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Cofactor Controlled Encapsulation of a Rhodium Hydroformylation Catalyst

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Abstract: *Supramolecular approaches in transition-metal catalysis, including catalyst encapsulation, have attracted considerable attention. Compared to enzymes, supramolecular catalysts in general are less complex. Enzyme activity is often controlled by the use of smaller cofactor molecules, which is important in order to control reactivity in complex mixtures of molecules. Interested in increasing complexity and allowing control over supramolecular catalyst formation in response to external stimuli, we designed a catalytic system that only forms an efficient supramolecular complex when a small cofactor molecule is added to the solution. This in turn affects both the activity and selectivity when applied in a hydroformylation reaction. This contribution shows that catalyst encapsulation can be controlled by the addition of a cofactor, which affects crucial catalyst properties.*

In nature, many chemical processes occur in parallel and although reactions take place in very complex mixtures of substrates, nature manages to have full control over the chemical outcome. In contrast to man-made catalysts, nature has evolved a plethora of mechanisms to control the chemistry, oftentimes through the use of cofactors and feedback loops.[1,2] Chemists are at the beginning of building synthetic catalysts with similar functions, with the long-term aim to control chemical pathways in more complex chemical mixtures.[3–9] In this context, there is increasing interest in synthetic catalysts that can be switched by external stimuli or cofactors.[10–18] Most of these studies have been carried out using relatively simple hydrolysis reactions and organocatalytic reactions, and the number of transition-metal catalysts that have a switching function is very limited.[19,20] On the other hand, the encapsulation of transition-metal complexes in confined spaces to control the activity and selectivity through the second coordination sphere, a strategy also inspired by enzymes, has received considerably more attention.[7,21–23] Indeed, reported examples demonstrate that rate acceleration can be achieved by transition-state stabilization, and both substrate-selective catalysis and unusual product selectivity has been obtained.[24,25] Along these lines, we have developed ligand template assembly strategies over the years to encapsulate catalysts as a new way to control metal-catalyzed processes.[26] Tris-3-pyridyl-based rhodium catalysts can be encapsulated by Zn^{II}TPP (TPP = tetrakis-*meso*-phenyl porphyrin) through coordination of the pyridyl moieties to the zinc atom of the porphyrin, resulting in a rate acceleration and branched-selective hydroformylation of terminal alkenes.[25,27,28] This was the first example of a branched selective hydroformylation catalyst for these type of substrates and few selective catalysts have been developed since.[29] The origin of the observed branched selectivity and rate acceleration was attributed to the supramolecular capsule formed, which preoganizes the substrate towards the transition state leading to the branched product.[25] Other supramolecular strategies that provide control over regioselectivity in hydroformylation catalysis[30] include the use of self-assembled bidentate ligands,[31–33] substrate-orientation effects using supramolecular interactions between the substrate and the functional groups of the ligand,[34–36] ligand scaffolding using dynamic covalent bonds,[37] and cyclodextrin-based strategies.[38–40]

With the aim to develop molecular catalysts in confined spaces for which both activity and selectivity can be switched, we designed a supramolecular catalyst system in which the coordination of the zinc porphyrin to the pyridine ligand, and thus the catalyst encapsulation event, can be controlled by the binding of a cofactor. As a result, the individual components of the catalyst are present in solution but only form an efficient catalyst upon introduction of the cofactor (Figure 1).

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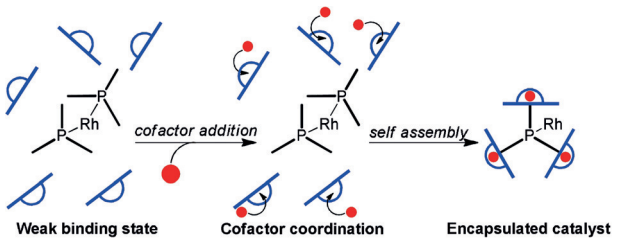


Figure 1. Schematic of cofactor-controlled encapsulation. The individual components present in solution form a bisphosphine rhodium complex, and the introduction of the cofactor activates the porphyrin for coordination, thereby initiating capsule formation around the catalyst.

For our purpose, zinc porphyrin clip molecule **2**, developed by Nolte et al.,[41] appeared an ideal building block, since the binding of a pyridine ligand to a zinc(II)porphyrin is relatively weak but becomes much stronger when a 4,4′-dimethylviologen dihexafluorophosphate guest is bound in the adjacent glycoluril-based cavity (Figure 2).[42,43] This

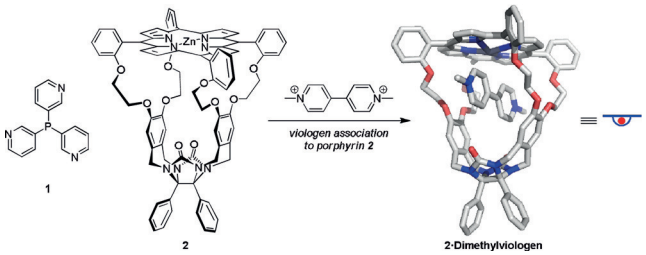


Figure 2. Ligand template **1**, which was previously used to generate encapsulated rhodium catalysts through pyridyl coordination to zinc-(II) porphyrins. Binding of dimethylviologen as a cofactor inside clip **2** activates the zinc porphyrin for binding, leading to a more than 100-fold enhancement in the association constant with the pyridine derivatives through so-called allosteric magnification.

enhanced binding is the result of an allosteric effect in which the bound viologen has a structural and electronic effect on the zinc porphyrin, as a result of which the association constant of the coordination of a pyridine ligand to the zinc atom via the outside of the cavity is enhanced by more than 2 orders of magnitude. By combining ligand template **1** with zinc porphyrin clip **2**, a system is generated in which coordination of the ligand template through the pyridyl groups, and therefore the encapsulation of the rhodium metal complex, is controlled by the viologen cofactor. As a result, the application of a rhodium complex based on ligand template **1** in the presence of zinc porphyrin clip **2** should provide a hydroformylation catalyst in which control over the selectivity and activity is achieved through binding of the cofactor molecule.

The influence of the cofactor on the binding of the zinc porphyrin clip to the tris-3-pyridylphosphine ligand template was investigated using UV/Vis titration experiments. Assuming a non-cooperative 3:1 binding model, the titration curves give very good fits (see Figures S1 and S2 in the Supporting Information), from which the association constant values are calculated to be $K_a = 390\,\text{M}^{-1}$ in the absence of viologen and $K_a = 71.000\,\text{M}^{-1}$ in the presence of viologen. This more than 180-fold increase in association constant is in line with the previously found allosteric magnification of the coordination of 4-*t*-butylpyridine to **2** in the presence of viologen[42] ($K_a =$ 400 and $100\,000\,\text{M}^{-1}$, in absence and presence of viologen, respectively). For the current system, the association constant in the absence of the viologen cofactor is too low for full encapsulation of the ligand by **2** at millimolar concentrations. Addition of the cofactor ensures full capsule formation and the titration data shows that a 3:1 complex of the zinc porphyrin clip is formed with the trispyridylphosphine ligand template when the cofactor is present. The formation of the 3:1 complex of the zinc porphyrin clip **2** with viologen and the ligand template **1** was further observed by CSI-MS, confirming the formation of the seven-component assembly to give a fully encapsulated species (see Figures S3–S5).

Having established that ligand encapsulation can be achieved upon binding of the viologen cofactor in zinc porphyrin clip **2**, in situ high-pressure infrared spectroscopy (HP-IR) studies were performed to further confirm catalyst encapsulation. The carbonyl stretch vibrations in the HP-IR spectra are powerful probes to monitor coordination around the rhodium atom.[44] The HP-IR spectrum of the rhodium catalyst formed by mixing $Rh(acac)(CO)_2$, 2.5 equivalents of ligand template **1** and 7.5 equivalents of zinc porphyrin clip **2** under catalytic conditions in the absence of the cofactor shows four bands in the carbonyl region (at 2064, 2041, 2017, and 1992 cm^{-1}; see Figure S6), which indicates the formation of the typical *bis*-phosphine coordinated rhodium complex. The four peaks show that the rhodium complex exists as a mixture of the ee and ea (equatorial-equatorial and equatorial-apical) coordination complexes, similar to that found in the control experiment where only $Rh(acac)(CO)_2$ and ligand **1** are present, thus indicating that in the absence of the cofactor, zinc porphyrin clip **2** has little influence on the coordination complex.[28,44] Upon addition of the cofactor, the four bands disappear and three new peaks are observed in the HP-IR spectrum, at 2089, 2040, and 2012 cm^{-1} (see Figure S7). These peaks indicate the formation of a *mono*-phosphine triscarbonyl rhodium complex, similar to the previously reported active species formed in the presence of zinc(II) tetraphenylporphyrin.[25,44,45] These experiments therefore establish that in the current system, catalyst encapsulation can be regulated by the addition of the viologen as a cofactor, which binds in the zinc porphyrin clip and induces strong coordination to the pyridyl moieties of **1**, thereby resulting in catalyst encapsulation (Figure 3, for further characterization of the encapsulated catalyst see Figures S8–15).

The cofactor-controlled catalyst encapsulation significantly changes the catalyst performance of the rhodium phosphine complex. The hydroformylation of 1-octene was studied with the catalyst mixture (Rh, Ligand **1**, and zinc porphyrin clip **2**) in the absence and the presence of the cofactor (Table 1). The rhodium catalyst formed by phosphine **1** in the presence of porphyrin **2** has a relatively low activity in the hydroformylation reaction, with 17% conversion after 24 h. The observed linear to branched product ratio of 2.4 is typical for catalysis by bis-phosphine rhodium complexes.[27] In sharp contrast, the encapsulated rhodium catalyst that is formed in the presence of the viologen cofactor achieves $>99\%$ conversion under the same conditions. Importantly, this catalyst system dominantly forms the branched aldehyde (l/b ratio of 0.71), a selectivity that is rather unique for these type of encapsulated catalyst systems.[27] To further monitor the effect of cofactor-induced activation of the catalyst, the reaction progress was measured by monitoring the aldehyde formation by in situ HP-IR spectroscopy. From the initial part of the reaction rate curve, the turnover frequency (TOF, in (mol aldehyde) (mol Rh)$^{-1}$) of the reaction was calculated, which is increased eightfold, from 3.7 to 29.1 h^{-1}, when the cofactor is present (Figure 4, see Figure S16–18 for full IR data).

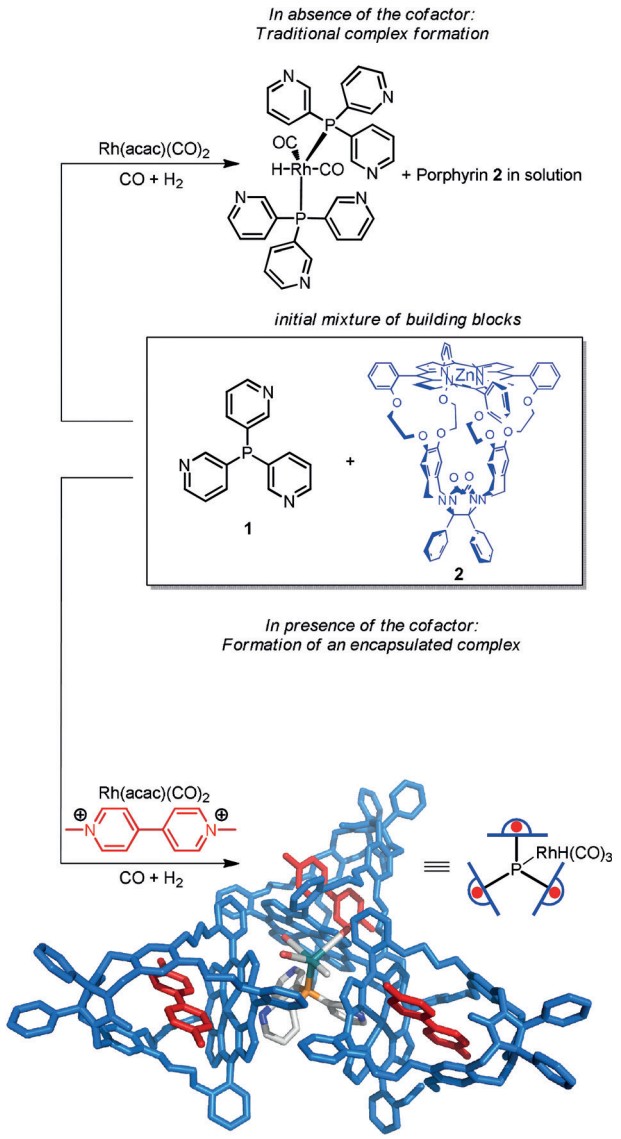
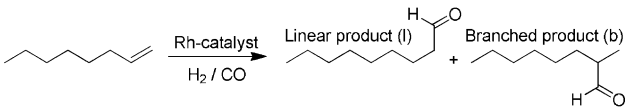


Figure 3. Cofactor controlled encapsulation of a rhodium complex for hydroformylation. When the viologen cofactor is not present, the pyridyl group of template ligand **1** has weak interactions with zinc porphyrin cage **2**, and bisphosphine rhodium complexes are formed in solution. Addition of the cofactor causes a much stronger interaction of the pyridyl groups of **1** with the zinc porphyrin, leading to the formation of an encapsulated monophosphine rhodium complex. An xTB-optimized structure is shown (for details, see the Supporting Information),[46] with the viologen shown in red, clips shown in blue, and the HRh(**1**)$(CO)_3$ complex shown in CPK colouring.

In conclusion, we present a supramolecular system in which the encapsulation of a rhodium phosphine catalyst is controlled by the presence of a cofactor in the solution. Upon binding a viologen cofactor in a cavity-containing zinc porphyrin, three porphyrins wrap around the tripyridylphosphine template ligand, effectively encapsulating the rhodium catalyst. When the catalyst is applied in the hydroformylation of 1-octene, the cofactor-induced encapsulation reverses the regioselectivity of the reaction and increases the activity of the rhodium catalyst by a factor of eight. We anticipate that this type of cofactor controlled reaction may impact the way we perform catalytic reactions in complex mixtures of catalysts.

Table 1: Hydroformylation of 1-octene with various combinations of ligands, capsule constituents, and cofactor.[a]



Ligand[b]	Cofactor	Yield [%][c]	l/b ratio[c]
Phosphine **1** + Porphyrin **2**	–	17	2.4
Phosphine **1** + Porphyrin **2**	viologen	> 99	0.71
Phosphine **1**	–	11	2.9
Phosphine **1**	viologen	13	2.9
Phosphine **1** + ZnTPP	–	> 99	0.60
Phosphine **1** + ZnTPP	viologen	44	0.67

[a] Conditions: [Rh(acac)$(CO)_2$] = 1.0 mM, T = 25 °C, t = 24 h, p = 20 bar (CO/H_2 = 1:1), solvent: dichloromethane/acetonitrile = 4:1. [b] phosphine/rhodium = 2.5:1, porphyrin/phosphine = 3:1, cofactor/porphyrin = 1.1:1; substrate/Rh = 800:1. [c] Yield of aldehyde products, determined by GC with decane as an internal standard, selectivity confirmed by NMR (Figures S20,21).

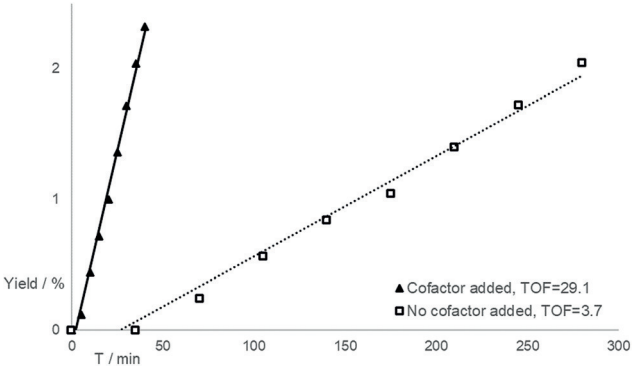


Figure 4. Yield of the hydroformylation of 1-octene (combined products) in the presence and absence of the cofactor in the initial phase of the reaction (up to 2.5% conversion). TOFs in (mol aldehyde) (mol Rh)$^{-1}$ h^{-1} were determined from the slopes of the curves.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: bioinspired catalysis · catalyst encapsulation · complex chemical systems · hydroformylation · supramolecular chemistry

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