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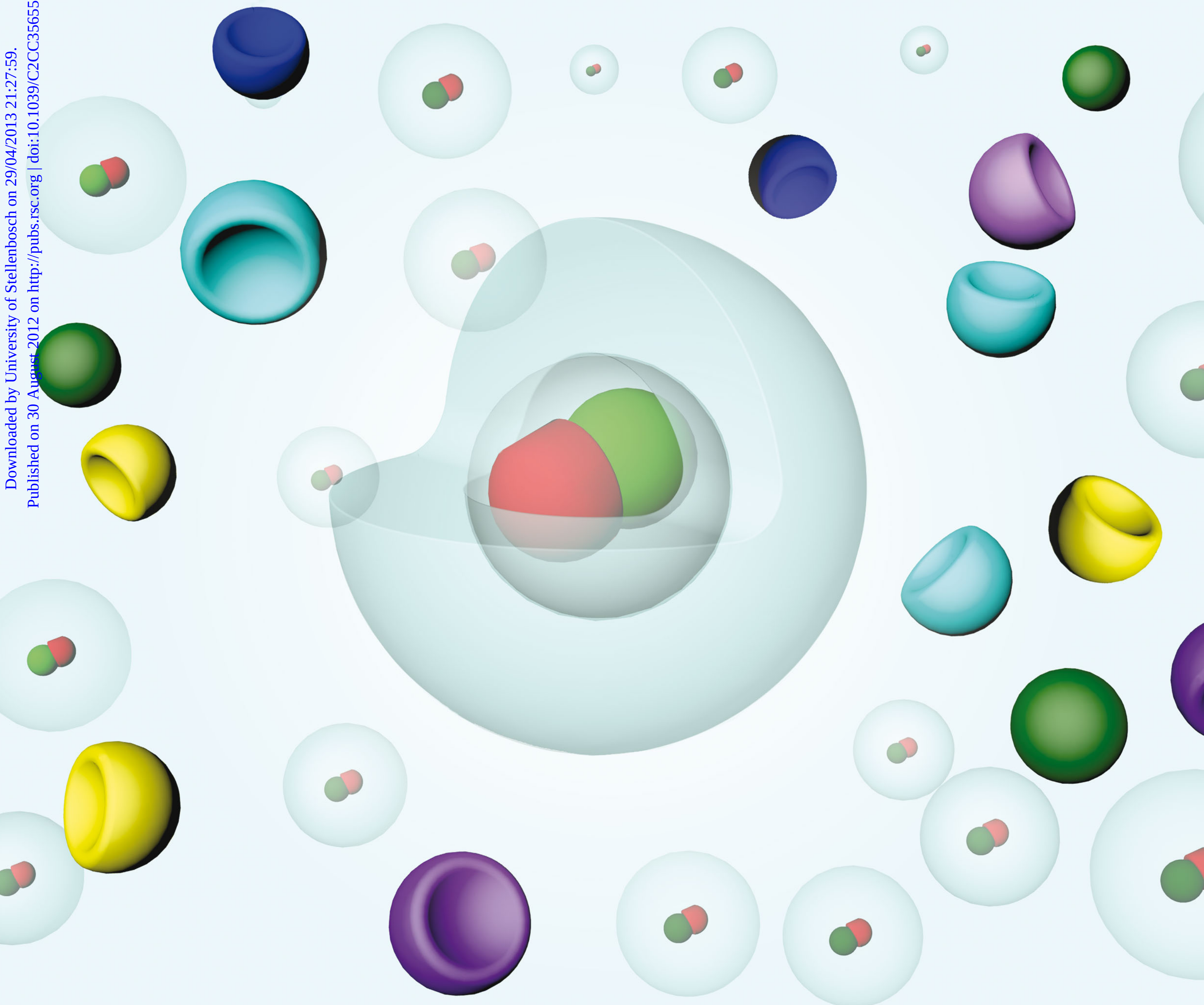

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COMMUNICATION

Molecular recognition driven catalysis using polymeric nanoreactors†

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The concept of using polymeric micelles to catalyze organic reactions in water is presented and compared to surfactant based micelles in the context of molecular recognition. We report for the first time enzyme-like specific catalysis by tethering the catalyst in the well-defined hydrophobic core of a polymeric micelle.

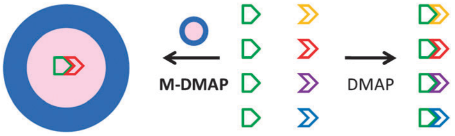
Specific interactions between biological molecules are essential in nature. Most of the chemical reactions in biological cells are catalyzed by enzymes, which act specifically with one substrate based on molecular recognition.[1] The complementarity between the substrates takes into account the shape of the molecules, hydrogen bonding, charges, dispersion forces and hydrophobic interactions. Enzymes generally make use of a compartmentalized hydrophobic cavity surrounded by a hydrophilic outer shell to allow specific catalysis.[2] Inspired by enzymes, several groups have designed a wide range of artificial catalytic systems where the catalyst is isolated from the environment through the use of core–shell structures using dendrimers and polymeric stars,[3] but the cases where these systems allow for efficient catalysis in water are rare.

We and others have studied the use of polymeric micelles in order to catalyze organic reactions in aqueous media through incorporation of a catalyst into the polymeric scaffold.[4] To prepare these materials, functionalized monomers can be covalently incorporated into the hydrophobic domain of a polymeric micelle *via* copolymerization techniques.[5] Advantages of these polymeric systems over the extensively studied surfactants are the possibility of facile catalyst recovery and the unique properties originated by the difference in polarity between the shell domain and the very stable hydrophobic pocket created in the core of polymeric nanoreactors.[6] Due to the kinetically frozen structure of polymeric micelles, the diffusion of the hydrophobic substrates to the stable hydrophobic core of the micelle is improved,[6] showing unprecedented enhancements of the reaction rates, while the water permeability within the core domain is significantly reduced compared to surfactant based micelles.[4e]

Several aqueous catalytic systems using surfactants have been reported to achieve substrate selectivity based on hydrophobicity.[7] However, the use of the unique properties originated by the difference in polarity core–shell in kinetically frozen polymeric nanoreactors is still at an early stage in terms of molecular recognition. A first approach was recently reported by Weck and co-workers for the selective hydrolytic kinetic resolution of epoxides using shell-crosslinked polymeric nanoreactors in water.[4a] Although different reactivities were found for different epoxides based on hydrophobicity, only initial experiments were carried out where a competitive reaction of two different substrates of similar reactivities was explored and overall moderate selectivity was observed.

Unfortunately, enzymatic catalysis is not so simple. Enzymatic reactions are specific rather than selective, distinguishing one single target from a mixture of several substrates of different reactivities; therefore, our challenge is to utilize a catalytic polymeric nanostructure as a yocto-litre reaction vessel, whose molecular recognition properties can be utilized to promote a specific reaction from a pool of reactants (Scheme 1). If the stable polymeric scaffold restricts the permeability such that only the most hydrophobic molecule can fit, specificity will be observed. To demonstrate the synthetic utility that this system affords, we have carried out the competitive reaction of different products using kinetically frozen catalytic nanoreactors in aqueous media. Our results clearly indicate that by tethering the catalyst in a confined hydrophobic environment, specific molecular recognition is achieved in the presence of several substrates and the reactivity can be significantly enhanced compared to that for surfactant based systems.

4-(N,N-dimethylamino)pyridine (DMAP, Scheme 2) is an important nucleophilic catalyst which can be used in a variety of reactions such as esterifications with anhydrides and many more.[8] Unfortunately, this powerful organocatalyst presents high dermal toxicity; hence, its incorporation to a solid support to avoid dissemination is an important target.[4c,9] In order to obtain stable micelles with DMAP functionality locked into the hydrophobic core, a styrenic monomer containing DMAP was synthesized (**sDMAP**) and copolymerized with styrene by RAFT, since styrene-based polymers chain extended with a water soluble



Scheme 1 Illustration of specific reaction of one substrate (from a pool of 4) using a polymeric nanoreactor as a reaction vessel (Green = 1 anhydride; yellow, red, purple and blue = 4 different alcohols).

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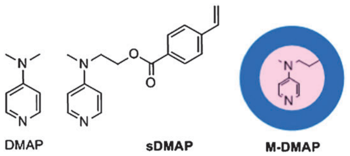


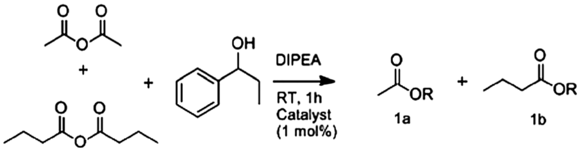
Scheme 2 Schematic representation of the catalysts used.

block are known to form kinetically frozen micelles in water.[10] The DMAP-containing hydrophobic block was chain extended with NIPAM to form a diblock copolymer with a permanently hydrophobic styrenic-DMAP block and a temperature responsive block as previously reported.[4e] The amphiphilic block copolymer was self-assembled in water by solvent switch from acetone. The resulting spherical micelles (**M-DMAP**) were found to be *ca.* 24 nm in diameter, determined by TEM analysis (see ESI†).

The chemical transformations selected for this system were the well-established DMAP-catalyzed acylation of alcohols with acid anhydrides. In homogenous systems this reaction is generally carried out in anhydrous conditions (since the anhydride slowly hydrolyzes upon contact with water) and preferentially in bulk or less-polar solvents to facilitate the recycling of the catalyst.[11] Previous results already prove that **M-DMAP** efficiently catalyzes this type of reactions in aqueous media with high reactivities and outstanding recycling properties and the tethering of the catalyst in the hydrophobic core of the micelle is key to overcome these issues.[4e]

In order to investigate the selective esterification in this system, the competitive reaction between two different anhydrides with 1-phenylpropanol in the presence of auxiliary base was studied (Table 1). When a 1 : 1 mixture of acetic anhydride and butyric anhydride was added to the reaction mixture using unsupported DMAP in neat conditions, 12% less of the ester from the bulkier anhydride **1b** was obtained (**1a**/**1b** = 1.3), probably due to steric effects.‡ On the other hand, when **M-DMAP** was used as a catalyst in aqueous media, the selectivity of the reaction was reversed and **1b** was formed preferentially (**1a**/**1b** = 0.4). As observed by Weck, the increase of the length of the carbon chain resulted in a remarkable increase of its reactivity. Although both reactions reached high conversions, as predicted, this first experiment clearly indicates that just **M-DMAP** exhibits molecular recognition based on hydrophobicity (the more hydrophobic, the more reactive) and independent of steric effects. Similar results were obtained in the competitive acylation of 1-phenyl-1-propanol with acetic and valeric anhydrides (ESI†).

Table 1 Competitive acylation of 1 equivalent of 1-phenyl-1-propanol using 2 different anhydrides (1 : 1 ratio)[a]



Catalyst	% Conversion (**1a** + **1b**)
M-DMAP	83 (22 + 61)
DMAP	92 (52 + 40)
sDMAP[b]	26 (2 + 24)

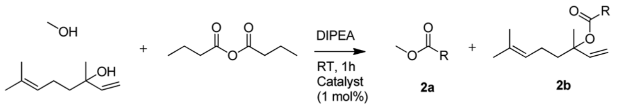
[a] Reaction contained 1 mol% of catalyst, 1 equivalent alcohol, 1.5 equivalents of auxiliary base (DIPEA) and 1.5 equivalents of each anhydride. Conversions determined by HPLC analysis with mesitylene as the internal standard. Calculation of % catalyst is described in the ESI. [b] 10 mg of SDS in 2 mL of nanopure water. R = $CH(C_6H_5)C_2H_5$.

To obtain further data about how the environment created inside the polymeric micelle **M-DMAP** affects selectivity and reaction rates, the same reaction was explored using sodium dodecyl sulfate (SDS) as a surfactant and a modified DMAP with high hydrophobicity (**sDMAP**). Although this new system also shows selectivity based on hydrophobicity, the acylation reaction was more than 3 times slower, achieving just 26% conversion after 1 hour compared to the 83% obtained for the polymeric system **M-DMAP**.

To further explore the selectivity of this system, **M-DMAP** was used in the 1 : 1 competition reaction of linalool and completely water-soluble methanol. Linalool is a compound present in many flowers and plants and its acylated products are commonly used as a scent for hygiene products and cleaning agents.[12] However, ordinary methods of acetylation cannot be used with linalool due to its unreactive nature and its tendency to cyclise upon heating. Despite this, in the case of **M-DMAP**, 60% conversion was reached after 1 hour compared to 2% for DMAP during the same period. Given the reactivity and hydrophilic nature of methanol, it is not surprising that the acylation was complete after 1 hour in the homogeneous system, but no conversion was observed in the nanoreactor, where the unique product formed was the acylated linalool **2b**. This new observation suggests that the encapsulation of the catalyst in the core of a polymeric micelle not only reverses selectivity based on hydrophobicity but facilitates the reaction of otherwise non-reactive alcohols by bringing the substrate in closer proximity to the catalyst. To our knowledge, this is the first example where the selectivity of the reaction is reversed and specificity is achieved by encapsulating the catalyst in a synthetic hydrophobic pocket, facilitating the reaction of otherwise non-reactive substrates while inhibiting the formation of the otherwise most favorable product. On the other hand, when the reaction was carried out in the presence of SDS using **sDMAP** as a catalyst, 40% of the methanol had reacted after 1 hour and only 20% of the product from the less reactive linalool was formed. As hypothesized, these control experiments confirm that the tethering of the catalyst in the hydrophobic core of a kinetically frozen polymeric micelle creates a unique hydrophobic environment able to completely inhibit the reaction of hydrophilic substrates and extraordinary enhance the reactivity of hydrophobic ones compared to that of the less stable surfactant-based systems (Table 2).

As a proof-of-principle that polymeric micelles can act as nano-vessels for specific molecular recognition in the presence of multiple substrates, we investigated how the presence of **M-DMAP** affected the substrate selectivity in a one pot acylation reaction of four different alcohols with similar reactivities. Preliminary experiments showed that, when equimolar amounts of two different alcohols were tested under these conditions, the ratio of products obtained was highly dependent on the hydrophobicity of the alcohols (ESI†). Following these initial experiments, the competitive DMAP-catalyze acylation between four primary alcohols (methanol, allyl alcohol, 1,4-butandiol and 1-decanol) with butyric anhydride in the presence of auxiliary

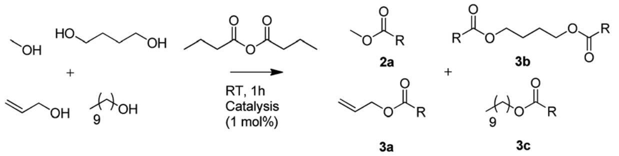
Table 2 Selective acylation of 2 different alcohols (1 : 1 ratio) with butyric anhydride[a]



Catalyst	% Conversion (**2a** + **2b**)
M-DMAP	60 (0 + 60)
DMAP	> 99 (> 99 + 2)
sDMAP[b]	65 (45 + 20)

[a] Reaction contained 1 mol% of catalyst, 1 equivalent of each alcohol, 1.5 equivalents of auxiliary base (DIPEA) and 3 equivalents of anhydride. Conversions determined by GC analysis with mesitylene as the internal standard. Calculation of % catalyst is described in the ESI. [b] 10 mg of SDS in 2 mL of nanopure water. R = $CH_2CH_2CH_3$.

Table 3 Selective acylation of 4 different alcohols with butyric anhydride[a]



Product	Conversion (%)	
	DMAP	**M-DMAP**
2a	> 99	Trace
3a	32	Trace
3b[b]	> 99	Trace
3c	75	> 99

[a] Reactions contained 1 mol% of catalyst, 1 equivalent of each alcohol, 1.5 equivalents of auxiliary base (DIPEA) and 4 equivalents of anhydride. Conversions determined by GC analysis with mesitylene as the internal standard. Calculation of % catalyst is described in the ESI. [b] Mixture of the mono- and di-alkylated products observed. R = $CH_2CH_2CH_3$.

base was studied. Initially a mixture of one equivalent of each alcohol was butyrylated using unsupported DMAP in neat conditions (Table 3). As expected, the conversions obtained for the different alcohols in this case simply depend on their reactivity. The primary alcohols were acylated and only the less reactive allyl alcohol and the bulkier 1-decanol were still present after 1 hour. When the same reaction was tested in the micellar system **M-DMAP**, just the hydrophobic 1-decanol formed the acylated product **3c** quantitatively in the same time. These results highlighting the specific acylation of one alcohol in the presence of several products significantly expand the utility of our organocatalytic nanoreactor.

In conclusion, we have shown that polymeric organocatalytic nanoreactors are not only very efficient supported catalyst for organic species in aqueous media (with all known advantages of these systems) but also show specific substrate recognition able to drastically modify the selectivity of the reactions based on the simple concept of hydrophobicity. Moreover, the hydrophobic core-substrate attraction induced by the unique nature of the polymeric micelle creates a concentrated catalytic environment that allows for the reaction of otherwise non-reactive species, significantly improving the effects observed for surfactant-based systems. This is the first example of polymeric nanoreactor capable of effectively distinguishing from a pool of substrates of similar or different reactivities and where specificity is achieved based on substrate hydrophobicity. We see these results as an initial approach towards enzyme mimics for organic reactions in water.

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Notes and references

‡ In our case, since the mol% catalyst is 1, the values given for percentage of conversion are also the turnover numbers.

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