Transition metals enclosed in supramolecular capsules: assembly, characterization and application in catalysis
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Chapter 6

Encapsulation of a Rhodium Hydroformylation Catalyst in a Diphosphine Based Capsule
6.1 Introduction

Enzymes, nature’s creation of catalysts, encapsulate multiple functionalities within their cavity where the catalytic conversion takes place, and as a result they can be extremely active and selective for a range of chemical conversions. The special microenvironment in the substrate binding pocket and the catalytically active site result for example in substrate preorganization, which restricts substrate motion. Also (covalent) binding of the transition state and desolvation of the substrate contribute greatly to an extraordinarily catalytic activity. Enzymes have served as the major source of inspiration for supramolecular catalysis, with a major focus on host-guest catalysis. Self-assembled nanocapsules with well-defined cavities can encapsulate smaller guest molecules and have been applied as nanosized reaction chambers, i.e. nanoreactors, for chemical transformations. Rebek and co-workers have reported that the cavity of a self-assembled hydrogen-bonded “softball” capsule can act as a catalyst for the bimolecular Diels–Alder reaction, which resulted in a tenfold rate enhancement. Raymond, Bergman and co-workers have encapsulated a cationic transition metal complex (iridium or rhodium) within a tetrahedral coordination cage, based on metal-ligand interactions, via non-directional noncovalent bonds. This encapsulated active-site was successfully used for thermal C–H bond activation of aldehydes and ethers (Ir), and allylic alcohol isomerization reactions (Rh), which resulted in substrate size and shape selectivities, and protection of the catalyst against decomposition.

Alkene hydroformylation, catalyzed by phosphorus-based rhodium complexes, is an important homogeneously catalyzed reaction in industry for functionalizing hydrocarbons. The regio-, stereo-, and chemoselectivity and overall catalytic activity of the catalyst in the hydroformylation reaction can be optimized by tuning the electronic and steric properties of the ligands. Implementing supramolecular strategies in the design of rhodium-phosphorus catalysts can drastically change the activity and reactivity of the hydroformylation reaction. Reek and co-workers have introduced the ligand-template approach as a new strategy for the encapsulation of transition metal catalysts. A hemispherical ligand-template capsule is created around the transition metal by applying pyridylphosphine ligands which coordinate to the transition metal via the phosphorus atom, and at the same time the nitrogen atoms of the pyridyl groups selectively coordinate to Zn(II)-porphyrins or Zn(II)-salphens. When tris(m-pyridyl)phosphine is applied as template ligand, the created steric hindrance around the metal results in decoordination of one of the two pyridylphosphine ligands. The encapsulated rhodium complex has a tenfold higher reactivity and unusual regioselectivity in the hydroformylation of terminal and internal alkenes. The unusual selectivity and increased rate observed for the encapsulated rhodium is caused by modification of the catalytically active species as well as by the novel nano-environment around the rhodium imposing steric restriction which influence the individual steps in the catalytic cycle. Monflier and co-workers have demonstrated that inclusion of a sulfonated xantphos in a cyclodextrin-based cavity increases the steric hindrance around the rhodium, compelling the alkene to react preferentially by its terminal carbon, which resulted in high regioselectivity for the linear aldehyde in the hydroformylation reaction.
Nolte and co-workers have applied the phosphine substituted “molecular basket” based on diphenylglycoluril framework in the rhodium catalyzed hydroformylation of various allylbenzene substituted substrates. Substrates can bind inside the basket’s cavity while the rhodium is situated above the cavity. The most strongly bound substrates gave the highest rate due to the raised effective molarity, but after 30% conversion product inhibition took place.

The generally accepted dissociative mechanism for alkene hydroformylation catalyzed by phosphine based rhodium complexes, first proposed by Heck and Breslow for cobalt, is depicted in Scheme 1. With bidentate phosphine ligands, the catalytic cycle begins with CO dissociation from the trigonal-bipyramidal [HRh(PP)(CO)₂] to form the square-planar 16-electron complex [HRh(PP)(CO)]. Alkene association yields the 18-electron complex, which undergoes hydride-migration to form either the linear or the branched rhodium-alkyl complexes and , respectively. Association of CO provides the rhodium complexes and , respectively, and migratory insertion of CO affords the corresponding rhodium-acyl complexes and . Hydrogenolysis of the rhodium-acyl complexes gives the respective linear and branched aldehyde and regenerates the rhodium complex . Wide bite angle ligands, such as xantphos, are known to give high selectivity in the hydroformylation of alkenes for the linear aldehyde.

In this Chapter we investigate whether encapsulation of a rhodium catalyst based on a wide bite angle diphosphine ligand (xantphos) influences its stability and its catalytic properties in the hydroformylation reaction, e.g. activity, substrate selectivity, product regioselectivity and product chemoselectivity. The novel nano-environment around the catalyst is created by rhodium encapsulation within a capsule formed by ionic interactions and composed of a tetracationic xantphos-type ligand and a tetravanionic calix[4]arene. We discuss the mechanism of the encapsulated rhodium catalyst in the hydroformylation reaction on the basis of molecular modeling and a kinetic study.

![Scheme 1 Dissociative mechanism for alkene hydroformylation.](image)
6.2 Diphosphine capsule

Supramolecular capsules are composed of two or more, not necessarily identical, building blocks programmed to self-assemble in solution into the desired structure.\cite{3a,10} We have previously reported the ionic-based diphosphine capsule A·C composed of the tetracationic xanthos-type diphosphine A and the complementary tetraanionic calix[4]arene C (Scheme 2).\cite{11}

Mixing methanol solutions of the neutral building blocks tetraamine-diphosphine a and tetrasulfonic acid-calix[4]arene C-SO$_3$H results in quantitative protonation of a by C-SO$_3$H, leading to capsule A·C. The observed single set of proton resonances for the free and associated building blocks in the $^1$H NMR spectrum of capsule A·C, indicates a fast exchange process on the NMR time scale between the building blocks that are in the monomeric form (free) and those in the capsular form. Upon capsule formation the diethylammoniummethyl substituents of A show significant upfield shifts in the proton NMR spectrum with respect to those of tetraammonium-diphosphine A-HOTs (in CD$_3$OD: $\Delta$δ(CH$_2$CH$_3$) = 0.37, $\Delta$δ(CH$_2$CH$_3$) = 0.34 and $\Delta$δ(NCH$_2$) = 0.25 ppm). This indicates that the substituents are partially included inside the hydrophobic cavity of the capsule.\cite{12}

The 2D NOESY spectrum of capsule A·C shows an intermolecular NOE contact between the NH$^+$CH$_2$CH$_3$ protons of A and the aromatic protons of C, confirming the 1:1 capsular structure of A·C (Figure 1).\cite{13}

The electrospray-ionization mass spectrum (ESI-MS) of capsule A·C shows a prominent ion peak of the capsule at $m/z$ 977.06 corresponding to [A·C + 2H]$^{2+}$, confirming capsule formation and stability in the gas-phase (Figure 1).\cite{14}

Encapsulation of a transition metal atom within capsule A·C can be achieved by using the metal complex of the tetracationic diphosphine ligand for the assembly process, or by the reaction of a transition metal precursor and the diphosphine capsule A·C.\cite{11c}

The encapsulated metal is still available for catalytic transformation as it is not involved in the assembly process.\cite{11a}

Scheme 2 Self-assembly of capsule A·C (a), and molecular structure of A-HOTs (b).
Encapsulation of a Rhodium Hydroformylation Catalyst in a Diphosphine Based Capsule

6.3 Rhodium capsules

The formation of free and encapsulated rhodium(I)-hydrides, the precursor to the active species in the hydroformylation reaction, was studied in situ by high-pressure (HP) NMR and IR spectroscopy in methanol.

Catalyst precursor: cationic rhodium species

The precursor of the rhodium hydride species [Rh(diphosphine)(CO)(acac)] is formed by mixing solutions of [Rh(acac)(CO)2] (acac = acetylacetonate) and a diphosphine ligand. We observed that mixing methanol solutions of [Rh(acac)(CO)2] with the tetracationic diphosphine A-HOTs resulted in the formation of the cationic rhodium species [Rh(A-HOTs)(CO)]+ (B1) (Scheme 3a), and that mixing methanol solutions of [Rh(acac)(CO)2] with the corresponding diphosphine capsule A·C resulted in the formation of the cationic rhodium capsule [Rh(A)(CO)]+·C (B1·C) (Scheme 3b). The formation of these species was evidenced by 31P{1H} NMR and IR spectroscopy. The 31P{1H} NMR spectra show a doublet at 38.3 ppm (J_P-Rh = 122 Hz) for B1 (Figure 2), and a doublet at 38.2 ppm (J_P-Rh = 126 Hz) for capsule B1·C (Figure 3). These phosphorus signals are in good agreement with the doublet at 37.2 ppm (J_P-Rh = 122 Hz) reported for the similar [Rh(xantphos)(CO)]+[BF4]– complex reported by van Leeuwen and co-workers.15a-b In the 31P{1H} NMR spectrum of capsule B1·C some additional broad signals at 17.4, 11.0 and –1.5 ppm were observed. The signal at 11.0 ppm could be assigned to capsule [Rh(A)(CO)(acac)]·C. The carbonyl vibration of B1 and B1·C in CH3OH were observed in the IR spectra at 2010 cm⁻¹ for both species.15a-b

The cationic rhodium species are formed by protonation of the intermediate species [Rh(A-HOTs)(acac)(CO)] and capsule [Rh(A)(acac)(CO)]·C. One of the acidic ammonium groups of the tetraammonium-diphosphine protonates acetylacetonate to acetylacetone, H(acac),
upon which acetylacetone dissociates and the cationic rhodium species is formed (Scheme 3). The counterions of the cationic rhodium species are probably a tosylate anion (OTs\(^-\)) for B\(_1\) and one of the four sulfonate monoanions (R–SO\(_3\)\(^-\)) of tetrasulfonatocalix[4]arene C for capsule B\(_1\)·C.

**Scheme 3** Formation of cationic rhodium species B\(_1\) and capsule B\(_1\)·C, rhodium hydrides B\(_2\) and capsule B\(_2\)·C, and rhodium-dimer B\(_3\) from: diphosphine A-HOTs (a) and capsule A·C (b).

**Rhodium hydride**

Pressurizing a methanol solution of the cationic rhodium species B\(_1\) with CO/H\(_2\) (1:1) provided the rhodium-hydride species [HRh(A-HOTs)(CO)\(_2\)] (B\(_2\)) (Scheme 3a). Pressurizing a methanol solution of the cationic rhodium capsule B\(_1\)·C with CO/H\(_2\) (1:1) provided the rhodium-hydride capsule [HRh(A)(CO)\(_2\)]·C (B\(_2\)·C) (Scheme 3b), as is evidenced by HP NMR and HP IR spectroscopy.\(^{15,16}\) The \(^{31}\)P{\(^1\)H} HP NMR spectra show a characteristic doublet at 20.6 ppm (\(J_{P,Rh} = 129\) Hz) for B\(_2\) (Figure 2), and a doublet at 20.2 ppm (\(J_{P,Rh} = 127\) Hz) for capsule B\(_2\)·C (Figure 3).\(^{17}\) In the \(^1\)H HP NMR spectra of B\(_2\) and B\(_2\)·C the hydride resonance was observed as a broad singlet at –9.38 respectively –9.39 ppm (Figure 4). Both cationic rhodium species transform into the rhodium(I)-hydrides in one hour (at 20 °C) and remain stable for at least sixteen hours. Heterolytic cleavage of dihydrogen at the cationic rhodium species results in the rhodium-hydride species and a proton which reprotonates the amine of the diphosphines into the ammonium moiety (Scheme 3).\(^{18a-c}\)
**Figure 2** $^{31}$P{$^{1}$H} NMR spectra in CD$_3$OD, Rh/PP = 1/1, [Rh] = 38 mM. *Top:* cationic-Rh $B_1$. *Bottom:* Rh-hydride $B_2$ and Rh-dimer $B_3$ (1:1) (20 bar CO/H$_2$).

**Figure 3** $^{31}$P{$^{1}$H} NMR spectra in CD$_3$OD, Rh/PP = 1/1, [Rh] = 38 mM. *Top:* cationic-Rh capsule $B_1$·C. *Bottom:* Rh-hydride capsule $B_2$·C (20 bar CO/H$_2$).

**Figure 4** $^1$H HP NMR spectrum in CD$_3$OD of Rh-hydride capsule $B_2$·C (8 bar CO/H$_2$). Asterisks indicate the $B_2$ building block.
[HRh(diphosphine)(CO)₂] can exist in two isomeric structures in which the diphosphine ligand coordinates in a diequatorial (ee) or an equatorial-apical (ea) fashion (Scheme 4). The carbonyl bands of the rhodium hydrides are observed in the HP IR spectrum of B₂ at 1947, 1972 and 1997 cm⁻¹, and in the HP IR spectrum of capsule B₂·C at 1947, 1970 and 1996 cm⁻¹. The absorption bands at 1997 cm⁻¹ of B₂ and 1996 cm⁻¹ of B₂·C are partly obscured by overlap with strong absorption bands of the solvent (CH₃OH, 20 bar CO/H₂). Comparison of the observed carbonyl bands of B₂ and B₂·C with those observed by van Leeuwen and co-workers for the similar [HRh(a)(CO)₂] complex in C₆D₆ (1938, 1970 and 1990 cm⁻¹) leads to the conclusion that both ee- and ea-complex isomers are present in solution. The HP IR and HP NMR results show the existence of a dynamic equilibrium between the ee- and ea-isomers of B₂. The same dynamic equilibrium between the ee- and ea-isomers is also observed for capsule B₂·C.

Scheme 4 ee-ea equilibrium of a rhodium trigonal bipyramidal complex.

**Rhodium-dimer**

Upon pressurizing the cationic rhodium species B₁ (at 38 mM concentration) with 20 bar syn gas, the carbonyl-bridged dimer [Rh(A-HOTs)(CO)(µ-CO)]₂ B₃ was formed next to the rhodium-hydride B₂ in a ratio of one-to-one, see Scheme 3. The ³¹P{¹H} HP NMR spectrum of B₃ consists of two apparent doublets (1:1) at 9.2 ppm (Jₚ-Rh = 152 Hz) and 0.4 ppm (Jₚ-Rh = 150 Hz), see Figure 2. The rhodium-dimer [Rh(diphosphine)(CO)(µ-CO)]₂ is inactive in the hydroformylation reaction and is in equilibrium with the rhodium-hydride. This equilibrium depends on the partial CO and H₂ pressures. In the HP NMR experiments, the rhodium-dimer species was clearly observed when the free ligand A-HOTs was used, but scarcely for capsule A·C (B₃·C: 9.2 d and 0.1 d), see Figure 3. The ³¹P{¹H} HP NMR spectra reported in Figure 2 and Figure 3 remained unchanged for at least 16 h. The steric hindrance around the encapsulated rhodium metal prohibits capsule B₂·C to form a rhodium-dimer species. The high concentration, small gas volume and different metal-ligand ratio used in HP NMR experiments ([Rh] = 38 mM, PP/Rh = 1) compared to those used in catalytic experiments result in different monomer/dimer equilibrium. Indeed, no rhodium-dimers were observed in the HP IR experiments of A-HOTs or capsule A·C for which the conditions ([Rh] = 1 mM, PP/Rh = 4) resemble more closely the hydroformylation conditions. In the HP NMR experiments also small amounts of phosphine oxide, free ligand and other species (~14 d ppm) were observed for A-HOTs as well as for capsule A·C.
Encapsulation of a Rhodium Hydroformylation Catalyst in a Diphosphate Based Capsule

**Capsule stability**

The formation of the cationic rhodium species, rhodium-hydrides and rhodium-dimers with the ammonium-diphosphine A-HOTs or capsule A·C as the ligand, was evidenced by (HP) NMR and (HP) IR studies. The $^1$H NMR spectra of B$_1$, B$_2$ and B$_3$ show downfield shifts for the diethylammoniummethyl substituents, CH$_2$NH$^+$ (CH$_2$CH$_3$)$_2$, with respect to those of the comparable [HRh(a)(CO)$_2$] species, containing neutral diethylaminomethyl substituents.$^{17b}$ This confirms that the ammonium moieties of the rhodium-diphosphine species B$_1$, B$_2$ and B$_3$ remain intact and do not protonate the hydride species. We have shown in Section 6.2 that upon formation of capsule A·C the diethylammoniummethyl substituents of A show significant upfield shifts in the $^1$H NMR spectrum with respect to those of free A-HOTs.$^{11a}$ The $^1$H NMR spectra of capsules B$_1$·C and B$_2$·C also show upfield shifts for their diethylammoniummethyl substituents with respect to those of B$_1$ and B$_2$, e.g. for capsule B$_1$·C $\Delta\delta$(CH$_2$CH$_3$) = 0.25, $\Delta\delta$(CH$_2$CH$_3$) = 0.22 and $\Delta\delta$(NCH$_2$) = 0.16 ppm. This confirms that the capsules remain intact upon inclusion of a rhodium metal.

**6.4 Hydroformylation catalyzed by encapsulated rhodium**

Hydroformylation experiments were carried out in the AMTEC SPR16 robot, consisting of sixteen parallel reactors and a mass-flow controller, suited for application of different reaction conditions in each individual reactor.$^{19}$ Hydroformylation of styrene, 1-octene and 4,4,4-triphenylbut-1-ene was carried out in 8 ml methanol at 60 °C under 20 bar of CO/H$_2$ (1:1) using a 1.00 mM solution of rhodium-catalyst prepared from [Rh(acac)(CO)$_2$] and 5 equivalents of ligand (Scheme 5). Reactions were all started with incubation of the catalyst under 16 bar of CO/H$_2$ (1:1) for 1 h at 80 °C. Reaction rates and turnover frequencies (TOF) were determined from the gas-uptake profiles and the product distribution was monitored by gas chromatography. In this section we describe the effect of rhodium encapsulation on its catalytic properties in the hydroformylation reaction. In order to confirm that rhodium encapsulation is responsible for the observed results rather than the acidic phosphine ligand or free calix[4]arene, we have conducted control experiments which are described in the first part of this section. In the next section (6.5) a discussion concerning the mechanism of the hydroformylation reaction catalyzed by the encapsulated rhodium is presented.

![Scheme 5](image)

**Scheme 5** Rhodium-catalyzed alkene hydroformylation.
Control experiments

Effect of acidic diphosphine. The acidic ammonium substituents and tosylate counterions of diphosphine A-HOTs facilitate solubility in polar protic solvents such as methanol, isopropanol and water. As can be seen in Table 1 (entry’s 1–2) and Figure 5, the rhodium catalyst based on tetraammonium diphosphine A-HOTs is more active than the rhodium catalyst based on the corresponding tetraamine diphosphine a in the hydroformylation of styrene in methanol (TOF after 5% conversion: 85.2 and 31.1, respectively). The product regioselectivities of A-HOTs and a are slightly different: selectivities for the branched aldehyde are 59% and 57%, respectively. The electronic effect of the ammonium groups of A-HOTs on the phosphorus atoms is negligible because of the presence of the benzylic methylene-spacer, as is confirmed by $^{31}$P$\{^1$H$\}$ NMR data in CD$_3$OD: A-HOTs: −16.9 (s) and a: −18.3 (s) ppm.

Table 1 Effect of calix[4]arene C-SO$_3$Na and of acidic diphosphine A-HOTs on the rhodium-catalyzed hydroformylation of styrene.$^a$

<table>
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<th>entry</th>
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<th>b/l (%)$^c$</th>
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<td>63.1</td>
<td>57/43</td>
</tr>
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<td>A-HOTs</td>
<td>64.4</td>
<td>87.1</td>
<td>95.5</td>
<td>59/41</td>
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<td>a + C-SO$_3$Na$^e$</td>
<td>30.7</td>
<td>50.4</td>
<td>63.7</td>
<td>57/43</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: [Rh(acac)(CO)$_2$], [Rh] = 1.00 mM, [styrene] = 873 mM, ligand/Rh = 5, CO/H$_2$ (1:1) = 20 bar, 60 $^\circ$C, 8 ml methanol. The reaction was stopped after 35 h. $^b$ Conversion of substrates into aldehydes and corresponding enol ethers (enol ethers are only formed with A-HOTs). Conversion is determined by syngas uptake. $^c$ Branched to linear ratio of aldehydes and corresponding enol ethers. $^d$ TOF = turnover frequency (mol product)/(mol Rh)$^{-1}$·h$^{-1}$. $^e$ Mol ratio of a/C-SO$_3$Na is 1/1.

Figure 5 Kinetic profiles: effect of calix[4]arene C-SO$_3$Na and of acidic diphosphine A-HOTs on the Rh-catalyzed hydroformylation of styrene. Conversion is determined by syngas uptake. Reaction conditions: [Rh] = 1 mM, [L] = 5 mM, [S] = 873 mM, CO/H$_2$ (1:1) = 20 bar, 60 $^\circ$C, methanol.
Hydroformylation of styrene, 1-octene and 4,4,4-triphenylbut-1-ene in methanol catalyzed by the Rh-complex based on A-HOTS resulted in branched and linear aldehydes and their corresponding branched and linear enol ethers with a methoxy substituent (identified by GC-MS), see Scheme 6. Changing the solvent from methanol to isopropanol resulted in aldehydes and their corresponding enol ethers with an i-propoxy substituent. The percentage of enol ethers in the products continued to grow after the hydroformylation reaction had been stopped (with a maximum of 47% for styrene, 70% for 1-octene and 40% for 4,4,4-triphenylbut-1-ene). The products of 1-octene hydroformylation catalyzed by the Rh-complex based on A-HOTS also contained 8–12% of two unidentified byproducts which might be assigned to the corresponding hemiacetals, acetals or the hydroformylation products of the enol ethers. We have not observed alcohol formation during the hydroformylation reactions. Remarkably, alkene hydroformylation in methanol catalyzed by Rh-complexes based on the tetraamine ligand a and on capsule A·C did not produce enol ethers or other unidentified byproducts. Various researchers reported consecutive hydroformylation-acetalization in alcoholic solvents to give the corresponding acetals. El Ali and co-workers reported the formation of small amounts of enol ethers next to the acetals. Nucleophilic addition of an alcohol to the formed aldehyde, catalyzed by an acid, gives a hemiacetal which can further react to an acetal, or can undergo dehydration to give the enol ether (Scheme 6). Capsule A·C and A-HOTS are based on the same tetraammonium diphosphine A, but capsule A·C yields solely aldehydes. This shows that under the used conditions, the rhodium catalyst based on capsule A·C has a remarkable higher product selectivity compared to the rhodium catalyst based on A-HOTS. This is probably caused by the strong interaction between A and C and therefore the unavailability of the ammonium groups of capsule A·C to catalyze the enol ethers formation.

![Scheme 6](image)

**Scheme 6** Alkene hydroformylation-acetalization and formation of enol ether in methanol (only shown for the linear aldehyde).

*Effect of calix[4]arene.* Concave calix[4]arenes contain an open cavity wherein smaller molecules can be encapsulated and have shown to influence activities and selectivities of several reactions. The tetrasodium salt of tetrasulfonated calix[4]arene (C-SO₃Na) and the neutral tetraamine-diphosphine a do not form a capsule and allow us to study the influence of unassociated calix[4]arene on the catalytic performance of the rhodium complex based on ligand
a. As can be seen in Table 1 (entry’s 1 and 3) and Figure 5, the activity and product regioselectivity of the Rh-complex based on ligand a remains the same in the presence of C-SO$_3$Na in the hydroformylation of styrene in methanol. Therefore, the capsule, rather than unassociated calix[4]arene, is responsible for the new activities and selectivities described in this chapter (vide infra).

**Catalyst encapsulation: effect on activity and regioselectivity**

Encapsulation of the rhodium metal within capsule A·C results in a significant drop in activity compared to the rhodium catalyst based on A-HOTs, in the hydroformylation of the small styrene and 1-octene, as well as the sterically demanding 4,4,4-triphenylbut-1-ene (Table 2 and Figure 6).$^{22}$ The turnover frequency (TOF) values at 5% conversion decrease due to rhodium encapsulation; for styrene from 45.4 to 2.5, for 1-octene from 52.1 to 0.8 and for 4,4,4-triphenylbut-1-ene from 21.7 to 1.1. Product regioselectivity in the hydroformylation reaction, i.e. branched to linear ratio of the aldehydes, is also affected by catalyst encapsulation. The selectivity for the branched aldehyde has increased upon rhodium encapsulation for styrene from 59% to 75% and for 1-octene from 2% to 4% (Table 2, entry’s 1–4). Styrene usually has a high preference for the formation of the branched aldehyde due to the stability of the benzylic rhodium species, induced by the formation of a stable $\eta^3$ complex.$^{23}$ Hydroformylation of 1-octene catalyzed by rhodium complexes based on xantphos-type ligands generally give very high selectivities for the linear aldehyde.$^{17a,17c-d}$ Therefore, the observed increased selectivity for the branched aldehyde in the hydroformylation of 1-octene upon catalyst encapsulation, is significant. Surprisingly, hydroformylation of 4,4,4-triphenylbut-1-ene, catalyzed by the Rh-complex based on A-HOTs, resulted in a decrease of linear aldehyde during the course of the reaction. After 10% conversion the selectivity provided by the catalyst based on A-HOTs was 89% for the linear aldehyde, and after 86% conversion the selectivity for the linear aldehyde decreased to 55% (Table 2, entry 5). Contrary, the encapsulated rhodium catalyst has a 100% selectivity for the linear aldehyde, which remained constant during the whole reaction (Table 2, entry 6). The new activities and product regioselectivities observed for the encapsulated catalyst show that the capsule remains intact during the catalysis.
Table 2: Effect of rhodium encapsulation within diphosphine capsule \( \text{A·C} \) on the catalyst activity and regioselectivity in the hydroformylation of styrene, 1-octene and 4,4,4-triphenylbut-1-ene.\(^a\)

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<th>entry</th>
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<td>capsule ( \text{A·C} )</td>
<td>triphenyl butene</td>
<td>396</td>
<td>2.9</td>
<td>5.4</td>
<td>7.9</td>
<td>0/100</td>
<td>1.1</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \([\text{Rh(acac})(\text{CO})_2]\), [\text{Rh}] = 1.00 mM, ligand/Rh = 5, CO/H\(_2\) (1:1) = 20 bar, 60 °C, 8 ml methanol. The reaction was stopped after 35–43 h. \(^b\) Conversion of substrates into aldehydes and corresponding enol ethers (enol ethers are only formed with \( \text{A·HOTs} \)). The products of 1-octene hydroformylation with \( \text{A·HOTs} \) also contained 5–8% of isomerization and hydrogenation products, and 8–12% of two unidentified byproducts which were used to calculate the conversion. The products of 1-octene hydroformylation with capsule \( \text{A·C} \) also contained 1% of isomerization and hydrogenation products. Conversion is determined by syngas uptake. \(^c\) branched to linear ratio of aldehydes and corresponding enol ethers. \(^d\) TOF = turnover frequency (mol product)/(mol Rh)\(^{-1}\)·h\(^{-1}\). \(^e\) Reaction mixture contained 2 ml of dichloromethane. \(^f\) Amount of formed linear aldehyde + linear enol ether decreased from 89% (after 10% conversion) to 55% (after 86% conversion).

Figure 6: Kinetic profiles: effect of rhodium encapsulation within diphosphine capsule \( \text{A·C} \) on the catalyst activity in the hydroformylation of styrene, 1-octene and 4,4,4-triphenylbut-1-ene. Conversion is determined by syngas uptake. Reaction conditions: [\text{Rh}] = 1 mM, [\text{L}] = 5 mM, [\text{styrene}] = 436 mM, [1-octene] = 478 mM, [4,4,4-triphenylbut-1-ene] = 396 mM, CO/H\(_2\) (1:1) = 20 bar, 60 °C, methanol.
Chapter 6

Catalyst encapsulation: substrate selectivity

The drop in activity by catalyst encapsulation is more than three times higher for the small 1-octene compared to styrene and the bulky 4,4,4-triphenylbut-1-ene (drop in TOF at 5% conversion: 65%, 18% and 20%, respectively) (Table 2). Apparently, the capsule does not display substrate selectivity solely on basis of size. According to the TOF values, the non-encapsulated catalyst based on A-HOTs has a higher preference for hydroformylation of 1-octene than styrene, and the encapsulated catalyst based on capsule A·C has a higher preference for hydroformylation of styrene than 1-octene (Table 3 entry’s 3–6). A substrate competition study in which a mixture of styrene and 1-octene (mol ratio = 10/11) is hydroformylated by a rhodium catalyst based on A-HOTs or capsule A·C made it possible to study the substrate selectivity properties of the encapsulated catalyst. After a reaction time of nine hours, the rhodium-catalyst based on A-HOTs gave a conversion of 60.2% for styrene and 68.2% for 1-octene while the rhodium-catalyst based on capsule A·C gave a conversion of 8.1% for styrene and 4.4% for 1-octene (Table 3 entry’s 1–2 and Figure 7). The ratio between styrene conversion and 1-octene conversion is 0.88 for A-HOTs and 1.84 for capsule A·C (after 9 h), meaning that the affinity of the encapsulated catalyst for the compact C₈ molecule of styrene is two times higher than that of the non-encapsulated catalyst. These results show that the encapsulated catalyst is substrate selective because it discriminates between substrates, on the basis of shape and size.

Table 3 Substrate competition study by simultaneous hydroformylation of styrene and 1-octene catalyzed by rhodium complexes based on capsule A·C and diphosphine A-HOTs.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>substrate</th>
<th>[sub] (mM)</th>
<th>conversion (%) b</th>
<th>b/l c (%)</th>
<th>TOF d at 5% conv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t = 9 h</td>
<td>t = 21 h</td>
<td>t = 31 h</td>
</tr>
<tr>
<td>1 e</td>
<td>A-HOTs</td>
<td>styrene</td>
<td>436</td>
<td>60.2 +</td>
<td>86.6 +</td>
<td>94.2 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-octene</td>
<td>478</td>
<td>68.2 +</td>
<td>90.1 +</td>
<td>95.7 +</td>
</tr>
<tr>
<td>2 e</td>
<td>capsule A·C</td>
<td>styrene</td>
<td>436</td>
<td>8.1 +</td>
<td>13.6 +</td>
<td>18.1 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-octene</td>
<td>478</td>
<td>4.4 +</td>
<td>7.0 +</td>
<td>10.0 +</td>
</tr>
<tr>
<td>3 f</td>
<td>A-HOTs</td>
<td>styrene</td>
<td>436</td>
<td>63.2 +</td>
<td>89.3 +</td>
<td>96.2 +</td>
</tr>
<tr>
<td>4 f</td>
<td>A-HOTs</td>
<td>1-octene</td>
<td>478</td>
<td>62.2 +</td>
<td>88.0 +</td>
<td>95.1 +</td>
</tr>
<tr>
<td>5 f</td>
<td>capsule A·C</td>
<td>styrene</td>
<td>436</td>
<td>6.3 +</td>
<td>11.8 +</td>
<td>15.6 +</td>
</tr>
<tr>
<td>6 f</td>
<td>capsule A·C</td>
<td>1-octene</td>
<td>478</td>
<td>2.4 +</td>
<td>4.2 +</td>
<td>5.8 +</td>
</tr>
</tbody>
</table>

a Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1.00 mM, ligand/Rh = 5, CO/H₂ (1:1) = 20 bar, 60 °C, 8 ml methanol. The reaction was stopped after 35–41 h. b Conversion of substrates into aldehydes and corresponding enol ethers (enol ethers are only formed with A-HOTs). Hydroformylation of 1-octene also resulted in isomerization and hydrogenation products, and in two unidentified byproducts (the later are only formed with A-HOTs), which were all used to calculate the conversion. c branched to linear ratio of aldehydes and corresponding enol ethers. d TOF = turnover frequency (mol product)·(mol Rh)⁻¹·h⁻¹. e Conversion is determined by GC data of the periodic samplings. f Conversion is determined by syngas uptake.
Figure 7 Kinetic profiles: substrate competition study by simultaneous hydroformylation of styrene and 1-octene catalyzed by rhodium complexes based on capsule A·C and diphosphine A-HOTs. Conversion is determined by GC data of the periodic samplings. Reaction conditions: [Rh] = 1 mM, [L] = 5 mM, [styrene] = 436 mM, [1-octene] = 478 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol.

Catalyst encapsulation: kinetic study

The kinetics of styrene, 1-octene and 4,4,4-triphenylbut-1-ene hydroformylation catalyzed by rhodium complexes based on A-HOTs and capsule A·C was studied by varying the substrate concentrations. The reaction rates and turnover frequencies were determined from the gas-uptake profiles and were used to calculate the orders in substrate concentrations. No incubation periods were observed after typical incubation of the catalysts for 1 h at 80 °C was applied. As can be seen in Table 4 all hydroformylation reactions catalyzed by encapsulated as well as non-encapsulated catalysts, have positive order dependencies in substrate concentration. The first-order dependencies in styrene concentration for A-HOTs (0.95) and in 4,4,4-triphenylbut-1-ene for capsule A·C (1.01) imply that Type I kinetics is applicable.\textsuperscript{5b,24} As can be seen in Equation 1, a reaction with Type I kinetics is first order in the alkene concentration, first order in the rhodium concentration, zero order in hydrogen, and negative order in ligand concentration (phosphine and/or carbon monoxide).

\[
\text{Rate(type-I)} = \frac{A_{[\text{alkene}][\text{Rh}]}}{B + [L]} \quad (\text{Equation 1})
\]

The observed positive orders in substrate concentration for alkene hydroformylation by rhodium catalysts based on A-HOTs and on capsule A·C indicate that all reactions involve a rate
determining alkene coordination followed by rapid alkene insertion into the Rh-H bond, or a fast alkene coordination followed by rate determining hydride migration, or an intermediate case in which the combination of the two is slower than any other step of the cycle.\textsuperscript{5b-c,24} We have not determined the orders in rhodium, ligand, CO and H\textsubscript{2}, and therefore we cannot exclude that other steps in the catalytic cycle may contribute slightly to the rate equation. Remarkably, styrene hydroformylation catalyzed by a rhodium complex based on A-HOTs has a first-order (0.95) dependency in substrate concentration while styrene hydroformylation catalyzed by a rhodium complex based on capsule A·C has an almost second-order (1.70) dependency in substrate concentration. The exceptionally high order in styrene concentration found for the encapsulated catalyst might suggest that two styrene molecules are involved in the rate limiting step of the catalytic cycle (vide infra). The orders in 1-octene concentration are less than one for rhodium complexes based on A-HOTs and on capsule A·C (0.68 and 0.41, respectively), which might point to saturation kinetics.\textsuperscript{5c}

**Table 4** Kinetics for alkene hydroformylation catalyzed by rhodium complexes based on A-HOTs and capsule A·C.\textsuperscript{a}

<table>
<thead>
<tr>
<th>ligand</th>
<th>substrate</th>
<th>order in substrate</th>
<th>at conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-HOTs</td>
<td>styrene</td>
<td>0.95</td>
<td>20</td>
</tr>
<tr>
<td>capsule A·C</td>
<td>styrene</td>
<td>1.70</td>
<td>15</td>
</tr>
<tr>
<td>A-HOTs</td>
<td>1-octene</td>
<td>0.68</td>
<td>20</td>
</tr>
<tr>
<td>capsule A·C</td>
<td>1-octene</td>
<td>0.41</td>
<td>4</td>
</tr>
<tr>
<td>A-HOTs</td>
<td>triphenylbutene</td>
<td>positive\textsuperscript{c}</td>
<td>-</td>
</tr>
<tr>
<td>capsule A·C</td>
<td>triphenylbutene</td>
<td>1.01</td>
<td>8</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The gas-uptake profiles and ln(TOF) versus ln[substrate] graphs are shown in the experimental section. 
\textsuperscript{b} The orders in substrate concentrations are determined from the TOF at the indicated conversion. 
\textsuperscript{c} Reaction progress kinetic analysis of the “graphical rate equation” (TOF versus substrate concentration) for the hydroformylation of 4,4,4-triphenylbut-1-ene catalyzed by a rhodium-catalyst based on A-HOTs has a straight line, suggesting a positive-order dependency in substrate concentration (only one substrate concentration was used), see experimental section.\textsuperscript{25}

**Reaction progress kinetic analysis**

The “graphical rate equation” (TOF versus substrate concentration) of styrene hydroformylation catalyzed by a rhodium-complex based on A-HOTs at four different initial styrene concentrations, shows overlapping straight line curves with fixed slopes (Figure 8a). Reaction progress kinetic analysis indicates that the reaction exhibits a steady state behavior, an overall first-order kinetics and that no product inhibition or catalyst deactivation occurs.\textsuperscript{25} Contrary, the “graphical rate equation” for styrene hydroformylation catalyzed by the encapsulated rhodium-complex based on capsule A·C at four different initial styrene concentrations, shows bent curves that do not overlap (Figure 8b). The ‘twist’ in the curves, i.e.
Encapsulation of a Rhodium Hydroformylation Catalyst in a Diphosphine Based Capsule

change in the slope after approximately 10–15% conversion, show a non-steady state behavior for the reaction (at least not during the measured conversions). The graphs do not overlap, suggesting that product inhibition or catalyst deactivation takes place (vide infra). The “graphical rate equation” for 1-octene and 4,4,4-triphenylbut-1-ene hydroformylation catalyzed by the encapsulated rhodium-complex based on capsule A·C, also show bent curves that do not overlap, suggesting that the encapsulated catalyst experience also for these substrates a non-steady state behaviour for the reaction as a result of product inhibition or catalyst deactivation.

![Graphical rate equations](image)

**Figure 8** “Graphical rate equations”: styrene hydroformylation catalyzed by rhodium complexes based on A-HOTs (a) and capsule A·C (b) at four different initial styrene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh] = 1 mM, [L] = 5 mM, [styrene] = 436, 655, 873 and 1309 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol.
Catalyst encapsulation: product inhibition

Reaction progress kinetic analysis indicates that the encapsulated catalyst experiences catalyst deactivation or product inhibition for all the substrates. In order to find out if product inhibition takes place we have performed hydroformylation experiments using various mixtures of the styrene hydroformylation products 2-phenylpropionaldehyde and 3-phenylpropylaldehyde (2/1 molar ratio) and styrene. As can be seen in Table 5 and Figure 9, the presence of aldehydes in the beginning of the reaction results in a decrease of the catalytic activity of the rhodium complex based on capsule A·C. The decrease in catalyst activity was linear with the aldehydes-to-styrene ratio. Upon addition of three equivalents of aldehydes with respect to styrene, the TOF at 10% conversion decreased from 6.0 to 2.4 and the conversion after 30 h decreased from 21.0% to 11.3% (Table 5 entry’s 1 and 4). In contrast, addition of three equivalents of aldehydes to the non-encapsulated rhodium catalyst did not alter the catalyst activity (Table 5 entry’s 5–6). These results show that the encapsulated rhodium catalyst experiences product inhibition in the hydroformylation of styrene. According to reaction progress kinetic analysis, product inhibition takes place with styrene and 1-octene, substrates that both fit inside the capsule’s cavity, as well as with 4,4,4-triphenylbut-1-ene which does not fit inside the capsule’s cavity (vide infra modeling studies). Therefore, we conclude that product inhibition can take place in two ways: a. the aldehydes interact with the ionic substituents of the capsule’s building blocks and consequently increase the steric hindrance around the encapsulated catalyst or b. when the catalytic conversion occurs inside the capsule and the cavity has a higher affinity for the product than for the substrate (vide infra).

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>equiv. aldehydes present</th>
<th>conversion (%) at 5% conv</th>
<th>TOF at 10% conv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>t = 10 h</td>
<td>t = 20 h</td>
</tr>
<tr>
<td>1</td>
<td>capsule A·C</td>
<td>-</td>
<td>8.6</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>capsule A·C</td>
<td>0.16</td>
<td>8.0</td>
<td>14.1</td>
</tr>
<tr>
<td>3</td>
<td>capsule A·C</td>
<td>0.97</td>
<td>6.6</td>
<td>11.5</td>
</tr>
<tr>
<td>4</td>
<td>capsule A·C</td>
<td>3.00</td>
<td>5.3</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>A-HOTs</td>
<td>-</td>
<td>64.4</td>
<td>87.1</td>
</tr>
<tr>
<td>6</td>
<td>A-HOTs</td>
<td>3.00</td>
<td>64.2</td>
<td>86.1</td>
</tr>
</tbody>
</table>

* Reaction conditions: [Rh(acac)(CO)2], [Rh] = 1.00 mM, [styrene] = 873 mM, ligand/Rh = 5, CO/H₂ (1:1) = 20 bar, 60 °C, 8 ml methanol. The reaction was stopped after 35 h. * Equivalents aldehydes present relative to styrene: hydroformylation experiments were performed using various mixtures of the styrene hydroformylation products 2-phenylpropionaldehyde and 3-phenylpropylaldehyde (2/1 molar ratio) and styrene (the aldehydes did not contain any stabilizers or other compounds which could have influenced the catalysis). * Conversion of substrates into aldehydes and corresponding enol ethers (enol ethers are only formed with A-HOTs). Conversion is determined by syngas uptake. * TOF = turnover frequency (mol product)·(mol Rh)⁻¹·h⁻¹.
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Figure 9 Kinetic profiles: product inhibition study of styrene hydroformylation catalyzed by a rhodium complex based on capsule A·C. Conversion is determined by syngas uptake. Reaction conditions: [Rh] = 1 mM, [L] = 5 mM, [styrene] = 873 mM, CO/H\textsubscript{2} (1:1) = 20 bar, 60 °C, methanol. Equivalents aldehydes (2-phenylpropionaldehyde and 3-phenylpropylaldehyde: 2/1 molar ratio) present relative to styrene.

6.5 Discussion

Molecular modeling

The structures of the rhodium complexes were first calculated using DFT and subsequently, the optimized structures were used as input to construct the capsule for PM3 calculations. The modeled structures of capsule ee-[HRh(A)(CO)(styrene)]·C with the diphosphine coordinating to rhodium in a diequatorial (ee) fashion and the double bond of styrene being in the equatorial plane (in-plane coordination), are depicted in Figure 10. When the phenyl group of styrene is pointing ‘down’ towards the apical CO then styrene is situated inside the capsule (Figure 10a), and when the phenyl group of styrene is pointing ‘up’ towards the apical hydride then styrene is situated outside the capsule (Figure 10b). The modeled structure of capsule ea-[HRh(A)(CO)(1-octene)]·C with the diphosphine coordinating to rhodium in an equatorial-apical (ea) fashion shows the opposite, i.e. when the phenyl group of styrene is pointing ‘up’ towards the apical hydride then styrene is situated inside the capsule. Modeling studies also show that when the phenyl group of styrene is situated outside the capsule, then the capsule’s cavity can easily accommodate a second non-coordinating styrene molecule or product. This might explain the observed nearly second-order (1.70) dependency in styrene concentration for capsule A·C. The modeled structure of capsule ee-[HRh(A)(CO)(1-octene)]·C shows that when the alkyl group of 1-octene is pointing ‘down’ towards the apical CO then 1-octene is also situated inside the capsule. Interestingly, the modeled structure of capsule ee-
[HRh(A)(CO)(triphenylbutene)]·C shows that when the triphenylalkyl substituent of 4,4,4-triphenylbut-1-ene is pointing ‘down’ towards the apical CO then triphenylbutene is situated outside the capsule, unlike styrene and 1-octene. Clearly, the capsule’s cavity is not big enough to accommodate triphenylbutene.

**Figure 10** Molecular and modeled structures of diequatorial capsule ee-[HRh(A)(CO)(styrene)]·C with equatorial-coordinating styrene is inside (a) and outside (b) the capsule (hydrogen atoms of the capsules are omitted for clarity).

**Catalyst encapsulation: mechanistic considerations**

The activities and regioselectivities displayed by the encapsulated catalyst suggest that the capsule remains intact during the reaction. Hydroformylation of 4,4,4-triphenylbut-1-ene catalyzed by encapsulated rhodium resulted in reduced activity and a high regioselectivity for the linear aldehyde compared to the non-encapsulated catalyst, even though this substrate does not fit inside the capsule’s cavity. The encapsulated rhodium catalyst showed reduced activities and higher regioselectivities for the branched aldehydes in the hydroformylation of styrene and 1-octene, which do fit inside the capsule’s cavity. These results indicate that the substrates are maybe, but not necessarily encapsulated during the catalytic cycle.

The almost second-order (1.70) in styrene concentration found for the encapsulated catalyst suggests that two styrene molecules are involved in the rate limiting step of the catalytic cycle (alkene complexation/insertion). Molecular modeling studies show that encapsulated rhodium can coordinate one styrene molecule situated partly outside the capsule, while a second non-coordinating styrene molecule can be accommodated in the capsule’s cavity. A second styrene molecule can be necessary when styrene is coordinating to ee-[HRh(A)(CO)(styrene)]·C in the apical position, which may have a slow hydride-migration due to hindered rotation. The apical-coordinating styrene can be stabilized by the capsule’s cavity and therefore a second equatorial-coordinating styrene molecule is needed in order to displace the apical-coordinating styrene, which can afterwards still be accommodated in the capsule’s cavity. Alternatively, a second styrene molecule may be involved in displacing the product from the capsule’s cavity.
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More kinetic experiments are required to distinguish between these different theories. Van Leeuwen en Nolte have proposed cooperative binding of functionalized styrene and resorcinol inside the cavity of a rhodium metallolhost based on diphenylglycoluril framework.\textsuperscript{8d}

Product regioselectivity in the hydroformylation reaction is determined early in the catalytic cycle during the hydride-migration reaction to form either the linear or the branched rhodium-alkyl complex.\textsuperscript{5b,27a} Rhodium encapsulation results in a novel nano-environment around the metal. The new steric restrictions are dictated by the insides of the capsule and by reducing the degrees of freedom of the phosphorus aryl groups due to their interactions with the tetraanionic calix[4]arene. It is likely that the steric constrains induced by the capsule dictate the orientation of the entering alkene, reduce the rotation freedom during alkene rotation from the in-plane coordination to a perpendicular coordination mode, and subsequently influence the hydride-migration reaction which results in new product regioselectivities.\textsuperscript{6c,17c,27b-c} The steric restrictions are different for each substrate, depending on the shape and size of the substrate, and consequently result in different product regioselectivity. Indeed, catalyst encapsulation resulted in more branched product for styrene and 1-octene (16\% and 2\% more branched, respectively), while 4,4,4-triphenylbut-1-ene resulted in more linear product (at least 11\% more linear). HP IR studies suggest that the capsule does not affect the coordination mode of the diphosphine to rhodium (\textit{ee} and \textit{ea}) and therefore the coordination mode (in the resting state) does not contribute to the observed new regioselectivities of the encapsulated catalyst.\textsuperscript{17c} Molecular modeling studies are currently in progress to unravel the way encapsulated rhodium give new product regioselectivities.

6.6 Conclusion

In this Chapter we have demonstrated that a rhodium catalyst with a wide bite angle ligand known to be active in the hydroformylation reaction, can be encapsulated within a capsule formed by ionic interactions and composed of a tetracaticonic xantphos-type ligand and a tetraanionic calix[4]arene. Reaction of the diphosphine capsule with a rhodium precursor in methanol and subsequently pressurizing with syn gas afforded the catalyst, \textit{i.e.} the rhodium hydride capsule. Encapsulation of the rhodium species protected the metal center against formation of the non-active rhodium dimer species at high concentrations. The activity of the encapsulated catalyst in the hydroformylation of styrene, 1-octene and 4,4,4-triphenylbut-1-ene decreased significantly compared to the non-encapsulated catalyst. The encapsulated catalyst exhibited high product chemoselectivity as it afforded solely aldehydes in the hydroformylation reaction in methanol, unlike the non-encapsulated catalyst. Substrate competition experiments between styrene and 1-octene indicate that the encapsulated catalyst exhibits substrate selectivity. Catalyst encapsulation also resulted in different product regioselectivities compared to the non-encapsulated analogue. The catalysis results and molecular modeling studies show that the substrate is not necessarily encapsulated during the catalytic cycle. The encapsulated
catalyst does display different regioselectivities and therefore dictates the orientation of the alkene or reduces the rotational freedom of the substrates required for hydride migration. Surprisingly, catalyst encapsulation also resulted in a system that displays product inhibition, likely due to interactions of the aldehydes with the capsule’s ionic substituents and/or due to a higher affinity of the aldehyde for the capsule’s cavity. The observed positive orders in substrate concentration for alkene hydroformylation by encapsulated as well as non-encapsulated rhodium catalysts indicate that all reactions involve a rate determining alkene coordination/hydride migration. The exceptionally nearly second-order in styrene concentration (1.70) found for the encapsulated catalyst suggests that two styrene molecules are involved in the catalytic cycle: one which undergoes hydroformylation and a second non-coordinating styrene molecule accommodated inside the capsule’s cavity. In conclusion, we have shown that the novel supramolecular strategy for catalyst encapsulation opens up new opportunities to control the catalyst stability, activity, substrate selectivity, product regioselectivity and product chemoselectivity in the hydroformylation reaction.

6.7 Experimental Section

**General remarks** All reactions were carried out under a dry, inert atmosphere of purified nitrogen or argon using standard Schlenk techniques, unless stated otherwise. Solvents were dried and distilled under nitrogen prior to use. Dichloromethane, methanol and isopropanol were distilled from CaH₂. Deuterated solvents were distilled from the appropriate drying agents. Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. 4,5-Bis[(diethylamino)methyl]phenylphosphino]-9,9-dimethylxanthene A, 4,5-bis[(diethylammonium-tosylate)methyl]phenylphosphino]-9,9-dimethylxanthene A-HOTs, 5,11,17,23-tetrakis(sulfonato)-25,26,27,28-tetraakis(2-ethoxyethoxy)calix[4]arene tetrasodiumsalt C-SO₃Na and 5,11,17,23-tetrakis(sulfonicacid)-25,26,27,28-tetraakis(2-ethoxyethoxy)calix[4]arene C-SO₃H²⁻ were synthesized according to reported procedures. NMR spectra were recorded on Varian Inova 500, Bruker Avance DRX 300 and Varian Mercury 300 NMR spectrometers. Chemical shifts are given relative to TMS (¹H and ¹³C NMR) and 85% H₃PO₄ (³¹P NMR). Chemical shifts are given in ppm. Electrospray ionization mass spectrometry (ESI-MS) measurements were carried out on a Q-TOF (Micromass, Waters, Whyttenshawe, UK) mass spectrometer equipped with a Z-spray orthogonal nanoelectrospray source, using Econo Tips (New Objective, Woburn, MA) to create an off-line nanospray, at the Department of Mass Spectrometry of Biomacromolecules at the University of Amsterdam. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrophotometer. High pressure FT-IR experiments were performed in a stainless steel 50 ml autoclave equipped with INTRAN windows (ZnS), a mechanical stirrer, a temperature controller and a pressure transducer. Gas chromatographic (GC) measurements were performed on a Shimadzu GC-17A apparatus (split/splitless, equipped with a FID detector and a BPX35 column: internal diameter of 0.22 mm, film thickness 0.25 μm, carrier gas 70 kPa He). Molecular modeling calculations were performed using Spartan ‘08 V1.0.3 software (B3LYP LACVP basic set).
Self-assembly of diphosphine capsule A·C

Methanol solution of the tetraacidic calix[4]arene C-SO₃H (1 equiv.) was slowly added to a methanol solution of the tetraamine diphosphine a (1 equiv.). The solution was stirred for 30 min. at room temperature and subsequently the solvent was evaporated resulting in capsule A·C. Observed upfield shifts of the proton resonances (Δδ(H)) of the CH₂NH+(CH₂CH₃)₂ protons of capsule A·C, with respect to those of the corresponding free A-HOTs, in CD₂OD: Δδ(CH₂CH₃) = 0.37, Δδ(CH₂CH₃) = 0.34 and Δδ(NCH₂) = 0.25 ppm (A/C = 1/1). ESI-MS (m/z, CH₃OH): [A·C + 2H]⁺ found 977.06, calcd. (C₁₀₃H₁₃₄N₄O₂₁P₂S₄) 976.90; [A·C + 3H]⁺ found 651.74, calcd. (C₁₀₃H₁₃₅N₄O₂₁P₂S₄) 651.60.

High pressure NMR experiments

High pressure NMR experiments were performed in a 10 mm outer diameter/8 mm inner diameter sapphire tube glued into a Ti (6A1-4V) alloy pressure head, which allows measurements up to 140 bar. An additional ¹H HP NMR spectrum of capsule B₂·C was measured with a New Era enterprises, NE-HP5-M, high pressure glass NMR tube of CortecNet with a Teflon closure (25 mM, 0.5 ml CD₂OD, 8 bar syngas) which results in proton spectra with a better resolution. In a typical experiment a solution of [Rh(acac)(CO)₂] (50 μmol) and diphosphine (50 μmol) in 1.3 ml CD₂OD was transferred into a 10 mm sapphire NMR tube flushed with argon. The tube was purged three times with 5 bar of CO/H₂ (1:1) and pressurized to 20 bar of CO/H₂. Catalyst formation was followed in time by ³¹P{¹H} and ¹H HP NMR, and was completed within 1 h at 20 °C. The HP NMR spectra remained unchanged for at least 16 h at 20 °C. The experiments were carried out in duplo.

High pressure FT-IR experiments

In a typical experiment a solution of [Rh(acac)(CO)₂] (15 μmol) and ligand (60 μmol) in 15 ml CH₃OH was transferred into the high pressure IR autoclave. After stirring for 30 min. at 20 °C and before pressurizing with syngas an IR spectrum was measured of the cationic rhodium species. Subsequently, the autoclave was purged three times with 10 bar of CO/H₂ (1:1) and pressurized to 20 bar. The rhodium hydride species were formed within 20 minutes at 20 °C. Upon heating the HP IR autoclave 60 °C the rhodium hydride species remained stable. The experiments were carried out in duplo. Spectra were recorded every 15 minutes.

[Rh(A-HOTs)(CO)]⁺: B₁

This compound was prepared in situ by stirring a solution of A-HOTs (50 μmol) and [Rh(acac)(CO)₂] (50 μmol) in 1.3 ml of CD₂OD for 30 min. at 20 °C. ³¹P{¹H} NMR (121.5 MHz, CD₂OD, 293 K): δ = 38.3 (d, J<sub>P,Rh</sub> = 122 Hz); ¹H NMR (300 MHz, CD₂OD, 293 K): δ = 8.00 (d, J = 7.5 Hz, 2H, PC₆H₃), 7.82 (m, 8H, PC₆H₄), 7.68 (d, J = 7.5 Hz, 8H, PC₆H₄), 7.63 (d, J = 8.5 Hz, 8H, OTs⁻), 7.51 (t, J = 7.3 Hz, 2H, PC₆H₄), 7.40 (br s, 2H, PC₆H₃), 7.16 (d, J = 8.2 Hz, 8H, OTs⁻), 4.19 (s, 8H, CH₂N), 3.00 (m, 16H, C₆H₂), 2.29 (s, 12H, CH₃, OTs⁻), 1.77 (s, 6H, C(CH₃)₂), 1.22 (t, J = 7.1 Hz, 24H, CH₂CH₃); IR (CH₃OH, 293 K, cm⁻¹): ν = 2010.

Capsule [Rh(A)(CO)]⁺·C: capsule B₁·C

This compound was prepared similarly to B₁. ³¹P{¹H} NMR (121.5 MHz, CD₂OD, 293 K): δ = 38.2 (d, J<sub>P,Rh</sub> = 126 Hz); ¹H NMR (300 MHz, CD₂OD, 293 K): δ = 7.97-7.05 (br m, 22H, PC₆H₃ and PC₆H₄, B₁).
7.49 (s, 8H, H₆, C), 4.74 (br t, 8H, CH₂CH₂, C), 4.03 (br s, 8H, CH₃N, B₁), 3.88 (br t, 8H, CH₂CH₂, C), 3.53 (q, J = 7.2 Hz, 8H, CH₂CH₃, C), 3.35 (br d, 4H, H₂O, C), 2.78 (br m, 16H, CH₂CH₃, B₁), 1.72 (br s, 6H, C(CH₃)₂, B₁), 1.19 (t, J = 7.3 Hz, 12H, CH₃, C), 0.97 (br t, 24H, CH₂CH₃, B₁); Observed upfield shifts upon capsule formation, with respect to B₁: Δδ(CH₂CH₃) = 0.25, Δδ(CH₂CH₃) = 0.22, Δδ(NCH₂) = 0.16 ppm (B₁ / C = 1/1); IR (CH₃OH, 293 K, cm⁻¹): ν = 2010.

[HRh(A-HOTs)(CO)₂]: B₂ and [Rh(A-HOTs)(CO)(μ-CO)]₂: B₃
This compound was prepared in situ by pressurizing a solution of [Rh(acac)(CO)₂] (50 μmol) and A-HOTs (50 μmol) in 1.3 ml CD₃OD to 20 bar of CO/H₂ (1:1) and leaving the NMR tube for 1 h at 20 °C.
In the HP NMR experiment an equivalent amount of a rhodium-dimer B₃ was formed next to the rhodium-hydride B₂.

[HRh(A-HOTs)(CO)₂]: B₂: 3¹P{¹H} HP NMR (121.5 MHz, CD₃OD, 293 K): δ = 20.6 (d, Jₚ-Rh = 129 Hz); ¹H HP NMR (300 MHz, CD₃OD, 293 K): δ = -9.38 (br, H Rh), 4.27 (br, CH₂N), 3.13 (br, CH₂CH₃), 1.23 (br CH₂CH₃). The ¹H HP NMR spectrum is a 1:1 mixture of B₂ and B₃ and displays broad averages signals, therefore not all the shifts are reported; HP IR (CH₃OH, 293 K, cm⁻¹): ν = 1947, 1972 and 1997.

[Rh(A-HOTs)(CO)(μ-CO)]₂: B₃: 3¹P{¹H} HP NMR (121.5 MHz, CD₃OD, 293 K): δ = 9.2 (apparent d, Jₚ-Rh = 152 Hz, 1P), 0.4 (apparent d, Jₚ-Rh = 150 Hz, 1P).

Capsule [HRh(A)(CO)₂]·C: capsule B₂·C: This compound was prepared similarly to B₂. 3¹P{¹H} HP NMR (121.5 MHz, CD₃OD, 293 K): δ = 20.2 (d, Jₚ-Rh = 127 Hz); ¹H NMR (300 MHz, CD₃OD, 293 K): δ = -9.39 (br, HRh), 7.83-6.94 (br m, 22H, PC₆H₃ and PC₆H₄, B₂), 7.48 (s, 8H, H₆, C), 4.72 (d, J = 12.7 Hz, 4H, H₆, C), 4.26 (br t, 8H, CH₂CH₂, C), 4.13 (br q, 8H, CH₂N, B₂), 3.86 (br t, 8H, CH₂CH₂, C), 3.52 (q, J = 6.8 Hz, 8H, CH₂CH₂, C), 3.36 (br d, 4H, H₆, C), 2.86 (br m, 16H, CH₂CH₂, B₂), 1.64 (br s, 6H, C(CH₃)₂, B₂), 1.19 (t, J = 7.3 Hz, 12H, CH₃, C), 0.94 (br t, 24H, CH₂CH₃, B₂); Observed upfield shifts upon capsule formation, with respect to the 1/1 mixture of B₂ and B₃ (therefore these upfield shifts are only an approximation): Δδ(CH₂CH₃) = 0.29, Δδ(CH₂CH₃) = 0.27, Δδ(NCH₂) = 0.14 ppm (B₂/C = 1/1); HP IR (CH₃OH, 293 K, cm⁻¹): ν = 1947, 1970 and 1996.

Hydroformylation experiments
The hydroformylation reactions were carried out in the AMTEC SPR16 robot consisting of 16 parallel reactors equipped with temperature and pressure sensors and a mass-flow controller. The apparatus is suited for monitoring gas-uptake profiles during the catalytic reactions for each reactor simultaneously (6 data points are recorded per minute). Four to sixteen autoclaves were heated to 110 °C and flushed with argon (22 bar) five times. Next, the reactors were cooled to 25 °C and flushed again with argon (22 bar) five times. The autoclaves were charged with the appropriate amount of catalyst precursor [Rh(acac)(CO)₂] (4.0–16.0 μmol) and 5 equivalents of diphosphine ligands or diphosphine capsule in methanol (4.20–6.80 ml) and the catalyst was incubated under 16 bar of syngas (CO/H₂ = 1/1) for 1h at 80 °C. Next, the temperature of the reaction mixtures was decreased to 60 °C and the pressure in the autoclave was reduced to 2.0 bar. Subsequently, substrate and if necessary methanol, dichloromethane, 2-phenylpropionaldehyde and 3-phenylpropionaldehyde were added under a flow of syngas and the reaction was started by pressurizing the reactor with 20 or 35 bar of syngas (CO/H₂ = 1:1). These reaction steps (pressure release, addition substrate and start of the reaction) were done for all reactors after each other. The pressure was kept constant during the whole reaction and the reaction mixtures were stirred at 60 °C.
Encapsulation of a Rhodium Hydroformylation Catalyst in a Diphosphine Based Capsule

for 34–44 h. The syngas uptake was monitored and recorded for every reactor. During the catalysis ten periodic samples of 0.1 ml (for GC analysis) were taken for every reactor using the auto-sampler. After the catalysis the pressure was reduced to 2.0 bar and samples of 0.3 ml (for GC analysis) were taken.

Total reaction volume is 8.00 ml. Styrene and 1-octene were freshly filtrated over basic alumina (2-phenylpropionaldehyde and 3-phenylpropionaldehyde were used as received). Decane was added as an external standard after the reaction (volume ratio substrate/decane 2/1). All the samples were analyzed by gas chromatography. The samples taken from the autoclaves at the end of the reactions were used to calibrate the gas-uptake profiles and the samples taken from the autoclaves during the reactions with the auto-sampler were used to monitor the products distribution. Unless stated otherwise, the branched to linear ratio (b/l) remained constant during the reaction course (b/l ratio of aldehydes and corresponding enol ethers). The conversion versus time graphs determined by gas-uptake profiles and by GC overlap and hence are in agreement with each other. The solubility of 4,4,4-triphenylbut-1-ene in methanol is too low and therefore the reaction mixtures contained 2 ml of dichloromethane. The hydroformylation of styrene in methanol catalyzed by rhodium complexes based on ligand **a** (S/C = 873), ligand **A-HOTs** (S/C = 873 and 1309) and capsule **A·C** (S/C = 873 and 1309) were performed in duplo and were reproducible. The branched and linear aldehydes of styrene: 2-phenylpropionaldehyde and 3-phenylpropionaldehyde; of 1-octene: 2-methyloctanal and nonanal; of 4,4,4-triphenylbut-1-ene: 2-methyl-4,4,4-triphenylbutanal and 5,5,5-triphenylpentanal.

**Kinetic study of the hydroformylation reaction**

<table>
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<th>[styrene] (M)</th>
<th>0.4364</th>
<th>0.6545</th>
<th>0.8728</th>
<th>1.3091</th>
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<tr>
<td>TOF (at 20% conv.)</td>
<td>38.26</td>
<td>58.53</td>
<td>72.27</td>
<td>110.99</td>
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**Figure 11** Gas-uptake profile (a) and plot of ln(ToF) versus ln[styrene] (b): styrene hydroformylation catalyzed by a rhodium complex based on **A-HOTs** at four different initial styrene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1 mM, [L] = 5 mM, [styrene] = 436, 655, 873 and 1309 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)¹·h⁻¹) have been determined from gas-uptake profiles.
Figure 12 Gas-uptake profile (a) and plot of ln(TOF) versus ln[styrene] (b): styrene hydroformylation catalyzed by a rhodium complex based on capsule A·C at four different initial styrene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1 mM, [L] = 5 mM, [styrene] = 436, 655, 873 and 1309 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)⁻¹·h⁻¹) have been determined from gas-uptake profiles.

<table>
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<tr>
<th>[styrene] (M)</th>
<th>0.4364</th>
<th>0.6545</th>
<th>0.8728</th>
<th>1.3091</th>
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<tr>
<td>TOF (at 15% conv.)</td>
<td>1.719</td>
<td>3.193</td>
<td>5.383</td>
<td>11.000</td>
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Figure 13 Gas-uptake profile (a) and plot of ln(TOF) versus ln[1-octene] (b): 1-octene hydroformylation catalyzed by a rhodium complex based on A-HOTs at three different initial 1-octene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1 mM, [L] = 5 mM, [1-octene] = 478, 956 and 1434 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)⁻¹·h⁻¹) have been determined from gas-uptake profiles.

<table>
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<tr>
<th>[1-octene] (M)</th>
<th>0.478</th>
<th>0.956</th>
<th>1.434</th>
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<tbody>
<tr>
<td>TOF (at 20% conv.)</td>
<td>41.52</td>
<td>63.94</td>
<td>87.80</td>
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</table>
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**Figure 14** Gas-uptake profile (a) and plot of ln(TOF) versus ln[1-octene] (b): 1-octene hydroformylation catalyzed by a rhodium complex based on capsule A·C at three different initial 1-octene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)\(_2\)], [Rh] = 1 mM, [L] = 5 mM, [1-octene] = 478, 956 and 1434 mM, CO/H\(_2\) (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)\(^{-1}\)·h\(^{-1}\)) have been determined from gas-uptake profiles.

| [1-octene] (M) | 0.4779 | 0.9558 | 1.434 |
| TOF (at 4% conv.) | 0.79 | 1.09 | 1.23 |

**Figure 15** Gas-uptake profile (a) and plot of ln(TOF) versus ln[4,4,4-triphenylbut-1-ene] (b): 4,4,4-triphenylbut-1-ene hydroformylation catalyzed by a rhodium complex based on capsule A·C at three different initial 4,4,4-triphenylbut-1-ene concentrations. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)\(_2\)], [Rh] = 1 mM, [L] = 5 mM, [4,4,4-triphenylbut-1-ene] = 396, 593 and 791 mM, CO/H\(_2\) (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)\(^{-1}\)·h\(^{-1}\)) have been determined from gas-uptake profiles.

| [triphenylbutene] (M) | 0.3955 | 0.5933 | 0.7912 |
| TOF (at 8% conv.) | 0.985 | 1.45 | 1.98 |
Ligand: A-HOTs

Figure 16 Gas-uptake profile (a) and “Graphical rate equations” (b): 4,4,4-triphenylbut-1-ene hydroformylation catalyzed by a rhodium complex based on A-HOTs. Conversion is determined by syngas uptake. Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1 mM, [L] = 5 mM, [4,4,4-triphenylbut-1-ene] = 396 mM, CO/H₂ (1:1) = 20 bar, 60 °C, methanol. TOF’s ((mol product)/(mol Rh)⁻¹·h⁻¹) have been determined from gas-uptake profiles.

6.8 Acknowledgments

Dr. Mark Kuil is gratefully acknowledged for his assistance with the robot-facilities at BASF and the fruitful discussions concerning the hydroformylation experiments. Jan Meine Ernsting is kindly acknowledged for his assistance with the high pressure NMR experiments.

6.9 References


Chapter 6


[29] See Chapter 3 of this Thesis.