Sustainable bio-based poly-N-glycines and polyesters

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"At our death beds, we will inevitably know that much in our life stories didn't work out, that there were dreams that didn't come to pass and loves that were rejected, friendships that could never be repaired, and catastrophes and hurts we never overcame. But as good story tellers, we will also know that there were threads of intense value that sustained us, that there was a higher logic we sometimes followed, that despite the agonies, our lives were not mere sound and fury; that in our own way, at select moments at least, our stories made sense."
The book of life, How to tell the story of our life.

I. Eidesstattliche Erklärung

Die vorliegende Arbeit wurde in der Zeit von Februar 2014 bis November 2017 am Max-Planck-Institut für Kolloid- und Grenzflächenforschung in Potsdam in der Abteilung Kolloidchemie unter der Leitung von Prof. Dr. Dr. h. c. Markus Antonietti und an der Universität Potsdam, Institut für Chemie, unter der Leitung von Prof. Dr. Helmut Schlaad angefertigt.

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig verfasst und nur unter Zuhilfenahme der ausgewiesenen Quellen und Hilfsmittel angefertigt habe. Beiträge von Kooperationspartnern wurden explizit gekennzeichnet.

Potsdam, den _____ _____

II. Abstract

Nowadays, the need to protect the environment becomes more urgent than ever. In the field of chemistry, this translates to practices such as waste prevention, use of renewable feedstocks, and catalysis; concepts based on the principles of green chemistry. Polymers are an important product in the chemical industry and are also in the focus of these changes. In this thesis, more sustainable approaches to make two classes of polymers, polypeptoids and polyesters, are described.

Polypeptoids or poly(alkyl-*N*-glycines) are isomers of polypeptides and are biocompatible, as well as degradable under biologically relevant conditions. In addition to that, they can have interesting properties such as lower critical solution temperature (LCST) behavior. They are usually synthesized by the ring opening polymerization (ROP) of *N*-carboxy anhydrides (NCAs), which are produced with the use of toxic compounds (e.g. phosgene) and which are highly sensitive to humidity. In order to avoid the direct synthesis and isolation of the NCAs, *N*-phenoxycarbonyl-protected N-substituted glycines are prepared, which can yield the NCAs *in situ*. The conditions for the NCA synthesis and its direct polymerization are investigated and optimized for the simplest N-substituted glycine, sarcosine. The use of a tertiary amine in less than stoichiometric amounts compared to the *N*-phenoxycarbonyl--sarcosine seems to accelerate drastically the NCA formation and does not affect the efficiency of the polymerization. In fact, well defined polysarcosines that comply to the monomer to initiator ratio can be produced by this method. This approach was also applied to other *N*-substituted glycines.

Dihydroxyacetone is a sustainable diol produced from glycerol, and has already been used for the synthesis of polycarbonates. Here, it was used as a comonomer for the synthesis of polyesters. However, the polymerization of dihydroxyacetone presented difficulties, probably due to the insolubility of the macromolecular chains. To circumvent the problem, the dimethyl acetal protected dihydroxyacetone was polymerized with terephthaloyl chloride to yield a soluble polymer. When the carbonyl was recovered after deprotection, the product was insoluble in all solvents, showing that the carbonyl in the main chain hinders the dissolution of the polymers. The solubility issue can be avoided, when a 1:1 mixture of dihydroxyacetone/ ethylene glycol is used to yield a soluble copolyester.

Keywords: ROP, N-alkyl-glycine, polypeptoids, activated urethane, dihydroxyacetone, polycondensation, polyesters

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1. Introduction

1.1. Green chemistry

Our society has changed drastically over the last 500 years and the advances of science and chemistry in particular have played a major role in that. Within this period, the population of humans has increased from around 500 millions to 7 billions.[1] Chemistry contributed to that in many ways. Fertilizers for example, have allowed for an important increase in the amount of food produced. Pesticides have been used for the protection of crops, but also for the elimination of diseases transmitted by insects like mosquitos. However, in the 20th century, people started realizing the consequences for the environment of the non-regulated use of chemicals.

In 1962 Rachel Carson's book "Silent spring" was published and soon a new, more sustainable view on chemistry started gaining ground in the scientific, and not only, community. It was a difficult to imagine achievement, when the success of pesticides was recent (Figure 1.1) and chemical weapons seemed crucial at the time of Cold War. Nevertheless, "green chemistry" was meant to become more and more popular. It was created to reduce the use of hazardous chemicals, prevent the pollution of the environment, and promote the use of sustainable resources.

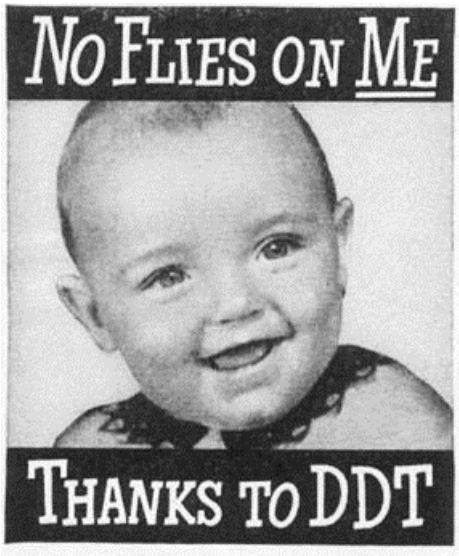


Figure 1.1: An advertisement from 1946 for the DDT-containing pesticide Black Flag. 60 years were enough for people to change entirely mindsets on the extensive use of toxic chemicals.

A good overview of the principles of green chemistry, as described in 1998 in the book “Green Chemistry: Theory and Practice” and summarized by the ACS Green Chemistry Insitute, is given in Table 1.1:

Table 1.1: The 12 principles of green chemistry according to the American Chemical Society.

The 12 Principles of Green Chemistry
1. Prevent Waste 2. Atom Economy 3. Less Hazardous Synthesis 4. Design Benign Chemicals 5. Benign Solvents & Auxiliaries 6. Design for Energy Efficiency 7. Use of Renewable Feedstocks 8. Reduce Derivatives 9. Catalysis (vs. Stoichiometric) 10. Design for Degradation 11. Real-Time Analysis for Pollution Prevention 12. Inherently Benign Chemistry for Accident Prevention

1.2. Green polymers

A very important field of chemistry, especially during the last centuries, is that of polymers. Due to their versatility in properties, polymers offer great advantages compared to other materials. They are materials of light weight, of high strength, and are not prone to corrosion, their properties making them ideal to substitute materials like metal, wood, and even glass. Smart phones, computers, and ever better aircrafts are produced thanks to polymeric materials.

Polymers are abundant in every aspect of our lives and therefore they are also a focus of green chemistry. Several aspects of polymer production and use make it necessary to make polymers more "green" and different approaches have been suggested, depending on the problem in question. The focus of the research on that regard can be either the optimization of the synthesis of known polymers or the synthesis of new polymers.

A significant concern regarding the sustainability of polymers is that the main source of monomers for the production of commercial polymers is petroleum. Petroleum is a finite resource and its extraction can be damaging to the environment. To avoid the oil refinery, biorefinery is suggested as an alternative. Biorefinery uses biomass for the production of fuels, heating, and value-added chemicals. Monomers based on biorefinery can be used for the production of "greener" polymers. These monomers can either be the conventional ones produced in alternative ways or new monomers. The use of conventional monomers based on renewable feedstock offers the advantage of the vast knowledge we already possess on how to polymerize them and the facilities for their processing are already in place.

An example of monomer that is already known and can be produced alternatively from renewable resources is ethylene synthesized from bio-ethanol. Several different fermentation processes from different sources, such as corn, wheat or sugar cane, are used to produce bio-ethanol with different efficacy.[2] For example, bio-ethanol production seems to be more efficient when sugar cane residues fermentation is used instead of corn.[3] The following reaction towards ethylene can be catalyzed using zeolite[4] or modified silica.[5] Applying the principles of green chemistry and using renewable feedstock for ethylene synthesis is essential, as it is not only the monomer for polyethylene

(PE), but also a precursor for the production of polystyrene (PS), polyvinyl chloride (PVC), and polyethylene terephthalate (PET).

Despite their advantages due to existing infrastructure, known monomers are not the only way to produce bio-based polymers. Compounds that can be easily derived from biomass are investigated as monomers for new polymers. An interesting example is 5-hydroxymethylfurfural (HMF), the derivatives of which have been reviewed in their uses as monomers from Gandini in 2010.[6] In addition, a collection of natural oils have been used as monomers, producing polymers that are often biodegradable and non-toxic.[7]

Apart from the fruitful research towards the more sustainable production of already popular monomers and the synthesis of new monomers, there is space for improvement in the polymerization process per se. Minimization of hazardous compounds and energy input are important goals for more environmentally-friendly polymerizations. Catalysis, for example, can increase the speed of a reaction, and even allow for lower reaction temperatures, making the polymerization reaction less energy demanding. Catalysis has also already enabled the creation of new polymers, for example via acyclic diene metathesis (ADMET) polymerization or ring-opening metathesis polymerization (ROMP). Enzymes, nature's catalysts, are a "greener" alternative and some have been used for the production of polymers via ring opening polymerization (ROP) or polycondensation.[8]

1.3. Objective of this work

In this work, two different approaches are investigated for the synthesis of polymers, having in mind the principles of green chemistry.

In the first part a new synthesis of polypeptoids is introduced. Polypeptoids constitute an interesting class of biocompatible and degradable polymers, isomers of polypeptides. The method used reduces the use of toxic substances and minimizes the number of reaction steps. This is possible due to the *in situ* formation of the sensitive monomer. Furthermore, the addition of a non-nucleophilic base in the reaction, which does not alter the product, decreases drastically the reaction time. The synthesis is initially optimized for the simplest monomer and the preparation of more complex monomers is described subsequently, as well as the influence of the chemical structure on the reaction kinetics.

In the second part of this work, new polymers are targeted using dihydroxyacetone as a monomer for step-growth polymerization. Dihydroxyacetone is a monomer that can be derived from renewable sources and contains two alcohol groups that make it an interesting monomer for polycondensation reactions. Enzymatic polymerization, as well as different approaches are used for its polymerization.

2. Introduction to Polypeptoids

2.1. Proteins and polypeptides

Proteins are naturally occurring macromolecules, which are responsible for a multitude of functions within the body, such as catalysis, transportation of molecules, and structural support. Their versatility is based on the different structures they can form based on 20 different monomer units, the amino acids. These can combine in a variety of ways in chains of lengths of 50-2000 monomer units in nature. The sequence of the chains defines their role.[9]

The substituents of the amino acids can differ significantly from each other in nature. They can be hydrophobic or hydrophilic, charged or not, aromatic or not, etc. For example, aspartic acid and glutamic acid carry carboxylic acid groups in their side chain, whereas histidine, arginine and lysine carry groups that can be positively charged at neutral pH (due to an amino group, a guanidinium group and an imidazolium respectively) (Figure 2.1).

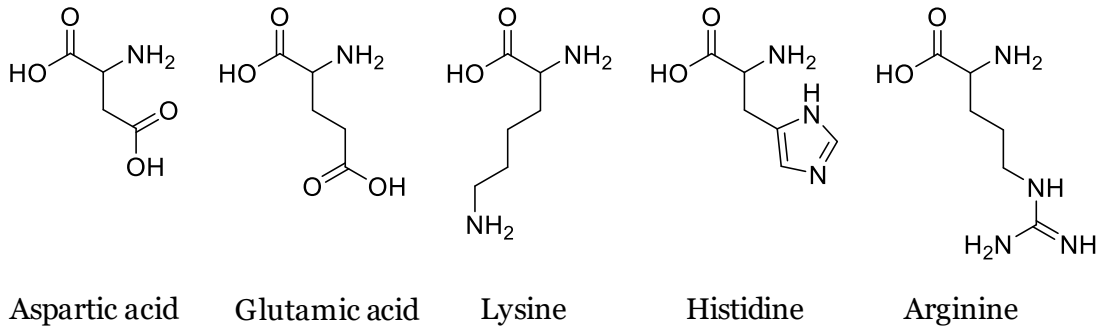
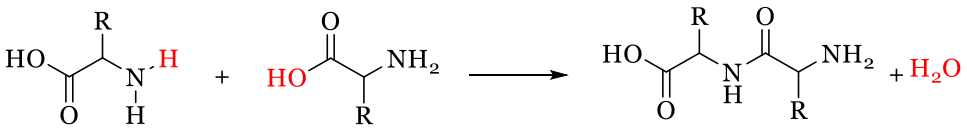


Figure 2.1: Structure of 5 amino acids: aspartic acid, glutamic acid, lysine, histidine, and arginine.

Amino acid units are connected with each other via a peptide bond (Scheme 2.1). Therefore, their macromolecular chains are called polypeptide chains. Amino acid units in a polypeptide are called residues.



Scheme 2.1: Condensation of two amino acids to form a peptide.

Nature produces polypeptides and proteins in living organisms using enzymes and ribosomes. In the lab, two main methods exist to prepare polypeptides, of which each offers advantages and disadvantages. One of them is the solid-state peptide synthesis. It allows for the synthesis of chains of controlled amino acid sequence. However, the chains produced in this way do not reach high molar masses. In contrast, the ring opening polymerization of *N*-carboxy-anhydrides (NCAs) of amino acids, allow for the preparation of polypeptides of high molar mass, but the sequence of residues cannot be controlled.

Despite not having a precisely defined sequence, the polypeptides prepared by NCA polymerization can demonstrate secondary structures (e.g. α-helices, β-sheets) like proteins and constitute interesting polymers for therapeutical applications.[10]

2.2. Polypeptoids

Polypeptoids are isomers of polypeptides, carrying the substituent on the amide nitrogen rather than the alpha carbon (Figure 2.2).

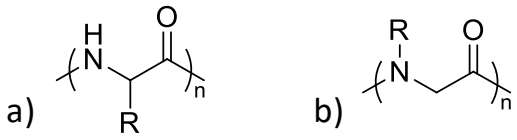


Figure 2.2: The basic structure of a) polypeptides and b) polypeptoids.

This change in the structure differentiates the structures they form. As mentioned, polypeptides can stabilize helices or β-sheets, because of the hydrogen-bond accepting carbonyl group and the hydrogen-bond donating NH group. The substitution of the nitrogen results in polypeptoids being less prone to form secondary structures and, therefore, being more soluble in a variety of solvents. Secondary structures can be promoted nevertheless with the choice of an appropriate substituent, which can either lead to a specific conformation due to steric repulsion or interactions with the backbone.[11]

The simplest polypeptoid is polysarcosine that carries a methyl group on the nitrogen, and it was also the first one that was reported in 1926.[12] It is a polymer of high potential in pharmaceutical applications as it was proved to be non-immunogenic when tested in rabbits.[13] Furthermore, when allergens are conjugated with polysarcosine, the production of antibodies can be suppressed, making polysarcosine a tolerogenic compound.[14] Adding to that, the fact that it can decompose in the body enzymatically by sarcosine dehydrogenase, together with its high solubility in water and many solvents, have made it the most widely used polypeptoid.

Although polysarcosine has been investigated the most, other polypeptoids also offer interesting and unique properties. Apart from being biocompatible[15] and degradable,[16] some of them show LCST (lower critical solution temperature) behavior in aqueous solutions. Specifically, poly(*N*-*n*-propyl-glycine), poly(*N*-allyl glycine), and poly(*N*-iso-propyl glycine) are soluble in water at room temperature and render insoluble at higher temperatures.[17] Their cloud point temperatures (T_{cp}) increase in the order of *n*-propyl (15–25 °C) < allyl (27–54 °C) < iso-propyl (47–58 °C), showing also correlation to the

chain length and polymer concentration, exhibiting Flory–Huggins type 1 behavior.[18]

In addition, polymers with adjustable cloud points can be prepared when hydrophilic and hydrophobic monomers are used for the synthesis of statistical copolymers. As an example, poly[sarcosine-ran-(*N*-butyl glycine)], prepared from the respective *N*-substituted glycine *N*-thiocarboxyanhydrides (NTAs) showed LCST behavior with a T_{cp} at 37 °C, making it a very appealing polymer for pharmaceutical applications.[19] Additionally, the cloud point temperature of linear and cyclic poly[(*N*-ethyl glycine)-ran-(*N*-butyl glycine)] random copolymers has been proved to depend on the fraction of the hydrophilic *N*-ethyl glycine and to be adjustable in a range of 20-60 °C. The addition of salts also led to a drop in cloud point temperatures according to the Hofmeister series (sulfate > chloride > iodide).[20]

Apart from demonstrating LCST behavior, polypeptoids can also be used for the formation of interesting structures in solution. Poly(ethylene glycol) (PEG) initiated sarcosine NTAs yield double hydrophilic copolymers that can form small spherical particles in addition to larger unstable aggregates.[21] An amphiphilic diblock copolypeptoid that forms micelles upon heating can be prepared from the block-polymerization of *N*-*n*-propylglycine and sarcosine due to the collapse of the thermosensitive poly(*N*-*n*-propylglycine).[22]

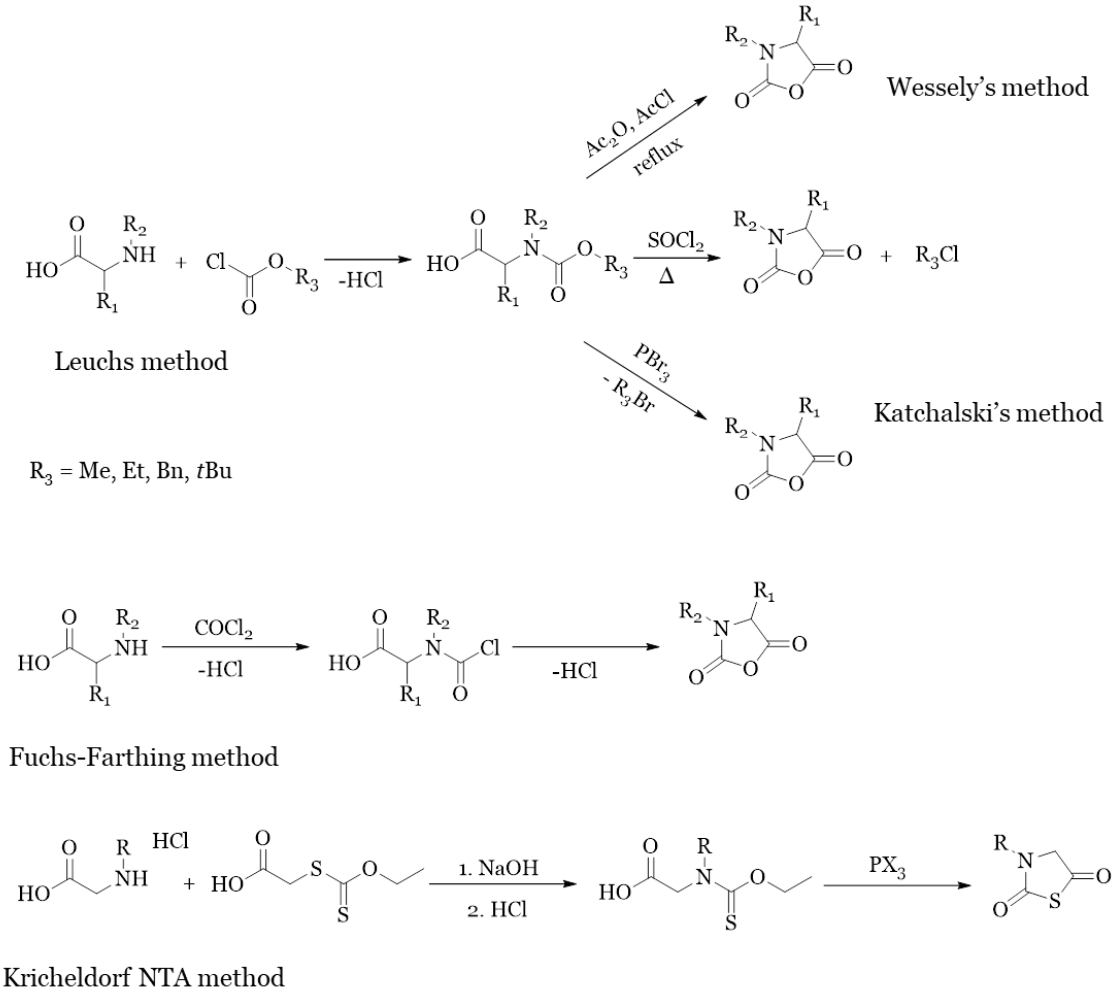
In total, polypeptoids give access to multiple properties and their monomer polymerization results in well-defined polymers. Adding to their biocompatibility and degradation in conditions that resemble these in the blood stream, polypeptoids would be interesting candidates for pharmaceutical applications.

PEG is the polymer that is majorly used for pharmaceutical applications. Peptides and proteins[23] as well as antibodies[24] have been conjugated with PEG (they have been PEGylated), in an attempt to produce better drug delivery systems. The reasons for the success of PEG include that it was reported to be safe for medical applications[25] and that it can be synthesized in a well-defined way in larger scales. Nevertheless, there have been reports about quick clearance of PEGylated proteins,[26] and since it can produce oxidative species that affect cells and tissues,[27] there is a need for alternatives.[28] Polypeptoids could be an interesting alternative.

The good control of the molar mass of polypeptoids that results from the polymerization of their respective *N*-substituted NCAs in combination with the interesting properties the polypeptoids offer make polypeptoids an attractive class of polymers. Nevertheless, the instability of the NCAs, which are highly susceptible to hydrolysis,[29] in addition to the use of hazardous chemicals for the NCA synthesis, make the synthesis of polypeptoids more challenging than expected.

2.3. Amino acid *N*-carboxyanhydride synthesis

As it is already mentioned, the most common way of preparing synthetic polypeptides of high molar mass, as well as polypeptoids, is via the ring opening polymerization of NCAs. The first report on the synthesis of an NCA was in 1906, when Hermann Leuchs synthesized the NCA of glycine.[30] NCAs are also called Leuchs anhydrides after him. Leuchs was reacting *N*-(methoxycarbonyl)-glycine with thionyl chloride to produce the respective acyl chloride. While trying to purify it, he realized that instead of the acyl chloride, he had produced the NCA of glycine. More efficient ways to synthesize NCAs were developed and the different pathways are summarized in Scheme 2.2:



Scheme 2.2: Synthetic pathways to NCAs and NTAs.[29–33]

Wessely et al., after observing low yields for the NCA of sarcosine (*N*-methyl glycine) when thionyl chloride was used, developed an alternative reaction. They reacted sarcosine with ethyl chloroformate, which after being refluxed in acetyl chloride/acetic anhydride 1:1 v/v, yielded the NCA in 63%

yield.[29] Katchalki and Sela, on the other hand, used phosphorous tribromide for the NCA synthesis.[32] The Fuchs-Farthing method reacts directly the amino acid with phosgene (or triphosgene, to avoid the toxic gas phosgene) to yield the NCA.[34]

Apart from NCA synthesis, Scheme 2.2 includes a synthesis of *N*-thiocarboxyanhydrides (NTAs).[31] NTAs can also be polymerized to yield polypeptoids and some examples of their products were mentioned in Section 2. However, NCA polymerization releases carbon dioxide (CO_2), whereas NTAs polymerization releases toxic carbonyl sulfide (COS).

Scheme 2.2 reveals that NCA synthesis requires the use of hazardous compounds, such as thionyl chloride, phosgene or phosphorus tribromide. A method that avoids such compounds would make the synthesis of NCAs much more environmentally friendly.

2.4. Polypeptoid and polypeptide synthesis

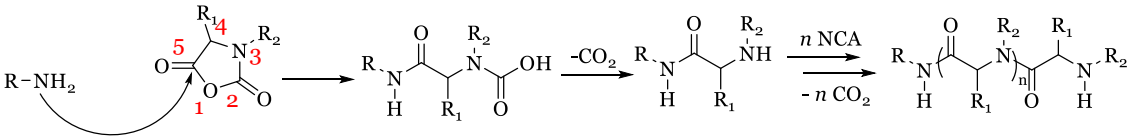
NCAs and their polymerization have been studied since more than a century. The most common initiators for the ring opening polymerization of NCAs are amines. In the case of *N*-substituted NCAs, the only mechanism that leads to polymerization is the normal amine mechanism. However, when the NCAs are substituted only on the α-carbon, deprotonation of the NCA leads to an additional mechanism, the activated monomer mechanism. The latter results in higher dispersities and several strategies have been used to avoid it. Rare-earth borohydrates and *N*-heterocyclic carbenes are also facilitated to initiate the polymerization of NTAs and NCAs respectively. A recent addition to the methods for the synthesis of polypeptoids takes advantage of the Ugi reaction to produce polymers with different functionalities.

Amine initiated polymerization

Normal amine mechanism (NAM)

The normal amine mechanism (NAM) is the mechanism involved in the polymerization of NCAs when protic nucleophiles, such as primary amines, alcohols or water are used. The mechanism was first suggested in 1949 and was based on an investigation of the polymerization of sarcosine NCA in acetophenone and nitrobenzene solution, using polysarcosine dimethylamide as an initiator.[35] Although tertiary amines cannot initiate the polymerization of *N*-substituted NCAs, the polymerization was probably a result of the reaction with deprotonated protic impurities, such as water.[36] Since then, multiple studies on the kinetics of the NCA polymerization have illuminated the nature of the NAM.[10,31,37]

NAM with primary amines as initiators allows for a product with low dispersity, when no additional mechanisms are observed, and the degree of polymerization can be easily controlled based on the monomer to initiator ratio. Although any nucleophile could be used to initiate the polymerization, primary amines are mostly used. The mechanism is shown in Scheme 2.3.



Scheme 2.3: Normal amine mechanism for the ring opening polymerization of NCAs. This mechanism applies both for NCAs and for N-substituted NCAs.

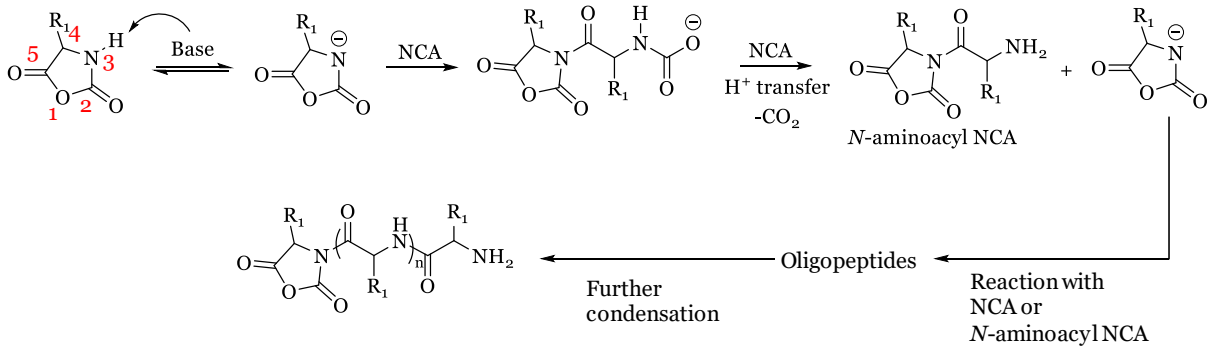
The initiation takes place due to the nucleophilic attack of the amine on the C-5 of the NCA. The NCA ring opens to form an unstable carbamic acid, which upon release of carbon dioxide, decomposes to yield an amine. The newly formed amine can subsequently attack another NCA.

In the case of *N*-substituted NCAs, their polymerization is a living polymerization, with the propagating center remaining intact and the reaction yielding products of low dispersity (Đ). Evidence for that was already accessible in 1977, when Sisido et al. polymerized sarcosine NCA using dimethylamine as an initiator in *N*,*N*-dimethylformamide (DMF) and showed that the reaction obeyed pseudo-first order kinetics and the molar mass distribution corresponds to a Poisson distribution.[38] A very detailed investigation by Luxenhofer et al. of the polymerization of methyl, ethyl, *n*-propyl, *n*- and *i*-butyl *N*-substituted NCAs, demonstrated that they also have living character.[39] Adding to the evidence supporting the living character of their ROP, the resulting polypeptoids could be fully functionalized by end-capping or be used to re-initiate polymerization, after the addition of NCA.[40] Despite the avoidance of other side reactions, *N*-substituted NCAs can dimerize,[31] particularly at lower concentrations.

In the case of amino acid NCAs, NAM can be accompanied by the activated monomer mechanism (AMM), which is analyzed next.

Activated monomer mechanism (AMM)

The fact that two mechanisms may influence the kinetics of NCA polymerization was first reported by Ballard et al. in 1958.[41] Szwarc et al. further elaborated on the mechanism, using primary amines in comparison to tertiary amines and other aprotic bases to initiate the polymerization of NCAs.[42] The additional mechanism that affects the polymerization of NCAs is called the activated monomer mechanism (AMM) (Scheme 2.4).



Scheme 2.4: Ring opening polymerization of NCAs according to the activated monomer mechanism. In this case, the initiator deprotonates the NCA, acting rather as a catalyst. The initiator is the deprotonated NCA. The oligopeptides include two reacting sites, leading to a high dispersity of the resulting polymer.

In the AMM, an amine or other base deprotonates the N-3 of the NCA, acting more as a catalyst rather than an initiator. The resulted deprotonated NCA can act as an initiator, attacking another NCA to form an *N*-aminoacyl NCA, after ring opening and release of CO_2. AMM leads to oligomers that contain both an amine, which can further react with other NCAs and propagate the polymerization in the same fashion as in the NAM, as well as an NCA ring, which can react with amines from other oligomeric chains. The probability of this condensation reaction increases at high conversions and leads to a broad molar mass distribution.[43]

NAM and AMM can take place simultaneously, depending on the nature of the initiator. Tertiary amines act as bases, leading to AMM, whereas primary and secondary amines can result in both of the mechanisms.[44] To yield polypeptides of defined molar mass and of a narrow distribution, it was thought necessary to suppress the AMM and many strategies were facilitated to circumvent the AMM.

An interesting method was suggested in 2003 and entailed the use of primary amine hydrochlorides.[45] The mechanism was assumed to include an equilibrium between the ammonium salt and the amine group of the initiator or the growing chain during propagation. The same group refined the use of ammonium salts as initiators to avoid the AMM and showed that the reaction can even be accelerated by the use of a tertiary amine without affecting the control of the reaction, challenging the need to entirely avoid tertiary amines.[46]

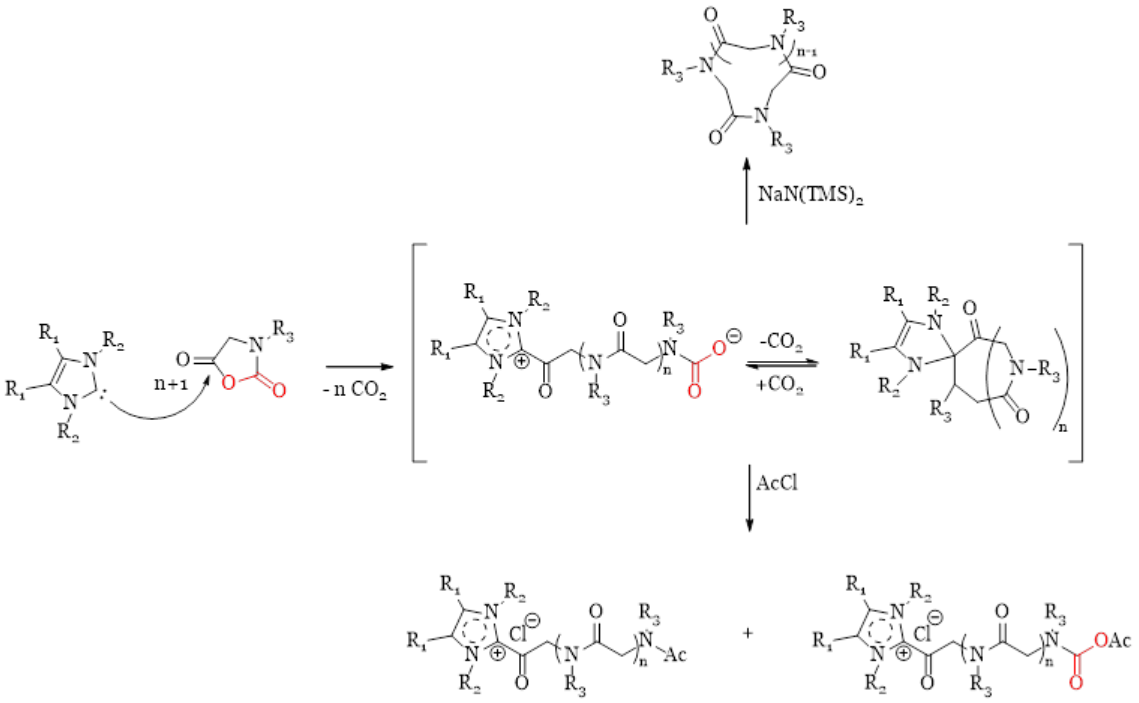
Rare-earth borohydrate-initiated ROP

In 2012, Ling et al. reported the polymerization of γ-benzyl-L-glutamate NCA and L-alanine NCA by rare earth catalysts (RE catalysts) (yttrium and scandium based). Rare earth isopropoxide ($RE(OiPr)_3$), rare earth tris(2,6-di-tert-butyl-4-methylphenolate) ($RE(OAr)_3$), rare earth tris(borohydride) ($RE(BH_4)_3(THF)_3$), and rare earth tris[bis(trimethylsilyl) amide] ($RE(NTMS)_3$) showed high catalytic activity and resulted in polymers with Đ of 1.2 to 1.6 in high yields (>90%).[47] To extend the use of rare earth metals to the synthesis of polypeptoids, they used *N*-substituted NTAs, which are more stable than their respective NCAs. Specifically, they homo- and copolymerized the NTAs of sarcosine and *N*-butyl glycine. The reactions resulted to low yields at 25 or 40 °C, which reached 65-99% at 60 °C. The polymers produced at 60 °C had a dispersity of 1.26 to 1.40.[21]

N-Heterocyclic carbene-initiated ROP

In 2009, Zhang et al. reported that *N*-heterocyclic carbenes (NHC) could initiate the ROP of *N*-substituted NCAs. They used *n*-butyl glycine NCA and *n*-methyl glycine NCA, which they polymerized with bis(2,6-diisopropylphenyl)imidazol-2-ylidene in THF to yield cyclic polypeptoids of narrow dispersity (Đ = 1.04-1.12).[48]

Further investigation on the NHC initiated ROP, revealed a dependency of the polymerization rate and molar mass of the products on the chosen solvent and illuminated the mechanism of the polymerization.[49] As seen in Scheme 2.5, the NHC initiate the polymerization, but also act as intramolecular counterions. Propagation takes place through monomer addition to the zwitterionic propagating species at the carbamate chain end. The formed zwitterionic anhydride is intramolecularly rearranged to regenerate the zwitterionic propagating intermediate after irreversible CO_2 release. The rate-determining step of the reaction is the equilibrium between the zwitterionic propagating species and the spirocyclic propagating species. Termination with electrophiles, such as acetyl chloride, yields the linear polymer, whereas sodium bis(trimethylsilyl)amide ($NaN(TMS)_2$) treatment yields the cyclic polypeptoid.

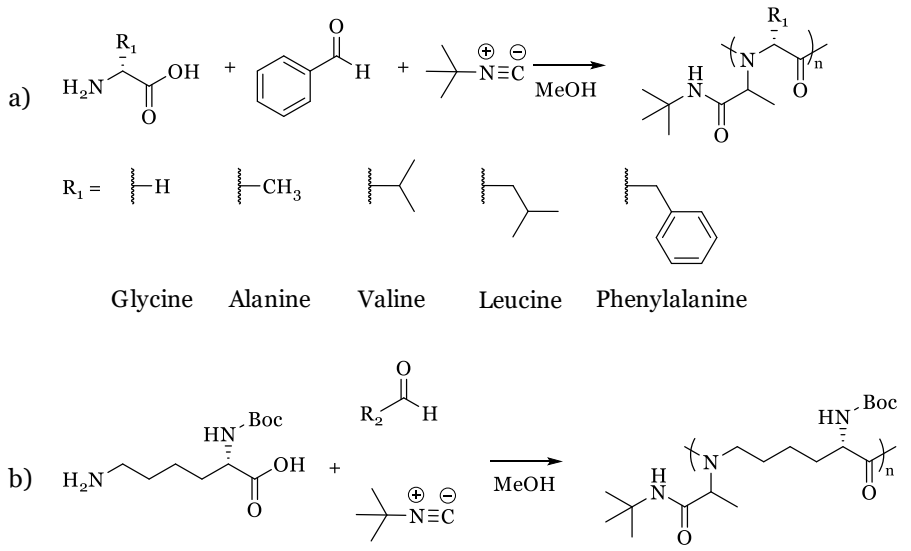


Scheme 2.5: N-Heterocyclic carbene initiated ROP of N-substituted NCAs.[49]

Ugi reaction

The Ugi reaction is a reaction in which a bis-amide is formed from a ketone or aldehyde, an amine, an isocyanide, and a carboxylic acid. In 2013, Wessjohann et al. used the Ugi reaction to synthesize peptoid-peptide hybrids.[50] In addition to that, the reaction has been also used to yield multiple different polymers that incorporate amides on their backbone.[51,52]

In 2016, polypeptoids were also prepared, based on natural amino acids, with the Ugi reaction.[53] As shown in Scheme 2.6, α-polypeptoids, as well as ε-polypeptoids based on N_{α}-*tert*-butyloxycarbonyl-lysine (N_{α}-Boc-lysine) were targeted. From the amino acids used, glycine and alanine yielded α-polypeptoids of molar mass of 3400 g/mol (Đ = 1.24) and 1600 g/mol (Đ = 1.24) respectively. The ε-polypeptoids reached molar masses of up to 11200 g/mol, depending on the aldehyde used, and the dispersities varied between 1.28 and 1.81. Regarding the synthesis of ε-polypeptoids, oligomeric cyclic species were observed, probably due to a ring-forming side reaction.[52]

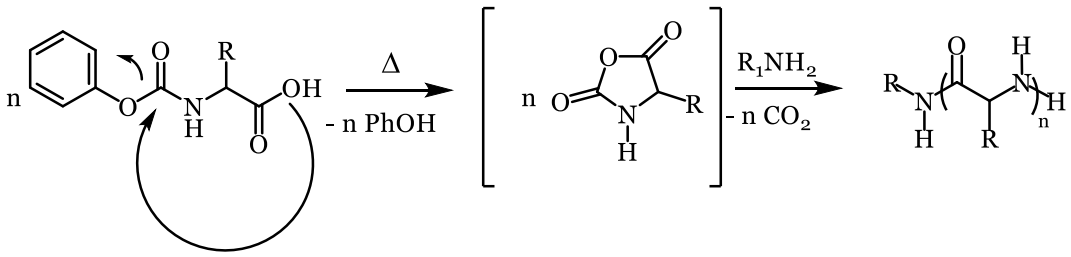


Scheme 2.6: Ugi reaction used for the synthesis of a) α-polypeptoids and b) ε-polypeptoids based on natural amino acids.[53]

2.5. Activated urethane derivatives of amino acids

In 2007 Endo et al. reported a new method for the synthesis of amino acid NCAs.[54] Their group prepared a series of NCAs based on L-glutamic acid γ-benzyl ester, benzyl cysteine, isoleucine, and *O*-benzyl-tyrosine. Reaction of the amino acids with bisarylcarbonates and subsequent heating in a variety of different solvents gave NCAs in yields of 55% to 100% according to ^{1}H-NMR analysis (internal standard 1,4-dioxane). However, the reaction towards the NCA was significantly accelerated in polar solvents, in which the NCAs are highly reactive and can polymerize easily. Soon, the first report of the synthesis of poly(γ-benzyl glutamate) from *N*-aryloxycarbonyl-γ-benzyl-L-glutamates without isolation of the NCA followed.[55] The produced polymers reached molar masses up to 15400 g/mol and their dispersities were between 2.34 and 2.89.

Since then, this method, which utilizes activated urethane derivatives of amino acids, has given access to many more polypeptides, based on e.g. *β*-benzyl-L-aspartate, L-leucine, L-phenylalanine, and L-proline,[56] Z-L-lysine,[57] and 3-{1-methyl-1-[2-(2,2,2-trifluoroacetylamino)ethoxy]ethoxy}-2-amino propionic acid.[58]



Scheme 2.7: Polypeptide synthesis from N-aryloxycarbonyl amino acids.

As shown in Scheme 2.7, the polymerization is based on the *in situ* synthesis of the NCA, after attack of the carbonyl group of the urethane group from the carboxylic acid oxygen. The fact that the polymerization proceeds in this way and not through polycondensation was supported by NMR analysis, which supported the formation of the NCA.[59]

This method enabled the synthesis of polypeptides without the use of phosgene or other toxic substances and without the need to isolate the NCAs. Although it was used for the synthesis of polyproline, an *N*-substituted polypeptide, the resulting polymer could not be characterized due to reduced

solubility and there was no report of the method being used for the synthesis of polypeptoids.[56]

In this chapter, we saw that proteins play a very important role in the function of living organisms and their synthetic equivalents, polypeptides, are thoroughly researched polymers with interesting properties. Their isomers, polypeptoids, similarly exhibit a great potential, especially for pharmaceutical applications. Nevertheless, their synthesis can be challenging due to the use of hazardous compounds and the instability of their monomers.

Polypeptoids are mainly prepared from their respective *N*-substituted NCAs, in the same fashion as polypeptides. In the case of polypeptides, the use of activated urethane amino acids has allowed for a more benign synthesis, skipping the use of compounds such as thionyl chloride or phosgene.

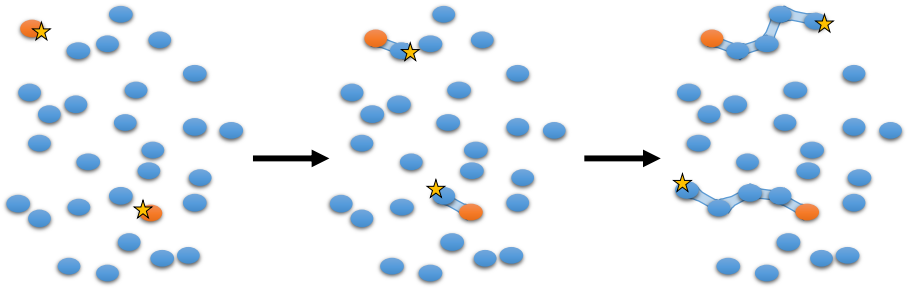
In this work, the method of the activated urethane amino acids is further extended to yield polypeptoids. In Chapter 4, the method is applied in the synthesis of polysarcosine, sarcosine being the simplest *N*-substituted glycine. The substitution of the amine influences the formation of the respective NCA. After optimization of the reaction for sarcosine, in Chapter 5, a variety of *N*-substituted glycines are synthesized and polymerized.

3. Introduction to Green Polyesters

3.1. Step-growth polymerization

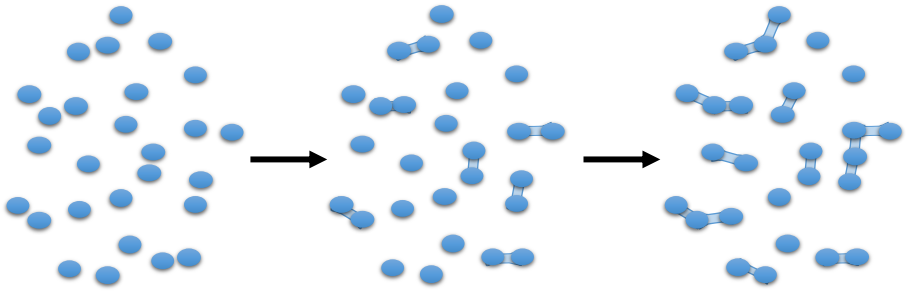
Although polymers can be classified according to a variety of criteria, a popular way to classify them is according to how they are produced. Specifically, the polymerization reactions can be divided into chain-growth and step-growth polymerizations.

Chain-growth polymerizations are characterized by the necessity for an initiator to start the reaction. After the formation of an initiating species that incorporates a propagating center (e.g. a cation, anion or radical), this species can react with a monomer. The propagating center is always at the end of the formed chain and can react with more monomers. Monomers cannot react with each other, but only with the propagating center (Scheme 3.1).



Scheme 3.1: A chain-growth polymerization. To start the polymerization an initiator (orange) is necessary. The monomers can only react with the propagating center (yellow star).

On the contrary, in step-growth polymerizations, the monomers can react with each other. Due to that, monomers can react to yield dimers, which can further react with monomers or dimers, and so on (Scheme 3.2). Furthermore, the polymerization reaction can be either an equilibrium or a non-equilibrium reaction.



Scheme 3.2: A step-growth polymerization. Depending on the polymerization, small molecules can be released from the reaction and the reaction can be an equilibrium or a non-equilibrium one.

Additionally to equilibrium and non-equilibrium reactions, step polymerization can also be divided based on the types of monomers used. The polymerization reaction can either entail two bifunctional monomers that each have one type of functional group or a bifunctional monomer that has two different functional groups that can react with each other (Scheme 3.3).

a) $n\,A\text{-}A + n\,B\text{-}B \rightarrow \text{-}(A\text{-}AB\text{-}B)\text{-}_n$

b) $n\,A\text{-}B \rightarrow \text{-}(A\text{-}B)\text{-}_n$

Scheme 3.3: Step polymerization involving a) two bifunctional monomers, each of which has the same type of functional groups, b) one bifunctional monomer with two different functional groups.

Because of the inherent differences in the mechanism, the kinetics of the chain and step-growth reactions are also very different. In the case of the step-growth polymerization, a very high conversion should be reached to access high molar mass (in Figure 3.1 for an AB monomer).

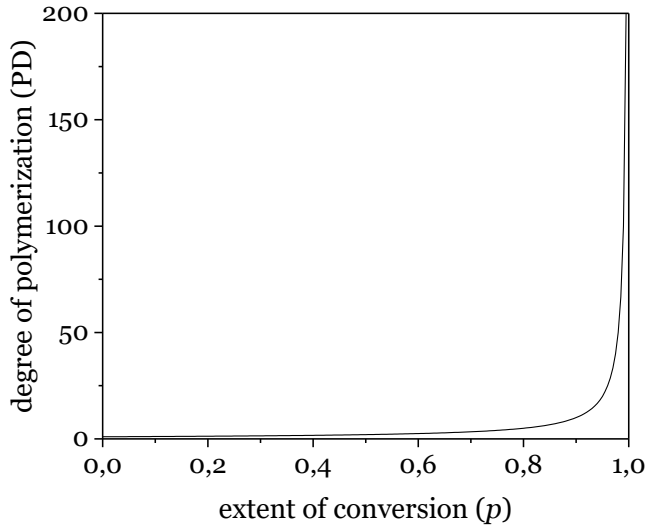


Figure 3.1: Degree of polymerization (DP) vs. % conversion according to Carother's equation for a step-growth polymerization of an AB monomer.

The average of the repeat units per macromolecular chain is given by the Carothers equation (here for AB monomers):

$$\bar{X}_n = \frac{1}{(1-p)},$$

in which p stands for the extend of conversion.

In the case of AA and BB monomers, the ratio of the two different monomers is crucial for the success of the polymerization. Even a slight deviation of 1:1 ratio can dramatically affect the molar mass of the produced polymer. The highest molar mass the polymer can reach, can be calculated according to the equation:

$$\bar{X}_n = \frac{1+r}{1-r-2rp},$$

where r can be calculated as follows:

$$r = \frac{N_A}{N_B},$$

where N_A and N_B are the moles of the functional groups A and B respectively. In this way, the molar mass of the product can be controlled, as well as the end-groups, based on the monomer used in excess. Alternatively, monofunctional monomers (carrying one A or B group) can be used to control the molar mass.

Step-growth polymerization can be used for the production of a variety of polymers. Polyamides, polyurethanes, and polyesters are just some examples. Although Bakelite (1909) was also a product of a step polycondensation,[60] it was mainly the work of Carothers that established the importance of polymer products of step-growth polymerizations (after *ca.* 1929).[61]

Polyesters are a very popular class of polymers that are products of step polymerization techniques. They exhibit a variety of properties important for various applications according to their structure. They can vary from low-melting, semicrystalline or even viscous fluid polymers (most aliphatic polyesters) to high-T_g amorphous or high-melting semicrystalline polymers (aromatic polyesters). Different properties can also be accessed in the case of cross-linked polyesters or hyperbranched polyesters.[62]

Poly(ethylene terephthalate) (PET) (Figure 3.2), for example, is a popular polyester, being used for food packaging, as well as textiles.

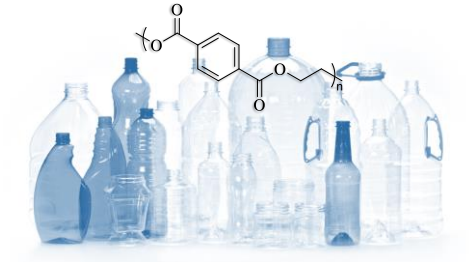


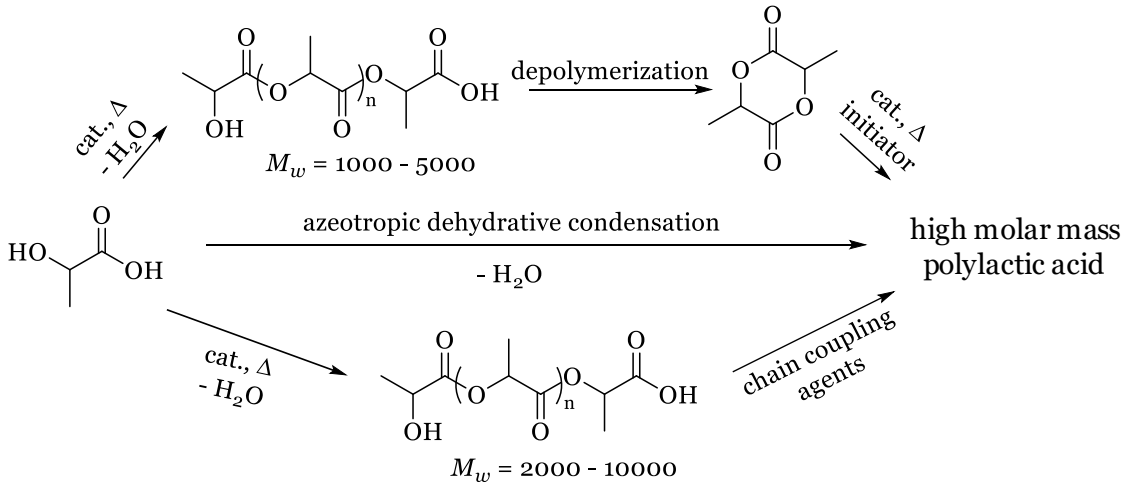
Figure 3.2: Poly(ethylene terephthalate), a popular polyester used in multiple applications, such as the production of bottles for soft drinks, detergents, etc.

Naturally, as research is turning to more environmentally friendly practices, solutions for "greener" polyesters are in need. Several approaches for the preparation of environmentally benign polyesters have been under investigation. Some environmentally friendly polyesters with interesting properties are briefly discussed here.

Poly(lactic acid)

Poly(lactic acid) is a polyester based on lactic acid. Carl Wilhelm Scheele was the first who isolated lactic acid from sour milk in 1780.[63] Nowadays, it is mainly prepared by bacterial fermentation from starch or sugar from tapioca, corn or other plants.[64]

Poly(lactic acid) can be produced by direct step-growth polycondensation of lactic acid in bulk. However, this method yields polymer of low molar mass (DP less than 100) with poor mechanical properties.[64] These short polymers can either be depolymerized to yield lactide (the cyclic dimer of lactic acid) or extended with chain coupling agents to yield poly(lactic acid) of high molar mass. Alternatively, high molar mass poly(lactic acid) is produced by ring opening polymerization (ROP) of the lactide (with metal catalysts) or by polymerization of the lactic acid in solution with constant water removal (Scheme 3.4).



Scheme 3.4: Production of high molar mass poly(lactic acid).[65]

Poly(lactic acid) can find applications in biomedicine, for example in dental implants or as a vehicle for controlled drug delivery. Additionally, it can be used for food packaging, especially for antimicrobial materials.[66] As a thermoplast, it can be extruded or molded into various products, which can then be recycled by melting to be processed again or can be hydrolyzed to lactic acid.[67]

Polyhydroxyalkanoates (PHAs)

Polyhydroxyalkanoates (PHAs) are linear polymers of hydroxyl derivatives of alkanoic acids and they can display different properties that resemble these of synthetic polymers according to their molar mass and structure.[68] PHAs are synthesized by bacteria, as well as by some Archaea, and polyester synthases are the main enzymes responsible for this polyester biosynthesis.[69]

PHAs are considered for a multitude of applications, such as medical implants, constituents of nanoparticles for drug delivery, and even as a source for biofuel. Poly(4-hydroxybutyrate) (P4HB), for example, is a resorbable polymer that can be used for tissue repair. It is flexible and can be processed to give oriented fibers, offering an important advantage in comparison to other resorbable thermoplastics. It eventually degrades producing carbon dioxide and water and does not cause inflammation.[70] To access structures for drug delivery, polyhydroxybutyrate (PHB), has been used in triblock copolymers with poly(ethylene oxide) (PEO),[71] as well as poly(hydroxybutyrate-co-hydroxyvalerate) (PHBHV) copolymer to form microspheres when emulsified with poly(ε-caprolactone) (PCL).[72] Additionally, after cleavage and reaction with methanol, PHAs form their respective methyl esters, which, interestingly, improve the combustion heat of ethanol and can be used as fuel additives.[73]

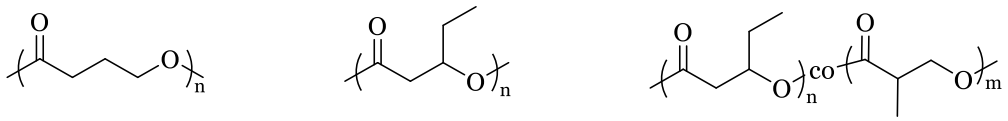


Figure 3.3: Examples of polyhydroxyalkanoates (PHAs), biodegradable polyesters synthesized by fermentation.

2,5-Furandicarboxylic acid (FDCA) based polyesters

2,5-Furandicarboxylic acid (FDCA) (Figure 3.4) is a diacid that can also be used for the production of environmentally friendly polyesters. It was first synthesized in 1786 from mucic acid,[74] but, nowadays it is mainly prepared from 5-hydroxymethylfurfural (HMF), a compound made of renewable resources.[75] FDCA is analogous to terephthalic acid and can be used for the synthesis of polyesters. One of its most interesting uses is the synthesis of poly(ethylene 2,5-furandicarboxylate) (PEF) (Figure 3.4). PEF is the furan equivalent of poly(ethylene terephthalate) (PET) and its properties have been thoroughly analyzed.[76] It is solely based on renewable feedstock and it is semicrystalline with a thermal stability up to 300 °C.[77] Its properties are comparable to those of PET and some studies support that it would be also economically viable to substitute PEF for PET, as long as it is produced in large scale and its by-products are also exploited.[78]

2,5-Furandicarboxylic acid (FDCA)

poly(ethylene 2,5furandicarboxylate) (PEF)

Figure 3.4: 2,5-Furandicarboxylic acid (FDCA), a biobased compound, and poly(ethylene 2,5-furandicarboxylate) (PEF), its polyester, which could be an alternative to PET.

3.2. Enzymatic polymerization

A very efficient way to accelerate chemical reactions is by metal catalysts. In the case of polyester synthesis, for example, bulk polyesterification reactions are rather slow at room temperature. However, they are accelerated at high temperatures, in the presence of catalysts, such as metal oxides or alkoxides.[62] Additionally to the catalyst and the high temperature, vacuum is also applied at the final steps of the polymerization to remove the by-product and shift the reaction towards the polymer.

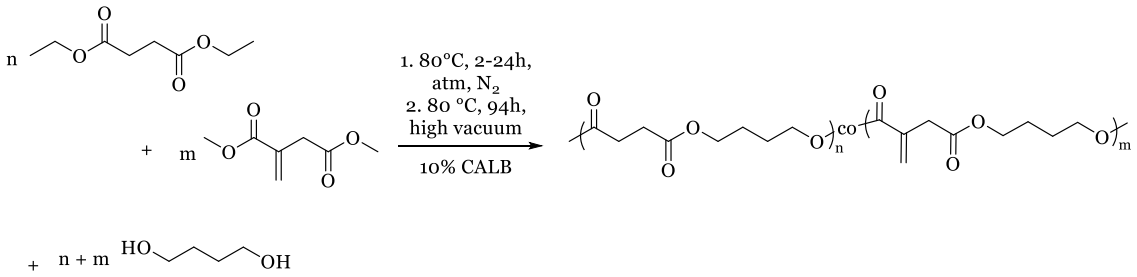
Despite the advantages they offer, most catalysts are difficult to remove and, especially in the case of biomedical applications, such contaminations might significantly affect the use of a polymer. In some cases, enzymes can be an alternative to metallic catalysts. Enzymes, in comparison to metal catalysts, require milder conditions, are more selective for specific reactions and can also exhibit stereoselectivity.

In the case of polyester synthesis, the enzymes of choice are lipases. Lipases normally catalyze the hydrolysis of fats. Pancreatic lipases, for example, digest triacylglycerol (the form in which most lipids are ingested) into free fatty acids and monoacylglycerol.[9] However, reactions in non-aqueous media and removal of by-products lead to bond formation rather than bond breaking, allowing for their use in polymerization reactions.[79] The first time that a lipase was used for the synthesis of oligoesteres was in 1984, when purified and crystallized lipase isolated from a strain of *Aspergillus niger* oligomerized 1,2-ethanediol with a variety of different dicarboxylic acids.[80] Soon thereafter, Yoshimoto et al. used a poly(ethylene glycol) (PEG)-modified lipase in benzene for the polycondensation of 10-hydroxydecanoic acid.[81] Recently, lipase was immobilized on a resin, Novozyme 435 (N435) being a highly popular commercial example, consisting of *Candida antarctica* lipase B (CALB) adsorbed within a poly(methyl methacrylate-co-butyl methacrylate) resin.[79] Immobilization of the enzyme on a resin allows for easy removal of it, as well as recycling, and increases its stability.

Gross et al.[82] investigated the effects of solvent (or absence thereof), as well as monomer chain length on lipase catalyzed polycondensations. According to their studies, diphenyl ether allowed for higher molar mass compared to other organic solvents or bulk polymerization reaching a M_n of 28500 g/mol

within 48 hours. The chain length of diacids and dialcohols seemed to have an effect on the reactivity, with longer chain lengths resulting in faster polymerization.

An example of CALB catalyzed polycondensation is given in Scheme 3.5, in which diethyl succinate is copolymerized with dimethyl itaconate and 1,4-butanediol. The reaction involves two steps. In the first step, the reaction mixture is heated up to 80 °C and is stirred for 2 up to 24 hours in nitrogen atmosphere, allowing for oligomerization of the monomers. In the second step, high vacuum is applied for removal of the by-products. Loos et al. investigated this system, optimizing it for solvent selection and time, reaching the conclusion that diphenyl ether was the best of the tested solvents and that the oligomerization step is complete within 30 minutes.[83]



Scheme 3.5: Exemplary use of lipase (N435) for the copolymerization of succinate, itaconate and 1,4-butanediol.[83]

3.3. Dihydroxyacetone (DHA)

Dihydroxyacetone (DHA) is a carbohydrate, the simplest ketose. It is commonly produced from glycerol. Glycerol is an abundant compound, obtained as a by-product of soap manufacture, the production of fatty acids or fatty esters,[84] or microbial fermentation.[85] DHA can also be produced in the human organism from glycerol during glycolysis.[86]

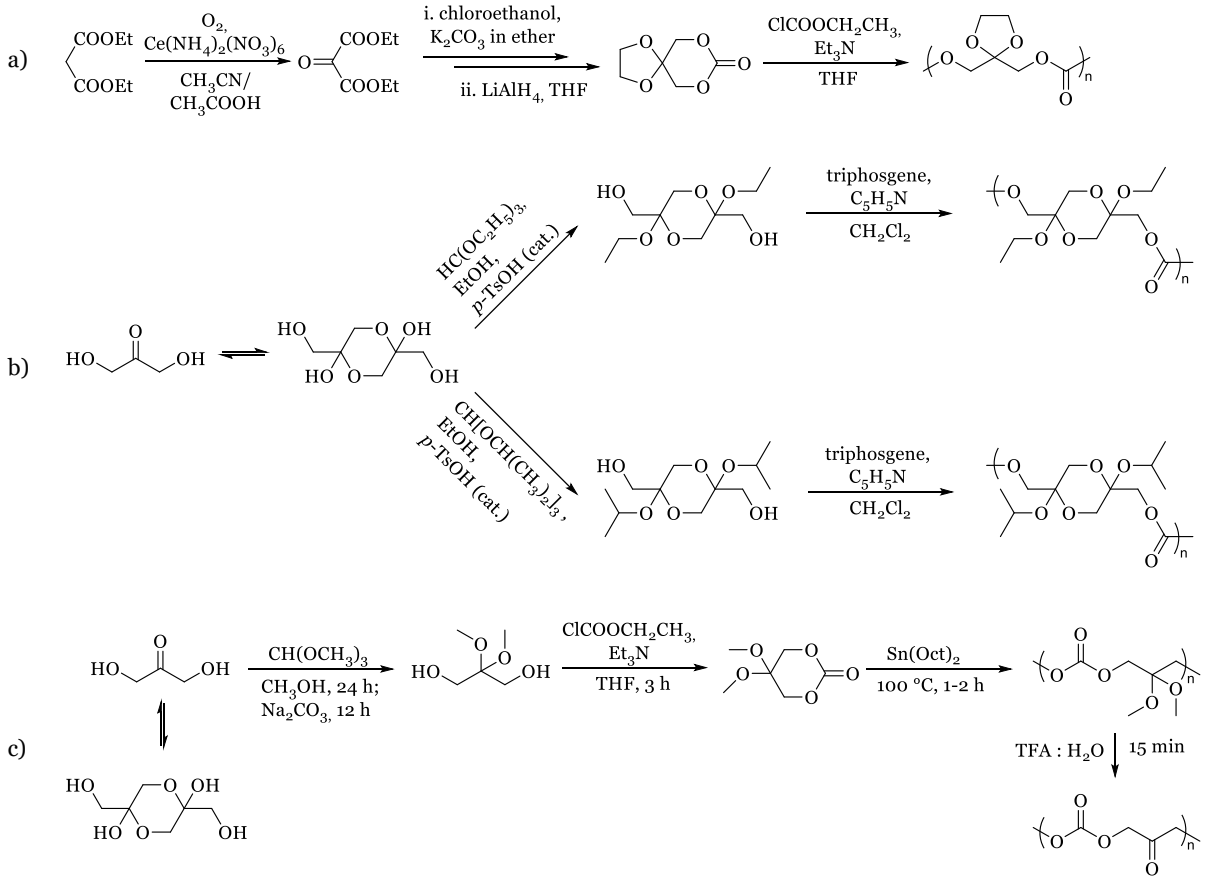
The production of DHA from glycerol is based on fermentation or catalysis. The first time that bacterial fermentation was reported to turn glycerol to DHA was in 1898,[87] and the bacterium responsible for the reaction was recognized a year later.[88] Since then, different approaches to increase the yield of the production based on fermentation have been taken, like adjusting the environmental conditions,[89] using innovative bioreactor systems,[90] or by genetically manipulating bacteria to overexpress glycerol dehydrogenase, the enzyme that leads to DHA production.[91]

DHA is also prepared by catalytic oxidation from glycerol. Waymouth et al., for example, reported a 97% conversion of glycerol to DHA with a selectivity better than 96%, when 5 mol% palladium and 3.0 equivalents of benzoquinone were used in acetonitrile and at room temperature.[92] In 2015,[93] Ramírez et al. reported the gas-phase oxidation of glycerol to dihydroxyacetone over iron-loaded zeolites, showing that a stable yield of almost 90% can be achieved with iron-containing silicate prepared by hydrothermal synthesis followed by steaming. Prior to that, the same group had used zeolites for the conversion of DHA to lactic acid.[94]

In addition to being a precursor for lactic acid, DHA has been used in cosmetic products. Its ability to stain the skin has led to its facilitation in self-tanning lotions. The staining is not permanent and can be removed by mechanical rubbing or tape stripping[95] and it is influenced by several factors, such as moisture content and the pH of the skin.[96]

Regarding polymeric products, dihydroxyacetone and its derivatives have been successfully polymerized to yield polycarbonates. Zhuo et al. reported in 2004 the synthesis of an aliphatic polycarbonate based on a cyclic acetal protected dihydroxyacetone.[97] Ethylene ketal protected dihydroxyacetone was converted to 2,2-ethylenedioxypropane-1,3-diol carbonate, the monomer, which was further subjected to ring-opening polymerization in bulk (Scheme 3.6a).

The resulting polymer was amorphous and could be hydrolytically degraded. A year later, Zelikin and Putnam prepared two different poly(carbonate-acetal)s based on the dimer of dihydroxyacetone.[98] Two different stabilized forms of the dihydroxyacetone dimer were treated with triphosgene to yield polymers with molecular weights up to 50000 g/mol, with dispersities of approximately 2 (Scheme 3.6b). The same group also investigated the ring-opening polymerization of a cyclic carbonate based on a stabilized form of DHA, 2,2-dimethoxy-1,3-propane diol (Scheme 3.6c),[99] a route to obtain polycarbonates that has since been investigated by more groups.[100]



Scheme 3.6: Examples of DHA based polycarbonates; a) ring-opening polymerization of 2,2-ethylenedioxypropane-1,3-diol carbonate,[97] b) polycondensation of stabilized DHA dimers with triphosgene,[98] and c) ring-opening polymerization of 2,2-dimethoxypropylene carbonate.

Additionally to linear polycarbonates, DHA has been used for the formation of hydrogels.[101] Glycerol ethoxylate, tri(ethylene glycol) bis(chloroformate) and DHA were reacted to form hydrogels and their degradation was studied. Interestingly, the degradation of DHA based material seems to be very rapid in aqueous conditions. Monomethoxy poly(ethylene

glycol)-poly(DHA) diblock copolymers were degraded in vitro within 24 h.[102] The content of DHA seems to influence the degradation of polymers, with random copolymers of lactic acid and DHA showing an increased degradation rate with increasing DHA content.[103]

As the need to move to more sustainable materials becomes more urgent, a variety of polymers based on renewable feedstock is under investigation. New materials based on old methods are reported from research groups continuously. Additionally, alternative synthetic methods add to the options for greener polymers. In the field of polyesters, poly(lactic acid) seems to dominate, finding application in multiple areas that reach from implants to food packaging. Polyhydroxyalkanoates (PHAs) constitute a versatile class of polyesters based on bacterial polymerization that could also substitute some traditional, synthetic polymers. An alternative to the popular poly(ethylene terephthalate) could be the bio-based poly(ethylene 2,5-furandicarboxylate) (PEF).

Dihydroxyacetone (DHA) a compound based on glycerol (an abundant resource) has already been investigated for the synthesis of polycarbonates. However, DHA being a diol, polycondensation would be an attractive option to obtain its polymers. DHA is also a product of the human metabolism, making its polymers less probable to result in toxicity or inflammation upon degradation.[101] Polymers based on DHA, additionally to being sustainable, are therefore also interesting candidates for medicinal applications.

In this work, dihydroxyacetone is investigated as a comonomer for polycondensation reactions. Equilibrium and non-equilibrium reactions are used for its polymerization, as well as a variety of comonomers.

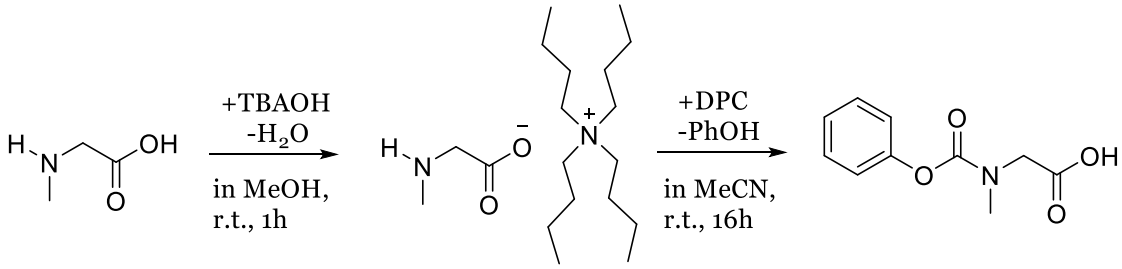
4. Alternate Synthesis of Polysarcosine

To assess the use of activated urethane monomers as an alternative way to synthesize polypeptoids, the first polypeptoid chosen was polysarcosine. Polysarcosine is biocompatible and degradable, and dissolves very well in a variety of solvents, including water. These properties make it highly popular as a homopolymer, or as a hydrophilic block in block-copolymers.[21,104]

Polysarcosine is normally prepared from the NCA of sarcosine (methyl-*N*-glycine). Sarcosine NCA (Sar-NCA) can be synthesized using triphosgene (in the presence of (+)-limonene)[39] or in a one-step synthesis from Boc-*N*-methyl glycine in anhydrous DCM with phosphorous trichloride.[22] The Sar-NCA can be purified by sublimation. Both of the methods include the use of hazardous chemicals and the resulting NCA is highly susceptible to the common problems of NCAs, dimerization and degradation. An alternative method that avoids the isolation of Sar-NCA would make polysarcosine easier to prepare and would pave the way for the synthesis of more complicated polypeptoids.

4.1. Monomer synthesis

Firstly, *N*-phenoxycarbonyl-*N*-methyl-glycine (Poc-Sar) was prepared, based on the synthesis of Poc-amino acids.[105] Sarcosine was stirred in methanol (MeOH) with tetrabutylammonium hydroxide (TBAOH) for 1 hour at room temperature (r.t.). After evaporation of the solvent, the formed tetramethylammonium salt was dissolved in acetyl chloride (MeCN) and diphenyl carbonate (DPC), also dissolved in MeCN, was added to the mixture to achieve *N*-carbamoylation. The reaction mixture was stirred for 16 hours at r.t. and the product could be isolated either by column chromatography or by double extraction. The reaction is shown on Scheme 4.1.



Scheme 4.1: Poc-Sar synthesis with tetrabutylammonium hydroxide (TBAOH).

The resulting Poc-Sar was analyzed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy (Figure 4.1). For the product isolation, double extraction and column chromatography resulted to similar yields (48% and 52% respectively). However, double extraction cannot entirely remove the tetrabutylammonium cation, as revealed by NMR spectroscopy.

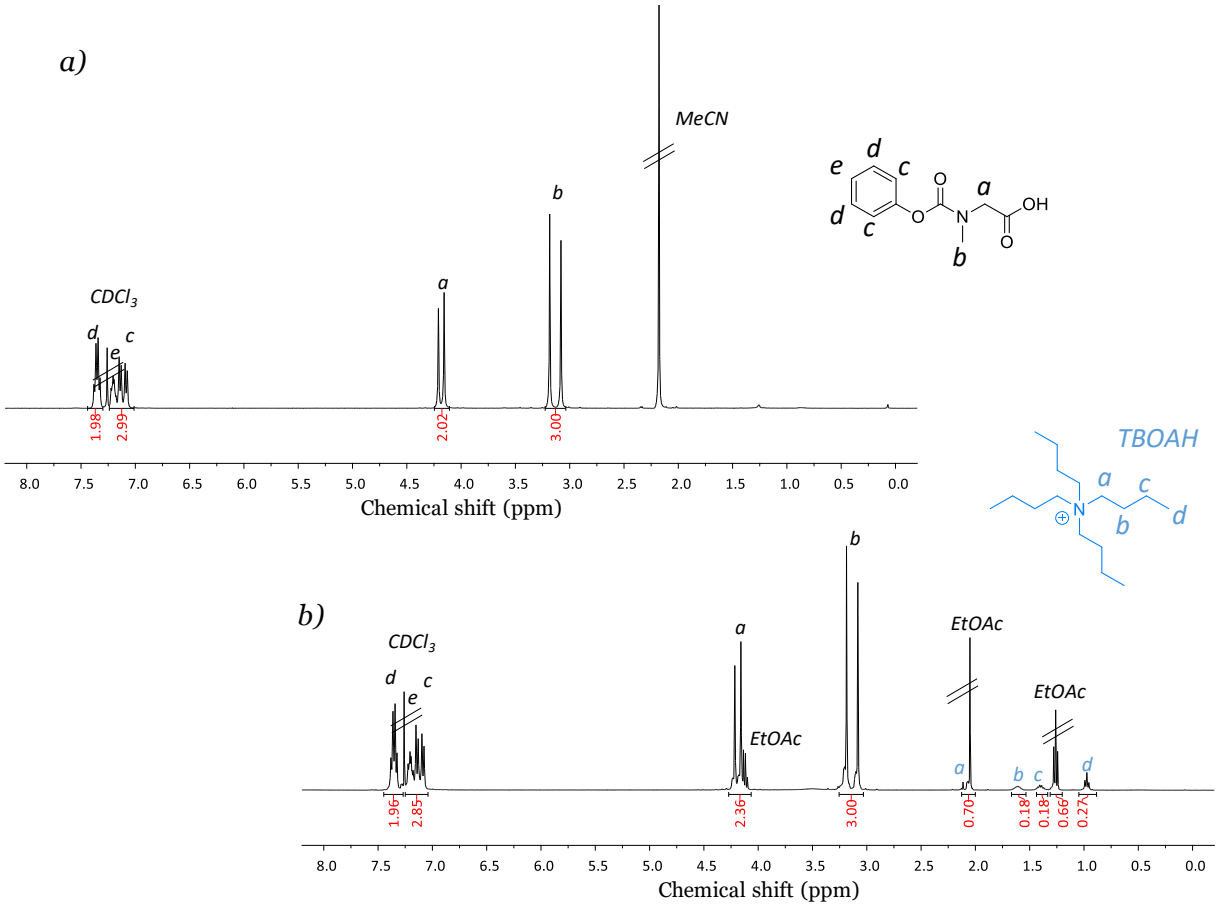
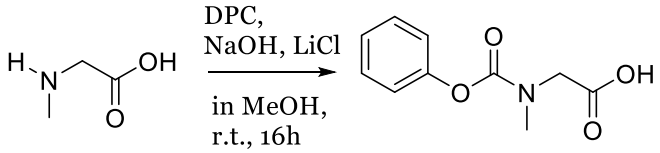


Figure 4.1: ^{1}H-NMR spectra ($CDCl_3$, δ 7.26) of Poc-Sar isolated by a) column chromatography and b) double extraction. The double extraction does not remove TBAOH in its entirety.

To avoid the use of TBAOH, Poc-Sar can also be synthesized using potassium hydroxide (KOH) (or sodium hydroxide (NaOH)), lithium chloride and diphenyl carbonate (DPC).[106] Sarcosine is dispersed in MeOH, and the base and salt are added. DPC is added to the mixture and the reaction is left to proceed for 16 hours. The product can be easily isolated by double extraction, in the form of a viscous liquid (Scheme 4.2).



Scheme 4.2: The second method for the preparation of Poc-Sar, without TBAOH.

4.2. The effect of the solvent

In order to study whether Poc-Sar could react to give polysarcosine, we chose an arbitrary concentration of 0.77 M, a temperature of 60 °C, and benzylamine ($BnNH_2$) as the initiator, which also acts to accelerate the reaction.[59] The reaction mixtures were analyzed by ^{1}H-NMR spectroscopy every day for 4 days. After 4 days the samples were precipitated in acetone, which is a non-solvent for polysarcosine.

The reaction is expected to consist of two different reactions, namely the conversion of the Poc-Sar precursor to the Sar-NCA and the polymerization of the formed NCA. Different solvents, which could be advantageous for the following reasons, were used for the reaction:

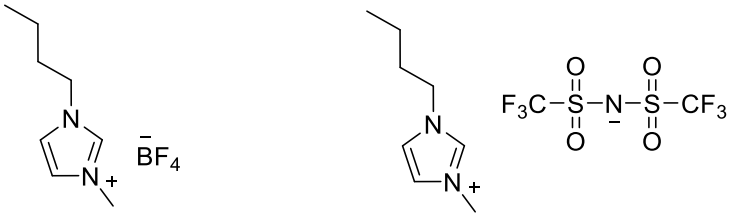
No solvent

Since the purpose of this work was to make the synthesis of polypeptoids "greener", the ideal choice would be to use no solvent for our reaction. An example of bulk polymerization to yield a polypeptoid already exists: the NCA of *N*-isopropyl glycine is reported to successfully polymerize in melt.[17] Furthermore, Poc-Sar is a viscous liquid, making its use in bulk polymerization easier.

Ionic Liquids

Ionic liquids are considered "green" solvents, mainly because of their low volatility and their recyclability. In addition, they can be of variable hydrophilicity, substituting a plethora of conventional solvents.[107] They have already been used for various applications, and they seem to be advantageous not just as solvents for multiple reactions, but also for extractions,[108] and for biocatalysis.[109]

For our investigation we used 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][TFN_2]) (Figure 4.2).



[bmim][BF4] [bmim][TFN2]

Figure 4.2: 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][TFN_2]).

Benzonitrile

Benzonitrile (BnCN) is the solvent of choice for polymerization of *N*-substituted NCAs. It is used for the synthesis of different polypeptoids and the kinetics of their polymerization in BnCN is well studied.[40]

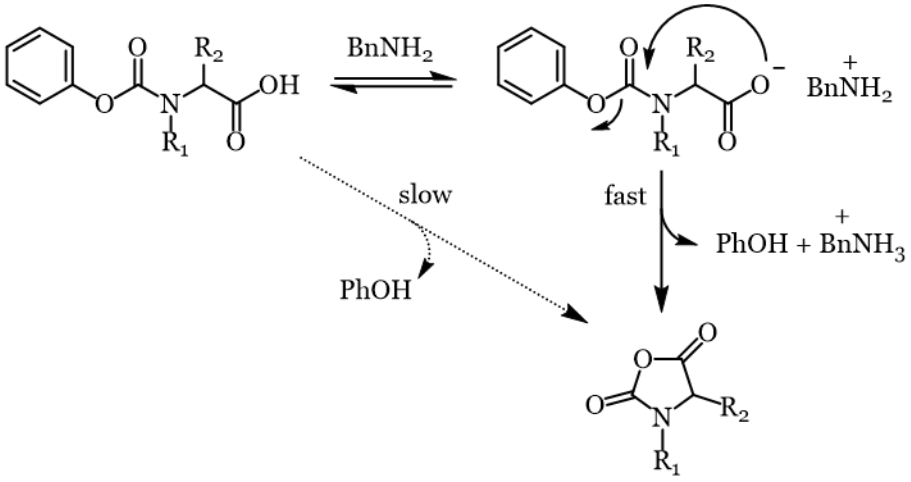
Polar solvents

In early studies of the activated urethane derivatives it was demonstrated that polar solvents are more efficient for the *in situ* formation of NCA. Specifically, it was shown that compared to 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF), in which 72 h were needed for quantitative conversion, 2-butanone and acetonitrile led to high conversions within 6 h. [54] More recently, even more polar solvents are used, such as *N,N*-dimethylacetamide (DMAc).[110]

In our studies, dimethyl formamide (DMF), *N,N*-dimethylacetamide (DMAc), and dimethyl sulfoxide (DMSO) were used. DMF is the solvent mostly used for the polymerization of amino acid NCAs,[33] and DMAc has been extensively used for the activated urethane derivatives polymerization, as already mentioned.

Assessing the efficiency of the solvents

According to Endo et al., in the case of the Poc-amino acids, the mechanism of the reaction in the presence of an amine includes the formation of NCA with the simultaneous release of phenol (Scheme 4.3).[59]



Scheme 4.3: The mechanism of polymerization of the activated urethane derivatives of amino acids based on the research of Endo et al.

Therefore, the reaction mixtures were analyzed by NMR to investigate whether phenol was formed. The signals of the aromatic protons of Poc-Sar and these of the released phenol differ significantly in ^{1}H-NMR. Indeed, for some solvents a release of phenol was observed. As an example (Figure 4.3), the ^{1}H-NMR spectra after 1 day and 2 days of reaction in bulk and in DMSO are shown. In the case of the bulk polymerization, the spectra do not show any change in the timescale of the experiment. On the contrary, in DMSO some phenol is already formed within the first day.

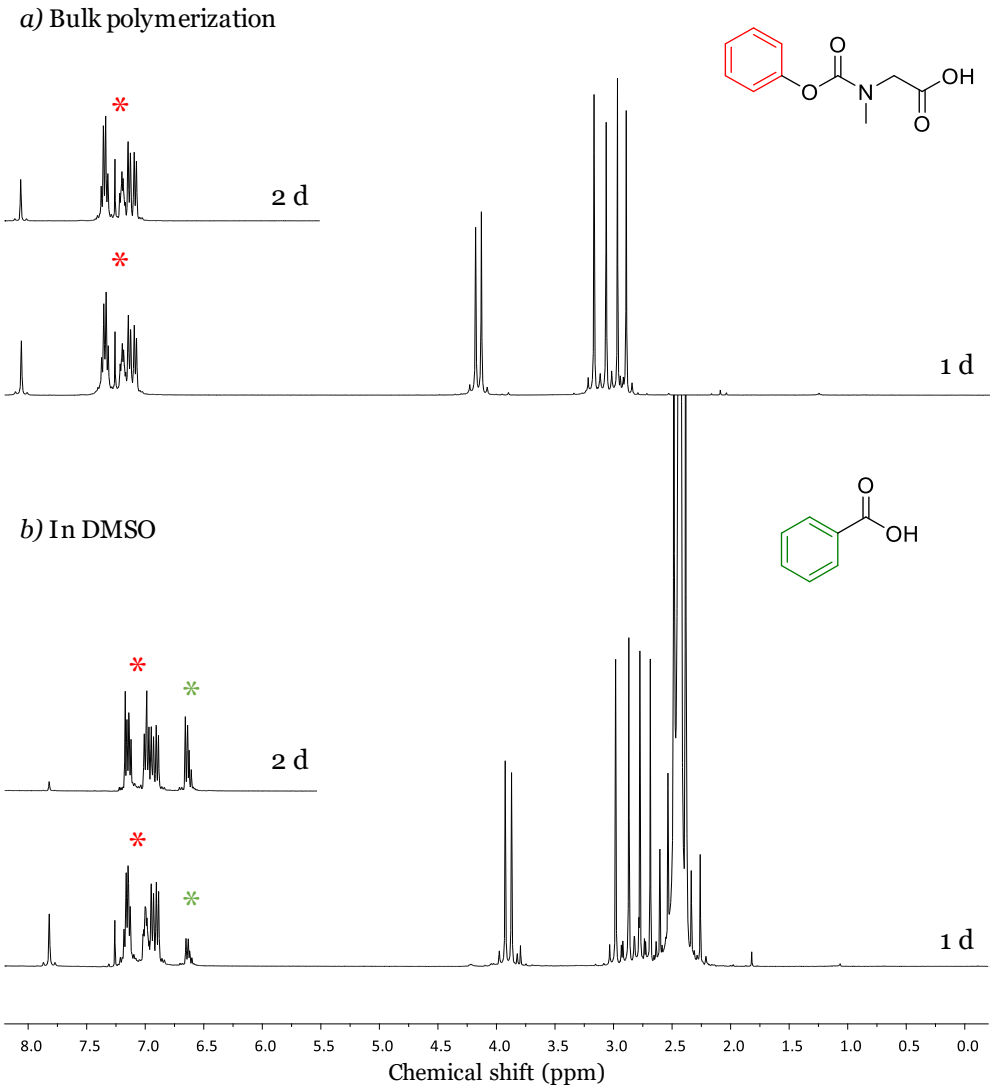


Figure 4.3: Exemplary ^{1}H-NMR spectra ($CDCl_3$, δ 7.26) of the attempts to polymerize Poc-Sar a) in bulk and b) in DMSO. In samples that do not polymerize within the tested time, the NMR spectra do not show changes in the shift of the aromatic protons. Whereas, when Poc-Sar reacts, it releases phenol (in green).

All of the samples were added dropwise in an excess of acetone after 4 days, to precipitate the potentially synthesized polysarcosine. The only sample that produced a solid was the one in DMSO. It was also the only one showing signals corresponding solely to phenol on the fourth day, based on its NMR spectrum, indicating a strong relation between the phenol production and the polymerization efficiency. Reactions in ionic liquids, benzonitrile, as well as in bulk showed hardly any evidence of reaction. In the polar solvents, some phenol was produced, but no precipitate could be isolated, except for DMSO.

The amount of precipitate that was produced was too low to be analyzed by ^{1}H end-group analysis, but was sufficient for gel permeation chromatography

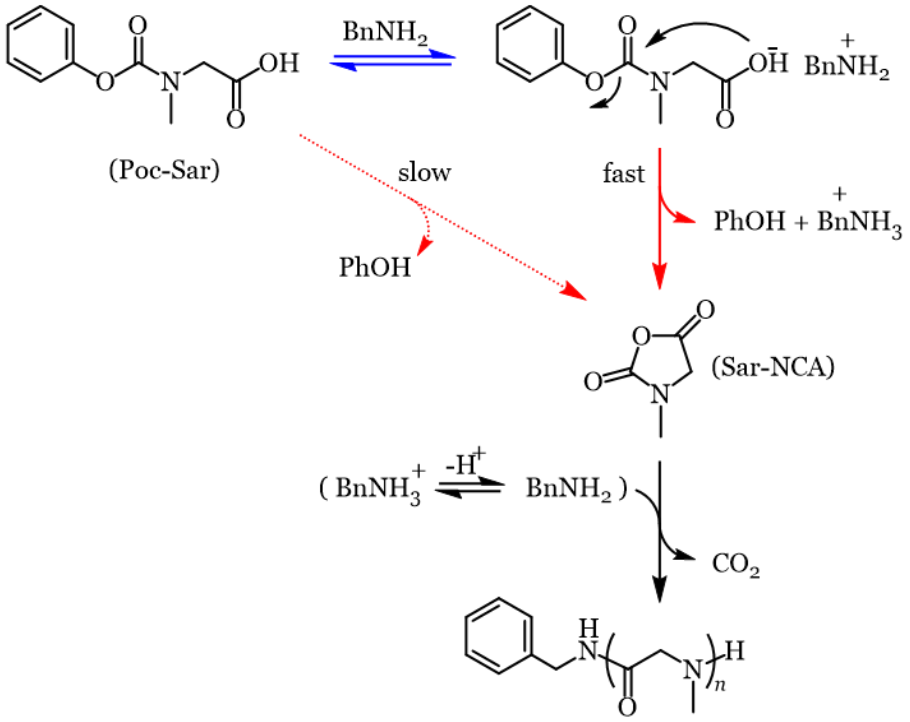
(GPC). It was measured in *N*-methyl-2-pyrrolidone (NMP) with polystyrene (PS) calibration to show a M_n of 1900 g/mol with a dispersity of 1.11.

The reaction seems to be significantly slower than the Sar-NCA polymerization reaction, as well as the reactions of the activated urethane derivatives of amino acids. Despite the use of benzylamine as an initiator, which is supposed to accelerate the reaction, it is of doubt whether the method could offer significant advantages for the synthesis of polypeptoids. It requires a long reaction time and the advantages of the more benign chemistry are undermined by the energy surplus it demands. Even in DMSO, which seems to be the best solvent for the reaction, it requires 4 days at 60 °C instead of few hours (3.5 h for a DP of 50) required for the Sar-NCA polymerization at room temperature.[40] Therefore, adjustments and optimizations are necessary, for this method to be advantageous enough for the preparation of polypeptoids. It is important, however, to notice that the dispersity seems to be comparable to the polymerization of Sar-NCA. This is contrary to the polymerization of activated urethane derivatives of amino acids, the products of which have a significantly higher dispersity, especially in less polar solvents.[59] In the next section, two different strategies are investigated to circumvent the challenges of the slow kinetics.

4.3. Acceleration of the reaction

Reaction mechanism

As already mentioned, according to the literature, the mechanism of the reaction is based on an *in situ* formation of the respective NCA.[55] The amine not only initiates the reaction but also helps to produce the deprotonated Poc-Sar. In this way, the NCA is produced faster than when in the absence of amine. Based on the fact that the only reaction producing a polymer, see previous section, was the one in which all of the Poc-Sar was consumed and phenol was released, the expected mechanism is shown on Scheme 4.4.



Scheme 4.4: The tentative mechanism for the polymerization of Poc-Sar. To accelerate the reaction either a carbonyl activator is used to enhance the reactions producing the NCA (indicated in red) or a tertiary amine that can result in a higher concentration of the deprotonated Poc-Sar (equilibrium indicated in blue).

The kinetics of Sar-NCA polymerization are well studied and, therefore, our attempts were focused on the acceleration of the transformation of Poc-Sar to Sar-NCA. A method already adopted in the case of polypeptides, when the respective Poc-amino acids did not react, was to add electron-withdrawing groups on the Poc-aromatic ring. For example, *N*-(4-chlorophenoxycarbonyl)-γ-benzyl-L-glutamate and *N*-(4-nitrophenoxycarbonyl)-γ-benzyl-L-glutamate were reported to react much faster than the Poc-γ-benzyl-L-glutamate.[55]

However, that would be less atom efficient, since we would simply add even more weight that is going to be lost during the polymerization reaction.

To increase the speed of the reaction we tried two different methods. Either activate the carbonyl that is attacked by the oxygen to produce the NCA or to shift the equilibrium towards the deprotonated Poc-Sar, so that the respective carboxylate is more nucleophilic.

Use of carbonyl activating agents

Carbonyl activating agents, tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) and scandium(III) triflate ($Sc(OTf)_3$), were used to activate the carbonyl of the Poc-Sar and that of its deprotonated state, making the reactions towards the NCA more efficient, either directly from the Poc-Sar or from its deprotonated form. If this strategy results in an acceleration of the NCA, it could also be used for the synthesis of polypeptides, as the compounds suggested should not affect the amino acid NCA polymerization.

To evaluate the compounds we chose, we decided to use one of the polar solvents that showed some reactivity, specifically DMF. DMSO was avoided in the case the reaction would become too fast to follow its kinetics. The conditions used were again 60 °C with a 50:1 ratio of monomer to $BnNH_2$. The concentration of the carbonyl activators was 1 mol%. The reaction was evaluated via NMR, according to the phenol released, and the results are summarized in Table 4.1.

Table 4.1: Carbonyl activators used for the acceleration of the in situ NCA synthesis and their effect in terms of conversion of Poc-Sar after 2 days.

Aiding reagent (concentration)	Conversion after 2 days
$Sn(Oct)_2$ (0.1 equiv)	2%
$Sc(OTf)_3$ (0.1 equiv)	No change detectable by NMR analysis

The carbonyl activators do not seem to significantly change the kinetics of the reaction.

Use of a non-nucleophilic base

When amines were used for the initiation of activated urethane derivatives, it was noticed that the kinetics were faster. However, an amine in

the case of amino acid NCAs is also an initiator, limiting the amount of amine that can be used. In our case, however, use of a non-nucleophilic base to deprotonate the Poc-Sar should not have an effect in the molar mass of the products. Tertiary amines are able to initiate amino acid NCAs, because they can deprotonate them and activated monomer mechanism (AMM) polymerization can take place. This also has a significant effect in the dispersity of the product. However, since Sar-NCA is substituted on the nitrogen, it cannot polymerize with AMM. The bases tried were triethylamine (TEA), *N,N*-diisopropylethylenamine (DIPEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Figure 4.4).

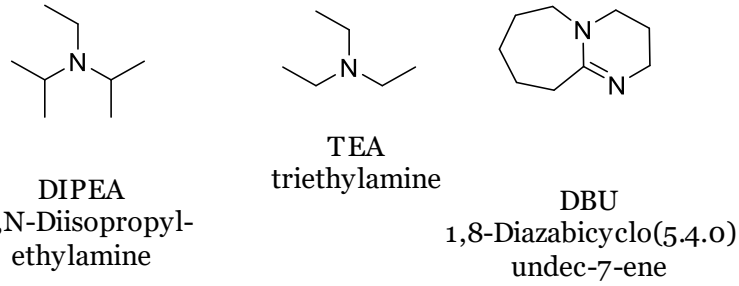


Figure 4.4: The non-nucleophilic bases used to accelerate the Poc-Sar conversion.

The concentration of the non-nucleophilic bases used was 2 mol%. The reaction was evaluated via NMR, according to the phenol released, and the results are summarized in Table 4.2.

Table 4.2: Non-nucleophilic bases used for the acceleration of the in situ NCA synthesis and their effect in terms of conversion of Poc-Sar after 2 days.

Aiding reagent (concentration)	Conversion after 2 days
TEA (0.2 equiv)	8%
DBU (0.2 equiv)	7%
DIPEA (0.2 equiv)	12%

The use of a non-nucleophilic base shows a noticeable advantage compared to the carbonyl activating agents. For the latter, the change in the conversion is within the statistical error. However, the bases result in a significantly faster conversion.

Among the bases, DIPEA seemed to yield the best results. However, the acceleration in DMF was not significant. In the next section, DIPEA or TEA are combined with DMSO to drastically accelerate the reaction.

4.4. Effect of the base on the kinetics and the polymer structure

Addition of a non-nucleophilic base in DMF was more effective in the conversion of Poc-Sar compared to carbonyl activators. However, the reaction was still not very fast. In this section, the tertiary amines are combined with DMSO. Poc-Sar is reacting with $BnNH_2$ at 60 °C, at a concentration of 0.77 M for 24 h, with different amounts of a tertiary amine. The kinetics of the reaction was studied by NMR analysis for 0.2, 0.5, 1.0 and 2.0 equiv of TEA compared to the monomer in DMSO.

The reaction in DMSO is significantly faster when a tertiary amine is added. The fast conversion of Poc-Sar, as phenol is released, when 0.5 equiv of TEA are used is shown in Figure 4.5.

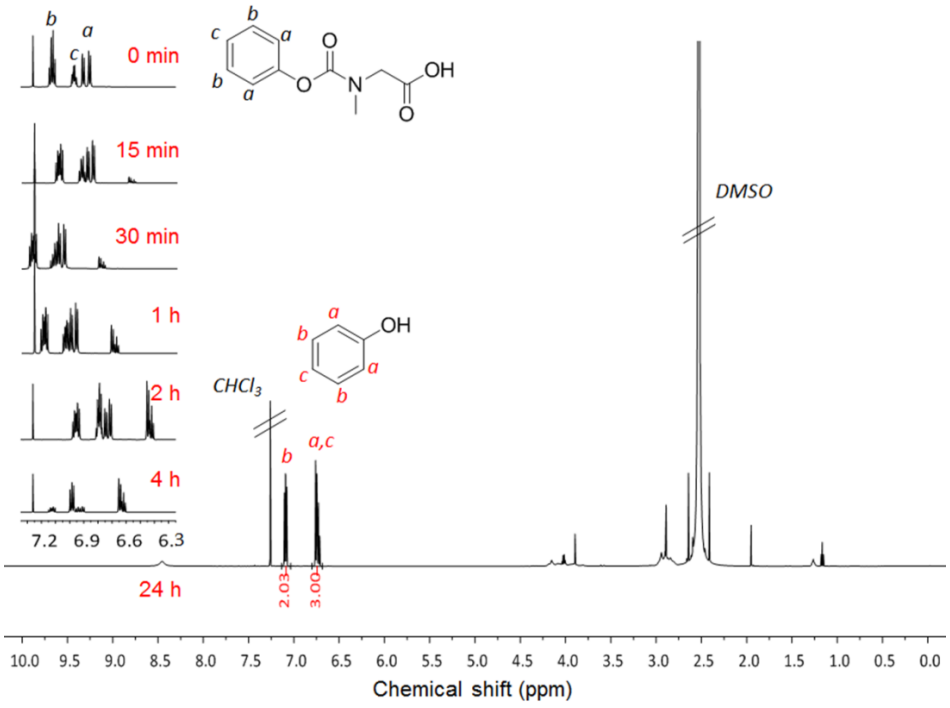


Figure 4.5: ^{1}H NMR spectra of the mixture of Poc-Sar with 0.5 equiv TEA in DMSO (in $CDCl_3$) for different reaction times (at 60 °C). Note: variations of peak positions are attributed to different compositions of DMSO/$CDCl_3$ solvent mixtures, because the crude reaction mixture was directly added to $CDCl_3$ for NMR analysis.

Adding a non-nucleophilic base to the reaction also enabled us to observe the NCA via infrared (IR) spectroscopy and confirm the mechanism. In Figure 4.6, the IR spectra of the reaction mixture with 0.5 equiv of TEA at room temperature (black line) and after 15 minutes at 60 °C (red line) are compared.

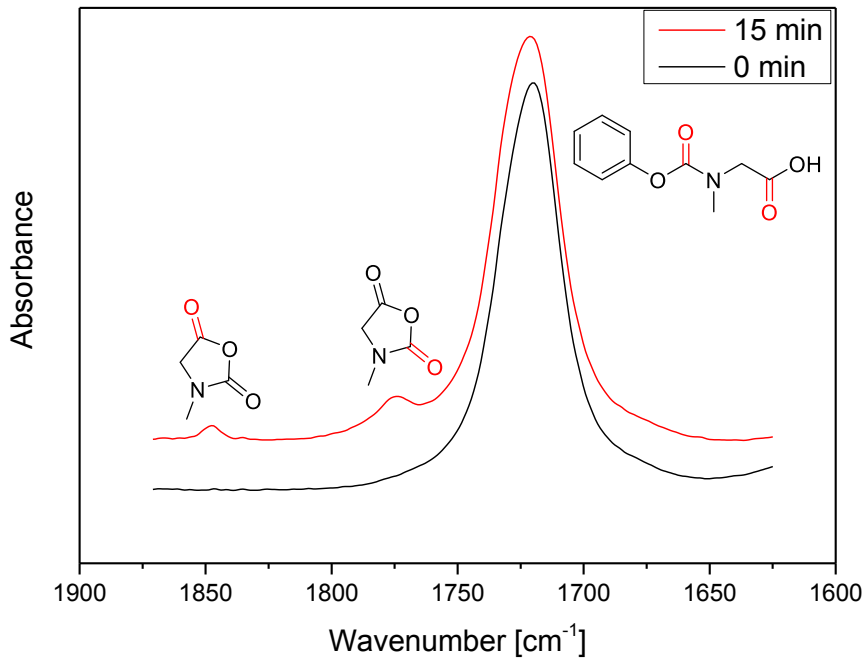
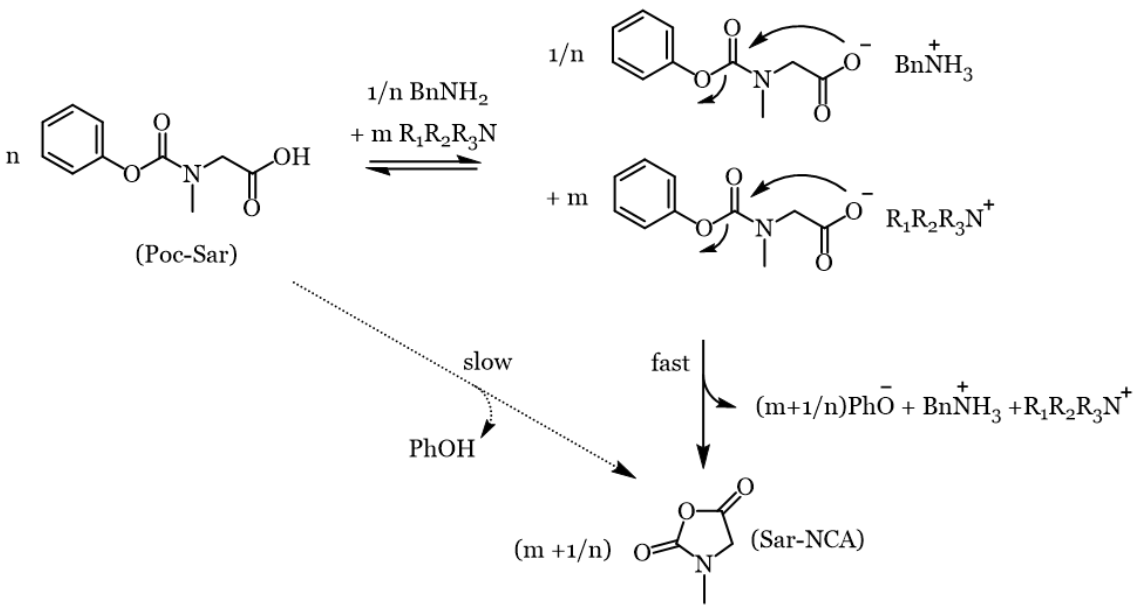


Figure 4.6: IR of the reaction mixture with 0.5 equiv TEA in DMSO at time 0 (black line) and after 15 minutes (red line). The distinct peaks of the NCA are present when heat is applied.

When no base is added to the reaction, there are no characteristic IR bands ($\bar{\nu}$ = ~1850 cm^{-1} and ~1780 cm^{-1} of the carbonyl bonds (C=O stretch)) indicating the presence of NCA. An explanation of this phenomenon is offered, if the rate of the NCA polymerization is higher than the rate of its synthesis under these conditions. Furthermore, the Poc-Sar to Sar-NCA reaction is relatively slow even at 60 °C (and slower at lower temperatures, as we will see in section 4.5), whereas the polymerization of Sar-NCA proceeds also at room temperature. This means that even when a sample is taken from the polymerization mixture to be analyzed by IR, the NCA polymerization can still take place.

The confirmation of the *in situ* NCA formation supports an equilibrium of the protonated and deprotonated form of Poc-Sar. Scheme 4.5 shows a tentative mechanism. The amount of the tertiary amine should determine the speed of the reaction.



Scheme 4.5: A tentative mechanism for the NCA formation when a tertiary amine is used.

Indeed, when a higher amount of the non-nucleophilic base is used, the reaction becomes significantly faster, as suggested by the kinetic studies on Figure 4.7:

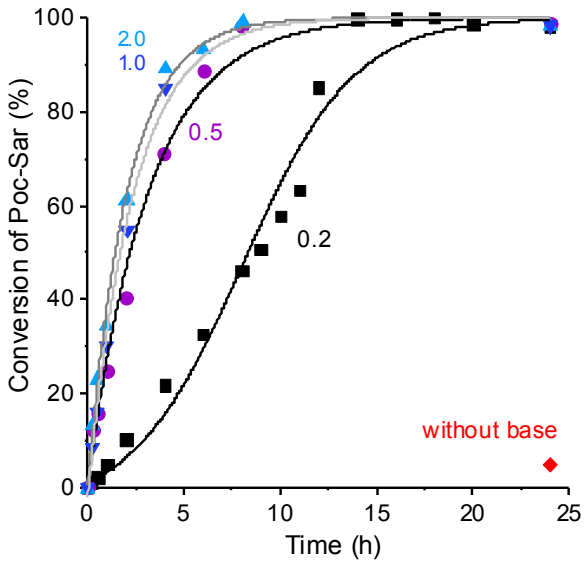


Figure 4.7: Conversion of Poc-Sar to Sar-NCA with 0.2 equiv, 0.5 equiv, 1 equiv and 2 equiv of DIPEA compared to Poc-Sar.

When a tertiary amine is used to accelerate the reaction in DMSO, the conversion of Poc-Sar to Sar-NCA is complete within 24 h, even when 0.2 equiv

of the base are used. When 0.5 equiv of the base are used, the reaction is still significantly faster than with 0.2 equiv. However, when more than 0.5 equiv are used (1 equiv and 2 equiv) the reaction does not accelerate significantly more. A reason for that, could be that the tertiary amine can be deprotonated again from the phenolate and act again to deprotonate Poc-Sar (TEA, conjugated acid in DMSO: pKa 9.0; DIPEA, pKa 8.5; PhOH, pKa 18.0 (DMSO)).[111] This makes the use of the base even more efficient, as it is not used up during the reaction. However, this is only the case, as long as it does not participate in the polymerization reaction. It is important, therefore, to investigate whether the use of a tertiary amine is affecting the structure of the product.

The effect of a non-nucleophilic base in the polymer structure

According to the NMR analysis, phenol is produced rapidly when a tertiary amine is added to the reaction mixture. ^{1}H-NMR analysis in D_2O of the product of polymerization with a tertiary amine, which was precipitated in acetone, shows that benzylamine is incorporated in the structure and end-group analysis shows a good control of the polymerization based on the monomer to initiator ratio (Figure 4.8).

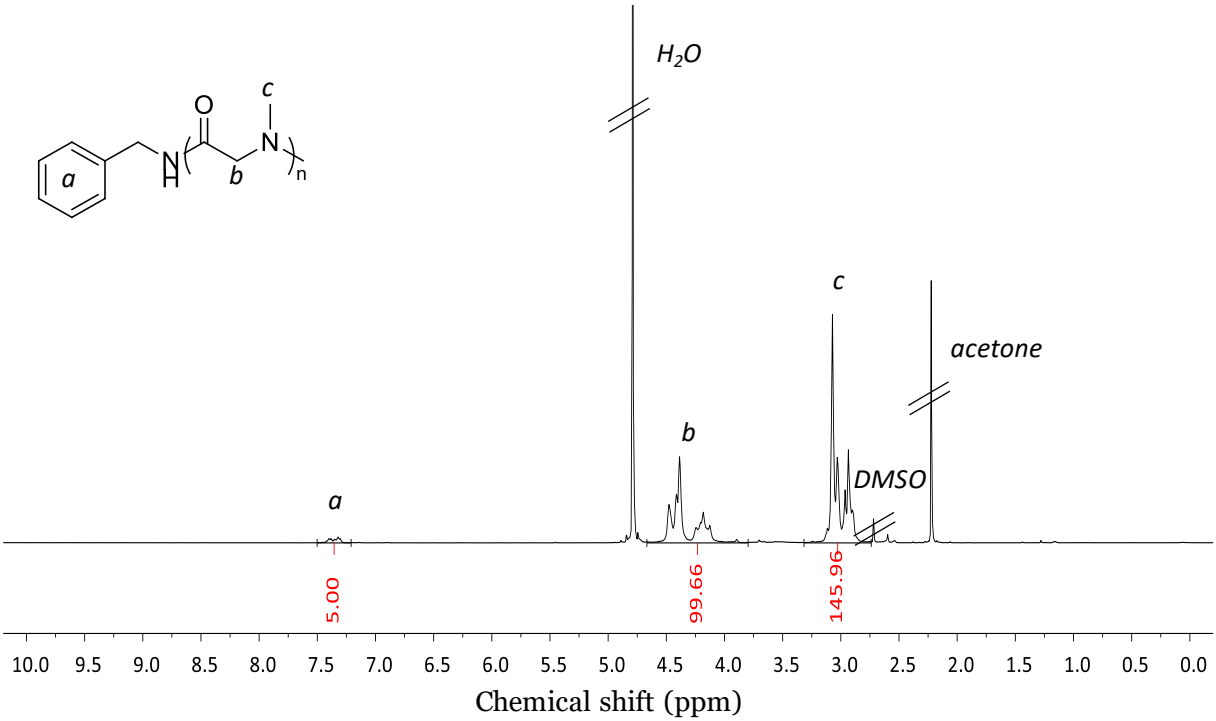


Figure 4.8: ^{1}H-NMR spectrum of the product of polymerization of Poc-Sar in DMSO in the presence of 0.2 equiv of DIPEA. The end-group analysis shows good control of the molar mass based on the monomer to initiator ratio. Signal of aromatic protons (δ 7.2-7.5 ppm, a, phenyl end group) was normalized to 5H and the molar mass calculated by M_n^{NMR} = (integral(CH_2, b)/2·71.1 + 107.2) g mol^{-1}.

Furthermore, analysis of the produced polymer with MALDI-ToF (Matrix-assisted laser desorption/ionization-Time of flight) mass spectrometry shows a monomodal and narrow distribution of polysarcosine (repeat unit mass = 71.1 Da) with α-BnNH and ω-H end groups (Figure 4.9).

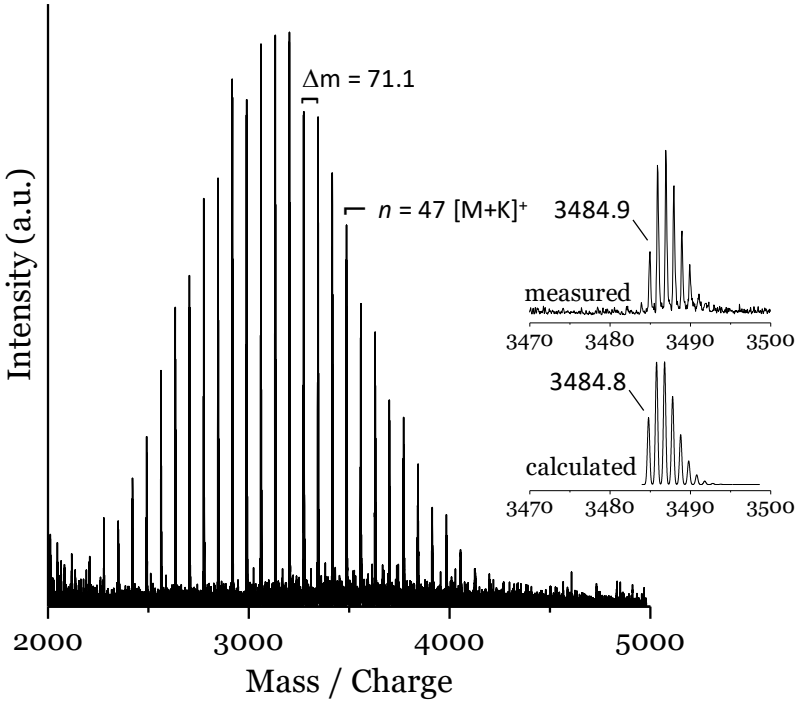


Figure 4.9: MALDI-ToF mass spectrum of the product of polymerization of Poc-Sar in DMSO in the presence of 0.2 equiv of DIPEA.

A collection of polymers was prepared in addition with higher amounts of amine (DIPEA) to check the amounts of base that could be added without affecting the efficiency of the polymerization. The monomer concentration is kept constant for all polymerizations at 0.77 M. The results are summarized on Table 4.3.

Table 4.3: Characteristics of polymers prepared using different amounts of DIPEA (monomer concentration 0.77 M, reaction time 1 day).

Experimental conditions ([M]/[I]/ [DIPEA])	Temper-ature	Theoretical molar mass	M_n (g/mol)[a]	M_n (g/mol)[b]	Đ[b]	Conversion[c]
1 / 0.02 / 0.3	60 °C	3630	3340	2040	1.18	~100%
1 / 0.02 / 3.5	60 °C	3550	3410	2220	1.12	~100%
1 / 0.02 / 7	60 °C	3700	3340	2100	1.13	~100%
1 / 0.02 / 11	60 °C	3480	3270	2210	1.15	~100%
1 / 0.02 / 14	60 °C	3480	2420	-		64%

[a] according to NMR end-group analysis

[b] according to GPC analysis in NMP with PS-standards

[c] conversion of Poc-Sar to Sar-NCA according to NMR analysis

As the results suggest, even a very high concentration of DIPEA (11 equiv) yields polymer. NMR end-group analysis shows a good control of the molar mass according to the amount of $BnNH_2$ used. GPC analysis shows a low dispersity. The only case in which there is a slower reaction and the reaction is not complete after the reaction time chosen (1 day) is when 14 equiv of base are used. However, since the concentration was kept constant, almost no DMSO was added (except for the initiator solution), indicating that despite DIPEA is accelerating the reaction it cannot substitute DMSO as a solvent.

4.5. Effect of the temperature

In addition to the effect of the amount of base, also the effect of temperature was investigated. Specifically, room temperature (r.t.), 40 °C, 60 °C, 80 °C, and 100 °C were used. The results are summarized in Table 4.4.

Table 4.4: Theoretical molar mass and characterization results for polymerizations in different ratios of DIPEA and DMSO. All reactions were run at a monomer concentration of 15 wt.% for a day.

Experimental conditions ([M]/[I]/ [DIPEA])	Temper-ature	Theoretical molar mass (g/mol)	M_n GPC (g/mol)/Đ[a]	M_n NMR (g/mol)[b]	Conversion[c]
1 / 0.02 / 3.5	r.t.	3200	-	-	7%
1 / 0.02 / 3.5	40 °C	3480	-	-	55%
1 / 0.02 / 3.5	60 °C	3550	2220 /1.12	3410	~100%
1 / 0.02 / 3.5	80 °C	3500	2380/1.15	3410	~100%
1 / 0.02 / 3.5	100 °C	3200	1950/1.14	2770	~100%

[a] GPC analysis in NMP with PS standards.

[b] ^{1}H-NMR end-group analysis in D_2O, δ=4.79

c According to ^{1}H-NMR

Temperature seems to play a very important role in the reaction of the Poc-Sar to Sar-NCA. In the case of polypeptides, the time required for the reaction was fairly short, but in the case of polypeptoids, a higher temperature and the use of a tertiary amine seem to be necessary for the polymerization. At 100 °C the molar mass observed seems to differ significantly from the expected one and at 80 °C the dispersity seems to be slightly higher than at 60 °C. High temperatures could potentially affect the sensitive NCA. For this reason, the next experiments were performed at 60 °C.

4.6. Effect of the monomer concentration

The monomer concentration used in our previous experiments was 0.77 M. However, NCA polymerization takes place normally at higher concentrations, which also result in faster reaction times due to the first-order kinetics of Sar-NCA polymerization.[38] To assess the effect of the monomer concentration, reactions were run at 60 °C with 0.2 equiv of DIPEA in DMSO. The results are presented in Table 4.5.

Table 4.5: Effect of the concentration on the Poc-Sar to Sar-NCA reaction, based on NMR analysis.

Experimental conditions ([M]/[I]/ [DIPEA])	Monomer Concentration	Conversion after 16 h
1 / 0.02 / 0.2	0.77 M	56%
1 / 0.02 / 0.2	1 M	35%
1 / 0.02 / 0.2	1.5 M	12%
1 / 0.02 / 0.2	2.6 M	7%
1 / 0.02 / 0.2	Bulk	4%

The higher the concentration of the monomer, the lower is the conversion to the NCA. Potentially, a further decrease of the concentration could be advantageous for the reaction of Poc-Sar. However, a very low concentration would affect the kinetics of the NCA polymerization as well.

A similar behavior was also noticed when Poc-amino acids were polymerized. The speculated reason for that was the formation of dimers of the Poc-amino acids via intermolecular hydrogen bonding.[55]

4.7. Polymerization of Poc-Sar to yield well-defined polysarcosine

The addition of a non-nucleophilic base made the polymerization of Poc-Sar feasible within less than 24 h. The polymers prepared showed initiation from $BnNH_2$. However, no polymers we studied exceeded a degree of polymerization (DP) of 50. It is important to investigate whether the method can also be used for the synthesis of polymers with longer chains. A hindering factor in the creation of larger polymers could be the low concentration (NCA polymerization is conducted in higher concentrations, like 3 M)[40], necessary for the initial transformation of the Poc-Sar to the NCA.

The dispersity of the polymers is also important to remain low, even when larger molar mass is targeted. Especially earlier literature on the polymerization of activated urethane derivatives reported high values of dispersity (Đ = 1.36-3.66)[59]. When solvents of higher polarity were used, the dispersities were significantly lower reaching values of Đ = 1.28-1.36.[57]

To study the efficiency of the method to produce longer polymers, we targeted a selection of molar mass based on monomer to initiator ratios 50:1, 70:1, 100:1, 200:1, 300:1, and 400:1.

NMR end-group analysis showed a good match to the expected molar masses. However, GPC analysis in NMP was hindered by potential interaction with the stationary phase, which resulted in significant tailing of the samples of higher molar mass. Additional GPC analysis was performed in water, to give eluograms with symmetrical peaks, suggesting that the tailing was indeed an artifact of the analysis method (Figure 4.11).

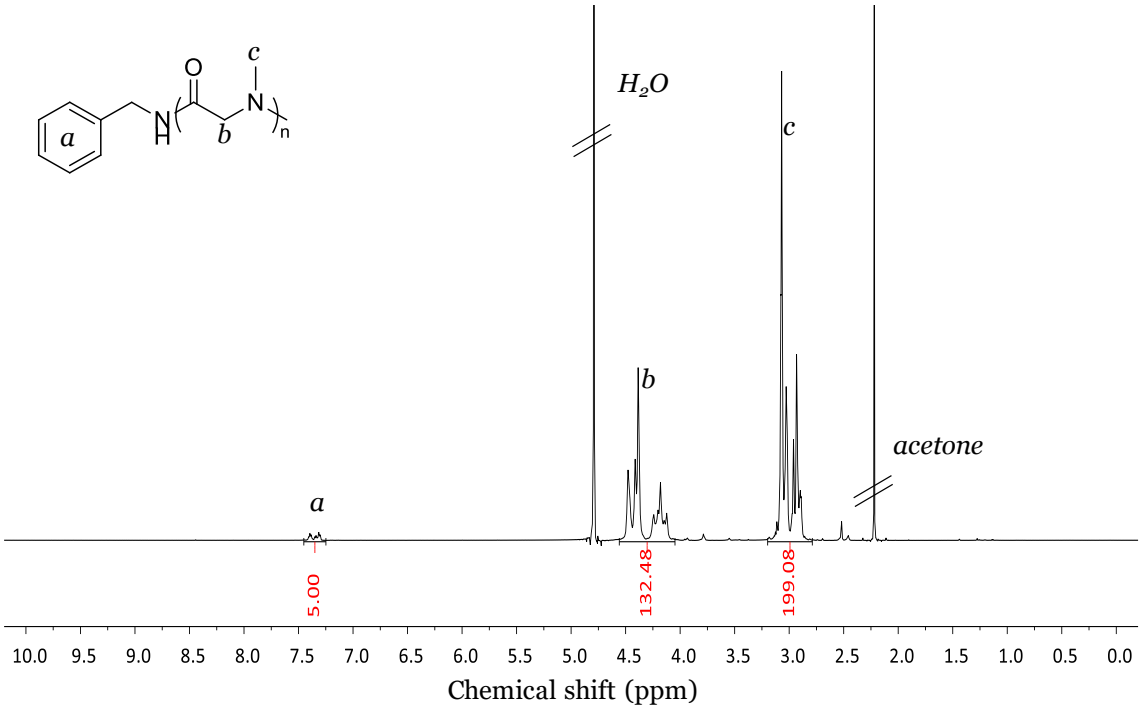


Figure 4.10: ^{1}H-NMR spectra (600 MHz, D_2O) of polysarcosine, Table 4.6 entry 2. Signal of aromatic protons (δ 7.2-7.5 ppm, a, phenyl end group) was normalized to 5H and the molar mass calculated by M_n^{NMR} = (integral(CH_2, b)/2·71.1 + 107.2) g mol^{-1}.

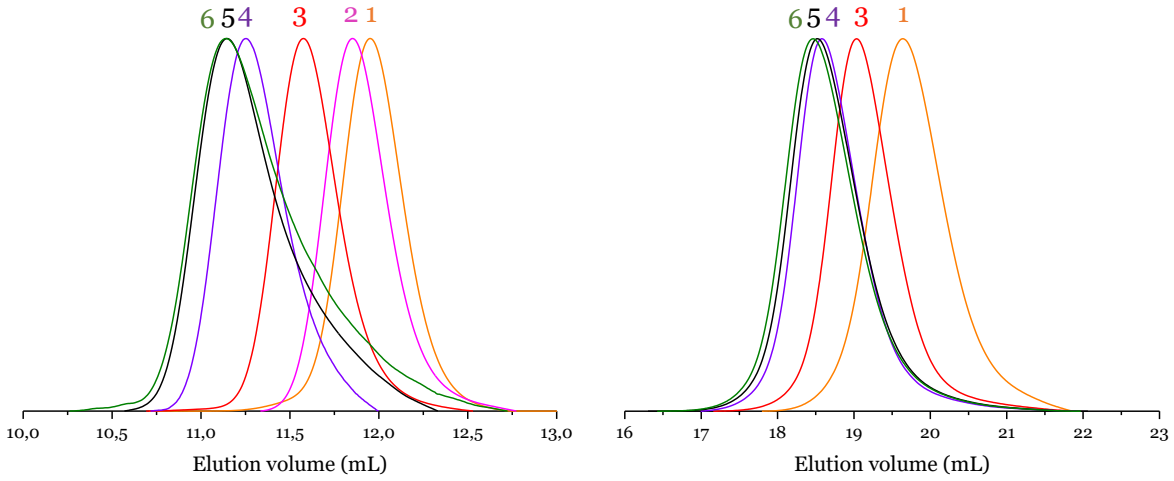


Figure 4.11: SEC RI traces of entries 1-6 (eluent: NMP) (left) and entries 1, 3-6 (eluent: 0.1 N aqueous $NaNO_3$) (right).

The polymers with a target DP of 50 to 100 could also be analyzed by MALDI-ToF mass spectrometry. The mass spectra are presented on Figure 4.12. They also indicate a good match to the theoretical molar mass. Longer polymers, however, could not be analyzed.

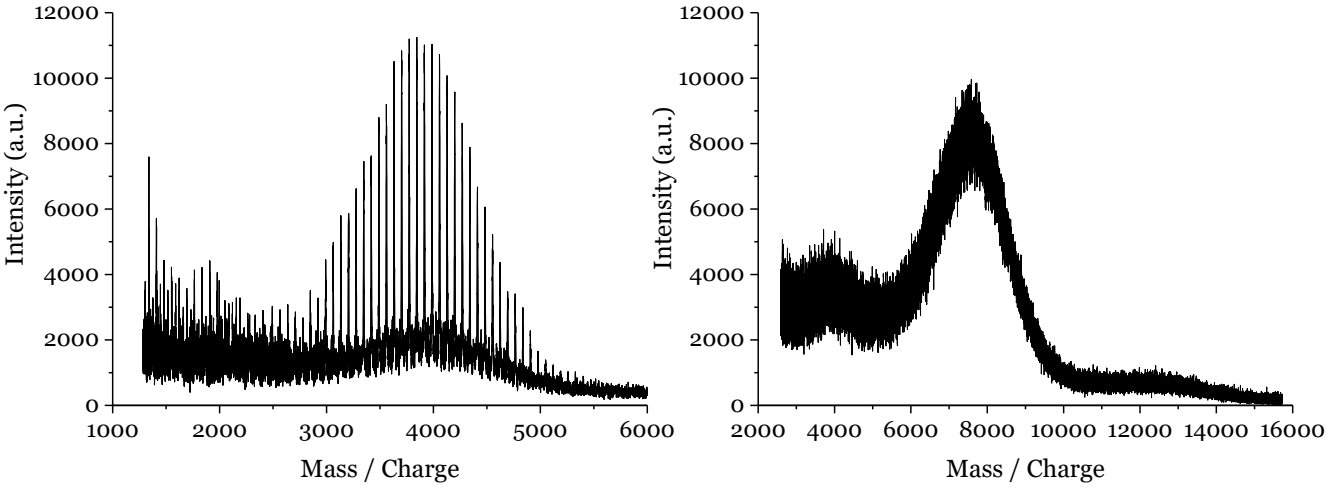


Figure 4.12: MALDI-TOF mass spectra of polysarcosine (Na^+/K^+ adducts), Table 4.6 entries 2 and 3. Note: Higher molar mass polysarcosines (entries 4-5) could not be analyzed.

The characteristics of the polymers are summarized in Table 4.6.

Table 4.6: Molecular characteristics of polysarcosines prepared by reaction of BnNH2 with Poc-Sar ([Poc-Sar]0 = 0.77 M) in 2 vol% tertiary amine base (TEA or DIPEA) in DMSO at 60 °C for 24 h.

entry	base	n [a]	M_n^{cal} (g mol^{-1})[b]	M_n (g mol^{-1})[c]	M_n (g mol^{-1})[d]	M_n (g mol^{-1})[e]	$Đ^{app}$ [e]
1	DIPEA	50	3660	3650	3200	4580	1.11
2	TEA	68	4940	4440	3900	5150	1.11
3	DIPEA	96	6930	7780	7600	8140	1.10
4	DIPEA	194	13900	16500	–	12970	1.08
5	DIPEA	307	21940	20000	–	(10920)	(1.2)[f]
6	DIPEA	400	28550	26500	–	(9540)	(1.33)

The results suggest a very good match of the M_n based on the end-group analysis of the NMR spectra with the calculated M_n, even for longer polymers. The dispersity of the polymers remains low for the polymers with a degree of polymerization up to 200, but longer polymers are challenging to characterize.

4.8. Conclusion

The activated urethane method was successfully applied to prepare polysarcosine. Although polymerizing the monomer with a primary amine initiator ($BnNH_2$) resulted in a very slow reaction, it was possible to accelerate the reaction by using a non-nucleophilic base. The base deprotonated the carboxylic acid group of the urethane sarcosine (Poc-Sar) to form a carboxylate, which reacts much faster to form the NCA. There was no influence of the tertiary amine on the polymer structure, which was confirmed by NMR and MALDI-ToF analysis. The conversion of Poc-Sar to Sar-NCA could be monitored by NMR spectroscopy by the release of phenol. Different polymerization conditions, regarding the amount of non-nucleophilic base, temperature, and monomer concentration were investigated for their influence on the reaction. Polysarcosines of various molar masses were prepared, the molar mass being in agreement with the initial monomer to initiator ratio. However, limited solubility of the longer chains made the characterization challenging.

The activated urethane derivatives seems to be a promising method for the preparation of polypeptoids, because the addition of a non-nucleophilic base can significantly alter the kinetics of the activated urethane glycine to monomer reaction. The same strategy cannot be applied in the case of polypeptides, due to the activated monomer mechanism initiated by tertiary amines. The next chapter, deals with the preparation and polymerization of other *N*-substituted NCA monomers, and how the substituent of the *N*-substituted glycine affects the reaction.

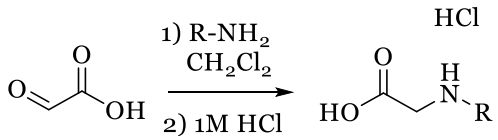
5. Application to other Polypeptoids

In this chapter, different monomers based on *N*-substituted glycines are synthesized and characterized. A variety of substituents is chosen thanks to the facile synthesis of *N*-substituted glycines. However, the synthesis of the activated urethane derivatives is more challenging than for Poc-Sar. Phenyl chloroformate is utilized to increase the yield, but the NCA synthesis remains overall "greener" than the usual procedure.

The kinetics of the conversion of the urethane derivative to NCA is studied for a selection of compounds. Finally, all of the compounds are polymerized in DMSO under the same conditions as Poc-Sar, and the products are characterized.

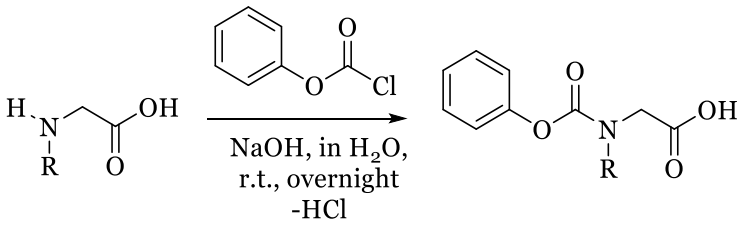
5.1. Synthesis of Poc-*N*-alkyl-glycines

To synthesize the activated urethane compounds, we started by preparing the *N*-substituted glycine, using glyoxylic acid and the respective amine, according to the literature (Scheme 5.1).[39]



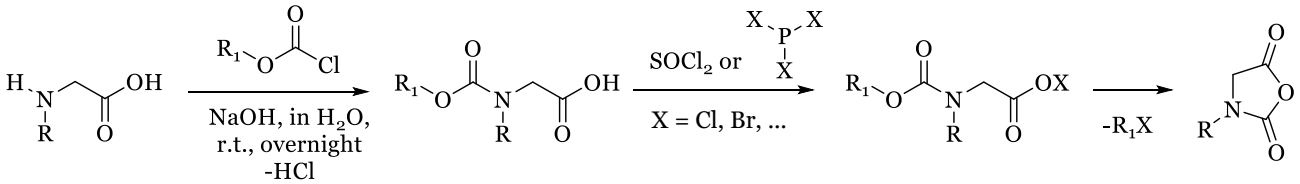
Scheme 5.1: N-glycine synthesis with glyoxylic acid and the respective amine.

In chapter 4, Poc-Sar is synthesized using either tetrabutylammonium hydroxide and diphenyl carbonate or direct addition of diphenyl carbonate in the presence of a base and lithium chloride. However, the synthesis of *N*-phenoxycarbonyl-*N*-substituted glycines with more complex substituents than the methyl group with the aforementioned methods proved to be challenging. The yields were as low as < 1% for some of the monomers. Therefore, direct reaction of the *N*-glycine with phenyl chloroformate was used to circumvent the problem of low yields (Scheme 5.2).



Scheme 5.2: Monomer synthesis using chloroformate.

Despite the fact that the use of chloroformate makes the method less "green", the full synthesis of the NCA remains advantageous compared to the traditional *N*-substituted NCA synthesis, as it avoids the additional use of thionyl chloride or phosphorus trichloride (Scheme 5.3).[22]



Scheme 5.3: Common synthesis of N-substituted glycine NCAs.

The compounds prepared included a variety of substituents, like alkyl chains (ethyl, *n*-propyl, *n*-butyl, isopropyl, isobutyl), aromatic groups (phenethyl and 1,3-benzodioxol-5-ylmethyl) and the allyl group, which can subsequently be used for further functionalization.[112] Most of the polypeptoids bearing the aforementioned substituents have already been explored either as homopolymers[17] or only as blocks of copolymers (phenethyl).[113] However, 1,3-benzodioxol-5-ylmethyl as a substituent on a polypeptoid has not been studied. It would be an interesting moiety, since deprotection of the pendant group could give a polypeptoid alternative to L-DOPA (L-3,4-dihydroxyphenylalanine). L-DOPA is an amino acid, it is a precursor to dopamine and plays also an important role in adhesive proteins found in mussles.[114] Except for their use in adhesives, catechol moieties have also been used for drug-carrying polymers, for example for the controlled release of bortezomib (BTZ), because of its pH sensitive nature.[115] Copolypeptoids containing the catechol moiety could potentially also be used for such pharmaceutical applications, thanks to their inherent biocompatibility and degradability.

The ^{1}H and ^{13}C NMR spectra of the *N*-Poc-*N*-1,3-benzodioxol-5-ylmethyl-glycine are shown in Figure 5.1 and Figure 5.2 respectively.

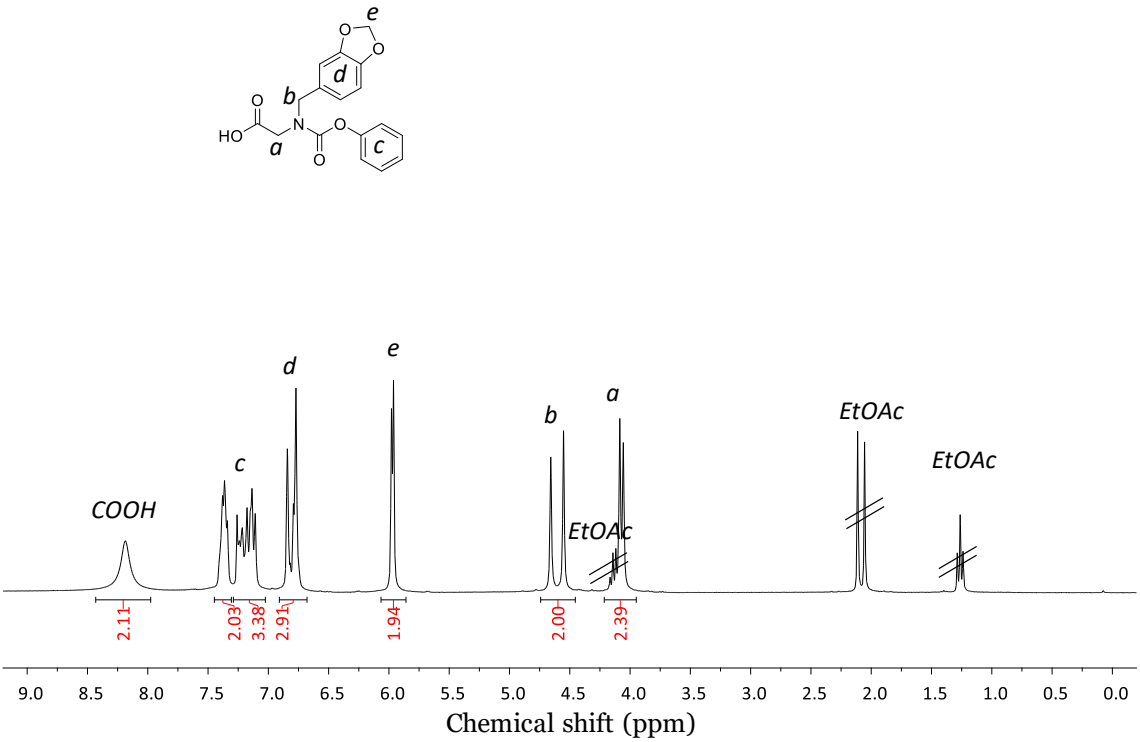


Figure 5.1: ^{1}H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-N-1,3-benzodioxol-5-ylmethyl glycine.

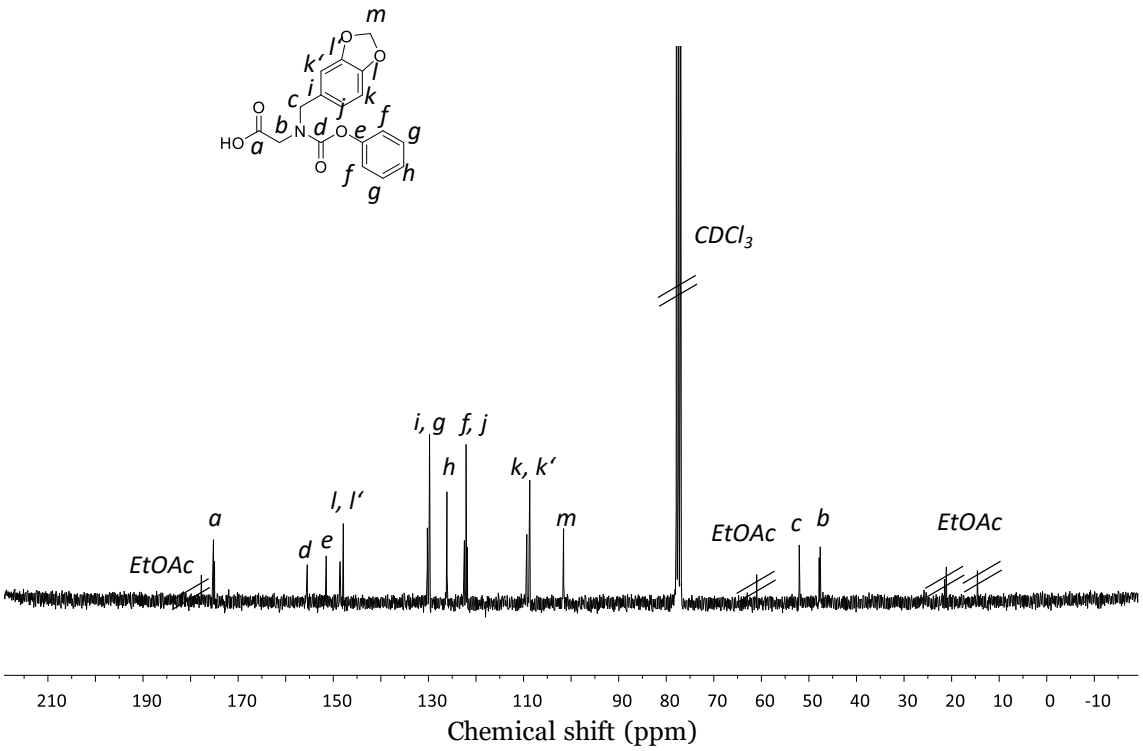
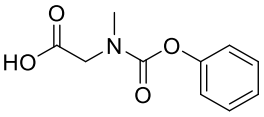
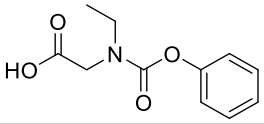
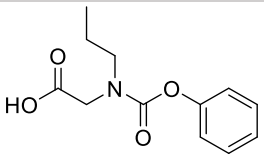
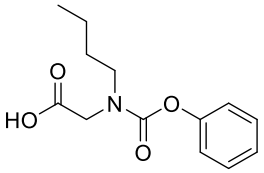
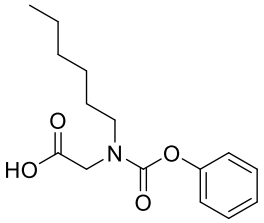
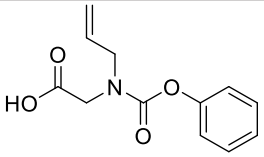
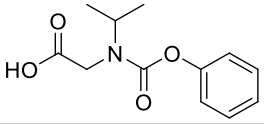
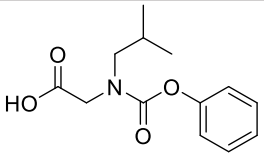
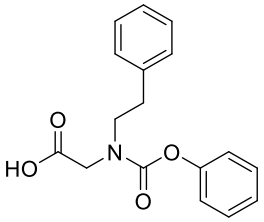
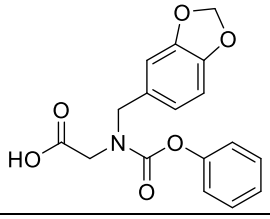


Figure 5.2: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-N-1,3-benzodioxol-5-ylmethyl glycine.

The compounds prepared and their yields according to the method used are summarized in Table 5.1.

Table 5.1: The monomers prepared with a) tetrabutylammonium hydroxide and diphenyl carbonate, b) diphenyl carbonate, base and lithium salt, and c) phenyl chloroformate.

Entry	Substituent	Compound	Method	Yield
1	Methyl		a b c	49% 52% 80%
2	Ethyl		c	64%
3	*n*-Propyl		c	90%
4	*n*-Butyl		c	71%
5	*n*-Hexyl		c	80%
6	Allyl		b	23%
7	Isopropyl		b	traces
8	Isobutyl		a	23%
9	Phenethyl		b c	15% 80%
10	1,3-benzodioxol-5-ylmethyl		b c	15% 41%

From the yield of the compounds synthesized by all methods, the advantage of the use of phenyl chloroformate is evident, reaching yields between 41 and 90%. Whereas the yield of Poc-Sar was around 50% when TBAOH is used, the same synthesis for *N*-Poc-*N*-isopropyl glycine leads to only 23% yield. Direct addition of diphenyl carbonate in the presence of a base and a lithium salt, also results in a maximum yield of 23% in the case of *N*-allyl glycine and to a yield as low as simply traces in the case of *N*-isopropyl glycine.

Overall, a variety of *N*-Poc-glycines were prepared in significant amounts, all of the compounds in Table 5.1 except for the *N*-Poc-*N*-isopropyl glycine, and characterized. The spectra of the compounds can be found in the Appendix.

5.2. Kinetic studies for a selection of monomers

In Chapter 4, it was shown that a hindering factor regarding the use of Poc-Sar for the synthesis of polysarcosine is the slow kinetics of the Poc-Sar conversion. However, a non-nucleophilic base could be used to significantly accelerate this conversion. Specifically, in Section 4.4, the kinetics of the conversion of Poc-Sar to Sar-NCA was studied. It was established that when a tertiary amine is added to the reaction, even for the smallest amount used (0.2 equiv compared to Poc-Sar), all Poc-Sar is consumed within 14 hours.

To expand the method to other compounds, it is important to study the conversion times of the *N*-Poc-glycines. The conversion of a selection of monomers was studied over time, as well as the conversion after 24 hours of all of the monomers synthesized in Section 5.1, using NMR analysis.

For the kinetic study, the compounds used were *N*-Poc-*N*-ethyl glycine, *N*-Poc-*N*-(*n*-propyl) glycine, *N*-Poc-*N*-(*n*-butyl) glycine, and *N*-Poc-*N*-phenethyl glycine. All of them were reacted at a concentration of 0.77 M, in DMSO, in the presence of 0.2 equiv of DIPEA. The results of the kinetic studies are summarized in Figure 5.3.

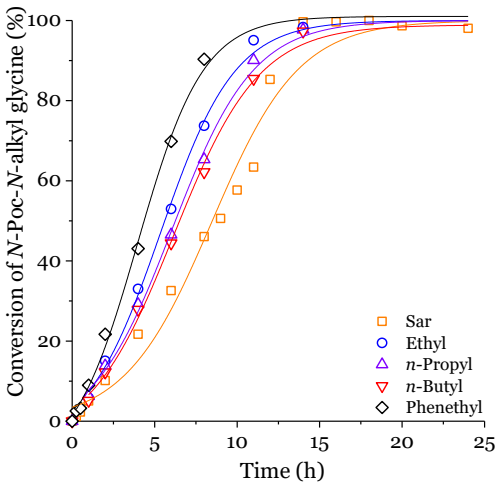


Figure 5.3: Conversion of Poc-monomers in relation to time in h.

Surprisingly, all of the compounds show a faster conversion compared to Poc-Sar. Between the ethyl-, *n*-propyl-, and *n*-butyl-substituted compounds, it seems that the longer the alkyl chain is, the slower is the conversion. Unexpectedly, the *N*-Poc-*N*-phenethyl-glycine is even faster. However, very fast

kinetics was also observed in the polymerization of the *N*-phenethyl-NCA compared to other *N*-NCAs in benzonitrile.[116] The high polymerization rate was attributed to the viscosity of the reaction mixture being low up to a higher DP compared to the products of other *N*-NCAs and to the probable proximity of the monomer molecules to the growing chains due to π-π interactions. However, such an effect was not observed in the case of the benzyl-*N*-NCA. This explanation would also not explain the fast conversion of the *N*-Poc-*N*-phenethyl-glycine. A potential reason is the reduced steric hindrance of the phenethyl group. Despite the bulkiness of the aromatic ring, the allowed conformations of the group keep the steric hindrance around the nitrogen low.[117]

Additionally to the kinetic studies, the conversion of all the Poc-*N*-glycines either after complete conversion or after 24 hours are summarized in Table 5.2:

Table 5.2: Conversion of Poc-N-glycines according to ^{1}H-NMR analysis after complete conversion or 24 hours. (Note: for the Poc-N-phenethy-glycine, the analysis was not possible after 8 hours, because of solubility problems of the reaction solution.)

Entry	Substituent	Time (hours)	Conversion
1	Methyl	24	99%
2	Ethyl	14	98%
3	*n*-Propyl	14	98%
4	*n*-Butyl	14	97%
5	*n*-Hexyl	24	90%
6	Allyl	24	99%
7	Isobutyl	24	76%
8	Phenethyl	8	90%
9	1,3-Benzodioxol-5-ylmethyl	24	< 3%

The Poc-*N*-glycines with ethyl-, *n*-propyl-, *n*-butyl- and allyl- groups as substituents, show complete conversion within less than 24 hours. The phenethyl-substituted compound could not be analyzed after 24 hours due to reduced solubility of the reaction mixture. Reduced solubility of the formed polymeric chains could also be the reason why the Poc-*N*-glycines with *N*-hexyl-

and isobutyl- moieties did not reach complete conversion within 24 hours. As it is analyzed in the next section, most of the formed polymeric chains do not dissolve well in DMSO. The precipitation of the polymer, which alters the ideal conditions for the conversion of the Poc-*N*-glycine, could hinder their reaction.

5.3. Polymerization results

The Poc-*N*-glycines prepared were also polymerized at a concentration of 0.77 M, at 60 °C, with 0.2 equiv of DIPEA and a 50:1 monomer to initiator ratio, with $BnNH_2$ as an initiator. The amount of Poc-group compared to released phenol was analyzed by ^{1}H-NMR analysis after 24 hours (as summarized in the Table 5.2) for all compounds and the products were isolated after 2 days. The results are shown in Table 5.3:

Table 5.3: Polymerization results of Poc-N-glycines after 2 days (0.77 M, 60 °C, 0.2 equiv DIPEA, $BnNH_2$ as initiator).

Substituent	n [a]	M_n^{cal} (g mol^{-1})[a]	M_n (g mol^{-1})[b]	M_n (g mol^{-1})	$Đ^{app}$
Ethyl	50	4360	2750	2400 [d]	1.2 [d]
n-Propyl	50	5060	3970	4000 [d]	1.1 [d]
n-Butyl	50	5770	4750	4000 [d]	1.1 [d]
n-Hexyl	50	7170	4770	4800 [e]	1.2 [e]
Allyl	50	4960	3120	2400 [e]	1.4 [e]
Isobutyl	50	5770	-*	-*	-*
Phenethyl	50	8170	-*	-*	-*

[a] Theoretical values, according to monomer to initiator ratio
[b] According to ^{1}H-NMR end-group analysis
[c] According to ^{1}H-NMR analysis
[d] According to GPC in THF with PS standards
[e] According to GPC in NMP with PS standards
[*] Non-soluble product

All of the polymerization reactions, except for these with ethyl- and allyl-substituents formed precipitate within 24 hours. This is a result of the low solubility of most polypeptoids in DMSO. Polypeptoids of a DP of around 25 are reportedly not dissolving in DMSO in the case of propyl-, *n*-butyl-, isobutyl- and phenethyl- moieties.[116] Surprisingly though, according to end-group analysis of the NMR spectra, the DP of the polymers of propyl-, *n*-butyl-, and *n*-hexyl-*N*-glycines is 39, 41 and 33 respectively, very close to the DP of the soluble poly(*N*-ethyl glycine), which was 31, and of the soluble poly(*N*-allyl glycine), which was also 31. All of the obtained products, except for the poly(*N*-allyl glycine), have a low dispersity below or equal to 1.2.

The products of the isobutyl- and phenethyl- substituted compounds could not be analyzed due to reduced solubility in all the solvents tried.

The polymerizations were stopped after two days, mostly, due to precipitation. However, the polymers had higher DP than expected in DMSO. Therefore, it would be interesting to have more studies of these polymerizations in different reaction times, to see whether they can reach higher molar masses despite the precipitation observed.

5.4. Conclusion

In this Chapter, an array of additional Poc-*N*-glycines with different substituents were prepared and then polymerized in the conditions optimized for polysarcosine synthesis. Initially, the *N*-substituted glycine hydrochlorides were synthesized according to the literature. To synthesize the Poc-compounds, the methods used for sarcosine gave just low yields. Therefore, phenyl chloroformate was used as a third, alternative method to access the new compounds, reaching yields double as high.

The kinetics of the conversion of a selection of Poc-*N*-glycines was studied to show that the reaction is also very fast with other substituents than methyl, when a tertiary amine is used to accelerate the reaction. However, not all of the compounds reached complete conversion after 24 hours. A potential reason for that is the precipitation of the forming polymer chains, which disturbs the optimized for the reaction system.

Most of the reactions showed precipitation within less than 24 hours. The reason for that is the reduced solubility of the forming polymers in DMSO. However, within only 2 days, DP of more than 30 was reached according to ^{1}H-NMR end-group analysis, which is very close to the targeted 50 (according to monomer/initiator ratio), even for the precipitating polymers.

5.5. Outlook

In this Chapter, the investigation of the new compounds was restricted to the conditions optimized for sarcosine. However, it is obvious from these preliminary results that the system becomes much more complicated for the synthesis of polypeptoids other than polysarcosine. An inherent difficulty is that the optimal conditions for the *in situ* synthesis of the NCA include a low concentration and the use of DMSO as solvent, as seen in Chapter 4. In the case of most polypeptoids this translates to precipitation of the forming polymeric chains due to their low solubility. Additionally, NCA polymerization is faster the higher is the concentration of the NCA.[116]

Despite the aforementioned difficulties, in practice, the polymers produced reached a relatively high molar mass. It would be interesting to investigate further the polymerization kinetics under the conditions chosen. It could be that the observed precipitation does not entirely hinder the polymerization. Furthermore, it would be interesting to study the effect of the temperature of the reaction on the reaction times in these low monomer concentrations.

To fully evaluate the method for the preparation of polypeptoids, additional studies including different polymerization times, eventually different solvents and even a combination of solvents would be necessary.

6. Dihydroxyacetone-based polyester

In this chapter, dihydroxyacetone, a sustainable compound, is investigated as a monomer for incorporation in polyesters, taking advantage of its two alcohol groups and using them in a polycondensation reaction. Two different approaches are in focus. Specifically, equilibrium and non-equilibrium polycondensation reactions are used. In the case of the equilibrium polycondensation, adipic acid, itaconic acid, and their derivatives are reacted with dihydroxyacetone under different conditions. In addition to that, a non-equilibrium polycondensation is used to obtain a polyester from dihydroxyacetone and terephthaloyl chloride.

Both equilibrium and non-equilibrium polycondensations present challenges, potentially due to the ketocarbonyl present on the backbone of the products that reduces their solubility. Finally, ethylene glycol is used in combination with dihydroxyacetone to yield soluble copolyesters, after reaction with terephthaloyl chloride.

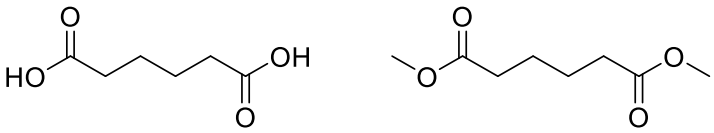
6.1. Monomers

A short overview of the monomers used to prepare a polyester based on dihydroxyacetone is presented here:

Adipic acid and dimethyl adipate

Adipic acid is a dicarboxylic acid, which is very important for the chemical industry. It is produced in huge amounts every year mainly for the production of nylon-6,6.[118] It is commonly produced using derivatives of benzene and a common by-product of its synthesis is nitrous oxide, a greenhouse gas. Because of its broad use, alternative, "greener" pathways have also been reported for its synthesis.[118,119] Additionally to its use for nylon production, it is a convenient co-monomer for the preparation of a variety of polyesters, and it has also been used in combination with glycerol for the synthesis of polyesters to add value in the biodiesel industry.[120]

In addition to the adipic acid, its diester, dimethyl adipate, was used as a co-monomer (Figure 6.1).



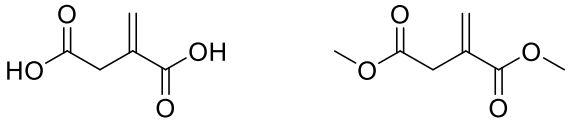
Adipic acid Dimethyl adipate

Figure 6.1: The structures of adipic acid and dimethyl adipate.

Itaconic acid and dimethyl itaconate

Itaconic acid is a bio-derived dicarboxylic acid. It is produced by the fungus *Aspergillus terreus*, although alternative organisms are also considered for its more efficient synthesis.[121] Itaconic acid has already been reported as a monomer either for polycondensation reactions or ROP.[122] Due to its unsaturation, it allows for post-polymerization reactions, as for example cross-linking of the prepared polymer.[123]

Due to their sustainability itaconic acid and dimethyl itaconate were also used in this work (Figure 6.2).

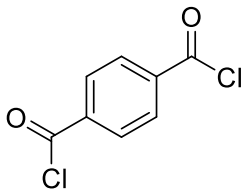


Itaconic acid Dimethyl itaconate

Figure 6.2: Itaconic acid and dimethyl itaconate.

Terephthaloyl chloride

A derivative of terephthalic acid, terephthaloyl chloride was the co-monomer used for the non-equilibrium polycondensation. Terephthalic acid is another very fundamental monomer for the plastics industry. Its main application is in the synthesis of poly (ethylene terephthalate) (PET). In addition to PET, terephthalic acid has also been used for the synthesis of different copolymers.[124] Interestingly, it can also be recovered from PET, for example via alkaline hydrolysis, and be used again as a monomer for PET or in alternative ways.[125] Here, the acyl chloride is used for a non-equilibrium polycondensation (Figure 6.3).



Terephthaloyl chloride

Figure 6.3: Terephthaloyl chloride.

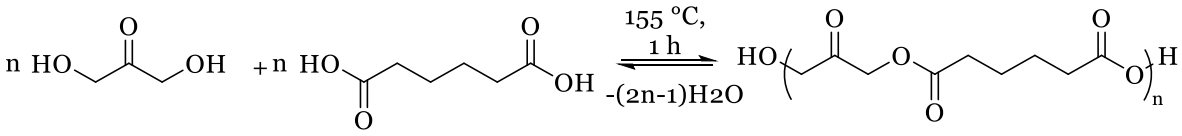
6.2. Polymerization methods

Equilibrium reactions with adipic acid, itaconic acid and their esters

Bulk polymerization without a catalyst

Bulk polymerization at elevated temperature is the simplest way to prepare polyesters. Carothers reported on bulk polymerization of succinic acid and ethylene glycol at elevated temperatures already in 1931.[126] It is a method applied more in the case of aromatic monomers, because they form good leaving groups.[62]

For this project, 1 equivalent of dihydroxyacetone and 1 equivalent of adipic acid were heated to 155 °C for 1 hour (Scheme 6.1).



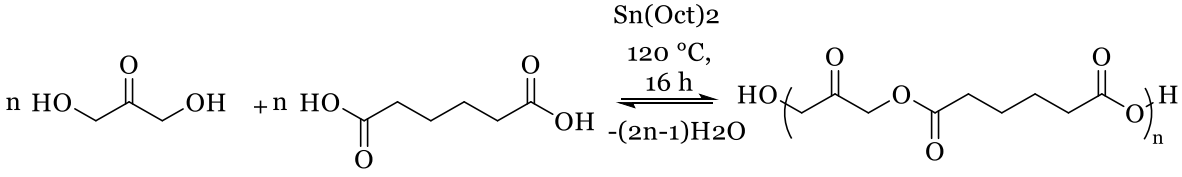
Scheme 6.1: Bulk polymerization of dihydroxyacetone with adipic acid without a catalyst.

Soon after elevating the temperature, the reaction mixture turned black and no polymer could be found by GPC. Therefore, alternative strategies that avoid the use of so high temperatures were explored.

Bulk polymerization with Sn(oct)2

To avoid the high temperatures used for bulk polycondensation, a bulk polymerization with a catalyst was chosen. Although there are numerous reports on polyesterification catalysis, and a broad variety of catalysts for the reaction, the nature of the mechanism of the different catalysts is not well defined.[62] For this project, tin (II) bis(2-ethylhexanoate) ($Sn(Oct)_2$) was used as a catalyst for the reaction. $Sn(Oct)_2$ is a low cost, low toxicity catalyst of high efficiency.[127]

Dihydroxyacetone was mixed with adipic acid at 1:1 molar ratio and 0.001 equivalent of $Sn(Oct)_2$ and the mixture was heated up to 120 °C for 16 hours (Scheme 6.2).



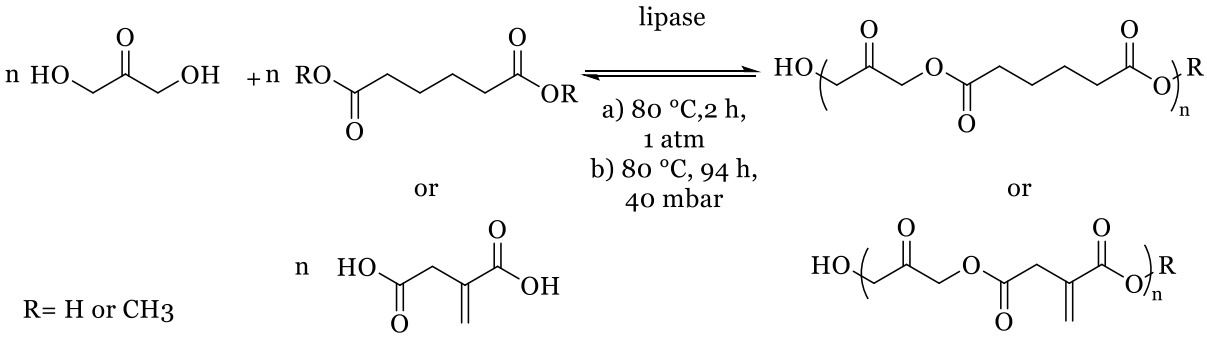
Scheme 6.2: Bulk polymerization of dihydroxyacetone and adipic acid with $Sn(Oct)_2$ as a catalyst.

Despite the fact that the temperature chosen was lower than at the bulk polymerization without a catalyst, the reaction mixture turned black also in this case and no compounds of adequately high molar mass were detected by GPC, stretching the need for a polymerization method that does not necessitate high temperatures. The dark color of the reaction mixture could be attributed to impurities in the dihydroxyacetone (purity 97%) that decomposed, as dihydroxyacetone is expected to decompose in higher temperatures.[128]

Bulk polymerization with lipase catalyst

To decrease further the polycondensation temperature, lipase from candida Antarctica stabilized on polymeric beads was used. Enzymatically catalyzed polycondensation is usually taking place at temperatures between 20 and 80 °C. The advantage of immobilized lipase is the easy removal after dissolution of the product.

Dihydroxyacetone was mixed at equimolar ratio with adipic acid, dimethyl adipate or itaconic acid and lipase corresponding to the 10 wt% of the total monomer weight. The mixture was heated up to 80 °C and after 2 hours vacuum was applied gradually to reach over the course of 1.5 hours a pressure of 40 mbars (Scheme 6.3).



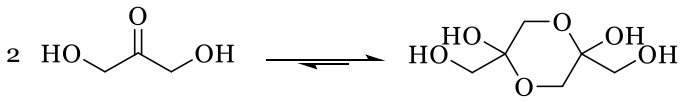
Scheme 6.3: Lipase catalyzed melt polycondensation of dihydroxyacetone and adipic acid, dimethyl adipate or itaconic acid.

At this temperature, there was no darkening of the polymerization mixture. However, the reactants were not mixing well, because dihydroxyacetone, adipic acid and itaconic acid have melting temperatures higher than 80 °C.[129] Hence, a solvent is necessary for the successful polycondensation of the monomers.

Enzymatic polycondensation in diphenyl ether

For an enzymatic polycondensation, the solvent chosen should, among others, retain the activity of the enzyme and have a sufficiently high boiling point, so that it is not removed during the polymerization. For our studies, diphenyl ether was chosen as a solvent. Diphenyl ether has been proven to give the highest molar mass products compared to other solvents, such as dodecane, hexyl ether, and isoamyl ether, when used for polycondensation reactions. Additionally, the enzyme activity seems to be retained better in diphenyl ether compared to the bulk polycondensation.[82]

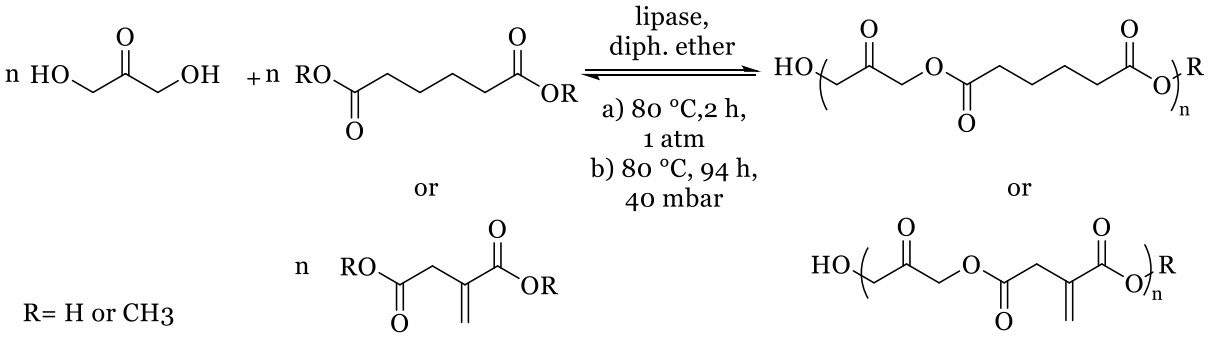
Besides using a solvent, the dihydroxyacetone was freeze-dried from its aqueous solution for this series of experiments. Dihydroxyacetone is a commercial monomer that can be purchased mainly in its dimer form. There is an equilibrium between the dimer and the monomer form of dihydroxyacetone, as indicated in Scheme 6.4.



Scheme 6.4: Equilibrium between dihydroxyacetone and its dimeric acetal.

In the case the polycondensation was hindered by the isomerization or the dihydroxyacetone being mainly in the form of its dimer, dihydroxyacetone was dissolved in water and freeze-dried before the reaction to ensure that it was in the monomer form.[130]

Freeze-dried dihydroxyacetone was mixed with 1 equivalent of adipic acid, dimethyl adipate, itaconic acid, or dimethyl itaconate and 10 wt% (according to the total monomer mass) lipase. The mixtures were dissolved in 150 wt% (corresponding to the total monomer weight) diphenyl ether and heated up to 80 °C. After 2 hours, vacuum was applied gradually to reach over the course of 1.5 hours a pressure of 40 mbars (Scheme 6.5).



Scheme 6.5: Lipase catalyzed polycondensation of dihydroxyacetone and adipic acid, dimethyl adipate, itaconic acid or dimethyl itaconate in diphenyl ether.

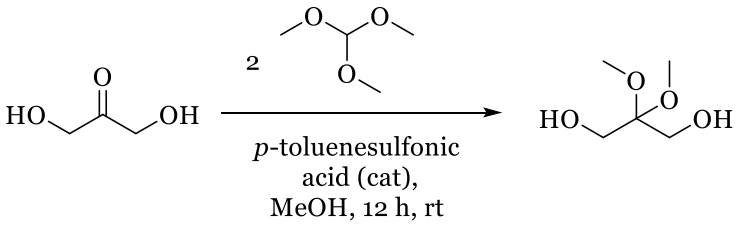
Despite the fact that condensate was formed during all of the reactions performed, the products were insoluble in all the solvents tried. Furthermore, due to their insolubility, it was not possible to remove the catalyst beads and isolate the products.

The insolubility of the products in common solvents, but also trifluoroacetic acid (TFA) or hexafluoroisopropanol (HFIP), could be a result of the carbonyl groups of the polymers forming strong hydrogen bonds. Although aliphatic polyesters are normally soluble in a variety of organic solvents, this is not the case for the products of these reactions. The reason for that might be the carbonyl group on the main structure. Polyketones, which also feature carbonyl groups on their chain structure, are polymers that are insoluble in most solvents,[131] although recently there have been even reports for soluble polyketones via incorporation of a cyclohexanone moiety on the π-conjugated main chain.[132]

Non-equilibrium polycondensation with terephthaloyl chloride

For the non-equilibrium polycondensation to access an analogue of PET, dihydroxyacetone was reacted with terephthaloyl chloride in THF in the presence of dry pyridine for 16 hours. The reaction did not yield polymer, therefore, 2,2-dimethoxy-propane-1,3-diol was synthesized from the dihydroxyacetone to be used for a reaction with terephthaloyl chloride.

The dimethyl acetal of dihydroxyacetone (2,2-dimethoxy-propane-1,3-diol) (Figure 6.4) was prepared according to literature as shown in Scheme 6.6.[99]



Scheme 6.6: Synthesis of 2,2-dimethoxy-propane-1,3-diol from dihydroxyacetone.

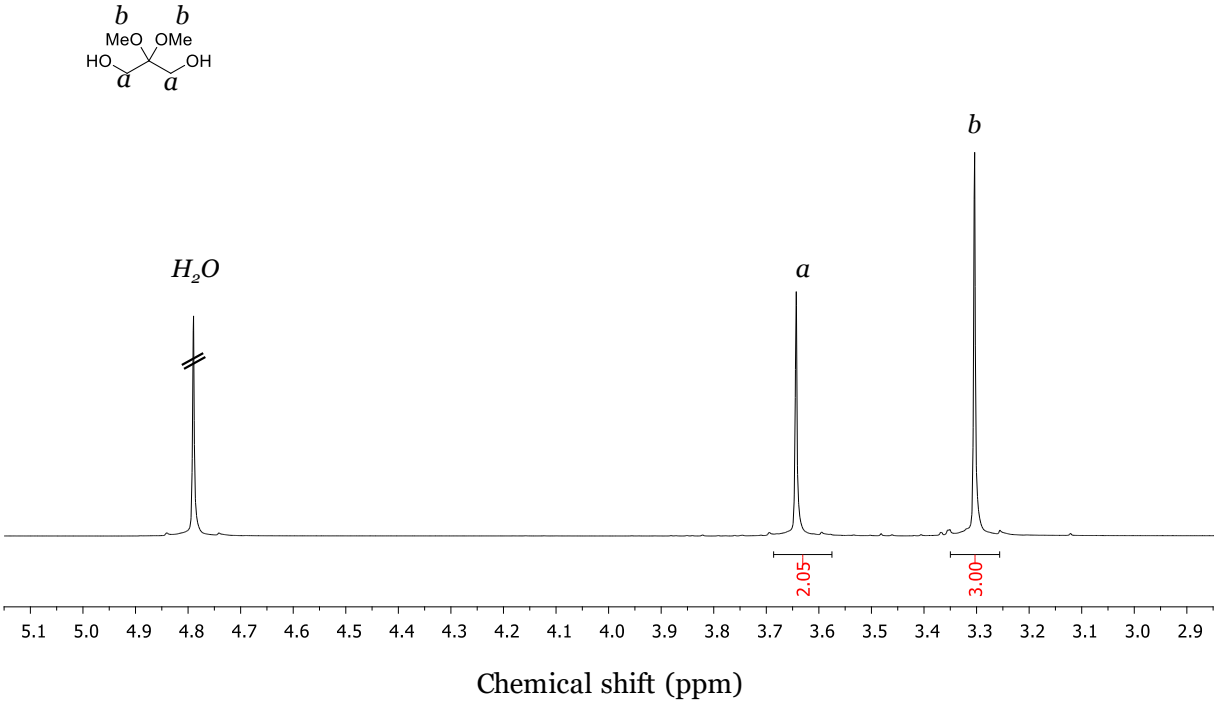
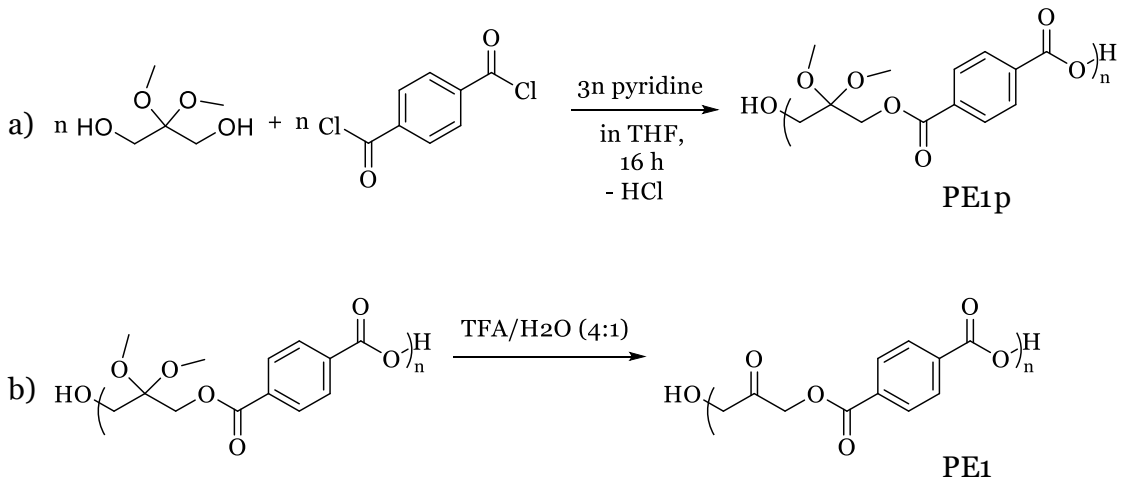


Figure 6.4: ^{1}H-NMR spectrum of 2,2-dimethoxy-propane-1,3-diol in D_2O (δ = 4.79).

For the polymerization, 1 equivalent of 2,2-dimethoxy-propane-1,3-diol was dissolved in dry THF and mixed with 3 equivalents of dry pyridine.

Terephthaloyl chloride dissolved in THF was added dropwise to their mixture and the reaction mixture was stirred for 16 hours. The reaction (Scheme 6.7a) yielded polymer (PE1p) that was washed with MeOH and H_2O, freeze-dried from dioxane, and analyzed with GPC, TGA, DSC, and NMR (Figure 6.5).



Scheme 6.7: a) Polycondensation of 2,2-dimethoxy-propane-1,3-diol and terephthaloyl chloride, b) deprotection of the product with a TFA/H_2O mixture.

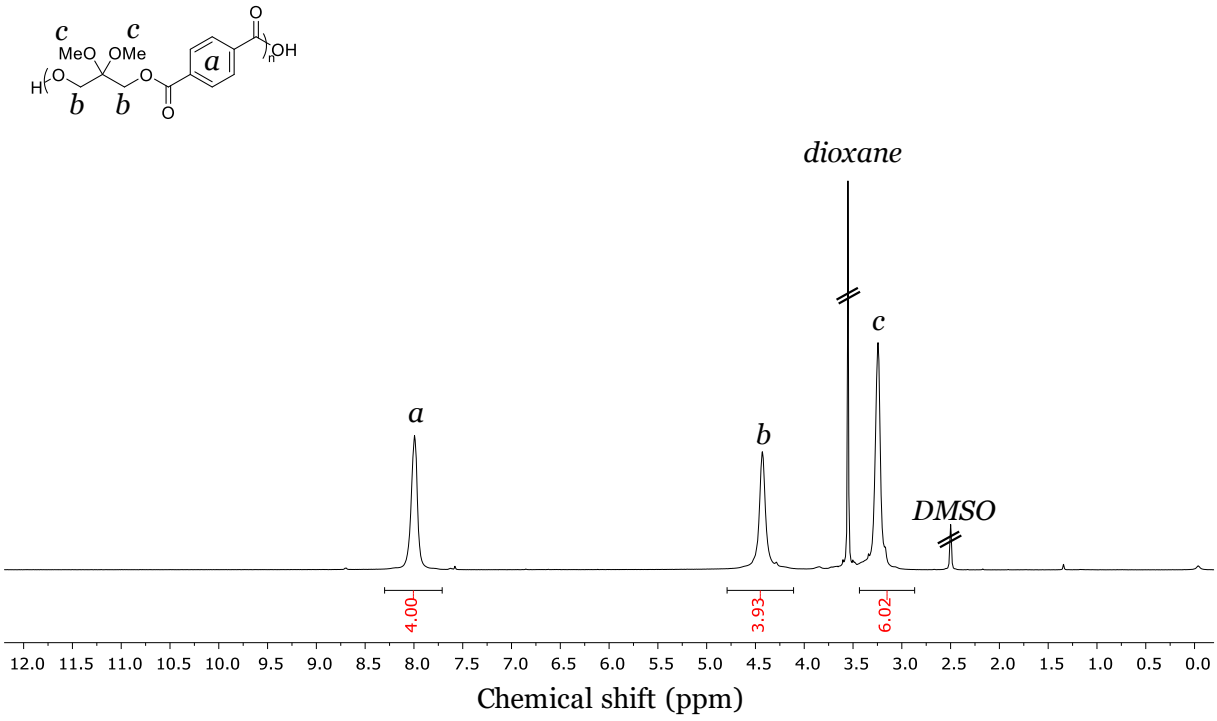


Figure 6.5: ^{1}H-NMR spectrum of the product of 2,2-dimethoxy-propane-1,3-diol and terephthaloyl chloride polymerization in DMSO (d = 2.5).

PE1p was deprotected with a mixture of trifluoroacetic acid and water (TFA/H_2O 4:1) to recover the carbonyl (PE1) (Scheme 6.7b). After the deprotection the resulting product is neither soluble in common solvents nor in TFA or HFIP. Elemental analysis indicates a composition with a C/H ratio lower than the expected, probably due to a high content of H_2O (Table 6.1). Polymers like polyketones, with a carbonyl on their main chain, are very hydrophilic and that could result to difficulties in water removal even after extended drying.[133]

Table 6.1: Elemental analysis of PE1p and PE1.

PE1p	PE1[a]
Theoretical: H [%] 5.3, C [%] 58.64	Theoretical: H [%] 3.66, C [%] 60.00
Experimental: H [%] 5.16, C [%] 58.53	Experimental: H [%] 3.57, C [%] 55.79

[a]*This sample probably contains some humidity.*

FT-IR spectroscopy shows a lower transmittance at around 1100 cm^{-1}, supporting a lower concentration of methoxy groups in addition to additional peaks in the area where carbonyl groups are expected (1750-1790 cm^{-1}). (Figure 6.6).

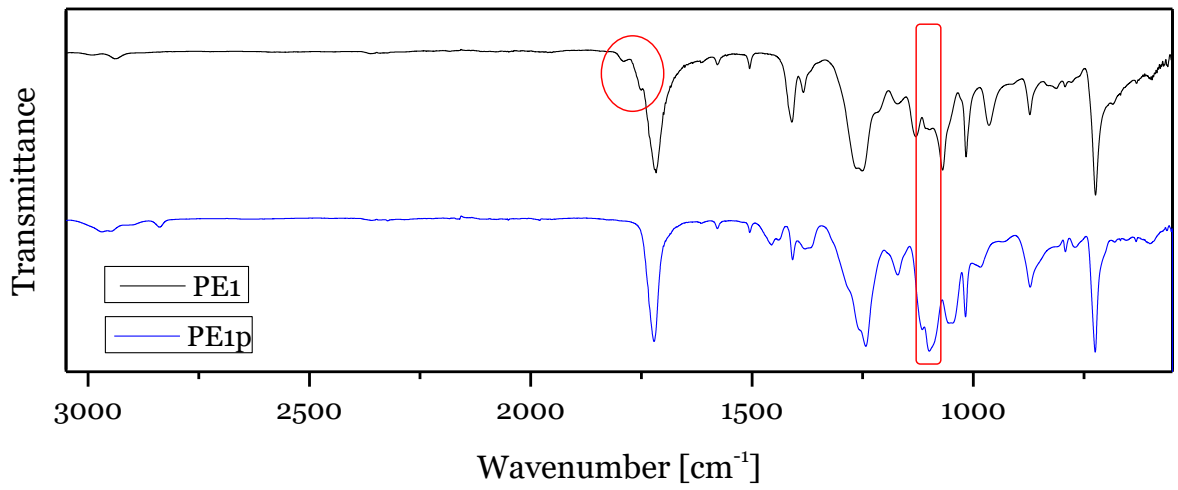


Figure 6.6: FT-IR spectra of the PE1p (blue) before and after deprotection to yield PE1 (black). The denoted area in the circle (1750-1790 cm^{-1}) shows additional carbonyl groups that were created and at around 1100 cm^{-1} the signal of the methoxy groups is clearly smaller.

Additionally to elemental analysis, the product was also subjected to solid state ^{13}C-NMR analysis. The resulting spectrum is shown in Figure 6.7.

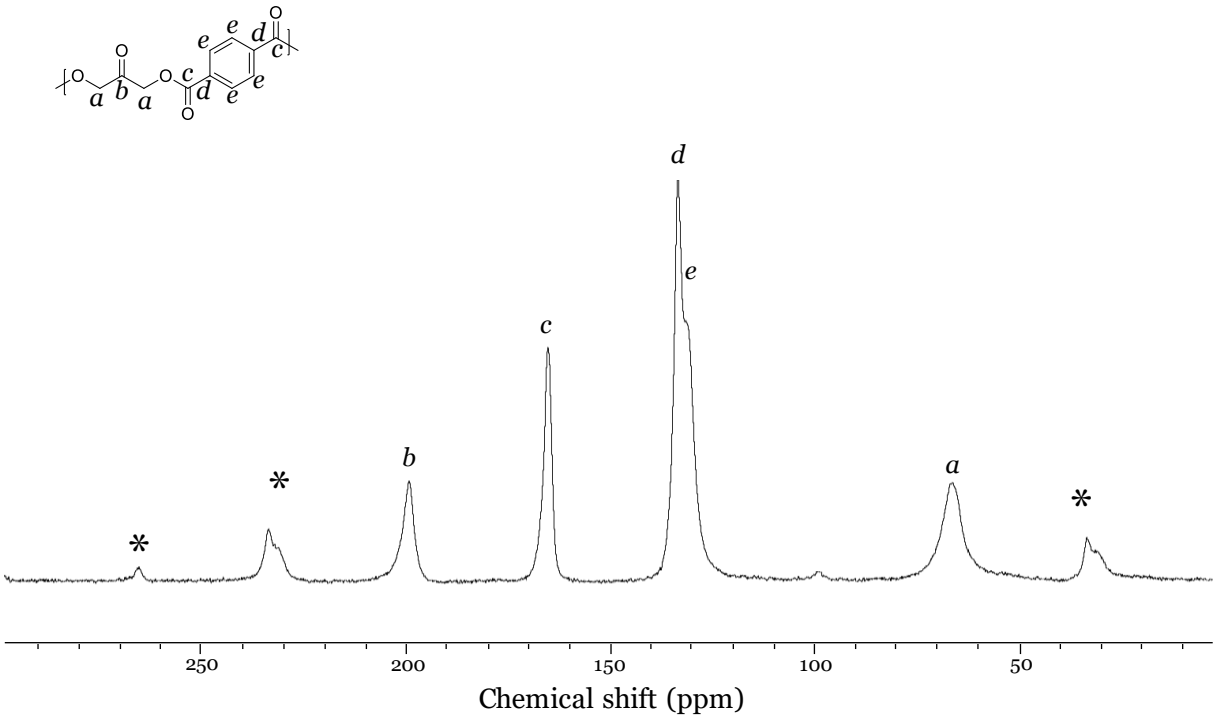


*Figure 6.7: solid state ^{13}C-NMR of the deprotected product. The * connoted signals are spinning sidebands.*

The spectrum seems to support the structure of the expected product, also in comparison to the corresponding spectrum of the protected polymer (Figure 6.5). On the spectrum, signals denoted with an asterisk correspond to spinning sidebands of the main signals, which are results of the rotation of the sample.[134]

The X-ray diffractogram of the polymer is shown on Figure 6.8, revealing a semicrystalline structure. As PE1 was insoluble and did not show a melting point before its decomposition temperature (Table 6.3), a preparation of a purely amorphous sample and a sample with a high degree of crystallinity was not possible and did not allow for the exact calculation of its degree of crystallinity (DOC).[135] However, the relative degree of crystallinity of the sample was calculated at 44% (Appendix).

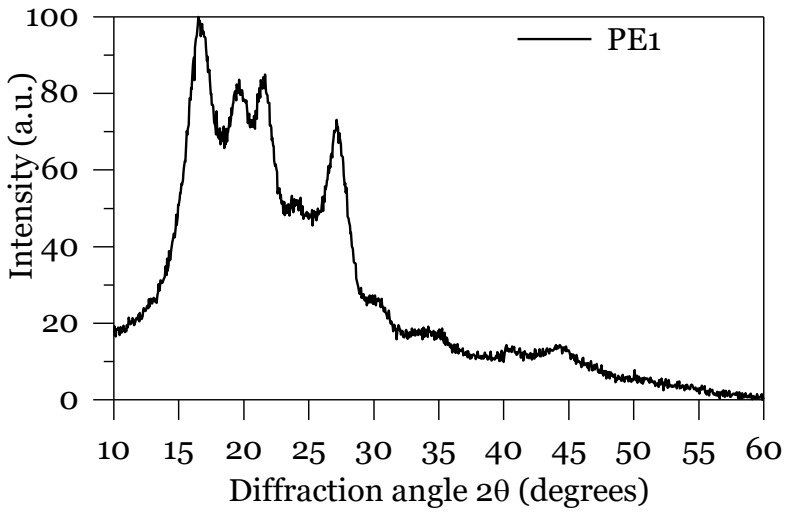


Figure 6.8: XRD diffractogram of PE1.

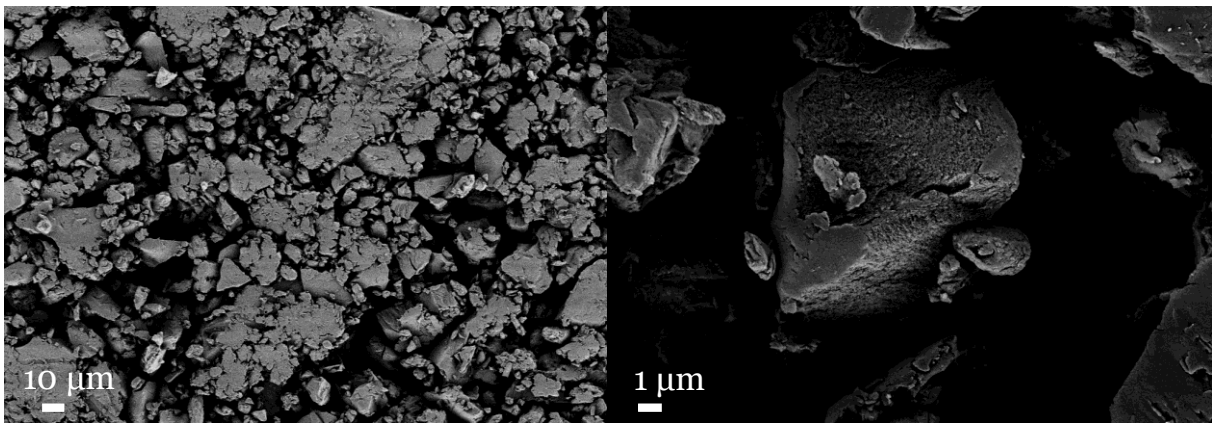


Figure 6.9: SEM pictures of PE1. The deprotection yielded a semicrystalline polymer that is insoluble in common, but also less common, solvents.

In total, the polycondensation of 2,2-dimethoxy-propane-1,3-diol with terephthaloyl chloride gave a polymer that after deprotection yielded an insoluble product. Characterization by means of NMR, FT-IR and elemental analysis supports the expected structure of the product. Its characteristics are a high degradation temperature, insolubility in all solvents tried, and no melting point visible before its degradation temperature (Table 6.2). All these characteristics are intercorrelated and depend on the structure of the polymer.

Table 6.2: Average molar masses and thermal properties of PE1p and PE1.

	M_n[a]	M_w[a]	T_g[b]	T_{dec}
PE1p	6600	14700	87 °C	318 °C
PE1	*	*	**	340 °C

[a]*As defined by GPC in THF with calibration according to PS standards.*

[b]*As defined by DSC.*

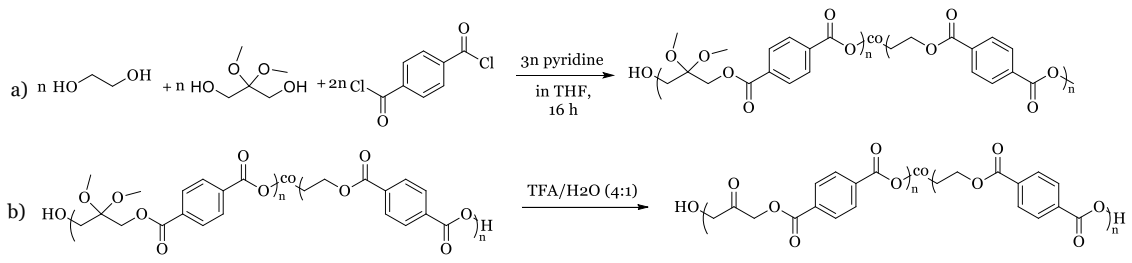
Not soluble in the solvents used for GPC.

**Material not showing T_g or T_m between -50 °C and 290 °C.*

The presence of aromatic groups leads to resonance interactions with the ester carbonyl (as is the case for PET), as well as probably the additional carbonyl groups of the main chain. Hydrogen bonds of the carbonyl groups, as in polyketones, can also lead to insoluble polymers. The symmetry of the structure and the short segments between the aromatic groups also affect the stiffness of the polymer chains and the conformation they adopt. Of course, in addition to the structure, the properties of the polymer depend on its molar mass and its degree of crystallinity.

To alter these properties of the polymer chain, different methods can be used; adding long, asymmetrical side-chains or copolymerizing can yield more easily processable polymers. The asymmetry added to the structure can disrupt the conformation of the polymer chains and copolymerization can add some structural flexibility changing the polymer characteristics. Specifically, random copolymerization gives polymers with T_m lower than that of the homopolymers, in the case of polyesters.[136] This method is also used in this work:

Additionally to the PE1p and PE1, a copolymer was also prepared, polymerizing terephthaloyl chloride with a combination of 2,2-dimethoxy-1,3-propane-diol and ethylene glycol (1:1 ratio of the two diols) (Scheme 6.8a). The polymer produced, PE2p, was characterized by NMR and GPC (Appendix and Table 6.3) and subsequently deprotected using again a TFA/H_2O mixture to give PE2 (Scheme 6.8b). The resulting polymer was soluble in a variety of organic solvents, which allowed for its characterization. NMR spectroscopy in TFA allowed for the evaluation of its structure, as shown in Figure 6.10.



Scheme 6.8: a) Polycondensation of 2,2-dimethoxy-propane-1,3-diol, ethylene glycol and terephthaloyl chloride and b) deprotection of the product with a TFA/H_2O mixture.

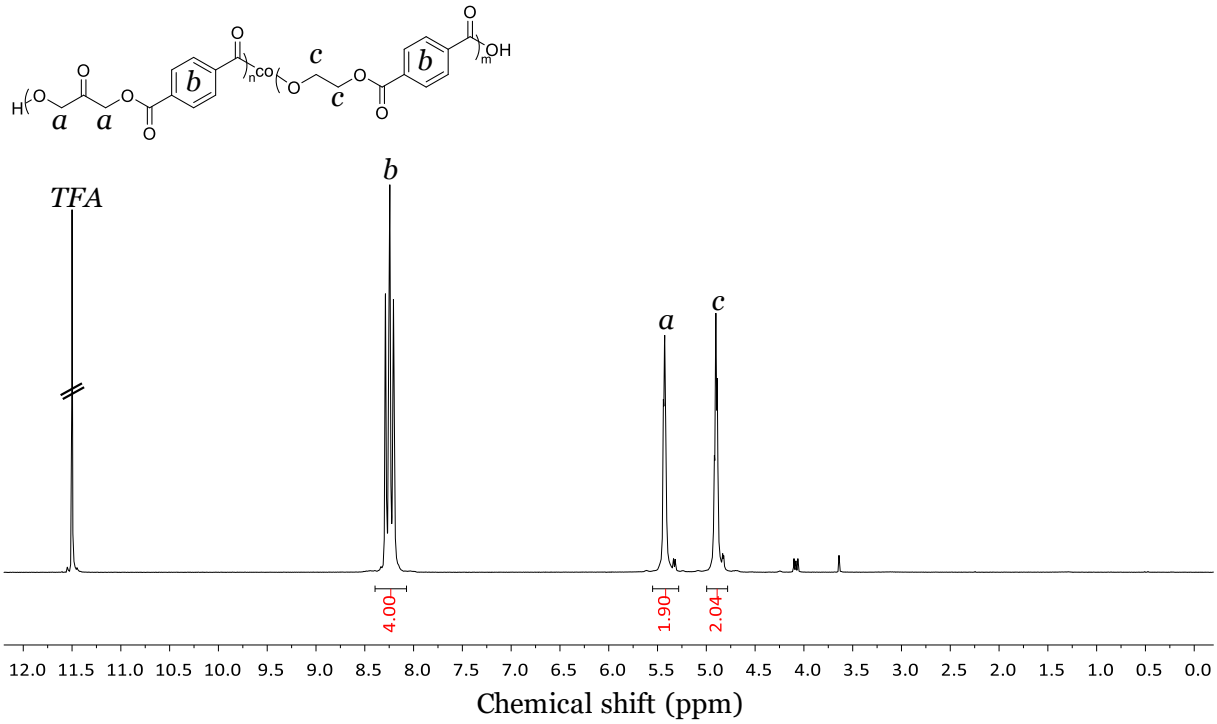


Figure 6.10: ^{1}H-NMR spectrum of PE2 in TFA. The spectrum supports the expected structure.

Except for the NMR and GPC, PE2 was also characterized by differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) (Table 6.3 and Figure 6.11 respectively).

Table 6.3: Average molar masses and thermal properties of the polymers.

	M_n[a]	M_w[a]	T_g[b]	T_{dec}
PE2p	7900	12100	36 °C	326 °C

PE2	2600	4600	36 °C	327 °C

[a]*As defined by GPC in THF with calibration according to PS standards.*

[b]*As defined by DSC.*

[*]*Not soluble in the solvents used for GPC.*

[**]*Material not showing T_g or T_m between -50 °C and 290 °C.*

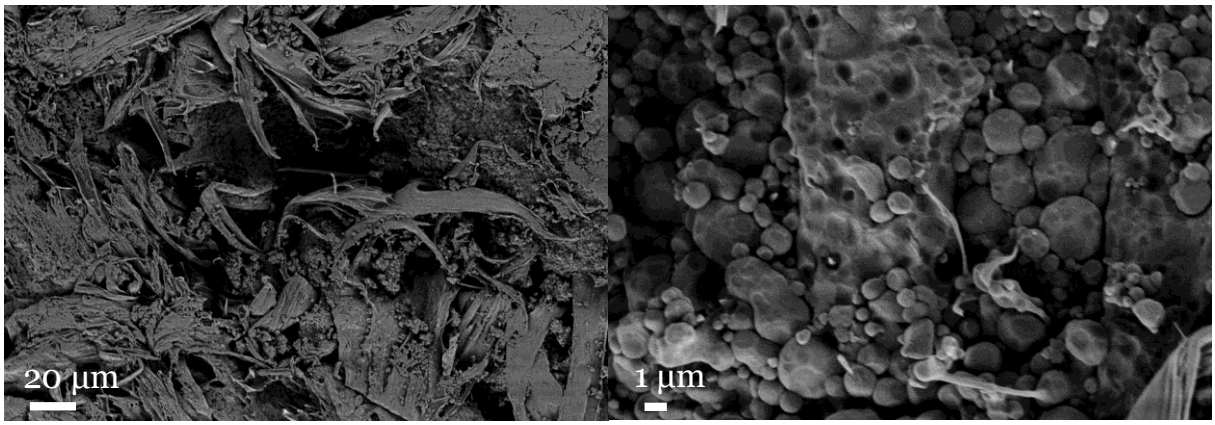


Figure 6.11: SEM of PE2 after precipitation in MeOH. The structure is very different from the one of PE1.

The deprotected copolyester, PE2, has, as expected, different properties than both PE1 and PET. Besides being soluble in a variety of organic solvents, it also shows a glass transition temperature (T_g) (Table 6.3) and shows an entirely different structure on SEM (Figure 6.11).

The molar mass of the deprotected polymer, however, seems to be much lower than the deprotected PE2p. This could be a result of different intramolecular interactions of the polymer chains in solution that lead to a more closely-packed polymer, with a small hydrodynamic volume for its length. Further analysis would be important to ensure that there is no chain scission during the deprotection reaction.

6.3. Conclusion and outlook

In this chapter, dihydroxyacetone was evaluated as a simple monomer for the production of polyesters. Its renewable nature and the potential biodegradability of its polymers could make dihydroxyacetone an interesting monomer. However, its polycondensation presented challenges, especially when equilibrium polymerization techniques were utilized.

High temperatures, as these used in the case of bulk polymerization with or without a catalyst, resulted to darkening of the reaction mixture and did not yield any polymer. Lipase, stabilized on polymer beads, was used alternatively as an enzymatic catalyst. When diphenyl ether was used as a solvent and dihydroxyacetone was freeze-dried to ensure that it was at its monomer form, condensation could be observed. However, the products of the reactions were insoluble and could not be isolated, since the enzyme-bearing beads could not be removed.

In contrast, a polyester based on dihydroxyacetone was prepared from the polymerization of 2,2-dimethoxy-propane-1,3-diol and terephthaloyl chloride and its subsequent deprotection with a TFA/H_2O mixture. The product was insoluble in all common solvents and it was characterized by solid state NMR analysis, FT-IR spectroscopy and elemental analysis. The material was semicrystalline and nonmeltable, properties that can be attributed to its symmetrical structure, its aromatic rings, and the presence of carbonyl groups on its backbone.

To access a polymer that would not present the same solubility issues and would be more easily processable, a copolyester of dihydroxyacetone was prepared. The polymer was a random copolyester containing a 1:1 ratio of dihydroxyacetone and ethylene glycol residues. It was soluble in a multitude of organic solvents, allowing for its characterization by NMR and GPC.

As an expansion of this work, it would be interesting to prepare copolyesters of different ratios of dihydroxyacetone and ethylene glycol and analyze the properties of the products in association with the ratio of the comonomers.

In addition to that, since copolymerization yielded processable polymers, it would be also of interest to employ the same method for the equilibrium

polycondensation. The copolyesters should be soluble and allow for the removal of the enzyme-beads after the completion of the polymerization.

Moreover, an investigation of the degradability of the produced polymers could reveal whether they share the same properties as polyketones and decompose under UV radiation. Norrish type I and II reactions lead to the degradation of polyketones and the carbonyl on the structure of the produced polymers are also expected to allow their degradation under the same conditions.[137]

In addition to making copolyesters with a high ratio of dihydroxyacetone, smaller amounts of it could be used, to make existent polymers more prone to UV degradation.[138]

7. Summary and outlook

7.1. Summary

This work described different approaches to more environmentally friendly polymer syntheses. The focus of these syntheses was either the use of sustainable monomers or the decrease in use of toxic substances. A new route for the preparation of poly-*N*-glycines gave well-defined polysarcosines and showed potential for a variety of monomers. Additionally, dihydroxyacetone was used as a monomer for the preparation of polyesters.

In the first part of the thesis, a new synthesis of poly-*N*-glycines was investigated. The purpose of this synthetic route was to decrease the use of hazardous compounds, such as phosgene, and to surmount the high sensitivity of the *N*-carboxyanhydrides (NCAs), the usual monomers of poly-*N*-glycines. This was achieved by the use of a Poc-*N*-glycine that can form the NCA *in situ*.

In Chapter 4, the method was tested for the simplest poly-N-glycine, polysarcosine. Sarcosine is reacted with diphenyl carbonate to yield Poc-Sar. Poc-Sar was expected to react in elevated temperatures, in the presence of an initiator, to form the NCA of sarcosine (Sar-NCA), which could subsequently polymerize. However, the reaction was very slow and did not lead to full conversion of Poc-Sar to Sar-NCA after 4 days. To accelerate the reaction, several compounds were tested, added in catalytic amounts in the reaction mixture. Tertiary amines proved to significantly accelerate the reaction. In contrast to the synthesis of polypeptides, *N*-substituted NCAs can not be initiated by tertiary amines via the activated monomer mechanism (AMM), allowing for the use of tertiary amines for the acceleration of the reaction. Diisopropylethylamine (DIPEA) was the main amine used and different reaction conditions were investigated to optimize the reaction. Temperature of 60 °C gave the best results and lower Poc-Sar concentrations led to faster reaction. Higher amounts of DIPEA led to faster polymerization, but when more than 1 equivalent of DIPEA compared to Poc-Sar was used, there was hardly any difference in the kinetics of the NCA formation.

Additionally to the optimization of the reaction conditions, polysarcosines of different molar mass were targeted. The resulting polymers were of low

dispersity (Đ) and the molar mass was well controlled according to the monomer to initiator ratio.

In Chapter 5, a collection of Poc-*N*-glycines with several substituents was prepared (ethyl-, *n*-propyl-, *n*-butyl-, *n*-hexyl-, allyl-, isobutyl-, phenethyl-, and 1,3-benzodioxol-5-ylmethyl-substituted). Due to low yields of the reaction with DPC, phenyl chloroformate was used for their synthesis. The kinetics of the NCA formation of a selection of them (ethyl-, n-propyl, n-butyl, and phenethyl) was studied to show a faster conversion of the respective Poc-*N*-glycine to its NCA compared to sarcosine. Most of the Poc-*N*-glycines reached a high degree of conversion to the corresponding NCAs within 24 hours. However, during polymerization most of them showed precipitation. The products of their polymerization were isolated after 2 days of polymerization and were characterized. The method seems to work well for the formation of the NCAs, but solubility is decreased as polymeric chains start forming, leading to relatively low molar masses.

In the second part of this work, dihydroxyacetone, a bio-derived compound, was used as a monomer for the synthesis of polyesters. It was reacted with adipic acid, dimethyl adipate, itaconic acid, and dimethyl itaconate in different conditions. Bulk and solution polymerization were used, with and without the addition of a catalyst, enzymatic or non-enzymatic. Of these methods, enzymatic polymerization in diphenyl ether led to formation of by-products, but resulted in insoluble products. The insolubility of the potential polymers or oligomers was attributed to the formation of hydrogen bonds due to the carbonyl on their main chain. To overcome the difficulties of the polymerization caused by the ketone carbonyl, 2,2-dimethoxy-propane-1,3-diol was prepared from dihydroxyacetone and was copolymerized with terephthaloyl chloride to yield a polymer. After characterization, the polymer was deprotected to recover the ketone on the main chain. The product was an insoluble polymer, supporting the assumption that the ketone carbonyl led to insolubility due to hydrogen bonding. However, when 2,2-dimethoxy-propane-1,3-diol was copolymerized with ethylene glycol (1:1 ratio) and terephthaloyl chloride, the resulting product was soluble even after deprotection.

7.2. Outlook

The first part of this work focused on an alternative, more sustainable synthetic route for poly-*N*-glycines, also known as polypeptoids. A synthetic path was optimized for the synthesis of polysarcosine and was tested for more complex *N*-substituted glycines. However, solubility problems of polypeptoids other than polysarcosine led to less than full conversion and molar masses smaller than the expected. To address the solubility problems, an addition of a good solvent during the polymerization, but after the full conversion to the NCA, could allow for complete polymerization. However, the addition of a solvent would result in a less concentrated NCA polymerization mixture and potentially a slower polymerization. Further investigations are therefore needed to improve the yield of the polymerization of Poc-*N*-glycines.

A particularly interesting characteristic of these polymerizations is that different *N*-glycines have different kinetics for the NCA formation. This feature could be used in the case of copolymerization, allowing for the synthesis of gradient copolymers. In the case of extreme differences of the conversion time, block copolymers could result, even if the Poc-N-glycines are added simultaneously to the reaction mixture. Additionally, copolymerization could improve the solubility of the formed chains.

As polypeptoids are biocompatible and some of them show interesting properties, such as LCST, copolymerization using the Poc-*N*-glycines could allow for the creation of a copolymer library and consequent study of their properties. The Poc-*N*-glycine method does not require the isolation of the NCAs and therefore, makes the polymerization much less demanding than the direct ROP of NCAs. The new copolymers could be used for pharmaceutical applications, such as drug or gene delivery.

Regarding the use of dihydroxyacetone for the synthesis of polyesters, this work has showed that using it in a 1:1 ratio with a comonomer results in insoluble products. However, when mixed with another diol, the resulting products are soluble and can be analyzed. Therefore, it would be interesting to study whether the ketone moiety on the main chain can result in fast degradation under UV radiation and what amount of it is necessary to make the polymers degradable.

A. Appendix

A.1. Experimental Part

Analytical Instrumentation

Nuclear magnetic resonance (NMR) spectroscopy. ^{1}H NMR spectra of polymer samples were recorded on a Bruker Avance III 600 MHz spectrometer in D_2O (δ 4.79 ppm); the number of scans was 128. ^{1}H and ^{13}C NMR spectra of all other materials were recorded on a Bruker Avance 300 MHz Spectrometer in DMSO-d_6 (δ 2.50 ppm (^{1}H), 39.5 ppm (^{13}C)) and $CDCl_3$ (δ 7.26 ppm (^{1}H), 77.0 ppm (^{13}C)). Unless otherwise mentioned, the number of scans was 128 (^{1}H) and 1024 (^{13}C).

Fourier transformation infrared (FT-IR) spectroscopy was performed on a Bruker Vertex 70 fitted with a PLATINUM ATR. Liquid samples were placed directly on the ATR diamond under an argon flow. The spectra were acquired and processed with the OPUS 7.0 software. The number of scans was 32, the built-in atmospheric correction function was turned on, and the background was automatically subtracted; in the case of liquid samples, the background was generated using the very same solvent as the one used for the sample.

Matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS). Mass spectra were acquired with an Autoflex III MALDI-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) which is equipped with a frequency tripled Nd:YAG laser (λ = 355 nm); spectra were recorded in linear mode. Samples were prepared by mixing matrix (trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile), DCTB) and analyte solutions (10 mg mL^{-1} in THF) in a ratio 10:1 (v/v) and spotting a volume of 0.5 µL of this mixture on the target using an Eppendorf pipette (dried-droplet method). Spectra were recorded without addition of salt or with addition of 0.5 µL potassium trifluoroacetate (2 mg mL^{-1} in THF) as dopant. Calibration was done with a mixture of two poly(ethylene glycol) standards (M_n = 1400 and 6000 g mol^{-1}).

Gel permeation chromatography (SEC). Measurements were performed with (*i*) eluent: 0.058 M LiBr in NMP at 60 °C, flow rate 0.5 mL min^{-1}, stationary phase: 300 × 8 mm^2 PSS-GRAM 7µ analytical linear or (*ii*) eluent: 0.1 N aqueous $NaNO_3$ at 25 °C, flow rate 1.0 mL min^{-1}, stationary phase: 300 × 8 mm^2 PSS-Suprema 10µ 30 + 300 Å; detectors: UV (λ = 270 nm or 265 nm) and RI. Solutions containing ~0.1-0.15 wt % polymer were filtered through 0.45 µm filters; the injected volume was 100 µL. Calibration curves were recorded with polystyrene or poly(ethylene oxide) standards,

respectively. Data analysis was done with the PSS WinGPC UniChrom software (PSS GmbH, Mainz, Germany).

^{13}C solid-state magic angle spinning (MAS) NMR was measured on a Bruker Avance 400 MHz Solid State at a MAS frequency of ν_{MAS} = 10 kHz. ^{13}C chemical shifts were referenced relative to tetramethylsilane (TMS; δ = 0 ppm).

Materials

Sarcosine (Sar, 98%), ethylene glycol (99%), trifluoroacetic acid (TFA, 99%) and *tert*-butylammonium hydroxide (40% w/w in methanol) were purchased from **Alfa Aesar**.

Dimethyl sulfoxide (DMSO, 99.7+%, extra dry, AcroSeal), methanol (MeOH, 99.8%, extra dry, AcroSeal), acetonitrile (99.9%, extra dry, over molecular sieves, AcroSeal), diphenyl carbonate (DPC, 99.5%), triethylamine (TEA, 99%, pure), p-toluenesulfonic acid monohydrate (*p*TsOH, 99% extra pure), methanol (MeOH, 99.8%, extra dry over molecular sieves), pyridine (C_5H_5N, 99.5%, extra dry over molecular sieves), tetrahydrofuran (THF, 99.5%, extra dry over molecular sieves), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 99.5+%, pure) were purchased from **ACROS Organics**.

N,*N*-Diisopropyl-ethylamine (DIPEA, ≥99%, for synthesis) and lithium chloride (≥99%) were purchased from **Roth**.

Potassium hydroxide (puriss. p.a., Reag. Ph. Eur., ≥85%, pellets), 1,3-dihydroxyacetone dimer (DHA dimer, 97%), trimethyl orthoformate ($CH(OCH_3)_3$, 99%), terephthaloyl chloride (TCL, >99%, flakes) were purchased from **Sigma-Aldrich**.

Benzylamine (for synthesis, dried with molecular sieves) was purchased from **Merck KGaA**.

Ethyl acetate (EtOAc), heptanes (Heptan Isomerengemisch), tetrahydrofuran (THF), and acetone were of technical grade quality from **VWR**.

Standard Silica 60 M (0.04-0.063 mm, particle size 230-400 mesh) was purchased from **Macherey-Nagel**.

All chemicals were used as received except for ethylene glycol, which was dried over sodium sulphate and distilled prior to use.

Experimental Procedures

N-phenoxycarbonyl-N-sarcosine (Poc-Sar):

Method A:[57] Sarcosine (5.0 g, 56.1 mmol) was suspended in 31 mL of MeOH, and then 56.1 mL of 40% solution of tetrabutylammonium hydroxide in MeOH (1 equiv) was added dropwise. After 1 h the MeOH was evaporated and 15.5 mL of acetonitrile was added. To this solution, a solution of 12.02 g of DPC (56.1 mmol) in 15.5 mL of acetonitrile (solution II) was added dropwise. The reaction was left to proceed overnight at room temperature, and then the solvent was evaporated. The product (Poc-Sar) was purified either by double extraction (initially pH around 9 and washing with EtOAc, then pH around 3 and extraction with EtOAc) or by extraction (after decrease of the pH to 3-4) with EtOAc and then column chromatography (silica) with a mixture of heptanes:EtOAc 7:3 (v/v). Yield: 49%.

Method B:[106] Sarcosine (1.0 g, 11.2 mmol) was suspended in 20 ml of MeOH, to which KOH (0.63 g) and LiCl (0.27 g,) were added. The opaque solution was combined with a solution of 2.4 g DCP (11.2 mmol, 1 equiv) in 20 mL of THF, and the reaction was left to proceed overnight at room temperature. The non-dissolved salts were filtered off and the solvents were evaporated. Water (~20 mL) was added to the flask and the pH was adjusted to 3-4 with 0.1 N aqueous HCl. The water was evaporated and the product (Poc-Sar) was purified by column chromatography (silica) with a mixture of heptanes:EtOAc 7:3 (v/v). Yield: 52%.

ethyl-N-glycine hydrochloride: glyoxylic acid monohydrate (10 g, 109 mmol) was dissolved in 110 ml H_2O. Ethylamine (3.08 ml, 54 mmol) was added and the reaction was stirred overnight. 3.96 ml hydrochloric acid (37%, 130 mmol) was added and the reaction mixture was refluxed for 8 h. The aqueous solution was evaporated and the mixture was dissolved in MeOH and precipitated in diethyl ether (Et_2O). The product was recrystallized in MeOH/Et_2O. Yield: 25%.

The following compounds were prepared accordingly:

n-propyl-N-glycine hydrochloride: yield: 25%.

n-butyl-N-glycine hydrochloride: yield: 35%.

and

N-phenoxycarbonyl-N-ethylglycine: ethyl-*N*-glycine hydrochloride (1 g, 7.16 mmol) was dissolved in 10 ml of H_2O and 0.86 g (2.15 mmol) of sodium hydroxide (NaOH) were added. The mixture was cooled down to 0 °C and phenyl chloroformate (0.9 ml, 7.16 mmol) were added dropwise. The reaction was stirred overnight. The product was

isolated by double extraction, in the same way as *N*-phenoxycarbonyl-*N*-methylglycine. Yield: 64%.

The following compounds were prepared accordingly:

N-phenoxycarbonyl-N-n-propyl glycine: yield: 90%.

N-phenoxycarbonyl-N-n-butyl glycine: yield: 71%.

2,2-Dimethoxy-propane-1,3-diol: Dihydroxyacetone dimer (50 g, 280 mmol) was suspended in 600 cm^3 of dry methanol. *p*-Toluenesulfonic acid monohydrate (200 mg, 1 mmol) and trimethyl orthoformate (60.8 cm^3, 560 mmol) were added. The mixture was stirred for 16 h and the reaction progress was followed by NMR spectroscopy. After the completion of the reaction, a Dowex Marathon basic resin (OH^-) was added to neutralise the mixture. The reaction mixture was then filtered and the filtrate was concentrated in vacuum. Upon recrystallisation from diethyl ether, the desired product was isolated with a 68% yield (52 g, 382 mmol).^{1}H-NMR (400 MHz, D_2O): δ (ppm) = 3.64 (s, 4H, -C**H**$_2$-OH), 3.30 (s, 6H, OMe).

PE1p: 2,2-dimethoxy-propane-1,3-diol (5.0 g, 36.7 mmol) was dissolved in 100 cm^3 dry THF and dry pyridine (8.9 cm^3, 110.2 mmol) was added. Terephthaloyl chloride (7.46 g, 36.7 mmol) was dissolved in 25 cm^3 dry THF was added dropwise over 20 min. The reaction mixture thus obtained was further stirred for 16 h. The precipitated pyridinium chloride was removed by filtration and the filtrate was precipitated in cold methanol (MeOH). The polymer was washed twice with cold MeOH and H_2O and freeze-dried from 1,4-dioxane. The product yield was 89% (9.78 g).^{1}H-NMR (400 MHz, DMSO): δ (ppm) = 8.01 (4H, Ar), 4.43 (4H, C(OCH$_3$)$_2$-C**H**$_2$-O), 3.25 (6H, OMe).

PE2p: 2,2-dimethoxy-propane-1,3-diol (5.0 g, 36.7 mmol) and ethylene glycol (2.28 g, 36.7 mmol) were dissolved in dry THF (200 cm^3) and dry pyridine (17.8 cm^3, 220.3 mmol) was added. Terephthaloyl chloride (14.91 g, 73.4 mmol) was dissolved in dry THF (50 cm^3) was added dropwise over 20 min. The reaction mixture thus obtained was further stirred for 16 h. The precipitated pyridinium chloride was removed by filtration and the filtrate was precipitated in cold MeOH. The polymer was washed twice with cold MeOH and H_2O and freeze-dried from 1,4-dioxane. The product yield was 95% (16.67 g).^{1}H-NMR (400 MHz, DMSO): δ (ppm) = 7.97 (4H, Ar), 4.60 (2H, O-C**H**$_2$-C**H**$_2$-O), 4.41 (4H, C(OCH$_3$)$_2$-C**H**$_2$-O), 3.24 (6H, OMe).

Deacetalation of the polymers: The method applied for this purpose was based on the procedure reported by Putnam *et al.*[1] The polymers were dissolved in a TFA:water solution (4:1 vol.%/vol.%) at a concentration of 10 mg cm^{-3} corresponding to monomeric units containing the acetal groups. After 15 min, the reaction mixture was

poured into excess MeOH, where the polymer precipitated. The solid product was filtered, washed thoroughly with MeOH and finally dried overnight under vacuum at 313 K.

DHA-TPA. ^{13}C-NMR (10 kHz, solid state): δ (ppm) = 195 (CH_2-**C**(O)-CH_2), 161 (-**C**(O)-O-), 130 (-**C**(O)-Ar), 129 (Ar), 62 (-O-**C**H_2-C(O)).

DHA-EG-TPA. ^{1}H-NMR (400 MHz, TFA-*d*): δ (ppm) = 8.24 (4H, Ar), 5.43 (2H, O-C**H**$_2$-C(O)), 4.41 (2H, O-C**H**$_2$-C**H**$_2$-O).

Supporting spectra

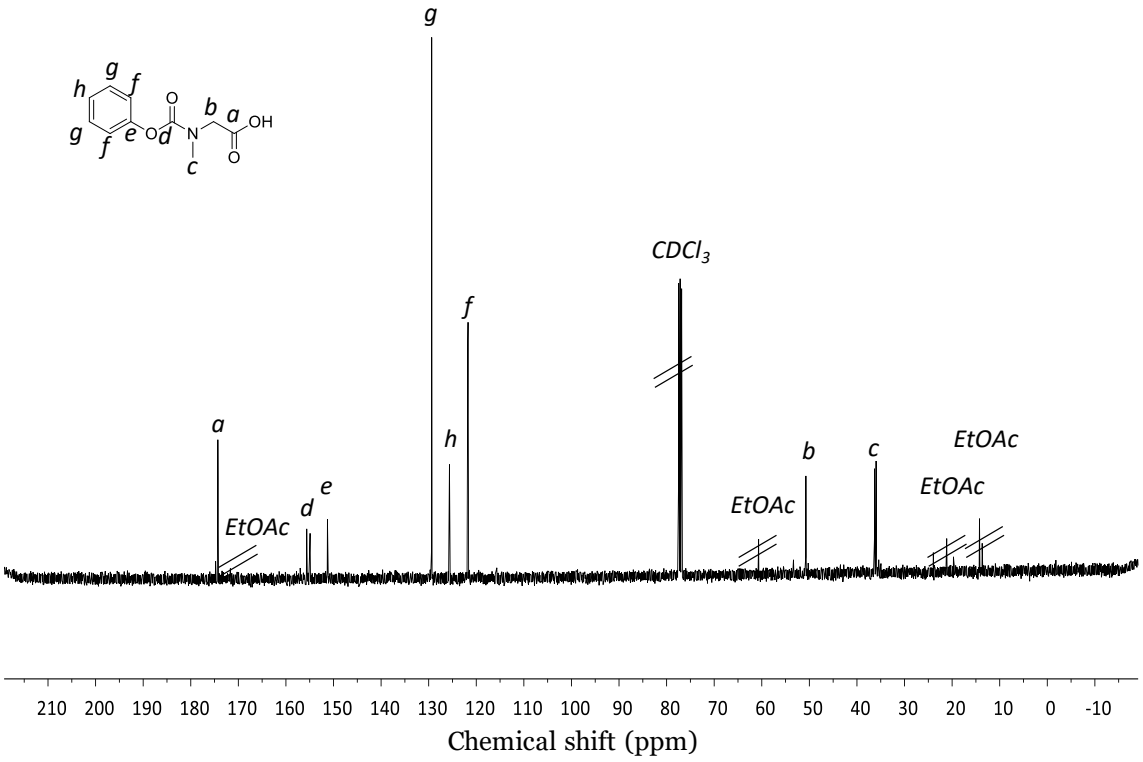


Figure A.1: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-Sar.

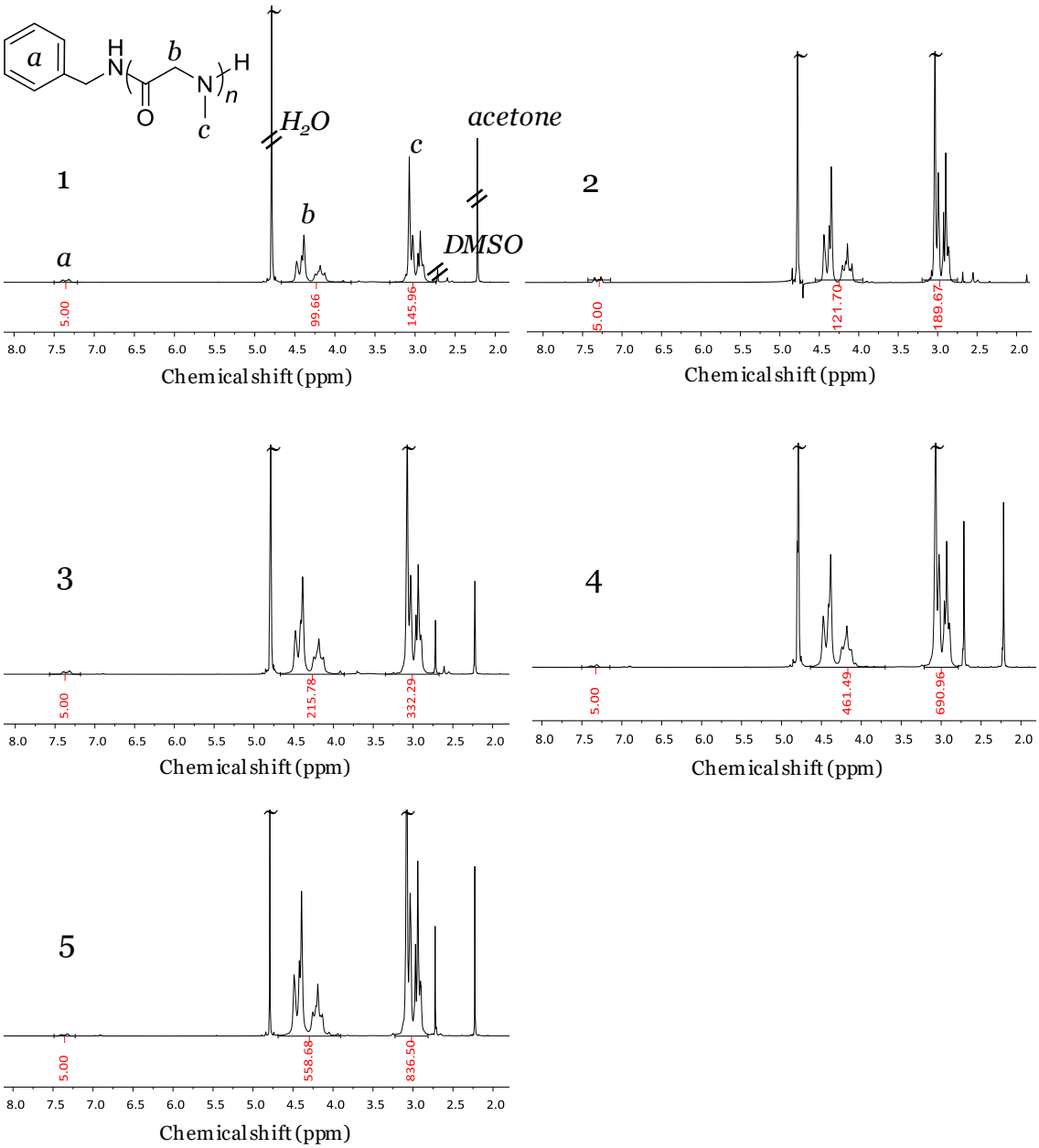


Figure A.2: ^{1}H-NMR (DMSO δ 2.50) of polysarcosine of different molar mass (4.7).

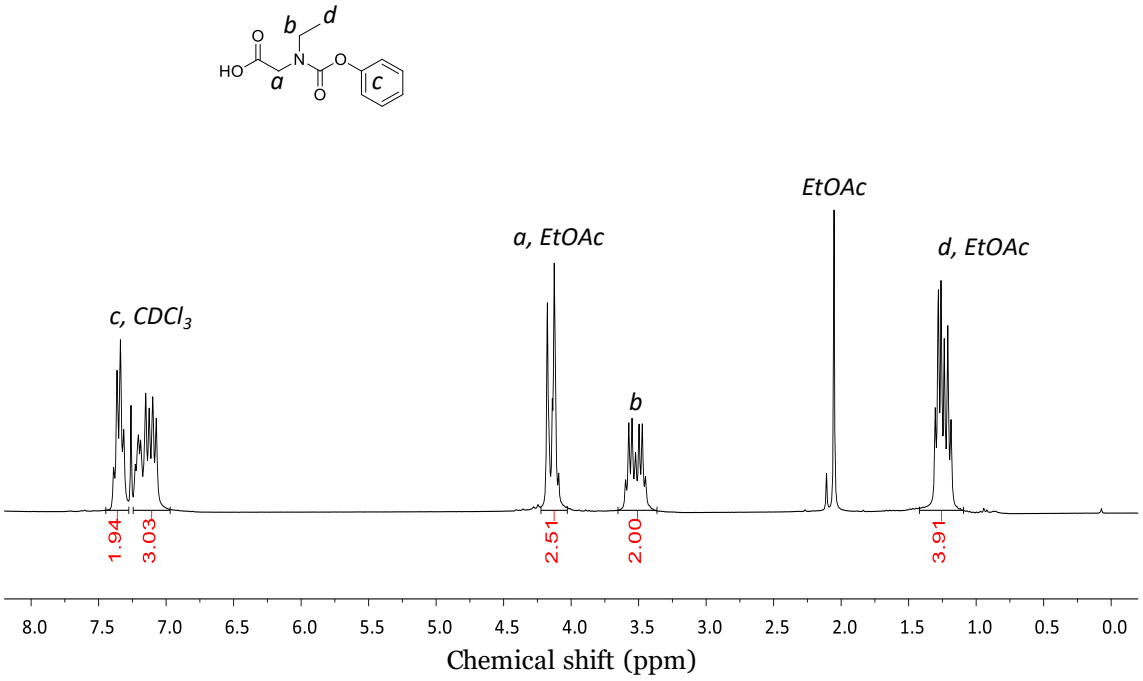


Figure A.3: ^{1}H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-N-ethyl-N-glycine.

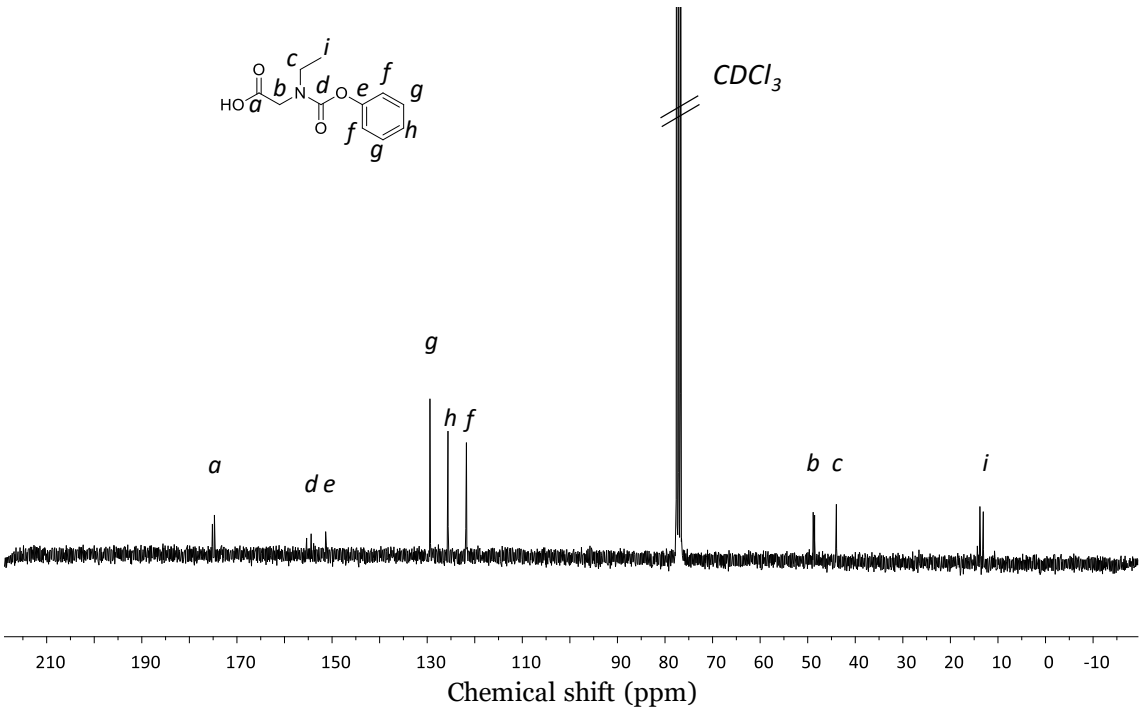


Figure A.4: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-ethyl-N-glycine.

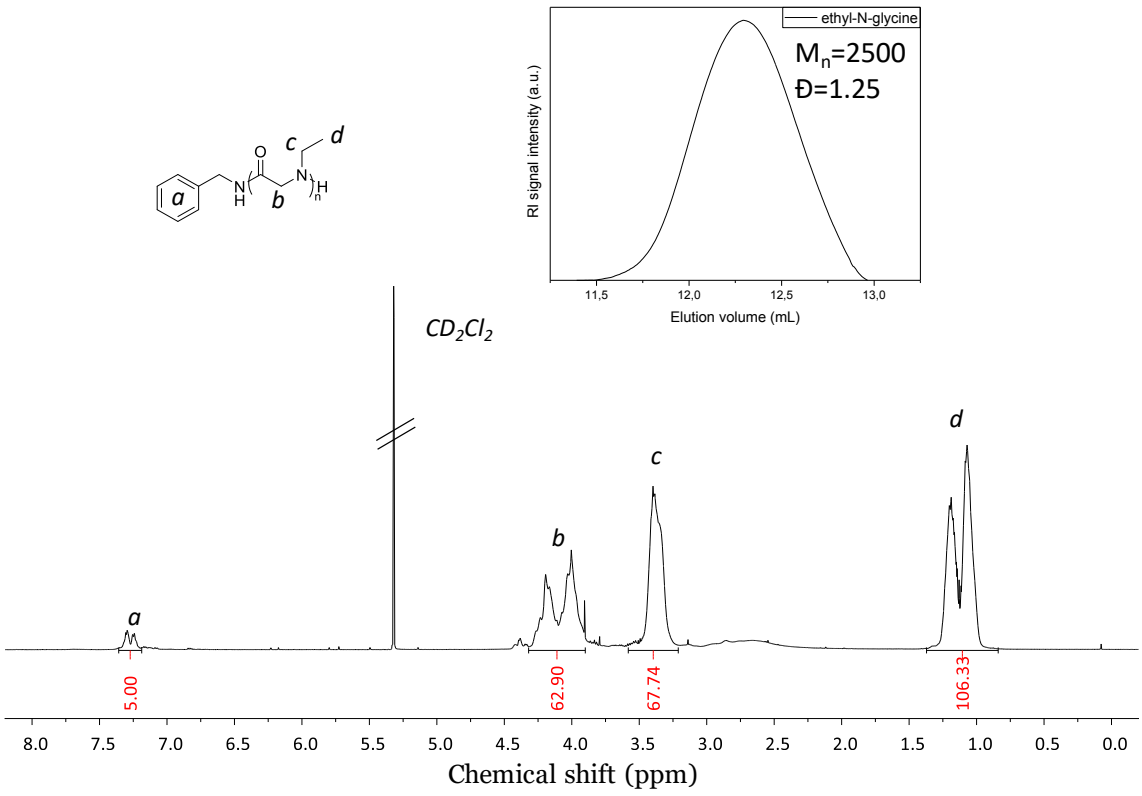


Figure A.5: : ¹H-NMR (CD_2Cl_2 δ 5.32) of poly-ethyl-N-glycine and GPC eluogram in NMP (PS standards).

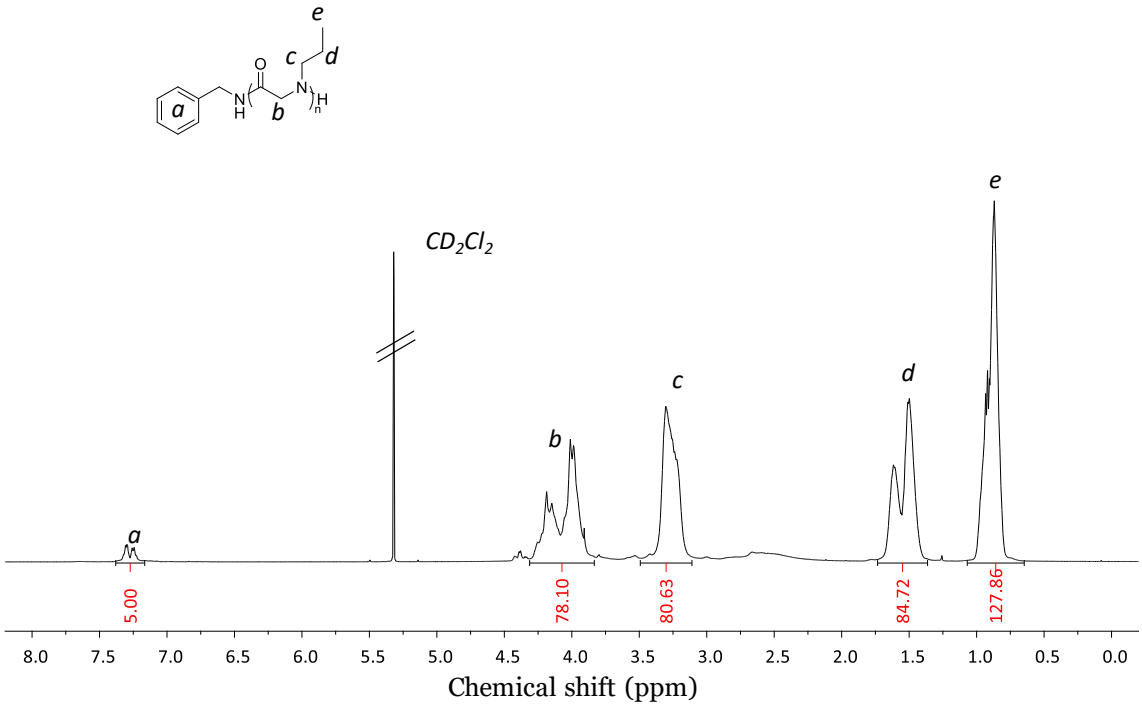


Figure A.6: ¹H-NMR (CD_2Cl_2 δ 5.32) of poly-N-propyl-N-glycine.

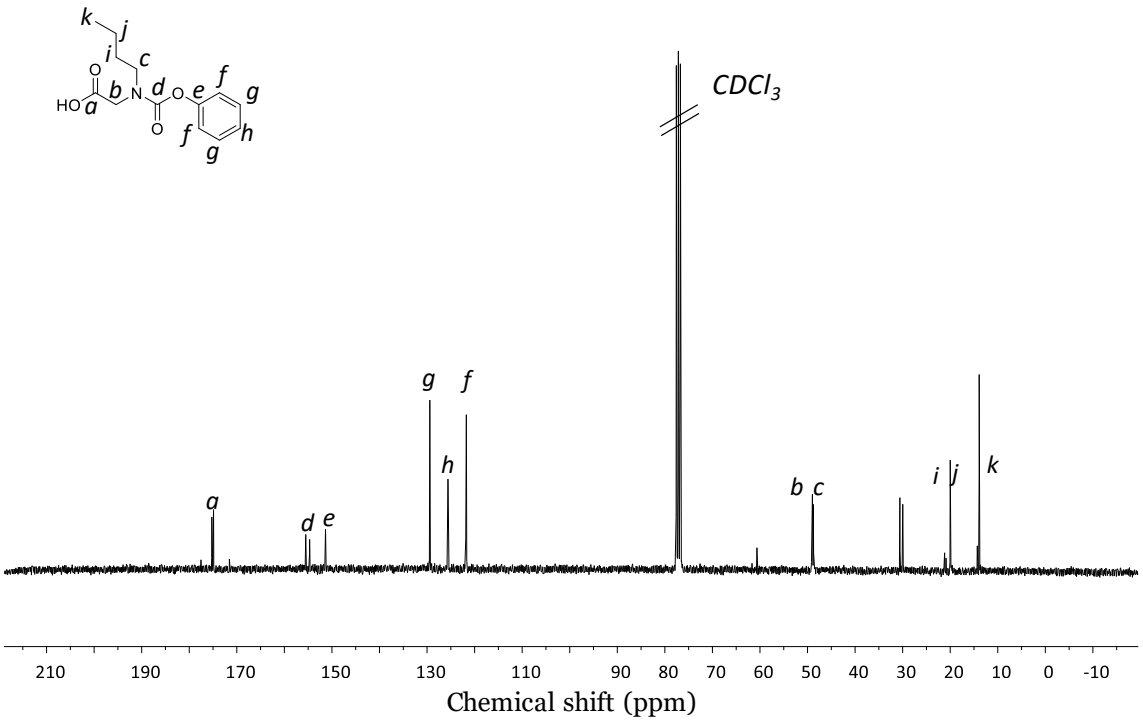


Figure A.7: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-N-butyl-N-glycine.

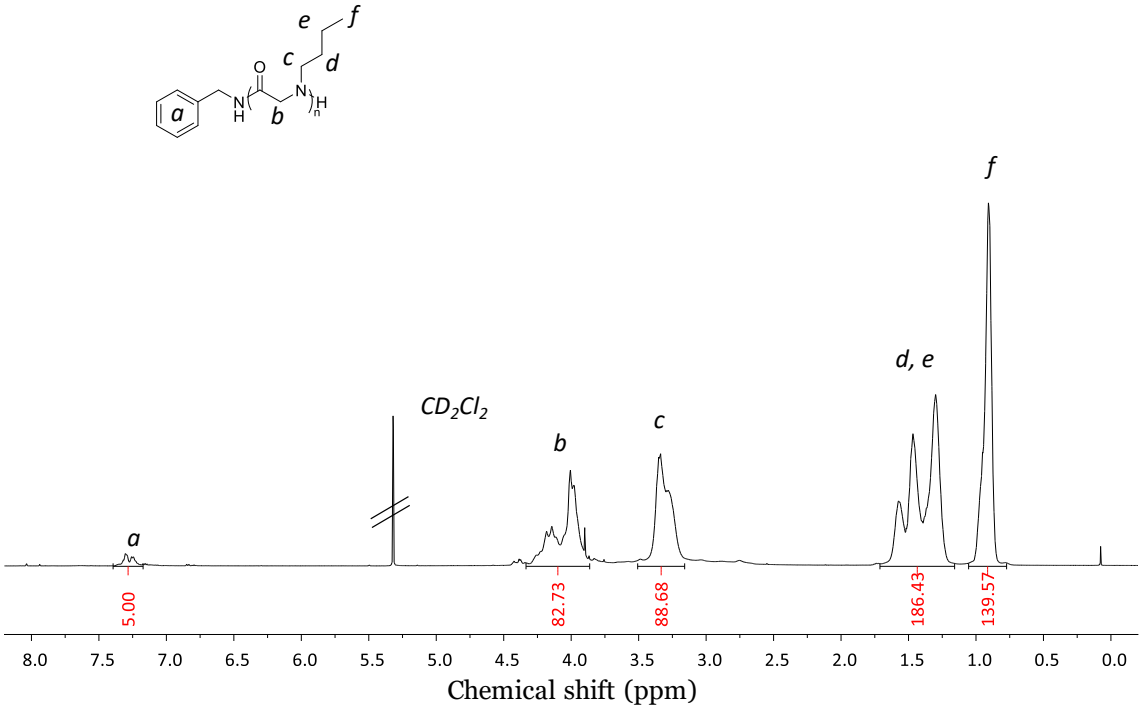


Figure A.8: ^{1}H-NMR (CD_2Cl_2 δ 5.32) of poly-N-butyl-N-glycine.

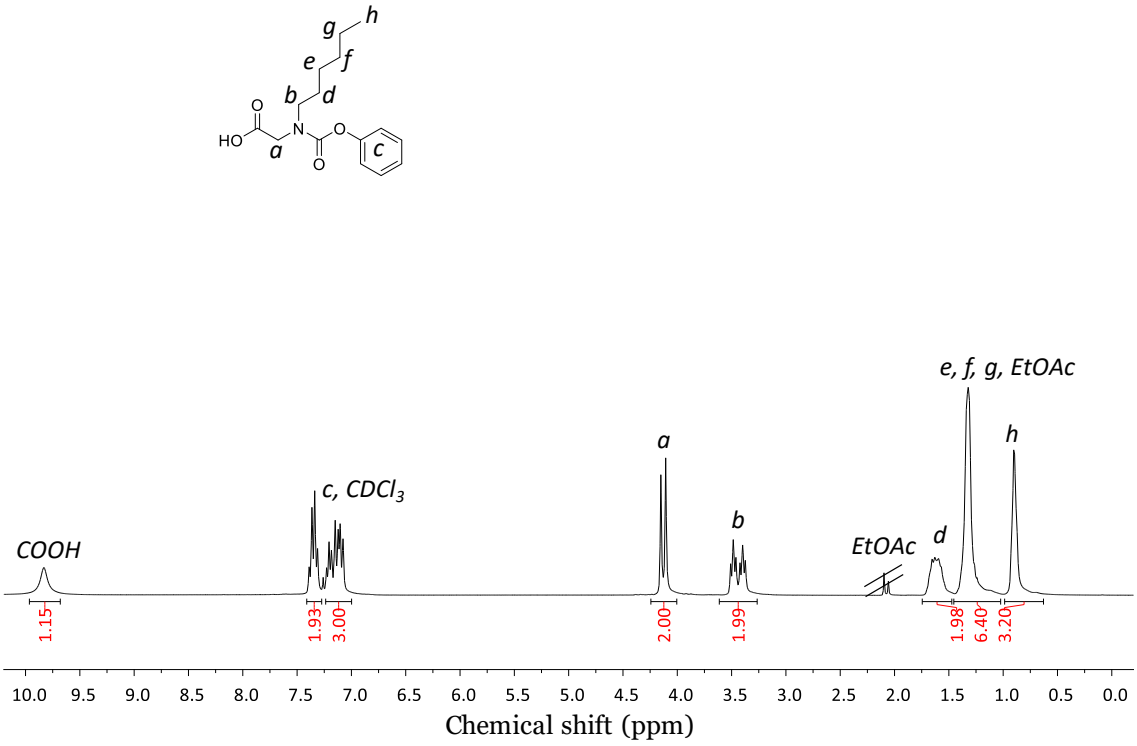


Figure A.9: ^{1}H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-hexyl-N-glycine.

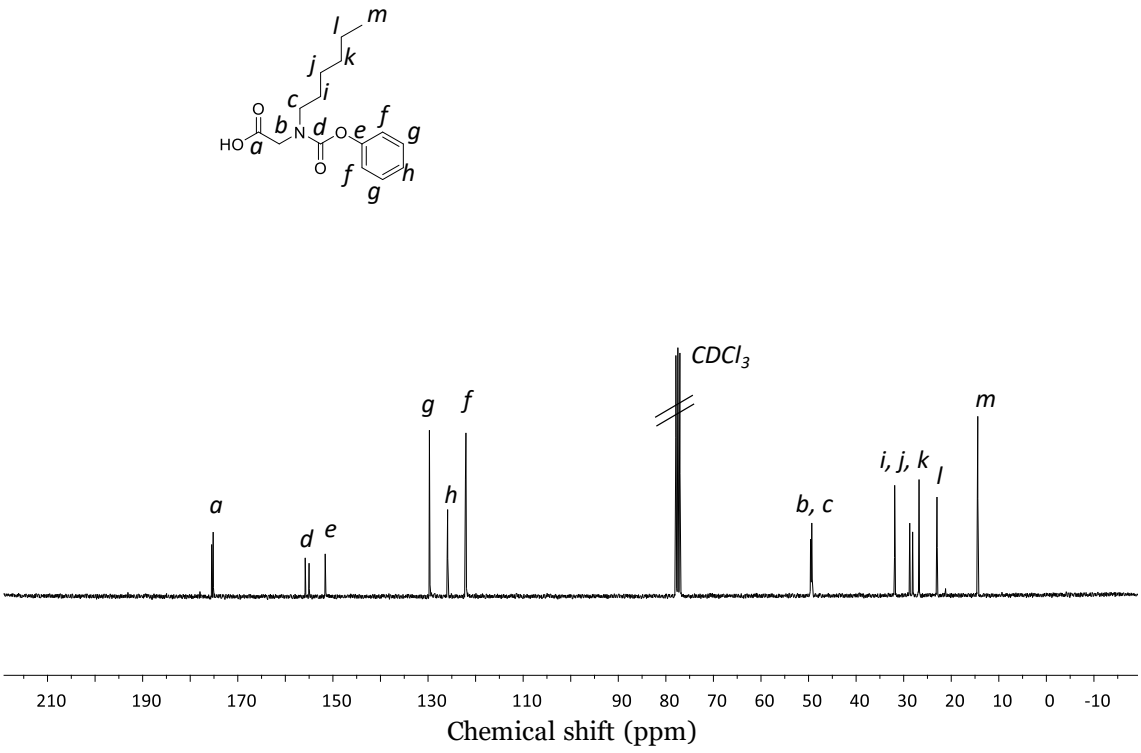


Figure A.10: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-hexyl-N-glycine.

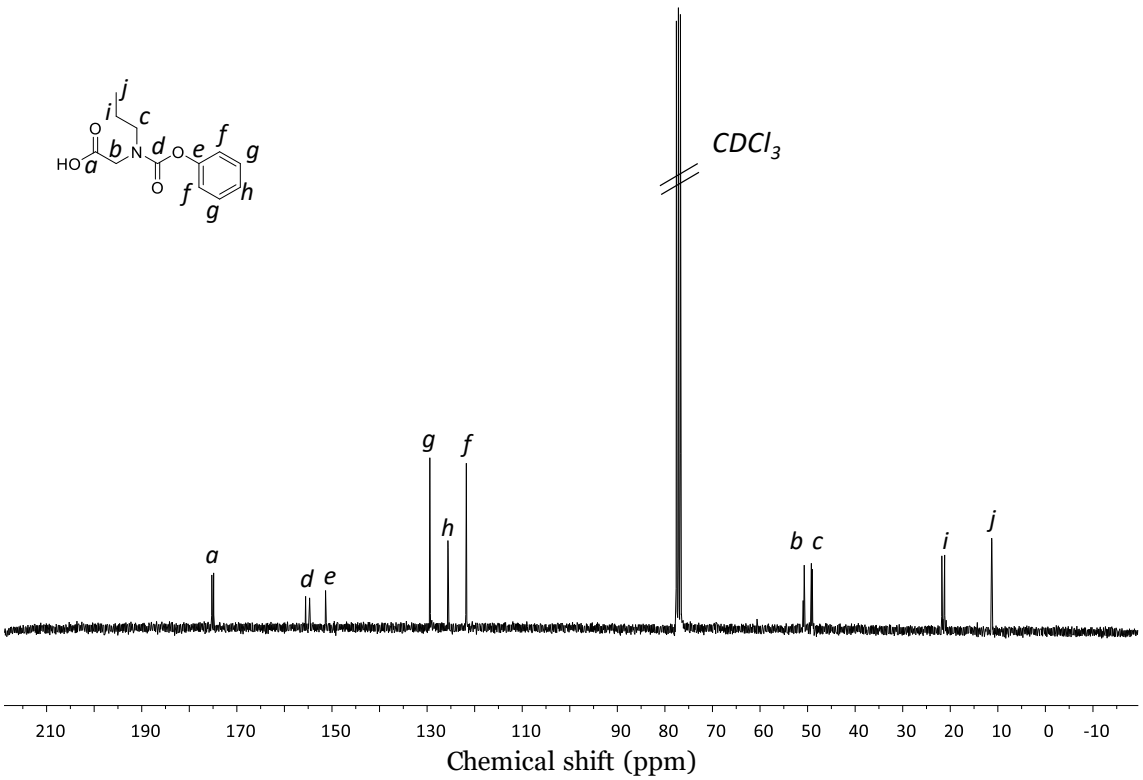


Figure A.11: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-N-propyl-N-glycine.

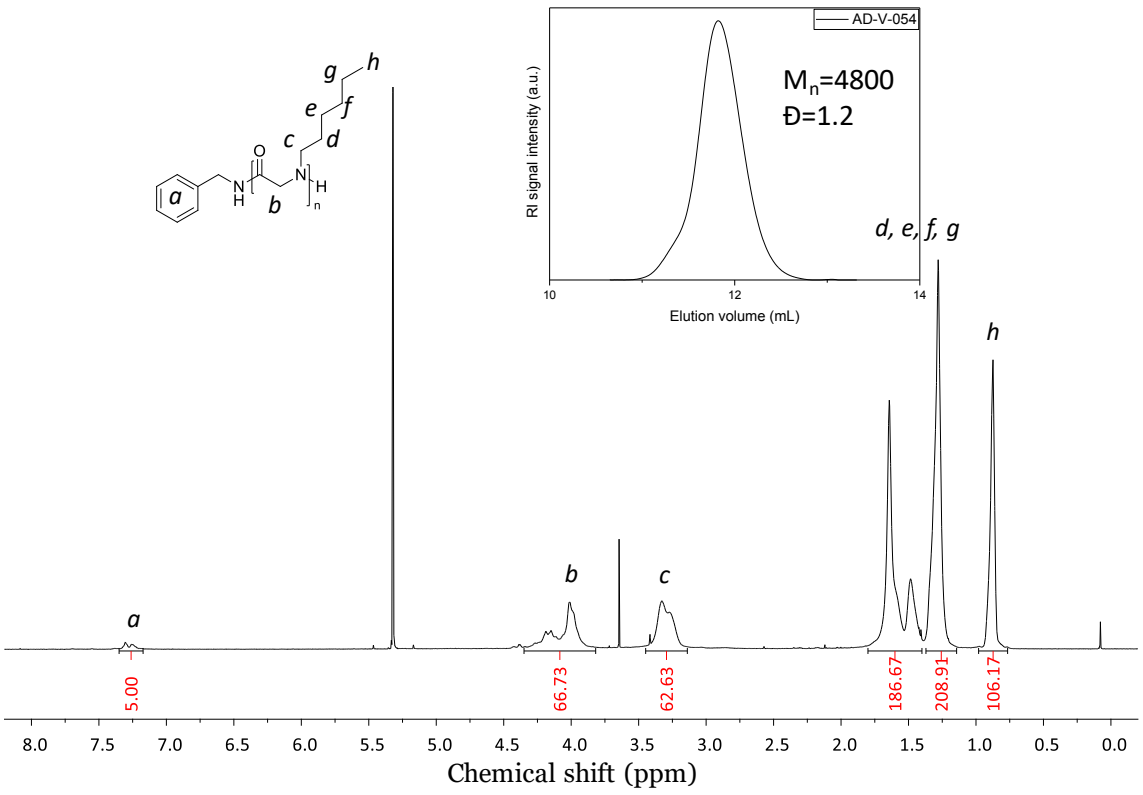


Figure A.12: ^{1}H-NMR (CD_2Cl_2 δ 5.32) of poly-ethyl-N-glycine and GPC eluogram in NMP (PS standards).

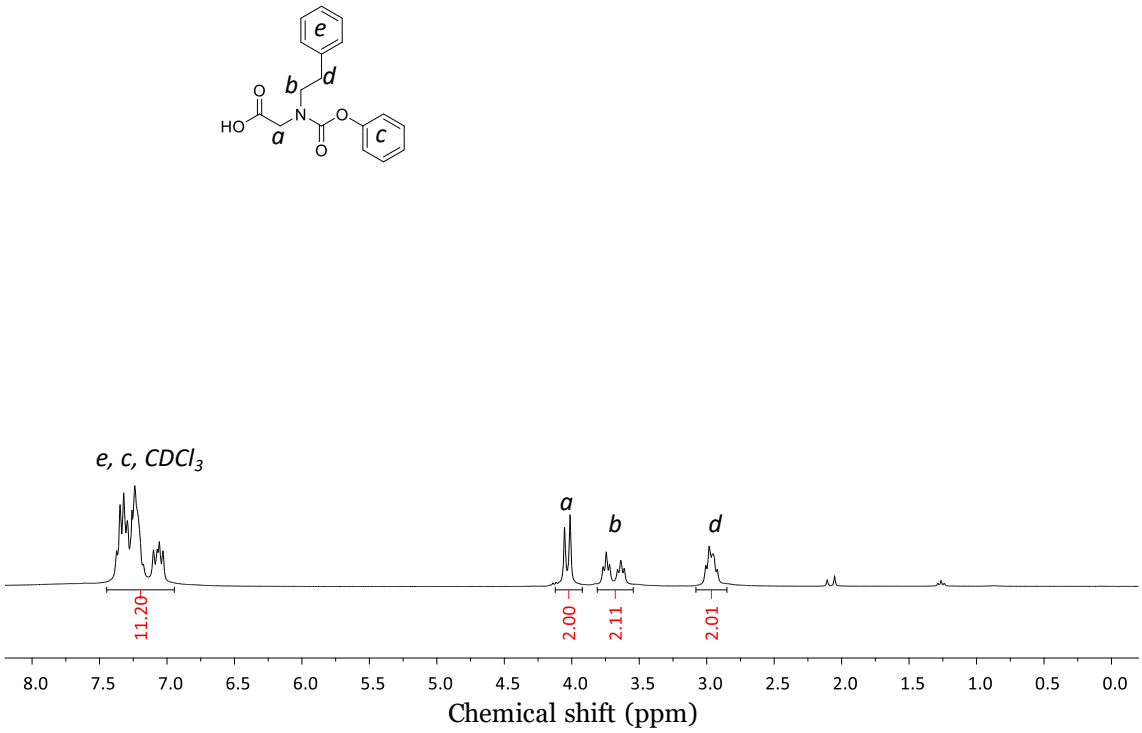


Figure A.13: ^{1}H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-phenethyl-N-glycine.

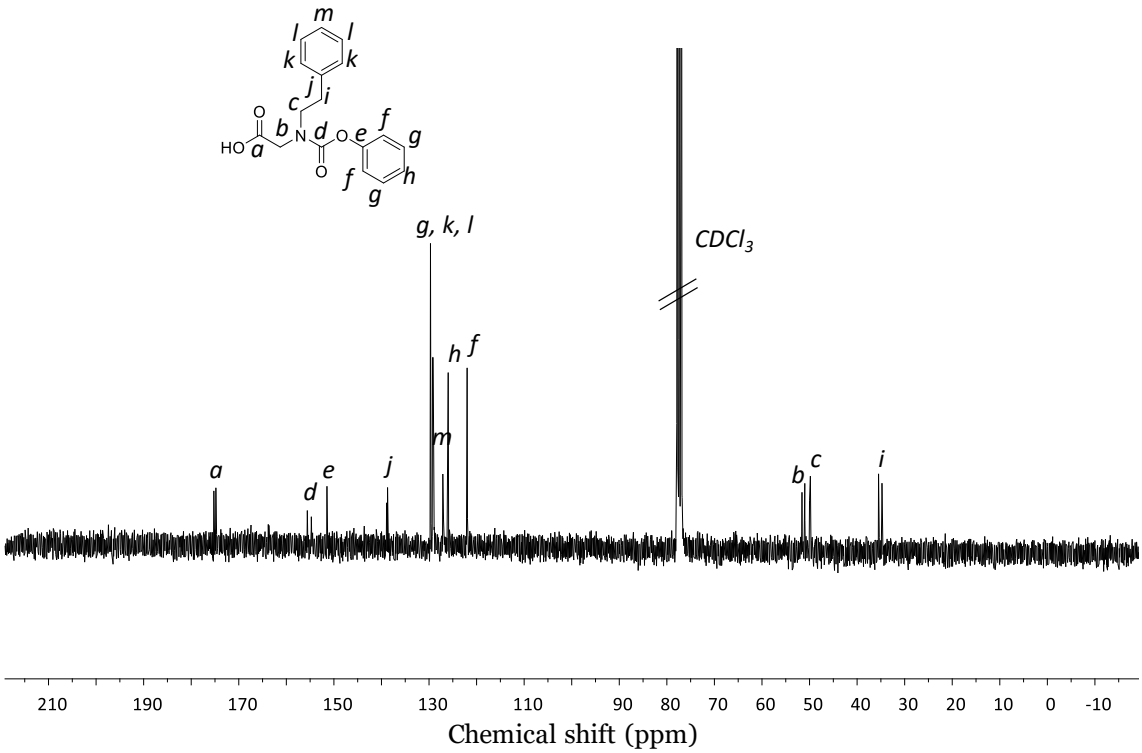


Figure A.14: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-phenethyl-N-glycine.

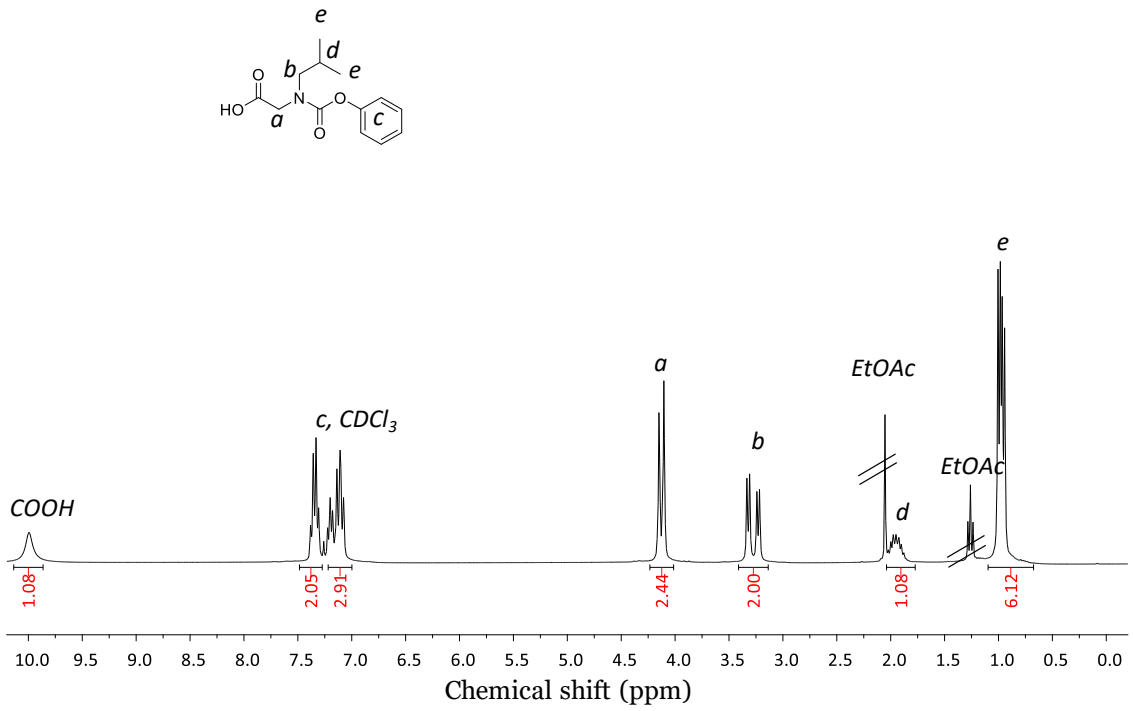


Figure A.15: ^{1}H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-isobutyl-N-glycine.

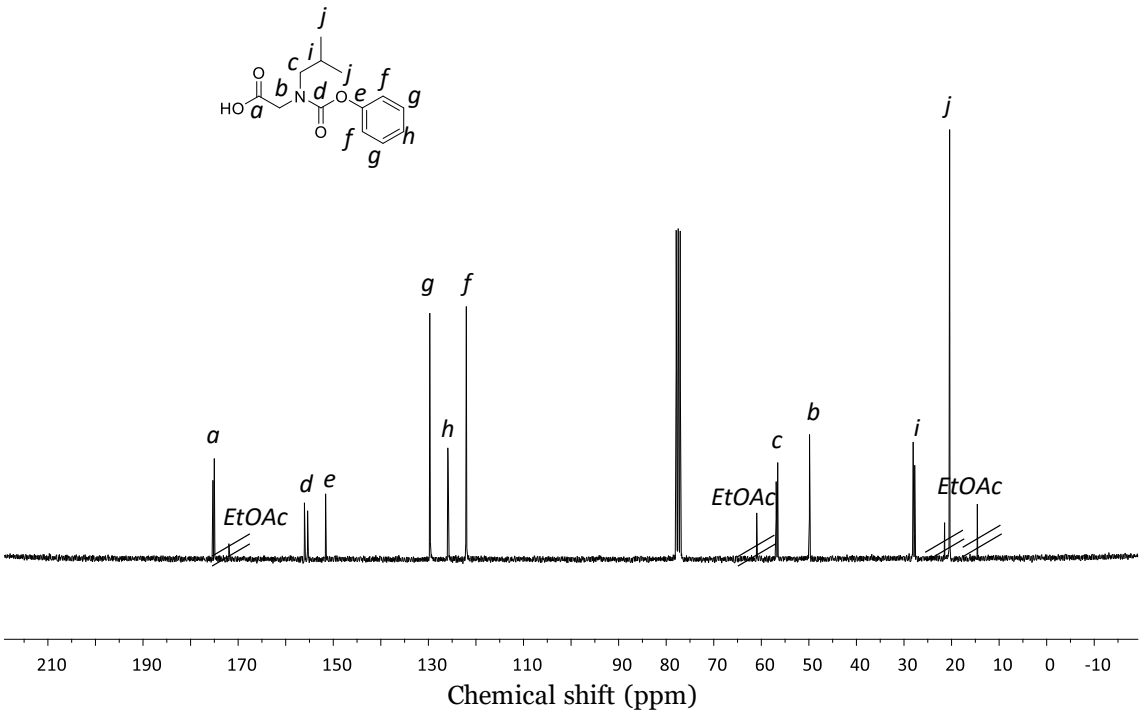


Figure A.16: ^{13}C-NMR spectrum ($CDCl_3$, δ 77.16) of Poc-isobutyl-N-glycine.

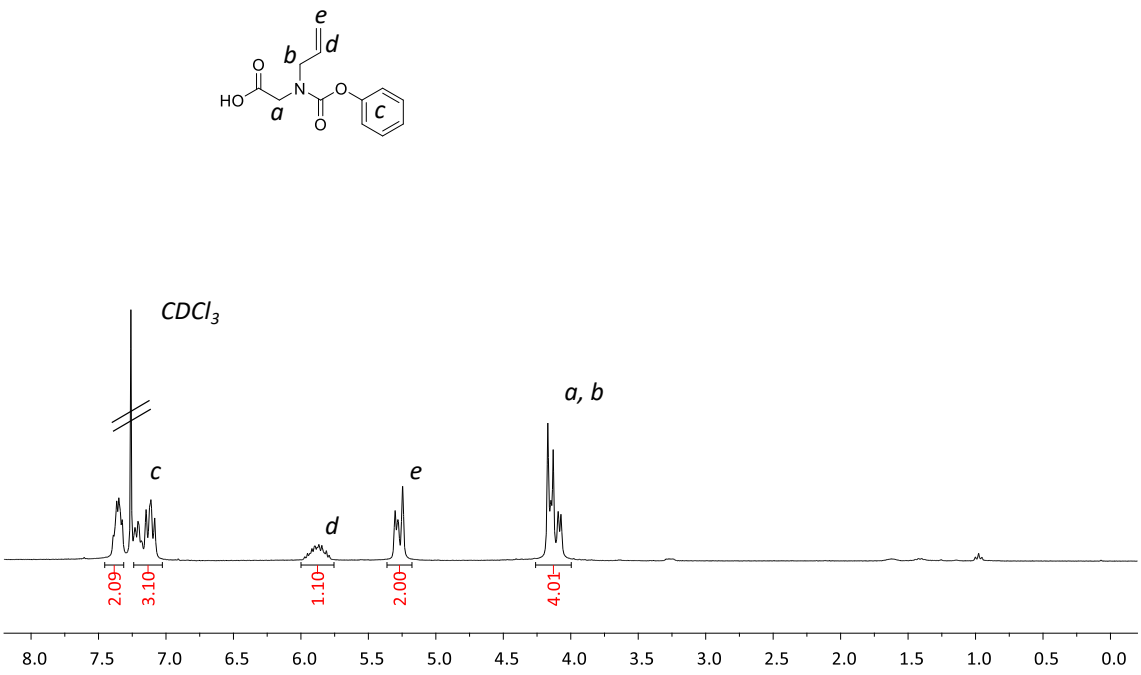


Figure A.17: ¹H-NMR spectrum ($CDCl_3$, δ 7.26) of Poc-allyl-N-glycine.

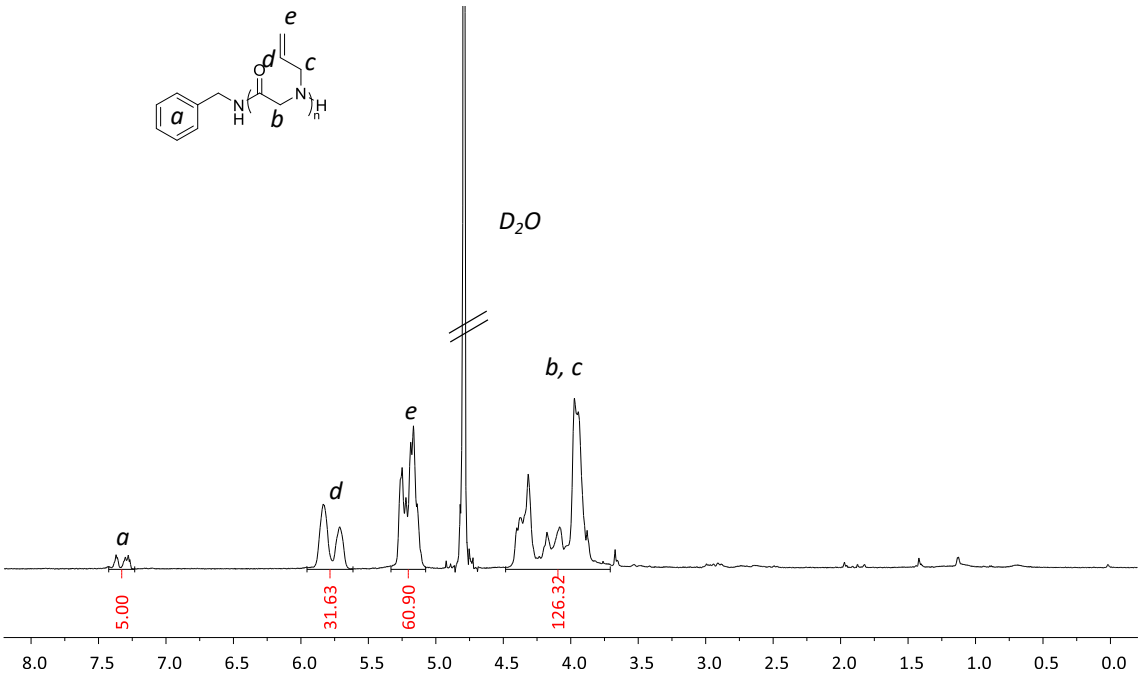


Figure A.18: ¹H-NMR (D_2O δ 4.79) of poly-allyl-N-glycine.

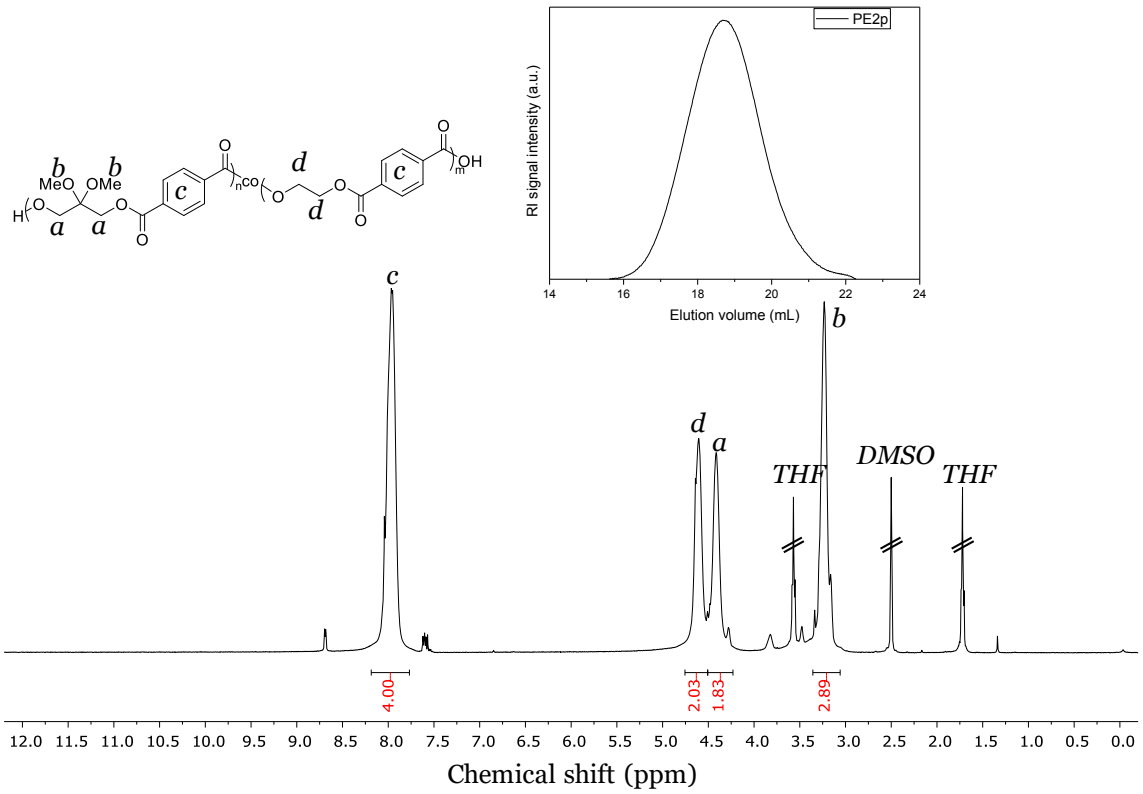


Figure A.19: ^{1}H-NMR (DMSO-d6 δ 2.50) of PE2p and GPC eluogram in NMP (PS standards).

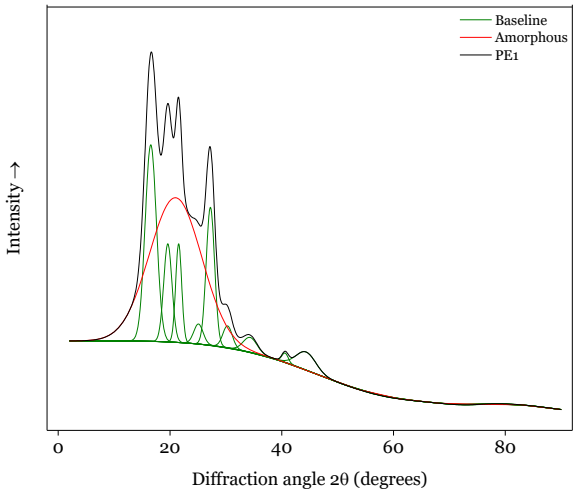


Figure A.20: XRD diffractogram of PE1 with fitted curves for the calculation of its degree of crystallinity (DOC).

B. List of Tables

C. List of Abbreviations

ADMET	Acyclic diene metathesis
AMM	Activated monomer mechanism
BnCN	Benzonitrile
BTZ	Bortezomib
CALB	Candida antarctica lipase B
Đ	Dispersity
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DHA	Dihydroxyacetone
DIPEA	Diisopropylethylenamine
DMAc	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DOC	Degree of crystallinity
DP	Polymerization degree
DPC	Diphenyl carbonate
DSC	Differencial scanning calorimetry
FDCA	2,5-Furandicarboxylic acid
FT-IR	Fourier-transform infrared spectroscopy
GPC	Gel permeation chromatography
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMF	5-Hydroxymethylfurfural
LCST	Lower critical solution temperature
L-DOPA	L-3,4-Dihydroxyphenylalanine
MALDI-ToF	Matrix-assisted laser desorption/ionization-Time of flight
MeCN	Acetyl chloride
MeOH	Methanol
NAM	Normal amine mechanism
NCA	*N*-carboxy anhydride
NHC	*N*-heterocyclic carbenes
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NTA	*N*-thiocarboxyanhydride

P4HB	Poly-4-hydroxybutyrate
PCL	Poly(ε-caprolactone)
PE	Polyethylene
PEF	Poly(ethylene 2,5-furandicarboxylate)
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PET	Polyethylene terephthalate
PHAs	Polyhydroxyalkanoates
PHBHV	Poly(hydroxybutyrate-co-hydroxyvalerate)
PLA	Poly(lactic acid)
Poc	*N*-phenoxycarbonyl
PS	Polystyrene
PVB	Polyhydroxybutyrate
PVC	Polyvinyl chloride
ROMP	Ring-opening metathesis polymerization
rt	Room temperature
SEM	Scanning electron microscopy
TBAOH	Tetrabutylammonium hydroxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tg	Glass transistion temperature
THF	Tetrahydrofuran

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I would like to thank Prof. Dr. Dr. h. c. Markus Antonietti for giving me the chance to conduct the research for my PhD. Additionally, I would like to thank Prof. Dr. Helmut Schlaad for being a knowledgeable and supportive supervisor, full of understanding for his students. I would also like to thank Prof. Dr. Andre Laschewsky for sharing some of his vast knowledge on polymers with us in our seminars. I would like to thank all of my group (Aleks, Andreas, Anna, Charlotte, Felix, Ina, Sascha, Scott, Sebastian, Tapas) and, in particular, Sarah Brosnan who was an incredible supervisor, even for a short time, teaching by example and keeping up her excitement even when nothing seemed to work as planned. Special thanks also go to Marlies Gräwert, Irina Shekova, Olaf Niemeyer, Rona Pitschke, and Sylvia Pirok for their help.

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