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# Synthesis of functional polymers by flow processes

Tesi di laurea sperimentale

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…Questa vita è bellissima

Anche se a volte ci tira giù

Qualcosa ci tira giù

E che Bologna è una regola

Che hai provato a spiegarmi tu

Non lo dimentico più…

(Luca Carboni)

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# 1. Introduction.

## 1.1 Flow Chemistry and Functional Polymers tools from Green Chemistry: a brief introduction

The "Green Chemistry" is a term recently coined to highlight a new trend in chemistry. For the US Environmental Protection Agency (EPA), Green Chemistry should *promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substance in the design, manufacture and use of chemical products*".[1] This concept is based on series of principles defined by Paul Anastas and John Warner, the following list outlines an early conception of what would make a greener chemical, process, or product (Box 1).[2]

**1. Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.

**2. Atom Economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

**3. Less Hazardous Chemical Syntheses:** Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

**4. Designing Safer Chemicals:** Chemical products should be designed to affect their desired function while minimizing their toxicity.

**5. Safer Solvents and Auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

**6. Design for Energy Efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

**7. Use of Renewable Feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

**8. Reduce Derivatives:** Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

**9. Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

**10. Design for Degradation:** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the

1 P. T. Anastas, J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
2 a) I. Horvath, P. T. Anastas *Chem. Rev*., **2007**, *107*, 2167; b) P. Anastas, N. Eghbali, *Chem. Soc. Rev*., **2010**, *39*, 301.

environment.

**11. Real-time analysis for Pollution Prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

**12. Inherently Safer Chemistry for Accident Prevention**: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

**Box 1** The 12 principles of Green Chemistry

Thus, a new Green Chemistry Process should be one that is able to provide a given chemical product with chemical efficiency and economic viability but, at the same time, produces less waste, less energy consumption, with less risks associated to it and generating and handling less toxic compounds than classical, known processes.

A factor that can contribute to implement the sustainability of a chemical transformation is the substitution of batch processes by flow processes.[3] Advantages associated to flow systems include the improvement in mass and heat transfer, a significant intensification of the process, making available systems working 24 h a day, 7 days a week, or their easier optimization through the adjustments of simple parameters such as flow, pressure or temperature. Additionally, the scale-up of flow processes is generally more easily attainable than for batch processes, via different approaches such as the scale-out or the number-up. Although the advantages of flow chemistry were soon realized by the bulk chemistry industry, the situation is quite different in the Fine Chemicals or Pharmaceutical industries. Most industrial petrochemical processes, and others for the preparation of bulk chemicals, are carried out in flow, but batch processes still dominate in other industrial areas, and a high pressure is currently being exerted to introduce flow processes there. In fact, the last years have seen the blossoming of new developments in the field of the application of flow processes in complex organic syntheses.[4] Nevertheless, the application of those approaches to asymmetric synthesis has been, up to date, much more limited.[5] Two main methodologies can be considered in this regard. The first one involves the use of microreactor technologies with the use of

3 S. V. Luis, E. Garcia-Verdugo, *Chemical Reactions and Processes under Flow Conditions*, RSC, Green Chemistry Series, 2009.

4 a) F. Venturoni, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem*., **2010**, *8*, 1798. b) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun*., **2010**, *46*, 2450. c) I. R. Baxendale, S. C. Schou, J. Sedelmeier, S. V. Ley, *Chem. Eur. J*. **2010**, *16*, 89. d) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed*. **2009**, *48*, 4017.

5 X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem*. **2009**, 5, No. 19. doi:10.3762/bjoc.5.19

either homogeneous or supported systems.[6] The second one is based in the use of what can be called mini-reactors, with dimensions being an order of scale larger than the microreactors.

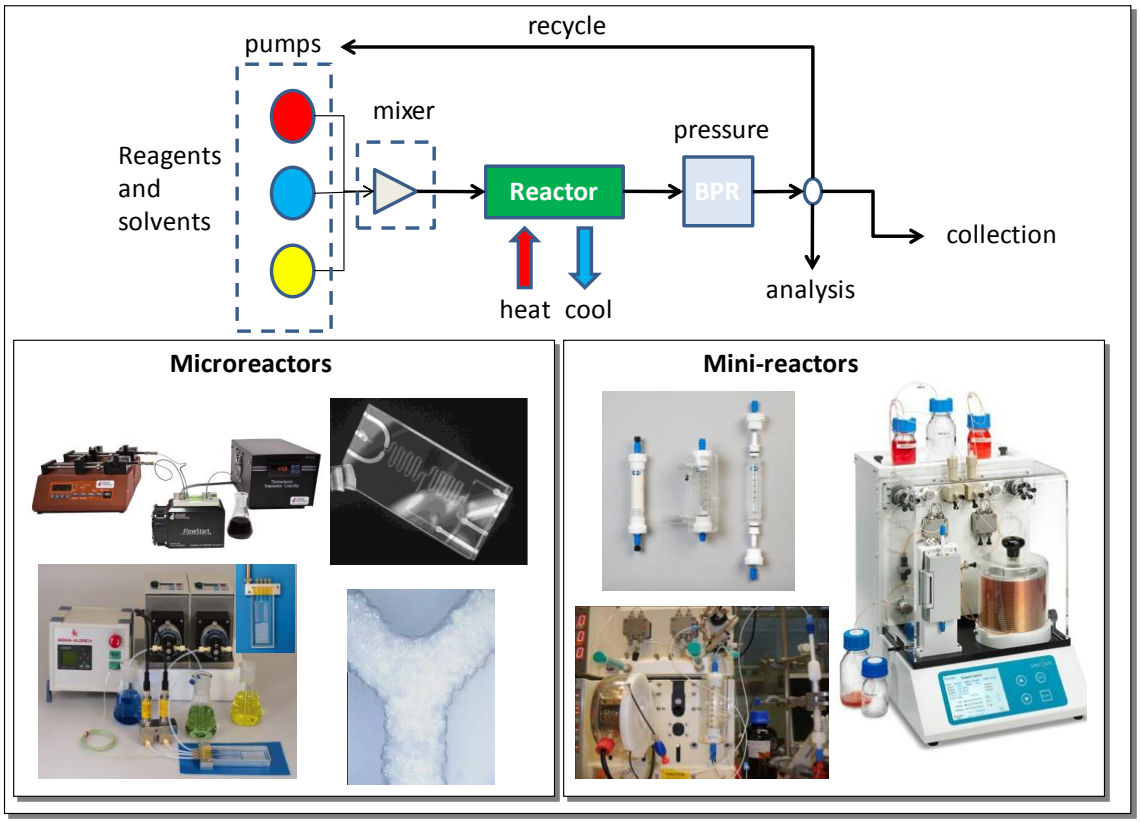



**Figure 1.** General scheme of the experimental set-up for continuous flow processes using either micro reactors or mini reactors for the catalyst immobilisation (from ref. 3).

In order to satisfy green chemistry requirements, another important aspect is catalysis. In a chemical reaction, the catalyst's presence improves the selectivity of the product so it is not necessarily a long and expensive separating process. Using a catalyst, the reaction can carries out without need of reagents in excess, consequently the amount of waste produced is reduced. The catalyst allows to perform reactions at lower temperature and pressure. In this way, a catalytic process reduces the hazard and contribute substantially to safe energy.

In this context, the use of functional polymers in organic synthesis is playing a very fundamental role. The immobilization of functional moieties into a solid support, here we will concentrate on polymeric supports, capable of acting as reagents, scavengers or catalysts produces some important advantages related to this issue. First of all, the use of a reagent or catalyst anchored to a phase that is different from the one containing the substrates and products greatly facilitates the separation and

6 a) K. Tanaka, K. Fukase, *Org. Process Res. Dev.*, **2009**, *13*, 983. b) R. L. Hartman, K. F. Jensen, *Lab Chip*, **2009,** *9*, 2495 c) K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett*, **2009**, 2382**.** d) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434.

work-up protocols, leading to increases in yields and important savings in solvents, energy and labor-time. The same factors also make easier the reuse and recycling of the spent supported reagents and catalysts, a key issue for sustainability. Moreover, immobilization of toxic or volatile compounds on a solid matrix will significantly reduce the hazards and "inconveniences" derived from their use.[7]

Many different types of insoluble matrices have been used for the immobilization of supported reagents or catalysts. Specific advantages have been claimed for each individual support, but those, necessarily, need always to be explicitly evaluated for each single application. In the case of insoluble organic polymers, those that are of interest for this project, materials derived from many different monomeric compositions have been studied (Figure 2), but the use of polystyrene based polymers has clearly dominated.

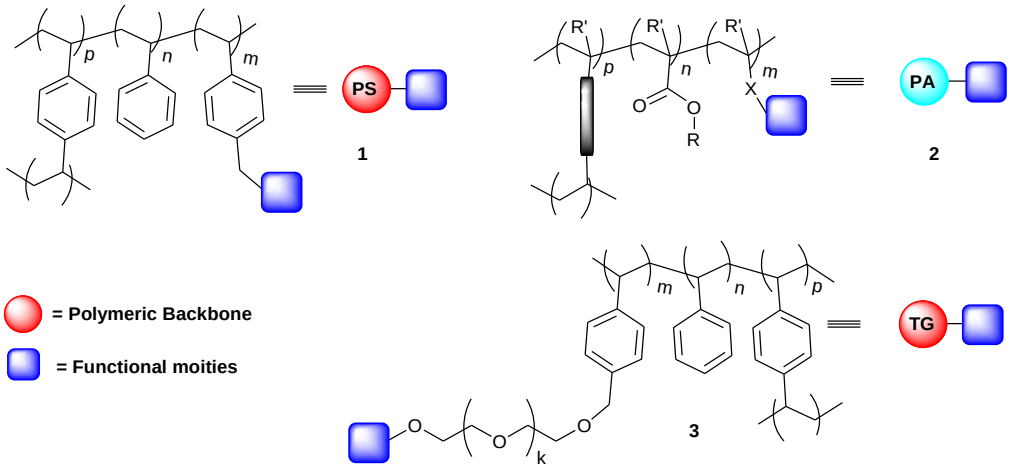



**Figure 2**. General structures of some common functional polymeric matrices.

This is based in two fundamental factors. First, on the easy functionalization of the polymeric matrix taking advantage of the chemical reactivity of the aromatic rings derived from styrene (or divinylbenzene).[8] Secondly, the "inert" chemical nature of the rest of the matrix, as the absence of any other organic functionality reduces the potential interferences for the chemical transformation to be carried out.[9]

The term "functional polymer" indicates a polymer whose polymeric backbone is modified in order to introduce new functional motives, which may act as catalytic sites. The introduction of these functional moieties can carry out, mainly, by two different approaches: i) Grafting: this process

7 A.P. Kybett, D.C. Sherrington, *Supported Catalysts and their Applications*, The Royal Society of Chemistry, Oxford, 2001.
8 D. Obrecht, J. M. Villalgordo, *Combinatorial and Parallel Synthesis of Small-Molecular-weight Compound Libraries*, Elsevier Science Ltd, Oxford UK, 1998.

consist in the chemical modification of a polymer already formed; ii) Polymerization of a monomer, which already contained in its structure the required functionality, with additional commercial monomers to provide the corresponding functionalized polymer.

The first one is the most widely used approach, since the resins are commercially available. The grafting protocols are chosen according to the polymer structure. For instance, resins of polystyrene-di-vinyl-benzene polymers (PS-DVD) allow an easy functionalization of the aryl groups by nucleophilic substitution. Chloromethylated polymers, known as Merrifield resins, are usually prepared through a Friedel-Crafts alkylation by reaction of the resin with chloromethylmethylether in the presence of a Lewis acid, like $SnCl_4$.[10] Nevertheless, the high carcinogenicity of this reagents has led to the development of different methodologies as the use of paraformaldehyde, $MeSiCl_3$ and $SnCl_4$.[11] After that, multiple reactions can be carried out to obtain a variety of functionalized resins.[12]

## 2. Objectives.

The main objectives of this work are to design and build ***a new synthetic technology platform*** that will allow us to design and produce functional polymers adapting to the needs and technologies of the XXI century and to design a new modifications of functional polymer obtained by plug-play flow to use in many applications.

The specific research objectives are the following:

**RO.1.** ***Synthesis and characterization of a polymeric system allowing the development functional materials by post-modification procedures.*** This polymeric system will be based on the soluble liner poly-(acrylamide-thiolactone) (Figure 3). This polymer will provide polymeric scaffold to build-up the hierarchic functional polymers by post-modification procedures. Thus, the aminolysis of the thiolactone with an amine will introduce the first level of substitution (Figure 3 in pink), while the second level of functionality will be introduced by thiol-ene reaction of the thiol generated in-situ by the aminolysis reaction (Figure 3 in blue). The high flexibility of the click reaction considered will allow to obtain a large variety of functional polymeric structures, in many cases through the synthetic manipulation of a reduced number of common simple intermediates that

9 B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral, A. J. Royo, M. J. Vicent, *Tetrahedron: Asymmetry,* **1997**, *8*, 2561.
10 K. W. Pepper, H. M. Paisley, M. A. Young,. *J. Chem. Soc.* **1953**, 4097.
11 S. Itsuno, K. Ito, *J. Org. Chem.* **1990,** *55*, 3950.
12 The Power of Functional Resins in Organic Synthesis, Editors: F. Albericio and J. Tulla-Puche, **2008**, Wiley ISBN: 978-3-527-62618-2

could be obtained even in large scale. The high modularity of the approach offer multiple possibilities, according to the required needs, to introduce chiral elements (catalyst), hydrophobic/hydrophilic residues, additional functional groups, ligands, etc. or even cross-linking units (Figure 3 in green). Commercial available cross-linkers have been used. The variation of the relative proportions of the above mentioned elements and modification conditions will define not only the fuctionalisation but also the morphological and mechanical properties of the resulting polymeric beads materials. (Figure 3).

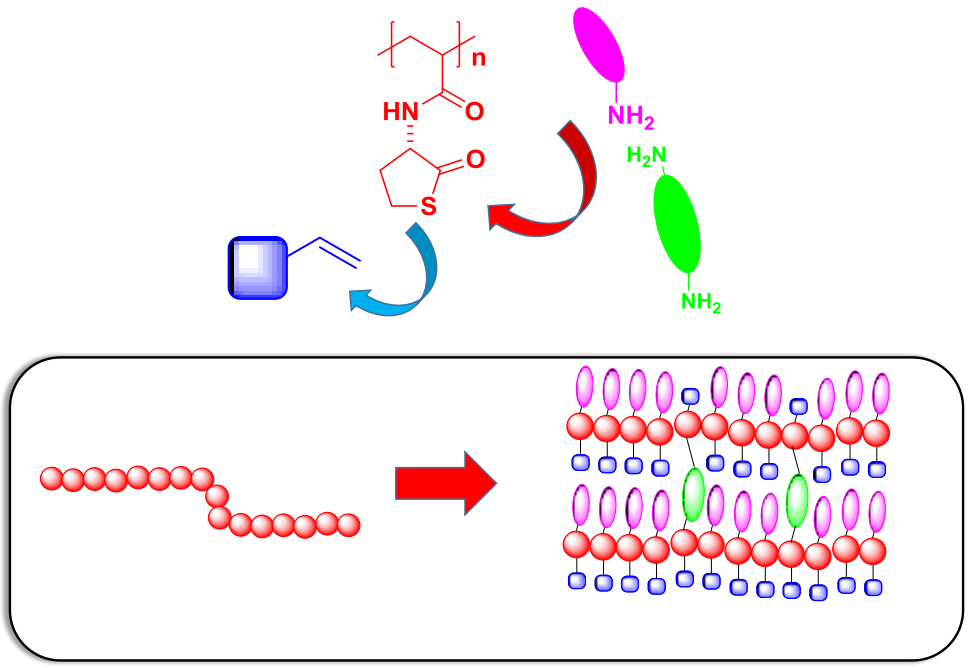



**Figure 3.** Modification with poly(acrylamide-thiolactone) by aminolysis with an amine (in pink) and click thio-ene reaction with a vinyl derivative (in blue). The polymers can be crosslinked for instance in presence of di-alkyl-amine (in green).

**RO.2.** ***Design and build a modular plug-play flow platform able to control reaction parameters required for the assembly and synthesis of the functional polymers in a highly controlled fashion enabling fast screening and simple scale-up of these types of materials.*** Recognizing the high versatility of the synthetic methodology here proposed, it has endeavored to adopt a machine assisted approach to more efficiently screening the different possibilities in the preparation of new functional polymers derived from poly(acrylamide-thiolactone) with complex architectures. A liquid–liquid multiphase flow synthesis will be targeted for the synthesis of crosslinked functional materials based on poly(acrylamide-thiolactone). This task of this project consists of the development of this modular flow platform. It will allow to perform the assembly and preparation of the functional polymers with regular and tailored sizes morphologies at macroscopic level in a highly controlled fashion and much faster than in traditional batch systems. The development of a platform where the reaction conditions will be modified in a rapid, facile and highly controlled

fashion will underpin the rest of the project. The platform will be divided in three main components: pumps, droplet generator, and reactor (Figure 4).

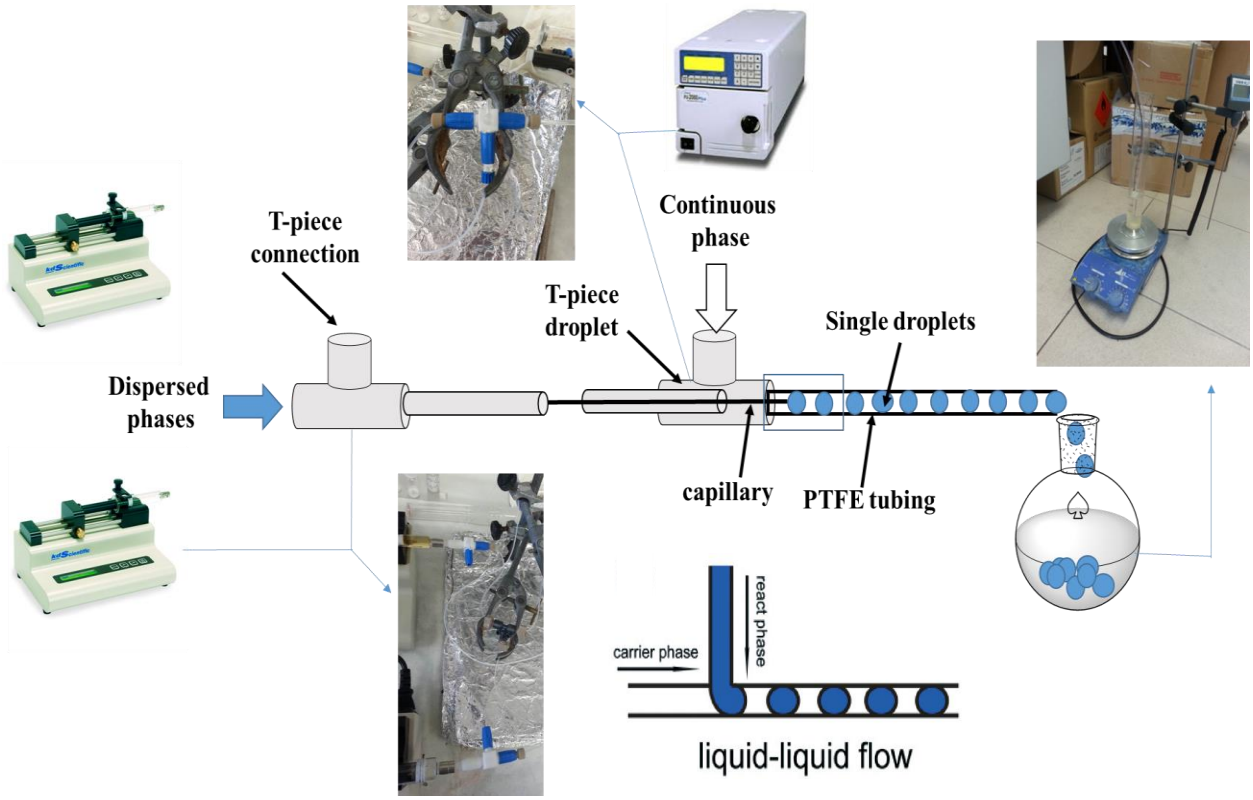



**Figure 4.** Schematic representation of the Modular plug-play flow platform for the synthesis of functional polymers

**RO.3.** ***Synthesis and characterization of different functional polymer materials using flow platform developed in the object RO.2.*** The optimal parameters (concentration, crosslinking, flow rates, type of mixing, residence time, etc.) will be established in order to achieve reproducible conditions for the preparation of functional polymers.

**RO.4.** ***Post-modification of the polymer obtained by the flow platform to introduce additional functionalization degree.*** The presence of the thiol group in the polymer allow the introduction of additional functionality, different type of functional sites will be introduce.

**RO.5.** ***Evaluation of some of the functionalized systems as catalysis.*** The polymers prepared will be evaluated as catalyst for model reaction already developed in the group.

# 3. Results and Discussion

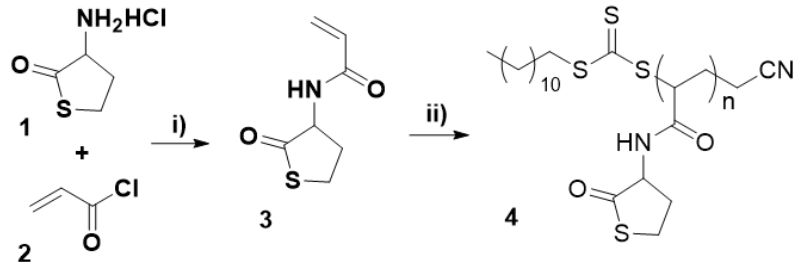
## 3.1 Synthesis of Poly(acrylamide-homocysteine thiolactone) by RAFT homopolymerisation

One of the most remarkable advantages of functional polymers is their potential for displaying a large level of chemical and structural diversity and, hence, physico-chemical characteristics. In the context of the objectives of this project is the development of synthetic strategies able to introduce a certain degree of orthogonality on their design of functional polymers. This will simultaneously allow introducing structural elements defining the morphology and physico-chemical properties of the polymers along with others targeting a specific function. For this purpose, we envisioned an extensive use of the so-called "***Click" chemistry***.[13] In particular, we have selected the thiol–alkene/alkyne reactions. The high flexibility of the click reaction considered will allow obtaining a large variety of functional polymeric structures, in many cases through the synthetic manipulation of a reduced number of common simple intermediates that could be obtained even in large scale. The high modularity of the approach offer multiple possibilities, according to the required needs, to introduce chiral elements (catalyst), hydrophobic/hydrophilic restudies, additional functional groups, ligands, etc. This design will help to define multi-functional hierarchically-ordered built around the catalytic motif and modulate its catalytic efficiency for a given application.

In order to achieve these goals we selected Poly(acrylamide-homocysteine thiolactone) (PAHT, **4**) as basic polymeric building block. The thiolactone groups of these polymer enables its simple post-modification through aminolysis reaction with a wide range of amines and the subsequent modification of the thiols groups generated in-situ by the ring opening of the thiolactone thiol–alkene/alkyne reactions. Thus, starting from the same initial polymer a wide variety of functional polymers can be design and synthetize.

To achieve the preparation of **4**, the monomer (**3**) (*N*-thiolactone acrylamide) was prepared in multigram scale by reacting acryloylchloride (**2**) with D,L-homocysteine thiolactone hydrocloride (**1**). (Sheme 1).[14]

13 A. B. Lowe, *Polym. Chem*. **2014**, 5, 4820.
14 S. Reinicke, P. Espeel, M. M. Stamenović and F. E. Du Prez, *ACS Macro Lett*., 2013, **2**, 539.




**Scheme 1.** Synthesis of the homopolymer PAHT (4) from D,L-homocysteine thiolactone hydrocloride. i) $NaHCO_3$ (5 equiv.) $H_2O$/dioxane (1/1) r.t., overnight. ii) AIBN, DMF, CMDTTC, 110°C, 24 h.

Monomer **3** was isolated in a > 90 % yield and was characterized by $^1$H-NMR. The spectrum showed the characteristic peaks expected for monomer **3**. Figure 5 shows the assignment of the different protons of the product isolated after the work-up processes.

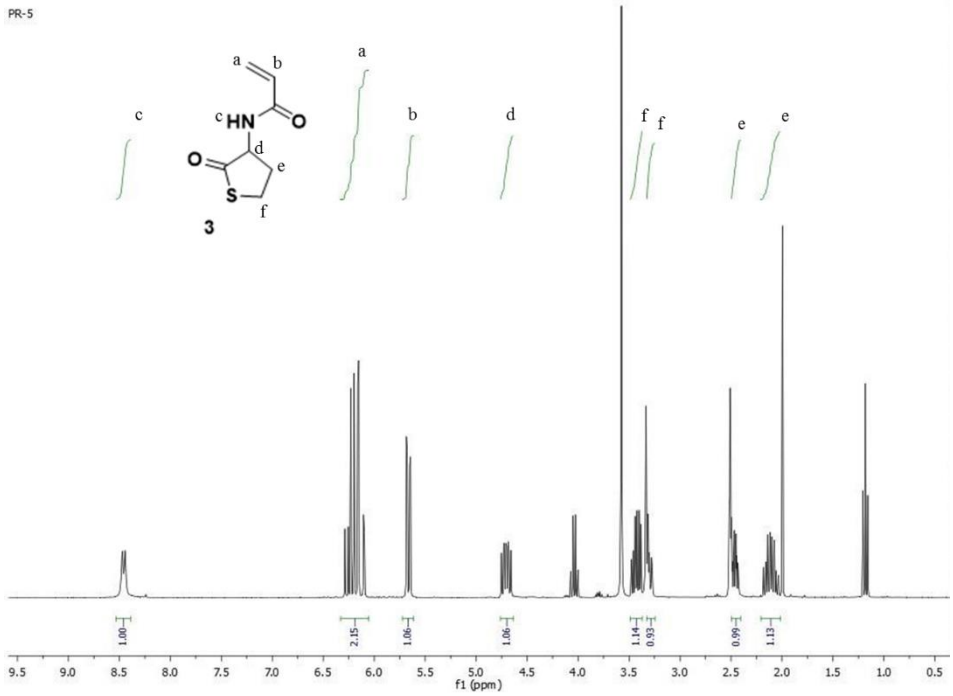



**Figure 5.** $^1$H-NMR of monomer **3**.

The polymerization of the monomer **3** was performed by RAFT polymerization in DMF as solvent using cyanomethyl dodecyl trithiocarbonate (CMDTTC) as CTA and AIBN ($[M]_0$/[CTA]/[AIBN] = 100/0.67/0.06 (Scheme 1). An appreciable increase on the viscosity of the reaction solution was observed during the polymerization process as well as a complete absence of any precipitate. After 24 hours, the $^1$H-NMR spectrum of the reaction crude confirmed that the polymerization had taken place with a monomer conversion higher than 95%. The polymer formed was precipitated with cold methanol, purified by re-precipitation from DMF with methanol and finally washed with diethyl ether to afford a solid (85 % yield by weight). The resulting polymer **4**, dissolved in DMF (8

mg/mL) containing 0.1% (w/w) of LiBr, was analysed by size exclusion chromatography (SEC) showing a molecular weight (Mn) of 20.7 kg/mol and a polydispersity (PDI) of 1.582. It is worth mentioning that this is the first time, to the best of our knowledge, that the polymerisation of **3** can be achieve through a RAFT process to yield to the corresponding homopolymer (**4**).

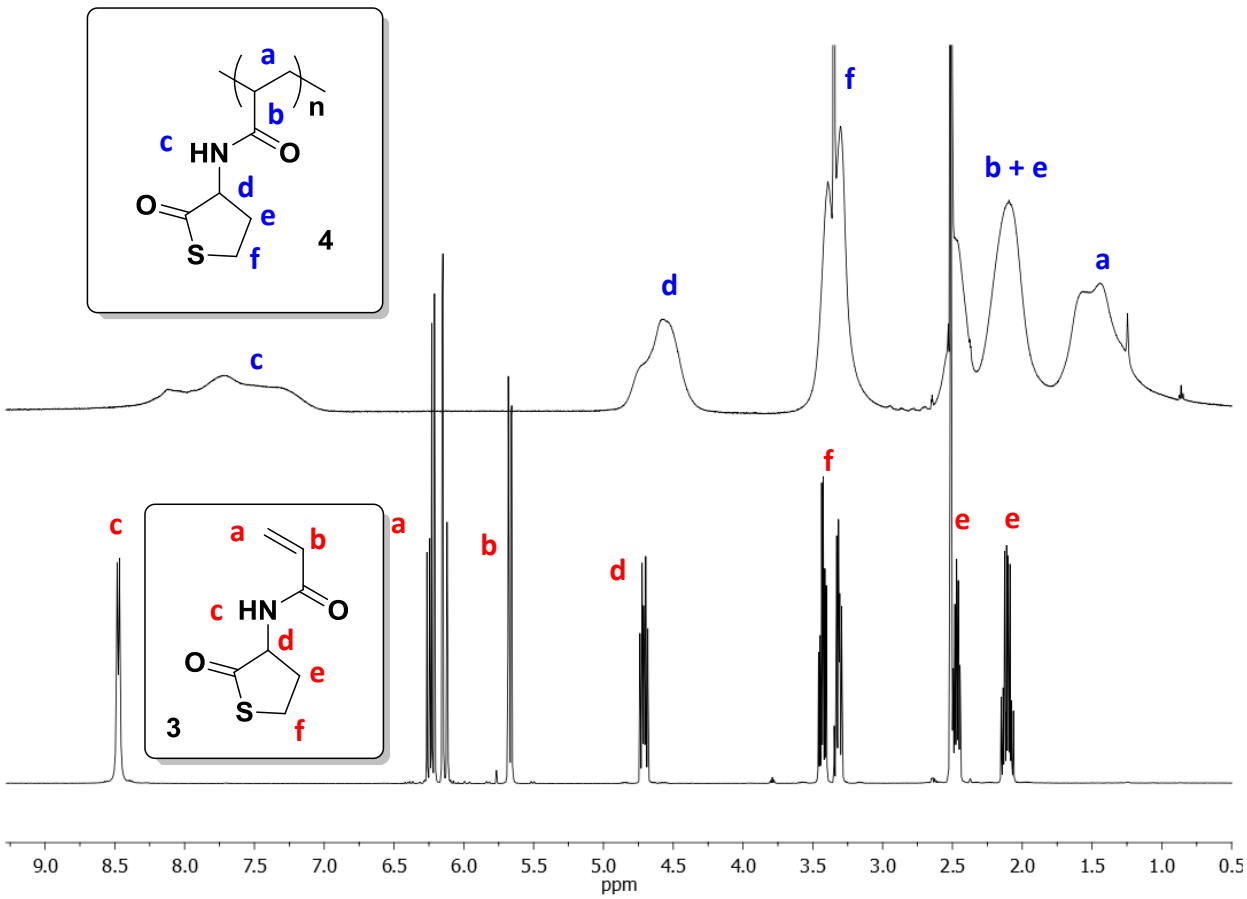



**Figure 6.** $^{1}$H-NMR Comparison between the monomer **3** and the homopolymer **4**

The $^{1}$H-NMR spectrum of the polymer **4** is presented in Figure 6. The characteristics bands of the amino-thiolactone can be observed as broad signals at 4.8-4.4, 3.4-3.3, 2.5 and 2.0 ppm. Besides, a new broad signal at 1.5 ppm from the aliphatic protons of the main chain is also present. The homopolymer **4** was also characterised by TGA and DSC. Two mass losses are observable on the TGA curve (Figure 7a). The first one (4.8 %) occurs from 50 to 120 °C and can be attributed to residual solvent loss. The second one takes place from 260 to 585 °C and corresponds to polymer decomposition. The curve has a well-defined S-shape, without any additional curvature, suggesting the absence of intermediate decomposition steps, being the polymer thermally stable up to 260 °C. On the other hand, the DSC presents a single glass transition at 195 °C (Figure 7b).

Once obtained a simple and reliable methodology for the multigram preparation of the homopolymer **4**, efforts focused on the evaluation of different methodologies for its post-functionalisation using a continuous flow platform.

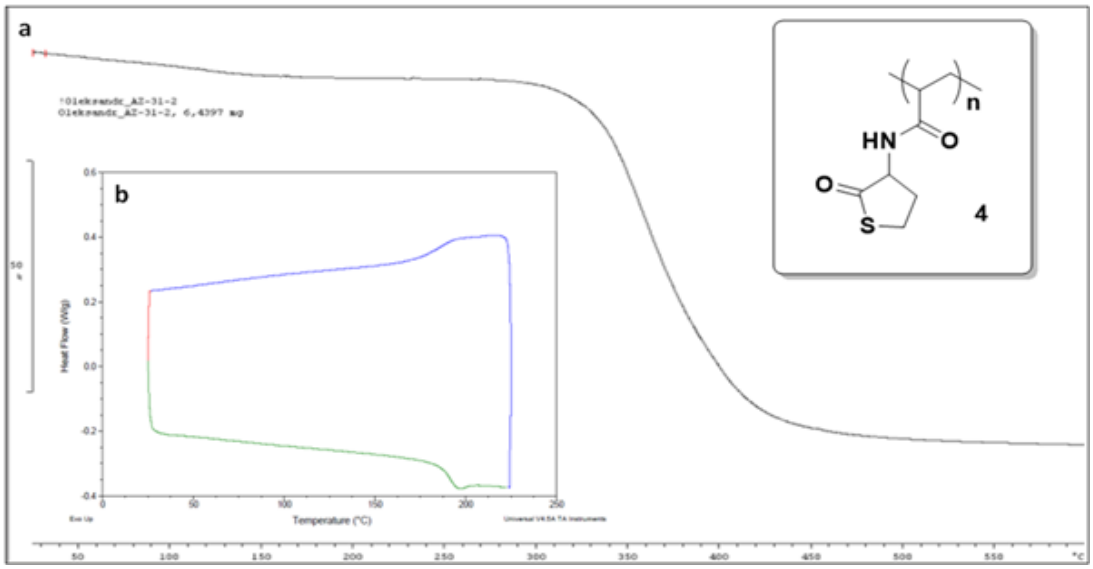



**Figure 7.** a: TGA obtained from 25 to 600 °C for 4. b: DSC obtained for 4 between 25 and 200 °C (1st cycle heating cooling)

## 3.2 Design and build a modular plug-play flow platform for synthesis of functional PAHT.

Since 1990s, a large amount of research efforts has been devoted to microfluidic synthesis of materials.[15] In particular, continuous-flow fluidic systems, in contrast to conventional batch systems, are widely studied. These systems can provide a precise control reaction conditions including rapid heat and mass transfer, high mixing efficacy, large reaction interfaces, and compatibility with online analysis. In particular, droplet-based microfluids are suitable technology for the preparation of polymeric beads materials. Taking into the account these antecedents, the first goal of this work was to build-up a plug-and-play system enabling the synthesis functional polymers under continuous flow conditions.

The reactor design in our case was based on preparation of a needle like droplets generator. The droplet generator can be built using a PTFE body three way connector valve, which was drilled to accommodate a stainless-steal cannula (43 mm length and 0.5 mm OD) through the three way connector valve. This simple device will be able, in principle, to produce drops when two immiscible flows will meet at the outlet of needle using an oil-oil approach (Figure. 8). The two solutions able to produce the droplets are pumped with two different pumps. A syringe pump was selected for the solution containing the polymer, while the second oil required for the droplet formation was pumped using a HPLC pump. This type of pump allows the use of a wide range of

15 J. Ma, S. Ming-Yuen Lee, C. Yi, C.-W. Li, *Lab Chip*, **2017**, 17, 209.

flow rates, which is one of the key parameters in the formation of stable and well-formed droplets. All the pumps and elements used were connected using a PTFE tubing of 1/8 inch.

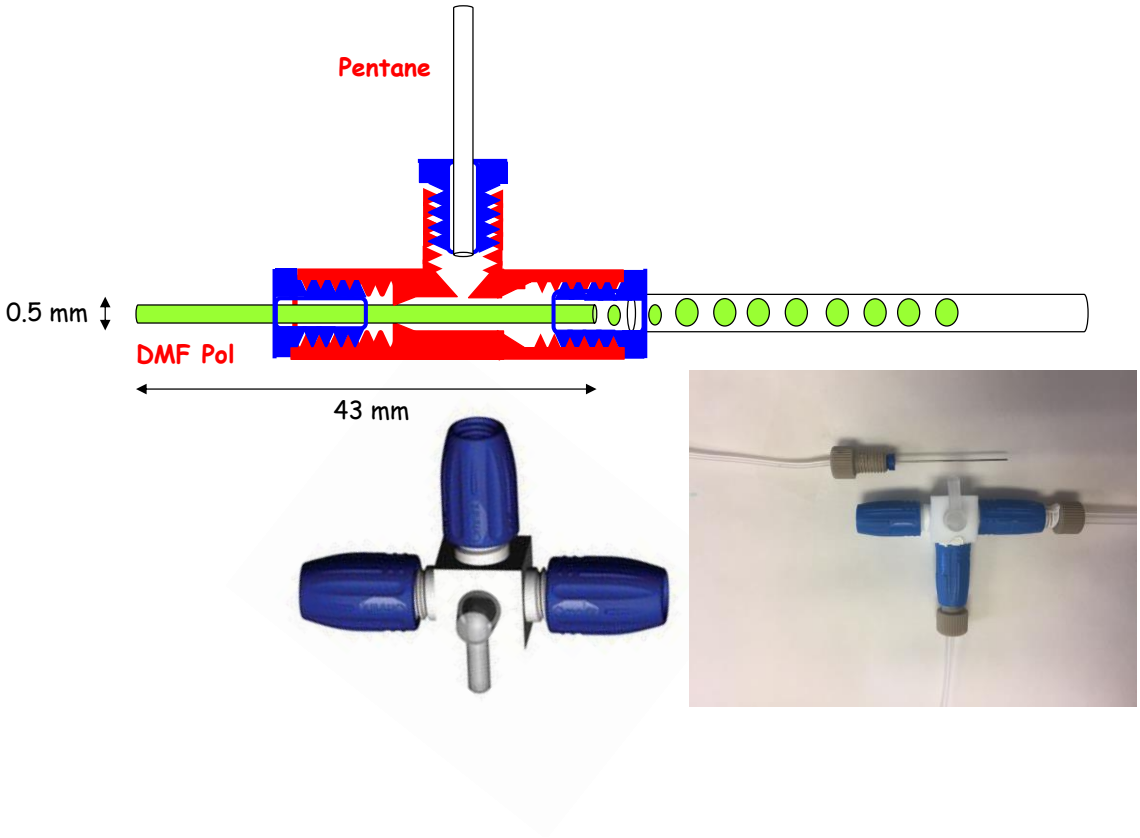



**Figure 8.** Droplet generator build-up using a modified three-way connector valve from Onmifit

In order to test the suitability of the device to produce drops, DMF colored with a dye (malachite green) is pumped through the device, while a second stream of pentane is pumped to produce the droplets. The two immiscible fluids (DMF and pentane) meet at the exit of the needle breaking up into droplets of DMF (blue) dispensed in a surrounding immiscible fluid (pentane). Figure 9 shows the droplets generated using a flow rate of 0.075 mL/min of DMF and 5 mL/min of pentane. In all the cases, together with the formation of the droplet, the generation of a gas, in this case air, slug was observed. The droplet generator is connected to a PTFE tube (678 cm of length and 0.16 cm ID) corresponding with a volume 13.62 mL, to provide the required residence time for the modification of the polymer to take place leading to the corresponding functionalized materials. Figure 9 shows how the droplets generated in the system are stable in this unit not showing any appreciable sign of collapse albeit of the long residence time.

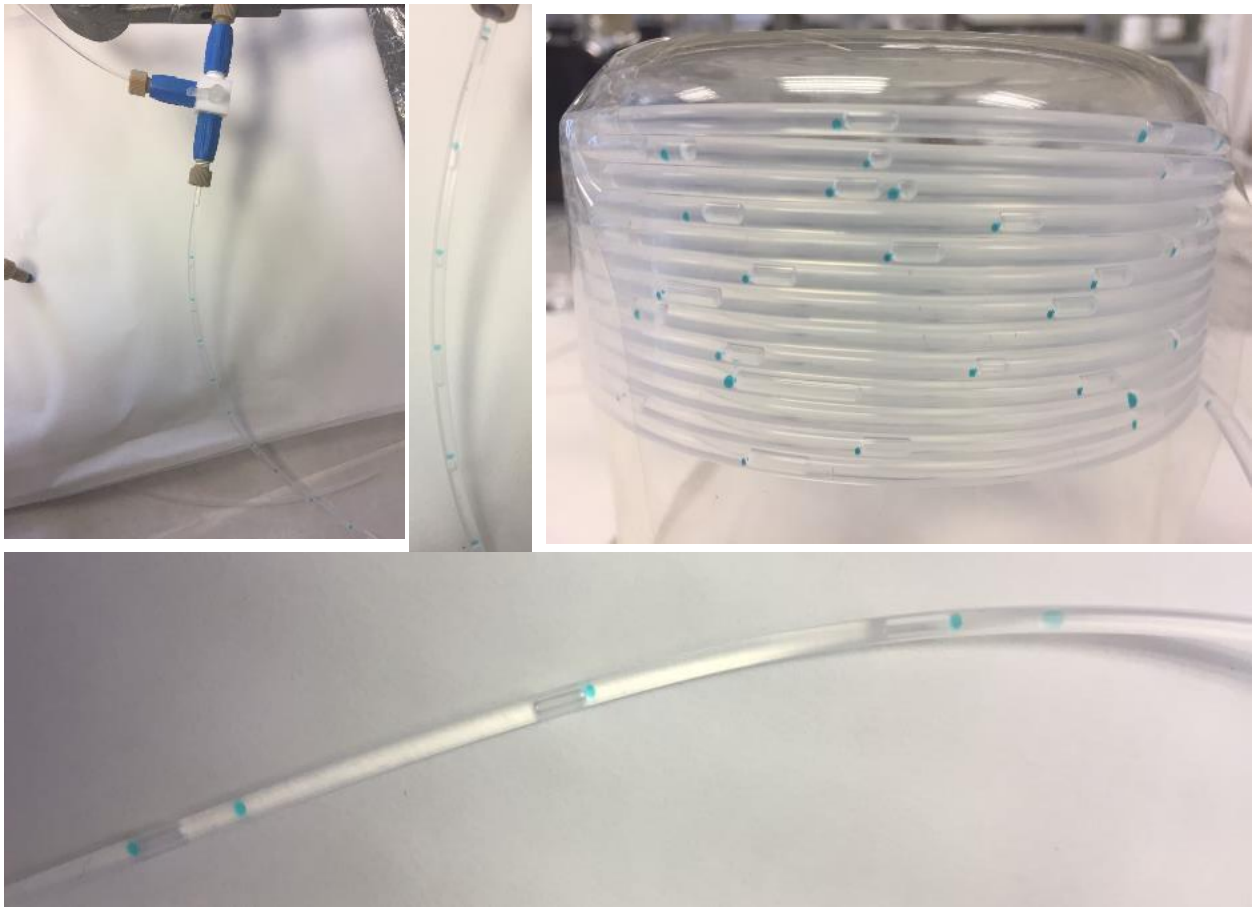


**Figure 9.** Droplets generated by the system using a flow rate of 0.075 mL/min of the DMF and 5 mL/min of pentane. DMF dye with malachite green.

In summary, the general scheme of the reactor contains two syringe pumps for feeding independently the polymer solution and the modifiers solution to functionalize the polymer (a in Figure 10). These two solutions prepared in DMF are mixed in a T-piece (b in Figure 10). A third pump (HPLC pump, c in Figure 10) is used to pump the oil (pentane) to generate the droplets in the droplet generator (d in Figure 10) where it meets the solution with the polymer and the modifiers in DMF. Finally a residence unit (reactor, e in Figure 10) is added at the exit of the droplets generator to provide require residence time.

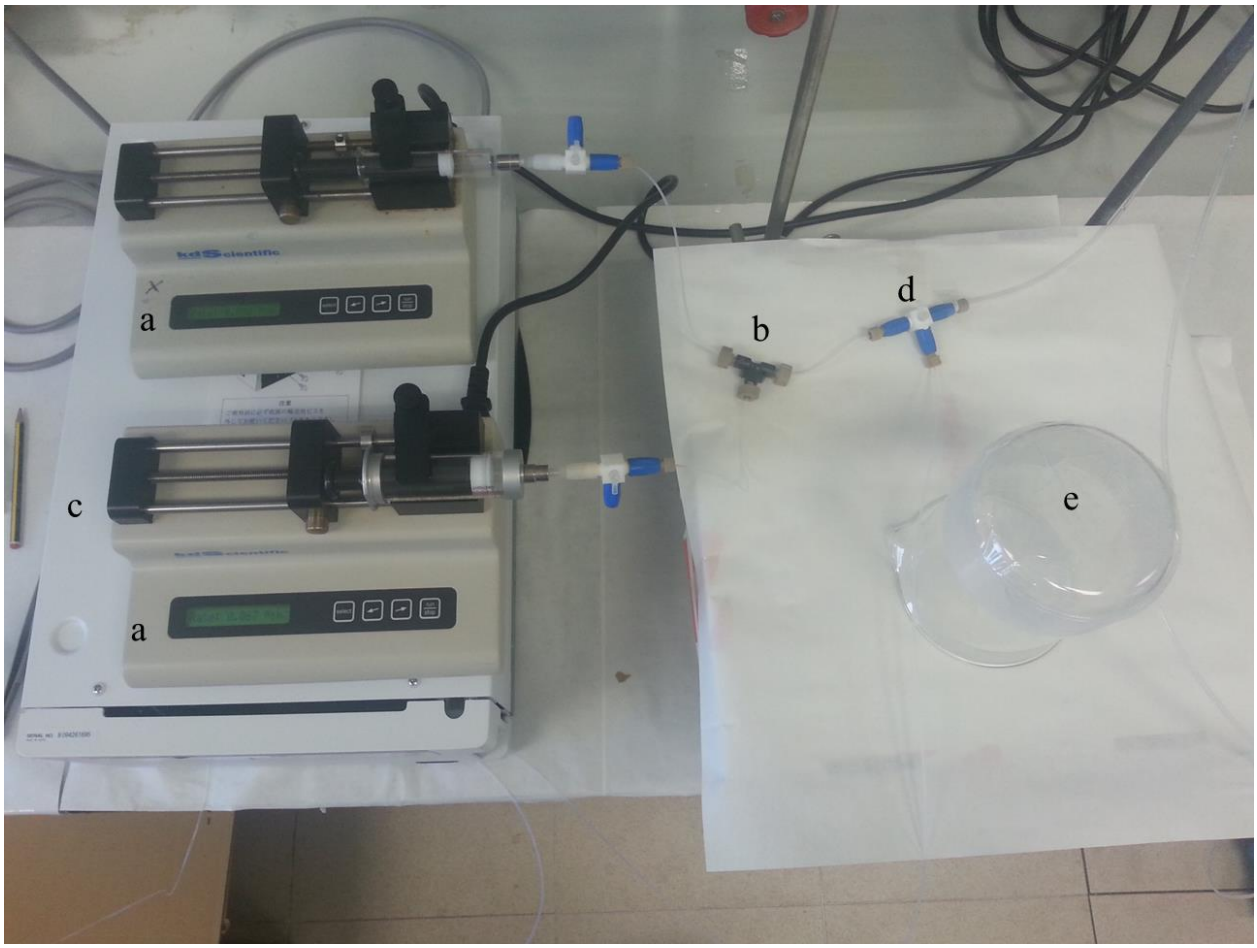
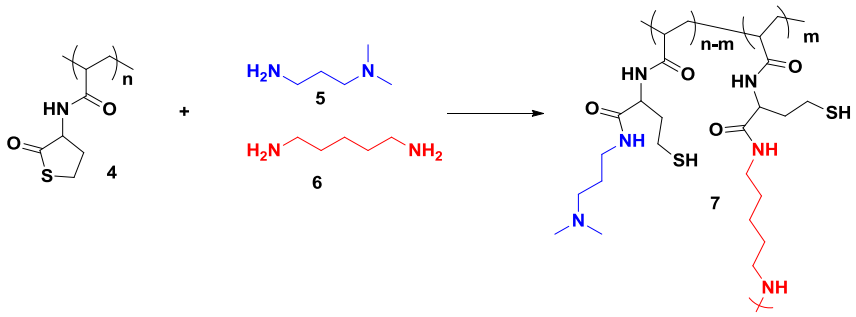



**Figure 10.** General scheme of reactor; a: syringe pumps, b: T-piece connection, c: HPLC pump, d: generator droplets, e: residence unit.

Before proceeding to the test with the continuous flow system, a series of initial experiments were performed in batch to establish the suitable initial conditions in terms of concentration and degree of crosslinking for the functionalization of **4**. These two factors determine the functionalization rate of the homopolymer. The polymeric chains of the PAHT in presence of the *N*-alkyl-amine and the *N*-alkyl-diamine can experiment the corresponding amylolysis reaction leading to the formation of two new amide bonds. In this process, the *N*-alkyl-di-amine leads to the covalent crosslinking of the polymeric chains, while the *N*-alkyl-amine only introduces the functionality. In this case, 3-(dimethylamino)-1-propylamine (**5**) was selected as *N*-alkyl-amine to introduce an amine (-$NR_3$), while 1,5-diaminopentane (**6**) was used as *N*-alkyl-di-amine providing the crosslinking unit (Scheme 2). The amylolysis reaction also produces in-situ thiol groups, which may also contribute, in absence of any additional modifier, to a dynamic crosslinking of polymers chains by the formation of sulfur bridge (R-S-S-R). These two crosslinking reactions (covalent and dynamic) can lead to the gelation of the polymer solution if the concentration of the polymer is high enough. Under continuous flow conditions, the gelation of the droplets, and therefore the crosslinking, can freeze the form of the crosslinked droplet. However, if the gelation is too fast and takes place before

the droplet formation the reactor can be blocked, especially in the point where the solution of the polymer and the solution of the *N*-alkyl-amine (**5**) and the *N*-alkyl-di-amine (**6**) are met (initial T-piece). The gelation rate can be influenced by the concentration of the polymer in the solution. To evaluate the gelation time, some experiments were performed in HPLC vials using the stable-to-inversion test. The gelation time was determined visually by this test. After a given time, 5 min, the vial containing the polymeric solution with the reactants was inverted and if a stable gel was observed, the sample was consider a gel. The gelation time was defined as the time for which the polymer solution does not flow under its own weight when the vial was turn upside-down. Table 1 shows the results obtained for these experiments. The tests were carried out using the same molar ratio of the polymer, *N*-alkyl-amine and the *N*-alkyl-di-amine (1:1.5:0.2 molar ratio for **4**:**5**:**6**) in order to stablish the effect of the concentration on the gelation time. In general, a decrease in the polymer concentration produces an increased in the gelation time, with gelation times going from 20-50 minutes with the decrease of the concentration from 1.114 to 0.826 M.




**Scheme 2.** Post-modification of PAHT (**4**) with 3-(di-methylamino)-1-propylamine (DMAPA, **5**) and 1,5 diaminopentane (**6**) to obtain functionalized cross-linked polymers.

**Table 1.** Effect of the concentration on the gelation time.[a]

| Entry | DMF (µL) | [PAHT] mol/L | Inversion test (time/ min)[b] | | |
|---|---|---|---|---|---|
| 1 | 92 | 1.114 | L (0) | L (10) | G (20) |
| 2 | 137 | 1.026 | L (0) | L (10) | G (25) |
| 3 | 229 | 0.884 | L (0) | L (10) | G (45) |
| 4 | 275 | 0.826 | L (0) | L (10) | G (50) |

**a:** 0.25 mL of a polymer solution of 2.34 mmol/mL (400 mg/mL) in DMF was added to different volumes of DMF containing the same amount of trimethylamine (121 µL, PAHT:$Et_3N$ 1:1.5 molar ratio), 3-(di-methylamino)-1-propylamine (DMAPA, **5,** 55 µL, PAHT:**5** 1:1.34 molar ratio) and 1,5-diaminopentane (**6**, 7 µL, PAHT:**6** 5:1 molar ratio). 40 % mol crosslinking. **b:** By the stable-to-inversion test L: liquid, G: gel

Other factor that can have strong influence on the gelation time is the amount of crosslinking agent used, in this case the ratio polymer to *N*-alkyl-di-amine. The Table 2 summarizes the results

obtained in batch for a different polymer to n-alkyl-di-amine ratios. As expected in absence of the *N*-alkyl-di-amine **6**, the gelation did not take place as there is not covalent crosslinking (Table 2, Entry 1). Under the conditions assayed in absence of oxygen the formation of S-S is not favored, therefore the dynamic crosslinking is not taking place and the modified polymer is soluble in DMF. The use of a large excess of the crosslinking agent (Table 2, Entry 4) led to the instantaneous gelation of the polymeric solution. In this case, as soon as the amine solution was added to the polymer solution the gelation took place. However, under the conditions assayed, for crosslinking degrees lowers than 20% (Table 1, Entries 2 and 3) gelation was not observed even after 24 hours. The gelation was taking place for nominal crosslinking degrees higher than 40%. The gelation time, under these conditions, can be controlled reducing the amount of crosslinking from a nominal crosslinking of 100% to 40 from 2 to 10 minutes (Table 1, Entries 5-7).

**Table 2.** Effect of the amount of crosslinking agent on the gelation time.[a]

| Entry | 5+6:PAHT | PAHT:6 | Crosslinking molar | [PAHT] M | Inversion test (time/ min)[b] | | |
|---|---|---|---|---|---|---|---|
| 1 | 1.49 | 0.00 | 0 | 0.69 | L (0) | L (0) | L (24 h) |
| 2 | 1.64 | 13.76 | 15 | 0.69 | L (0) | L (10) | G (24 h) |
| 3 | 1.69 | 10.12 | 20 | 0.69 | L (0) | L (10) | G (24 h) |
| 4 | 4.49 | 0.67 | 299 | 0.69 | G (0) | - | - |
| 5 | 2.49 | 2.00 | 100 | 0.69 | L (0) | G (2) | / |
| 6 | 2.09 | 3.34 | 60 | 0.69 | L (0) | G (3) | / |
| **7** | 1.90 | 4.98 | 40 | 0.69 | L (0) | G (10) | **/** |

**a:** 0.25 mL of a polymer solution of 1.17 mmol/mL (200 mg/mL) in DMF was added the same amount of trimethylamine (121 μL, PAHT:$Et_3N$ 1:3 molar ratio), 3-(di-methylamino)-1-propylamine (DMAPA, **5,** 55 μL, PAHT:**5** 1:1.5 molar ratio) and a variable volume of 1,5 Diaminopentane (**6**). **b:** By the stable-to-inversion test L: liquid, G: gel

From these initial experiments, we can concluded that the gelation time is highly dependent on the concentration of the homopolymer and the amount of crosslinking agent (1,5-di-amino-pentane, **6**) used. At the view of these results, we started to study the preparation of crosslinking functional materials assisted by the flow platform above introduced. All the experiments were performed at room temperature, and the effect of different experimental parameters as residence time, concentration of the homopolymer and ratio of *N*-alkyl-amine **5** and *N*-alkyl-di-amine **6** with respect to the homopolymer were assayed. The conditions tested are summarized in Table 3.

| Entry | Oil 1 | | Oil 2 | Sol. A | Sol. B | | | Ratio | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Flow A (mL/min) | Flow B (mL/min) | Pentane (mL/min) | **4**[b] (M) | **5**[c] (M) | **6**[d] (M) | $Et_3N$[e] (M) | **5+6**:**4**: | **4:6** | Res. Time (min) |
| 1 | 0.075 | 0.109 | 4 | 2.34 | 2.39 | 0.32 | 4.77 | 1.88 | 5.0 | 3.25 |
| 2 | 0.075 | 1.500 | 5 | 2.34 | 1.92 | 0.26 | 3.83 | 20.85 | 0.5 | 2.07 |
| 3 | 0.050 | 0.067 | 2 | 2.34 | 1.58 | 0.21 | 3.20 | 1.15 | 8.3 | 1.35 |
| 4 | 0.050 | 0.067 | 10 | 1.75 | 1.58 | 0.21 | 3.20 | 1.53 | 6.2 | 6.38 |
| 5 | 0.050 | 0.083 | 2 | 1.17 | 1.19 | 0.16 | 2.39 | 2.14 | 4.4 | 2.66 |
| 6 | 0.050 | 0.067 | 5 | 1.17 | 1.58 | 0.21 | 3.20 | 2.29 | 4.2 | 6.43 |

**Table 3.** Synthesis of functional crosslinked polymers from **4**.[a] **a:** Oil 1: Solution formed by mixing Sol A (**4** in DMF) with Sol B (**5**+**6**+$Et_3N$ in DMF) and Oil 2: Pentane; **b:** Concentration of **4** in DMF) before the mixing point; **c:** concentration of 3-(di-methylamino)-1-propylamine (DMAPA, **5**) in DMF before the mixing point; **d:**concentration of 1,5-diaminopentane (**6**) before the mixing point; **e:** concentration of $E_{t3}N$ before the mixing point.

The initial experiments were performed with a polymer solution of 2.34 M in DMF (Sol A, Table 3, Entries 1-3). This solution was pumped at different two flow rates 0.075 mL/min and 0.050 mL/min (flow A). This solution was diluted in the T-piece connection (b in Figure 10) with a second solution (Sol. B). The solution B presented a variable concentration of the $Et_3N$, **5** and **6** pumped and is pumped with a second pump at different flow (flow B and Sol B, Table 3, Entries 1-3). The final concentration of all of reactants depended of the flow rates used (flow A and B). Under the conditions reported in the Entry 1, a blockage of the needle of the droplet generator was observed. The blockage is likely due to a fast reaction between the polymer **4** and the amines (**5** and **6**). The concentration of the polymer in the mixing point is higher (0.95 M vs 0.69 M) than the reported for the Entry 7 of the table 2 for the same nominal crosslinking 40% leading to the fast gelation of the polymeric solution blocking the system. Similar results were observed when the conditions of the Entry 2 were assayed, although this time the blockage was located directly in the T-piece where Sol A and Sol B met. In this case, a larger flow rate of B (1.5 mL/min) was used to try to reduce the concentration of the polymer (0.11 M) to avoid the gelation. However, under such condition a large amount of amines was used. This can also induce the crosslinking and precipitation of the modified polymer. Finally, reducing the flow rates of solution A and B to 0.050 and 0.065 mL/min (Table 3, Entry 3) the formation of droplets was achieved. Under these conditions, the concentration of the polymer after the mixing point was 1 M in DMF and a nominal crosslinking of *ca*. 25 % was expected. Unfortunately, the droplets of polymer formed in the droplet generator tended to fuse together in the reactor to form an insoluble filament, which can be collected at the exit of the reactor (Figure 11a). We tried to reduce the residence time by increasing the flow rate of the oil 2 (pentane) from 2 to 10 mL/min in order to avoid the fusion of the droplets, however the same effect was found.

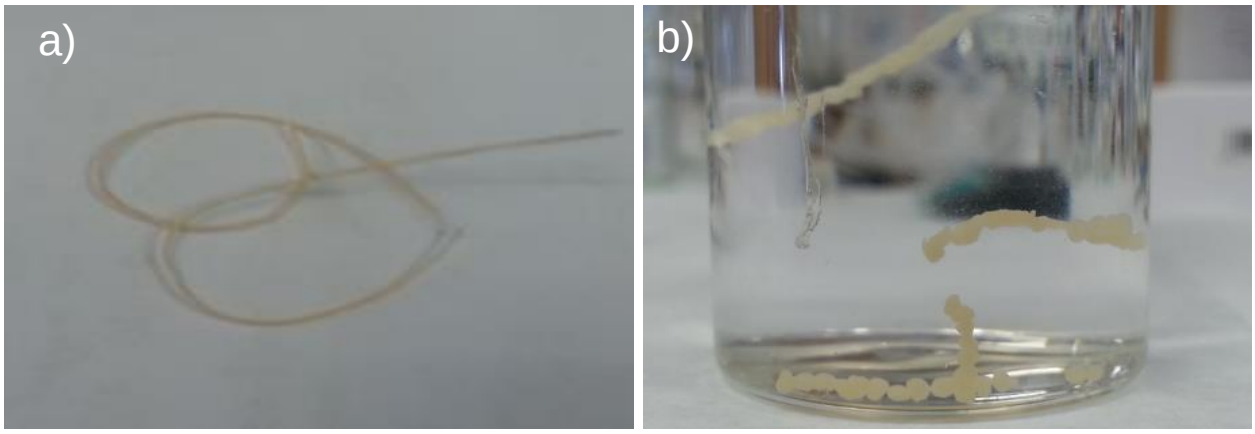



**Figure 11** Functional insoluble polymers obtained by modification of **4**. a) Obtained with the conditions reported in Table 3, Entry 3. B) Obtained with the conditions reported in Table 3, Entry 4.

Encouraged from this result, we decided to use similar conditions than those of Entry 3 keeping the flow rates for solution A and B at 0.050 and 0.065 mL/min (Table 3, Entry 4) but reducing the initial concentration of the polymer form 2.34 to 1.75 M. The flow rate of the oil 2 (pentane) was set to a high flow rate (10 mL/min). Furthermore, the reactor was introduce in ultrasonic bath in order to avoid the possible fusion of the polymeric droplets formed. In this case, the concentration of the polymer **4** after the mixing was 0.75 M and a nominal crosslinking of *ca*. 30% was expected. Under these conditions, the droplets were formed and some individual spherical particles were obtained and collected but most of polymer was obtained as an insoluble pearl necklace type system (Fig. 10b) resulting of the partial fusion of the polymeric droplets inside of the reactor unit.

An additional experience was carried out (Table 3, Entry 5) reducing the concentration of the polymer from 0.75 to 0.44 M after the mixing point by increasing the flow rate of solution B and increasing the nominal crosslinking to *ca*. 47%. In this case, the flow rate of the pentane was reduce to 2 mL/min. Unexpectedly, under these conditions a soluble polymer was obtained, the gelation and crosslinking of polymer did not take place under the concentration assayed. Thus, in a final attempt, the concentration of the polymer **4** was slightly reduce in comparison with the conditions reported in Entry 4 from 0.75 to 0.50 M but the same flow rates of sol A and B were used (Table 3, Entry 6). Under these conditions, the system was able to generate a continuous production of polymeric mainly spherical particles of crosslinking functional polymer with a nominal crosslinking of *ca*. 47%. Under these experimental conditions, the obtained yield of functional polymer after filtration, washing and drying was of *ca*. 62 %. The modification and crosslinking of the polymer **4** was repeated two times achieving comparable results showing the robustness of the methodology to produce the functional polymers in beads form.

## 3.3 Characterization of crosslinked functional PAHT beads.

The polymeric beads were analyzed to verify the nature and properties of the functionalized polymer formed. Thus, in the first place, the obtained functional PAHT beads were characterized by ATR FT-IR and compared with corresponding spectra of unmodified polymer (Figure 12). The spectra show significant changes confirming the amylolysis reaction in presence of the amines **5** and **6**. For instance, the disappearance of the signals at 1696 $cm^{-1}$ and at 919 $cm^{-1}$ corresponding to the C=O and the C-S bonds of the thiolactone suggest the complete conversion of the this group by amylolysis of **4** induce by **5** and **6**.

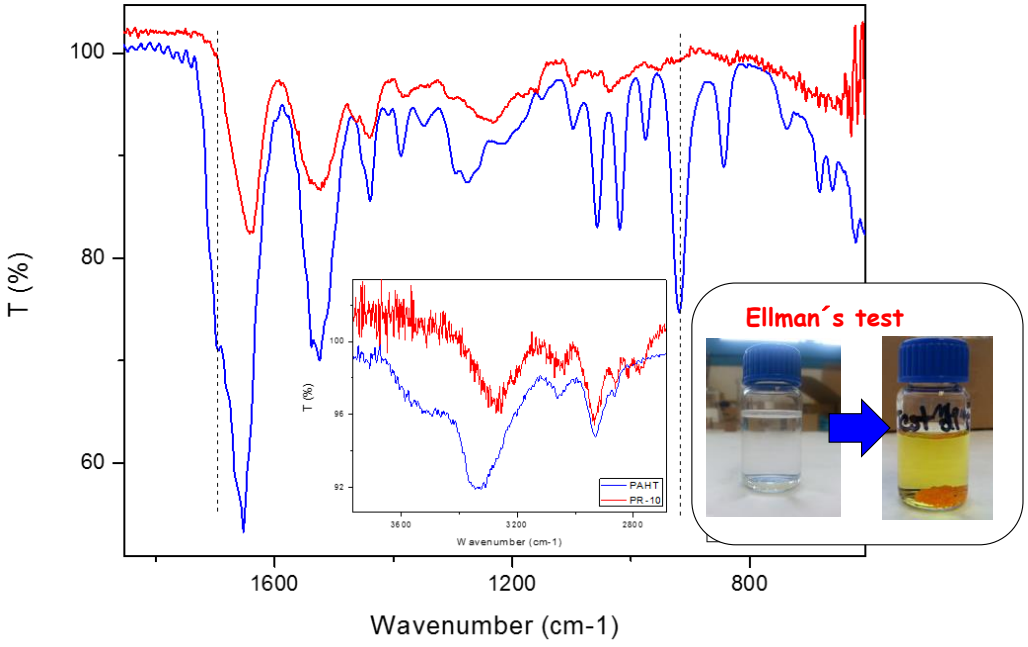



**Figure 12.** Structure of functional PAHT and ATR FT-IR (blue: **4**. Red: **7**). Insert Ellman´s test

Furthermore, the carbonyl functional group at 1652 $cm^{-1}$ and NH of amide at 3325 $cm^{-1}$ changed their absorption respectively at 1642 $cm^{-1}$ and 3273 $cm^{-1}$. The modified polymer also showed new signals at 2817 $cm^{-1}$ and 2862 $cm^{-1}$ corresponding to the CH of methyl group of 3-(dimethylamino)-1-propylamine and 2776 $cm^{-1}$ assignable to the thiol group. Indeed, the presence of free thiol groups was confirmed by positive test obtained under Ellman's test conditions.[16,17] This test consists in monitoring the appearance of a color in both solution and polymers caused by the reaction of –SH groups with Ellman's reagent (Figure 12, insert ). Altogether, the FT-IR and the Ellman´s test

16 G. L. Ellman, *Arch. Biochem. Biophys*., **1958**, *74*, 443-450
17 F Gaggini , A. Porcheddu , G. Reginato, M. Rodriquez, and M. Taddei, *J. Comb. Chem*., **2004**, 6, 805–810

suggests a successful conversion of the homocysteine thiolactone groups of the initial polymer by amylolysis reaction in presence of the amines **5** and **6**.

Swelling experiments are a simple and low cost methodology to characterize the nature of a polymeric network. A simple experiment to evaluate the degree of swelling consists in introduce the dry volume of polymer beads in a syringe and to observe the expansion of the volume in presence of a given solvent. Thus, the dry polymer was introduced in three different syringes (dry volume 0.2 mL) and 2 mL of dichloromethane, methanol and water were added to each syringe (Figure 13). After 1 hours, the polar solvents increases beads volume up to 0.3 mL, while the polymers beads in dichloromethane retained at their original volume. The change in volume for the polar solvents was *ca*. of 50% in agreement with the polar nature of the polymeric backbone. The same tests were repeated in presence of 1,4-dithiothreitol (DTT), an agent able to break the possible sulfur bridge (R-S-S-R). Under these conditions, the same swelling was observed suggesting that the main crosslinking is due to the covalent amide bonds formed by the amylolysis of the thiolactone and *N*-alkyl-di-amine **6**.

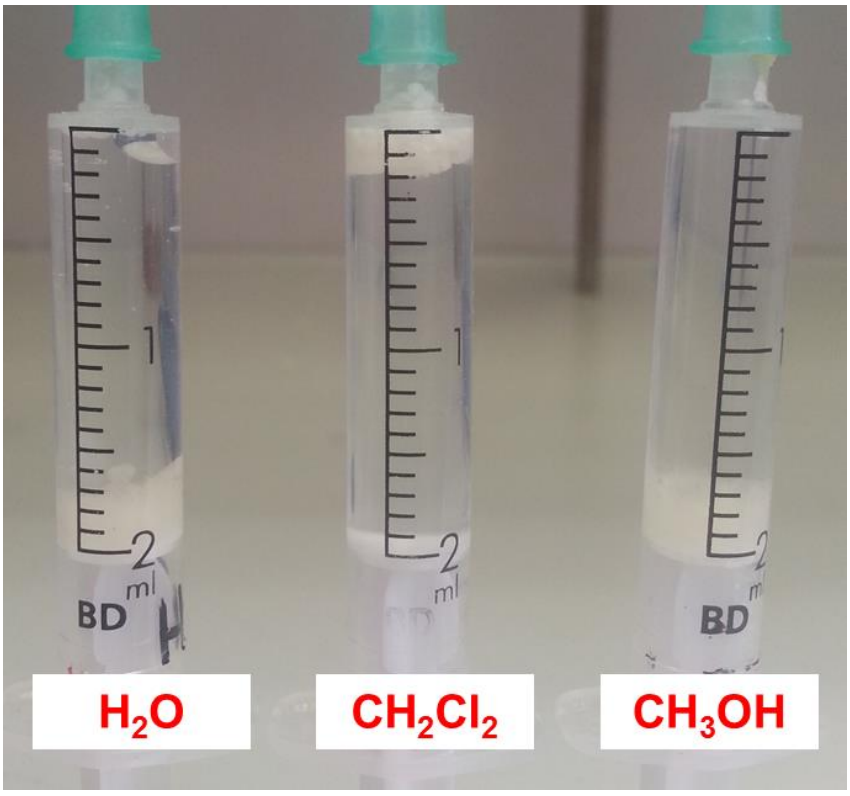



**Figure 13.** Swelling of the functional polymer 7 in different solvents.

Finally, the size of the particles obtained was analyzed using a Coulter system, where laser diffraction is used to determine the particle size distributions by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample. As we can see in the Figure 13, the functional polymer obtained presented a bimodal size distribution, where

*ca*. of 20% of the particles were centered at 829 μm and *ca*. 80% at 1426 μm leading to a mean size distribution of 1345 μm. It seems that the sizes of the particle obtained is mainly due to the internal diameter of the tube used to build the reactor (0.16 cm ID).

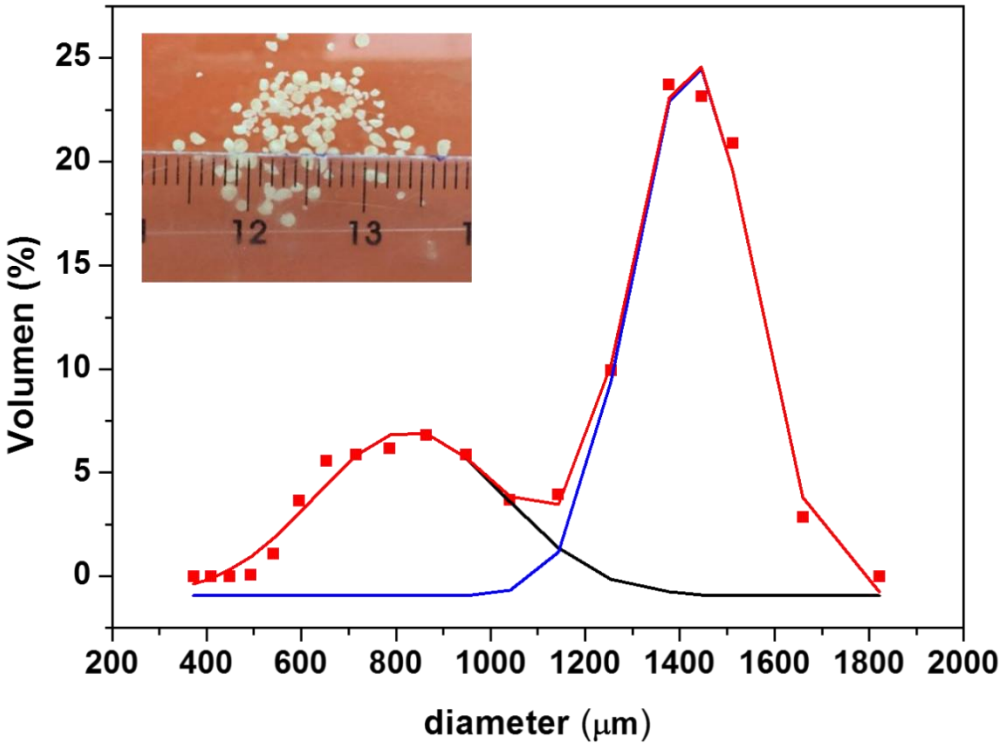



**Figure 13** Size distribution of functional polymer beads

## 3.4 Modifications and catalysis study of functional PAHT beads.

PAHT obtained using the flow platform described in the second chapter present in its structure different functional groups (thiol and tertiary amine), which represent the first level of functionalization. A second level of functionalization, in order to obtain materials with advanced properties, may be achieved through the modification of the thiol group. In this chapter, we present our efforts in this regard.

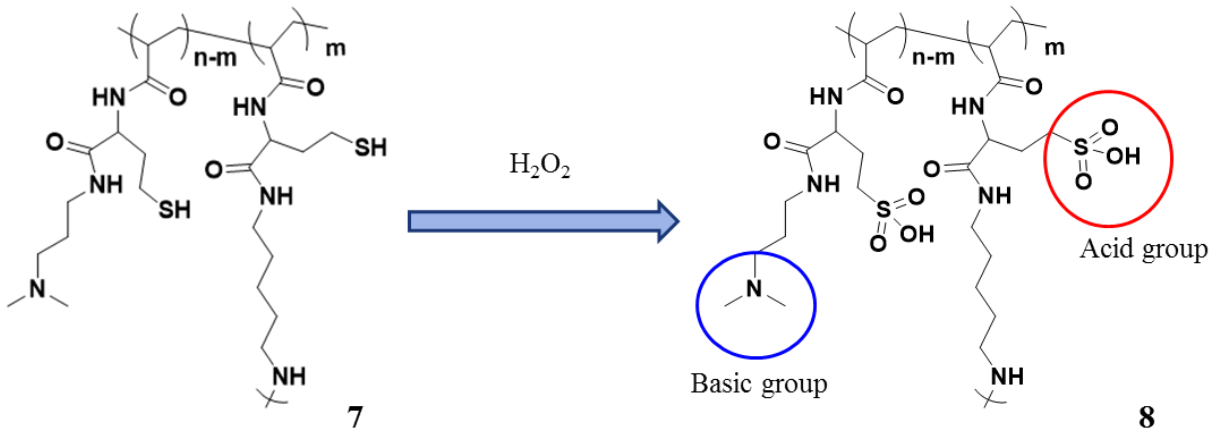
### 3.4.1 Oxidation of thiol group to sulfonic acid.

The oxidation of the -SH groups of the PAHT into $SO_3H$ is highly attractive as it can lead to bifunctional heterogeneous catalysis with the coexistence of incompatible catalytic species, such as acid and base, nearby on a same solid particle surface (Scheme 3). According with principles of Green Chemistry, hydrogen peroxide was chosen as oxidant agent to transform the thiol into the corresponding $SO_3H$ groups. The two different methodologies tested are summarized on Table 2.

| Entry | Polymer beads (mmol) | $H_2O_2$ (mmol) | Solvent (µL) | Temperature (°C) | Time (h) |
|---|---|---|---|---|---|
| 1 | 0.29 | 2.90 | Acetic Acid | 60 | 2 |
| 2 | 0.29 | 0.68 | Methanol | r.t. | 2 |

**Table 2**. Different reactions for the oxidation of 7.

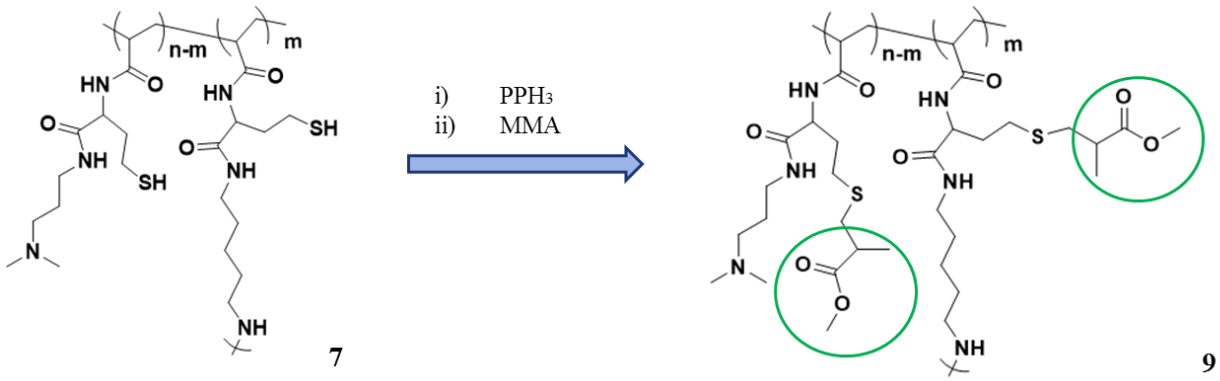
Under the conditions reported for the entry 1, a high molar ratio (1:10) polymer hydrogen peroxide is used. Additionally, the temperature (60 °C) also help to decompose the oxidant agent to generate oxygen. Under these conditions, although the reaction seems to take place to transform SH into $SO_3H$, the bead structure of the polymer collapsed leading to the final polymer as fine white powder. Therefore, these conditions were not suitable for the oxidation of the SH groups while maintaining the polymer morphology. On the contrary, under the conditions reported in the Entry 2 of the Table 2, the morphology of the polymer was maintained after modification. In this case, hydrogen peroxide (0.68 mmol) was added to polymer beads (0.29 mmol) drop by drop at 0 °C and the reaction carried out at room temperature. With these milder conditions, polymeric beads kept their shape and the new functionalization was confirmed by IR spectra (see Figure 24 of Experimental part) The appearance of new peaks at 1037 $cm^{-1}$, 1175 $cm^{-1}$ and 1203 $cm^{-1}$ confirm the oxidation of the SH groups into the corresponding SO·H groups . With this simple reaction, the product can be used like bifunctional catalyst because acid and basic groups are present in the same structure. (Scheme 3)




**Scheme 3.** Oxidation of thiol group with hydrogen peroxide

### 3.4.2 Thiol-Michael addition click reaction.

Thiol is a versatile functional group able to react with different reagents to introduce new functionality. One of most important reaction is thiol-Michael addition click reaction.[18]. This reaction is accepted as a click chemistry reaction due to the reactions' high yield, stereoselectivity, high rate, and thermodynamic driving force. Among the different thiol reaction, we have assayed the reaction between the thiol present in the polymeric beads with methyl methacrylate in order to achieve a new degree of functionalization (Scheme 4).




**Scheme 4**. Thiol-ene reaction with MMA

Although Ellman's test was positive indicating the presence on the beads of free thiol group, polymer was treated with triphenylphosphine as reducing agent able to break all of sulfur bridges (-S-S-) that form dynamic cross-linking. Then, beads reacted with methyl methacrylate under inert atmosphere and 80° C for 24 hours. The beads were filter off and washed. The FT-IR of the resulting beads showed the presence of a new carbonyl band assignable to the ester at 1733.7 $cm^{-1}$ (Figure 22 of Experimental part) suggesting the successful modification.

18 D.P. Nairt, M. Podgorski, S. Chetonit, T. Gong, W. Xi, C. R. Fendi, C. N. B *Chem. Mater.*, **2014**, *26* (1), pp 724-744

### 3.4.3 Nanoparticles of Gold.

The presence of the functional groups in the polymer **7** (-SH and -$NR_3$) can be used for the immobilization and stabilization of gold nanoparticles (Au-NPs). Au-NPs can be used in different fields such as catalysis, and sensors. The reaction scheme is very simple: tertiary amine was protonated by hydrochloric acid, chloroauric acid was added and the solution was stirred. The change of color from yellow to no-color was observed and confirmed anion change between chloride of the polymer and $AuCl_4^-$ anions was achieved. (Figure 15b) The last reaction was the reduction of Au(III) to Au(0) by sodium borohydride. Beads showed the typical pink color of Au-NPs and the shape was not altered. (Figure 15a). Further analysis (UV-Vis, TEM) will be undertaken to fully characterize these systems. However, these initial results suggest the suitability of the polymers here prepared for the immobilization and stabilization of different NPs.

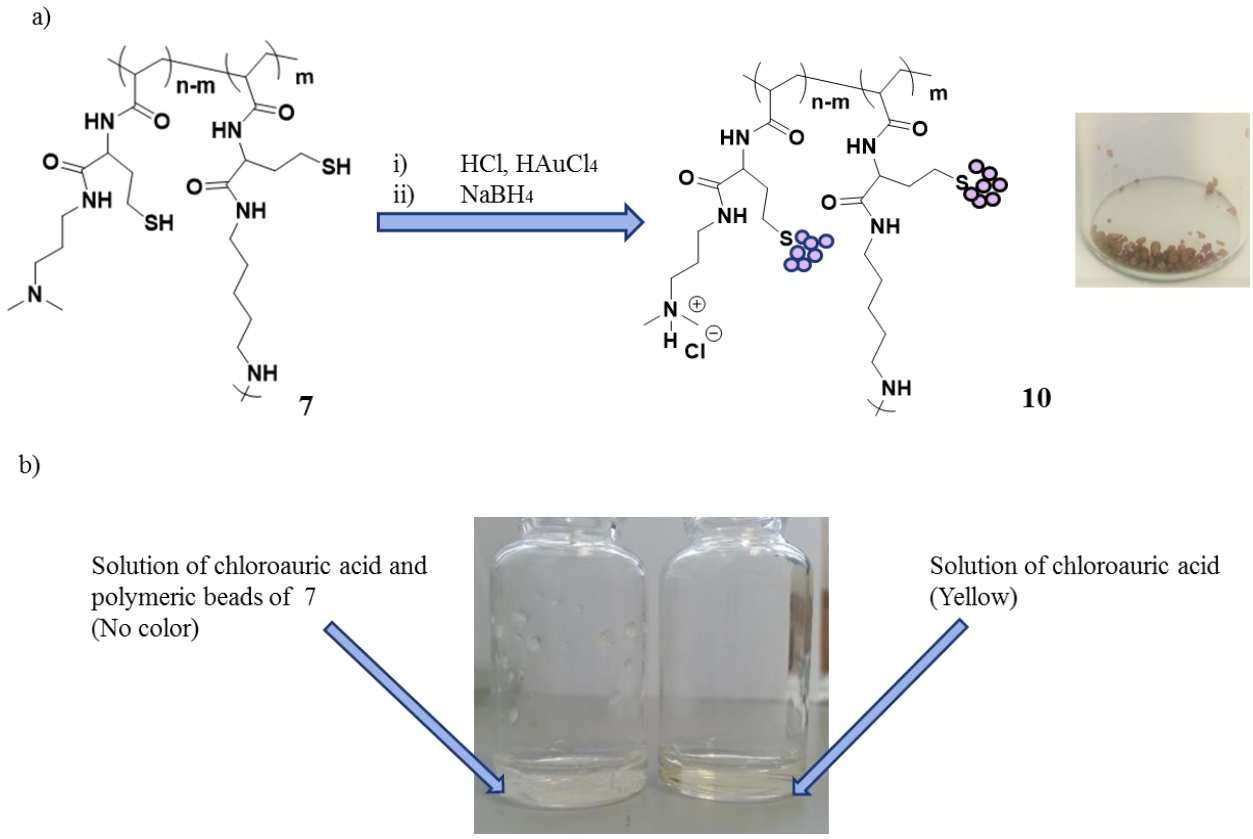
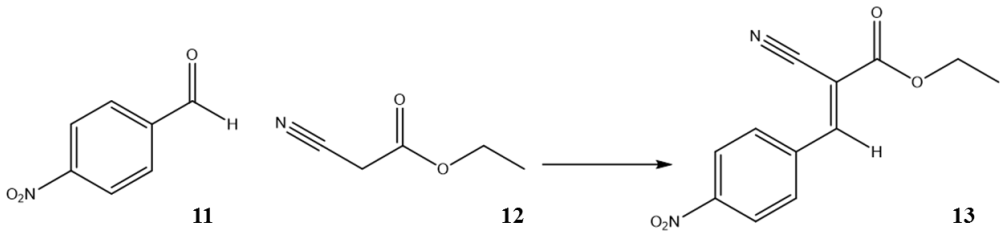



**Figure 15**. a) Substrate with Au-NPs b) Change of color during reaction

### 3.4.4 Catalytic test.

Finally, the polymeric beads (**7**) were tested without other modifications for a Knoevenagel condensation between *p*-nitro-benzaldehyde with active methylene compound (Scheme 5). The reaction was carried out in three different solvents under the same conditions in presence and absence of the polymer **7**. The results obtained after 24 hours are summarized in Table 3. The reaction did not proceed in absence of the catalyst when DCM and 2-Me-THF were used as solvent (Entries 1-2, Table 3). However, a 70% of yield was achieved when water was used as solvent (Entry 3, Table 3) likely due to a hydrophobic effect. The presence of the polymer improved the yields obtained for the model reaction for all the solvents assayed (Entries 4-6, Table 3) showing the catalytic effect of the basic units (-$NR_3$) presented in the polymer **7**.




**11** **12** **13**

**Scheme 5** Reaction used to investigate catalyst activity of beads polymer.

| Entry | Catalyst | Solvent | Conversion (%) |
|---|---|---|---|
| 1 | x | DMC | 0 |
| 2 | x | 2-MeTHF | 0 |
| 3 | x | $H_2O$ | 70 |
| 4 | yes | DMC | 75 |
| 5 | yes | 2-MeTHF | 80 |
| 6 | yes | $H_2O$ | 95 |

**Table 3** Experiments carried out. The conversion was calculated by $^1$H-NMR from the crude reaction

# 4. Conclusions.

In this work we have designed, built and tested a continuous flow platform for the efficient and reproducible modification of poly(acrylamide-homocysteine thiolactone) into crosslinked functionalized polymers.

We can conclude that:

- RAFT polymerization is an efficient and reproducible method for the preparation of the homopolymer poly(acrylamide-homocysteine thiolactone) **4**.
- Modular play-plug flow platform was built and tested. The platform allows, under the optimized conditions, a fast, simple and reproducible synthesis of crosslinked functional polymers derived from **4**.
- The *N*-alkyl-di-amine 1,5-diaminopentane is an efficient cross-linking agent for the synthesis of functional polymers derived from **4**.
- The sizes distribution of the polymer beads are defined by the internal diameter of the tube used in the construction of the flow reactor.
- The polymeric beads prepared bearing at least to functional groups such as the amine ($–NR_3$) and the thiol (R-SH) groups, which can be use either as catalytic sites or as modification units allowing the immobilization of additional catalytic motives.
- New functional groups ($-SO_3H$ and MMA derivate) were introduced according with Green Chemistry principles.
- Because of high affinity between thiol and amine groups, AuNPs can be obtained by ionic exchange and reduction.
- Polymeric beads shown catalytic activity for the Knoevenagel condensation.

# 5. Experimental Part.

## 5.1. Chemicals

DL-homocysteine thiolactone hydrochloride, acryloyl chloride, cyanomethyl dodecyl trithiocarbonate (CMDTTC), triethylamine, 3-(dimethylamino)-1-propylamine, 1,5-diaminopentane, azobisisobutyronitrile (AIBN), hydrogen peroxide, acetic acid, methyl methacrylate, triphenyphosphine, chloroauric acid, sodium borohydride, 4-nitro-benza1dehyde, ethyl cyanoacetate, 1,4-dioxane, N,N-Dimethylformamide (DMF), Dimethyl sulfoxide (DMSO), diethyl ether, dimethylcarbonate (DMC), 2-Methyl tetrahydrofuran (2-MeTHF) were purchased from Sigma Aldrich and used without further purification. Sodium hydrocarbonate were purchased from Riedel-de Haën (Seelze, Germany) and used without further purification.

## 5.2. Characterisation methods

The NMR spectroscopic experiments were carried out at Varian 500 MHz and Bruker 400 MHz (1H NMR) and 101 MHz (13C NMR). The chemical shifts are reported using trimethylsilane as the internal standard. IR spectroscopy was used to monitor the synthesis of the monomers and polymers. The FT-IR spectra were obtained at 4 $cm^{-1}$ resolution for the 4000 to 600 $cm^{-1}$ spectral range using a spectrometer (JASCO FT/IR-6200) equipped with an ATR (MIRacle singlereflection ATR diamond/ZnSe). Calorimetry studies were performed using a differential scanning calorimeter (DSC) (DSC8, Perkin Elmer or alternatively DSC Q2000 TA) in a nitrogen atmosphere at 10 ºC/min heating rate. TGA curves were measured on TGA 850 Mettler Toledo Star - 70 µl alumina crucible with approximately 5 mg of the polymer and the reference crucible of the same material were placed in the instrument. Temperature scan was performed in a range 30-600 C at constant heating rate of 10 C/min, purge gas - nitrogen 50 ml/min.

Molecular weight distribution and polydispersity index (PDI) were analyzed by GPC using a Viscotek TDA 302 series system as an integrated instrument, including three HEMA-based columns (105/103/102 Å porosity) from MZ-Analysentechnik GmbH, a dual LS detector (7 and 90º), viscosimeter and RI detector. The samples were run in DMF, HPLC grade containing 1g/L of lithium bromide as an additive with a flow rate of 0.8 mL/min at 60 °C The apparatus was calibrated with well-defined poly(methyl methacryl.

Elemental analyses were obtained with a CHN Euro EA 3000 instrument. Distribution dimension was obtained with a LS particle size analyzer Beckman Coulter.

**5.3 Modular plug-play flow platform**.

A schematic representation of the reactor is found in the Figure 10. The reactive solutions were put in two different glass Hamilton syringes (5 and 10 ml). Two syringe pumps are Model 100 Series of KD Scientific Inc. (USA). All of components are in PEEK and the tube is in PTFE.

**Synthesis of acryl homocysteine thiolactone (3).**

Sodium hydrocarbonate (19.15 g, 227.9 mmol) was slowly added to an ice-cooled solution of D,L-homocysteine thiolactone hydrochloride (**1**, 7.0 g, 45.6 mmol) in a 1:1 mixture of water/dioxane (100 mL). The resulting mixture was stirred for 30 min at 0 ºC. After this, acryloyl chloride (2, 8.3 g, 91.2mmol) was added to the mixture in several portions. The reaction mixture was allowed to reach room temperature overnight. Brine (100 mL) was added and the mixture was extracted with ethyl acetate (3x200 mL). The organic fractions were dried with magnesium sulphate and the solvent concentrated in vacuum. $^{1}$H NMR (500 MHz, DMSO-d6, ppm) δ 8.45 (d, 1H), 6.23 (dd, 1H), 6.12 (dd, 1H), 5.65 (dd, 1H), 4.70 (ddd,1H), 3.42 (dt, 1H), 3.30(ddd, 1H), 2.44 (m, 1H), 2.09 (m, 1H).$^{13}$C NMR (125 MHz, DMSO-d6, ppm) δ 205 (C=O), 131.0 (CH), 126.2 ($CH_2$), 58.2 (CH), 30.3 ($CH_2$), 26.8($CH_2$).

**Synthesis of Poly (acryloyl homocysteine thiolactone) (4).**

Acrylhomocystheine thiolactone **3** (171 mg, 1 mmol), CMDTTC (2.12 mg, 6.6 μmol) and AIBN (0.1 mg, 0.6μmol) were dissolved in DMF. The mixture was degassed through 3 freeze-thaw cycles. The reaction was allowed to proceed for 24 hours at 110 ºC. The polymerization was stopped by freezing the mixture in liquid nitrogen. The product was precipitated in methanol, purified by reprecipitation from DMF to methanol and washed with diethyl ether. Yield of crude product: 85-90 %.$^{1}$H NMR (500 MHz, DMSO-d6, ppm) δ 7.21-8.25 (br. m, 1H), 7.58 (br. d, 1H), 3.40 (br. d, 2H), 2.47 (br. s, 1H), 2.11 (br. s, 2H), 1.52 (br. d, 2H). $^{13}$C NMR (500 MHz, DMSO-d6, ppm) δ 206.4 (C), 174.3 (C), 58.9 (CH), 41.5 (CH), 36.0 ($CH_2$), 30.3 ($CH_2$), 27.2 ($CH_2$).

**Modification of 4 with plug-play flow platform (7)**

Poly(acryloyl homocysteine thiolactone) (3 g, 1.2 mmol) was dissolved in 15 ml of DMF. Triethylamine (8.7 ml, 62.5 mmol), 3-(dimethylamino)-1-propylamine (3.9 ml, 31.2 mmol), 1,5-diaminopentane (490 μL, 4.2 mmol) was dissolved in 6.5 ml of DMF. The flow conditions were adjusted as reported in the Entry 6 Table 3.

**Oxidation of 7 with Hydrogen peroxide (8).**

Polymeric beads (50 mg, 0.3 mmol) were put in a flash bottom of 5 ml with Methanol (440 µL). The system was cooled at 0 °C and hydrogen peroxide (21.32 µL of $H_2O_2$ solution at 32 %) was added drop to drop. Cold bath was removed and the solution was stirred at room temperature for two hours. At the end of this time, beads ware filter off and dried.

**Mofidication of 7 by Thiol – ene reaction (9).**

Polymeric beads (50 mg, 0.29 mmol) were put in a 50 mL round bottom flask with 1,4-dioxane (30 mL), ultra-pure water (15 mL) and triphenylphosphine (228.2 mg, 0.9 mmol). The solution was stirred for four hour, at room temperature under inert atmosphere ($N_2$). Beads were filtered off and put in a 10 mL round bottom flask with methyl methacrylate (155µL, 1.4 mmol) and dry DMF (5 mL). The obtained solution was stirred for 24 h at 80 °C and under inert atmosphere ($N_2$). Beads were filtered off and dry.

**Modification of 7 by Nanoparticles of Gold (10).**

Polymeric beads (50 mg, 0.3 mmol) were put in a 10 mL vial with a solution of chloroauric acid (1 mL of a solution composed by 9 mL of ultra-pure water, 1 mL of chloridric acid 37 %, 5.1 µL of chloroauric acid 30% in HCl). The obtained solution was stirred for ten minutes at room temperature. Beads were filtered off and put in a vaial with ultra-pure water (2.5 mL) and sodium borohydride (250 mg, 6.61 mmol). Beads were filtered off.

**Catalysis test.**

All the reactions were carried out under the same conditions: **7** (50 mg, 0.3 mmol), 4-nitrobenzaldehyde (22.3 mg, 0.2 mmol), ethyl cyanoacetate (15.5 µL, 0.2 mmol), solvent (dimethyl carbonate, 2-methyl tetrahydrofuran, ultra-pure water, 725 µL). The solutions were stirred in orbital stirring at 40 °C and 180 rpm for 24 hours.

| Muestra | Mn (Da) | Mw (Da) | Polydispersity (MW/Mn) | Volumen de retención (min) |
|---|---|---|---|---|
| SM_4P97 | 20669 Da | 32709 Da | 1,582 | 17,616 |

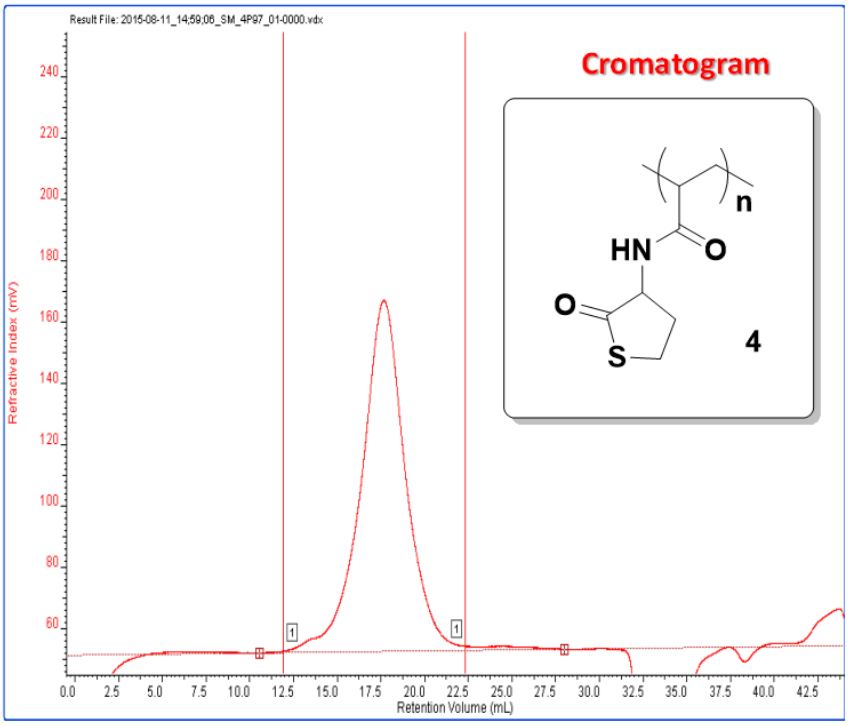



**Figure 15** Size exclusion chromatography obtained for 4 in DMF (8 mg/mL) and 0.1% (w/w) of LiBr.

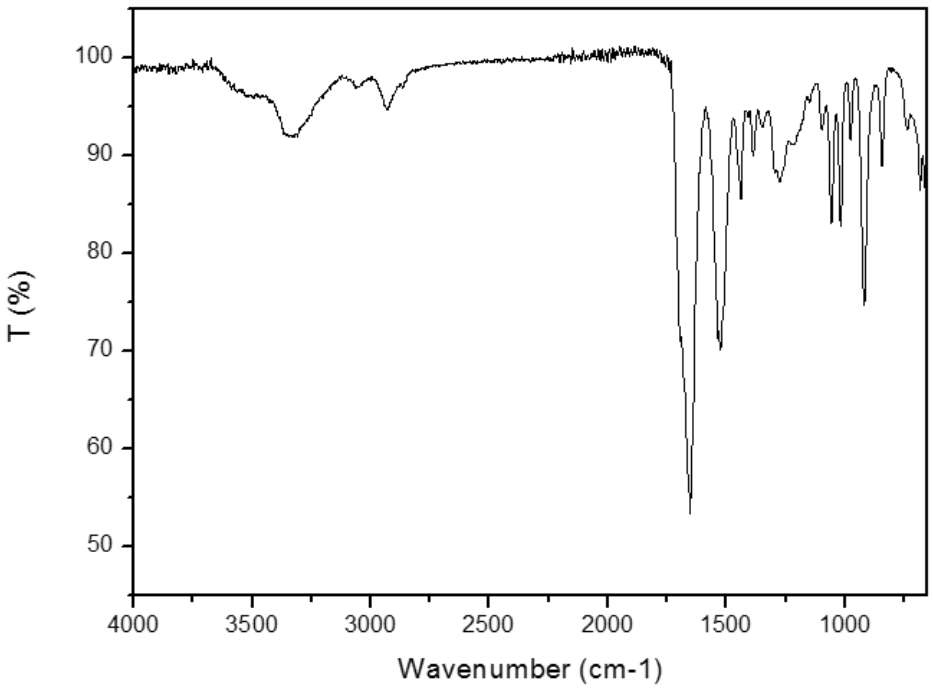



**Figure 17** ATR FT- IR spectra of PAHT (**4**)

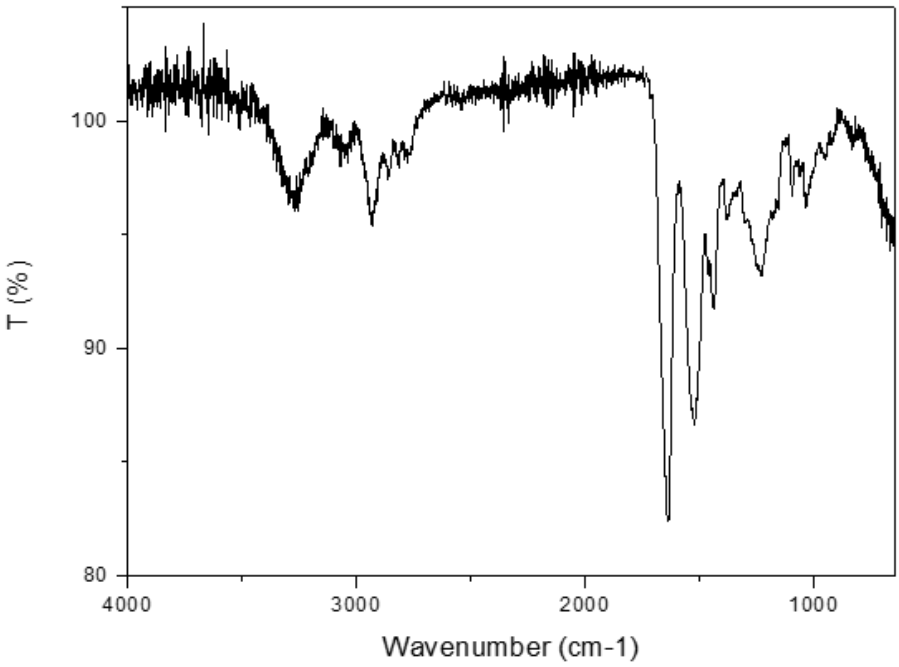



**Figure 18** ATR FT- IR spectra of crosslinked polymer 7.

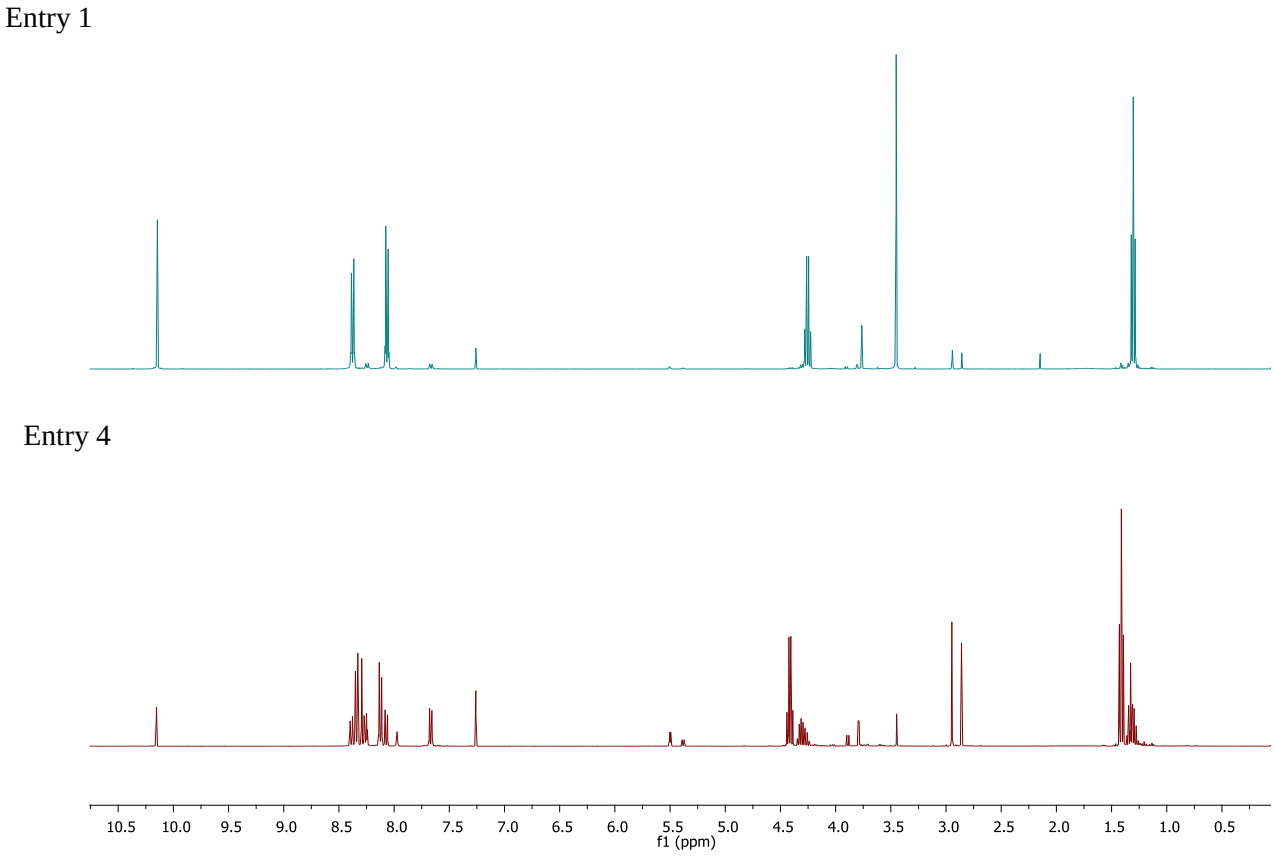
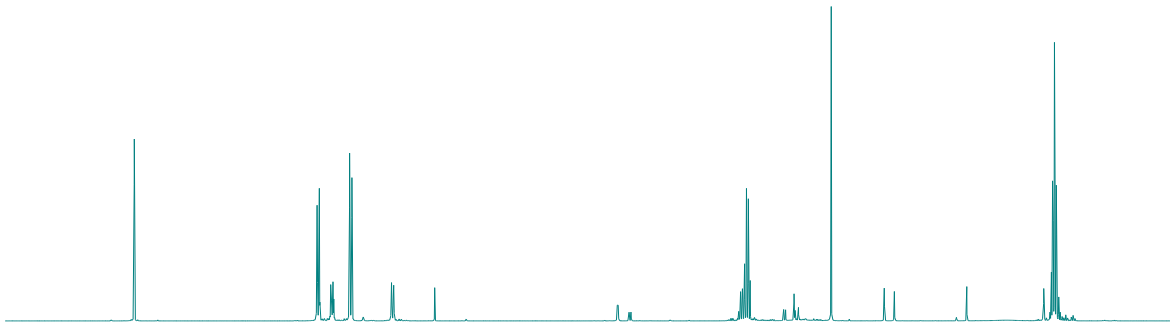



**Figure 19** $^{1}$H-NMR of entries 1 and 4 of table 3

Entry 2



Entry 5

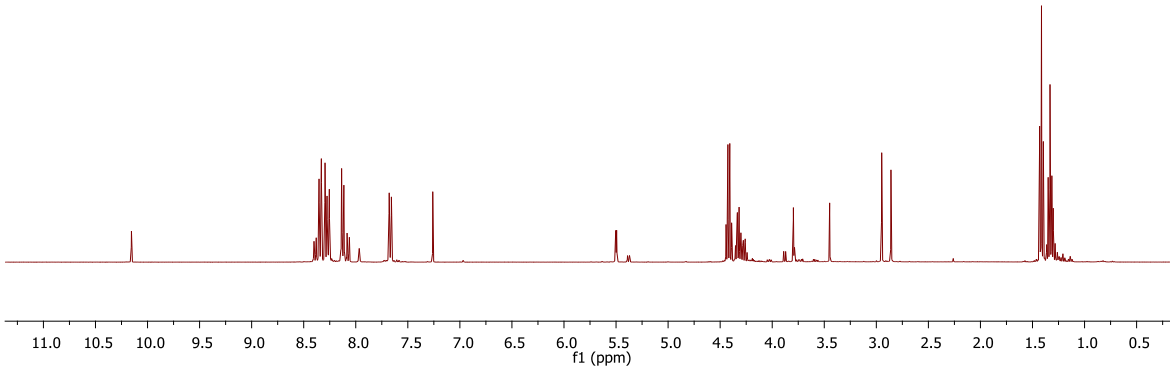



**Figure 20** $^{1}$H-NMR of entries 2 and 5 of table 3.

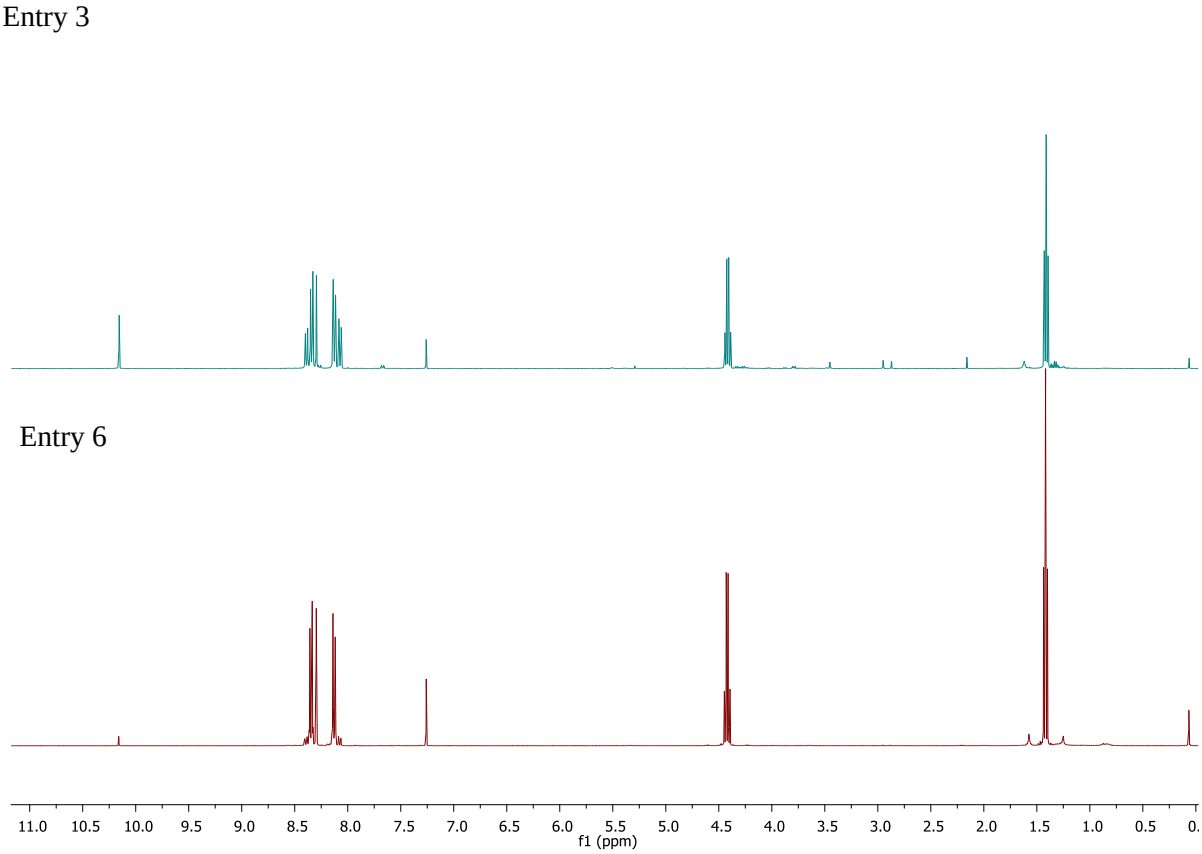



**Figure 21** $^{1}$H-NMR of entries 3 and 6 of table 3.

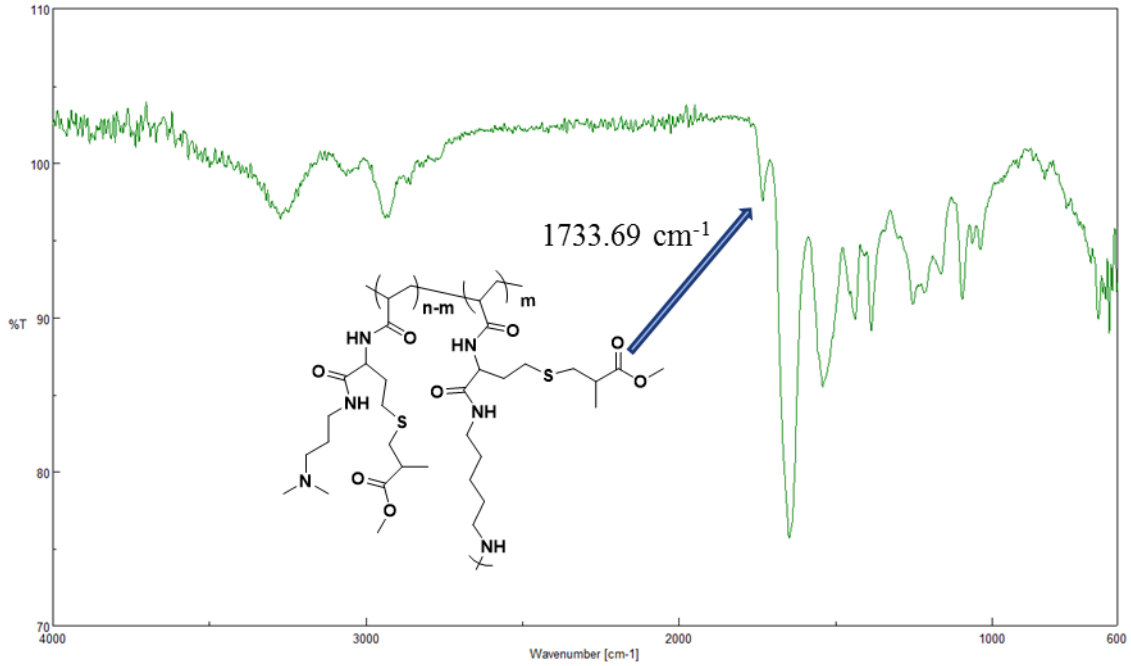



**Figure 22** ATR FT- IR spectra of polymer 9.

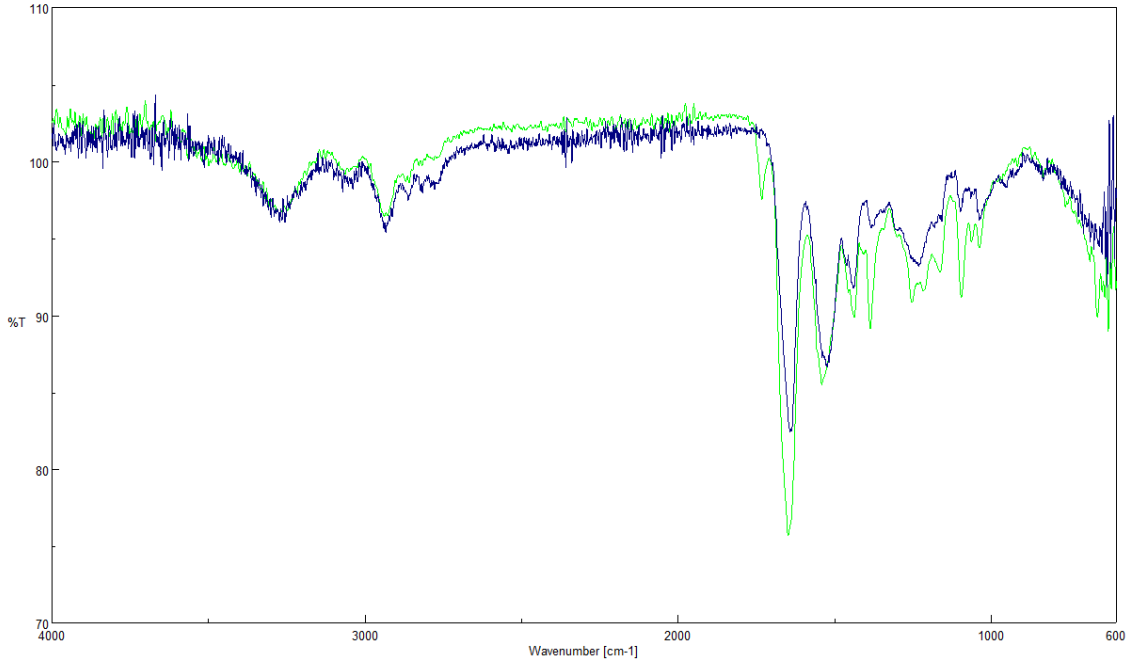



**Figure 23** ATR FT- IR spectra comparison between polymer 7 (blue) and polymer 10 (green).

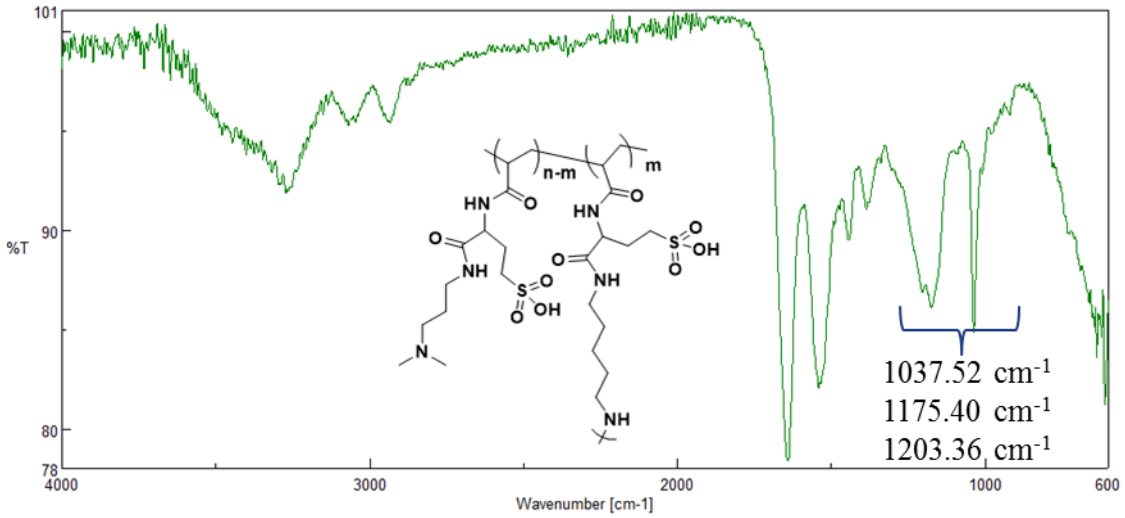



**Figure 24** ATR FT- IR spectra of polymer 9.

# RINGRAZIAMENTI

Finalmente sono giunta anche alla fine di questo percorso universitario. È stato più difficile del previsto, ho pensato di non farcela e di mollare tutto ma con il sostegno della mia famiglia e dei miei amici ce l'ho fatta! Iniziamo con i famigliari; ringrazio mia madre per la sua presenza costante e mi scuso per tutte le preoccupazioni che le ho dato specialmente durante il mio periodo in Spagna, mio padre per avermi sempre fatto sentire la sua principessa, mia sorella Francesca per gli incoraggiamenti non sempre gentili che mi ha dato, mio nonno Pippo per essere stato il mio primo sostenitore soprattutto nell'ultimo periodo e per le mitiche videochiamate in dialetto durante il mio periodo Erasmus, mia zia Lavinia e mio zio Giovanni per l'incoraggiamento e la vicinanza sempre dimostratami e tutta la frutta speditami nei meravigliosi pacchi da giù, mio cugino Fabio per i consigli giusti sebbene detti in maniera non molto tenera e mio cugino Sergio per tutte le uscite magnifiche fatte a Bologna anche quando non volevo varcare la soglia di casa. Davvero grazie di cuore! Lasciare la mia città qualche anno fa non è stato semplice soprattutto per gli amici rimasti lì ma sempre pronti a fare baldoria ad ogni mio ritorno. Ringrazio quindi Ferdinando per avermi supportato e sopportato in qualunque punto del mondo ci trovassimo, per avermi fatta sentire a casa durante il periodo all'estero, per avermi spronata a farcela e a non mollare nonostante tutto, Clara la super amica con cui divertirsi e fare ogni cavolata possibile ed inimmaginabile ma sempre pronta a tendermi una mano nel momento del bisogno, e Marina per il sostegno e le lunghe chiamate fatte da Milano. Anche a Bologna ovviamente ho trovato persone che mi sono state accanto dall'inizio alla fine di questa avventura, ringrazio le ragazze della famosa 117, Melissa Monia Paola e Cristiana, per aver sopportato tutti i miei scleri, Walid per tutte le tazze di the che mi ha preparato, Enrico per la compagnia assidua in sala studio e tutte le puntate di Sex & the City viste insieme, i portieri Roberto e Fabrizio per tutto l'aiuto che mi hanno offerto e tutte le attività di teatro, cineforum e lettura che hanno organizzato, in cui sono stata coinvolta e a cui mai avrei pensato di partecipare, e Althea per tutti i caffè preparati per me nei pomeriggi di studio. Inoltre ringrazio le colleghe e amiche di questo percorso, Benni per tutti gli appunti passatemi, per l'accoglienza che mi ha riservato nella sua vita e tutto l'aiuto possibile ricevuto ed Alessandra per il sostegno soprattutto nell'ultimo periodo quando studiare era diventato pesante e sclerante. Ringrazio inoltre Casa Fiorita con i suoi componenti, Lorenzo Marco e Joklaus, per aver sopportato i miei capelli, il mio ripetere sulle piastrelle della cucina e per aver monopolizzato la cucina stessa con tutti i miei appunti ed i miei fogli. Un ringraziamento speciale va alla mia relatrice, Dott.ssa Mariafrancesca Fochi per aver risolto ogni mio problema burocratico riguardo l' Erasmus e per essere stata presente professionalmente nonostante la distanza. Os agradesco también a todos los profesores, Santiago

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*Roberta Prinzi*