Chapter Six

Encapsulation of Hydrophilic NCN-Pincer Platinum Complexes in Amphiphilic Hyperbranched Polyglycerol Nanocapsules

Abstract
Hydrophilic NCN-pincer platinum(II) complexes with sulfonate groups are encapsulated in amphiphilic hyperbranched polyglycerols with a core-shell structure (‘nanocapsules’). In apolar solvents, these macromolecules exhibit a reverse micelle-type architecture. The maximum loading of the polar NCN-pincer complexes in the nanocapsules depends on the molecular weight of the hyperbranched polymers. The non-covalently encapsulated Pt(II) complexes show catalytic activity in double Michael additions, albeit with decreased activities compared to the free NCN-pincer complex. Hyperbranched polymer based microenvironments are promising supports with respect to the application of homogeneous NCN-pincer catalysts in membrane reactors.
6.1. Introduction

The study of catalytically active dendritic materials has become an attractive subject of interest.¹ Such materials can be obtained either upon attachment of the appropriate catalyst (precursor) at the core or periphery of dendrimers, or by the immobilization of metal nanoclusters in dendritic compartments.² Unfortunately, the preparation of dendrimers requires multi-step syntheses, which limits their large-scale (industrial) application. In contrast, hyperbranched polymers are conveniently prepared on large scales in one-pot procedures via polymerization of AB₄-type monomers.³ Controlled polymerization of glycidol by anionic ring-opening multibranching polymerization results in the formation of highly hydrophilic hyperbranched polyglycerols.⁴ Esterification of a certain fraction (40-60%) of the hydroxyl groups of these hyperbranched polyether polyols with hydrophobic alkyl chains yields amphiphilic molecular nanocapsules with a reverse micelle-type architecture. These low polydispersity (1.3<\(M_w/M_n<1.5\)) amphiphilic molecular nanocapsules are soluble in apolar organic solvents and irreversibly encapsulate various polar, water-soluble dye molecules in their hydrophilic interior by liquid-liquid extraction.⁵ Our interest in the immobilization of homogeneous transition metal catalysts by soluble support systems has motivated us to prepare hydrophilic transition metal complexes which can be encapsulated inside these amphiphilic nanocapsules in a noncovalent manner. Due to their chemical integrity, metal complexes of the pincer-ligand (3,5-bis[(dimethylamino)methyl]phenyl anion) have proven to be especially potent candidates for immobilization purposes.⁶,⁷ The introduction of suitable substituents at the \(para\)-position of these NCN-pincer complexes permits to tailor their solubility in solvents ranging from apolar to highly polar and protic (see chapter 2). This chapter describes the noncovalent encapsulation of sulfonated pincer platinum(II) complexes in readily available amphiphilic nanocapsules based on hyperbranched polyglycerol (Scheme 1). The encapsulated platinum(II) complexes have been applied as catalyst in double Michael additions to demonstrate their potential as homogeneous catalysts in continous membrane reactors.

6.2. Results and Discussion

Synthesis

The nanocapsules P(G₂₅C₁₆₀.₅) ¹ and P(G₁₀₆C₁₆₀.₆) ² investigated in this study, were synthesized by partial esterification of hyperbranched polyglycerols with molecular weights of \(M_n=2,000\) and \(M_n=8,000\), respectively.⁸ Esterifications were performed with palmitoyl chloride in a mixture of pyridine and toluene,⁵ᵃ and the products were characterized by \(^1\)H- and \(^{13}\)C-NMR spectroscopy, IR-spectroscopy, and SEC analysis. While nanocapsule ¹ possesses a molecular weight of \(M_n=5,200\) (\(M_w/M_n=1.2\)), with a degree of substitution of
50%, nanocapsule 2 has a molecular weight of $M_n = 23,500$ ($M_w/M_n = 1.3$) with 60% degree of substitution with palmitoyl tails. Polymers 1 and 2 are completely and homogeneously soluble in apolar solvents such as dichloromethane, chloroform and toluene. It should be emphasized that the analogous linear polyglycerols after partial esterification (60%) afford chloroform-soluble materials unable of transporting polar guest molecules.9

**Scheme 1.** Molecular nanocapsule synthesis, structure, and non-covalent encapsulation of NCN-pincer platinum complexes.

*Hydrophilic NCN-platinum complexes*

The hydrophilic pincer-platinum(II) complexes 3 and 4 (Chart 1) can be dissolved in polar (protic) solvents such as water, methanol or DMSO. Their solubility in aqueous solvents can be enhanced by the addition of base.

**Chart 1.** Structures of hydrophilic NCN-platinum complexes.

Since encapsulation of 3 and 4 by liquid-liquid extraction involves solubilization of the organometallic complexes in aqueous solution, we investigated their behaviour in aqueous solution in more detail. Carboxylic acid complex 4 is slightly soluble, and sulphonie acid 3 is reasonably soluble in water. However, their solubility is enhanced in aqueous solutions with
pH >7 due to more efficient deprotonation of the acidic functional group. A $^1$H-NMR spectrum of a saturated solution of platinum complex 3 in D$_2$O shows, apart from the aromatic and benzylic resonances, a large signal from the NMe$_2$ protons at 2.99 ppm, corresponding with the sulfonate. In a saturated 0.5M NaOH/D$_2$O solution this resonance disappears, and two new signals appear for the NMe$_2$ protons at higher field (2.88 ppm and 2.59 ppm). $^{195}$Pt-NMR in 0.5M NaOH/D$_2$O shows two signals located at -1795 and -1849 ppm. These shifts correspond to the dehalogenation of 3, as confirmed by halide abstraction with AgBF$_4$, followed by the formation of an equilibrium between presumably the aqua and the hydroxyl analogues of 3, in a ratio dependent on the pH of the solution (Scheme 2). In D$_2$O, the solubility of 3 is too low for observation by $^{195}$Pt-NMR. Similar behaviour, i.e. dehalogenation under basic aqueous conditions, was observed for platinum complex 4.

![Scheme 2. Dehalogenation of NCN-platinum complex 3 under basic aqueous conditions.](image)

**Non-covalent Encapsulation**

Using UV/Vis spectroscopy, we monitored the extent to which molecular nanocapsules 1 and 2 were able to encapsulate the platinum complexes 3 ($p$-SO$_3$H) and 4 ($p$-COOH) by extraction from aqueous solutions (0.5 M NaOH) into dichloromethane solutions. Dichloromethane solutions of the nanocapsules (c = 5 x 10$^{-5}$ M) were shaken thoroughly with aqueous solutions of the pincer complexes 3 and 4, respectively, with various concentrations in the range of 10$^{-5}$ to 10$^{-4}$ M. The clear organic phase obtained after phase separation was studied by UV/Vis spectroscopy. While the sulfonated complex 3 shows very little solubility in neat dichloromethane, it could be extracted from the aqueous phase into dichloromethane solutions of the amphiphilic polyglycerols 1 and 2. UV/Vis spectra from solutions of 3 in the nanocapsules showed two strong bands ($\varepsilon_{\pi-\pi^*} \approx 10^4$ M$^{-1}$cm$^{-1}$) at 262 and 275 nm. The intensity of these bands increased at higher ratios of [3]/[nanocapsule]. Selected UV/Vis spectra from the extractions of 3 by nanocapsules 1 and 2, together with the corresponding titration curves, are depicted in Figure 1. The corresponding UV/Vis spectra from the aqueous phase, showing incomplete uptake of 3 by the nanocapsules, are given in Figure 2.
Figure 1. UV/Vis spectra (organic phase) and titration curves (insets) of the extractions of NCN-platinum complex 3 by nanocapsules (a) 1 and (b) 2 at various [3]/[nanocapsule] ratios.

Figure 2. UV/Vis spectra from the aqueous phase for extractions with nanocapsules (a) 1 and (b) 2, corresponding to Figure 1.

A change in slope of absorbance versus concentration ratio (inflection point) was reached at ratios of 1.5 ([3]/[1]) and 9.0 ([3]/[2]), clearly demonstrating the effect of molecular weight on the loading capacity of the amphiphilic hyperbranched polyglycerol. The incorporation behavior of 3 in the molecular nanocapsules is similar to that observed for sulfonated organic dyes.5 At concentrations above the inflection point the nanocapsules take up more 3 from the aqueous solution, but clearly by a different mechanism. This behavior deviates from the sulfonated dyes reported previously,5a and we explain this tentatively by the aggregation of nanocapsules to form larger micelle-type structures, most probably assembled around the polar NCN-platinum complex, which possesses two polar moieties (SO$_3^-$ and HO$^-$) and a Lewis-acidic center. It should be pointed out that all our observations to date suggest that the unimolecular nature of the solvating nanocapsules depends on the nature of the guest.
Encapsulation of hydrophilic NCN-pincer platinum complexes

A molecule studied. UV/Vis analysis of the aqueous phase showed that at concentrations exceeding the inflection point, 3 is not extracted quantitatively into the organic phase any more. Preparative loading of nanocapsules 1 and 2 with NCN-pincer platinum complex 3 was carried out using concentration ratios of [3]/[nanocapsule] equal to 1.5 and 9, respectively. The resulting yellowish solids were analyzed by 1H-, 13C-, and 195Pt-NMR, and SEC-chromatography. 1H-NMR integration of the NMe2 signals (δ(CH3)= 3.02 ppm) originating from complex 3 and hydrophobic shell protons (δ(CH3)= 0.84 ppm) of the nanocapsule afforded an estimate for the loading of the nanocapsules. Nanocapsule 1 was found to encapsulate 0.9-1.1, and nanocapsule 2 3.8-4.1 molar equivalents of 3. More accurate loadings of 1.3 for 1 and 2.4 for 2 were determined based on the platinum content quantified by elemental analysis. The loaded nanocapsules will be denoted as 1·31.3 and 2·32.4.

The carboxylate platinum(II) NCN-pincer 4 is not encapsulated in the hyperbranched nanocapsules. Dichloromethane solutions of 1 and 2 remained unchanged after shaking them with aqueous (0.5M NaOH) solutions of 4. UV/Vis-spectra of the organic phase showed no phase transfer of the complex. Furthermore, the band at 308 nm in the spectrum of 4 in the aqueous phase did not decrease upon repeated extractions with the nanocapsules. Attempts to encapsulate 4 with other counterions, e.g. in 0.5 M KOH and CsOH, were also unsuccessful. It should be noted that the encapsulation behavior observed for the carboxylate pincer complexes is similar to that of carboxylate-substituted organic dye molecules, which have a low affinity for the polyether-polyol interior of the nanocapsules compared to sulfonate substituted dyes.11

Double Michael Addition

The isolated loaded nanocapsules 1·31.3 and 2·32.4 were applied as catalyst in the double Michael addition of methyl vinyl ketone to ethyl cyanoacetate. Although cationic NCN-pincer platinum complexes are, in contrast to their highly active palladium analogues, not considered to be catalytically active in Lewis-acid catalysed processes,6 they do accelerate selected examples to some extent. This offers the opportunity for a model-study of the non-covalently assembled system towards catalysis. The platinum loadings determined by elemental analysis were used to calculate the amount of catalyst applied in the double Michael addition. The results from the catalysis experiments are summarized in Table 1.
Table 1. Catalytic results of the double Michael addition, catalyzed by the encapsulated complexes.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>(k) ((10^{-3} \ h^{-1}))</th>
<th>Conversion (% after 40 h)</th>
</tr>
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<tbody>
<tr>
<td>a</td>
<td>([\text{Pt(OH}_2\text{CN}]\text{(BF}_4\text{)}])</td>
<td>280</td>
<td>99</td>
</tr>
<tr>
<td>b</td>
<td>none</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>c</td>
<td>1</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>d</td>
<td>2</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>e</td>
<td>1·3(_{1,3})</td>
<td>73</td>
<td>95</td>
</tr>
<tr>
<td>f</td>
<td>2·3(_{2,4})</td>
<td>62</td>
<td>81</td>
</tr>
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</table>

\(^a\) for conditions see experimental section.

Amphiphilic polyglycerols \(\text{P(G}_{25}\text{C}_{160.5})\) and \(\text{P(G}_{106}\text{C}_{160.6})\) without encapsulated catalyst do not result in a significant rate enhancement compared to the blank reaction (entries b,c,d).\(^1\) The loaded nanocapsules 1·3\(_{1,3}\) as well as 2·3\(_{2,4}\) considerably increased the reaction rate compared to the blank reaction (entries e,f), albeit that the observed activity is lower than observed for the unsubstituted NCN-pincer platinum(II) complex (entry a). This may be due to the fact that the catalysts are shielded from the environment by the core of the nanocapsules, their fatty acid substituents preventing fast exchange of products and substrates. Interactions between the hydroxyl groups of the polyglycerol core and the platinum cation can also render the catalyst less accessible for the coordination of ethyl cyanoacetate. The catalytic activity of 1·3\(_{1,3}\) and 2·3\(_{2,4}\) supports the finding that 3 is dehalogenated in 0.5M NaOH, prior to the encapsulation, since the halide platinum(II) pincers are not Lewis acidic and not active in the Michael addition.\(^3\) Due to the size of the nanocapsules, we were able to separate the products from the encapsulated catalysts by dialysis, and recover >97% of the catalytic material.\(^4\) These results show the suitability of the presented hyperbranched systems as catalyst carriers in continuous membrane reactors.\(^5\)

6.3. Conclusion

In conclusion, hydrophilic NCN-pincer platinum(II) complexes have been encapsulated in amphiphilic nanocapsules based on hyperbranched polyglycerols, possessing a reverse micelle-type architecture. The loading of the pincer complexes in the nanocapsules depends on the molecular weight of the hyperbranched polymer as well as on the functionality of the pincer. The incorporated platinum(II) complexes show catalytic activity in a double Michael addition, albeit with decreased activities compared to the parent NCN-pincer complex. To our knowledge this is the first example of the use of a hyperbranched polymer-based micro-environment for homogenous catalysis in a non-covalent strategy. This strategy is also promising with respect to the application of catalysts in a membrane reactor set-up.
6.4. Experimental

General
All solvents were distilled from and stored over molsieves (4Å) under a dry nitrogen or argon atmosphere. All other reagents were obtained commercially and were used without further purification. Elemental Analyses were performed by Kolbe, Mikroanalytisches Laboratorium (Müllheim, Germany). $^1$H and $^{13}$C ($^1$H) NMR spectra were recorded on a Varian Inova 300 spectrometer (operating at 300 and 75 MHz respectively) or a Varian Mercury 200 spectrometer (operating at 200 and 50 MHz respectively). Spectra were recorded in chloroform-d or benzene-d$_6$ at room temperature, unless stated otherwise, and were referenced to TMS ($\delta = 0.00$ ppm). The syntheses of NCN-platinum complexes 3 and 4 is described in chapter 2.

Synthesis of nanocapsules 1 and 2.
Partially esterified polyglycerols P(G$_{25}$C$_{160.5}$) (1) and P(G$_{106}$C$_{160.6}$) (2) were prepared as followed: To a pyridine solution (80 mL) of hyperbranched polyglycerol (DP$_n$= 25; 1.52 g; 20.51 mmol of OH groups), was added dropwise a toluene solution (100 mL) of palmitoyl chloride (3.6 mL; 12 mmol) at 80°C within 1h. The mixture was refluxed for 20h at 130°C. A stoichiometric amount of NaHCO$_3$ (10.28 mmol; 1.03 g) was added to the cold solution and most of the volatiles were removed in vacuo. Residual pyridine was removed by azeotropic distillation in 100 mL of toluene. The remaining solution was filtered and concentrated in vacuo. The residue was washed several times with ethyl acetate to remove traces of free palmitoyl carboxylic acid and was further purified by dialysis (MWCO 1000) in CHCl$_3$. The polymer was obtained as white solid.

**Polymer P(G$_{25}$C$_{160.5}$) (1):** Yield 85%. $^1$H NMR (CDCl$_3$): 0.81 (t, CH$_3$), 1.11-1.25 (br , 24H, CH$_2$), 1.53 (m, COCH$_2$CH$_2$), 2.24-2.28 (m, CH$_2$, CH$_2$CO), 3.44-4.03 (br , 5H, glycerol moiety), 5.04 (br, OH). $^{13}$C NMR (CDCl$_3$): 14.08, 22.66, 24.88, 29.16, 29.51, 29.64, 31.90, 34.10, 65.12, 68.65, 69.81, 70.16, 173. IR (NaCl)$\nu$= 1738.43 (C=O), 3441.81 (O–H). $\alpha$ (Degree of substitution per hydroxyl group)= 50%; $M_m$ = 5,230; $M_w/M_n$ = 1.2.

**Polymer P(G$_{106}$C$_{160.6}$) (2):** Dried hyperbranched polyglycerol (DP$_n$=106; 10g, 134.95 mmol of OH groups) and palmitoyl chloride (24.54 mL; 80.97 mmol) were reacted following the same procedure as polymer 1, to give polymer P(G$_{106}$C$_{160.6}$), 2 as a white solid. Yield: 90%. $^1$H NMR (CDCl$_3$): 0.84 (t, CH$_3$), 1.21 (br, 24H, CH$_2$), 1.57 (m, 2H, CH$_2$CH$_2$CO), (m, 2H, CH$_2$CO), 2.26-2.3 (m, CH$_2$, CH$_2$CO), 3.52-4.07 (br , 5H, glycerol), 5.10 (br, OH). $^{13}$C NMR (CDCl$_3$): 14.10, 22.67, 24.94, 29.13, 29.43, 29.66, 31.91, 34.10, 65.12, 68.65, 69.81, 70.16, 173. IR (NaCl)$\nu$ = 1636.76 (C=O), 3388.06 (O–H). $\alpha$ (Degree of substitution per hydroxyl group)= 60%; $M_m$ = 23506; $M_w/M_n$ = 1.3.
UV/Vis-titrations

Solutions of 3 and 4 in aqueous 0.5 M NaOH were prepared in concentrations ranging from $10^{-3}$-$10^{-4}$ M. Nanocapsules 1 and 2 were dissolved in dichloromethane with concentrations in the range of $10^{-5}$ M. In a typical UV/Vis experiment, 3 mL of the aqueous solution was mixed thoroughly for 1 hour with 3 mL of the dichloromethane solution. The phases were allowed to settle completely and were subsequently separated and both analysed by UV/Vis-spectroscopy.

**Loading of Nanocapsules 1 and 2**

Equimolar amounts (50 mL) of an aqueous solution of 3 (5.0 mM, 0.5 M NaOH) and dichloromethane solutions of 1 (3.3 mM) or 2 (0.6 mM) were mixed vigorously for 30 minutes. The phases were allowed to settle overnight and subsequently separated. The organic phase was dried over MgSO$_4$, filtered, and dried in vacuo to obtain the loaded nanocapsules as yellowish solids in near quantitative yields. 1·3$_{1.3}$: $^1$H NMR (CDCl$_3$): 0.83 (t, CH$_3$), 1.24 (br, CH$_2$), 1.58 (br. m, COCH$_2$CH$_2$), 2.28 (br. m, CH$_2$, CH$_2$CO), 3.00-3.18 (NMe$_2$ pincer), 3.40-4.13 (br, glycerol moiety), 4.01 (CH$_2$N pincer), 5.04 (br, OH). 7.60 (ArH pincer); $^{13}$C NMR (CDCl$_3$): 174.0-173.0, 123.4, 119.4, 80.0-78.0, 74.0-68.0, 66.0-63.0, 54.6, 34.5, 32.1, 30.0-29.0, 25.1, 22.9, 14.3; Elem. Anal.: C 65.64, H 10.37, Pt 4.45.

2·3$_{2.4}$: $^1$H NMR (CDCl$_3$): 0.84 (t, CH$_3$), 1.24 (br, CH$_2$), 1.59 (br. m, COCH$_2$CH$_2$), 2.29 (br. m, CH$_2$, CH$_2$CO), 3.00-3.20 (NMe$_2$ pincer), 3.40-4.20 (br, glycerol moiety), 4.01 (CH$_2$N pincer), 5.06 (br, OH). 7.62 (ArH pincer); $^{13}$C NMR (CDCl$_3$): 174.0-173.0, 143.5, 123.4, 119.4, 80.0-78.0, 74.0-68.0, 66.0-63.0, 54.6, 34.5, 32.1, 30.0-29.0, 25.1, 22.9, 14.3; Elem. Anal.: C 64.52, H 10.63, Pt 3.25.

**Double Michael Addition**

General conditions for the double Michael addition: 1.6 mmol ethyl cyanoacetate, 4.8 mmol methyl vinyl ketone, 0.16 mmol Et$_3$P$_2$, 1 mol% catalyst based on its platinum content, 5 mL CH$_2$Cl$_2$, room temperature. The reaction was followed by $^1$H-NMR, and the products were characterized by $^1$H-NMR and GC-MS. Lewis acidic palladium(II) and platinum(II) pincer complexes of the type [(M(OH)$_2$)NCN](BF$_4$) can be applied as catalyst in aldol-type reactions.

### 6.5. References and Notes

Encapsulation of hydrophilic NCN-pincer platinum complexes


7. Pincer complexes from the nickel triad (Ni, Pd, Pt) are applicable as catalyst in various carbon-carbon coupling reactions, such as the Kharasch addition, the Heck reaction and aldol condensations.

8. Nomenclature P(G xCYz): x = DP₉ of polyglycerol, Y: number of carbon atoms of the palmitoyl acid, z: degree of alkyl substitution per hydroxyl group.


12. Neat dichloromethane, shaken thoroughly with an aqueous solution of 3, was also not catalytically active in the double Michael addition.

13. In a control experiment, the encapsulated pincer systems were treated with AgBF₄, which is a normal procedure for dehalogenation. The resulting materials did not show significant rate enhancements compared to 1·3₁,₃ and 2·3₂,₄.

14. Benzoylated dialysis tubing (D-7884 Sigma) in dichloromethane/methanol 95/5, overnight stirring at room temperature has been used.