UNIVERSITAT ROVIRA i VIRGILI

Well-defined Thermoresponsive Lactic Acid-based Polymers

Bachelor's thesis
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"Chemistry itself knows altogether too well that
– given the real fear that the scarcity of the
global resources and energy might threaten
the unity of mankind –
Chemistry is in a position to make a contribution
towards securing a true peace on Earth."

Kenichi Fukui.

Content

1. ABSTRACT

The problems derived from the accumulation of plastic waste and the dependence on non-renewable resources for its production, has led to the search for new biobased polymers as an alternative to conventional plastics. In this work, we synthesized a series of smart thermoresponsive homo and random copolymers based on lactamide acrylic monomers prepared from ethyl lactate solvent, a lactic acid derivative. Lactic acid is one of the top biobased feedstocks for the production of polymers given its readily availability from carbohydrates, biodegradability and reduced toxicity.

Els problemes derivats de l'acumulació de residus de plàstic i la dependència de recursos no renovables per a la seva producció, han conduït a la recerca de nous polímers amb base biològica com a alternativa als plàstics convencionals. En aquest treball, vam sintetitzar una sèrie de copolímers homo i aleatoris termoresponsius intel·ligents basats en monòmers acrílics de lactamida preparats a partir de dissolvent de lactat d'etil, un derivat de l'àcid làctic. L'àcid làctic és una de les primeres matèries de base biològica per a la producció de polímers, atesa la seva disponibilitat fàcil d'hidrats de carboni, la seva biodegradabilitat i la seva toxicitat reduïda.

2. INTRODUCTION

A polymer is a chemical made of many repeating units, called monomers, linked by covalent bonds. The synthesis of this type of macromolecular structure is made by the polymerization reaction of monomers (Figure 1). Over the last decades, polymer science has significantly developed, making available durable and versatile polymeric materials for daily-life applications including textile, electronic, toys and food packaging. Although polymers also are present in nature, e.g., deoxyribonucleic acid (DNA) and ribonucleic acid (RNA),[1] synthetic alternatives, designed to serve for specific needs, are widespread.

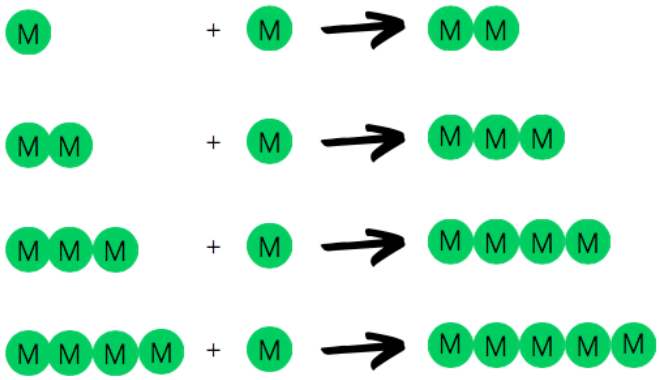


Figure 1. Schematic of a polymerization reaction.

Nowadays, polymerization of biobased monomers is having a big impact in the production of polymers.[2] The derivation of polymeric materials from sustainable and annually renewable resources, such as vegetable oils, sugars, terpenes, among others, has attracted increasing interest to limit the utilization of finite resources and to decrease carbon dioxide emissions. Bio-based polymers are an interesting alternative to traditional petroleum-based plastics, as they are often less toxic and sometimes offer appealing biodegradable characteristics.[3] An outstanding example of biobased and biodegradable polymer, which is already commercially available, is polylactic acid (PLA) (Figure 2).[4]

The straightforward PLA synthesis is the direct polycondensation of lactic acid at high temperature. However, the most convenient method to produce PLA is the ring-opening polymerization (ROP) of lactide (Figure 2). In fact, the industrial production of PLA mostly relies on the latter route in which the lactide monomer is first prepared from L- and/or D-lactic acid and subsequently subjected to ROP.[5]

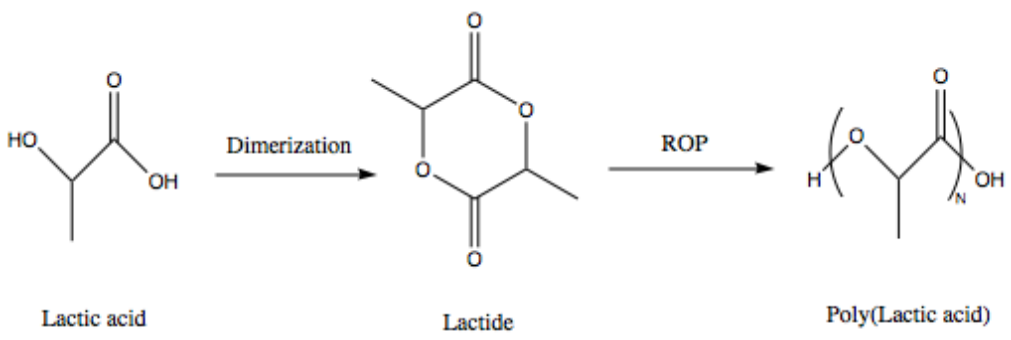


Figure 2. Synthetic process to obtain PLA via ROP of lactide.

PLA is a bioabsorbable polymer with many applications in the medical field. For example, PLA filaments as used for suturing, wool for hemostatic, and rods for bone fixation. Moreover, as a biodegradable plastic is also useful for short-term applications as rigid and flexible packaging film, cold drink cups, cutlery, filament and staple fibers, bottles, injection and extrusion molds and so on, and as durable and specialty materials such as car parts and electric appliances.[4]

Lactic acid is one of the most known bio-synthons mainly because of PLA. The Swedish chemist Carl Wilhelm Scheele was the first person to isolate lactic acid in 1780 from sour milk. The chemical route for the synthesis of lactic acid is based on the hydrolysis of lactonitrile, a byproduct of acrylonitrile production. However, the resulting product is a racemic mixture of L-(+)-lactic acid and D-(-)-lactic acid. In fact, lactic acid has a chiral carbon that originates two possible configurational isomers (enantiomers) (Figure 3).

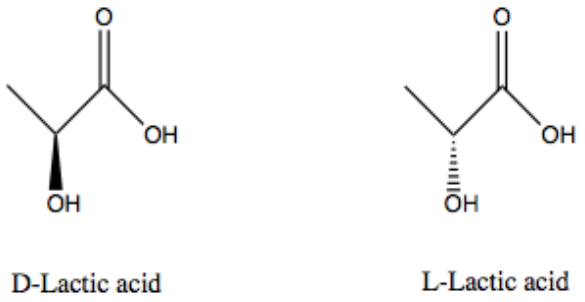


Figure 3. Chemical structure of the two enantiomeric forms of lactic acid.

Nevertheless, currently about 90% of the lactic acid is produced by the fermentation of refined carbohydrates with the appropriate microorganisms.[5] This appealing approach produces enantiomerically pure lactic acid, which is more valuable than the D/L racemic mixture. It is important to highlight that this approach is based on renewable resources, has low energy consumption and low temperature requirements.

Lactic acid is also a valuable platform chemical for the production of green solvents. Ethyl lactate (EL) and *N,N*-dimethyl lactamide (DML) are in the portfolio of available green biosolvents suitable to replace traditional chemicals because they offer an appealing combination of properties including high boiling point, high solvency power, negligible toxicity, and 100% biodegradability that translate into important environmental benefits and performance advantages.[7] The secondary alcohol group of these two abundantly available chemicals offers a simple access to vinylic biobased monomers suitable for use in radical polymerization. Suspol laboratory at URV recently reported the upgrading of these two biobased solvents into acrylic polymeric materials for specialty applications (Figure 4).[2,8] Interestingly, poly(EL acrylate) is a hydrophobic and water-insoluble polymer whereas poly(DML acrylate) is a highly hydrophilic and water-soluble polymer with no soluble-insoluble transition in aqueous media up to 100 ºC.

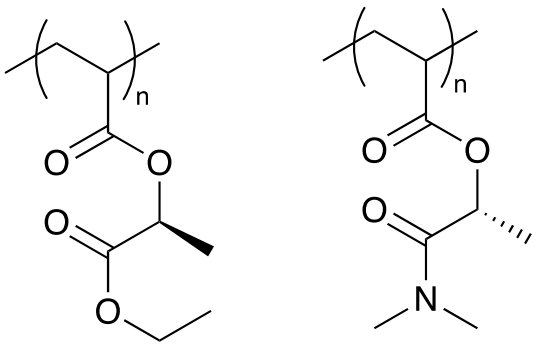


Figure 4. Chemical structure of the repetitive unit of poly(EL acrylate) (left) and poly(DML acrylate) (right).

Vinylic derivatives of *N*-alkyl lactamides and polymers thereof are only reported in the old patent literature[9] and no study on their physical properties is yet available to best of our knowledge. With the final goal of synthesizing smart biobased materials based on lactic acid, herein we seek to enable the development of thermoresponsive (co)polymers based on lactamide acrylic derivatives. Thermoresponsive polymers have a wide range of applications because of their interesting properties, which change depending on the environmental conditions, namely, temperature. The most popular applications of thermoresponsive polymers are drug delivery and injectable gels.[10] There are other applications as 3-D printing and synthesis of inorganic particles.[11]

3. OBJECTIVES

The main objective of this project is to synthesize well-defined thermoresponsive polymers, i.e., homopolymers and random copolymers, based on acrylic lactic acid derivatives. These polymers will be designed to exhibit conformational changes in response to temperature stimuli.

More specifically, the objectives of this work are the following:

· To synthesize and characterize a series acrylic lactamide monomers using ethyl lactate solvent as starting material.

· To conduct the controlled radical polymerization and copolymerization of these biobased monomers using RAFT polymerization.

· To study the thermoresponsiveness of the synthesized (co)polymers by variable-temperature optical transmittance measurements.

4. EXPERIMENTAL PART

4.1. Materials

The following chemicals were purchased from Merck and used as received: ethyl lactate (EL, ≥ 98%), 1,5,7-triazobicyclo[4.4.0]dec-5-ene (TBD, 98%), isopropylamine (≥ 99.5%), triethylamine (TEA, ≥ 99%), acryloyl chloride (≥ 97 %), propylamine (99%), ethylamine solution 2M in THF, dimethylsulfoxide (DMSO, ≥ 99%), 2-(dodecylthiocarbonothioylthio) propionoic acid (DTPA, 97%), hydroquinone (≥ 99%)Azabisisobutironitrilo (AIBN) was purchased from Fluka. Hydrochloric acid (HCl, 37.5%), sodium carbonate anhydrous ($NaHCO_3$, extra pure) and sodium chloride (NaCl, 99%) were purchased from Scharlab. Deuterated water (D_2O, 99.96%) and deuterated chloroform ($CDCl_3$) were purchased from Euriso-top. Ethyl acetate (99%), hexane, ethanol (96%), dichloromethane, diethylether, silica, *N,N*-dimethylformamide (DMF), tetrahydrofurane (THF) and acetone (synthesis grade) were purchased from Scharlab. Anhydrous dichloromethane was freshly distilled over CaH_2 prior to use.

4.2. Methods

4.2.1. Nuclear Magnetic Resonance (NMR) spectroscopy

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded at a 400 MHz (for ^1H) and 100.6 MHz (for ^{13}C) in a Varian VNMR-S400 NMR instrument at 25 ºC in $CDCl_3$. All chemical shifts are quoted on the δ scale in ppm using the residual non-deuterated solvent as an internal standard (^1H NMR: $CDCl_3$ = 7.26 ppm and ^{13}C NMR: $CDCl_3$ = 77.16).

4.2.2. Gel Permeation Chromatography (GPC)

The determination of the number-average molecular weight (M_n), the mass-average molecular weight (M_w) and molecular weight dispersity (D) of the synthesized polymers was performed via GPC. The analyses were carried out using DMF as a mobile phase in an Agilent 1260 isocratic pump equipped with a manual injector Rheodyne Model 7125 with 20 μL loop, two PLgel 5 μm Mixed-D 30x7.5 mm linear columns (MW 200-400.000) of 75970 and 97293 plates/m (1/2 ht) with an Agilent 1100 series refractive index detector. The flow rate was fixed at 1 mL/min and toluene was used as an internal standard. The M_n and M_w values are given based on a calibration curve prepared using poly(methylmethacrylate) (PMMA) standards (ReadyCal kit purchased from PSS).

4.2.3. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) measurements were carried out on a Mettler DSC3+ instrument using N_2 as a purge gas (50 mL/min) at a scanning rate of 20 °C/min in the -80 to 120 °C temperature range. Calibration was made using an indium standard (heat flow calibration) and an indium-lead-zinc standard (temperature calibration).

4.2.4. Infrared Spectroscopy

Infrared spectra were recorded on a FTIR-6700 spectrophotometer with a resolution of 4 cm^{-1} in the transmittance mode.

4.2.5. UV-VIS Spectrophotometer

The cloud point of the (co)polymers was analyzed on a UV-2401PC UV-VIS Recording Spectrophotometer using a wavelength of 500 nm equipped with a thermocontrolled cell. The samples were prepared at a concentration of 5 mg/mL.

4.3. Aminolysis reaction of ethyl lactate with primary amines

EL solvent was used as a starting lactic acid derivative to prepare a series of secondary amides via aminolysis reaction[12,13] (Figure 5). Different reaction conditions were used based on the chemical structure/nucleophilicity of all the investigated primary amines, i.e., isopropylamine, propylamine, ethylamine and 2-methoxyethan-1-amine.

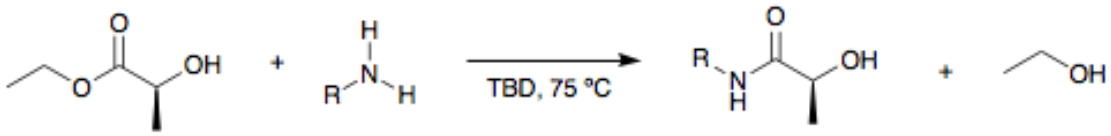


Figure 5. Aminolysis reaction of EL with primary amines.

The synthesis of 2-hydroxy-*N*-isopropylpropanamide and 2-hydroxy-*N*-(2-methoxyethyl) propanamide was achieved following the same procedure. In both cases, the reaction was carried using 1,5,7-triazobiciclo[4,4,0]dec-5-ene (TBD) as catalyst and a temperature of 75 ºC. Into a round-bottomed flask containing a magnetic bar, TBD (1 g, 7.15 mmols) was dissolved in EL (5.49 mL, 48 mmols). The resulting solution was magnetically stirred under argon flow for 5 min before adding the corresponding amine (57.47 mmols).

The calculations done for the experiment with isopropylamine are the following one:

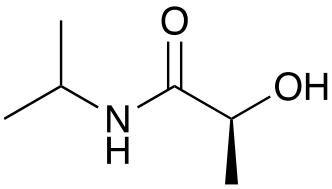
$$1g\ TBD \cdot \frac{1\ mol\ TBD}{139.2\ g\ TBD} \cdot \frac{100\ mols\ EL}{15\ mols\ TBD} \cdot \frac{118.13g\ EL}{1\ mol\ EL} \cdot \frac{1\ mL\ EL}{1.031g\ EL} = 5.49\ mL\ EL$$

$$1g\ TBD \cdot \frac{1\ mol\ TBD}{139.2\ g\ TBD} \cdot \frac{100\ mols\ EL}{15\ mols\ TBD} \cdot \frac{1.19\ mols\ IPA}{1\ mol\ EL} \cdot \frac{59.11\ g\ IPA}{1\ mol\ IPA} \cdot \frac{1mL\ IPA}{0.688g\ IPA}$$

$$= 4.91\ mL\ IPA$$

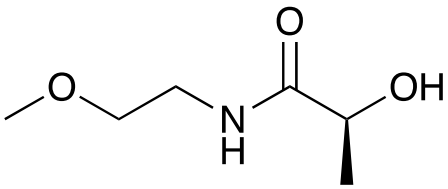
The reaction was allowed to proceed during 12 hours at 75 ºC. The conversion of the reaction was determined by ^{1}H NMR spectroscopy. The mixture was rotaevaporated to remove the ethanol formed and the excess of amine added. Then, a distillation under reduced pressure was carried out to isolate the lactamide product.

2-Hydroxy-*N*-isopropylpropanamide (IPA)



^{1}H NMR (401 MHz, Chloroform-d) δ: 4.17 (q, J = 6.8 Hz, 1H), 4.05 (dhept, J = 8.20, 6.60 Hz, 1H), 1.41 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.6 Hz, 6H).
^{13}C NMR (101 MHz, Chloroform-d) δ: 173.89, 68.24, 41.03, 22.67, 21.25.
FTIR-ATR (ν_{max}): 3300, 2973, 2934, 2876, 1641.

2-Hydroxy-*N*-(2-methoxyethyl)propanamide

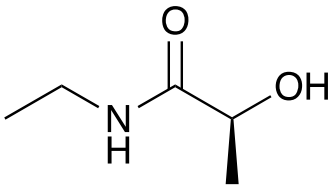


^{1}H NMR (401 MHz, Chloroform-d) δ: 4.21 (q, J = 6.90 Hz, 1H), 3.54-3.39 (m, 4H), 3.36 (s, 3H), 1.42 (d, J.= 6.9 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ: 174.97, 71.10, 68.19, 58.72, 38.27, 20.69.
FTIR-ATR (ν_{max}): 3321, 2978, 2931, 2884, 2830, 1644,1118.

The synthesis of *N*-ethyl-2-hydroxypropanamide was conducted according to the following procedure. This reaction was performed using TBD as catalyst and a temperature of 75 ºC. A mixture of TBD (1 g, 7.20 mmols) in EL (5.50 mL, 48.00 mmols) was magnetically stirred under argon flow for 5 minutes. Then, 36.00 mL (72.00 mmols) of a commercially available solution of 2 M ethylamine in THF was added. The reaction was allowed to proceed for 12 hours at 65 ºC. The conversion of the reaction was determined by ^{1}H NMR spectroscopy. The mixture was rotaevaporated to remove the

ethanol formed and the excess of amine added. Then, it was performed a column using ethyl acetate:hexane (9:1) as eluent to isolate the pursued lactamide product.

N-Ethyl-2-hydroxypropanamide



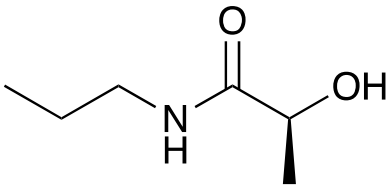
^{1}H NMR (401 MHz, Chloroform-d) δ: 4.28-4.17 (m, 1H), 3.33 (qd, J = 7.30, 5.70 Hz, 2H), 1.44 (d, J = 6.80 Hz, 3H), 1.17 (t, J = 7.30 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ: 174.36, 68.37, 34.00, 21.31, 14.77.

FTIR-ATR (ν_{max}): 3315, 2976, 2934, 1639.

The synthesis of 2-hydroxy-*N*-propylpropanamide is described. Into a flask with a magnetic bar, it was added EL (17.10 mL, 149.10 mmols). After 5 minutes of magnetically stirred under argon flow, it was added propylamine (14.70 mL, 178.20 mmols). The reaction was allowed to proceed during 12 hours at 75 ºC. The conversion of the reaction was determined by ^{1}H NMR spectroscopy. The mixture was rotaevaporated to remove the ethanol formed and the excess of amine added.

2-Hydroxy-*N*-propylpropanamide



^{1}H NMR (401 MHz, Chloroform-d) δ: 6.77 (s, 1H), 4.20 (q, J = 6.80 Hz, 1H), 3.29-3.16 (m, 2H), 1.54 (h, J = 7.40 Hz, 2H), 1.42 (d, J = 6.80 Hz, 3H), 0.93 (t, J = 7.40 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ: 174.84, 68.33, 40.78, 22.77, 21.29, 11.29.

FTIR-ATR (ν_{max}): 3313, 2965, 2934, 2876, 1641.

4.4. Acrylation reaction of lactamides

All the above synthesized lactamides were used as starting materials for the preparation of the corresponding acrylic monomers via acrylation reaction. In all cases, acryloyl chloride was used as acrylating reagent (Figure 6). This procedure described herein is generic for all the targeted monomers.[2]

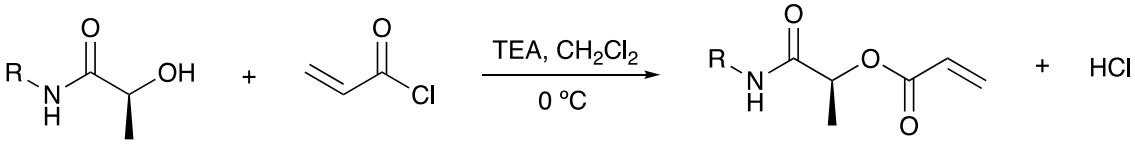
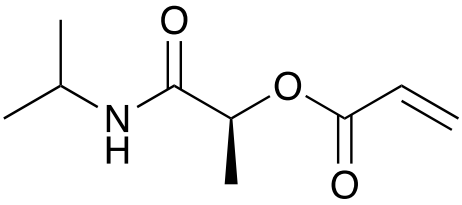


Figure 6. Acylation reaction of lactamide derivatives.

The synthesis of 1-(isopropylamino)-1-oxopropan-2-yl acrylate is described as a representative procedure. 2-Hydroxy-N-isopropylpronamide (5.68 g, 40.00 mmols) and TEA (8.69 mL, 66.00 mmols) were dissolved in dry DCM (22.00 mL) in a round-bottomed flask under argon flow. After stirring the solution for 10 min, it was cooled at 0 ºC and acryloyl chloride (3.78 mL, 0.05 mols), dissolved in anhydrous DCM (18 mL), was added dropwise with an addition funnel. The reaction was allowed to proceed for 16 h at room temperature. The mixture was filtered and sequentially washed with a 1 M HCl, saturated $NaHCO_3$ and saturated NaCl solutions. Then, the organic layer was separated and dried over anhydrous $MgSO_4$. The final residue was purified by vacuum distillation in the presence of 5 w/w % of hydroquinone to afford the monomer as a colorless liquid. The product crystallized as a white solid while storing in the fridge.

1-(Isopropylamino)-1-oxopropan-2-yl acrylate (IPLA)

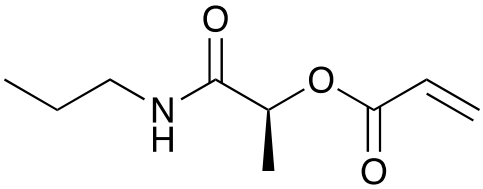


^{1}H NMR (401 MHz, Chloroform-d) δ: 6.49 (dd, J = 17.30, 1.30 Hz, 1H), 6.19 (dd, J = 17.30, 10.40 Hz, 1H), 5.93 (dd, J = 10.50, 1.30 Hz, 1H), 5.26 (q, J = 6.8 Hz, 1H), 4.09 (dp, J = 8.00, 6.50 Hz, 1H), 1.50 (d, J = 6.80 Hz, 3H), 1.17 (dd, J = 8.40, 6.60 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ: 169.30, 164.65, 132.13, 127.77, 70.75, 41.25, 22.65, 17.85.

FTIR-ATR (ν_{max}): 3289, 3105, 2970, 2940, 2880, 1726, 1656.

1-Oxo-1-(propylamino)propan-2-yl acrylate (PrLA)

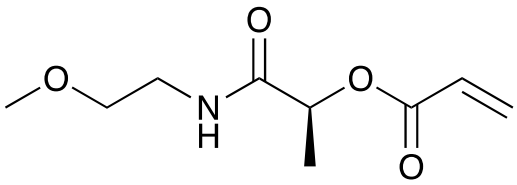


^{1}H NMR (401 MHz, Chloroform-d) δ: 6.49 (dd, J = 17.30, 1.30 Hz, 1H), 6.18 (dd, J = 17.30, 10.50 Hz, 1H), 5.93 (dd, J = 10.40, 1.30 Hz, 1H), 5.29 (q, J = 6.80 Hz, 1H), 3.29-3.20 (m, 1H), 1.52 (dd, J = 12.3, 7.00 Hz, 5H), 0.92 (t, J = 7.40 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform- d) δ:170.23, 164.69, 132.00, 127.73, 70.67, 40.22, 22.68, 17.85, 11.16.

FTIR-ATR (ν_{max}): 3289, 3109, 2967, 2936, 2876, 1728, 1659, 1567.

1-((2-Methoxyethyl)amino)-1-oxopropan-2-yl acrylate (MeOEtLA)

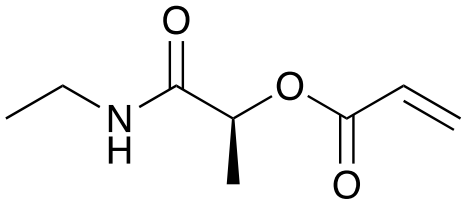


^{1}H NMR (401 MHz, Chloroform-d) δ: 6.49 (dd, J = 17.40, 1.30 Hz, 1H), 6.19 (dd, J = 17.30, 10.40 Hz, 1H), 5.93 (dd, J = 10.50, 1.30 Hz, 1H), 5.30 (q, J = 6.80 Hz, 1H), 3.56 – 3.40 (m, 4H), 3.36 (s, 2H), 1.52 (d, J = 6.90 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ: 170.36, 164.62, 132.10, 128.12, 71.00, 70.73, 58.84, 38.96, 17.88.

FTIR-ATR (ν_{max}): 3289, 3104, 2974, 2935, 2893, 2813, 1725, 1654, 1618.

1-(Ethylamino)-1-oxopropan-2-yl acrylate (EtLA)



^{1}H NMR (401 MHz, Chloroform-d) δ: 6.50 (dd, J = 17.30, 1.30 Hz, 1H), 6.19 (dd, J = 17.30, 10.40 Hz, 1H), 5.94 (dd, J = 10.40, 1.30 Hz, 1H), 5.29 (q, J = 6.80 Hz, 1H), 3.33 (qd, J = 7.30 Hz, 5.70 Hz, 2H), 1.51 (d, J = 6.90 Hz, 3H), 1.16 (t, J = 7.30 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ: 170.07, 164.64, 132.19, 127.73, 70.73, 34.17, 17.86, 14.75.

FTIR-ATR (ν_{max}): 3288, 3100, 2983, 2935, 2875, 1725, 1654.

4.5. Controlled RAFT polymerization of lactamide acrylate monomers

The controlled radical polymerization of all the synthesized monomers was conducted via RAFT polymerization (Figure 7). This following experimental procedure is generic for all the polymerization reactions conducted herein.

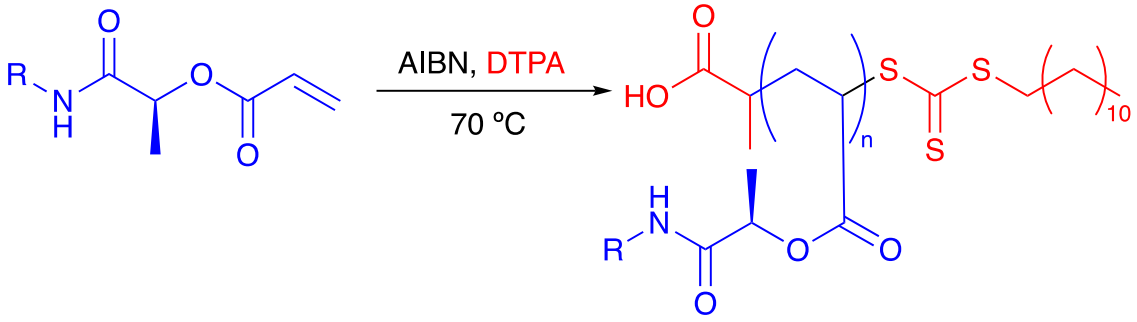


Figure 7. RAFT polymerization of lactamide acrylate monomers using DTPA as a chain transfer agent and AIBN as a radical initiator.

The polymers were prepared by solution RAFT polymerization in DMF at 70 ºC employing 2-(dodecylthiocarbonothioylthio)-2-methylpropinoic acid (DTPA) as the chain-transfer agent (CTA). Herein, a typical experimental procedure to conduct the RAFT polymerization of 1-(dimethylamino)-1-oxopropan-2-yl acrylate under the following conditions: $[M]_o$:$[DTPA]_o$:$[AIBN]_o$ = 50:1:0.1 and $[M]_o$ = 7 M, is described in detail. The monomer (400 mg, 2.16 mmols) and DTPA (15.15 mg, 0.04 mmols) were introduced into a Schlenk tube equipped with a rubber septum. Simultaneously, a stock solution of AIBN (2.84 mg, 0.02 mmols) in DMF (1.2 mL) was prepared. Next, 0.3 mL (0.005 mmol) of this solution were introduced into the Schlenk tube containing monomer and CTA. The following calculations were done:

$$400\ mg\ monomer \cdot \frac{1\ mmol\ monomer}{185.11\ mg\ monomer} \cdot \frac{1\ mmol\ DTPA}{50\ mmols\ monomer} \cdot \frac{350.60\ mg\ DTPA}{1\ mmol\ DTPA} = 15.15\ mg\ DTPA$$

$$400\ mg\ monomer \cdot \frac{1\ mmol\ monomer}{185.11\ mg\ monomer} \cdot \frac{0.1\ mmol\ AIBN}{50\ mmols\ monomer} \cdot \frac{164.21\ mg\ AIBN}{1\ mmol\ AIBN} = 0.71\ mg\ AIBN$$

$$400\ mg\ monomer \cdot \frac{1\ mmol\ monomer}{185.11\ mg\ monomer} \cdot \frac{1\ mol\ monomer}{1000\ mmols\ monomer} \cdot \frac{1000\ mL\ DMF}{7\ mols\ monomer} = 0.3\ mL\ DMF$$

After that, the solution was deoxygenated during 30 minutes by bubbling Ar with continuous stirring. Then, the Schlenk was introduced to a polyethylenglycol bath at 70 ºC for 2 hours. The reaction was stopped by cooling the reaction mixture using a liquid nitrogen bath and opening the Schlenk tube to the air. The monomer conversion was determined by ^{1}H NMR analysis by comparing the integral areas of the monomer protons of C=C-H at δ= 5.95 ppm and the integral area of the polymer protons of -CO-CH-OCO at 5.32 ppm. The signal for one proton of the monomer is directly proportional to the signal for the protons of the polymer. The monomer conversion was calculated using the following equation (1):

$$Conversion\ (\%) = \frac{integration_{polymer} - integration_{monomer}}{integration_{polymer}} \cdot 100 \qquad (1)$$

Therefore, if the integration is normalized considering that the integration for the proton of the monomer corresponds to 1.00, the conversion can be obtained from the following equation (2):

$$Conversion\ (\%) = \frac{integration\ of\ the\ polymer - 1}{integration\ of\ the\ polymer} \cdot 100 \qquad (2)$$

M_n, M_w and D index values were measured using small aliquots of the polymer solution by GPC using PMMA standards. To isolate the synthesized polymer, it was proceeded as follows: the crude polymer solution was diluted in CH_2Cl_2, immediately introduced into a dialysis bag and dialyzed against acetone overnight. The acetone was replaced each 30 minutes during the first 2 h. Finally, the polymers were isolated as white or pale-yellow powders after evaporating the solvent under reduced pressure.

5. RESULTS AND DISCUSSION

The experimental results from the different stages of the work will be presented and discussed in the next paragraphs.

5.1. Aminolysis reaction of ethyl lactate with primary amines

The first step for the preparation of the targeted lactamide acrylic derivatives was the aminolysis reaction of EL solvent with various primary amines: ethylamine, propylamine, isopropylamine and 2-methoxyethanamine (Figure 8).

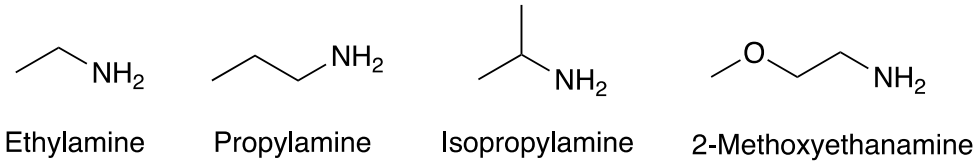


Figure 8. Chemical structure of the different primary amines used in this study.

The aminolysis reaction conditions were optimized while trying to maximize the green angle of the process. In this way, we tried to avoid the use of solvents, metallic catalysts and harsh reaction conditions. Hence, we tested different conditions in order to achieve the desired product with high conversion, while minimizing the amount of catalyst/solvents. As will be discussed below, for each aminolysis reaction, the conditions were varied due to the different structure of the primary amines used.

Propylamine was the first primary amine studied. The extent of the EL ester amidation process was determined by ^{1}H NMR analysis of the reaction mixture after predetermined periods. As can be seen in Figure 9, the conversion could be calculated using characteristic signals of both the desired amide product and the starting material.

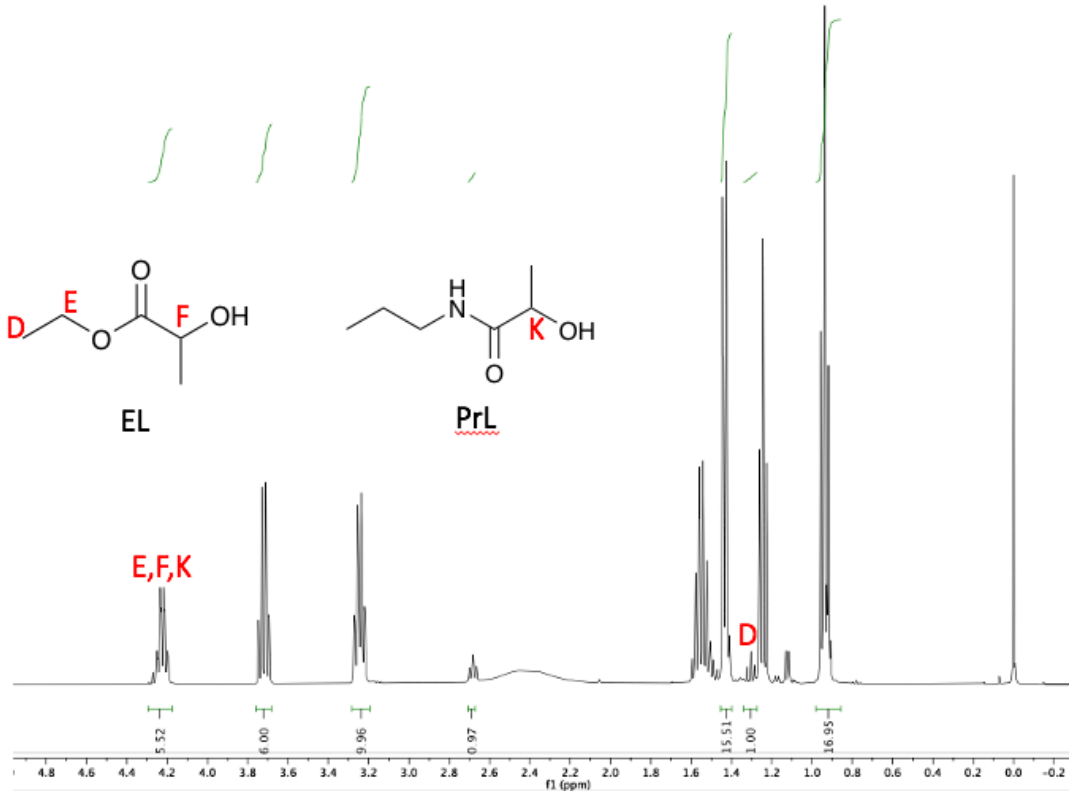


Figure 9. NMR spectra after 24h for the aminolysis of EL with propylamine (82% ester aminolysis).

The conversion of the aminolysis process was calculated using the following equation (3). In this equation it was taken into account the overlapping of the peaks E, F and K as they appeared in the same chemical shift. The integration was normalized considering the 3 protons of the signal D as 1.00.

$$Conversion\ (\%) = \frac{int.H^E + int.H^F + int.H^K - int.H^D}{int.H^E + int.H^F + int.H^K - int.H^D + int.H^D} \cdot 100 \qquad (3)$$

$$Conversion\ (\%) = \frac{5.52 - 1.00}{5.52 - 1.00 + 1.00} \cdot 100 = 82\ \%$$

As can be seen in Table 1, ~80% conversion could be achieved after 24 h in absence of catalyst/solvent at room temperature using 20% excess of amine reagent. Interestingly, conversion higher than 90% could also be achieved after only 15 h when the reaction was conducted at 75 ºC.

Table 1. Aminolysis of EL with propylamine.

Amine	*EL:amine molar ratio*	*Temperature (ºC)*	*Time (h)/ Conversion (%)*
Propylamine	1:1.2	Room Temperature	18 h: 78% 24 h: 82%
	1:1.2	75	15 h: 92%

Next, we investigated the aminolysis of EL using 2-methoxyethylamine and isopropyl amine (see Tables 2 and 3, respectively).

Table 2. Aminolysis of EL with N-methoxyethylamine.

Amine	*EL:amine molar ratio*	*% mol TBD*	*Temperature (ºC)*	*Time (h)/ Conversion (%)*
2-Methoxyethyl amine	1.5	0	Room Temperature	24 h: 61%
	1.2	15	75	15 h: 100%
	1.2	30	75	19 h: 100%

Table 3. Aminolysis of EL with isopropylamine.

Amine	*EL:amine molar ratio*	*% mol TBD*	*Temperature (ºC)*	*Time (h)/ Conversion (%)*
Isopropylamine	1.2	25	75	17h: 100%
	1.2	15	75	16h: 100%
	1.2	5	75	17h: 75%

Interestingly, despite using 50% excess of amine, the aminolysis of EL using N-methoxyethylamine only proceed up to 60% conversion at room temperature after 24 h. The lower reactivity of this primary amine is related to the decreased N nucleophilicity due to the electron-withdrawing inductive effect generated by the methoxy group. Accordingly, we decided to use 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a catalyst to improve aminolysis conversion. It is well known in the literature that the bicyclic guanidine TBD is an effective organocatalyst for the formation of amides from esters and primary amines.[14] Mechanistic and kinetic investigations support a nucleophilic mechanism where TBD reacts reversibly with esters to generate an acyl-TBD intermediate that acylates amines to generate the amides (Figure 10).

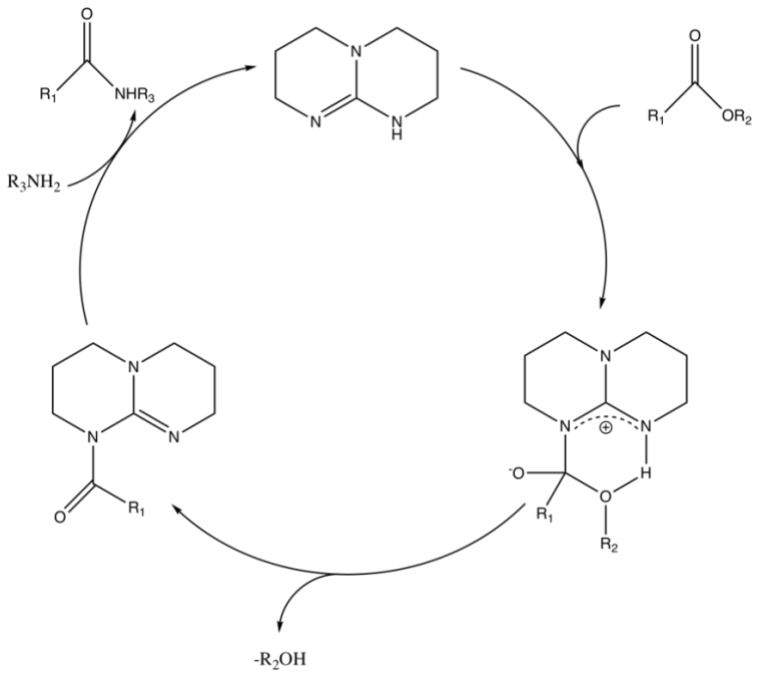


Figure 10. Proposed mechanism for TBD-catalyzed for the formation of amides from esters and primary amines.[15]

As can be seen in Table 1, the use of 15 % mol of TBD combined with a 20%-mol excess of amine at 75 ºC enabled to achieve near quantitative aminolysis. Under these conditions, the aminolysis of EL was also successful using isopropylamine (see Table 3). Unfortunately, we could not replicate the same reaction conditions when using ethylamine. Ethylamine is in the gas state at room temperature, and we purchased it as a 2 M solution in THF. As expected, the presence of THF in the reaction mixture reduced the extent of the aminolysis reaction due to the dilution effect (Table 4). After several attempts, the maximum aminolysis conversion using ethylamine was ~70%.

Table 4. Conditions and conversion for aminolysis of ethylamine.

Amine	*EL:amine molar ratio*	*% mol TBD*	*Temperature (ºC)*	*Time (h)/ Conversion (%)*
Ethylamine	1.2	15	Room Temperature	16 h: 48%
	1.2	15	75	20 h: 68%
	1.5	15	75	23 h: 62%
	1.5	15	65	16 h: 60%

The purification of the four synthesized lactamides is described in detail in the experimental section. Briefly, vacuum distillation or column chromatography was used to isolate the pursued products in moderate yields.

The chemical structure of the synthesized intermediate products was confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as FTIR. As a representative example, Figures 11 and 12 show the NMR spectra of the 2-hydroxy-N-isopropylpropanamide (see the supporting information section for other compounds).

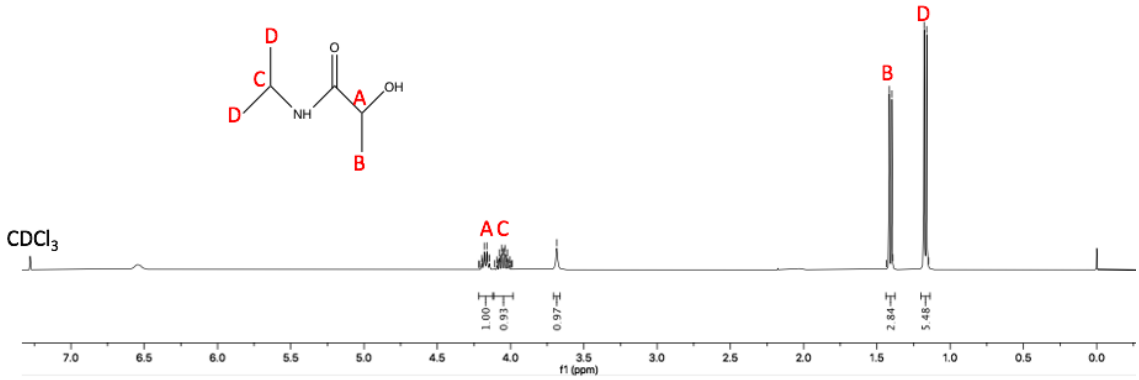


Figure 11. ^{1}H NMR spectrum for 2-hydroxy-N-isopropylpropanamide in $CDCl_3$.

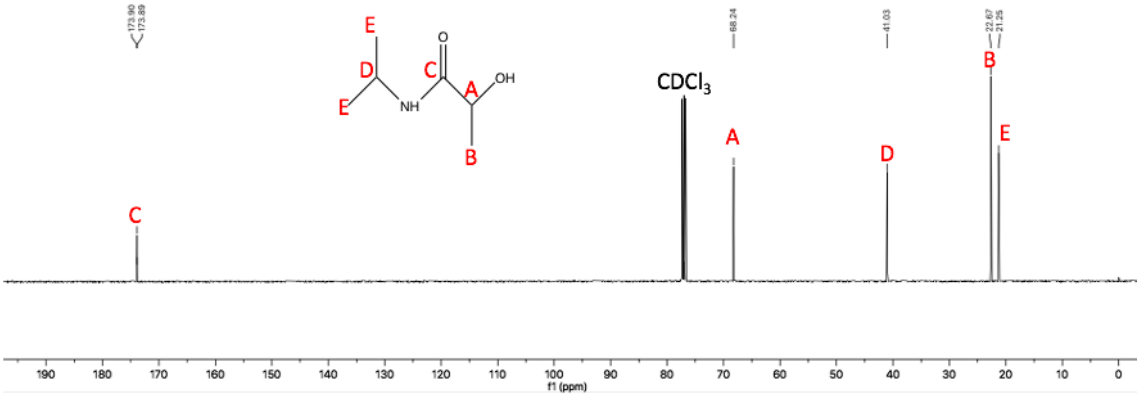


Figure 12. ^{13}C NMR spectrum for 2-hydroxy-N-isopropylpropanamide in $CDCl_3$.

In the ^{1}H NMR spectrum, the signal A appears at 4.17 ppm and corresponds to the proton of one of the methines (CO-CH-OH). This signal is a quadruplet due to the presence of the methyl group in the neighboring carbon. Very close to this signal, at 4.05 ppm there is the signal C, that corresponds to the proton of the other methine ($(CH_3)_2$-CH-NH). This signal is a multiplet due to the two methyls group in the neighboring carbons and the coupling with the proton of the amide. The signal B appears at 1.41 ppm and corresponds to the methyl group bonded to the methine of the signal A. For this reason, this signal is a doublet. The signal D appears at 1.17 ppm and corresponds to the two equivalent methyl group ($(CH_3)_2$-CH-). This signal is a doublet due to proton of the closest carbon. On the other hand, the ^{13}C NMR spectrum revealed 5 signals assigned to each of the carbons of the product. The chemical shift and the assignment of each signal is depicted in Figure 12.

The product was also characterized by FTIR. The broad peak at 3300 cm^{-1} corresponds to the O-H. The three bands that appear in the 3000-2850 cm^{-1} range are assigned for the CH_3, CH_2 and CH groups. There is a strong band at 1641 cm^{-1} that corresponds to the C=O of the amide. In the range 1500-1560 cm^{-1} there is a band with a medium intensity corresponding to the N-H group of the secondary amide.

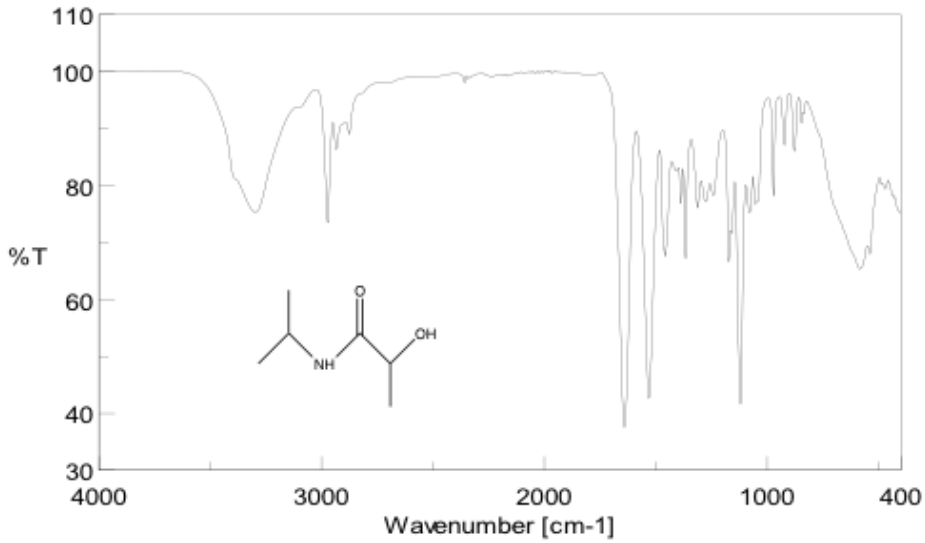


Figure 13. IR spectra for 2-hydroxy-N-isopropylpropanamide.

5.2. Acrylation reaction of lactamides

With the four targeted lactamides in our hands, we proceeded to synthesize the corresponding acrylic derivatives. The synthesis of these monomers was conducted following a conventional procedure that uses acryloyl chloride as an acylating reagent, dichloromethane as a solvent and triethylamine as a base to neutralize the generated acid (Figure 14).

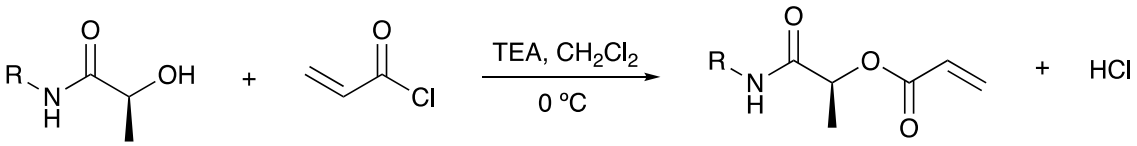


Figure 14. Synthesis of lactamide acrylic monomers.

All the produced monomers were purified by vacuum distillation in the presence of hydroquinone as a radical inhibitor to minimize polymerization during the distillation process. This experimental procedure produced the targeted monomers in moderate yields (Table 5). All the products crystallized as white solids after storing at room temperature.

Table 5. Yields obtained after purification of the acrylation reactions.

Acrylic Monomer	Yield	Physical state at Room Temperature	Melting point (°C)
PrL acrylate	63%	Solid	32.2 – 33.8
iPrL acrylate	68%	Solid	53.0 – 56.0
MeOEtL acrylate	63%	Solid	38.7 - 40.2
EtL acrylate	47%	Solid	31.8 – 33.5

The chemical structure of all the synthesized products was confirmed by measuring the corresponding FTIR, ^{1}H and ^{13}C NMR spectra. As a representative example, Figures 15-17 show the structural characterization for the 1-(isopropylamino)-1-oxopropan-2-yl acrylate. As can be seen in Figure 15, the FTIR spectrum is consistent with the expected structure.

The narrow band at 3300 cm^{-1} corresponds to the stretching of N-H amide bond. The peaks at 3100-3020 cm^{-1} correspond to the =C-H and $=CH_2$ groups of the acrylate moiety. In the range 3000-2850 cm^{-1} there are the characteristic bands for the stretching of the CH_3, CH_2 and CH groups. Finally, it is important to highlight that there are two peaks (1728 cm^{-1} and 1659 cm^{-1}) in the carbonyl region.

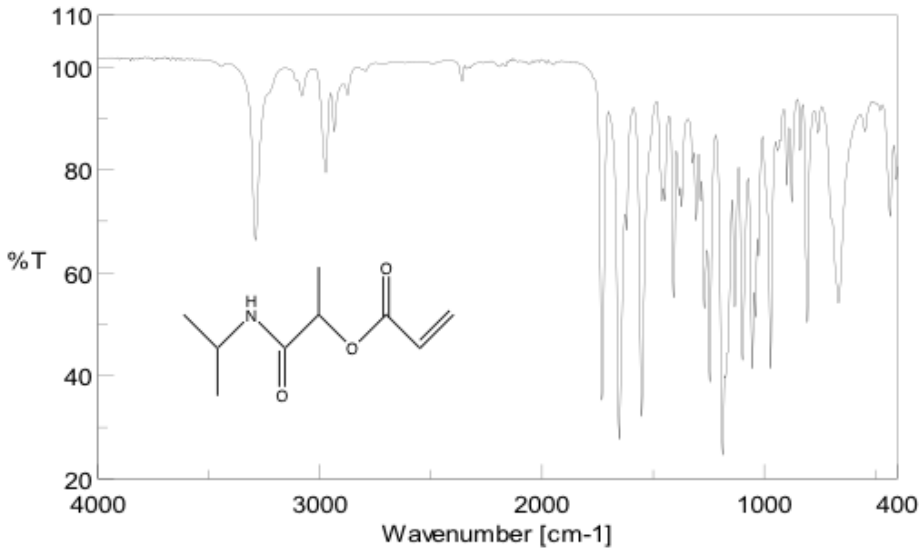


Figure 15. IR spectrum for the 1-(isopropylamino)-1-oxopropan-2-yl acrylate monomer.

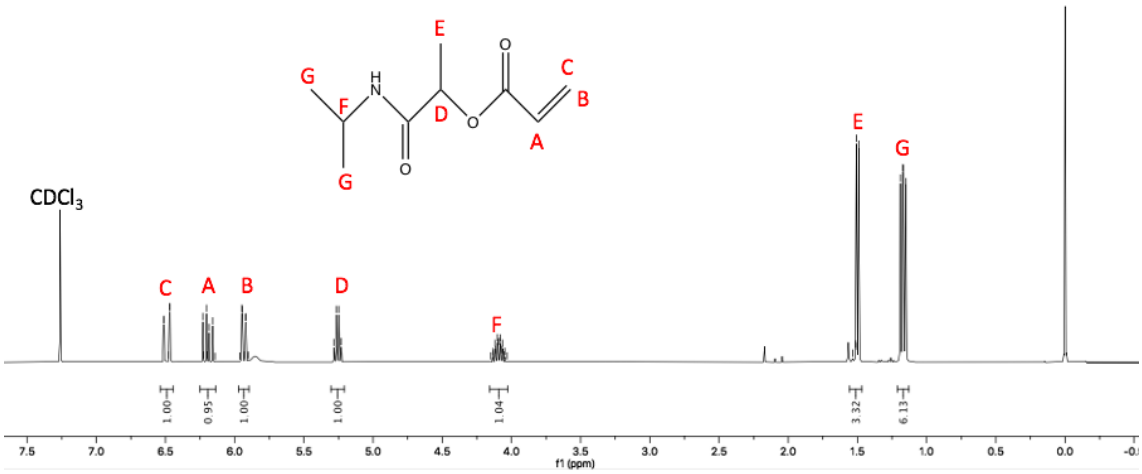


Figure 16. ^{1}H NMR spectra for 1-(isopropylamino)-1-oxopropan-2-yl acrylate

NMR analysis was also consistent with the proposed structure. In the ^{1}H NMR spectrum, the signals A, B and C (founded at 6.48, 6.20 and 5.9 ppm, respectively) corresponds to the protons of the double bond (Figure 16). The protons of the terminal carbon are not equivalent. The signal A is a doublet of doublet due to the protons in *cis* and *trans* position to the carbonyl. The signal B corresponds to the proton in cis position to the carbonyl and is a doublet of doublet because is coupled with the proton in trans and in geminal to the carbonyl. The signal C is a doublet of doublet and corresponds to the proton in trans position to the carbonyl. The signal D appears at 5.5 ppm and corresponds to the proton of the methine group of the unit -CO-CH-O-. The multiplicity of this signal is a quadruplet due to the methyl group in the closest carbon. The following signal founded at 4.15 corresponds to the signal F. It corresponds to the methine group closer to the amide and it is a multiplet, because is coupled with the protons of the methyls of the neighboring carbons. The signal G and E appears in the same chemical shift. This signal integrates 5 protons (two for the signal G and 3 for the signal E). The small signals in the range between 2.25 and 2.05 ppm corresponds to small amount of ethyl acetate.

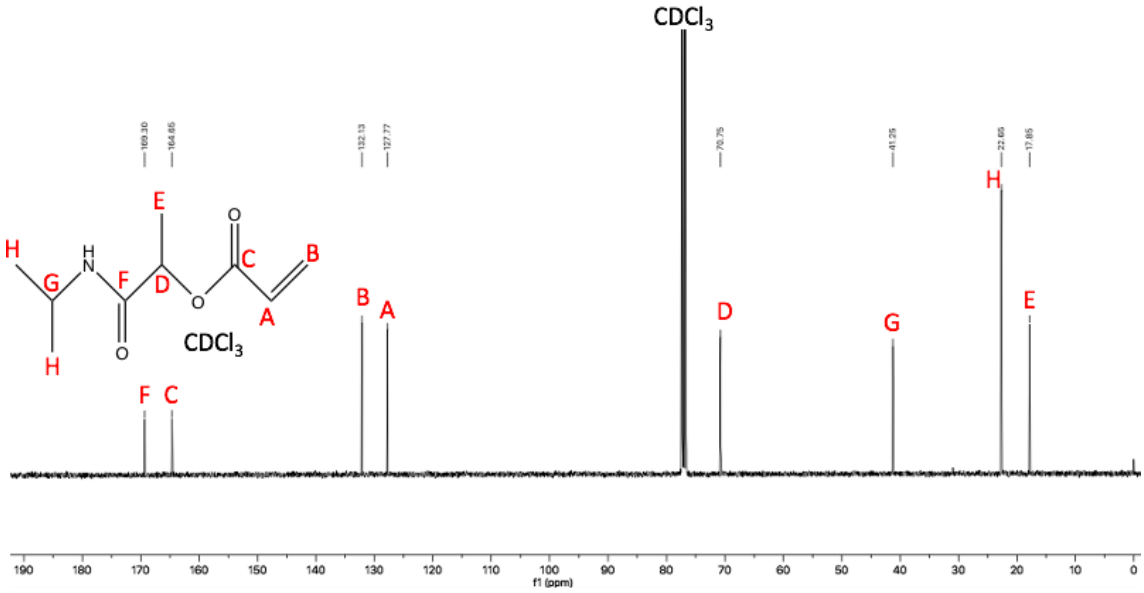


Figure 17. ^{13}C NMR spectra for 1-(isopropylamino)-1-oxopropan-2-yl acrylate.

The ^{13}C NMR spectra for 1-oxo-1-(propylamino)propan-2-yl acrylate is represented in the Figure 17. The chemical shift and the assignment of each carbon is represented.

5.3. Synthesis and characterization of homopolymers

Reversible addition-fragmentation chain transfer (RAFT) polymerization is well-known methodology to perform the controlled radical polymerization of vinylic monomers.[16] This method allows synthetic tailoring of macromolecules with complex architectures including block, graft, comb and star structures with predetermined molecular weight. RAFT polymerization is applicable to a very wide range of monomers under a large number of experimental conditions, including the preparation of water-soluble materials.

RAFT polymerization requires the use of a radical source and a RAFT agent commonly known as a chain transfer agent (CTA). The RAFT polymerization processes involve conventional free radical polymerization of a substituted monomer in the presence of a suitable CTA. In this work, we selected as a CTA the commercially available 2-(dodecylthiocarbonothioylthio)propinoic acid (DTPA) based on unpublished results of the Suspol group. The use of the proper RAFT agent is expected to allow the synthesis of polymers with high functionality and low polydispersity index (PDI), as can be seen in Figure 18. Conversely, in conventional radical polymerization processes, the heterogeneity of sizes of the polymers is much higher and the control on the degree of polymerization is not good.

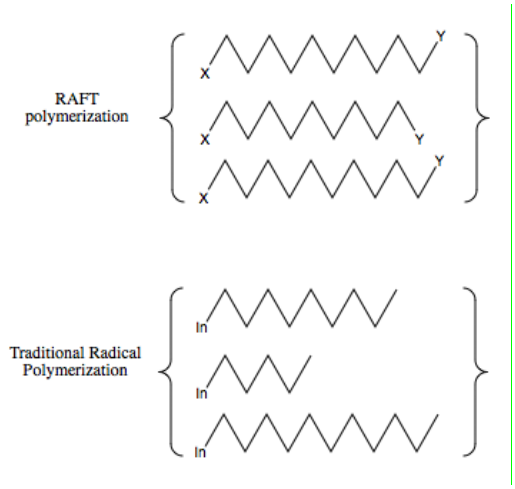


Figure 18. Schematic comparison between polymers prepared by RAFT polymerization and a conventional radical polymerization.

Figure 19 depicts the proposed mechanism for a RAFT polymerization.[17] First, the radical source, which is commonly azobisisobutyronitrile (AIBN) is decomposed to form two radical fragments ($I^{\bullet}$) that propagates with monomer (M) to give a polymeric radical ($P_n^{\bullet}$).

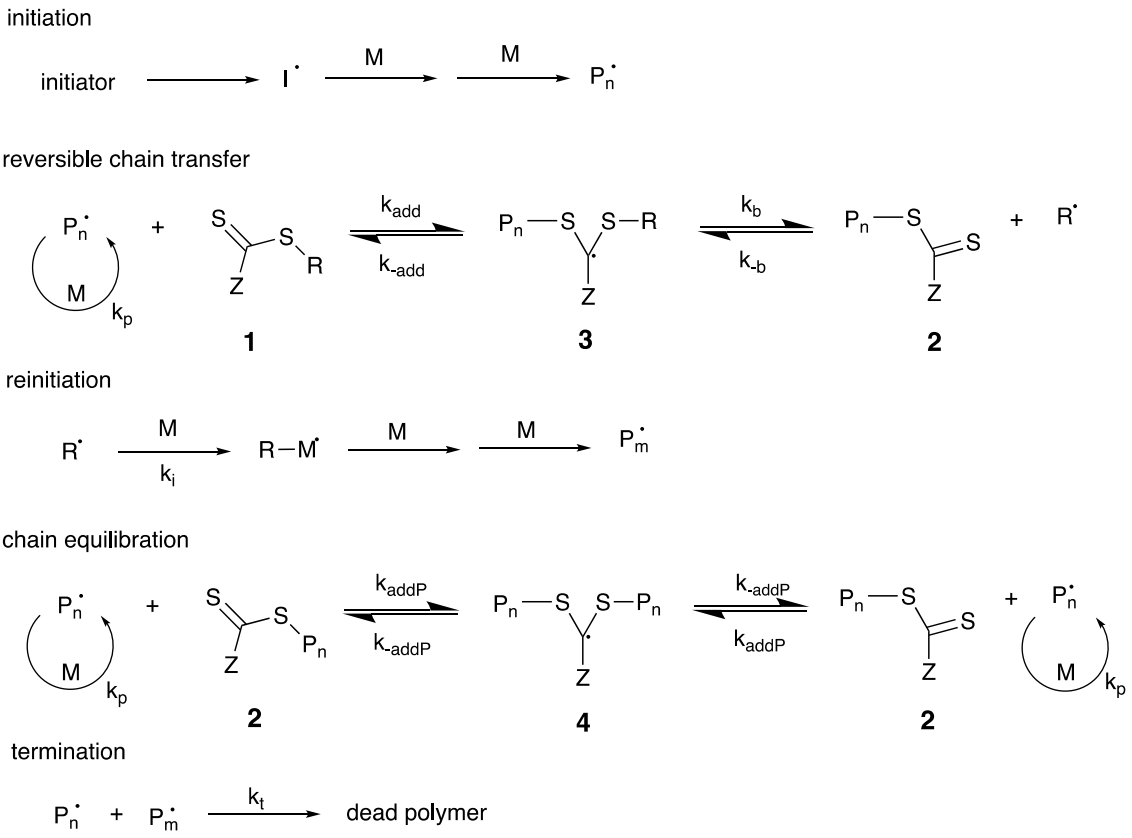


Figure 19. General mechanism for RAFT polymerization processes.

In the early stages of the polymerization, addition of a propagating radical ($P_n^{\cdot}$) to the thiocarbonylthio compound (RAFT agent 1) followed by fragmentation of the intermediate radical provides a polymeric thiocarbonylthio compound (macro-RAFT agent 2) and the expelled RAFT agent-derived radical ($R^{\cdot}$), which re-initiates polymerization.

The homopolymerization of all the synthesized lactamide acrylic monomers was conducted by RAFT polymerization targeting a degree of polymerization of 50. The proportion of monomer, CTA, and AIBN was fixed at [Monomer]:[DTPA]:[AIBN] = 50:1:0.1 with a [Monomer] = 2.7 M in DMF. The theoretical molecular weight expected for each of the polymerizations can be calculated with the equation (2).

$$Th.Mn\ (Polymer) = Mw\ (CTA) + DP \cdot Mw(Monomer) \qquad (2)$$

After preliminary experiments, all the polymerizations were left to proceeded for 2 h at 100 ºC to achieve high conversion. Next, the monomer conversion was determined by ^{1}H NMR, and M_n and D of the produced polymer were measured by GPC using DMF as a mobile phase. The results of the different polymerizations performed are summarized in Table 6.

Table 6. Theoretical and experimental molecular weight in number and polydispersity of the polymers.

Polymer	*Conversion (%)*	*Mn^{Th} (g/mol)*	*$Mn^{GPC,DMF}$ (g/mol)*	*D_{DMF}*
Poly(IPLA)	83%	7973	9019	1.17
Poly(MeOEtLA)	91%	9474	10922	1.13
Poly(EtLA)	83%	7396	9831	1.51
Poly(PrLA)	92%	8842	8841	1.20
Poly(DMLA)	98%	8727	12091	1.44

All the synthesized polymers were isolated by dialysis against acetone to perform further analyzes. Poly(MeOEtLA) was analyzed in detail by ^{1}H NMR to confirm the expected structure (Figure 20).

The theoretical molecular weight expected for a degree of polymerization of 50 can be calculated with the equation (2). The experimental molecular weight was calculated using ^{1}H NMR with the equation (4). The integration of protons H^A (normalized to 1) and H^F are represented in the Figure 20.

$$Exp\ Mn\ (Polymer) = Mw\ (CTA) + \frac{int.H^A}{(\frac{int.H^F}{3})} \cdot Mw\ (Monomer) \qquad (4)$$

Then, the experimental molecular weight for Poly(MeOEtLA) is calculated:

$$Exp\ Mn\ (Poly(MeOEtLA) = 380.6\frac{g}{mol} + \frac{1}{\frac{0.05}{3}} \cdot 201.10\frac{g}{mol}$$

$$Exp\ Mn\ (Poly(MeOEtLA) = 12447\frac{g}{mol}$$

However, for the rest of the polymers, the peaks for the protons H^E and H^F appeared overlapped and therefore precise determination of M_n by NMR was inaccurate. As can be seen in Table 6, RAFT polymerization under the reported conditions was an efficient methodology to control the degree of polymerization while retaining low polydispersity index.

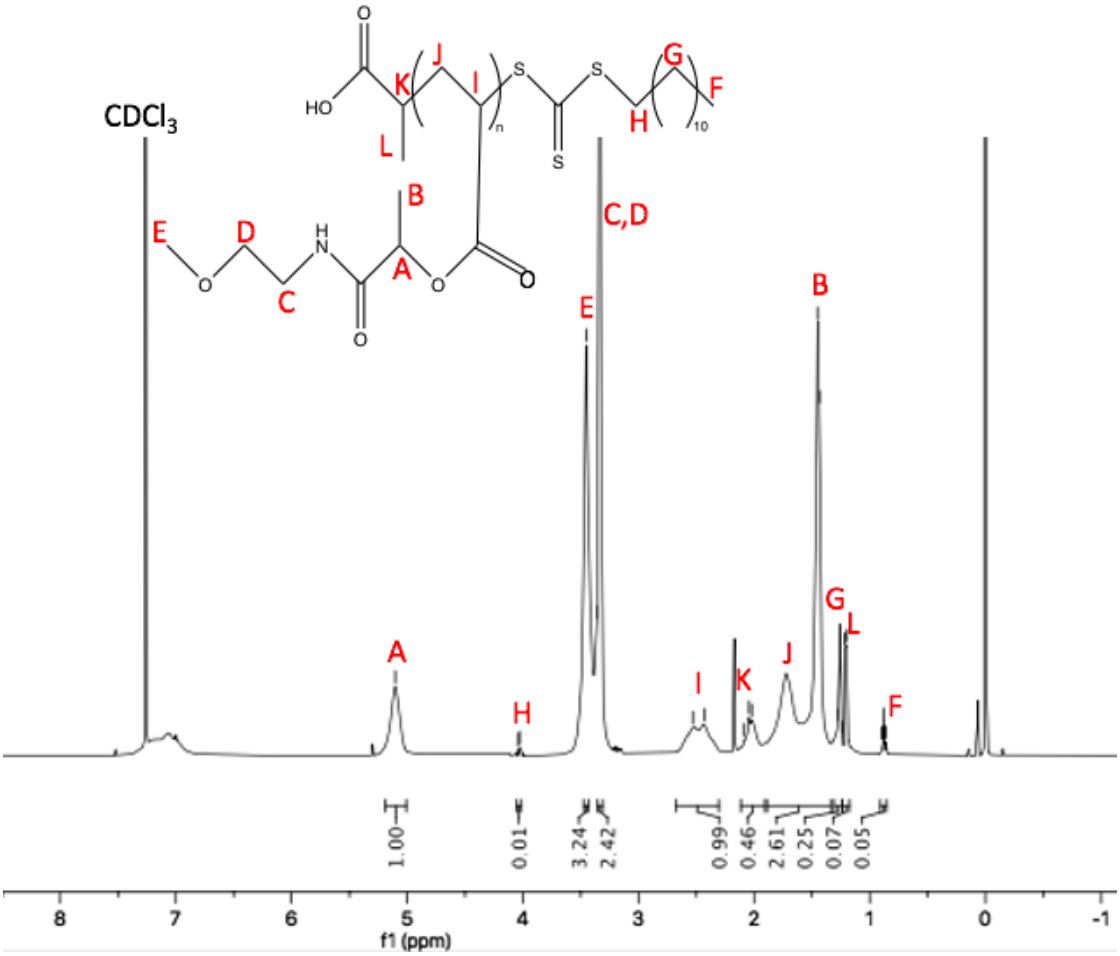


Figure 20. ^{1}H NMR spectrum of Poly(MeOEtLA).

The signal A, founded at 5.05 ppm, corresponds to the proton of the methine group (-CO-CH-O-). The multiplicity should be a quadruplet as it has a methyl group in the neighboring carbon, but the signal is theoretically repeated 50 times, so it becomes broad. The signal H has a very low integration and corresponds to the methylene closest to the sulfur. The signal E is a singlet and corresponds to the protons of the methoxy

group. The signals C and D appears in the same chemical shift at 3.30 ppm. The signal I corresponds to the methine group where initially were a double bond. The signal K corresponds to the methine group closest to the carboxylic acid. The signal J corresponds to the methylene group where initially were a double bond. The signal B comes from the protons of the methyl group of the repeated unit. The signal G and L appears in the same chemical shift. The signal F has a low integration and corresponds to the protons of the methyl group of the chain termination.

Finally, the thermal and water solubility properties of the synthesized homopolymers was investigated. Differential scanning calorimetry (DSC) revealed that all the obtained polymers are amorphous, and no significant differences were observed in their glass transition temperature (T_g). The T_g is the temperature at which a polymer changes from hard and brittle to soft and pliable nature. At the point of the T_g, the segmental movements of the chains increase, resulting in an increase in the free volume between the chains. As can be seen in Table 7, the T_g values ranged from 40 to 90 ºC.

Table 7. Glass transition temperature of the polymers synthesized.

Compound	T_g (ºC)
Poly(IPLA)	90.8
Poly(MeOEtLA)	41.8
Poly(PrLA)	70.6
Poly(EtLA)	40.0
Poly(DMLA)	67.8

Next, the thermoresponsiveness of the produced polymers was qualitatively evaluated by analyzing the solubility/turbidity change of a 5 mg/mL aqueous solution (Table 8).

Table 8. Solubility/turbidity change of the synthesized homopolymers upon heating a 5 mg/mL aqueous solution.

Polymer/Temperature	*5 °C*	*20 °C*	*40 °C*	*60 °C*
Poly(PrLA)	✗	✗	✗	✗
Poly(IPLA)	✗	✗	✗	✗
Poly(EtLA)	✓	✗	✗	✗
Poly(MeOEtLA)	✓	✓	✓	✗
Poly(DMLA)	✓	✓	✓	✓

Both poly(PrLA) and poly(IPLA) were insoluble in water between 5 and 60 ºC. On the other hand, poly(EtLA), poly(MeOEtLa), and poly(DMLA) were soluble in H_2O at 5 ºC. However, only poly(EtLA) and poly(MeOEtLA) showed clear thermoresponsive sensivity upon heating. Above approximately 10 ºC, the aqueous transparent solution of poly(EtLA) turned opaque suggesting a phase transition whereby the polymer aggregates. In the case of poly(MeOEtLa), qualitative analysis of the solution indicated that the cloud point temperature (T_{cp}) of the solution must be at around 45 ºC. Figure 21 shows the reversible thermsensitivity of a 5 mg/mL aqueous solution of poly(MeOEtLa).

Figure 21. Qualitative analysis for the thermoresponsive behavior of poly(MeOEtLA): on the left the polymer soluble at 40 ºC, in the middle the polymer heated to 60 ºC and in the right it was cooled to 40 ºC again.

The difficulty to fine-tuning the thermoresponsive properties (cloud point temperature) of this family of polymers by monomer design encouraged us to investigate the possibility to do it by using a random copolymerization approach between two different monomers.

5.4. Random copolymerization of DMLA a PrLA via RAFT

A series of random copolymers of DMLA and PrLA were prepared by RAFT polymerization using the same reaction conditions described for the above prepared homopolymers (Figure 22). The different copolymer proportions prepared were 90% DMLA – 10% PrLA, 80% DMLA – 20% PrLA, 75% DMLA – 25% PrLA, 70% DMLA – 30% PrLA and 60% DMLA – 40% PrLA. In all cases, the degree of polymerization was fixed at 50.

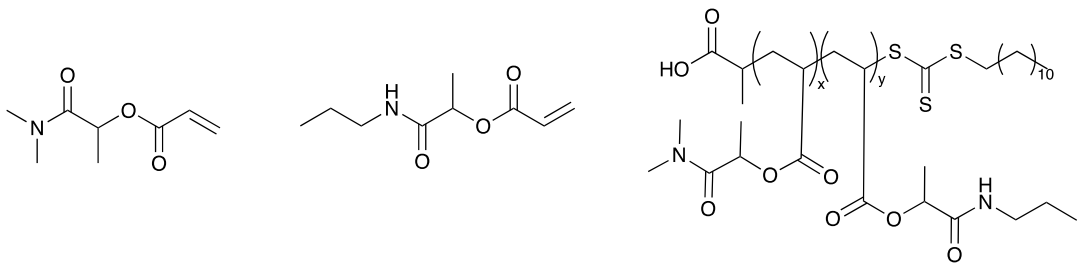


Figure 22. Chemical structures of DMLA (left), PrLA (right) monomers and representative random copolymer prepared by RAFT.

The synthesis of the targeted copolymers was confirmed by NMR and GPC (Table 9). In all cases, almost quantitative conversion was observed, and GPC analysis of the dialyzed materials revealed molecular weight values close to the theroretical values and low dispersity values. These results indicated that RAFT polymerization resulted in poly(DMLA-*r*-PrLA)s with well-controlled structures.

Table 9. RAFT random copolymerization of DMLA and PrLA.

Polymer	*Conversion (%)*	*Mn^{th} (g/mol)*	*$Mn^{GPC, DMF}$ (g/mol)*	*D_{DMF}*
Poly($DMLA_{45}$-r- $PrLA_5$)	95	8527	7296	1.18
Poly($DMLA_{40}$-r-$PrLA_{10}$)	94	8503	7827	1.19
Poly($DMLA_{37}$-r-$PrLA_{13}$)	97	8809	8186	1.23
Poly($DMLA_{35}$-r-$PrLA_{15}$)	95	8658	8375	1.19
Poly($DMLA_{30}$-r- $PrLA_{20}$)	94	8636	9157	1.19

Next, thermoresponsive properties of the copolymers were evaluated. In this case variable-temperature optical transmittance experiments to precisely determine the cloud point temperature[17] determined as the point at which the aqueous solution exhibits 50% transmittance. All the obtained copolymers were soluble in water at 5 ºC but delightfully solutions turned opaque at different temperatures (Figure 22). All the copolymers exhibited sharp transitions with T_{cp} between 10 and 58 ºC. For example, the T_{cp} was determined to be 9 ºC for poly($DMLA_{30}$-*r*- $PrLA_{20}$). The T_{cp} of the copolymers raised with the content of DMLA monomer, due to the fact that a higher content of more hydrophilic monomer would cause an increase of the hydrophilicity of poly(DMLA-*r*-PrLA), resulting in a higher T_{cp}. Interestingly, the T_{cp} varied linearly with composition which is important result in order to prepare thermoresposive polymers with predefined T_{cp} (Figure 23). Thinking about future biomedical applications, the random compolymer poly($DMLA_{37}$-*r*- $PrLA_{13}$) is particularly interesting because shows a T_{cp} close to body temperature.

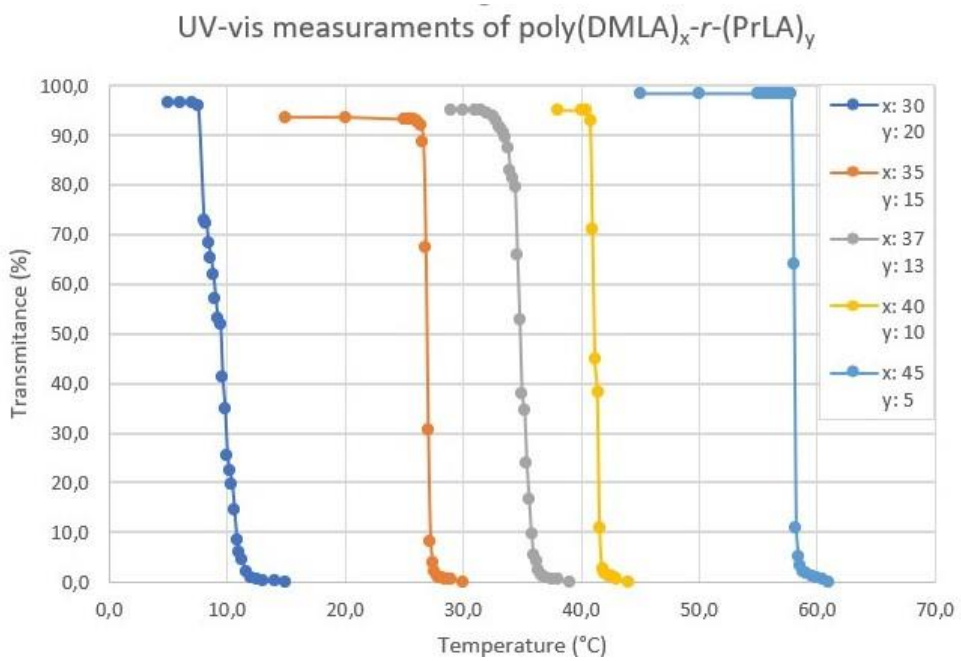


Figure 23. Temperature dependent of transmittance for the aqueous solution of poly(DMLA-r- PrLA)s with different DMLA and PrLA ratios.

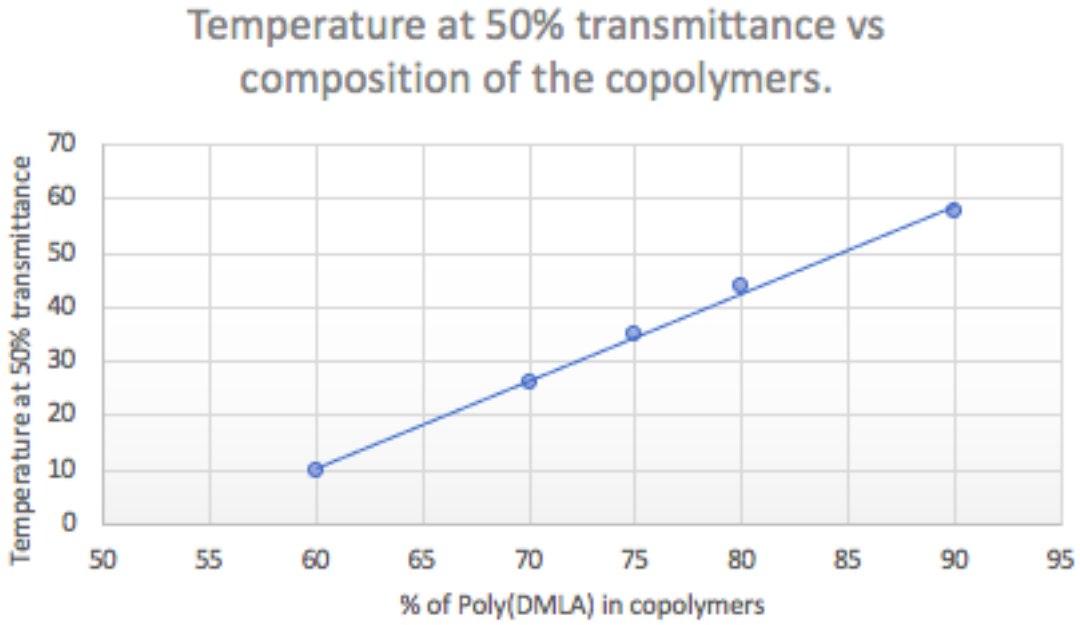


Figure 24. Plot of the temperature at 50 % of transmittance with the composition of the copolymers.

6. CONCLUSIONS

In brief, we have demonstrated that:

· Ethyl lactate solvent can be used as starting material for the preparation of acrylic lactamide-type monomers using commercially available primary amines.

· These monomers are suitable for controlled RAFT polymerization and produce polymers with controlled molecular weight and low dispersity.

· Poly(EtLA) and poly(MeOEtLA) prepared by RAFT are thermoresponsive polymers with T_{cp} around 10 and 45 ºC. On the other hand, poly(IPLA) and poly(PrLA) are water-insoluble whereas poly(DMLA) is water-soluble and did not show thermoresponsive behavior.

· The random RAFT copolymerization of DMLA and PrLA via RAFT has been demonstrated an effective approach for the preparation of smart materials with thermoresponsive behavior between 10 and 58 ºC.

· The random compolymer poly($DMLA_{37}$-*r*- $PrLA_{13}$) is particularly interesting for biomedical applications because shows a T_{cp} close to body temperature.

· These results are very significant toward the utilization of lactic acid-derived solvents as precursors for stimuli-responsive materials.

En resum, hem demostrat que:

· El dissolvent de lactat d'etil es pot utilitzar com a material de partida per a la preparació de monòmers de tipus lactamida acrílica mitjançant amines primàries disponibles en el comerç.

· Aquests monòmers són adequats per a la polimerització RAFT controlada i produeixen polímers amb pes molecular controlat i baixa dispersitat.

· Poly (EtLA) i poly (MeOEtLA) preparats per RAFT són polímers termoresponsius amb Tcp al voltant de 10 i 45 ºC. D'altra banda, poli (IPLA) i poli (PrLA) són insolubles en aigua mentre que poli (DMLA) és soluble en aigua i no va mostrar un comportament termoresponsiu.

· La copolimerització RAFT aleatòria de DMLA i PrLA mitjançant RAFT ha demostrat un enfocament eficaç per a la preparació de materials intel·ligents amb comportament termoresponsiu d'entre 10 i 58 ºC.

· El compolímer aleatori poli (DMLA37-r-PrLA13) és particularment interessant per a aplicacions biomèdiques, ja que mostra un Tcp proper a la temperatura corporal.

· Aquests resultats són molt significatius per a la utilització de dissolvents derivats d'àcid làctic com a precursors de materials sensibles als estímuls.

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8. SUPPORTING INFORMATION

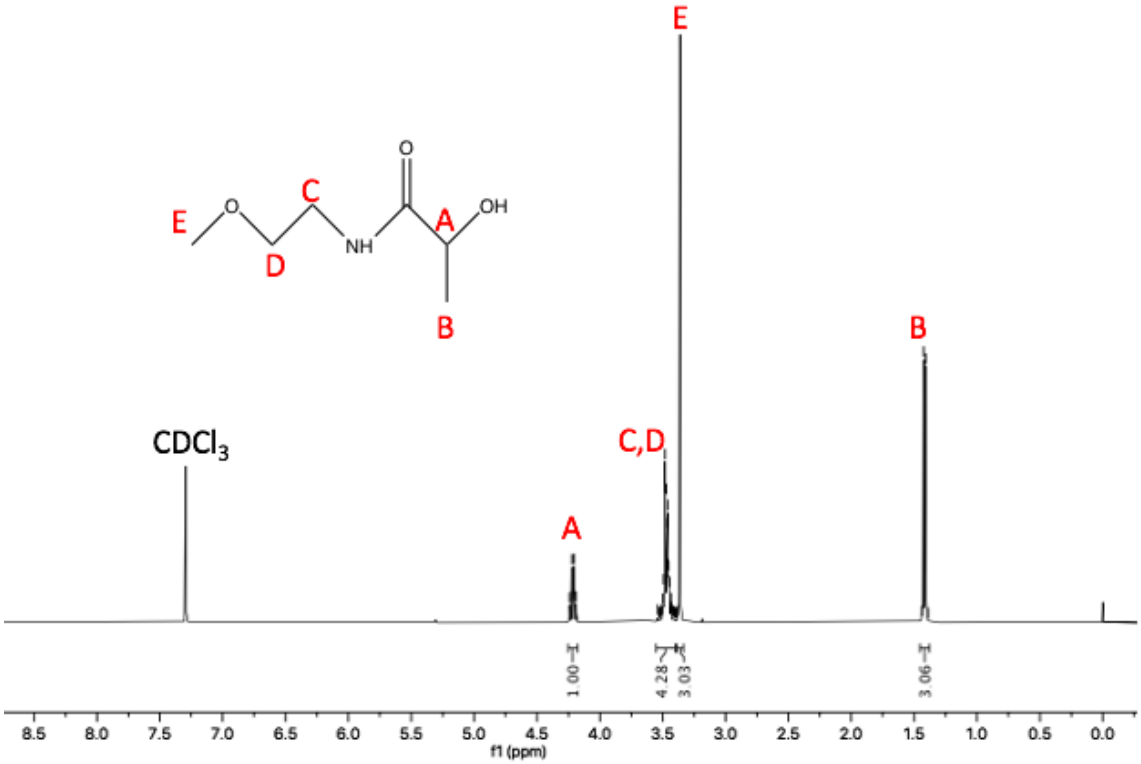

Figure S1. [1]H NMR spectra for 2-hydroxy-N-(2-methoxyethyl)propanamide.

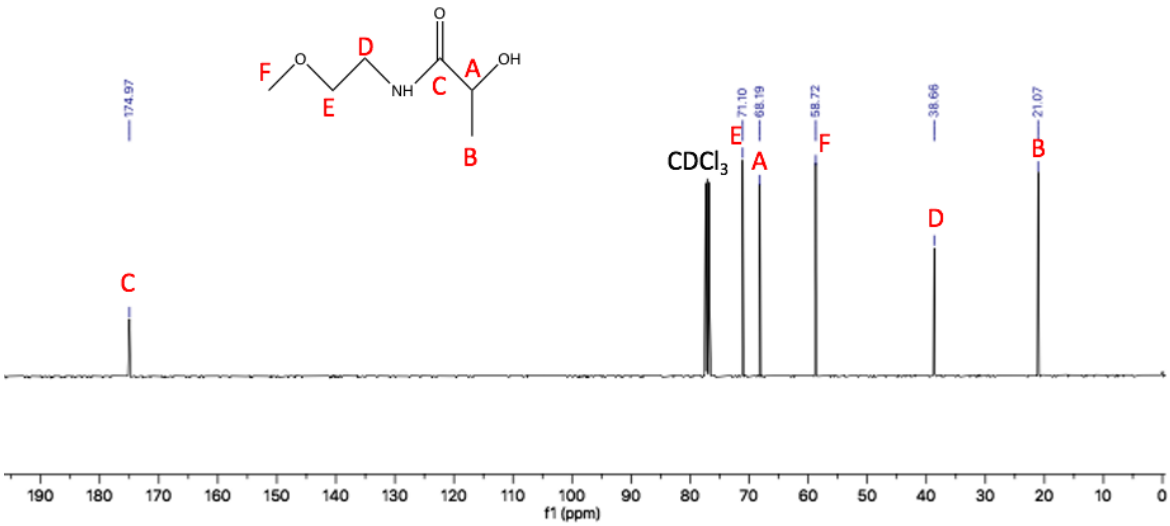

Figure S2. [13]C NMR spectra for 2-hydroxy-N-(2-methoxethyl)propanamide.

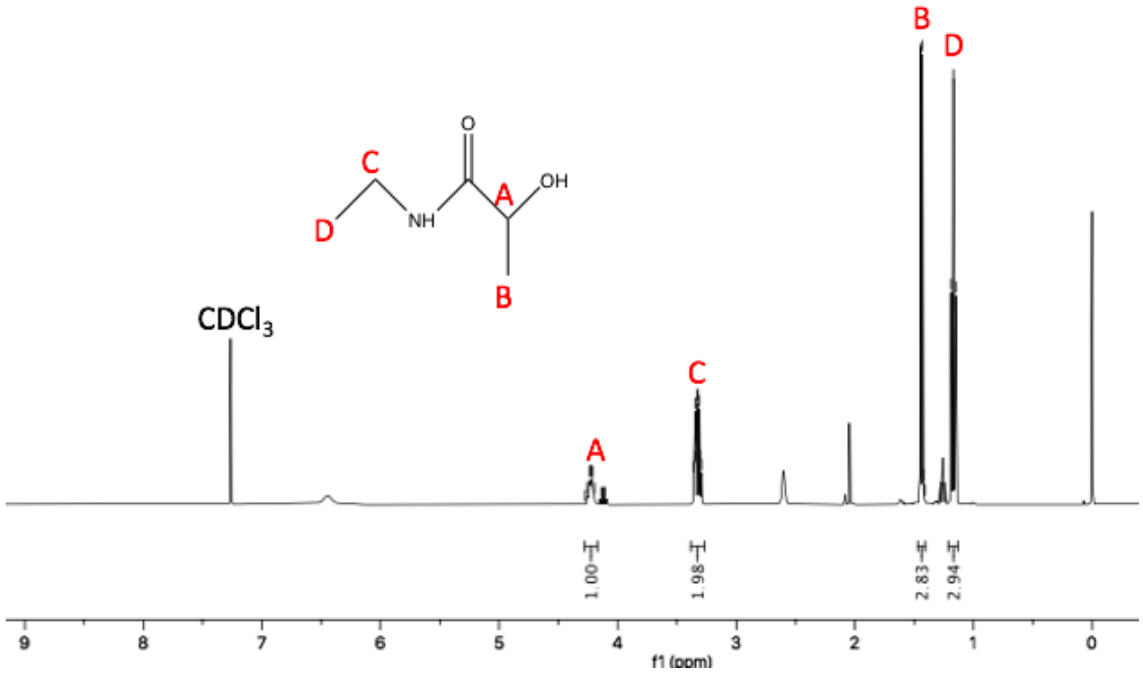

Figure S3. ^{1}H NMR spectra for N-ethyl-2-hydroxypropanamide.

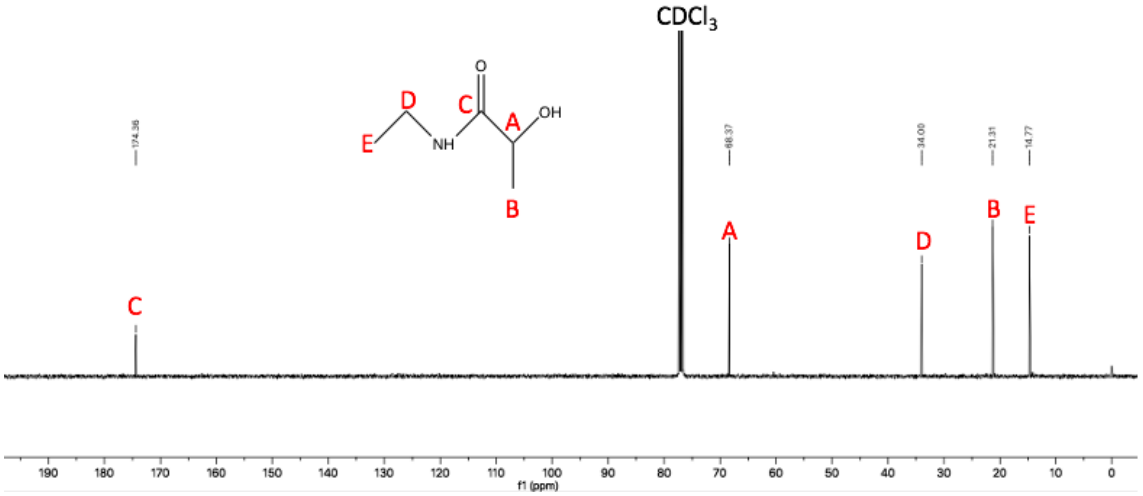

Figure S4. ^{13}C NMR spectra for N-ethy-2-hydroxypropanamide.

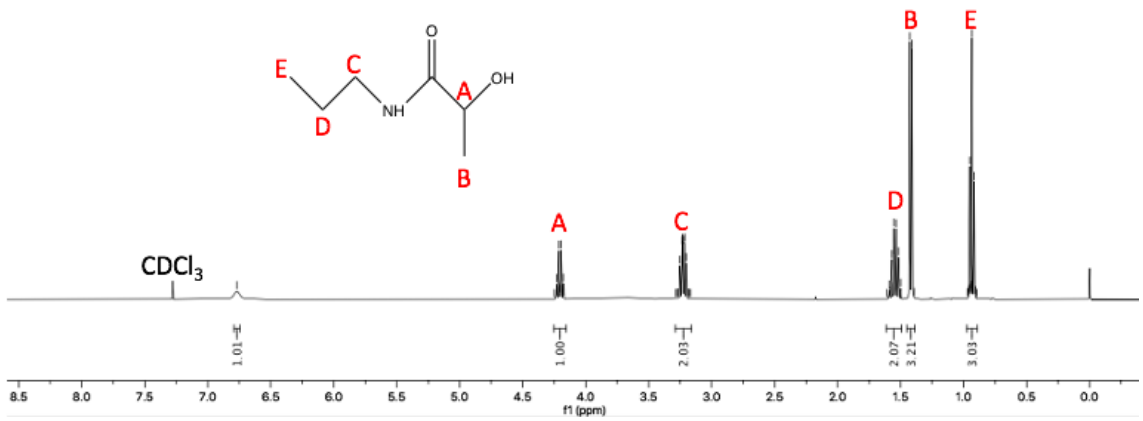

Figure S5. ^{1}H NMR spectra for 2-hydroxy-N-propylpropanamide.

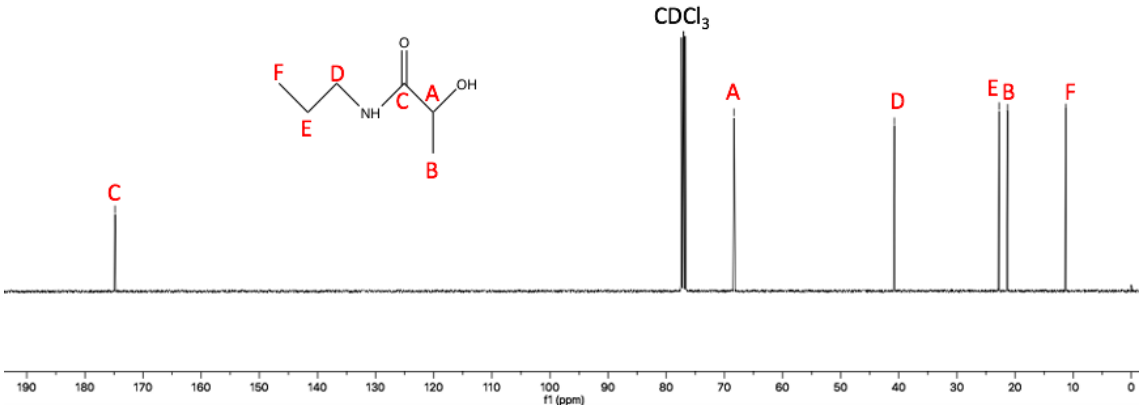

Figure S6. ^{13}C NMR spectra for 2-hydroxy-N-propylpropanamide.

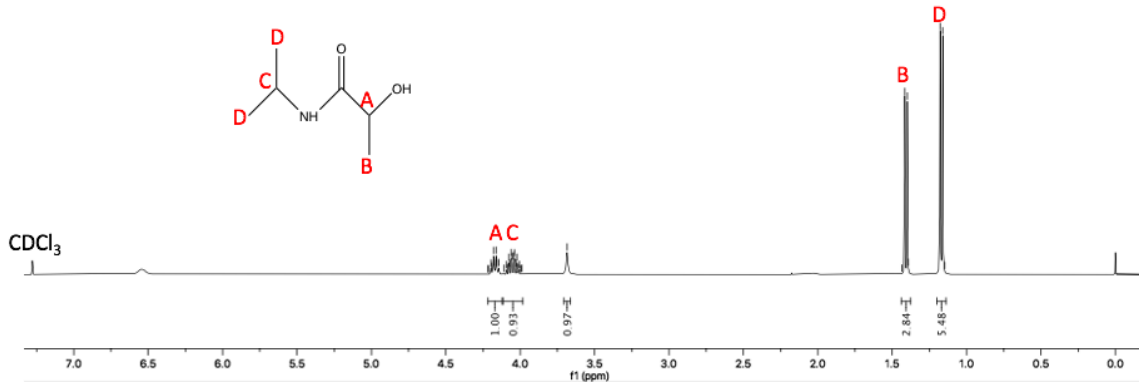

Figure S7. ^{1}H NMR spectra for 1-(isopropylamino)-1-oxopropan-2-yl acrylate.

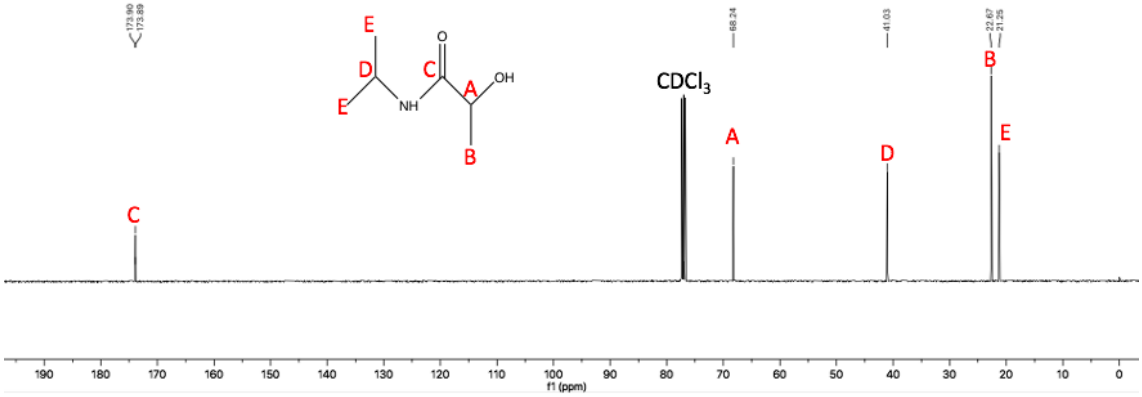

Figure S8. ^{13}C NMR spectra for 1-(isopropylamino)-1-oxopropan-2-yl acrylate.

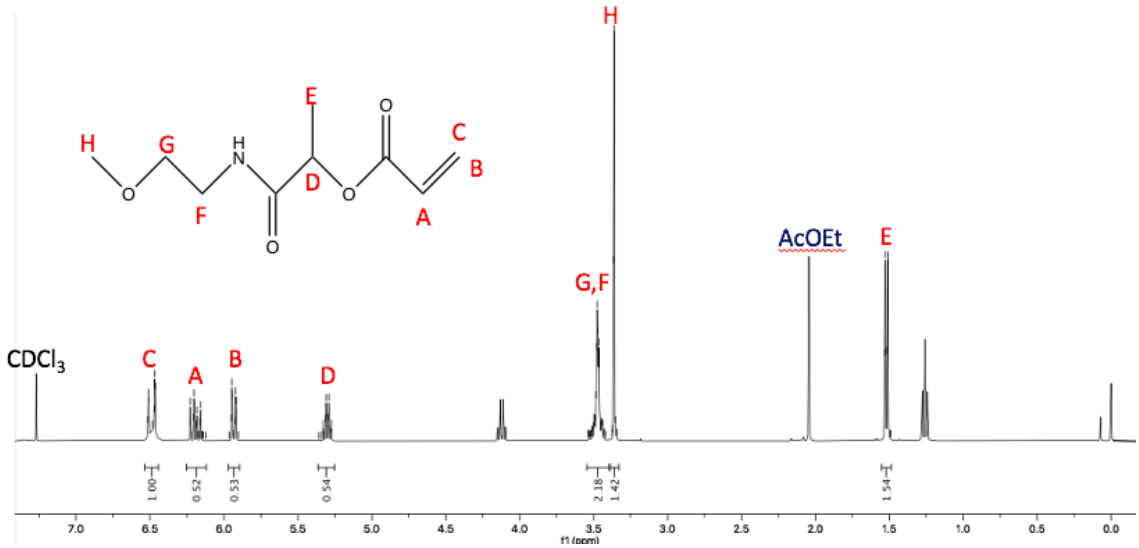

Figure S9. [1]H NMR spectra for 1-((2-methoxyethyl)amino)-1-oxopropan-2-yl acrylate.

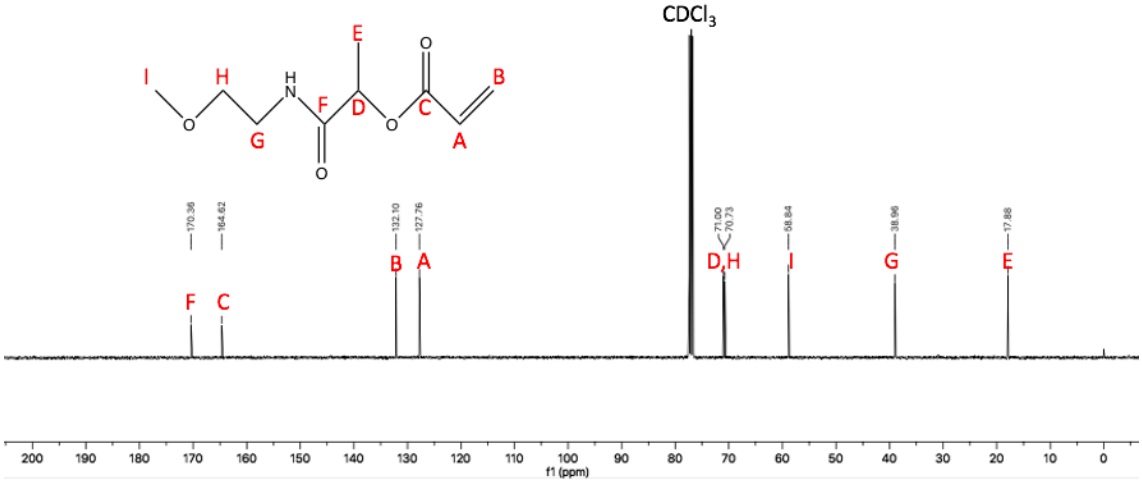

Figure S10. [13]C NMR spectra for 1-((2-methoxyethyl)amino)-1-oxopropan-2-yl acrylate.

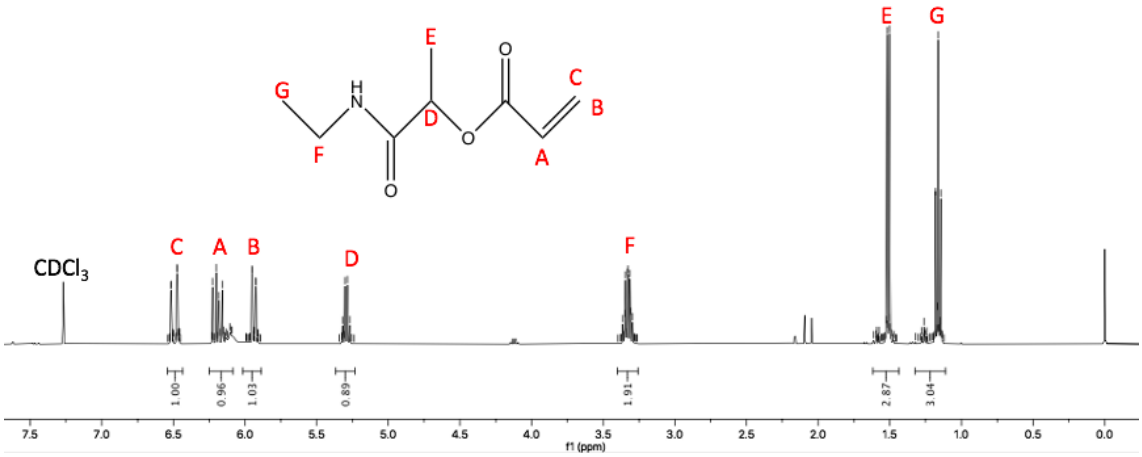

Figure S11. [1]H NMR spectra for 1-(ethylamino)-1-oxopropan-2-yl acrylate.

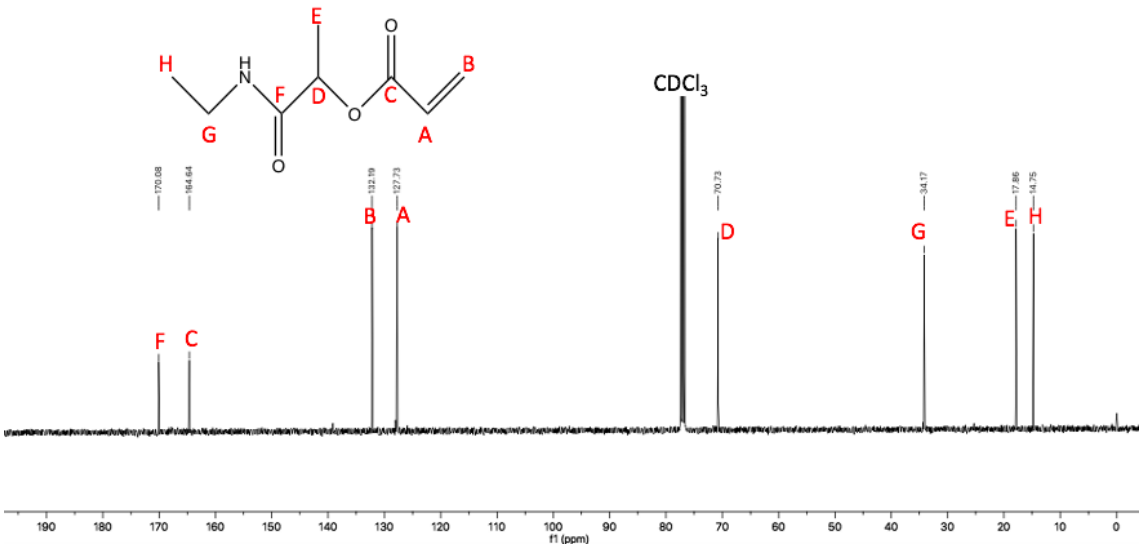

Figure S12. 13C NMR spectra for 1-(ethylamino)-1-oxopropan-2-yl acrylate.

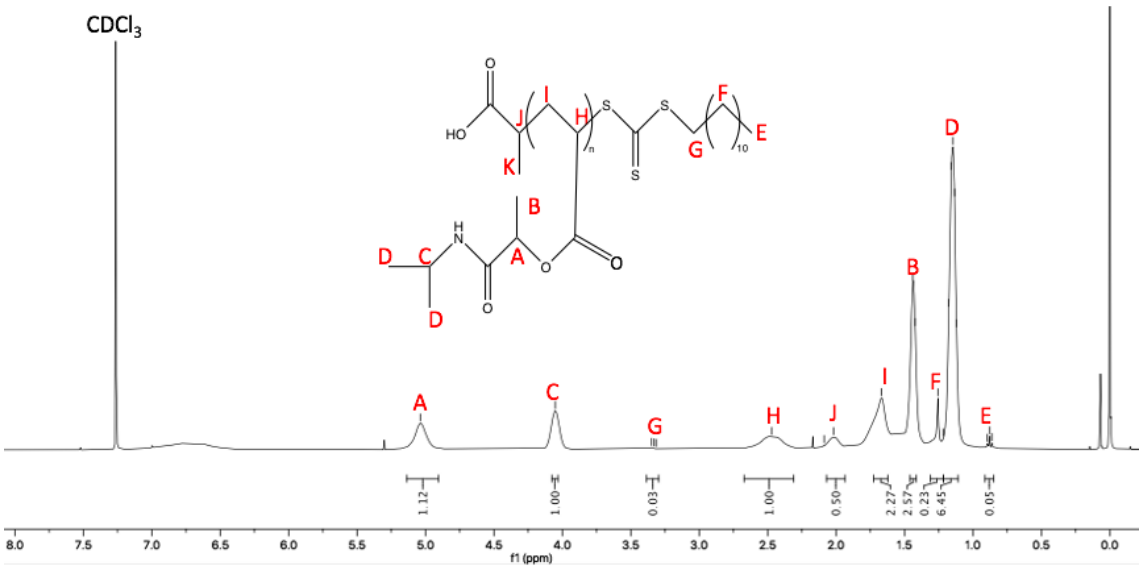

Figure S13. ^{1}H NMR spectra for the polymerization of 1-(isopropylamino)-1-oxopropan-2-yl acrylate.

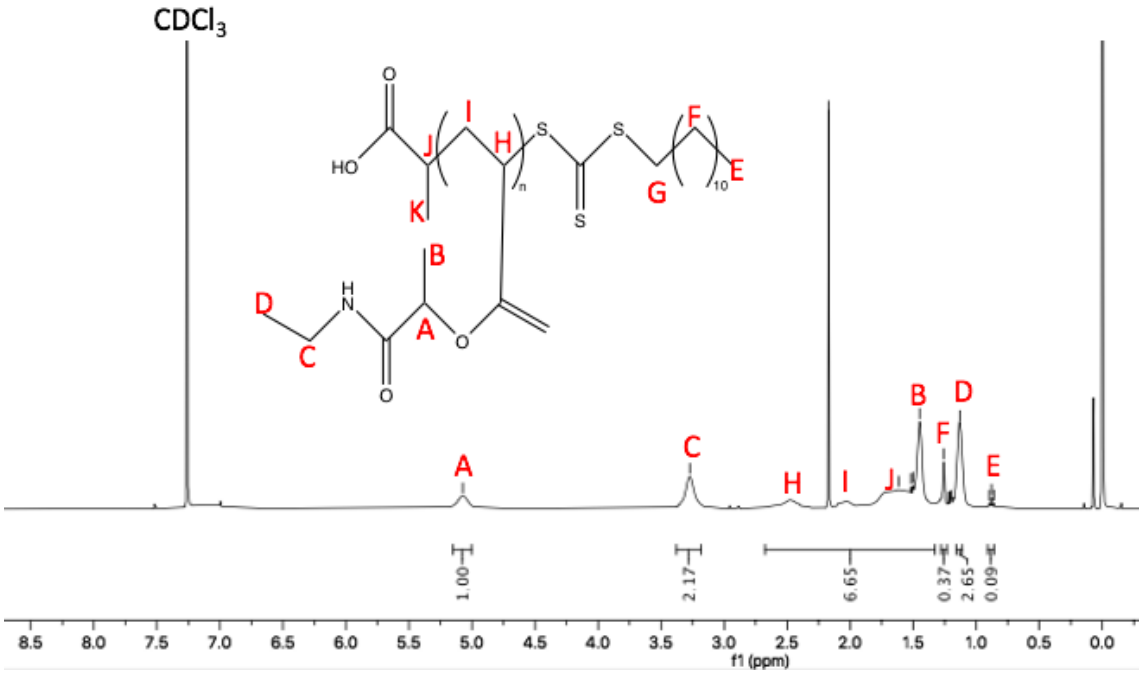

Figure S14. ^{1}H NMR spectra for the polymerization of 1-(ethylamino)-1-oxopropan-2-yl acrylate.

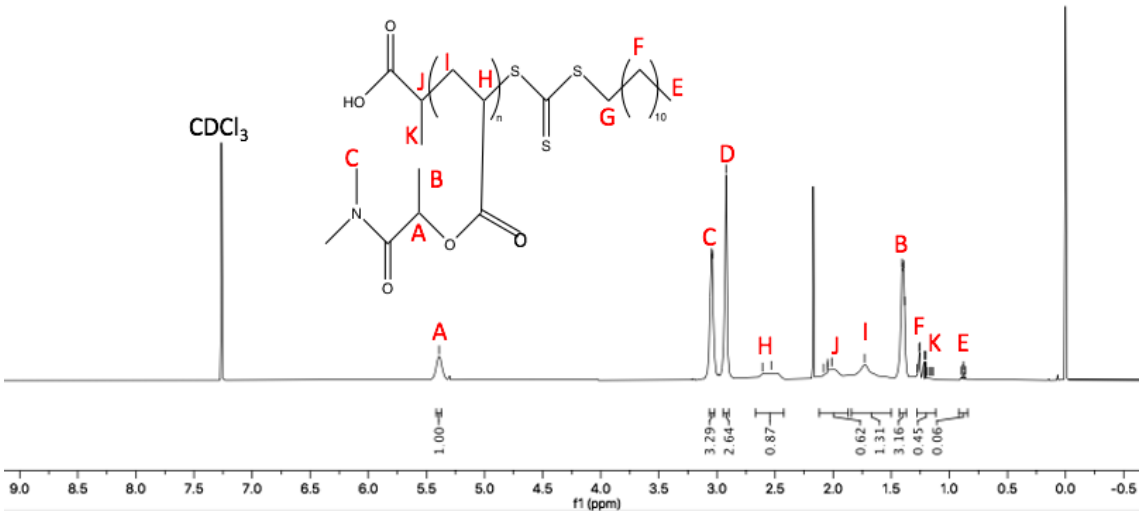

Figure S15. ^{1}H NMR spectra for the polymerization of 1-(dimethylamino)-1-oxopropan-2-yl acrylate.

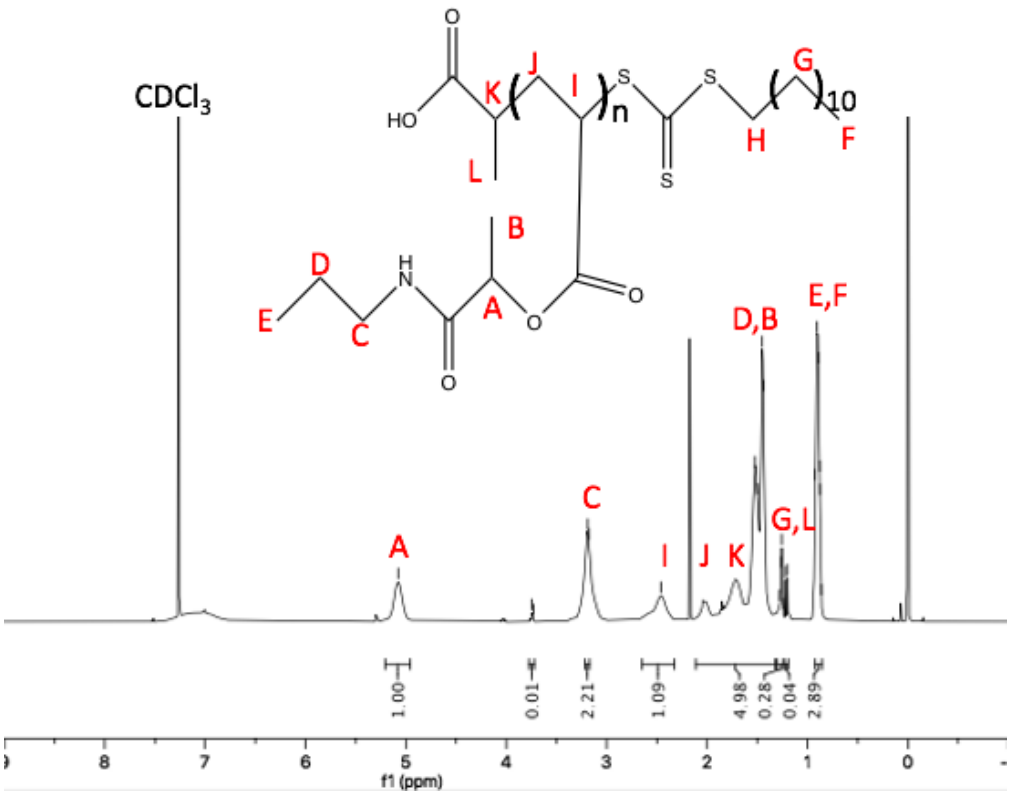

Figure S16. ^{1}H NMR spectra for the polymerization of 1-oxo-1-(propylamino)propan-2-yl acrylate.