metabolic pathways are highly regulated by effector molecules that influence the rate of enzymatic reactions. Inspired by the catalytic regulation found in living cells, we report a Pt$_4$L$_4$ cage of which the activity can be controlled by effectors that bind inside the cage. The cage shows catalytic activity in the lactonization of alkynoic acids, with the reaction rates dependent on the effector guest bound in the cage. Some effector guests enhance the rate of the lactonization by up to 19-fold, whereas one decreases it by 5-fold. When mixtures of specific substrates are used, both starting materials and products act as guests for the Pt$_4$L$_4$ cage, enhancing its catalytic activity for one substrate while reducing its activity for the other. The reported regulatory behavior obtained by the addition of effector molecules paves the way to the development of more complex, metabolic-like catalyst systems.

Regulation of catalytic activity plays a crucial role in biology, as it leads to controlled metabolism. Numerous enzymatic reactions are controlled by effectors, providing handles to regulate activity. In biological systems, such effector-controlled processes provide handles to control complex metabolic pathways. These effectors are typically inducing changes in the tertiary structure of an enzyme, which changes the rate of transformation of the substrate. In contrast to systems found in biology, only a limited number of synthetic catalysts are known to be regulated by effector molecules. The precise regulation of catalytic systems by effectors can enhance the applicability of catalysts in complex systems allowing for new strategies for chemical transformations.

We envisioned that self-assembled M$_4$L$_4$ cages would be ideal candidates for the development of catalyst systems regulated by effector molecules as they typically contain a binding cavity and metal nodes. These types of cages are formed by complexation of palladium or platinum with ditopic, banana-shaped pyridine building blocks. The interior space of some cages has been used for catalysis. Moreover, M$_4$L$_4$ cages are capable to encapsulate a variety of neutral and charged guests through either hydrophobic interactions or hydrogen-bonding. Both the catalytic activity displayed by the M$_4$L$_4$ cages and the rich host–guest chemistry makes M$_4$L$_4$ cages ideal candidates for studies into regulatory catalytic applications. Here we report a Pt$_4$L$_4$ cage in which both the inner volume (Figure 1, S1) and the exotopic space (Figure 1, S2) can be used for guest encapsulation and substrate transformation, which is the basis for effector regulated catalytic transformations.

For our investigations into regulatory catalytic systems, Pt$_4$L$_4$ cages were chosen. These are more robust in comparison to the palladium based analogues, allowing for a bigger variety of substrates and reaction conditions. Complexation of a ditopic building block (1 equiv) with a restrained amount platinum (0.49 equiv) was used to prepare cages in absence of impurities of platinum precursor (Figure 1). The desired Pt$_4$L$_4$ cage formation was supported by spectroscopic features that are in accordance to literature. The connectivity of the cage structure is furthermore supported by X-ray analysis of single crystals.

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**Figure 1.** A) Synthesis of the cage C$^{Pt}$ and molecular counterpart M$^{Pt}$. Display of the two distinct sites for catalysis and guest encapsulation/complexation (S1 vs. S2).

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(Section SI9). For comparison, also a molecular analogue (MPh), with similar electronic and steric features to the nanocage, was prepared using standard procedures (Figure 1).

The counterions were exchanged by salt metathesis to the large BarF− counterion according to reported procedures[8,9] (Section SI2). After counterion exchange, pure stock solutions of the cage CPh and MPh in DCM are obtained as judged by 1H-, DOSY NMR and MS analysis and used for further investigations.

With the nanocage CPh and the molecular analogue MPh in hand, we focused on platinum catalyzed cyclization of alkynoic acids. The inner cavity (S1) was envisioned for effector encapsulation and the exotopic space S2 for the catalytic transformation. To receive no competition of the substrate during effector binding in the inner cavity (S1), we decided to study the cyclization of a sterically demanding substrate SPh which does not fit in the cavity (S1) (Figure 1, Table 1). The cyclization of SPh is catalyzed in a water saturated solution of dcm (to promote proto-demetallation) by MPh (TOFcat = 1 h−1, Table 1, Entry 1) and by CPh (TOFcat = 2 h−1, Table 1, Entry 2). The inner pyridine protons of the cage show no shift in 1H NMR during the cyclization of SPh using CPh (Figure S19), in contrast to experiments in the presence of smaller molecules that do bind (vide infra), confirming that SPh/PPh are not efficiently encapsulated by CPh. This makes SPh a suitable substrate for studies on the influence of effectors on the catalytic performance of CPh.

Having demonstrated the catalytic activity of CPh in the cyclization of SPh, we used a combination of optimization, molecular dynamics simulations, and reaction-path modeling (Figure 2A/B) to produce an estimated free-energy pathway for the cyclization process (Section SI7). The calculation of the reaction pathway is anticipated to provide information for the rational choice of effector guests.[9] The calculations suggest that the proto-demetallation is the rate determining step (rds) (Figure 2B, red trace), which is in line with the catalytic results that show pseudo zero-order rate dependency on the substrate concentration (until 75 % conversion, Figure S21). Furthermore, the formed product PPh contains deuterium on the Z-5-methylene position (Table 1, Figure S18), indicative of a proto-demetallation step in the catalytic cycle (Int2, Figure 2A). In addition, we observe a kinetic isotope effect (KIE) of 3 when the reaction is performed in H2O instead of D2O, further supporting that the proto-demetallation is the rds (Table 1, Entry 3). Furthermore, water is anticipated to play a prominent role as it may facilitate the rds proto-demetallation and potentially form hydrogen-bonding networks close to the catalytic sites (also with guests, as observed for one potential transition state, Figure S59). The calculations together with the kinetic analysis of the cyclization suggest that a more active catalyst can be obtained by facilitation of the proto-demetallation step. Generally, this step can be facilitated by increasing the concentration of protons and enhancement of the nucleophilic character of the Pt-vinyl carbon (Int2, Figure 2A). This provides a rationale for the choice of effectors that can bind in the cage.

The cage CPh was anticipated to bind, in agreement to previously reported PdL4 cages,[10–13] different guests inside its cavity (S1) through hydrogen bonding of the inner eight pyridine protons to hydrogen bond acceptors (Figure 3A). As suitable effectors to boost the proto-demetallation, we choose maleic acid, levulinic acid and acrylic acid (Figure 3D). The acidic groups of those three effectors will increase the local concentration of protons. Hydrogen bonding of the oxygen to the pyridine protons (Figure 3A) can tune the electronic properties of the metal-complex which is anticipated to enhance the nucleophilic character of

### Table 1: Catalytic cyclization of SPh.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>TOFcat [h−1]</th>
<th>Conversion [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>MPh</td>
<td>1</td>
<td>95%</td>
</tr>
<tr>
<td>2[a]</td>
<td>CPh (8% D2O)</td>
<td>2</td>
<td>95%</td>
</tr>
<tr>
<td>3[a]</td>
<td>CPh (8% H2O)</td>
<td>6</td>
<td>95%</td>
</tr>
<tr>
<td>4[a]</td>
<td>CPh (1.25% cat)</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>5[a]</td>
<td>CPh (2.5% cat)</td>
<td>2</td>
<td>15%</td>
</tr>
<tr>
<td>6[a]</td>
<td>CPh (5% cat)</td>
<td>2.4</td>
<td>30%</td>
</tr>
</tbody>
</table>

[a] Reactions performed at 15 mM substrate with 10 mol% MPh (1 μmol) in 50 μL D2O and 600 μL DCM at r.t. for 18 h. [b] 15 mM substrate with 5 mol% CPh (0.5 μmol) in 50 μL D2O or H2O and 600 μL DCM at r.t. for 18 h. [c] 30 mM substrate with different amount of CPh in 50 μL D2O and 600 μL DCM at r.t. for 2 h. [d] Conversion and TOF were determined with 1H NMR using mesitylene as internal standard. [e] TOF displayed per 2 Pt complexes for better comparison with CPh.
Chemical catalysis is performed in the presence of maleic acid but to a lesser extend (TOF \textsubscript{pol} = 3 h\textsuperscript{-1} versus 1 h\textsuperscript{-1}, Table 2, Entry 1 and 2). Although \textsuperscript{M} and \textsuperscript{C} have comparable metal complexes, the well-defined inner cavity of \textsuperscript{C} allows for a 19-fold rate increase, whereas molecular analogue \textsuperscript{M} experiences 3-fold rate increase only. Importantly, in the presence of maleic acid as an effector, the nanocage \textsuperscript{C} is about 16-times more active compared to \textsuperscript{M} which is a unique feature obtained from the defined arrangement of the Pt\textsubscript{4}L\textsubscript{4} nanocage.

In contrast to the rate enhancing properties of the different electron donating acid effectors (Table 2, Entry 4–6), the presence of benzoquinone or dicyanobenzene result in a reduced turnover frequency (TOF \textsubscript{pol} = 2–0.5 h\textsuperscript{-1}, Table 2, Entry 7–8) as expected from their electron withdrawing character reducing the nucleophilicity of the Pt-vinyl carbon. These experiments show that the activity can be modulated in the range of 0.2–19-TOF\textsubscript{pol} when using different guests as effector, in analogy to effectors that change the rate of enzymatic reactions.

Having established that we can use effectors to control the catalytic activity of \textsuperscript{C}, we were wondering if such effectors could also be generated in situ using the cage as catalyst. The two most promising effectors (maleic and levulinic acid) are anticipated to be formed by hydrolysis of the corresponding anhydrides. The furanone derivative \textsuperscript{P} is structurally related to \textsuperscript{P} and was anticipated to be cyclized by \textsuperscript{C} from pentyneoic acid \textsuperscript{S} (Figure 4).

We first set up experiments to provide evidence that under catalytic conditions, maleic anhydride can be hydrolyzed. Indeed, when maleic anhydride is applied as effector in the \textsuperscript{C} catalyzed cyclization of \textsuperscript{S}, a similar TOF\textsubscript{pol} is observed as for maleic acid (TOF \textsubscript{pol} = 48 h\textsuperscript{-1}). The similar catalytic activity displayed by \textsuperscript{C} in the presence of maleic acid and maleic anhydride, as well as the MS study and \textsuperscript{1}H NMR shifts that reveal binding (Figure S35) all indicate...
that maleic anhydride is a suitable effector precursor which is hydrolyzed in the presence of water to provide the effector maleic acid.

A similar hydrolysis pathway is envisioned for the furanone $\text{S}^\text{H}$. The cyclization of $\text{S}^\text{H}$ and the consecutive hydrolysis of $\text{S}^\text{P}$ to the effector levulinic acid was studied. $\text{S}^\text{H}$ is cyclized by $\text{C}^\text{P}$ to $\text{P}^\text{H}$ (TOF$_\text{int}$ = 6.4 h$^{-1}$). However, little consecutive hydrolysis to the desired effector levulinic acid is observed within 14 h (less than 5%, Figure S40–41). In contrast to that, the presence of maleic acid as an effector allows faster conversion of $\text{S}^\text{H}$ (in the mixture $\text{S}^\text{H} + \text{S}^\text{P}$) is used, allowing substrate $\text{S}^\text{H}$ to be the effector for the conversion of $\text{S}^\text{P}$. Indeed, under these conditions, $\text{S}^\text{P}$ is converted more rapidly than $\text{S}^\text{H}$. As such, the activity for $\text{S}^\text{P}$ cyclization is enhanced 2-fold (TOF$_\text{int}$ = 2.5 to 6.7 h$^{-1}$) compared to the single substrate experiment, whereas the rate for $\text{S}^\text{H}$ is reduced by 65% (TOF$_\text{int}$ = 6.4 h$^{-1}$ to 2.2 h$^{-1}$). The enhanced activity for the conversion of $\text{S}^\text{P}$ is in line with the binding of the acid substrate $\text{S}^\text{H}$ inside the cage that operates as effector, and the $\text{S}^\text{H}$-$\text{C}^\text{P}$ catalysts results in $\text{S}^\text{P}$ cyclization with a higher rate k2 (Figure 5C). As binding of $\text{S}^\text{P}$ to the outside of the sphere and its cyclization is typically higher, it outcompetes the $\text{S}^\text{H}$ cyclization in the competition experiment.

**Figure 4.** (Top) Proposed synthesis of different effectors by $\text{C}^\text{P}$. (Bottom) Cyclization of $\text{S}^\text{H}$ by $\text{C}^\text{P}$ in the presence and absence of 50 equiv of maleic anhydride. Reaction conditions: 0.5 μmol $\text{C}^\text{P}$ (5 mol%), 10 μmol $\text{S}^\text{H}$, 5μmol maleic anhydride in 600 μL DCM and 50 μL D$_2$O. Concentrations were determined via $^1$H NMR using mesitylene as an internal standard.

**Figure 5.** A) Cyclization of $\text{S}^\text{H}$ and $\text{S}^\text{P}$ by $\text{C}^\text{P}$ in single-substrate experiments (dotted line) and in a 1:1 mixture (solid line). Reaction conditions: 0.5 μmol $\text{C}^\text{P}$ (5 mol%), 10 μmol $\text{S}^\text{H}$ or $\text{S}^\text{P}$ (in the mixture 5 μmol $\text{S}^\text{H}$ and $\text{S}^\text{P}$) in 600 μL DCM and 50 μL D$_2$O. Conversion was determined via $^1$H NMR . B) Proposed rate Scheme for the individual cyclization of $\text{S}^\text{H}$. C) Proposed rate scheme for the mixed cyclization of $\text{S}^\text{H}$ and $\text{S}^\text{P}$.
With this information in hand, we studied the effect of substrate \( \text{S}^\text{P} \), the product \( \text{P}^\text{P} \) and its ring opened structure levulinic acid as effector on the rate of the cyclization of \( \text{S}^\text{P} \).

In the presence of these effectors, the TOFs were respectively 6.7, 8.6 and 11.5, which is all higher than in absence of effectors (Figure 6). Finally, we studied if the cage quantitatively in the reaction mixture. Under these conditions \( \text{S}^\text{P} \) was added after 12 h, \( \text{C}^\text{P} \) cyclized \( \text{S}^\text{P} \) to furanone \( \text{P}^\text{P} \) which now operates as effector. Indeed, the observed TOF_{init} is identical to the experiment carried out in the presence of \( \text{P}^\text{P} \) (TOF_{init} = 8.4 h^{-1}). When the cage is not allowed to react for 5 days with \( \text{S}^\text{P} \) before adding the final batch of substrate \( \text{S}^\text{P} \), the effector levulinic acid is formed quantitatively in the reaction mixture. Under these conditions with levulinic acid as effector, \( \text{S}^\text{P} \) is now converted with a of TOF_{init} = 11 h^{-1}, which is the same as the control experiment. This demonstrates that \( \text{C}^\text{P} \) converts substrate \( \text{S}^\text{P} \), which is already an effector, into more efficient effectors (\( \text{P}^\text{P} \) or levulinic acid) leading to enhanced catalytic activity in \( \text{S}^\text{P} \) cyclization. It shows the complexity that can be reached with these relatively simple \( \text{Pt}_{14} \) cages, generating various systems in time with feedback loops as products generated act as effectors.

We have presented a \( \text{Pt}_{14} \) cage which is active in the cyclization of alkynoic acids. The catalyst activity can be modulated by encapsulation of guests within the cage, increasing the overall activity by 19-fold or decreasing it by 5-fold. The effector can also affect to rate of the follow-up reaction, and thereby the product selectivity. As for the cyclization reaction also the substrate and products can act as effectors, autoregulation in more complex substrate mixtures comes in sight. With the high tunability and complexity of effector controlled catalytic application of \( \text{Pt}_{14} \) cages we envision to pave the way to more complex bio-mimetic and metabolic catalyst systems. We anticipate that this proof-of-concept study may provide inspiration for studies into new reactivity of metal nodes used for supramolecular cages, especially when precious transition metals are utilized (e.g., Pt, Pd, Rh). We show that enhanced catalytic activity is obtained using host–guest chemistry which provides a new handle for cage catalyzed reactions.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the SI and from the corresponding author upon reasonable request.

Keywords: Catalysis · Effector · Feedback Loops · Host–Guest · Nanocages


Figure 6. Preparation of different effectors from pentynoic acid by the cage \( \text{C}^\text{P} \) and the rates of consecutive cyclization of \( \text{S}^\text{P} \). Reaction conditions: 0.5 μmol \( \text{C}^\text{P} \) (5 mol%), 10 μmol \( \text{S}^\text{P} \) in 600 μL DCM and 50 μL D$_2$O. TOF$_{init}$ were determined via $^1$H NMR.


[8] Deposition Number 2189698 (for (C^6)(BF_4) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.


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