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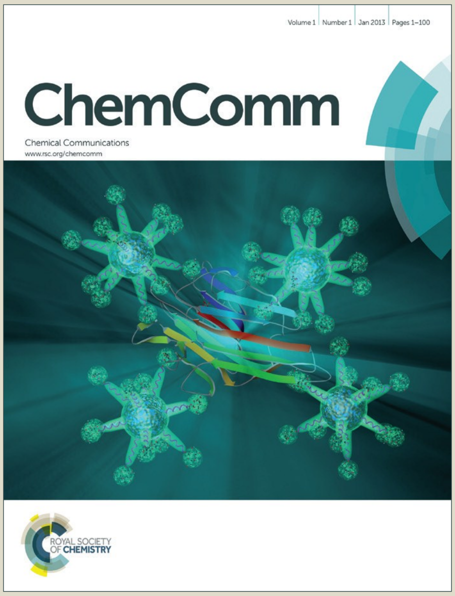

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Thermoresponsive self-assembled cyclodextrin-end-decorated PNIPAM for aqueous catalysis

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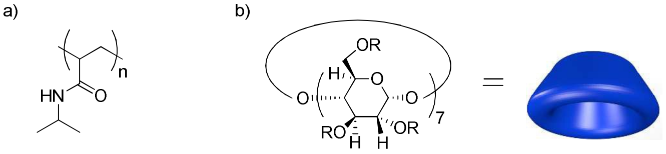
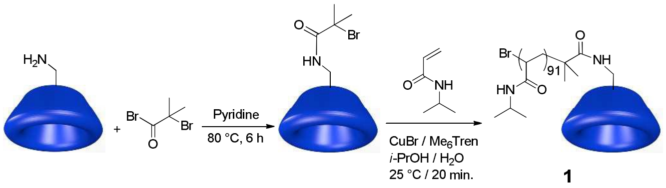
The catalytic performance of thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAM) functionalized at the terminal position with randomly methylated β-cyclodextrin was demonstrated in the aqueous Rh-catalysed hydroformylation of higher olefins.

In a green chemistry context, the development of novel chemical processes in water is currently central to environmental science. As such, aqueous catalysis has become one of the main levers to optimize chemical processes, both economically and environmentally, with beneficial effects on the activities, selectivities and reusability of the catalytic system.[1-4] Among the industrial processes developed in this context, the aqueous biphasic hydroformylation of propene to butyraldehyde (Ruhrchemie/Rhône-Poulenc process) is undoubtedly the most famous example.[5] This process is particularly suitable for hydrophilic or partially hydrophilic substrates such as propene or butene. However, conversion of more hydrophobic "higher" olefins is a much more delicate task as the reaction rate is too low because of solubility problems. In this context, the use of additives such as ligands with amphiphilic properties,[6-9] cosolvents[10] or thermomorphic solvents,[11] surfactants,[12,13] supramolecular receptor,[14,15] polymers[16] or dispersed particles[17,18] is often required. Recently, the use of phosphane-grafted polymers have also been reported as a promising approach to solve mass transfer limitations in aqueous two-phase hydroformylation.[21-24]

Herein, we describe the synthesis of a poly(*N*-isopropylacrylamide (PNIPAM, Scheme 1) end-decorated by the randomly methylated β-cyclodextrin (RAME-β-CD, Scheme 1)[25,26] and its catalytic application in the challenging aqueous Rh-catalyzed hydroformylation of strong hydrophobic C12-C18 alkenes. PNIPAM has been chosen because it is thermoresponsive[27] and shows a lower critical solution temperature (LCST) at around 32 °C (transition of the hydrophilic to hydrophobic state). Above the LCST, a coil-to globule transition is observed with formation of aggregates of micrometer size range. The choice of RAME-β-CD was directed by its high solubility in water and its ability to supramolecularly interact with appropriate organic susbtrates.[28] Below we show that the conjugate properties of both PNIPAM and RAME-β-CD in a single material allow for overcoming the mass transfer limitations in aqueous Rh-catalyzed hydroformylation of higher olefins.



Scheme 1. General structures of a) PNIPAM and b) RAME-β-CD (R = H or CH_3, average substitution degree = 1.8).



Scheme 2. Synthesis of RAME-β-CD-Br initiator and polymer **1**.

The RAME-β-CD end-functionalized PNIPAM (**1**) was synthesized in two steps through an Atom Transfer Radical Polymerization (ATRP) procedure (Scheme 2) as follows. RAME-β-CD-NH_2[16] was reacted with 2-bromoisobutyrate bromide in the presence of pyridine for 6 h at 80 °C. It was then engaged in the polymerization of NIPAM in the presence of the catalytic system based on CuBr and tris[2-(dimethylamino)ethyl]amine (Me_6Tren) in a *t*-butanol/water mixture (1.5/5 % v/v) for 20 minutes at 25 °C. The molar ratio NIPAM/RAME-β-CD-Br/CuBr/Me_6Tren was set to 100/1/1/2.[29] **1** was purified by precipitation and characterized by SEC ($M_{n\mathrm{SEC}}$ = 16000 g/mol, $Đ$ = 1.38, ESI) and ^{1}H NMR ($M_{n\mathrm{NMR}}$ =

11700 g/mol). In order to state about the catalytic performance of **1**, a PNIPAM without any RAME-β-CD at its extremity was also synthesized (**2**, $M_{n\mathrm{NMR}}$ = 9800 g/mol, $M_{n\mathrm{SEC}}$ = 12400 g/mol, $Đ$ = 1.18, ESI). Moreover, as the hydroformylation temperature was set to 80 °C, the thermal responsiveness of both polymers **1** and **2** were investigated through UV-Vis turbidimetry experiments. In water solution (polymer concentration of 1 g/L), polymer **1** exhibited a cloud point at 36.6 °C whereas polymer **2** displayed a lower cloud point (T_{cp} = 32.1°C). This difference is likely due to the hydrophilicity provided by the presence of the RAME-β-CD at the extremity of polymer **1**. On the other hand, Dynamic Light Scattering (DLS) experiments were carried out at different temperatures, *i.e.* 20 °C and 80 °C. The hydrodynamic radius of polymer **1** went from 7 nm to 368 nm when the temperature raised from 20 to 80 °C, thereby suggesting the formation of large aggregates above the LCST (ESI). Interestingly, addition of the water soluble ligand TPPTS (used thereafter for the catalytic study) led to a significant decrease in the hydrodynamic radius at 80 °C (from 368 to 263 nm). TEM images were next recorded to investigate the morphology of aggregates above the LCST of **1** (at 40 °C and 80 °C) and revealed the presence of collapsed spherical particles with an average hydrophobic core diameter of 200 nm (Fig. 1). This value was in good agreement with literature data.[30] Note that the high contrast observed on the TEM images characterized highly densely packed PNIPAM chains.

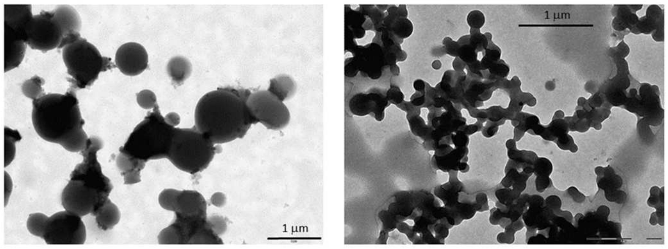


Fig. 1 Transmission electron microscopy (TEM) of **1** at 40 °C (left) and 80 °C (right).

To get additional information about the system in the presence of an organic substrate, mixtures of **1** in water/1-decene and RAME-β-CD in water/1-decene were observed by optical microscopy at 80 °C. In the presence of **1**, a well-dispersed oil in water (O/W) emulsion was observed (Fig. 2a). After cooling to 50 °C, a coalescence of small droplets led to larger ones to such an extent that the adsorption of **1**-based particles onto the droplet surface became visible (Fig. 2b). Conversely, no emulsion could be detected using RAME-β-CD as an additive. These observations strongly suggested the formation of an emulsion stabilized by the **1**-based particles. Fluorescence microscopy realized at 80 °C in the presence of the lipophilic fluorescent indocarbocyanine probe confirmed this hypothesis as particles were visualized onto the surface of 1-decene droplets (Fig. 2c).

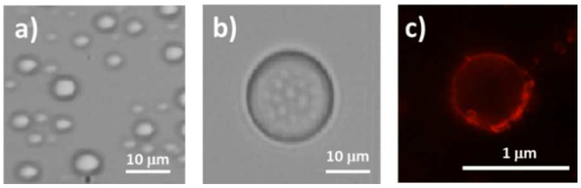


Fig. 2 a) Optical microscopy of a mixture containing 1-decene (1.2 mL), water (6 mL) and **1** (100 mg) at 80 °C; (b) optical microscopy of a mixture containing 1-decene (1.2 mL), water (6 mL) and **1** (100 mg): emulsion sampled at 80 °C and observed at 50 °C; c) fluorescence microscopy of a mixture containing 1-decene (1.2 mL), water (6 mL) and **1** (100 mg) at 80 °C.

Similar observations were recently reported by our group using Pickering emulsions stabilized by α-CD/PEG crystallites.[18,20]

The catalytic performance of **1** was evaluated in the Rh-catalyzed hydroformylation of 1-decene and 1-hexadecene at 80 °C under 50 bar of CO/H_2. To this end, **1** was compared to i) **2** (PNIPAM polymer free from RAME-β-CD), ii) RAME-β-CD and iii) a 1/1 physical mixture of **2** and RAME-β-CD. The sodium salt of the trisulfonated triphenylphosphane (TPPTS) was used as a ligand to retain the catalytic Rh-species in water. A preliminary study showed that the conversion linearly increased with the amount of **1** for a **1**/Rh molar ratio between 0 and 0.5 (ESI). Beyond, the conversion levelled off suggesting a saturation of the aqueous/organic interface. Whatever the substrate, **1** appeared to be the best additive to promote the conversion of the terminal alkene function into aldehydes (Fig. 3). Interestingly, when the results were translated in terms of gain in conversion (ratio of the conversion measured with **1** to the conversion measured with other components), the role of **1** appeared under a new light. While the less hydrophobic 1-decene was converted faster than 1-hexadecene, the gain in conversion was higher for 1-hexadecene than for 1-decene. For example, when comparing **1** and RAME-β-CD or the 1/1 physical mixture of PNIPAM and RAME-β-CD, a gain of 4 was measured for 1-hexadecene (from 11% to 43% conv.) while it was only 2 for 1-decene (from 43% to 85% conv.).

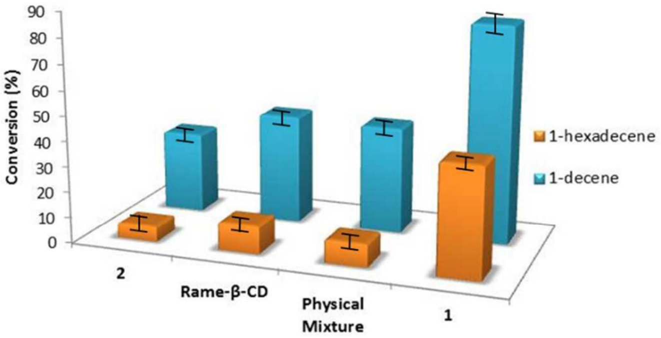


Fig.3 Effect of different additives on the Rh-catalyzed hydroformylation of 1-decene (blue) and 1-hexadecene (orange). Conditions: Rh/TPPTS/additive/substrate (1:5:0.75:140), 80 °C, 50 bar of CO/H_2, 3 h.

The gains were even higher when comparing **1** with the PNIPAM polymer devoid of RAME-β-CD unit thereby clearly indicating the propensity of **1**-based Pickering emulsion to efficiently convert very hydrophobic long alkyl-chain alkenes. As described in Fig. 4 (red curves), the conversion levelled off after 3 h reaction time. Hence, a saturation phenomenon occurred over time as previously described in the literature for silica- and alumina-based Pickering emulsions.[31,32] This saturation of the aqueous/organic interface was an indirect proof of the existence of a Pickering emulsion. Indeed, no saturation of the interface would have been observed if, for example, **1** behaved like a surfactant. To overcome the saturation phenomenon and improve the alkenes conversion, we exploited the thermal reversibility of the LCST transition. By cooling down the autoclave when the conversion leveled off, the interface between the aqueous and the organic compartments was no longer saturated because of the diassembling of the **1**-based particles. Indeed, the thermoresponsive RAME-βCD-end decorated PNIPAM chains were no longer interacting with their congeners and they regained their solubility in water. The Pickering emulsion was then broken and a rapid decantation occurred. Then, reheating the sample allowed the regeneration of **1**-based particles and the restoration of exchanges between both phases. This step-by-step procedure allowed us to greatly improve the conversion in 1-decene and 1-hexadecene. However, while a total conversion of 1-decene was readily obtained after one heat-and-cool, the heat-and-cool sequence should be repeated several times to achieve a full conversion of 1-hexadecene. Only three heat-and cool cycles were considered in Fig. 4 for clarity.

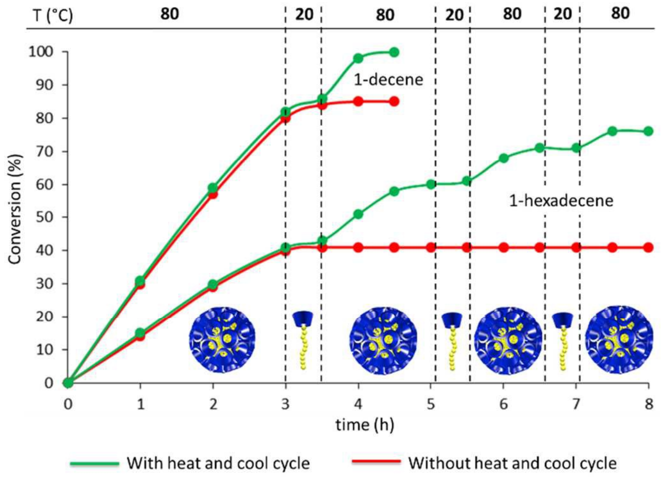


Fig. 4 Step-by-step procedure (heat-and-cool cycle) in Rh-catalyzed hydroformylation of 1-decene and 1-hexadecene. Conditions: 1/5/0.75/140 Rh/TPPTS/additive/substrate mixture, 80 °C, 50 bar of CO/H_2.

The thermoresponsive character of **1** was also exploited to trigger the easy recovery of the product and the catalyst in two different phases. While the decantation of an aqueous biphasic catalytic system could lead to the formation of emulsions when surfactants were used as additive, the current catalytic system allowed for a phase separation within a few seconds by simply cooling down the system. Eventually, the reusability of the catalytic system was successfully examined without any loss of its catalytic activity (ESI). Note that no trace of Rh could be detected in the organic phases after three catalytic tests, thus highlighting the stability of the Rh-catalyst under these experimental conditions.

In summary, we combine the structuring properties of thermoresponsive PNIPAM and the interfacial properties of RAME-β-CD in a single molecular entity to perform the Rh-catalyzed hydroformylation of higher olefins in aqueous media. The catalyst can be recovered once the reaction is complete by disaggregation of the transient Pickering emulsion. This approach provides an effective way to get rid of the mass transfer limitations in aqueous biphasic catalysis.

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