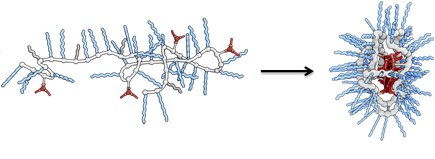
In this project we are exploring the possibility to combine the attractive features of self-assembly with classic polymer chemistry. From this, an exciting new field of chemistry to study emerges namely the field of Single Chain Polymer Nanoparticles (SCPN). The project is dealing with the synthesis of polymer chains that are able collapse into nanoparticles from a supramolecular approach. To the date, collapse of random coil polymer is done through covalent cross-linking of the chain. In our approach, we are first synthesizing copolymers with suitable functionalization. Two different approaches are being followed:

1. Copolymerization of monomers to obtain polymers with the desired functionality.
2. Post funtionalization strategy, in which a given functionality can be attached to the polymer.

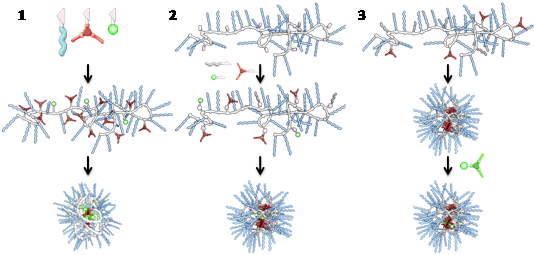
The different supramolecular units attached (*via* the two methodologies described) promote, when triggered, the folding and collapse of a random coil into a well defined nanoparticle (Figure 1). The folding process is being studied with a large variety of techniques such as gel permeation chromatography, several NMR techinques, dynamic light scattering (DLS), ultraviolet (UV) and circular dicroism (CD) spectroscopies and/or atomic force microscopy imaging. Moreover, we are aiming to control the folding process, as Nature does with biomacromolecules, in order to create well defined architectures.



***Figure 1:*** *Cartoon representing the unfolded polymer bearing supramolecular units depicted in red (left) and polymer collapsed into a well defined nanoparticle (right).*

At the same time, we are exploring the potential applications of these new compartmentalized systems. Thus, catalysis is one of the most challenging topics, due to folding promotes the existence of different environments to perform reactions. Inspired by enzymes, which are the ultimate (enantio)selective catalysts, we have prepared polymers with (protected) recognition moieties that can fold on demand when triggered with an external stimulus. By incorporating a catalytically active species in water soluble polymers, and compartmentalizing the system by secondary interactions, such as hydrogen bonding, it is possible to create a well-defined three-dimensional structure with a hydrophobic interior in which catalysis can occur. We have developed different strategies to incorporate catalytically active sites in our system and thus perform catalysis in aqueous media (Figure 2).

* Strategy 1: Copolymerization of catalytically active units.
* Strategy 2: Post-funtionalization of reactive polymers.
* Strategy 3: Incorporation of catalytically active site through supramolecular interactions.



***Figure 2:*** *Cartoon illustrating the strategies developed towards catalytically active SCPN: 1) copolymerization, 2) post-funtionalization and 3) post-incorporation of active site via supramolecular interactions.*

These three different strategies have been successfully employed in the design and synthesis of catalytically active SCPN. Different catalytic systems have been investigated in parallel. We have paid special attention to two different systems:

1. L-Proline functionalized polymers for aldol reaction;
2. Phenyl boronic acid functionalized polymers for catalysis in water and organic solvents.

To the date, L-Proline functionalized polymers bearing benzene-1,3,5-ticarboxamide (BTA) as recognition units has been synthesized *via* copolymerization strategy (Strategy 1). The folding of these catalytically active polymers has been thoroughly studied using techniques such as circular dichroism (CD), ultraviolet (UV), dynamic light scattering (DLS), gel permeation chromatography (GPC), nuclear magnetic resonance (NMR) among others. Besides, the catalytic activity has been tested against the aldol reaction in aqueous environment. These new compartmentalized systems exhibit a remarkable activity in water, resembling to that found in natural enzymes: in both cases activity is only expressed in the folded state. However, due to the *randomicity* of these polymers, full control over L-Pro positioning is not achieved. The diastero- and enantioselectivity observed in the aldol reaction is moderate as a result of the different environments surrounding the catalytic sites. In order to gain control over catalyst positioning we attached a proline unit to a BTA scaffold (L-Pro-BTA). The BTAs in the polymer chain can recognize and incorporate the L-Pro-BTA in the stack (Strategy 3). In this way we gained control over the selectivity of the aldol reaction, with *ee* ranging 97-98% and *de* 90-94%.

On the other hand, boronic acid derivatives are known to catalyze a wide number of reactions. Polymers bearing phenyl boronic acid derivatives as catalytic unit and BTA as supramolecular structuring unit were synthesized using either strategies 1 or 2. The folding of these polymers was studied in organic solvents and in water. In one of the cases, very high activities towards direct amidation reaction, *i.e.* the reaction between a carboxylic acid and an amine, were found in organic solvent (tetrachloroethane). A water soluble version of this polymer displayed no activity towards the same reaction in water. However, this polymer showed to be active towards Diels-Alder reactions in water using acrylic acid as dienophile. We are currently working on different versions of this polymer with the final goal of catalyzing direct amidation reaction in water.

These new compartmentalized systems in which the catalytic site is isolated into a hydrophobic cavity are very promising to perform cascade reactions.