CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS

Cristina Lluch Porres

Dipòsit Legal: T.182-2014

Cristina Lluch Porres

Click and Click-type chemistries in castor and sunflower oil-based monomers and polymers

PhD Thesis

Supervised by Dra. Marina Galià i Clua and Dr. Gerard Lligadas i Puig

Departament de Química Analítica i Química Orgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona 2013

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

UNIVERSITAT ROVIRA I VIRGILI

Departament de Química Analítica i Química Orgànica

c/Marcel·lí Domingo, s/n

Campus Sescelades

43007, Tarragona

Telf. 977 559 769

Fax. 977 558 446

Marina Galià i Clua, catedràtica d'Universitat, i Gerard Lligadas i Puig, professor lector, ambdós del Departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili,

Fem constar:

Que aquest treball, titulat "Click and Click-type chemistries in castor and sunflower oil-based monomers and polymers", que presenta Cristina Lluch Porres per a l'obtenció del títol de Doctor, ha estat realitzat sota la nostra direcció en el Departament de Química Analítica i Química Orgànica d'aquesta Universitat i que acompleix els requeriments per poder optar a la Menció Europea.

Tarragona, 9 de setembre de 2013

Dra. Marina Galià i Clua

Dr. Gerard Lligadas i Puig

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Table of Contents

Chapter 1

Click Chemistry and Polymer Science

This chapter discusses the contribution of Click Chemistry in the specific field of Polymer Chemistry and especially in those polymers prepared from vegetable oils and fatty acids as raw materials.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

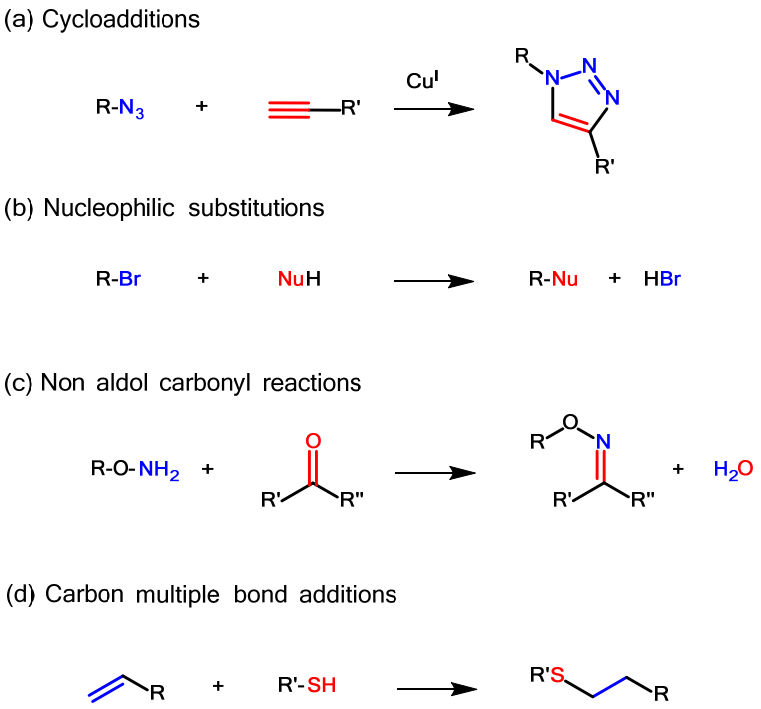
1.1. The Click chemistry concept

The introduction of the Click chemistry concept by Sharpless in 2001 was the starting point of the paradigm shift that chemistry has experienced in the last decade.[1]

The main vision of this research group was to simplify to the maximum the drug discovery process which has been traditionally slow, costly and labor intensive. An inspiration for their research was Nature's strategy of generating complex bio(macromolecules) (i.e. nucleic acids, proteins and polysaccharides) by simply joining small molecules together (nucleotides, aminoacids and sugars) via carbon-heteroatom linkages. Set this on their minds, they identified a toolbox of chemical transformations that undergo simple "fusions" to create new molecules, and coined them as Click reactions. They also established a set of stringent criteria that reactions should comply to be considered as Click:

"The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification -if required- must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions... Click processes proceed rapidly to completion and also tend to be highly selective for a single product: we think of these reactions as being "spring-loaded" for a single trajectory".[1]

These stringent requirements are only met by few selected reactions, which originate from four main classes of reactions: (a) cycloadditions of unsaturated species, (b) nucleophilic substitutions, (c) carbonyl reactions of the non-aldol type and (d) additions to carbon-carbon multiple bonds (Scheme 1).



Scheme 1. Examples of the four categories of Click reactions (a) Cu^{I}- catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes (CuAAC); (b) halogen nucleophilic substitution; (c) O-hydroxylamine–carbonyl addition and (d) thiol addition to alkenes.

While initially developed to meet the demands of drug discovery,[2] Click philosophy rapidly received a warm welcome by researchers in nearly all areas of modern chemistry[3] including bioconjugation,[4] nanotechnology[5] and especially polymer science,[6] providing new opportunities in all these areas.

1.2. Strategies Based on Click Reactions in Polymer Chemistry

Click chemistry reactions were rapidly integrated into the field of polymer chemistry. The distinctive features of these reactions, such as high efficiency, selectivity and easy purification, are of strong practical value in this discipline.

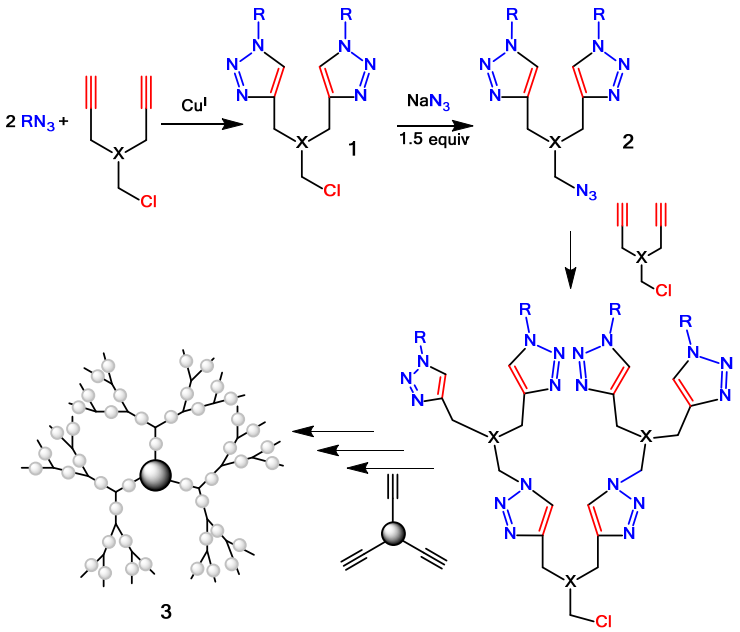
The efficiency of chemical transformations is very important in the macromolecular framework. If the functionalization reaction is intended to take place at multiple sites within a single macromolecule or to the polymer end-groups, inefficiency leads to a final product in which reacted units are covalently linked to unreacted units. In these cases, no simple methods of separation lead to pure products, and the only manner to ensure purity is achieving quantitative transformations. Likewise, orthogonality is also of major concern. If multiple transformations on a single polymer are desired, an ideal Click functionalization procedure would allow simultaneous reactions to occur with no interference.

As these characteristics are of special relevance in macromolecular synthesis, whereas in other fields probably not as much, the requirements of a reaction to achieve Click status were adapted to this specific field.[7] According to the revisited concept, Click reactions should use equimolar amounts of reagents to avoid complex purification techniques. For the same reason, reactions should reach very high conversions. Moreover, the reactions should proceed in a reasonable timescale and require no tedious fine-tuning of reaction conditions. These outlined requirements together with the unquestionable modularity, wide scope and chemoselectivity should be fulfilled. Satisfying or not these criteria would differentiate a Click reaction from just an efficient or Click-type reaction.

Considering these aspects, it is not surprising that the first application of the emerged Click technologies was in the synthesis of dendrimers, as the preparation of these structures demands a high degree of functionalization and easy purification.

In 2004, Wu and coworkers prepared a variety of AB_2 monomers based on terminal alkynes and alkyl halides (Scheme 2).[8]

CuAAC was performed using alkyne and azide in equimolar ratio in presence of $CuSO_4$ (2-5% mol) and sodium ascorbate (5-10% mol) in a 1:1 mixture of water and tert-butyl alcohol at room temperature (RT), generating the desired bistriazoles **1** in near quantitative yields. First generation dendron **2** was efficiently obtained through the subsequent conversion of the pendant primary chloride to azide at 60ºC using 1.5 equiv of NaN_3. Following this strategy, they constructed each generation and obtained up to fourth-generation well-defined dendrimers **3** in high yielding manner (>90%) and with different chain-end groups (R) and internal repeating units (X).



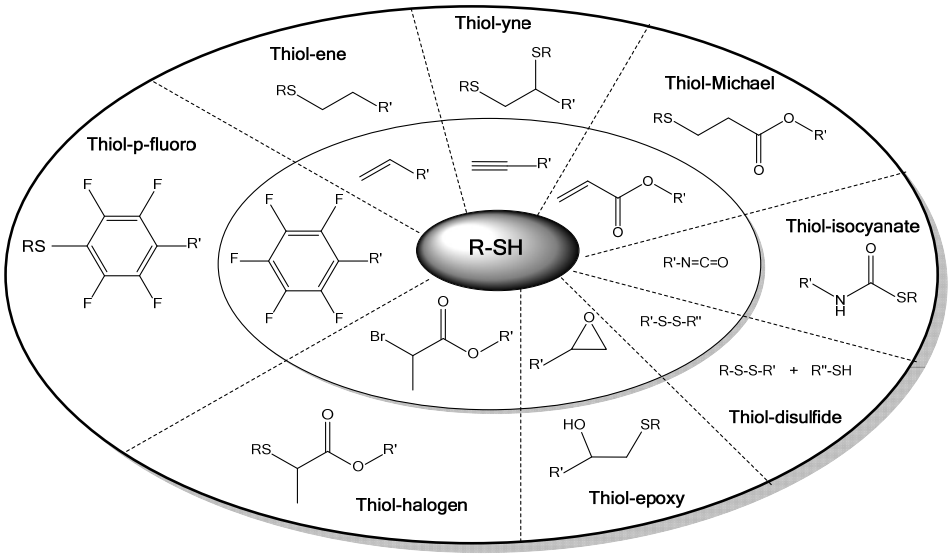
Scheme 2. Convergent Dendrimer Synthesis using CuAAC.

Since then, the application of CuAAC in polymer chemistry was extended and a wide range of functional complex materials have been synthesized.[9] The impressive efficiency and broad utility of CuAAC encouraged researchers to evaluate the potential of other reactions that possess Click characteristics. Besides this, the potential toxicity of the Cu metal catalyst is considered a major issue when the products are targeted to be used for biological applications, and thus efforts moved to the development of metal-free variation of this reaction[10] but also other Click reactions.[11]

Hence, other cycloaddition reactions, such as Diels Alder (DA) reactions attracted great interest in this field due to the high efficiency and unique reversibility features.[12] Indeed, all of the four outlined categories of Click reactions, to a greater or lesser extent, have been applied in the field of polymer chemistry. But with no doubt, reactions involving thiols, especially thiol-ene[13] and thiol-yne[14] chemistries, offers the greatest versatility and have been the most widely exploited. Indeed, a new nomenclature has been used to refer to this expanding toolbox of reactions, being generalized as thiol-Click reactions.[15] Certainly, thiols can react to high yields and under benign conditions with a wide range of chemical species through radical mediated or base/nucleophile-initiated processes (thiol-ene and thiol-yne) or nucleophilic substitution reactions (thiol-epoxy, thiol-isocyanate and thiol-halogen) at extremely fast reaction rates.

Nonetheless, the high reactivity and efficiency that make them so attractive can be also considered disadvantageous due to susceptible multiple simultaneous reactions. However, selective reaction with a particular substrate can be promoted using specific catalysts or photoinitiators, as these reactions follow different reaction mechanisms.

Also of particular importance is the commercial availability of the reagents involved in these reactions, from thiols to activated and unactivated double bonds, as well as organic bromides, isocyanates, etc. In Scheme 3 are depicted all the diverse thiol-Click reactions.



Scheme 3. Schematic illustration of thiol-Click reations.

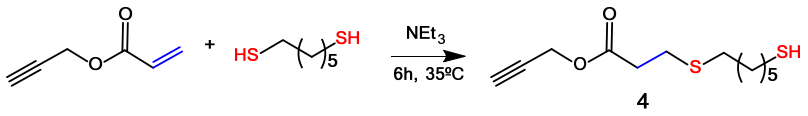
Click and Click-type chemistries have been implemented in all levels of polymer science, having an important role in the functionalization of simple starting materials for monomer synthesis purposes, but also in their polymerization and even in the modification of polymers.[16] Thus, the main fields in which they are involved can be encompassed in these three categories: monomer synthesis, polymerization and post-polymerization functionalization.

In the following section, general and relevant examples in each category will be presented to provide context of the different possibilities that Click chemistry reactions offer in the field of polymer chemistry.

1.2.1. Monomer Synthesis

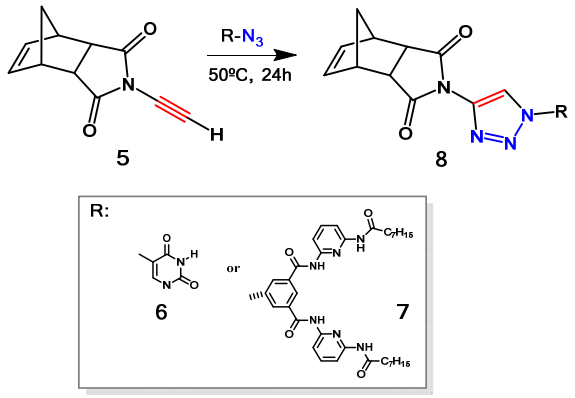
In the macromolecular field, the properties and performance of the polymers is basically dictated by the nature of their building blocks. In this sense, the structure and functionalities of the monomers should be judicious chosen according to the targeted polymer. Certainly, the availability of natural and/or synthetic monomers is wide but limited, and often it is necessary to functionalize the starting materials (a) to introduce polymerizable moieties or (b) to render them specific features. In this context, the use of Click reactions hold great interest as novel molecules can be synthesized in quantitative yields and with a reduced number of reaction and purification steps.

One successful example applying the first strategy was reported by Han and coworkers (Scheme 4).[17]They synthesized a new AB_2 monomer **4** for the synthesis of hyperbranched polymers, through thiol-Michael addition of hexanedithiol to propargyl acrylate using equimolar amounts in the presence of triethylamine (NEt_3) as catalyst. After 6 hours at 35ºC the reaction was complete and the resulting monomer, without further purification, was directly polymerized by thiol-yne reaction. This approach is clearly advantageous respect to the classical preparation of AB_2 monomers for the synthesis of hyperbranched polymers, in which low efficient conventional reactions are involved resulting in impure and low yielding monomers.



Scheme 4. Synthesis of an AB_2 monomer through Thiol-Michael addition.

As mentioned above, Click reactions have been also applied in the modification of monomers to render them specific features. Binder and Kluger used this strategy in the functionalization of alkyne bearing 7-oxynorbornene monomers **5** with azido compounds bearing hydrogen bonding donor/acceptor moieties **6** and **7** (Scheme 5).[18] The reactions proceeded at 50ºC in DMF using bromotris(triphenylphosphine)copper (I) and N,N-diisopropylethylamine as the catalytic system obtaining quantitative conversions after 24h. The library of monomers **8** obtained was subsequently polymerized by Ring-Opening Metathesis Polymerization (ROMP) furnishing self-assemble complex polymers.

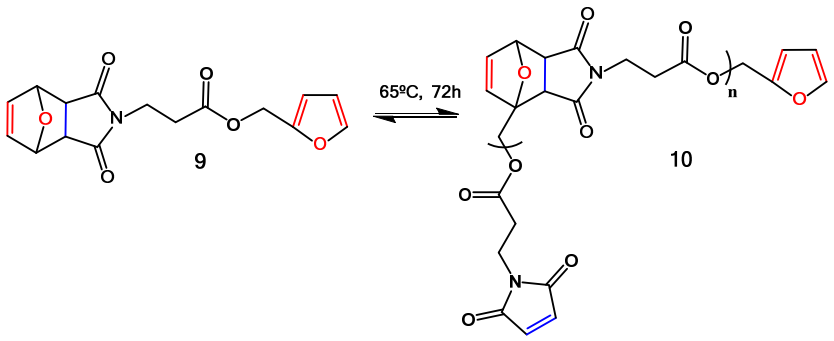


Scheme 5. CuAAC Click functionalization of alkyne bearing 7-oxynorbornenes.

1.2.2. Polymerization

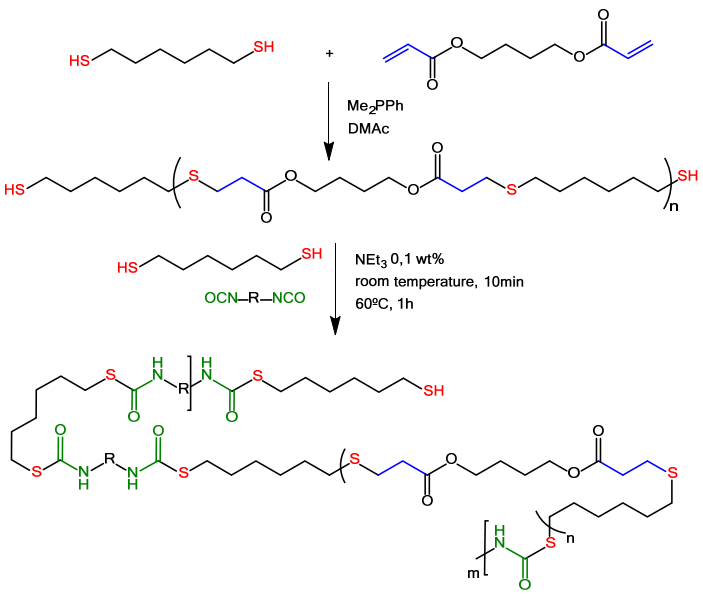
Exploration of efficient polymerization reactions is a subject of enduring interest in the area of polymer chemistry. Most, if not all polymerization processes have been developed from known organic reactions of small molecules. Hence, the advantageous features of Click chemistry reactions prompted polymer chemists to use Click reactions as powerful polymerization techniques. Indeed, Click reactions have been proven effective for the construction of a broad range of linear and crosslinked polymers.

For example, DA polymerization has been explored for the preparation of linear polymers possessing thermoreversible, mendable and recycling features. Gandini and coworkers have widely investigated DA reactions between furan and maleimides.[19] Recently, they reported the polycondensation of furan-maleimide monomers by means of DA reaction (Scheme 6). Monomer **9** was used with the maleimide group protected in the form of a furan DA adduct in order to obtain a stable monomer and thus avoid premature polymerization during the synthesis, purification and storage.[20] Stepwise polymerization was conducted at 65ºC for 24h, obtaining low molecular weight oligomers **10** (> 2000 g/mol), and thermal reversibility was observed at 110ºC.



Scheme 6. DA polymerization of a furan-maleimide monomer.

Shin and coworkers described the synthesis of novel segmented polythiourethane elastomers employing a combination of phosphine catalyzed thiol-Michael chemistry along with NEt_3-catalyzed thiol-isocyanate coupling (Scheme 7).[21] First, reaction of slight excess of 1,6-hexanedithiol with butanediol diacrylate under dimethylphenylphosphine (Me_2PPh) catalysis in dimethylacetamide (DMAc) resulted in the rapid and quantitative formation of thiol-terminated oligomeric species as soft segment (*Mn*=1000-3000 g/mol). The molecular weight of such oligomers was readily controlled by varying the ratio of both monomers. Subsequent reaction of the prepolymer and hexanedithiol with 0,1 wt% NEt_3 in DMAc with a range of commercially available diisocyanates yielded quantitatively, the targeted segmented polythiourethanes.

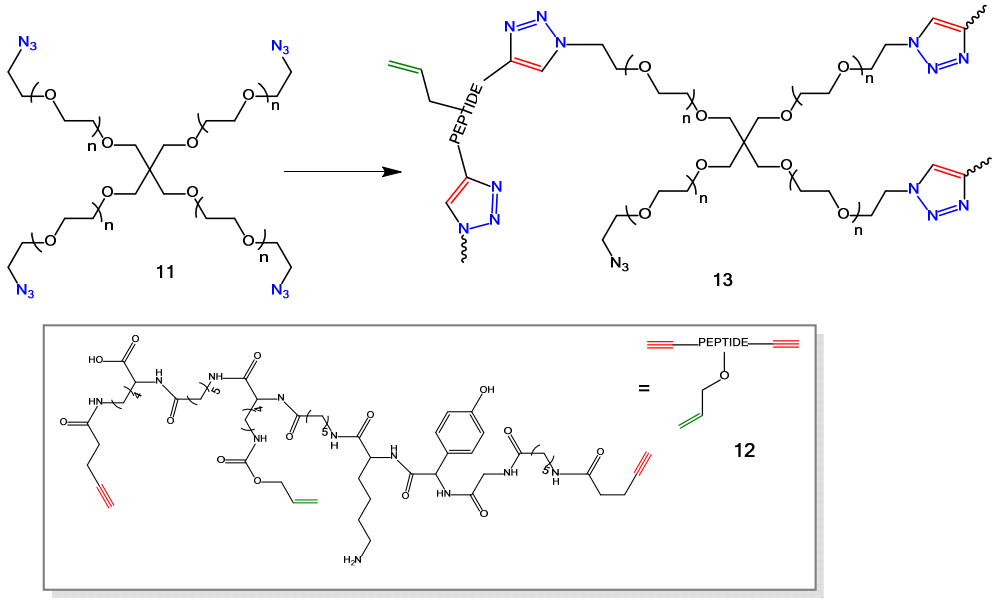


Scheme 7. Synthetic procedure for segmented polythiourethane elastomers.

The high efficiency of Click reactions has been also exploited in the synthesis of crosslinked systems. The attractive features of such reactions have allowed achieving much greater degree of control of the polymerization, leading to ideal networks that can attain superior mechanical properties compared with the conventional networks. Moreover, the high tolerance of these reactions to different functional groups allows the incorporation of active moieties in the crosslinked matrix that significantly impact the properties of the final material.

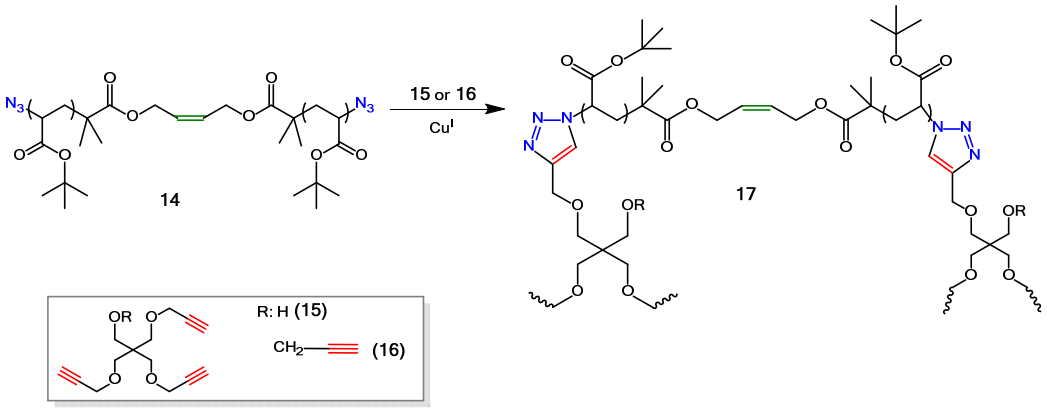
Polizzoti and coworkers exploited the specificity and fidelity of Click reactions to synthesize hydrogels with controlled architectures and improved mechanical properties.[22] They utilized a tetraazide-multiarm polyethylenglycol (PEGtetraazide) **11** and diacetylene-functionalized allyl ester containing polypeptides **12** to generate well-defined polyethylenglycol-peptide hydrogels **13** (Scheme 8). Hydrogel formation was facilitated via reaction of the PEGtetraazide with 2.0 equiv of the photoreactive crosslink at RT and using 0.5 equiv of copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) and 5.0 equiv of sodium ascorbate as catalytic system. Under these conditions, hydrogels were formed within minutes. Taking advantage of the orthogonality of CuAAC reaction, the remained intact alkenes were used in a subsequent step to pattern a fluorescently labeled cysteine

containing peptide on the hydrogel surface by photochemical thiol-ene coupling. This approach provided a facile way to independently tune the 3D chemical and physical properties of the material, which is important for applications directed at controlling cell interactions and cell function.



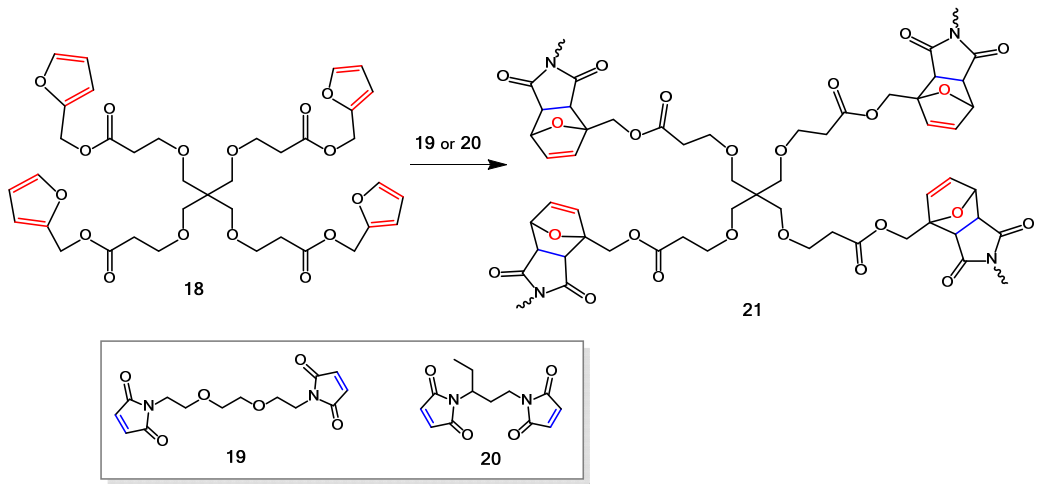
Scheme 8. Photo-functionalizable hydrogels synthesized through CuAAC crosslinking.

In another example, Johnson and coworkers reported the preparation of degradable networks.[23] Thus, they synthesized an α-ω-diazido-telechelic poly(t-butyl acrylate) **14** (M_n=14100 g/mol; M_w/M_n=1.12) (Scheme 9) by Atom Transfer Radical Polymerization (ATRP) methods which was further crosslinked into gels **17** by CuAAC reaction with trivalent and tetravalent acetylenes **15** and **16**. Complete crosslinking reaction was achieved in only 5 min at 80ºC, using as catalytic system CuBr/ N,N,N′,N′′,N′′-pentamethyldiethylenetriamine (PMDETA) with sodium ascorbate and N,N′-dimethylformamide (DMF) as solvent. An interesting structural feature in this system is that the initial telechelic prepolymer contained an internal alkene, and thus under such mild and efficient polymerization conditions, the alkene moieties were also present in the final polymer. Then, ozonolysis was employed to degrade the network into soluble polymeric byproducts by selective cleavage of these alkenes.



Scheme 9. Degradable polymer networks through CuAAC polymerization.

DA reaction has been also used to prepare crosslinked networks. By careful choice of the diene and dienophile, Chen and coworkers developed systems showing thermally reversible bonding, which allow for the self-healing of cracks or fractures by a simple heating and cooling cycle (Scheme 10).[24] The heating cycle serves to initiate retro-DA reactions leading to a decrease in crosslink density, and upon cooling, the crosslinks are reformed in a less mechanically strained and more energetically favorable configuration. Thus, polymerization of tetrafuran monomer **18** and bismaleimides **19** and **20** at 115-120ºC for 20 min yield thermally re-mandable polymers **21**, exhibiting a crack-healing recovery as much as 83% of the polymer's original strength.



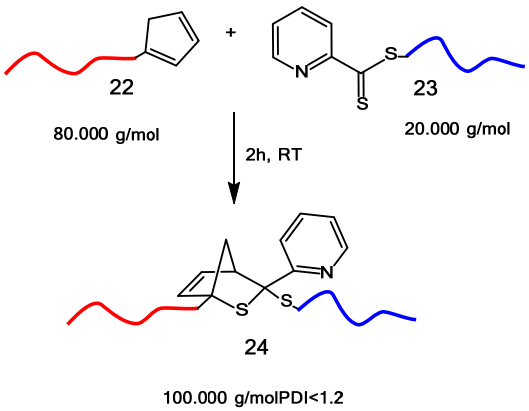
Scheme 10. Formation of self-reparable networks using reversible DA reactions.

1.2.3. Post-polymerization modification

A traditional approach for generating new materials has been the design of one polymer for one particular application. In order to streamline the discovery process, a more efficient strategy would be to design versatile materials capable of successful performance in diverse applications. Polymers that contain functional groups are very versatile as they can be modified to meet specific requirements. Moreover, functional groups that can be modified by highly selective and efficient reactions are of outmost importance to obtain high degrees of functionalization and avoid side products.

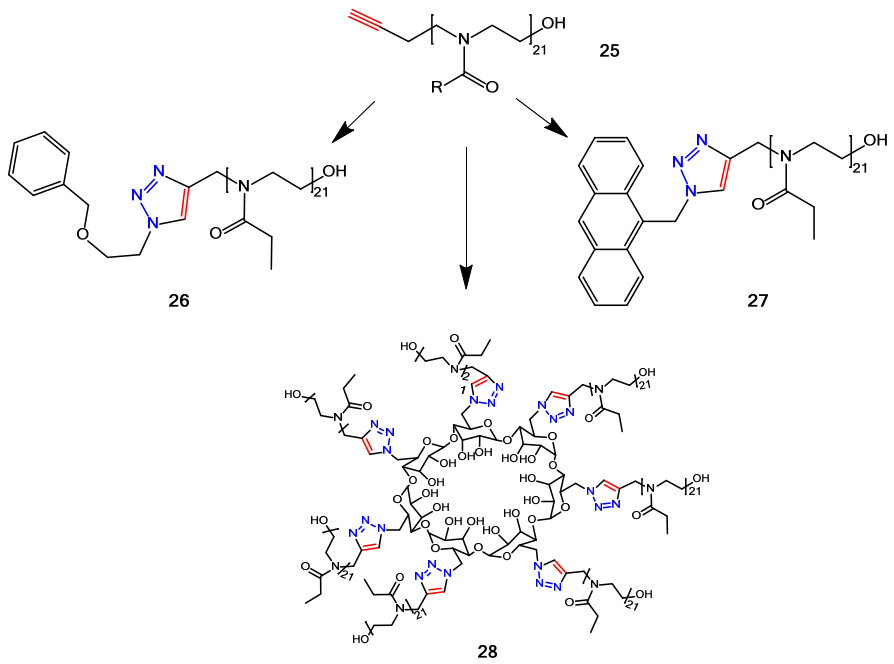
Thus, Click reactions have also played an effective role in this particular area. Modification of the polymer chain-ends has been widely applied in polymers with well-defined end-groups such as those prepared by controlled/living polymerization techniques.[25] Through this approach, small moieties or even polymer chains can be conjugated through Click reactions.[26] Indeed a highly efficient methodology to prepare block copolymers consists in the conjugation of the end-groups of two or more polymers by Click reactions.

In a noteworthy contribution, Inglis and coworkers were able to obtain a well-defined block copolymer **24** (Scheme 11), conjugating a polystyrene block **22** (80.000 g/mol) and a poly(isobornyl acrylate) block **23** (20.000 g/mol) in a 1:1 molar ratio stoichiometry at RT in only 2h, without any added catalyst.[27] The conjugation involved a hetero Diels Alder (HDA) mechanism with the sulfur-carbon double bond end-groups of **23** (prepared by Reversible Addition-Fragmentation chain Transfer (RAFT)) as dienophile and the cyclopentadienyl end groups of **22** (prepared by ATRP) serving as diene. This Click coupling is really advantageous as no end group transformation of the RAFT chain transfer is necessary and the Click reaction is directly performed to the polymer end-group. Besides, the necessary diene compounds were reported to be easily accessible by quantitative functionalization of polymer bearing electrophilic end-groups (e.g. polymers bearing a terminal bromide moiety obtained by ATRP) with sodium cyclopentadienide. Thus, RAFT-HDA chemistry has proved to be highly efficient by using 1: 1 stoichiometry between the reactants, a characteristic that becomes highly desirable as purification of macromolecular clicked products is often problematic.



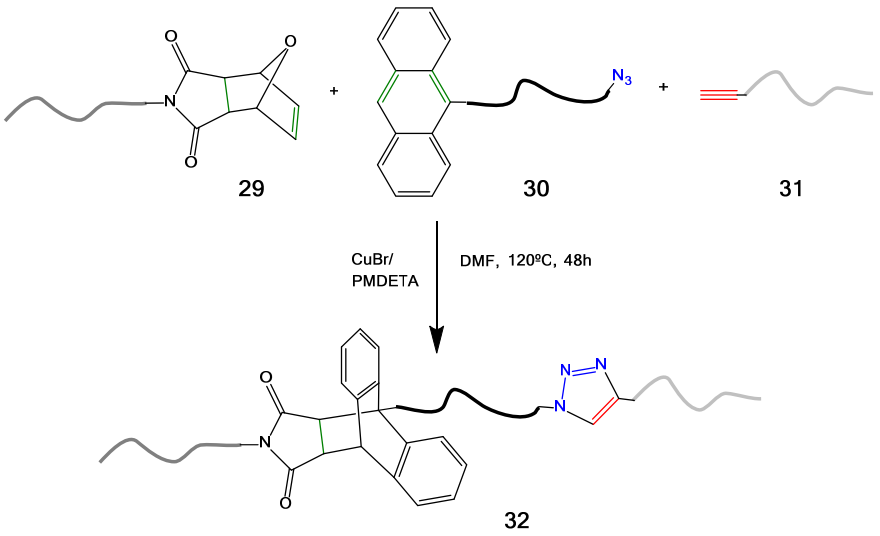
Scheme 11. Schematic illustration of RAFT-HDA coupling between two functional blocks.

The use of functional initiators is also an alternative approach to incorporate functionalities at the end groups of the polymer.[28] Nonetheless, care should be taken to avoid interference of the introduced functionalities during the polymerization, so often protective groups are used. An example in which the functional initiator is successfully used with no need of protective groups was reported by Schubert and coworkers.[29] The authors prepared acetylene end-functionalized poly(2-oxazoline)s **25** (Scheme 12) by using 3-butynyl toluene-4-sulfonate and propargyl toluene-4-sulfonate as functional initiators. They demonstrated the livingness of the polymerization with the latter initiator, under microwave irradiation at 140ºC in acetonitrile. In contrast, polymerization initiated with the former resulted in slow initiation, and polymers with broad molecular weights distributions were obtained. Post-polymerization modification of these polymers was evaluated on the basis of CuAAC reaction with benzyl-2-azidoethylether and 9-azidomethylanthracene using excess of azide (1 to 1.5 equiv) at RT in presence of Cu^{I} giving a benzyl-containing polymer **26** and an anthracene bearing polymer **27**. Moreover, the acetylene-bearing polymer **25** was also coupled to a star polymer (heptakis-azide-β-dextrin) using an excess of the former (1 to 9 equiv) to obtain the copolymer **28**.



Scheme 12. 1,3-Dipolar cycloadditions between acetylene-functionalized poly(2-ethyl-2-oxazoline) and different azide compounds.

Double Click strategies involving polymeric precursors with wide range of functional groups, have been also applied for the synthesis of complex macromolecules. In this context, Durmaz and co-workers utilized the combination of CuAAC and DA reactions to synthesize linear ABC triblock copolymers in a one pot reaction (Scheme 13).[30] The strategy benefits from the orthogonal nature of the azide-alkyne and anthracene-maleimide cycloaddition. As middle block, they utilized a hetero-telechelic polystyrene **30**, containing an anthracene and an azide functional group at the chain termini. Treatment of this polymer with a furan protected maleimide-terminated poly(methyl methacrylate) **29** and an alkyne-terminated poly(ethylene glycol) or poly(3-caprolactone) **31** provided the linear triblock copolymers **32** in a one-pot methodology. In the preparation of the triblock copolymer slight excess amounts of **29** and **31** were used compared to **30**, because they are completely soluble in methanol in the range of the molecular weights studied and therefore, are easily removed by precipitation. The reaction was carried out in the presence of CuBr/PMDETA in DMF at 120 ºC for 48 h and it was observed a coupling efficiency of 89-91%.

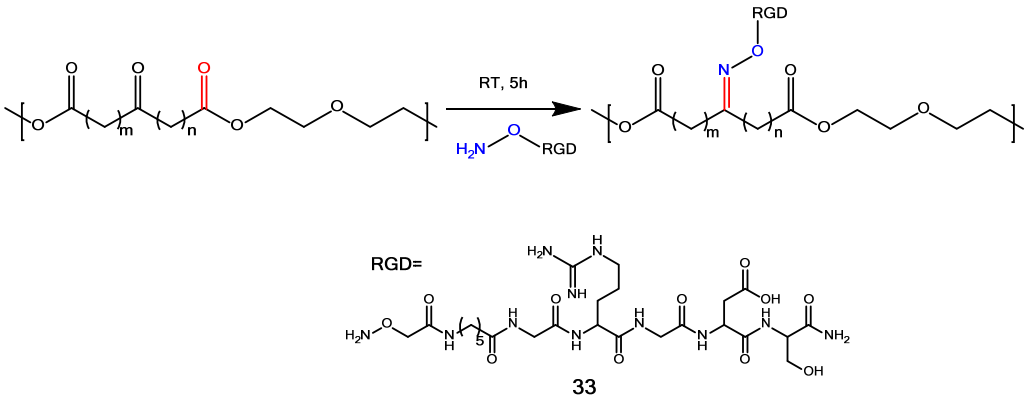


Scheme 13. Orthogonal one-pot synthesis of ABC triblock copolymers by simultaneous DA and CuAAC.

Modification of polymers can be also carried out on the functional groups present on their main chain. In this case functionalities are usually incorporated using functional monomers. The use of clickable monomers for the synthesis of functionalized polymers is an approach that offers a high degree of functionalization. Homopolymerization of a clickable monomer yields a polymer with as many functionalities as the number of repeating units. However, the incompatibility of many reactive functional groups under certain polymerization conditions is often a considerable synthetic challenge. Moreover, steric hindrance is a major issue, and complete post-polymerization functionalization is challenging.

Nonetheless, high degrees of polymer functionalization have been reported using different Click reactions.[31] A straightforward and versatile approach was reported by Barret and coworkers.[32] In their work, they polymerize a series of ketone-containing diacids and diesters with diethyleneglycol to obtain a family of amorphous polyketoesters (Scheme 14). Through the oxime-forming reaction, a wide variety of functionalities were appended onto the biodegradable polymers. For instance, a H_2NO-RGD **33** was attached to the polymer to take advantage of its well-known ability to bind to cell surface integrin receptors and mediate biospecific cell-adhesion and migration.

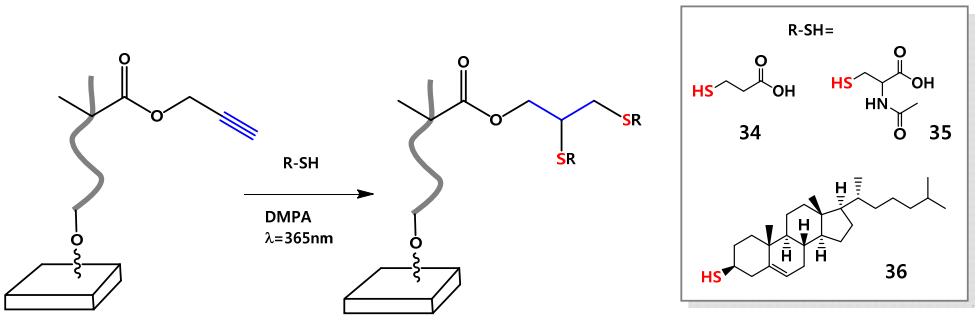
Oxyamine **33** was added in a 50% excess relative to the concentration of the ketones and complete conversion to the corresponding oxime was observed after 5h at RT. On the other hand, by using longer reaction times (10h) complete conversion was achieved using equimolar amount of oxyamine and ketone.



Scheme 14. Polyketoesters functionalization with RGD oxyamine.

Modification of polymeric surfaces is also important in many areas, including the fabrication of microelectronics, optoelectronics and sensors.[33] Besides, modified surfaces also play a key role in various aspects of biological engineering, for example as scaffolds for tissue engineering, stem-cell differentiation and cell culture. Thus, the use of Click reactions to achieve efficient surface modifications of materials has been also a subject of great interest.

Hensarling and coworkers prepared alkyne-containing scaffolds that were subjected to thiol-yne modifications with a variety of thiols to furnish dithiol-functionalized brushes (Scheme 15).[34] Thiols, including 3-mercaptopropionic acid **34**, N-acetyl-L-cysteine **35**, and thiocholesterol **36**, were used to demonstrate the feasibility to obtain polymers with pH responsive surfaces, peptide attachment and to show membrane compatibility, respectively. All thiol-yne reactions were carried out in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) at 365 nm at RT using different excess of thiols.



Scheme 15. Schematic illustration of surface thiol-yne photopolymerization.

In view of the numerous works involving these efficient reactions, Click chemistry can be considered as a well-established tool in polymer science. Nonetheless, its vast potential is unlimited and new avenues are yet to be explored which will facilitate the preparation of increasingly advanced macromolecules.

1.3. Click Chemistry and Plant Oils: Sustainable Polymer Chemistry

As we early introduced, Click chemistry has had a tremendous impact in the field of Polymer Chemistry. The unique synthetic opportunities afforded by the Click chemistry concept have been fully embraced by material scientists for the synthesis of new monomers as well as the development of advanced polymers with increased functionality and unique properties.

Although the high efficiency, atom economy, orthogonality and simplified purification procedures inherent to Click reactions are consistent with the green standards, its combination with renewable resources has not been materialized until recently.

Indeed, the use of renewable resources is identified as a primary driver towards sustainability within the framework of the 12 Principles of Green Chemistry. These Principles were established by Anastas and Warner in 1998,[35] to serve as a guideline for chemists to achieve sustainability in the development of chemical processes.[36]

Today's, polymer production relies almost exclusively on fossil feedstocks. However, due to the depleting fossil resources and the ever increasing crude oil prices, polymers prepared from alternative renewable resources are desirable on the long-term.

Renewable raw materials can offer several advantages over conventional petrochemical feedstocks, such as lowered demand for diminishing crude oil supplies, favorable CO_2 balance, reliable supply, competitive prices and a source of new structurally building blocks with new properties and applications.

Nature offers a broad window of renewable resources which have been already used as precursors of polymeric materials,[37] being the most exploited: polysaccharides, sugars, terpenes and fats and oils.

Polysaccharides, mainly cellulose, starch and chitin, have a remarkable potential to provide unique macromolecular materials.[38] The broad capacity of chemical modification that offers the abundant hydroxyl groups present in these structures (especially by means of esterification and etherification) and the high crystallinity and biodegradability that they display, makes them valuable polymeric building blocks.

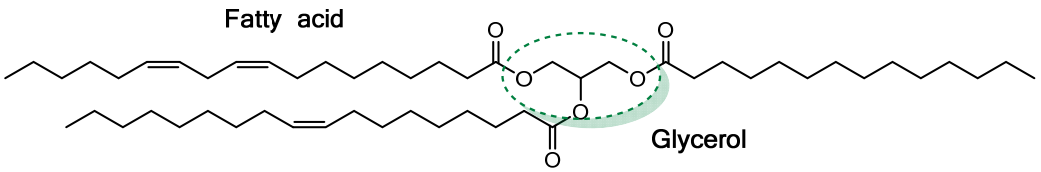
Sugars, as well as their natural oligomers and polymers, also play a fundamental role as precursors to other monomers, namely furan derivatives and lactic acid. In particular, C5 and C6 sugars can be converted into two basic furan monomer precursors: furfural and 5-hydroxymethylfurfural. The interest of these two monomers is related with their dienic character, making them amenable to participate in DA reactions with dienophiles like maleimides. On the other hand, polylactide (PLA) is one of the most prominent examples of biobased and biodegradable polymers, which is obtained from lactic acid.

Terpenes, terpenoids and resin acids are a class of hydrocarbon-rich natural biomass, produced by many plants and trees.[39] They are derived biosynthetically from isoprene units, which consist of five carbon atoms. Due to their high abundance and diverse structures, they have attracted attention as a class of natural products that can be converted into novel and valuable compound building blocks.

Vegetable oils and derived fatty acids, are very attractive raw materials for polymer chemistry, due to their natural abundance, relatively low price, high functionality and

purity.[40] Indeed, oils together with starch, make up the greatest proportion of the current consumption of renewable raw materials in the chemical industry.[41]

Vegetable oils are composed of triglycerides which under hydrolysis yield glycerol and free fatty acids. The general structure of a triglyceride is depicted in Scheme 16.



Scheme 16. Representative structure of a triglyceride.

Glycerol is an important intermediate in the synthesis of a large number of industrial chemicals. The current boom associated with biodiesel production has generated a spectacular rise in glycerol availability and significant efforts are being made to find value-added opportunities to this by-product.[42]

Fatty acids are aliphatic acids with 12 to 22 carbon atoms in a linear chain, some of them are totally saturated, although more interesting for polymer chemistry are those with other functionalities in the main chain. Hence, some fatty acids present double bonds and in less extent other functionalities such as hydroxyl or epoxide groups.

Thus, in the last few years some research groups have focused their research interest in preparing sustainable monomers and polymers derived from vegetable oils and fatty acids, taking advantage of different Click chemistry approaches.[43]

Great part of the work reported has been focused in the exploitation of CuAAC, DA and thiol-ene/yne Click chemistry. With no doubt, thiol-ene chemistry[44] has had the greatest impact, which is obvious considering that many natural vegetable oils and fatty acids present in their structure double bonds. Moreover, the commercial availability of thiols is wide, which also broadens the scope of application.

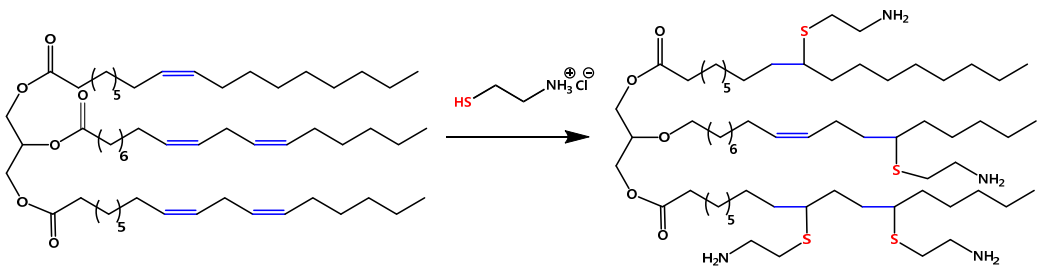
In the previous section we have described the main applications of Click chemistry in the field of polymers. As mentioned, these reactions have played important roles in the synthesis of monomers and in their polymerization, but also in the modification of polymers. The following section will present the contributions of Click chemistry in the field of polymers prepared from plant oil-derivatives.

1.3.1. Monomer Synthesis

Although vegetable oils and fatty acids are widely used as polymer's raw materials due to the high functionality that they present, the reactivity towards polymerization is often limited. It is well-known that C=C bonds in the triglyceride structure are not sufficiently reactive for any viable polymerization process, except for cationic polymerization.[45] In this sense, chemical transformations onto these groups are generally performed to increase their reactivity.

Indeed, special efforts have been made during the last decades, in functionalizing these feedstocks to serve as reactive polymeric precursors.[46] Although major part of the work has been focused on chemical transformations onto these double bonds, chemical transformations onto the carboxylic groups have been also investigated.[47]

Undeniably, a major breakthrough in the sustainable transformation of double bonds to obtain new reactive monomers has been achieved by using thiol-ene chemistry.
Thus, some groups have demonstrated the straightforward functionalization of the inactivated double bonds of triglycerides by means of thiol-ene addition. For example, Stemmelen and coworkers functionalized grapeseed oil triglycerides with cysteamine hydrochloride (Scheme 17) (thiol to C=C molar ratios of 3:1) under UV and RT, using DMPA as initiator and a mixture of 1,4-dioxane/ethanol 70/30 v/v as solvent. In this case, conversions up to 87% were achieved and the resulting vegetable-oil based polyamines were used as hardeners for epoxidized linseed oil.[48]



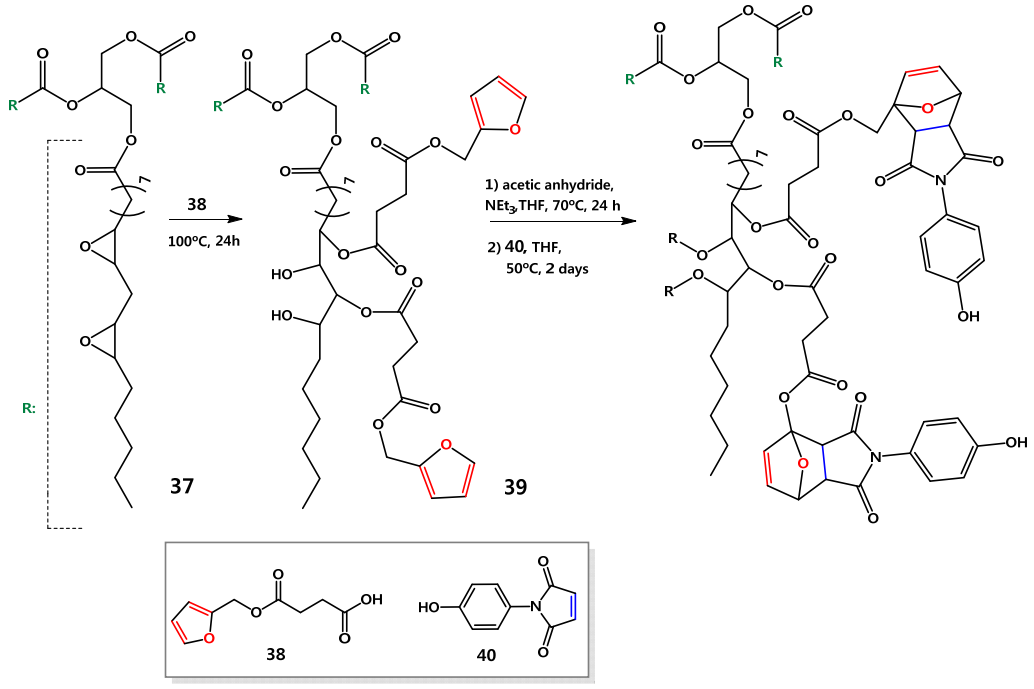
Scheme 17. Thiol-ene functionalization of grapeseed oil with cysteamine hydrochloride.

Employing the same approach Desroches et al.[49] functionalized rapeseed oil triglycerides with hydroxyl functionalities, adding mercaptoethanol (thiol to C=C molar ratios of 3:1) without any added solvent nor photoinitiator, and reported complete conversion in 1h. Additionally, the authors systematically performed model studies to determine for the first time the byproducts derived from thiol additon to fatty acid compounds and, in this way, sulfide formation and intermolecular recombination were identified. Nevertheless, the confirmed byproducts exhibited also hydroxyl functionalities and thus the mixture of polyols were successfully used for the preparation of crosslinked polyurethanes.

Therefore, it has been demonstrated that high functionalization degrees of the internal double bonds of these triglycerides can be obtained using slight excess of thiol. Nevertheless, this excess could be easily removed in both cases by non-chromatographic methods, such as crystallization or liquid/liquid extraction, respectively.

Recently, Amato and coworkers prepared a soybean based coating with thermally responsive Diels-Alder linkages (Scheme 18).[50] First, epoxidized soybean oil **37** reacted with 4-(furfuryl oxycarbonyl) butanoic acid **38** to obtain the monomer **39** with pendant furan moieties. Then, furan-based monomer was acetylated with anhydride acetic and further reacted with phenolic maleimide **40** to obtain soybean oil with reversible DA linkages. Alternatively, the non-acetylated furan-maleimide based monomer was also prepared to serve as irreversible crosslinks in the coating formulations. Thus, polyols reacted with different isocyanates, Desmodur N3330, isophorone diisocyanate (IPDI) and hexamethylene diisocyanate (HMDI) to obtain polyurethane coatings incorporating reversible and irreversible crosslinks. Through the analysis of rehealabilty, hardness, gloss, and adhesion they concluded that the optimal combination was an acetylated resin (no

irreversible crosslinks) with 54% reversible Diels Alder linkages at an NCO:OH ratio of 5:1 using isophorone diiscocyanate. The resulting coatings displayed the capability to be healed following physical deformation by a thermal stimulus.

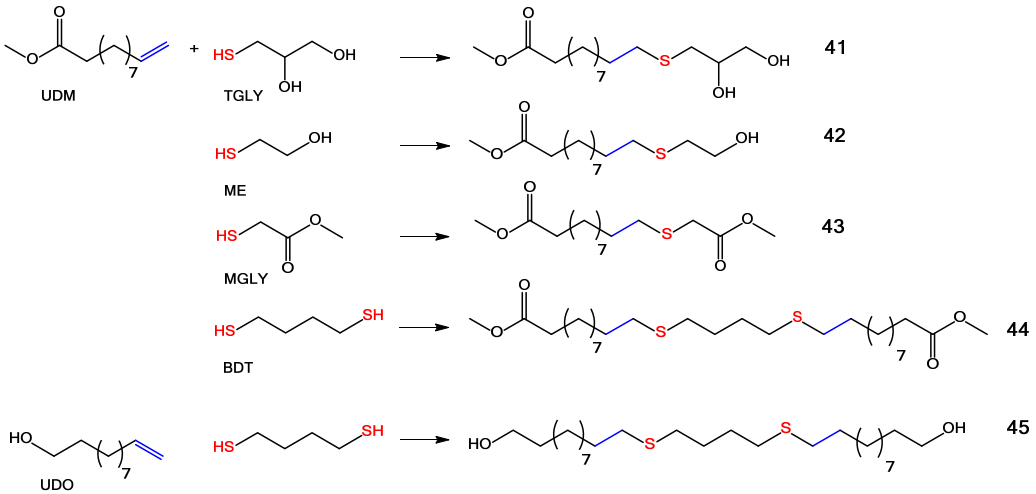


Scheme 18. DA functionalization of soybean oil.

Similarly, several research groups have taken advantage of the double bonds of unsaturated fatty acids to introduce new functionalities through thiol addition. By this approach, several AA and AB monomers have been synthesized and used in the preparation of different polycondensable linear polymers (polyesters, polyurethanes, polyamides, polyanhydrides).

For example, Türünç and Meier synthesized novel polyester precursors by addition of different thiols and dithiols to different undecylenic acid derivatives, methyl 10-undecenoate (UDM) and 10-undecenol (UDO) (Scheme 19).[51] In this case, hydrothiolation was performed using as thiols, 1-thioglycerol (TGLY), 2-mercaptoethanol (ME), methyl thioglycolate (MTGLY) and 1,4-butanedithiol (BDT), obtaining monomers **41-45**. They carried out the reactions using equimolar ratio of thiol and double bond and reaction temperatures ranging RT to 75ºC without using initiator. High to complete conversions

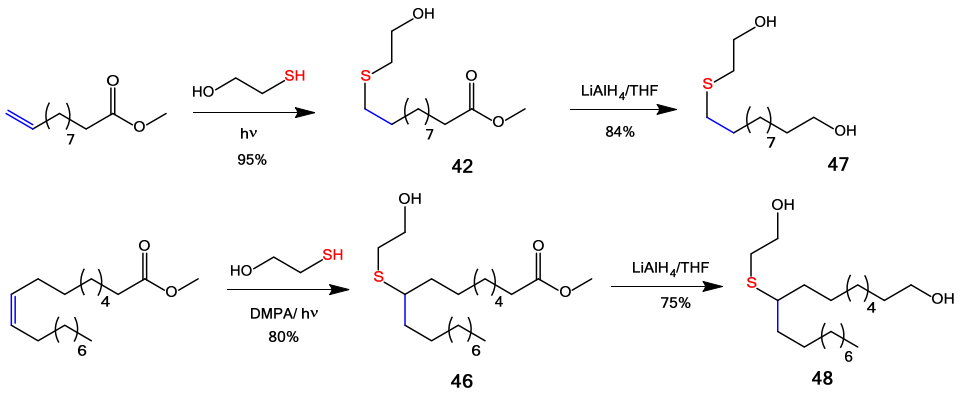
were achieved after quite prolonged reaction times (8h – 6days). The resulting monomers were polymerized to linear as well as hyperbranched polyesters at 120ºC using triazabicyclodecene (TBD) as catalyst, yielding polymers of 4-16 KDa after 8h.



Scheme 19. Thiol-ene Click chemistry to methyl undecenoate and undecenol.

Similarly, Bao and coworkers demonstrated that quantitative addition of TGLY to UDM can be achieved under UV at 35ºC using a catalytic amount of photoinitiator DMPA (0.5 wt% to methyl 10-undecenoate) in 30 min.[52] The resulting monomer **41** were then polymerized using different catalysts and high temperatures (160-170ºC) obtaining polymers with molecular weights ranging from 11-60 KDa.

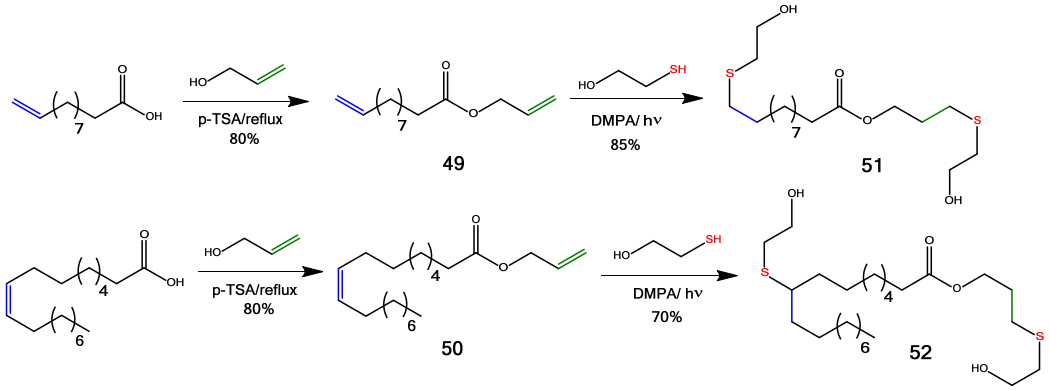
Hydrothiolation of UDM and methyl oleate (OLM) was investigated by González-Paz and coworkers in order to obtain new diols as precursors of linear polyurethanes (Scheme 20).[53] In this sense, they performed the addition of ME to UDM at RT and under UV. Complete conversion was achieved after few minutes, using slight excess of thiol (thiol to C=C molar ratio 1.8:1) without need of initiator. Thiol addition to methyl oleate was performed under the same conditions, but in this case, the presence of photoinitiator (1.7% mol init./mol C=C) was necessary to not compromise reaction times. It is worth noting that the excess of thiol was removed in both cases by liquid/liquid extraction with water, avoiding chromatographic separation. In a second step, the methyl ester groups of **42** and **46** were reduced with $LiAlH_4$ to introduce another primary hydroxyl functionality and afford novel diols **47** and **48**.



Scheme 20. Synthesis of diols via thiol-ene addition to undecylenic and oleic acid derivatives and subsequent reduction.

Alternatively, novel ester containing diols were prepared through an approach based on esterification and double thiol-addition (Scheme 21). In this sense, undecylenic acid (UD) and oleic acid (OLA) were first esterified with allyl alcohol and the resulting dienic monomers **49** and **50** were doubly-functionalized with ME yielding diols **51** and **52**.

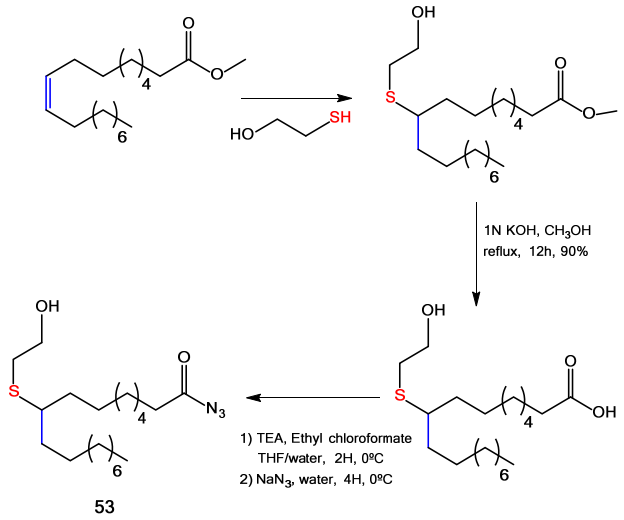
All the obtained diols were subsequently reacted with methylene diphenyl diisocyanate (MDI) at 50ºC for 24h to afford linear polyurethanes of high molecular weight (36-83 KDa).



Scheme 21. Synthesis of diols via double thiol-ene addition to undecylenic and oleic acids.

Addition of ME to UDM and OLM was also performed by More and coworkers as the initial step of the preparation of hydroxy-acyl azide monomers **53** (Scheme 22).[54] They investigated the hydrothiolation (thiol to C=C molar ratio of 3:1) under both thermal and photochemical conditions, observing faster reaction rates under UV conditions. Thus, under the latter conditions, addition was completed in 1h, whereas thermal conditions

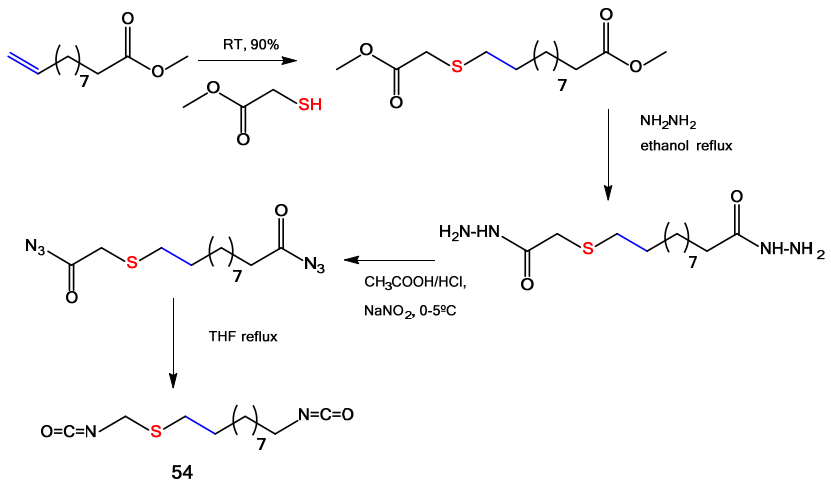
requiered 48h. Finally, the ester groups were converted to azide groups and the resulting monomers were self-polymerized under different reaction conditions, 60 or 80ºC either with or without tetrahydrofuran/dibutyltin dilaurate (THF/DBTDL), obtaining molecular weights around 10.000 g/mol. This work is presented as a green approach towards isocyanate-free polyurethanes.



53

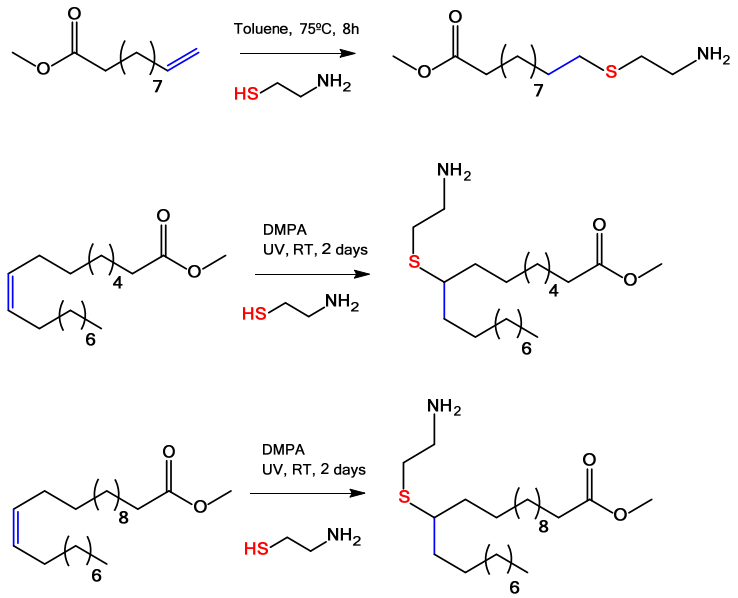
Scheme 22. Synthesis of an hydroxy-acyl azide monomer derived from methyl oleate using thiol-ene chemistry.

Following a different approach, the same group applied thiol-ene addition of TGLY to UDM, as initial step in the preparation of fatty acid-derived isocyanates **54** via Curtius rearrangement (Scheme 23).[55] The authors opted again to use a slight excess of thiol (thiol to C=C molar ratio 2.5:1) to accelerate the hydrothiolation. This time, complete conversion was observed at RT after 6h without added photoinitiator. In this case, the excess of thiol was removed by distillation, avoiding again chromatographic purification steps.



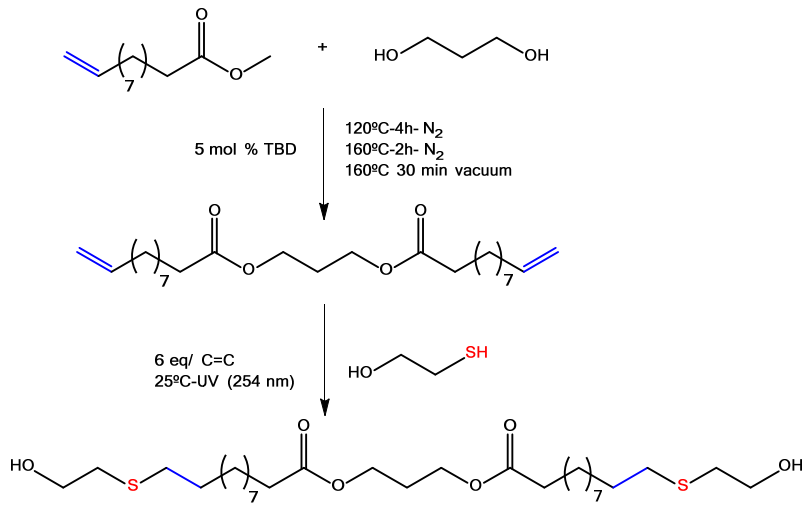
Scheme 23. Synthesis of a diisocyanate via thiol-ene chemistry.

Türünç and coworkers also demonstrated that α,ω-aminomethylesters based on UDM, OLM and methyl erucate are also easily accessible by thiol-ene addition of cysteamine hydrochloride (Scheme 24).[56] Also, in this work excess of thiol (thiol to C=C molar ratio 3:1) was used for reaction with internal double bonds of OLM and methyl erucate. By contrast, hydrothyolation of UDM was performed using equimolar amounts of reagents. These monomers were used to prepare polyamides of varying thermal properties by TBD-catalyzed copolymerization with adipic acid and 1,6-hexamethylene diamine.



Scheme 24. Synthesis of ester-amide monomers by thiol-ene chemistry.

Maisonneuve and coworkers reported the preparation of different diols containing ester, amide, or ester/amide linkages taking also advantage of both carboxyl and double bond groups of UDM and OLM (Scheme 25).[57] First step consisted in UDM esterification or amidation at 120ºC in presence of TBD as catalyst, using large excess of different diamino or diol compounds: 1,3 propanediol, 1,3-propanolamine, isosorbide, 1,4-diaminobutane. Then, the obtained mono- or di- unsaturated esters or amides were functionalized by reaction with different excess of ME (thiol to C=C molar ratio 3-18/1) under UV without initiator. Higher amounts of thiol were necessary to perform thiol-ene reactions on amide-containing precursors. Moreover, because of solubility problems, thiol-ene addition of 1,4-diaminobutane to UDM was carried out at 80ºC in N-methylpyrrolidone using thermal initiation in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN). Finally, the obtained diols were further reacted with MDI or IPDI to yield polyurethanes of high molecular weight (30-70KDa).



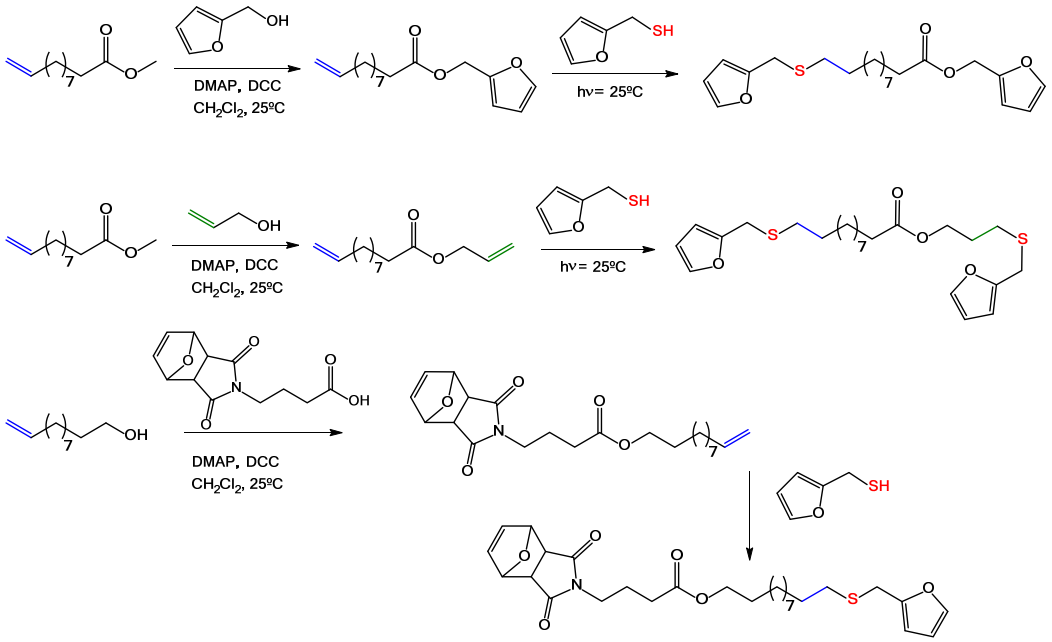
Scheme 25. Synthesis of novel diols by double thiol-ene addition to methyl undecenoate.

Desroches and coworkers extended this synthetic pathway to an oleic acid-rich fatty methyl esters mixture prepared by methanolysis of soybean oil.[58] In this case authors esterified the acid groups with ethyleneglycol, 1,4-butanediol, 1,6-hexanediol, 2-aminoethanol, 5-aminopentanol and 1,8-octanediamine. Subsequently, AIBN-thermally initiated addition of 2-mercaptoethanol using moderate excess of thiol (thiol to C=C

molar ratio 5:1) at 60ºC for 8 days. Later, they used the same approach to obtain diols from methyl esters of rapeseed oil.[59]

Functionalization of similar oleic acid-based structures with 1,5-pentanediol and polyethyleneglycols of different lengths, was reported by Palaskar and coworkers.[60] In this case, conversions up to 90% were achieved at 0ºC after 2h, using photochemical initiation (225 nm) and thiol to C=C molar ratio of 6:1.

Vilela and coworkers prepared different reactive DA monomers by functionalization of UDM derivatives with 2-furfuryl thiol (Scheme 26).[61] Photochemical reaction was initiated with DMPA using slight excess of thiols (thiol to C=C molar ratio 2:1). The reactions took 4 hours to be complete, and then the monomers were obtained in near quantitative yields after simple removal of the thiol excess under vacuum.

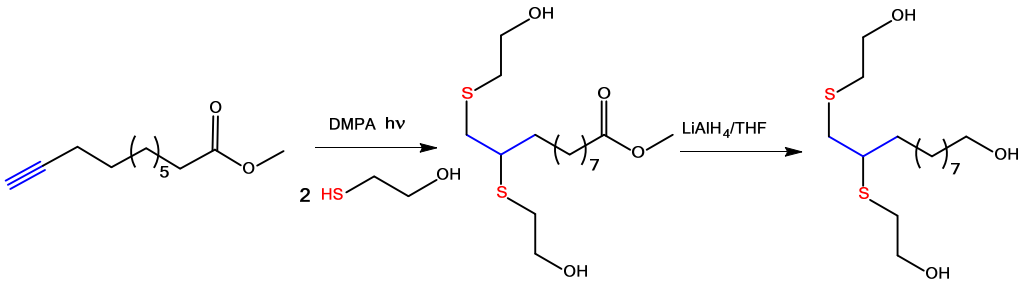


Scheme 26. Synthesis of novel furan and furan-maleimide monomers.

While thiol-ene chemistry has had a tremendous impact on the functionalization of fatty acids, thiol-yne chemistry has been practically overlooked, basically because acetylenic fatty acids are not naturally occurring.

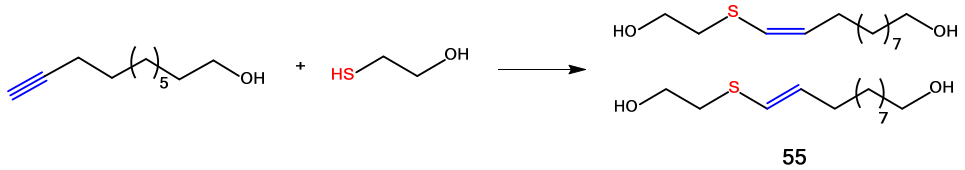
The beauty of this reaction is that it combines the readily available building blocks of the azide–alkyne and the thiol-ene reactions. Interestingly, unlike azide–alkyne cycloaddition, it does not need any potentially toxic metal catalyst. Moreover, it is normally much more efficient when carried out with equimolar amounts of reagents than thiol-ene addition, because intermediate vinyl radicals are formed in a virtually irreversible manner and they abstract a hydrogen atom from the thiol reagent more rapidly than their alkyl counterparts.

In fact, there is only two examples in the literature that deals with the functionalization of fatty acids via thiol-yne chemistry. In this sense, González-Paz and coworkers investigated thiol-yne addition of ME (3:1 thiol: triple bond) to methyl 10-undecynoate (MUDY) and methyl 9-octadecynoate (Scheme 27).[62] Double thiol addition in presence of DMPA was faster for the terminal triple bond, reaching complete conversion in 5 min whereas the absence of initiator extended the reaction to approximately 60 min. For the internal alkyne, it required 60 min to be completed in the presence of DMPA although reached a plateau around 40% conversion without photoinitiator. The synthesized diols were successfully used to prepare thermoplastic polyurethanes containing pendant methyl esters. Moreover, reduction of the methyl ester groups yielded fatty acid-derived triols suitable for the preparation of polyurethane networks.



Scheme 27. Synthesis of a novel diol and triol via thiol-yne addition of ME to MUDY and subsequent ester-groups reduction.

In another work, the same authors synthesized a vinyl sulphide containing diol **55** via thiol-yne addition of ME to 10-undecynol (UDYO) (Scheme 28).[63] In this case, reaction conditions were optimized to allow only one equivalent of 2-mercaptoethanol to add to the alkyne-fatty alcohol. Thus, coupling between the two components was carried out using different alkyne/thiol molar ratios under thermal and photoinitiated conditions. Reactions performed under thermal conditions (80ºC) were carried out using AIBN (5 or 10 % mol init./mol C≡C), whereas photoinduced reactions were carried out at RT under UV irradiation (365 nm) using DMPA (0.5 or 3.6 % mol init./mol C≡C) as a photoinitiator. All reactions were performed for 15 min. The highest amount of vinyl sulphide diol (80%) was obtained using 10 % mol AIBN as a thermal initiator and a slight excess of thiol (thiol to C≡C molar ratio of 1.05:1). The vinyl sulphide-containing diol was isolated by column chromatography as a mixture of E and Z isomers and used in the preparation of linear polyurethanes at 50ºC for 12h (Mn=66 KDa) using MDI as diisocyanate.



55

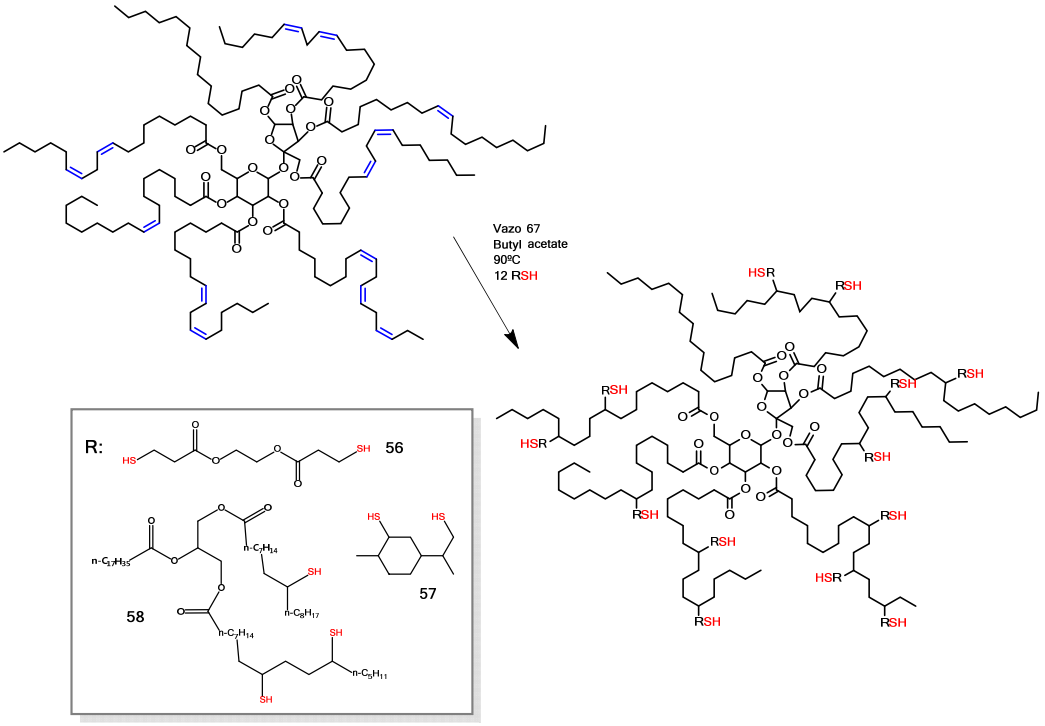
Scheme 28. Synthesis of a vinyl sulphide diol by thiol-yne addition of ME to UDYO.

1.3.2. Polymerization

As previously introduced, Click polymerization has demonstrated to be feasible to obtain well-defined linear and crosslinked polymers following a step-growth polymerization mechanism. Thus, researchers have also made efforts in investigating the polymerization of fatty acid derivatives via Click polymerizations, mainly thiol-ene polymerization.

Vegetable oils have been also oligomerized by thiol-ene polymerization. For instance, Wu and coworkers oligomerized soybean oil by AIBN-thermally initiatiated thiol-ene reaction using different commercially available multifunctional thiols (R-SH): ethyleneglycol di-3-mercaptopropionate, trimethylolpropane tri-3-mercaptopropionate, and pentaerythritol tetra-3-mercaptopropionate.[64] Using this latter polythiol, oligomers up to 6 KDa have been obtained using high thiol to ene ratios (thiol to C=C molar ratio

9-19: 1) at 90ºC for 20h. An analogous strategy was employed by the same group to examine the oligomerization of sucrose soya ester incorporating eight unsaturated fatty acid chains (Scheme 29) with different thiols: glycol di-3-mercaptopropionate **56**, di-pentene dimercaptan **57**, mercaptanized soybean oil **58** in the presence of 2,2′-azobis(2-methylbutyronitrile) (Vazo 67).[65] The resulting high molecular weight biobased thiols were used as a base of thiourethane coatings by means of isocyanate reactions, with different isocyanate trimers.



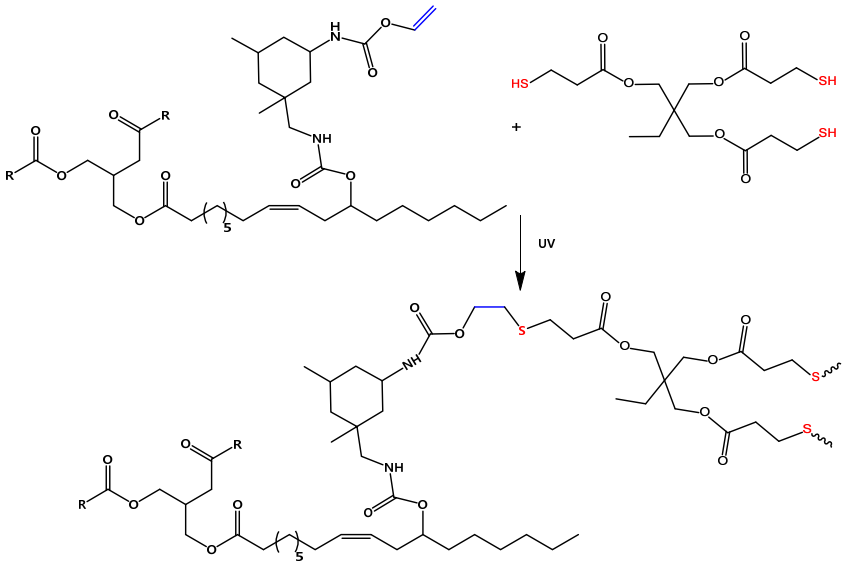
Scheme 29. Thiourethane thermoset coatings prepared by thiol-ene polymerization.

To the same end, Upshaw reported a different approach to prepare di-, tri-, and tetrathiols with high renewable content.[66] In this case, terminal C=C bonds of 9-decenoic and 10-undecenoic ester derivatives of cyclohexane diol, glycerol, trimethylol propane, pentaerythritol, or combinations were functionalized with thiol groups by thiol-ene addition of hydrogen sulfide (H_2S) at 40ºC under UV light.

Thiol-ene coupling as a crosslinking reaction of natural triglycerides has been barely exploited. The reported low reaction rates for thiol-ene addition to internal double

bonds has oriented the research towards the activation of the internal double bonds functionalizing them with more reactive double bonds such as acrylate, allyl, vinyl or anhydride maleic, for facile crosslinking.

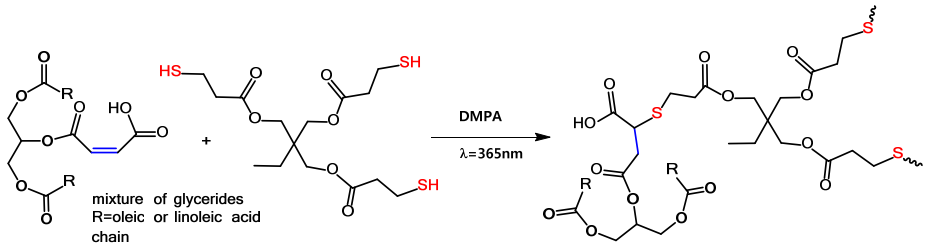
As such, vinyl ether, allyl ether, and acrylate functionalities were introduced to castor oil by Black and Rawlins through urethane linkages.[67] Such macromonomers were cured with trimethylolpropane tri-3-mercaptopropionate (TMPTA) via UV-initiated radical thiol-ene addition (Scheme 30). Notably, the authors determined that vinyl ether and acrylate radical homopolymerizations are competitive processes under thiol-ene conditions. Cured films exhibited high solvent resistance and hardness, as well as excellent adhesion and flexibility, regardless of the different macromonomer functionality, thus evidencing a successful crosslinking. Acrylated castor oil also showed noteworthy reactivity in the presence of oligomeric silsesquioxane-containing thiol derivatives.[68]



Scheme 30. Thiol-ene photopolymerimerization of vinyl ether-based castor oil.

Alternatively, Echevarri and coworkers demonstrated that maleated soybean oil triglycerides, prepared in two steps through glycerolysis of soybean oil followed by reaction with maleic anhydride, are reactive enough to afford elastomeric materials at RT under UV (365 nm)/DMPA-initiated thiol-ene crosslinking (Scheme 31).[69] Curing reactions were performed with multifunctional thiols: TMPTA and pentaerythritol tetrakis(3-

mercaptopropionic acid) using stoichiometric thiol to C=C ratio and insoluble fractions as high as 89% were reached after 12 h.

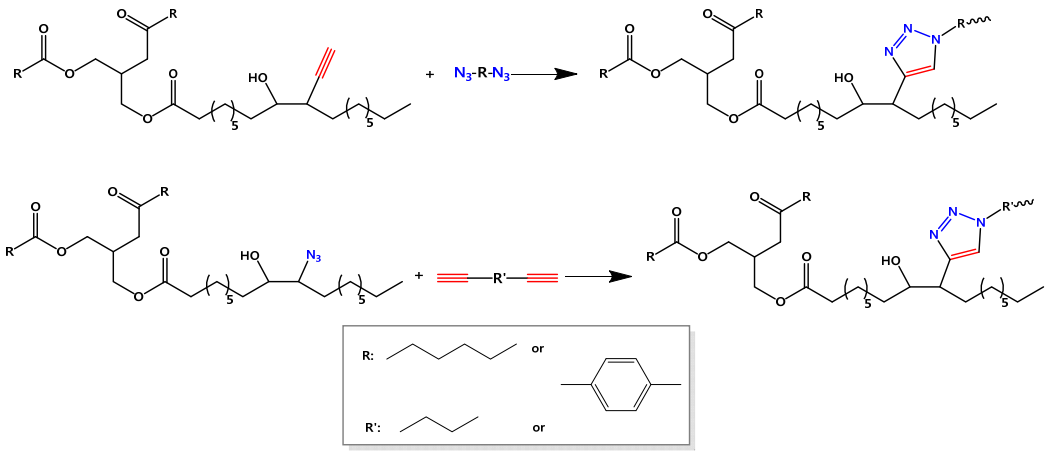


Scheme 31. Thiourethane thermoset coatings prepared by thiol-ene polymerization.

On the other hand, Chen and coworkers synthesized novel soybean oil-based thiols and enes through the Lewis acid-catalyzed ring opening reaction of epoxidized soybean oil with multifunctional thiols or hydroxyl functional allyl compounds.[70] Subsequently, soy-based thiols and enes were formulated with petrochemical-based enes and thiols, respectively, to make thiol–ene UV-curable coatings.

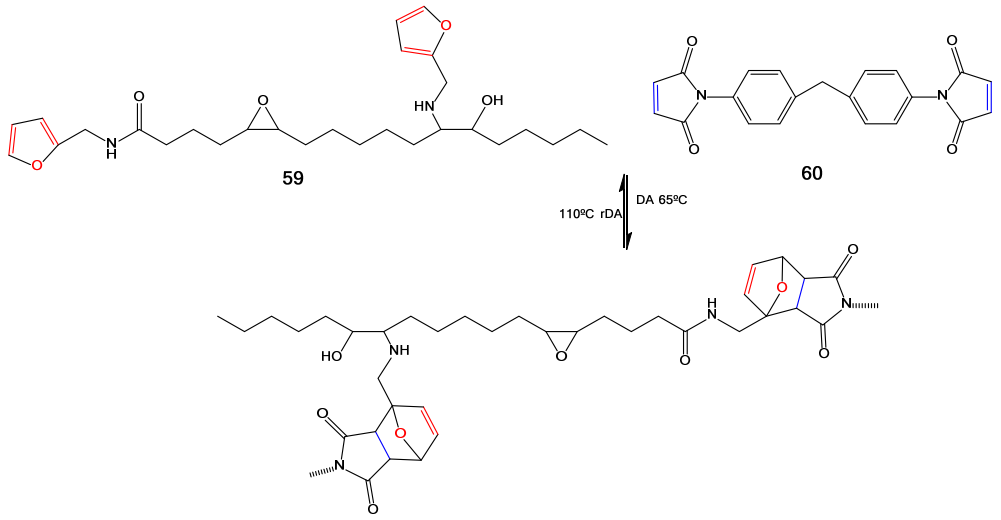
Sharma and coworkers demonstrated that thiol addition to epoxidized soybean oil by means of thiol-epoxy chemistry, proceeds in an effective way under mild acid catalysis conditions.[71] Thus, for instance, ring opening of epoxidized soybean oil with butanethiol was highly efficient (95% as determined by ^{1}H NMR spectroscopic analysis), although competitive epoxy hydrolysis was also identified. Additionally, the distinguishing feature of this process is the formation of a reactive hydroxyl group upon coupling reaction.

CuAAC polymerization has been also investigated by Hong and coworkers.[72] Azidated natural oils such as castor, canola, corn, soybean and linseed oils have shown to readily undergo CuAAC polymerization at RT with diynes as well as alkynated soybean oils (Scheme 32). It is worth pointing out that the synthesized monomers undergo more efficient and rapid polymerization in a catalyst-free and solvent-free environment at 100ºC, which represents an interesting green procedure to make polymers. Generally, under these conditions, polymerizations were faster (12–24 h) and high yielding (>90%), affording highly crosslinked polymers which exhibit behaviors ranging from soft rubbers to hard plastics.



Scheme 32. CuAAC polymerization of azidated and alkynated soybean oils.

Recently, Gandini and coworkers reported the polymerization of linseed oil fatty acids.[73] Epoxidized linseed oil triglycerides were reacted with an excess of furfuryl amine through the ester groups (aminolysis) and through the oxirane groups (ring opening) to afford monomer **59** bearing two or more furan rings in their structure (Scheme 33). Then, monomer **59** was polymerized with 1,1′-(methylenedi-4,1-phenylene) bismaleimide **60** in 1,1,2,2-tetrachloroethane, at 65ºC for 48 hours, obtaining polymers of average *Mw* values ranging from 35KDa to 40KDa and with PDIs around 5. Retro-DA reaction was performed at 110ºC, regenerating the two heterocycles after 48 hours.



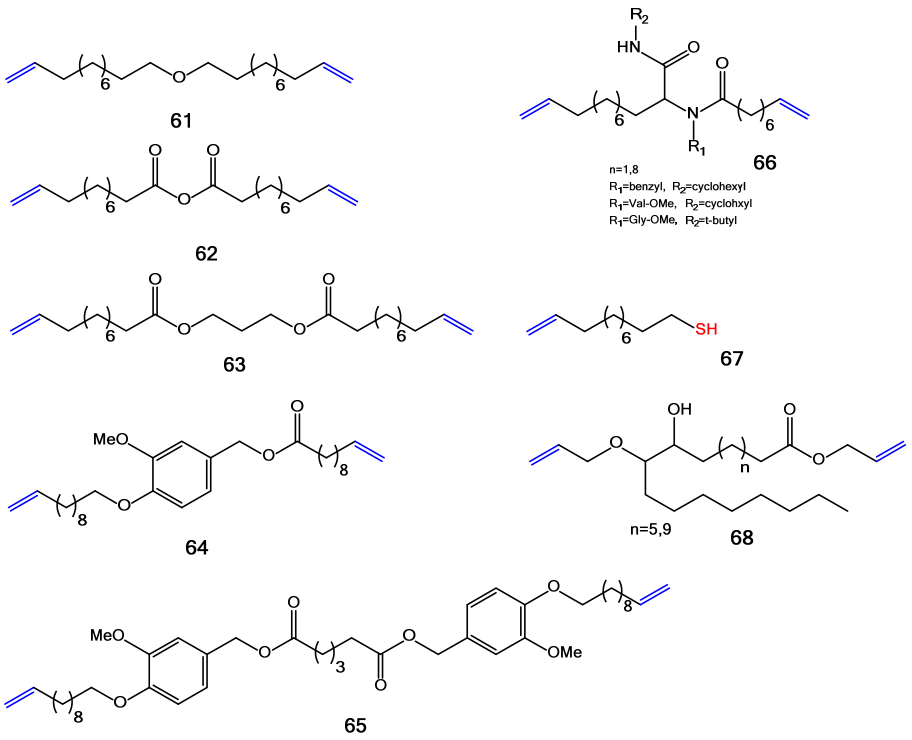
Scheme 33. DA polymerization of furan-functionalized linseed oil triglycerides.

The outstanding efficiency and high reaction rate demonstrated by thiol-ene addition performed on terminal C=C bonds encouraged several researchers to investigate its performance as oligomerization/polymerization tool of α,ω-dienic monomers using bifunctional thiols. As these monomers are not naturally occurring, their synthesis has relied on performing different transformations onto the carboxylic group of fatty acids to introduce an additional double bond.

In this context, the Meier's Group have made important contributions in the synthesis of novel α,ω-dienic monomers (**61-68**, Scheme 34), mainly derived from undecylenic acid, suitable to be polymerized by thiol-ene chemistry.

For instance they prepared an ether containing diene **61** by Williamson etherification of 11-bromo-1-undecene and 10-undecenol. Polymerization of this monomer with BDT was performed at 80ºC in presence of AIBN for 1 hour, yielding a polymer of 18KDa.[74]

The anhydride functional α,ω-dienic monomer **62** was prepared from 10-undecenoic acid and 10-undecenoyl chloride, whereas ester functional monomer **63** was prepared from methyl 10-undecenoate reaction with excess of 1,3-propanediol.[75] These monomers were polymerized with bis(2-mercaptoethyl)ether at 80ºC for 2h using AIBN (2.5% mol). Polymers of molecular weight of 12KDa were obtained from **63**. However, polymers of lower molecular weight (5000 KDa) were obtained from **62**, due to the high reactivity of the anhydride functionalities toward nucleophilic thiols, causing the scission of either monomer or polymer backbone via thioester formation.



Scheme 34. Synthesis of α,ω-diene monomers based on fatty acids for thiol-ene polymerization.

Firdaus and Meier reported the polymerization of dienes **64** and **65**, obtained from vanillin alcohol and 10-undecenoic acid, with BDT and 2-mercaptoethylether in presence of AIBN (2.5 % mol) at 80ºC for 2h, resulting in polymers of 9-16 KDa.[76]

Kreye and coworkers synthesized diene **66** via an Ugi four-component reaction (Ugi-4CR), which was polymerized with BDT under UV irradiation at RT for 2 hours using DMPA as photoinitiator (0.05 equiv) to obtain polymers of molecular weight ranging 3000-9000 g/mol.[77]

Van den Berg and coworkers prepared an α-olefinic-ω-thiol monomer **67** based on undecylenic acid which was self-polymerized under thermal and photochemical conditions. Thus, UV polymerizations at 75ºC for 40min in presence of DMPA (0.75 % mol) and thermal polymerization at 95ºC for 300 min using 1,1′-azobis(cyclohexan-1-carbonitrile) yield polymers with molecular weight as high as 40 KDa.[78]

Finally, polymerization of monomer **68**, obtained from allyl alcohol-ring opening of epoxidized OLM and MER, was performed with BDT at 75ºC in presence of AIBN (2.5% mol) for 4 hours, obtaining polymers of molecular weight up to 14.000 g/mol.[79]

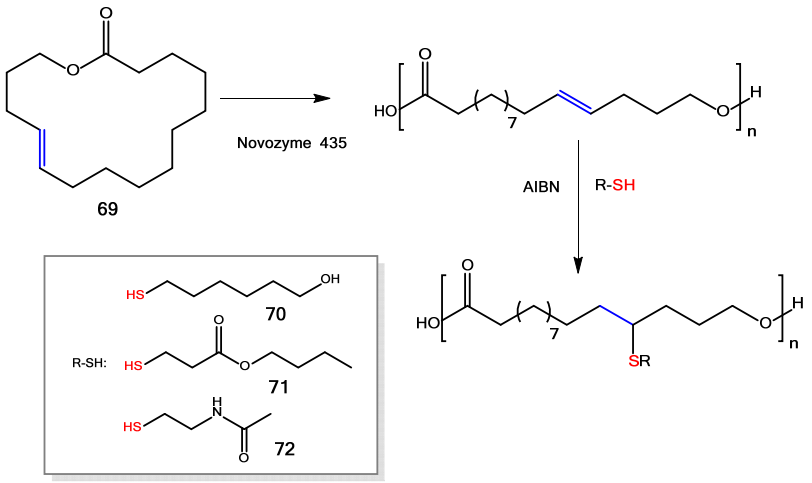
Additionally, although in much lesser extent, other Click reactions have been explored to polymerize functional fatty acids and vegetable oils. For instance, thiol-yne polymerization of alkyne functionalized fatty acids has been investigated by Türünç and coworkers.[80] Model polymerization of 1-octyne with octanethiol was studied in absence and presence of initiator (thermal or photochemical), giving best results the UV-initiated reaction at RT conditions. Then, under optimal conditions, fatty acid-based monoalkynes, such as undecynoic acid, have been polymerized using aliphatic dithiols affording polymers of medium molecular weight (11 KDa).

DA has been exploited recently by Gandini and coworkers to efficiently polymerize furan/maleimide fatty acid based monomers synthesized via hydrothiolation of furfuryl thiol to undecylenic acid derivatives (Scheme 26, page 30).[65] Polymerization was performed at 65ºC yielding low molecular weight materials (< 10 KDa) after several days. Thermoreversibility character of the synthesized polymers was demonstrated to take place at 110ºC, and the regenerated monomers were able to be polymerized again by heating at 65ºC.

1.3.3. Post-polymerization modification

Beyond the synthesis and polymerization of fatty acid-based monomers, the radical-mediated thiol-ene addition has been also used by several research groups as a facile and convenient tool for the post-polymerization modification of the functional groups present in the main and side chain of well-defined plant oil derived polymers.

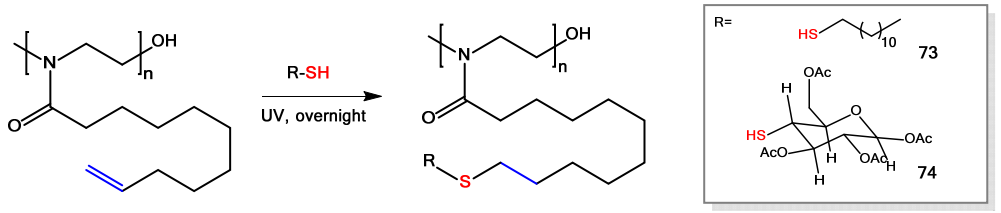
Ates and coworkers described the thiol-ene functionalization of polyester synthesized by enzymatic ring-opening polymerization of globalide **69**, an unsaturated macrolactone synthesized from hydroxyl fatty acid (Scheme 35).[81] The aliphatic polyester (Mn=16 kDa and PDI=2.5) was prepared and modified on the main chain with a range of thiols: 6-mercapto-1-hexanol **70**, butyl-3-mercapto propionate **71** and N-acetylcysteamine **72**. Thiol-ene additions were performed with 6.6–11.0 equiv of thiol in the presence of AIBN at 80 ºC for 24 h, and high degrees of modification were achieved (75-95%).



Scheme 35. Post-polymerization modification of the main chain.

Kempe and coworkers also investigated the modification of well-defined ene side-chain functional polymers prepared from 2-(dec-9-enyl)-2-oxazoline, based on 10-undecenoic acid (Scheme 36).[82] Using ^{1}H NMR spectroscopy and MALDI-TOF MS investigations, the authors demonstrated that C=C bond of the monomer stayed unaffected after the polymerization initiated by methyl tosylate under both conventional heating (100 ºC) and microwave irradiation, allowing their use for subsequent thiol-ene modifications with dodecanethiol **73** and 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glycopyranose **74**.

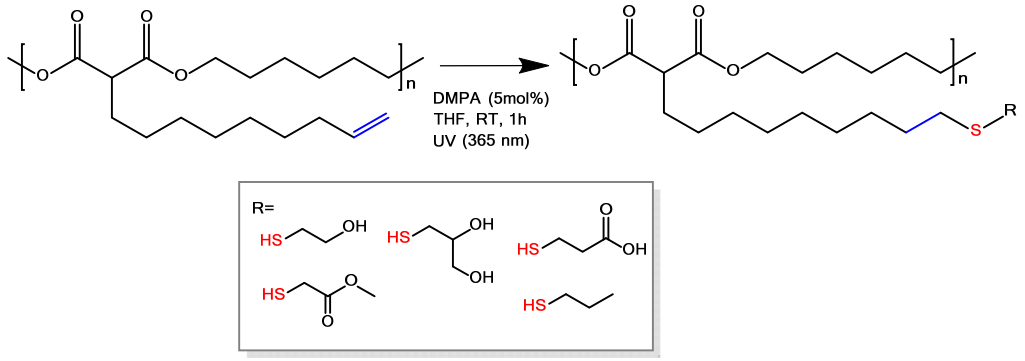
Both modifications were performed using slight excess of thiol (thiol to C=C molar ratio 1: 1.3–3.0), under irradiation with UV light for 24 h in 2-methyl-THF and methyl laureate as "green" solvents. A quantitative addition of both thiols onto the pendant double bonds could be confirmed by NMR spectroscopy.



Scheme 36. Post-polymerization modification of the side chains of alkene-functionalized poly(oxazoline)s.

Similarly, del Rio and coworkers reported the thiol-ene modification of unsaturated polyoxazolines using 2-mercaptoethanol.[83] Side chain modification of the double bonds was performed under UV at RT using excess of thiol (thiol to C=C molar ratio 1: 2.5) and obtaining quantative modification after 2h. Subsequently, the produced polyoxazoline–polyols were reacted with MDI yielding a series of amorphous and semicrystalline polyurethane networks.

High degrees of modification (>99%) were also reported by Kolb and Meier during the thiol-ene modifications of side chains of poly(malonate) (10.2 kDa) bearing C9 unsaturated pendant moieties with several commercially available thiols (Scheme 37).[84]



Scheme 37. Post-polymerization modification of the side chains of alkene-functionalized poly(malonate)s.

This polyester was prepared by condensation of 9-nonenyl malonate, a methyl 10-undecenoate derivative, with 1,6-hexanediol catalyzed by 1.0 mol % titanium (IV) isopropoxide. For all the investigated thiols, bearing different functionalities such as hydroxyl, carboxylic acid, and ester, equimolecular amounts of the thiol with 5.0 mol % DMPA and UV irradiation were reported to be convenient for a quantitative conversion of the C=C bond after 1 h with very low polymer–polymer radical coupling (<5%) and no other side reactions such as radical-initiated ring closure of the side chains.

1.4. Objectives and Scope

The main objective of this thesis was to develop new polymers with high sustainable value combining renewable resources and Click/Click-type transformations.

The development of polymeric materials from renewable resources is receiving considerable attention as a consequence of the depleting of fossil resources and environmental issues. Moreover, maximizing the benefits of using renewable feedstocks requires the utilization of sustainable and efficient chemical transformations, exemplified by Click chemistry reactions. In addition, the design of highly functionalized polymers with adjustable properties and thus, broader applicability is also consistent with the concept of sustainability.

To this aim, we have explored the wide opportunities that some of these efficient transformations can offer in the different steps involved in the production of polymers based on undecylenic and oleic acids, as castor and sunflower oil derivatives. In particular, we have applied thiol-ene, thiol-yne and nucleophilic substitutions as efficient transformations. As we explained in the introduction, these chemistries have shown great promise in the efficient synthesis of monomers as well as their polymerization. Moreover, they have also demonstrated great versatility and efficiency in the modification of polymers, contributing thus to extent the applicability of polymers.

In **Chapter 1** we have presented a brief introduction of Click chemistry in the context of polymer science, focused especially on those polymers based on vegetable oils and fatty acids.

In **Chapter 2** we aim at exploiting the potential of Click chemistry in the synthesis of new monomers based on fatty acid derivatives. We have particularly explored thiol-ene couplings to prepare new polycarboxylic monomers based on undecylenic and oleic acids. The novel reactive monomers have been used in the preparation of polyanhydrides and their potential application as drug delivery carriers has been evaluated.

The experimental procedures and the results of the studies described in this chapter have been published in the journal Macromolecular Rapid Communications, 2011, 32, 1343–1351.

The objective of **Chapter 3** was to explore the feasibility of polymerizing alkynic fatty acids with dithiols applying thiol-yne Click chemistry. The methyl ester-containing biobased polyols have been used in the preparation of polyurethane coatings. Further surface modification of the ester functionalities pending from the polyurethane's chains has been performed to extent the application of these polymers as antimicrobial coatings.
The work corresponding to this part will be submitted for publication.

The aim of **Chapter 4** was to apply the potential of thiol-ene Click chemistry to both polymerize fatty acid derivatives as well as post-modify the chain-ends of the new synthesized biobased macromonomers, all in a one-pot fashion. The developed approach consists in the thiol-ene photopolymerization of an undecylenic acid derived α -ω-diene and the subsequent end-group postpolymerization modification of a telechelic diene with different thiols containing acid, hydroxyl or trimethoxysilane groups.
The experimental procedures and the results of the studies described in this chapter have been published in the journal Biomacromolecules, 2010, 11, 1646-1653.

Taking advantage of the previously synthesized hydroxyl functional telechelics, our objective in **Chapter 5** was to use these oligomers as soft segments in the preparation of segmented polyurethanes. In addition, we have studied the potential application of the resulting polymers as drug delivery vehicles.
The experimental procedures and the results of the studies described in this chapter have been published in the journal Macromolecular Bioscience, 2013, 13, 614-622.

In **Chapter 6** we have focused our research on developing new versatile polymers based on castor oil. The objective was to study the nucleophilic substitution of a bromine containing polyester by using thiols, amines and carboxylic acids. Thus, we describe the synthesis of a sebacic acid-based diester which incorporates bromine functionalities. The

synthesized monomer has been polymerized with decanediol, via enzymatic polymerization as a sustainable alternative to conventional metal-catalyzed polycondensation, affording a functionalized polyester. Post-polymerization modifications of this polyester have been studied to develop polymers with new potential applications. The work corresponding to this part will be submitted for publication.

Finally, in **Chapter 7** the conclusions drawn from the results obtained in this thesis are presented.

[1] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, 40, 2004-2021.

[2] A. D. Moorhouse and J. E. Moses, *Chem. Med. Chem.* **2008**, 3, 715 – 723; H. C. Kolb, K. B. Sharpless, *Drug Discovery Today*, **2003**, 8, 24**,** 1128–1137; G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, 28, 2, 278-308.

[3] J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, 36, 1249-1262.

[4] S. S. Van Berkel, F. L. Van Delft, *Drug Discovery Today: Technologies*, **2013**, 10, 1, 45-51; M. Van Dijk, D. T. S. Rijkers, R. M. J. Liskamp, C. F. Van Nostrum, W. E. Hennink, *Bioconjugate Chem.* **2009**, 20, 11, 2001-2016; M. H. Stenzel, *ACS Macro Lett.* **2013**, 2, 14-18.

[5] E. Lallana, A. Sousa-Herves, F. Fernandez-Trillo, R. Riguera, E. Fernandez-Megia, *Pharm. Res.* **2012**, 29, 1-34; S. Peretz, O. Regev, *Curr. Opin. Colloid Interface Sci.* **2012**, 17, 360-368; D. T. Baviskar, C. M. Tamkhane, A. H. Maniyar and D. K. Jain, *Int. J. Pharmacy and Pharm. Sci.* **2012**, 4, 11-15; G. Clave, S. Campidelli, *Chem. Sci.* **2011**, 2, 1887-1896; N. G. Sahoo, S. Rana, J. W. Cho, L. Li, S. H. Chan, *Prog. Polym. Sci.* **2010,** 35, 837-867.

[6] W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2008**, 29, 952-981; W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, 28, 15–54; E. Lallana, F. Fernandez-Trillo, A. Sousa-Herves, R. Riguera, E. Fernandez-Megia, *Pharm. Res.* **2012**, 29, 902-921.

[7] C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp, *Angew. Chem. Int. Ed.* **2011**, 50, 60-62.

[8] P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.* **2004**, 43, 3928-3932.

[9] L. Liang, D. Astruc, *Coordin. Chem. Rev.* **2011**, 255, 2933–2945; M. Meldal, *Macromol. Rapid Commun*. **2008**, 29, 1016–1051; J. A. Johnson, M. G. Finn, J. T. Koberstein, N. J. Turro, *Macromol. Rapid Commun*. **2008**, 29, 1052-1072; J-F. Lutz, *Angew. Chem. Int. Ed*. **2007**, 46, 1018 – 1025; R. A. Evans, *Austral. J. Chem*. **2007**, 60, 6, 384–395.

[10] J-F. Lutz, *Angew. Chem. Int. Ed.*, **2008**, 47, 2182 – 2184.

[11] C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed*. **2009**, 48, 4900-4908.

[12] M. A. Tasdelen, *Polym. Chem*. **2011**, 2, 2133–2145.

[13] A. B. Lowe, *Polym. Chem*. **2010**, 1, 17-36; C. E. Hoyle, C. N. Bowman, *Angew. Chem, Int. Ed.* **2010**, 49, 1540-1573; M. J. Kade, D. J. Burke, C. J. Hawker, *J. Polym. Sci., Part A: Polym. Chem*. **2010**, 48, 743-750; C. E. Hoyle, T. Y. Lee, T. Roper, *J. Polym. Sci. Part A: Polym. Chem*. **2004**, 42, 5301-5338.

[14] A. B. Lowe, C. E. Hoyle, C. N. Bowman, *J. Mater. Chem.* **2010**, 20, 4745–4750; R. Hoogenboom, *Angew. Chem. Int. Ed*. **2010**, 49, 3415 – 3417; B. D. Fairbanks, T. F. Scott, C. J. Kloxin, K. S. Anseth, C. N. Bowman, *Macromolecules* **2009**, 42, 211-217.

[15] C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, 39, 1355-1387.

[16] R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade, C. J. Hawker, *Chem. Rev.* **2009**, 109, 5620-5686; A. Inglis, C. Barner-Kowollik, *Macromol. Rapid. Commun*. **2010**, 31, 1247-1266.

[17] J. Han, B. Zhao, Y. Gao, A. Tang, C. Gao, *Polym. Chem*. **2011**, 2, 2175-2178.

[18] W. H. Binder, C. Kluger, *Macromolecules* **2004**, 37, 9321-9330.

[19] A. Gandini, *Prog. Polym. Sci*. **2013**, 38, 1-29.

[20] A. Gandini, A. J. D. Silvestre, D. Coelho, *Polym. Chem*. **2011**, 2, 1713-1719.

[21] J. Shin, H. Matsushima, J. W. Chan, C. E. Hoyle, *Macromolecules* **2009**, 42, 3294-3301.

[22] B. D. Polizzotti, B.D. Fairbanks, K. S. Anseth, *Biomacromolecules* **2008**, 9, 1084-1087.

[23] J. A. Johnson, D. R. Lewis, D. D. Diaz, M. G. Finn, J. T. Koberstein, N. J. Turro, *J. Am. Chem. Soc.* **2006**, 128, 6564-6565.

[24] X. Chen, F. Wudl, A. K. Mal, H. Shen and S. R. Nutt, *Macromolecules* **2003**, 36, 1802-1807.

[25] P. J. Roth, C. Boyer, A. B. Lowe, T. P. Davis, *Macromol. Rapid Commun*. **2011**, 32, 1123–1143.

[26] A. Goldmann, M. Glassner, A. Inglis, C. Barner-Kowollik, *Macromol. Rapid. Commun*. **2013**, 34, 810-849; K. Kempe, A. Krieg, C. R. Becer, U. S. Schubert, *Chem. Soc. Rev*. **2012**, 41, 176-191; P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev*. **2010**, 39, 1338-1354; U. Mansfeld, C. Pietsch, R. Hoogenboom, C. R. Becer, U. Schubert., *Polym. Chem*. **2010**, 1, 1560-1598; N. Akeroyd, B. Klumperman, *Eur. Polym. J.* **2011**, 47, 1207-1231; P. J. Roth, C. Boyer, A. B. Lowe, T. P. Davis, *Macromol. Rapid Commun*. **2011**, 32, 1123–1143; D. Fournier, R. Hoogenboom, U. Schubert, *Chem. Soc. Rev.* **2007**, 36, 1369-1380.

[27] A. J. Inglis, S. Sinnwell, M. H. Stenzel, C. Barner-Kowollik, *Angew. Chem. Int. Ed*. **2009**, 48, 2411-2414; A. Inglis, M. H. Stenzel, C. Barner-Kowollik*, Macromol. Rapid. Commun*. **2009**, 30, 1792-1798.

[28] K. T. Wiss, P. Theato, *J. Polym. Sci., Part A: Polym. Chem*. **2010**, 48, 4758-4767; N. V. Tsarevsky, B. S. Sumerlin, K. Matyjaszewski, *Macromolecules*, **2005**, 38, 3558-3561.

[29] M . W. M. Fitjen, C. Haensch, B. M. Van Lankvelt, R. Hoogenboom, U. S. Schubert, *Macromol. Chem. Phys*. **2008**, 209, 1887-1895.

[30] H. Durmaz, A. Dag, O. Altintas, T. Erdogan, G. Hizal and U. Tunca, *Macromolecules*, **2007**, 40, 2, 191-198.

[31] K. A. Günay, P. Theato, H.A. Klok, *J. Polym. Sci., Part A: Polym. Chem*. **2013**, 51, 1-28.

[32] D. G. Barrett, M. N. Yousaf, *Biomacromolecules* **2008**, 9, 2029-2035.

[33] R. M. Arnold, N. E. Huddleston, J. Locklin*, J. Mater. Chem*. **2012**, 22, 19357-19365; L. Nebhani, C. Barner-Kowollik, *Adv. Mater*. **2009**, 21, 3442-3468; H. Nandivada, X. Jiang, J. Lahann, *Adv. Mater*. **2007**, 19, 2197-2208.

[34] R. M. Hensarling, V. A. Doughty, J. W. Chan, D. L. Patton, *J. Am. Chem. Soc*. **2009**, 131, 41, 14673–14675.

[35] P. T. Anastas and J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, New York, **1998**.

[36] P. T. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, 39, 301-312; E. S. Beach, Z. Cui, P. T. Anastas, *Energy Environ. Sci*. **2009**, 2, 1038-1049.

[37] A. Gandini, *Green. Chem.*, **2011**, 13, 1061-1083; A. Gandini, *Macromolecules* **2008**, 41, 24, 9491-9504.

[38] M. N. Belgacem, A. Gandini; *Monomers, Polymers and Composites from Renewable Resources*; Elsevier: Oxford, **2008**.

[39] W. Schwab, C. Fuchs, H. Fong-Chin, *Eur. J. Lipid Sci. Technol*. **2013**, 115, 3–8; K. Yao, C. Tan, *Macromolecules* **2013**, 46, 1689-1712; P. A. Wilbon , F. Chu , C. Tang, *Macromol. Rapid Commun.* **2013**, 34, 8–37.

[40] M. A. R. Meier, J. O. Metzger, U. S. Schubert, *Chem. Soc. Rev.* **2007**, 36, 1788–1802; F. S. Güner, Y. Yagci, A. T. Erciyes, *Prog. Polym. Sci.* **2006**, 31, 633–670.

[41] A. Jering, J. Günther, A. Raschka, M. Carus, S. Piotrowski, L. Scholz, ETC/SCP report 1/ 2010, 2010.

[42] A. Behr, J. Eilting, K. Irawadi, J. Leschinski, F. Lindner, *Green Chem*. **2008**, 10, 13–30.

[43] G. Lligadas, J. C. Ronda, M. Galia, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem*. **2013**, 51, 2111-2124.

[44] O. Türünç, M. Meier, *Eur. J. Lipid Sci. Technol.* **2013**, 115, 41–54.

[45] D. D. Andjelkovic, R. C. Larock, *Biomacromolecules* **2006**, 7, 927-936.

[46] U. Biermann, W. Friedt, S. Lang, W. Lühs, G. Machmüller, J. O. Metzger, M. R. Klass, H. J. Schäfer, M. P. Schneider, *Angew. Chem. Ind. Ed.* **2000**, 39, 2206-2224; U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. Schäfer, *Angew. Chem. Int. Ed.* **2011**, 50, 3854-3871.

[47] F. D. Gunstone, *Eur. J. Lipid Sci. Technol.* **2001**, 103, 307-314; A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, 107, 2411–2502.

[48] M. Stemmelen, F. Pessel, V. Lapinte, S. Caillol, J. P. Habas, J. J. Robin, *J. Polym. Sci. Part A: Polym. Chem.* **2011**, 49, 2434–2444.

[49] M. Desroches, S. Caillol, V. Lapinte, R. Auvergne, B. Boutevin, *Macromolecules* **2011**, 44, 2489–2500.

[50] D. N. Amato, G. A. Strange, J. P. Swanson, A. D. Chavez, S. E. Roy, K. L. Varney, C. A. Machado, D. V. Amato, P. J. Costanzo, *Polym. Chem.* **2013**, DOI: 10.1039/C3PY01024D

[51] O. Türünç, M. A. R. Meier, *Macromol. Rapid Commun.* **2010**, 31, 1822–1826.

[52] Y. Bao, J. He, Y. Li, *Polym. Int.* **2013**, 62, 1457-1464.

[53] R. J. González, C. Lluch, G. Lligadas, M. Galià, J. C. Ronda, V. Cádiz, *J. Polym. Sci. Part A: Polym. Chem.* **2011**, 49, 2407-2416.

[54] A. S. More, L. Maisonneuve, T. Lebarbé, B. Gadenne, C. Alfos, H. Cramail, *Eur. J. Lipid Sci. Technol.* **2013**, 115, 61–75.

[55] A. S. More, T. Lebarbé, L. Maisonneuve, B. Gadenne, C. Alfos, H. Cramail, *Eur. Polym. J.* **2013**, 48, 823-833.

[56] O. Türünç, M. Firdaus, G. Klein, M. A. R. Meier, *Green Chem.* **2012**, 14, 2577–2583.

[57] L. Maisonneuve, T. Lebarbé, T.H.N. Nguyen, E. Cloutet, b. Gadenne, C. Alfos, H. Cramail, *Polym. Chem.* **2012**, 3, 2583–2595.

[58] M. Desroches, S. Caillol, R. Auvergne, B. Boutevin, G. David, *Polym. Chem.* **2012**, 3, 450-457.

[59] M. Desroches, S. Caillol, R. Auvergne, B. Boutevin, *Eur. J. Lipid Sci. Technol*. **2012**, 114, 84–91.

[60] D. V. Palaskar, A. Boyer, E. Cloutet, J-F. Le Meins, B. Gadenne, C. Alfos, C. Farcet, H. Cramail, J. Polym. Sci. Part A: *Polym. Chem*. **2012**, 50, 1766-1782.

[61] C. Vilela, L. Cruciani, A. J. D. Silvestre, A. Gandini, *Macromol. Rapid Commun.* **2011**, 32, 1319–1323; C. Vilela, L. Cruciani, A. J. D. Silvestre, A. Gandini, *RSC Adv*. **2012**, 2, 2966–2974.

[62] R. J. González, G. Lligadas, M. Galià, J. C. Ronda, V. Cádiz, *Polym. Chem*. **2012**, 3, 2471–2478.

[63] R. J. González, G. Lligadas, M. Galià, J. C. Ronda, V. Cádiz*, J. Renew. Mater*. **2013**, 1, 3, 187-194.

[64] J. F. Wu, S. Fernando, D. Weerasinghe, Z. Chen, D. Webster, *ChemSusChem* **2011**, 4, 1135–1142.

[65] J. Yan, S. Ariyasivam, D. Weerasinghe, J. He, B. Chisholm, Z. Chen, D. Webster, *Polym. Int.* **2012**, 61, 602–608.

[66] P. Upshaw, WO Patent 132010 A1, **2009**.

[67] M. Black, J. W. Rawlins, *Eur. Polym. J.* **2009**, 45, 1433–1441.

[68] A. Luo, X. Jiang, H. Lin, H. Yin, *J. Mater. Chem.* **2011**, 21, 12753–12760.

[69] D. A. Echeverri, V. Cádiz, J. C. Ronda, L. A. Rios, *Eur. Polym. J.* **2012**, 48, 2040–2049.

[70] Z. Chen, B. J. Chisholm, R. Patani, J. F. Wu, S. Fernando, K. Jogodzinski, D. C. Webster, *J. Coat. Technol. Res.* **2010**, 7, 603–613.

[71] B. K. Sharma, A. Adhvaryu, S. Z. Erhan, *J. Agric. Food Chem.* **2006**, 54, 9866–9872.

[72] J. Hong, Q. Luo, B. K. Shah, *Biomacromolecules* **2010**, 11, 2960-2965; J. Hong, Q. Luo, X. Wan,Z. S. Petrovic, B. K. Shah, *Biomacromolecules* **2012**, 13, 261-266; J. Hong, K. Shah, Z. Petrovic, *Eur. J. Lipid Sci. Technol.* **2013**, 115, 55–60.

[73] A. Gandini, T. M. Lacerda, A. J. F. Carvalho, *Green Chem.* **2013**, 15, 1514–1519.

[74] O. Türünç, L. Montero de Espinosa, M. A. R. Meier, *Macromol. Rapid. Commun*. **2011**, 32, 1357-1361.

[75] O. Türünç, M. A. R. Meier, *Green Chem*. **2011**, 13, 314-320.

[76] M. Firdaus, M. A. R. Meier, *Eur. Polym. J*. **2013**, 49, 156-166.

[77] O. Kreye, O. Türünç, A. Sehlinger, J. Rackwitz, M. A. R. Meier, *Chem. Eur. J*. **2012**, 18, 5767-5776.

[78] O. van den Berg, T. Dispinar, B. Hommez, F. E. Du Prez, *Eur. Polym. J.* **2013**, 49, 804-812.

[79] O. Kreye, T. Tóth, M. A. R. Meier, *Eur. Polym. J.* **2011**, 47, 1804-1816.

[80] O. Türünç, M. A. R. Meier, *J. Polym. Sci. Part A: Polym. Chem*. **2012,** 50, 1689–1695.

[81] Z. Ates, P. D. Thornton, A. Heise, *Polym. Chem*. **2011**, 2, 309–312.

[82] K. Kempe, R. Hoogenboom, U. S. Schubert, *Macromol. Rapid Commun*. **2011**, 32, 1484–1489.

[83] E. del Rio, G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *J. Polym. Sci. Part A: Polym. Chem*. **2011,** 49, 3069-3079.

[84] N. Kolb, M. A. R. Meier, *Eur. Polym. J.* **2013**, 49, 843-852.

Chapter 2

"Click" Synthesis of Fatty Acid Derivatives as Fast Degrading Polyanhydride Precursors

This chapter is focused on studying the potential of thiol-ene Click chemistry in the synthesis of monomers based on unsaturated undecylenic and oleic acids. The monomers obtained have been polymerized into biobased polymers with potential biomedical applications.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

"Click" Synthesis of Fatty Acid Derivatives as Fast Degrading Polyanhydride Precursors

Cristina Lluch, Gerard Lligadas, Joan C Ronda, Marina Galià, Virginia Cadiz*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili,

C/ Marcel.lí Domingo s/n, 43007 Tarragona, Spain

* To whom correspondence should be addressed: marina.galia@urv.cat

Abstract:

Fast-degrading linear and branched polyanhydrides were obtained by melt-condensation of novel di- and tri-carboxylic acid monomers based on oleic and undecylenic acid synthesized using photoinitiated thiol-ene click chemistry. ^{1}H nuclear magnetic resonance (NMR), size exclusion chromatography (SEC), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and fourier transform infrared spectroscopy (FTIR) have been used to fully characterize these polymers.

The hydrolytic degradation of these polymers was studied by means of weight loss, anhydride bond loss and changes in molecular weight, showing fast degrading properties. Drug release studies from the synthesized polyanhydrides were also conducted, using rhodamine B as a hydrophobic model drug, to evaluate the potential of these polymers in biomedical applications.

Keywords: renewable resources, thiol-ene, biodegradable, plant oils, polyanhydrides

Introduction

The field of polymers derived from non-petrochemical feedstocks has recently attracted a great deal of interest for both economic and environmental reasons.[1] In this context, increasing efforts have been focused in the use of vegetable oils as monomers.[2–5] Plant oils, made up of triglyceride molecules, are considered to be one of the cheapest and most abundant biological sources available, and their use as annually renewable platform chemicals has numerous advantages, including low toxicity and inherent biodegradability.[4] There is a broad palette of chemical pathways for the preparation of thermosets based on triglyceride molecules.[2–4] Fatty acids that can be easily isolated from oils are also attractive since they can also be used as building blocks for the synthesis of linear polymers, such as polyesters,[5] polyethers,[6] and polyanhydrides (PAs).[7] PAs have emerged as an important class of biodegradable polymers.[8] The fast-degrading properties of PAs can find interesting applications in the controlled delivery of drugs.[9] Fatty acids are good candidates for the preparation of biodegradable and biocompatible PAs, as they are natural body components.[10] Unfortunately, fatty acids are monofunctional and cannot serve as monomers for polymerization. One methodology to convert fatty acids into PA precursors is by dimerization of unsaturated fatty acids such as oleic and erucic acid.[11] Alternatively, dicarboxylic fatty acid derivatives can also be obtained by modification of ricinoleic acid, a hydroxy-containing fatty acid, with cyclic anhydrides.[12] The concept of click chemistry, introduced by Sharpless and colleagues in 2001, describes chemistry tailored to generate substances quickly and reliably by joining small units together.[13] The century old addition of thiols to alkenes, which is currently called thiol-ene coupling, has recently emerged as an attractive click process.[14] The click status of this reaction is supported by being highly efficient and orthogonal to a wide range of functional groups, as well as being compatible with water and oxygen. This versatile tool has been recently applied to fatty acids for the preparation of various renewable monomers and polymers.[15]

Experimental Section

Separation of Fatty Acids from High Oleic Sunflower Oil

High oleic sunflower oil (15 g) and an ethanolic solution of 0.5 M KOH were refluxed in a 250mL round bottom flask for 90 min. The solution was then acidified with aqueous HCl and extracted with chloroform. The organic phase was dried over anhydrous magnesium sulfate and the solvent was eliminated under vacuum to obtain 10 g of a mixture of fatty acids. The fatty acid composition of this mixture was determined by gas chromatography mass spectrometry (GC-MS) analysis to be 82.5% (oleic acid), 7.2% (linoleic acid), and the rest of the mixture was composed of other saturated acids.

^{1}H NMR ($CDCl_3$, δ (ppm)): 0.88 (t,-CH_3), 1.20–1.40 (m,-CH_2-), 1.61 (m,-CH_2-), 2.02 (m,-CH_2-CH=), 2.34 (t,HOOC-CH_2-), 5.34 (m,CH=CH-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 14.39 (q), 22.97 (t), 24.93 (t), 27.20 (t), 27.42 (t), 27.49 (t), 29.31 (t), 29.34 (t), 29.43 (t), 29.60 (t), 29.81 (t), 29.95 (t), 30.04 (t), 32.19 (t), 34.38 (t), 129.99 (d), 130.28 (d), 180.77 (s).

Synthesis of 11-(2-Carboxyethylthio)undecanoic Acid (UDS)

Undecylenic acid (20 g, 108.5 mmol), 3-mercaptopropionic acid (13 mL, 152 mmol), 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator (0.083 g, 0.33 mmol), and the minimum amount of acetonitrile necessary to dissolve the catalyst were introduced into a 100mL round bottom flask. The reaction mixture was irradiated with two 9W lamps (λ=365 nm). A white solid appeared after 15 min indicating the completion of the reaction. UDS was purified by crystallization from methanol, filtered off ,and washed with cold methanol and diethyl ether, to obtain 27.8 g of 11-(2-carboxyethylthio) undecanoic (UDS, 88%).

^{1}H NMR ($CDCl_3$, δ (ppm)): 1.18–1.32 (m,-CH_2-), 1.46–1.60 (m,-CH_2-), 2.22 (t,HOOC-CH_2), 2.46 (t,-CH_2-S-), 2.52 (t,-CH_2-COOH), 2.70 (t,-S-CH_2-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 24.59 (t), 26.63 (t), 28.47 (t), 28.78 (t), 28.82 (t), 28.92 (t), 29.01 (t), 29.04 (t) 29.19 (t), 31.70 (t), 33.87 (t), 34.51 (t), 173.67 (s), 175.61 (s).

Synthesis of 9,10-(2-Carboxyethylthio)octadecanoic Acid as a Mixture of Isomers (OLS)

Oleic acid isolated from sunflower oil (9.5 g, 33.6 mmol), 3-mercaptopropionic acid (5.3 mL, 60 mmol), DMPA (0.73 g, 2.9 mmol), and the minimum amount of acetonitrile necessary to dissolve the catalyst were placed into a 50 mL round bottom flask. The reaction mixture was irradiated at λ=365nm for 2h. The product was purified by dissolving with dilute NaOH solution and washing the aqueous phase with diethyl ether. Finally, the aqueous layer was acidified and extracted with chloroform to obtain 11.2 g of a yellowish viscous oil (86%).

^{1}H NMR ($CDCl_3$, δ (ppm)): 0.88 (t,-CH_3), 1.20–1.44 (m,-CH_2-), 1.51 (m,-CH_2-), 1.58–1.70 (m, CH_2-CH-), 2.35 (t,HOOC-CH_2-), 2.58 (m,-S-CH-), 2.63 (t,CH_2-COOH), 2.75 (t,-S-CH_2-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 14.11 (q), 22.93 (t), 24.85 (t), 25.12 (t), 26.95 (t), 27.02 (t), 29.22 (t), 29.30 (t), 29.41 (t), 29.56 (t), 29.69 (t), 29.80 (t), 29.95 (t), 32.14 (t), 34.36 (t), 34.94 (t), 35.05 (t), 35.26 (t), 46.54 (d), 178.96 (s), 180.99 (s).

Synthesis of 11-(2-Carboxyethylthio)undecanoic Triglyceride (UDTGS)

Undecylenic acid triglyceride (UDTG, 20 g, 33.9 mmol), 3-mercaptopropionic acid (12.4 mL, 142 mmol), DMPA as photoinitiator (0.078 g, 0.30 mmol), and the minimum amount of acetonitrile necessary to dissolve the catalyst were introduced into a 100 mL round bottom flask. The reaction mixture was irradiated with two 9W lamps (λ=365 nm). A white solid appeared after 15 min indicating the completion of the reaction. UDTG was purified by crystallization from acetone, filtered off, and washed with cold acetone and hexanes, to obtain 19.3 g of 11-(2-carboxyethylthio)-undecanoic triglyceride (UDTGS, 70%).

^{1}H NMR ($CDCl_3$, δ (ppm)): 1.27–1.39 (m,-CH_2-), 1.54–1.60 (m,-CH_2-), 2.31 (t,-CO-CH_2-), 2.54 (t,-CH_2-S-), 2.66 (t,-CH_2-COOH), 2.79 (t,-S-CH_2-), 4.21 (dd,-CH_2-O-), 5.26 (m,-CH-O-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 25.1 (t), 26.9 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (t), 29.8 (t), 32.4 (t), 34.3 (t), 34.5 (t), 35.0 (t), 62.4 (t), 69.2 (d), 173.7 (s), 178.3 (s).

Prepolymer Synthesis

First, the polycarboxylic monomers were activated by refluxing in acetic anhydride for 45 min with constant stirring. UDS (8 g, 27.6 mmol) was refluxed with acetic anhydride (1: 10, w/v). The excess acetic anhydride was evaporated at 60ºC to product dryness. The hot clear viscous product was dissolved in chloroform and precipitated in 100mL of dry diethyl ether at -20ºC for 24 h. The white precipitate was collected by filtration, washed with cold diethyl ether, and dried under vacuum at room temperature for 3 h, to obtain the diacetylated product in 80% yield.

^{1}H NMR($CDCl_3$, δ (ppm)): 1.12–1.40 (m,-CH_2-), 1.57 (m,-CH_2-), 1.65 (m,-CH_2-), 2.21 (s,H_3C-CO-), 2.24 (s,-CO-CH_3), 2.44 (t,-CO-CH_2-), 2.53 (t,-CH_2-S-), 2.78 (m,-CH_2-CO-;-S-CH_2-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 22.46 (q), 22.52 (q), 24.36 (t), 26.36 (t), 28.78 (t), 29.02 (t), 29.36 (t), 29.49 (t), 29.59 (t), 29.68 (t), 32.46 (t), 35.47 (t), 36.14 (t), 36.25 (t), 166.45 (s), 166.88(s), 168.00 (s), 169.63(s).

In the case of the dicarboxylic acid derived from oleic acid, 11.2 g of OLS (28.8 mmol) were refluxed with acetic anhydride (1: 10, w/v) and the product was purified as described for the acetylated UDS to give 12.8 g (94%) of a yellowish viscous oil.

^{1}H NMR ($CDCl_3$, δ (ppm)): 0.88 (t,-CH_3), 1.20–1.44 (m,-CH_2-), 1.52 (m,-CH_2-), 1.65 (m,-CH_2-CH-), 2.21 (s,CH_3-CO-), 2.24 (s,-CO-CH_3), 2.45 (t,-CO-CH_2-), 2.58 (m,-S-CH-), 2.75 (m,-S-CH_2-,-CH_2-CO-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 14.33 (q), 22.42 (t), 22.48 (t), 22.87 (t), 24.31 (t), 4.64 (t), 26.83 (t), 26.89 (t), 28.99 (t), 29.31 (t), 29.33 (t), 29.49 (t), 29.69 (t), 29.74 (t), 29.81 (t), 32.09 (t), 34.88 (t), 34.97 (t), 35.36 (t), 36.28 (t), 46.57 (d), 166.44 (s), 166.84 (s), 169.58 (s), 169.59 (s).

Different prepolymeric mixtures were prepared to obtain branched polymers. UDTGS, UDS:UDTGS (80:20), and OLS:UDTGS (80:20) were one-pot acetylated and the excess acetic anhydride was evaporated at 60ºC to product dryness.

UDTGS Prepolymer

^{1}H NMR ($CDCl_3$, δ(ppm)): 1.19–1.34 (m,-CH_2-), 1.49–1.52 (m,-CH_2-), 2.17 (s,-CO-CH_3), 2.24 (t,-CO-CH_2-), 2.47 (t,-CH_2-S-), 2.70 (m,-CH_2-CO-;-S-CH_2-), 4.15 (dd,-CH_2-O-), 5.19 (m,-CH-O-).

UDS:UDTGS (80:20) Prepolymer

^{1}H NMR ($CDCl_3$, δ(ppm)): 1.20–1.39 (m,-CH_2-), 1.55–1.70 (m,-CH_2-), 2.19 (s,CH_3-CO-), 2.21 (s,-CO-CH_3), 2.30 (t,-CO-CH_2-), 2.43 (t,-CO-CH_2-), 2.52 (t,-CH_2-S-), 2.76 (m,-CH_2-CO-;-S-CH_2-), 4.20 (dd,-CH_2-O-), 5.25 (m,-CH-O-).

OLS:UDTGS (80:20) Prepolymer

^{1}H NMR ($CDCl_3$, δ(ppm)): 0.85 (t,-CH_3), 1.23–1.67 (m,-CH_2-), 2.19 (s,H_3C-CO-), 2.21 (s,-CO-CH_3), 2.28 (t,-CO-CH_2-), 2.43 (t,-CO-CH_2-), 2.51 (t,-CH_2-S-), 2.56 (m,-CH-S-), 2.73 (m,-CH_2-CO-; -S-CH_2-), 4.17 (dd,-CH_2-O-), 5.24 (m,-CH-O-).

The different prepolymers have typical IR absorptions at 1740 and 1800 cm^{-1} (symmetrical and asymmetrical anhydride C=O stretching bands).

Polymer Synthesis

PAs of undecylenic and oleic acids were prepared by melt condensation of the corresponding purified prepolymers at high temperatures under intermittent vacuum and argon supply. Crosslinked and branched PAs were prepared by one-pot melt condensation of UDTGS homopolymer and UDS:UDTGS (80:20) and OLS:UDTGS (80:20) copolymers. UDS prepolymer (8 g) was introduced to a Schlenk flask and heated at 140ºC for 4 h and 150ºC for 1 h with constant stirring supplying intermittent vacuum and argon. Isolation of 6.4 g of the polymer (PA-UDS) gave a yield of 80%.

^{1}H NMR ($CDCl_3$, δ (ppm)): 1.12–1.40 (m,-CH_2-), 1.56 (m,-CH_2-), 1.63 (m,-CH_2-), 2.43 (t,-CO-CH_2-), 2.51 (t,-CH_2-S-), 2.76 (m,-CH_2-CO-; -S-CH_2-).

^{13}C NMR ($CDCl_3$, δ (ppm)): 22.46 (q), 22.52 (q), 24.38 (t), 26.36 (t), 28.78 (t), 29.03 (t), 29.38 (t), 29.53 (t), 29.62 (t), 29.70 (t), 32.47 (t), 35.47 (t), 36.20 (t), 36.25 (t), 166.45 (s), 166.88(s), 168.00 (s), 169.63(s).

Following the same methodology, 3.2 g of oleic prepolymer were polymerized in a Schlenk flask to obtain 2.5 g of PA-OLS (90%).

^{1}H NMR ($CDCl_3$, δ (ppm)): 0.88 (t,-CH_3), 1.20–1.44 (m,-CH_2-), 1.52 (m,-CH_2-), 1.65 (m,-CH_2-CH-), 2.45 (m,-S-CH-), 2.58 (t,-CH_2-COO-), 2.75 (t,-S-CH_2-).
^{13}C NMR ($CDCl_3$, δ (ppm)): 14.36 (q), 22.90 (t), 22.91 (t), 24.34 (t), 24.37 (t), 24.62 (t), 26.87 (t), 26.93 (t), 29.28 (t), 29.49 (t), 29.53 (t), 29.55 (t), 29.59 (t), 29.82 (t), 29.84 (t), 29.92 (t), 32.15 (t), 35.10 (t), 35.46 (t), 36.39 (t), 46.56 (d), 166.44 (s), 166.84 (s), 169.58 (s), 169.59 (s).

In the case of UDTGS homopolymerization, UDS:UDTG (80:20), and OLS:UDTG (80:20), the prepolymer mixtures were polymerized at 140ºC (4 h) and 150ºC (1 h) without purification to avoid composition modifications.
PA UDS:UDTGS (80:20) ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.20–1.40 (m,-CH_2-), 1.52–1.70 (m,-CH_2), 2.31 (m,-CO-CH_2-), 2.45 (m,-CO-CH_2-), 2.53 (t,-CH_2-S-), 2.77 (m,-CH_2-CO-; -S-CH_2-), 4.20 (dd,-CH_2-O-), 5.25 (m,-CH-O-).
PA OLS:UDTGS (80:20) ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.85 (t,-CH_3), 1.23–1.67 (m,-CH_2-), 2.30 (m,-CO-CH_2-), 2.44 (m,-CO-CH_2-), 2.53 (t,-CH_2-S-), 2.58 (m,-CH-S-), 2.76 (m,-CH_2-CO-; -S-CH_2-), 4.17 (dd,-CH_2-O-), 5.24 (m,-CH-O-).

The anhydride group hydrolyzes easily in the presence of humidity, therefore, polymers were stored at low temperatures (–20ºC) under an inert atmosphere.

Hydrolytic Degradation of PAs

Hydrolytic degradation of the PAs was evaluated by immersing cylindrical samples (3.5 x 8.5 mm^2, 200 mg) into glass bottles containing 100 mL of phosphate buffer solution (pH 7.4 at 37ºC). Devices were prepared by the melt-casting method at 80ºC. At each time point, the polymer sample was taken out of the buffer solution, dried at room temperature under vacuum and weighed. The hydrolytic degradation was studied by monitoring the mass loss, the percentage of anhydride bonds, and the change in polymer molecular weight during hydrolysis. The mass loss was defined as follows: mass loss (%)= $(M_0-M_t)/M_0$ x 100, where M_0 represents the weight of the dry sample before

degradation and *Mt* represents the weight of the dry sample after degradation at different time intervals (t). Anhydride bond hydrolysis was determined by IR spectroscopy from the peak size ratio of the anhydride peak that appears at around 1815 cm^{-1} and the peak of the free acid at 1700 cm^{-1}. The morphology of the polymer samples during the degradation was observed by scanning electron microscopy (SEM).

Drug Release of Rhodamine B from PAs

Rhodamine B (5 wt%) was mixed with the polymer (200 mg) and melt-casted into cylindrical devices (3.5 x 8.5 mm^2). Drug release studies were conducted placing each polymer sample in 100 mL o phosphate buffer (pH 7.4) at 37ºC. At each time point, polymer was removed from the incubation solution. The rhodamine B concentration in the solution was determined by UV detection at a wavelength of 550 nm. The concentration was determined from a standard curve by measuring the absorption at 550 nm of pure rhodamine B at concentrations ranging from 0.2–15 ppm.

Results and Discussion

Monomer Synthesis

Thiol-ene coupling has been extensively studied and is known to follow a radical mechanism, in which the addition of a thiyl radical to a double bond is followed by chain transfer to thiol.[16] The addition of a variety of mercapto-compounds to unsaturated fatty acids was studied in the 1960s.[17] Because of its ability to add a broad range of functionalities in lieu of a double bond, the thiol-ene click chemistry of fatty acids is a promising route that can be used for the synthesis of novel chemical intermediates from renewable resources. Here we report the synthesis of novel polycarboxylic acid monomers based on oleic and undecylenic acids using photoinitiated thiol-ene click chemistry. It is important to mention that the oleic acid used in this work was isolated by saponification of the high oleic sunflower oil sample. The composition of the fatty acid mixture was analyzed by GC-MS and was as follows: 82.5% oleic acid, 7.2% linoleic acid, 6.1% palmitic acid, and 4.2% stearic acid. Initially, the kinetics of the coupling between pure undecylenic and oleic acids with 3-mercaptopropionic acid was studied. Reactions were carried out at room temperature under UV-light in the presence

of DMPA as photoinitiator. The reaction was conducted with an excess of thiol (1.8 equiv. relative to the double bond) in the presence of a small amount of acetonitrile. Figure SF1, Supporting Information, compares the C=C conversion, measured by ^{1}H NMR spectroscopy, as a function of time. As expected, the addition of 3-mercaptopropionic acid to undecylenic acid reaches 100% conversion in a few minutes, whereas the addition to oleic acid requires longer reaction times (90 min to reach 99% conversion). Thus, a remarkable difference in reactivity is observed between undecylenic (terminal ene) and oleic acid (internal ene). This difference in reactivity is attributable to the ene susceptibility to thiyl attack and subsequent hydrogen abstraction. Moreover, according to literature data, there is good reason to believe that the addition of a thiyl radical to a double bond maybe reversible depending on the specific structure of the thiol and ene.[18]

A detailed analysis of the evolution of ^{1}H NMR spectra during the 3-mercaptopropionic acid addition to oleic acid confirmed that this reversible process takes place. As shown in Figure 1A, the pure oleic acid double bond with *cis* configuration gives signal *a* at around 5.35 ppm. After 5min (15% conversion) a new signal *b* appears at 5.40 ppm, which is attributed to the chemical shift characteristic of C=C double bond with *trans* configuration. The appearance of this signal confirms that under these conditions, the addition of a thiyl radical to oleic acid is a reversible process that generates the more thermodynamically stable *trans* double bond. At 34% conversion the intensity of both signals is similar and at the point of 84% conversion (Figure 1D) only the signal of the *trans* ene remains. The signal corresponding to the *trans* ene completely disappears after 120 min. This insertion–isomerization–elimination reaction sequence is also responsible for the reduced reactivity observed for oleic acid. The *cis/trans*-isomerization process under thiol-ene conditions has been recently studied by FT-IR spectroscopy.[19]

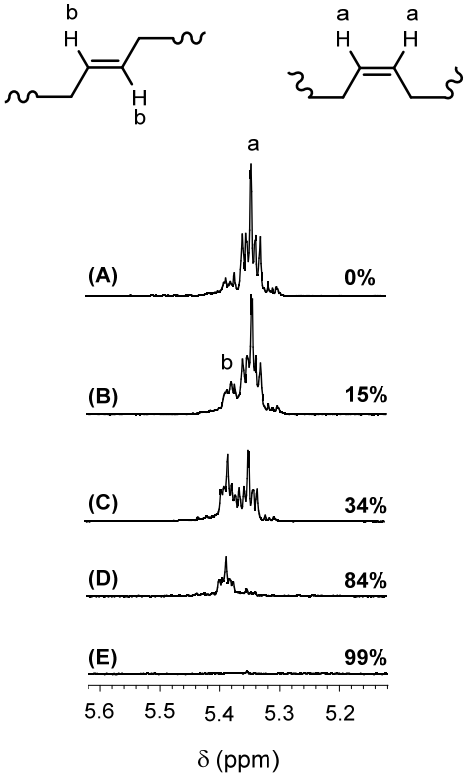


Figure 1. Expanded region (5.2-5.6 ppm) of the 400 MHz ^{1}H-NMR spectra ($CDCl_3$) during the photoinitiated thiol-ene click addition 3-mercaptopropionic acid to oleic acid as a function of conversion.

An additional experiment was carried out to study the behavior of pure linoleic acid, which is the major reactive impurity in the oleic acid mixture, toward thiol-ene coupling with 3-mercaptopropionic acid. Linoleic acid contains two C=C double bonds in its fatty acid chain. If both double bonds are active under thiol-ene coupling conditions with 3-mercaptopropionic acid, this would lead to a tricarboxylic acid derivative. A trifunctional acid could interfere with the polymerization step because of the formation of unwanted crosslinked material. However, the addition of 3-mercaptopropionic acid under the above reported conditions to pure linoleic acid only reached 50% double bond conversion showing that only the addition of equivalent of thiol takes place. These results are in agreement with previous investigations.[18c] Following the above reported conditions, UDS and OLS diacids were synthesized applying thiol-ene click chemistry with 3-mercaptopropionic acid (see chemical structures A and B in Figure 2). The thiol addition to undecylenic acid was quantitative even using a slight excess of thiol (1.4 mol

relative to the double bond) and lower photoinitiator load (0.3 mol% relative to the double bond). Under these conditions, thiol addition was also performed to UDTG. UDTG, which can be obtained by esterification of glycerol with undecylenic acid, has been previously used as a raw material for the preparation of a broad range of branched and crosslinked polymers.[20–23] 3-Mercaptopropionic acid addition to UDTG proceeds quantitatively leading to a trifunctional carboxylic acid UDTGS (see chemical structure C in Figure 2), a precursor of branched and crosslinked PAs. The chemical structure of the synthesized monomers was confirmed by ^{1}H and ^{13}C NMR analysis. Figure 2 shows the fully assigned ^{1}H NMR spectra of UDS, OLS, and UDTGS.

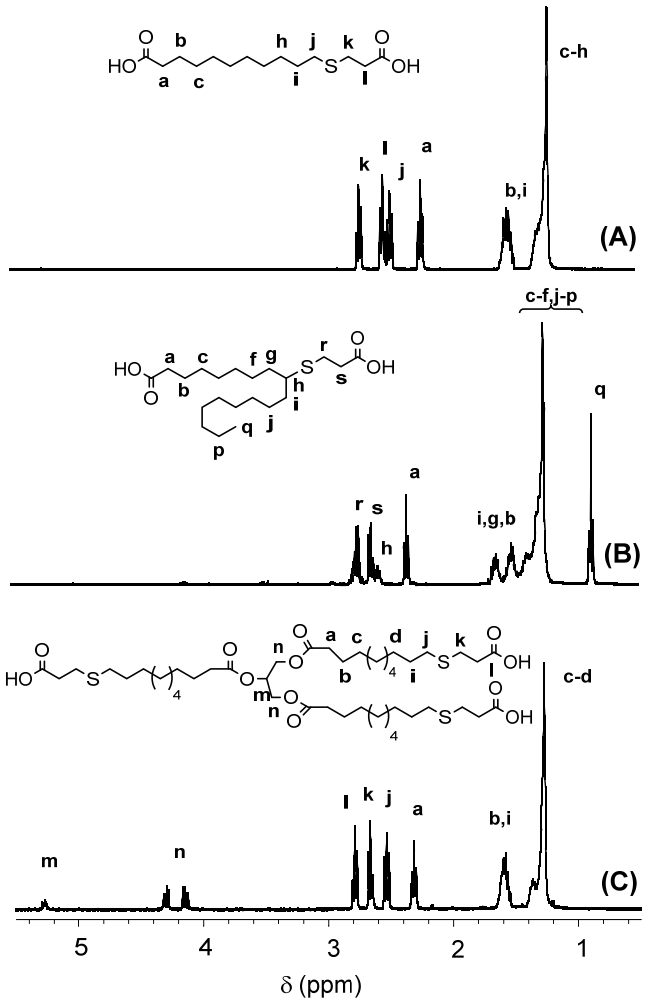


Figure 2. 400 MHz 1H-NMR spectra ($CDCl_3$) of biobased carboxylic acids synthesized via thiol-ene addition: (A) UDS, (b) OLS, and (C) UDTGS.

The success of the coupling was noted from the appearance of signals at 2.3 and 2.8 ppm, which corresponds to the newly formed carbon–sulfur bonds. Further evidence of successful coupling was obtained from ^{13}C NMR spectra with the appearance of two signals at around 175–180 ppm confirming the proposed structure. UDS and UDTGS were obtained as white solids with melting points at 106ºC (ΔH=-188.2 J/g) and 75.8C (Δ H=-101.7 J/g) respectively, whereas the Y-shaped oleic acid derivative was a viscous oil at room temperature and showed a melting– cold crystallization–melting process at around -78ºC (ΔH=-15.5 J/g), -64ºC (ΔH=-31.5 J/g), and -42ºC (ΔH=-26.0 J /g).

Polyanhydride Synthesis and Characterization

UDS, OLS, and UDTGS were used to prepare monocomponent PAs (PA-UDS, PA-OLS, and PA-UDTGS, respectively) by melt-condensation under vacuum. First the carboxylic acid groups were activated using an excess of acetic anhydride to prepare the polymer precursor. The displacement of the signals corresponding to the methylene protons next to the acid groups indicates a successful acetylation. For UDS anhydride, the acetyl-terminated end groups appear at 2.21 and 2.24 ppm (Figure SF2A, Supporting Information). Moreover, the area ratios of the repeating units and the acetyl-terminated end groups indicate that oligomerization took place during the acetylation process. The degree of oligomerization was calculated showing that UDS anhydride has 2.3 repeating units, and OLS anhydride consists of about 2.4 OLS repeating units.

In the second step, the polymer precursors were polymerized at 150ºC under vacuum to remove the melt condensation by-product, acetic anhydride. During the polymerization, the viscosity of the reaction mixture gradually increased, and in the case of PA-UDTGS the formation of a gelatinous product was observed after 2 h. The ^{1}H NMR spectra of PA-UDS and PA-OLS homopolymers showed significant peak broadening compared to the precursor. Moreover, the signal intensity of the acetyl end groups (2.2 ppm) significantly decreased in relation to the integrals of the repeating units, indicating that polymerization took place (Figure SF2B, Supporting Information). The UDS-based PA was isolated as a white powder whereas PA-OLS was a yellowish sticky oil. As expected, in the case of monocomponent PA-UDTGS, an insoluble and non-processable crosslinked gummy material was obtained. The preparation of a branched PA derived from UDS and

OLS could be interesting in order to modulate PA properties such as hydrolytic stability. Thus, the trifunctional carboxylic acid UDTGS was copolymerized with UDS and OLS diacids in different ratios by a one-pot method. Both monomers were refluxed in a flask with acetic anhydride. The excess acetic anhydride was evaporated under vacuum to product dryness and the liquid transferred to a silanized vial. The mixtures were polymerized at 140ºC (4h) and 150ºC (1 h) under vacuum to obtain polymers with different properties. A set of reactions was performed in order to investigate some important parameters concerning the reaction conditions, especially the optimal UDS/ UDTGS and OLS/UDTGS ratio that produces branched structures avoiding crosslinking. When UDTGS was polymerized with OLS (80:20, OLS:UDTG), a viscous branched polymer was obtained whereas the copolymerization of UDS:UDTGS (80:20) yielded a solid branched polymer. More than 20% w/w UDTGS in the copolymer systems produced gelatinous insoluble materials. Thus, 80% UDS or OLS and 20% UDTGS as a branching agent were fixed as optimal conditions. Key properties of the synthesized PAs are summarized in Table 1.

Table 1. Physical properties of UDS, OLS, and UDTGS mono and dicomponent biobased polyanhydrides.

						DSC[b]			TGA[c]	
	M_w^{SEC} (g/mol)[a]	PDI	Yield (%)	T_g (ºC)	T_{m1} (ºC)	$\Delta H_{f\,1}$ (J/g)	T_{m2} (ºC)	ΔH_{f2} (J/g)	$T_{10\%}$ (ºC)	T_{max} (ºC)
PA-UDS	22350	2.0	80	-38	64	57	72	42	279	413
PA-OLS	13100	3.0	90	-65	-	-	-	-	277	370
PA- UDTGS	-	-	93	-18	12	29	-	-	350	388
PA-UDS:UDTGS 80:20	8200	2.7	91	-25	55	16	-	-	271	404
PA-OLS:UDTGS 80:20	10100	4.1	92	-60	-19	14	-	-	270	388

[a] Determined using polystyrene as standard in THF; [b] Determined from the first DSC scan (20ºC/min); [c] N_2 was used as the purge gas (10ºC/min).

PA-UDS and PA-OLS were obtained as linear polymers with molecular weights (Mw) of approximately 22300 and 13100 Da respectively. PA-OLS has a lower molecular weight compared with the UDS-based polymer. This difference could be explained by the fact that undecylenic acid was used as a pure product whereas the oleic acid used in this study was a mixture of fatty acids isolated from high oleic sunflower oil. Saturated fatty acids such as palmitic and stearic, act as chain terminators during the polymerization thus decreasing the molecular weight and increasing the polydispersity. SEC analysis revealed that UDTGS incorporation into linear PAs significantly decreases its molecular weight to values close to 10.000 Da. Nevertheless it must be pointed out that SEC usually significantly underestimates the molar mass of branched polymers because the calibration is performed with linear standards. Crosslinked PA-UDTGS could not be analyzed by SEC. As expected the different polymers have completely different DSC behaviours. PA-UDS shows a glass-transition temperature (Tg) at -38ºC and a melting process as the merger of two peaks at 64 and 72ºC. On the other hand, DSC analysis of the OLS-derived PA shows a Tg at -65ºC. The incorporation of 20% of UDTGS into OLS induces the appearance of a low temperature melting point at -19ºC whereas the incorporation of the same amount of branching agent to UDS-derived PA slightly decreases the melting temperature and enthalpy. The highest Tg value for the prepared PAs was obtained for the crosslinked PA-UDTGS. TGA revealed that the degradation of these polymers under nitrogen atmosphere begins at around 250ºC, except for the crosslinked system that shows a higher thermal stability. Concerning the maximum weight loss rate, it was observed at around 400ºC for all the synthesized PAs. PAs are well known as useful biodegradable vehicles for localized drug delivery. Linear UDS-PA and branched UDS:UDTG (80:20) PA formulations show melting points at around 60ºC and therefore can be considered to be suitable for drug incorporation by melting and delivery through a degradation process. In fact, sebacic acid-based PAs synthesized from naturally occurring sebacic acid with melting temperatures close to 80ºC have been widely used for drug incorporation by a melting process and have shown excellent drug carrier properties in addition to good biocompatibility.[24,25]

Hydrolytic Degradation and Drug Release Properties

First, the hydrolytic degradation of the linear UDS-based and branched UDS:UDTGS (80:20) PAs was carried out in 100 mL of phosphate buffer solution (pH 7.4) at 37ºC and studied in terms of anhydride bond loss, weight loss, molecular weight loss, and surface morphology. The FT-IR spectra of both PAs varied significantly during the degradation process. Initially, the PA FT-IR spectra were dominated by peaks at 1815 and 1742cm^{-1}, characteristic of C=O anhydride bonds. During the hydrolytic degradation, a broad carboxylic hydroxy band between 3500 and 2500cm^{-1} and a strong carboxylic carbonyl band at 1701cm^{-1} appeared, and their intensities became stronger with prolonged degradation time. The intensities of the characteristic anhydride bond absorption bands at 1815 and 1742cm^{-1} and the C-O-C stretching band at 1101cm^{-1} obviously become weaker. These changes can be seen for PA-UDS in Figure SF3, Supporting Information.

The evolution of the percentage of anhydride bonds to the acid as a function of time for both PAs is shown in Figure 3A.

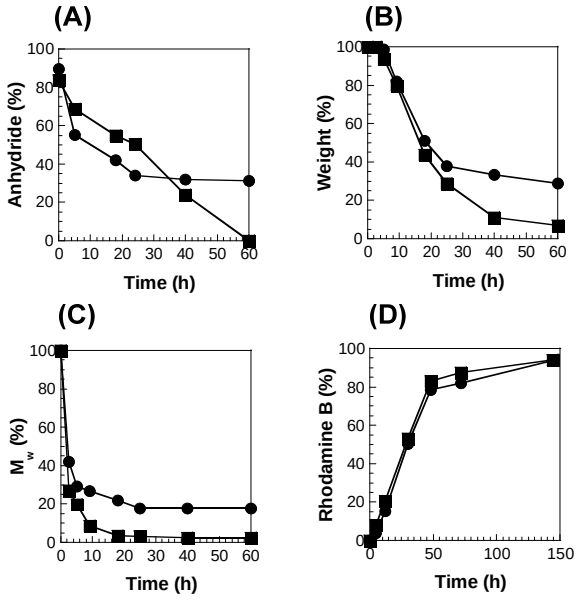


Figure 3. Evolution of % anhydride bonds (A), % weight (B), % M_w (C) during the hydrolytic degradation of PA-UDS (■) and PA-UDS:UDTGS (80:20) (●) conducted at 37 ºC in phosphate buffer solution (pH 7.4). (D) Rhodamine B release studies carried out with polymer devices of PA-UDS and PA UDS-UDTGS (80:20) containing 5% of hydrophobic dye in phosphate buffer (pH=7.4) at 37ºC.

PA-UDS showed fast and progressive percentage anhydride bond decay. It was found that the polymer loses around 50% of its anhydride bonds within 24 h and complete disappearance of the anhydride FT-IR bands was observed after 60 h. Concerning the PA UDS:UDTGS (80:20) copolymer, we expected that the inclusion of UDTGS into the copolymer slowed down the degradation rate since UDTGS produces a branched PA and is significantly more hydrophobic than UDS. However, polymer degradation is a complex phenomena influenced by multiple factors, including the hydrophilic/hydrophobic balance, crystallinity of the polymer matrix, and the water solubility of the degradation products. Figure 3A shows that the percentage copolymer anhydride bond loss curve follows a two-stage degradation profile: rapid hydrolysis of approximately 70% of the anhydride bonds followed by much slower hydrolysis of residual bonds. This can be explained by the degradation and release of UDS from the matrix, leaving a more hydrophobic UDTGS-rich framework. The more hydrophobic the PA matrix, the more difficult the cleavage of anhydride bonds in an aqueous environment. Nevertheless, a carefully analysis of the first 20 h of degradation shows that copolymer degradation is faster loosing around 50% of the anhydride bonds within 24 h. This can be related to the reduced crystallinity of the branched polymer in comparison to the PA-UDS. Crystalline regions are more resistant to hydrolysis than amorphous regions. As shown in Table 1, the enthalpy of the UDS-PA system is significantly higher than that in the copolymer system and, therefore, the addition of UDTGS segments hinders the crystallization of UDS domains, and thus accelerates the hydrolysis. The hydrolysis of the fatty acid-based PAs was also studied by monitoring the weight loss and molecular weight loss as a function of degradation time. The rate of polymer weight loss depends on the hydrolysis of anhydride linkages and solubility of the released carboxylic acid monomers. Weight loss data for both PAs are consistent with anhydride bond hydrolysis data. According to the limited solubility of UDTGS, weight loss data for PA UDS:UDTGS reaches a plateau after 24 h (Figure 3B). In Figure 3C, a similar decrease can be seen from the percentage Mw decrease data: the UDS-based linear PA decreases much faster in molecular weight. It can be seen that after 25 h the polymer degraded back to the molecular weight level of the monomer. The drop in molecular weight was accompanied by a narrowing of the polydispersity. Concerning the UDS:UDTGS copolymer, again a two-stage degradation profile is observed, a sharp decrease of the weight and Mw

within 24 h is followed by a slow rate of polymer weight loss probably determined by the hydrophobicity of the UDTGS-rich framework. These results correlate with the anhydride bond loss data presented above. It is important to mention that through-out the study the devices did not crumble, nor were there any visible cracks, but the device volume decreased as the polymer degraded. These observations together with mass loss data revealed surface erosion characteristics. In order to see how the microstructure changes during erosion and to visualize the erosion front, the outer surface and cross section of samples before and during degradation were observed by SEM. After erosion the smooth surface of the PA-UDS sample becomes very rough as shown in Figure 4A and B. The outer eroded layers consist of loosely associated polymer plates separated by medium to large pores. To visualize the erosion front, polymer samples were broken up and the cross-section was visualized by SEM.

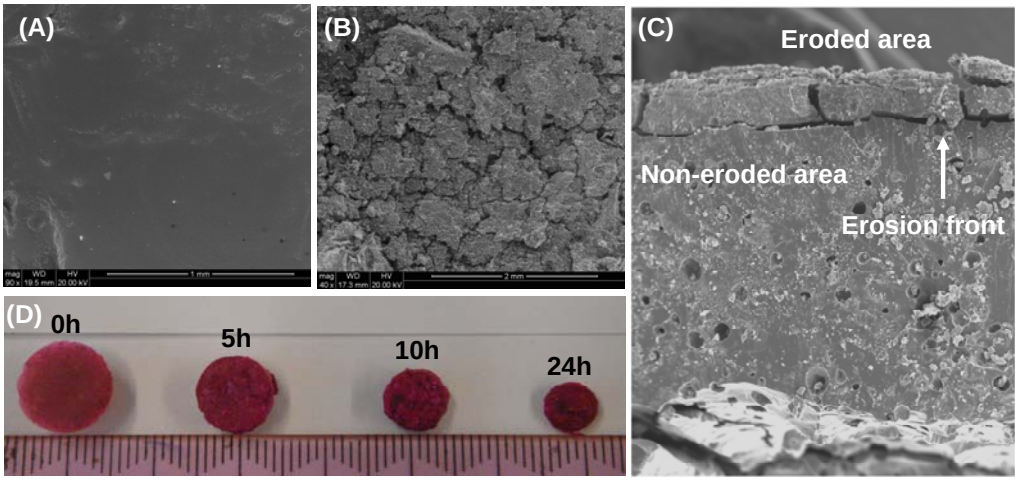


Figure 4. SEM micrographs of the outer surface and cross section of PA-UDS discs before and after degradation for 16 h in a phosphate buffer solution (pH 7.4) at 37ºC. (A) Outer surface before degradation; (B) outer surface after degradation for 16 h; (C) cross section after degradation for 16h.

In Figure 4C, there is a clear erosion front between the eroded portions and the remaining specimen. The fragile porous materials formed on the surface of the specimens are a typical indicator of a surface erosion degradation mechanism. Finally, UDS-based PAs were investigated for their release kinetics. Release studies were carried out with polymer devices of PA-UDS and PA UDS-UDTGS, containing 5% rhodamine B as

a hydrophobic dye, in phosphate buffer (pH 7.4) at 37ºC. The results of the release study are shown in Figure 3D. There was no significant difference between both polymers and the study was characterized by a rapid release of rhodamine B over the course of 60 h. As can be seen in Figure 4D, dye-loaded polymer devices showed progressive reduction in size with time indicating that delivery is governed by surface erosion.

Conclusions

In summary, by taking advantage of the recent advances in click chemistry we report the synthesis of novel polycarboxylic monomers based on oleic acid, undecylenic acid, and 10-undecenoyl triglyceride. Photoinitiated thiol-ene click chemistry was applied to these fatty acid compounds using 3-mercaptopropionic acid. This synthetic methodology leads to new biobased polyacids which have been used in the preparation of PAs. The synthesized PAs exhibit fast degradation and release properties making them suitable for fast-acting applications such as wound care. The results presented here demonstrate that thiol-ene click chemistry is a promising route that can be used for the synthesis of novel monomers and polymers from plant oils as renewable resources.

Acknowledgement. Financial support by the MICINN (Ministerio de Ciencia e Innovacion) (MAT2008-01412) is gratefully acknowledged.

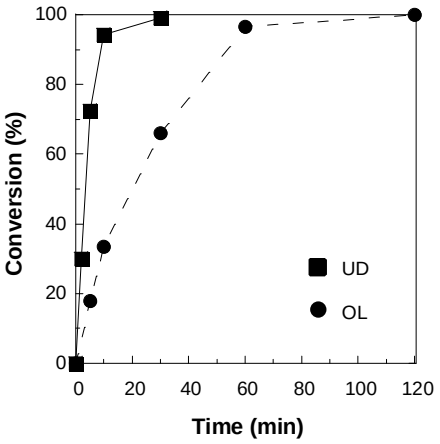
Supporting Information

Materials

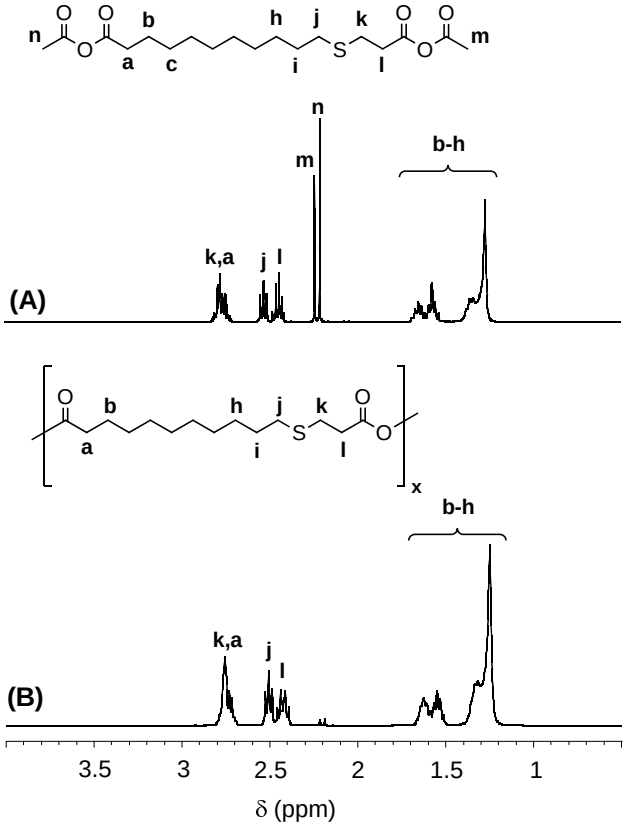
The following chemicals, acetic anhydride, undecylenic acid (98%), linoleic acid (>99%), 3-mercaptopropionic acid (99%) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) (99%) were purchased from Aldrich and used as received. High oleic sunflower oil was kindly supplied by Borges and 10-undecenoyl triglyceride (UDTG) by DOW Chemical Company.

Instrumentation

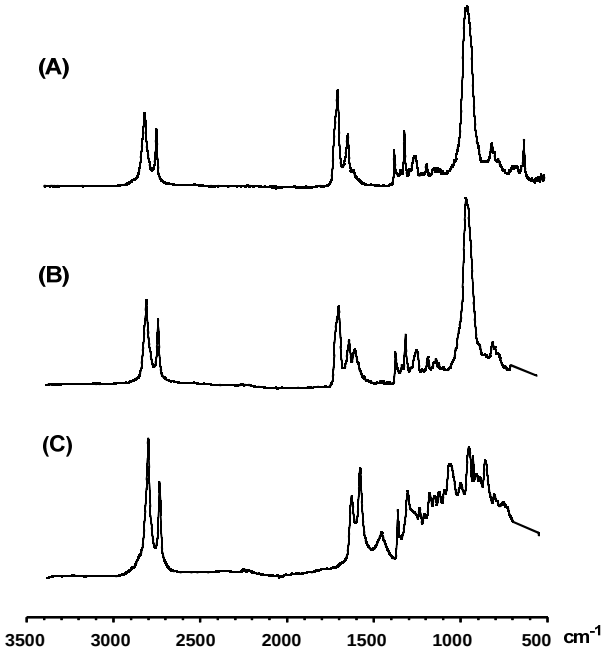
NMR spectra were recorded on Varian NMR Systems 400. Samples were dissolved in deuterated chloroform ($CDCl_3$), and ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature (with TMS as an internal standard). Size exclusion chromatography (SEC) analysis was carried out with an Agilent 1200 series system equipped with an Agilent 1100 series refractive-index detector. THF was used as eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained with polystyrene standards. Calorimetric studies were carried out with Mettler DSC821 and Mettler 27 DSC822e thermal analysers with N_2 as the purge gas. A heating rate of 20ºC/min was applied. Thermal stability studies were carried out with a Mettler TGA/SDTA851e/LF/1100 with N2 as the purge gas at a scanning rate of 10ºC/min. GC-MS measurements were carried out using a HP6890 Gas Chromatograph coupled to a HP5973 Mass Selective Detector. Ultraviolet (UV) light irradiation of the samples for thiol-ene coupling was carried out with two 9W bench lamps which emit around 365 nm wavelength. Infrared (IR) spectra of the samples were recorded on a Bomem Michelson MB 100 FTIR spectrophotometer with a resolution of 4 cm^{-1} in the absorbance mode. An attenuated total reflection (ATR) accessory with thermal control and a diamond crystal (Golden Gate heated single-reflection diamond ATR, Specac-Teknokroma) was used. Scanning electron microscopy (SEM) was performed on a JEOL JSM 6400 scanning electron microscope, at an activation voltage of 10kV. UV spectrophotometry measurements were carried out in a Hewlet Packard 8452 using HP 89531 A software.



Supporting Figure SF1. Kinetic plots for the photoinitiated thiol-ene click coupling between 3-mercaptopropionic acid and (■)10-undecenoic acid and (●) oleic acid.



Supporting Figure SF2. 400 MHz 1H-NMR spectra ($CDCl_3$) of (a) acetylated UDS and (b) PA-UDS.



Supporting Figure SF3. FTIR spectra of PA-UDS degrading in phosphate buffer (pH 7.4) at 37ºC. (A) Before degradation; (B) after degradation of 5 h; (C) after degradation of 60 h.

[1] A. Gandini, *Macromolecules* **2008**, 41, 9491.

[2] M. A. R. Meier, J. O. Metzger, U. S. Schubert, *Chem. Soc. Rev.* **2007**, 36, 1788.

[3] F. S. Güner, Y. Yagci, A. T. Erciyes, *Prog. Polym. Sci.* **2006**, 31, 633.

[4] U. Biermann, W. Friedt, S. Lang, W. Luhs, G. Machmuller, J. O. Metzger, *Angew. Chem., Int. Ed.* **2000**, 39, 2206.

[5] Y. Xu, Z. Petrovic, S. Das, G. L. Wilkes, *Polymer* **2008**, 49, 4248.

[6] G. Lligadas, J. C. Ronda, M. Galià, U. Biermann, J. O. Metzger, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, 44, 634.

[7] A. J. Domb, R. Nudelman, *J. Polym. Sci., Part A: Polym. Chem.* **1995**, 33, 717.

[8] L. S. Nair, C. T. Laurencin, *Prog. Polym. Sci.* **2007**, 32, 762.

[9] J. P. Jain, D. Chitkara, N. Kumar, *Expert Opin. Drug Delivery* **2008**, 5, 889.

[10] J. P. Jain, M. Sokolsky, N. Kumar, A. J. Domb, *Polym. Rev.* **2008**, 48, 156.

[11] A. J. Domb, M. Maniar, *J. Polym. Sci. Polym. Chem.* **1993**, 31, 1275.

[12] [12a] T. Eren, S. H. Küsefoglu, *J. Appl. Polym. Sci.* **2004**, 91, 4037; [12b] S. N. Khot, J. J. La Scala, E. Can, S. S. Morye, G. R. Palmese, G. I. Williams, S. H. Küsefoglu, R. P. Wool, *J. Appl. Polym. Sci.* **2001**, 82, 703; [12c] J. P. Jain, S. Modi, N. Kumar, *J. Biomed. Mater. Res. A* **2008**, 84, 740.

[13] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2001**, 40, 2004.

[14] M. J. Kade, D. J. Burke, C. J. Hawker, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, 48, 743.

[15] [15a] C. Lluch, J. C. Ronda, M. Galià , G. Lligadas, V. Cádiz, *Biomacromolecules* **2010**, 11, 1646; [15b] O. Türünç, M. A. R. Meier, *Macromol. Rapid Commun.* **2010**, 31, 1822; [15c] O. Türünç, M. A. R. Meier, *Green Chem.* **2011**, 13, 314.

[16] A. F. Jacobine, ''Thiol-ene Photopolymerization in Radiation Curing'', in Polymer Science and Technology, Vol. 3, (Eds: J. P. Fouassier, J. F. Rabek), Chapman and Hall, London 1993.

[17] H. J. Harwood, *Chem. Rev.* **1962**, 62, 99.

[18] [18a] K. Griesbaun, *Angew. Chem., Int. Ed.* **1970**, 9, 273; [18b] T. M. Roper, C. A. Guymon, E. S. Jönsson, C. E. Hoyle, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, 42, 6283; [18c] J. Samuelsson, M. Jönsson, T. Brinck, M. Johansson, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, 42, 6346; [18d] C. Chatgilialoglu, A. Altieri, H. Fischer, *J. Am. Chem. Soc.* **2002**, 124, 12816; [18e] C. Chatgilialoglu, A. Samadi, M. Guerra, H. Fischer, *Chem. Phys. Chem.* **2005**, 6, 286.

[19] M. Claudino, M. Johansson,M. Jönsson, *Eur. Polym. J.* **2010**, 46, 2321.

[20] G. Lligadas, L. Callau, J. C. Ronda, M. Galià, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem.* **2005**, 43, 6285.

[21] G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, 44, 6717.

[22] U. Biermann, M. A. R. Meier, W. Butte, J. O. Metzger, *Eur. J. Lipid Sci. Technol.* **2011**, 113, 39.

[23] J. D. Earls, J. E. White, L. C. López, Z. Lysenko,M. L. Dettloff, M. J. Null, *Polymer* **2007**, 48, 712.

[24] R. Teomim, A. J. Domb, *J. Polym. Sci. Part A: Polym. Chem.* **1999**, 37, 3337.

[25] [25a] C. Monoharan, J. Singh, *J. Pharm. Sci.* **2009**, 98, 4237; [25b] A. J. Domb, R. Wartenfeld, *Polym. Adv. Technol.* **1994**, 5, 577; [25c] D. Chickering, J. Jacob, E. Mathiowitz, *Biotechnol. Bioeng.* **1996**, 52, 9.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Chapter 3

Synthesis and Evaluation of Antimicrobial Polyurethane Coatings based on Undecylenic Acid

This chapter is devoted to the preparation of polyester-polyols via thiol-yne photopolymerization of undecylenic acid derivatives with dithiols. The prepared functionalized oligomers have been used in the preparation of polyurethane networks with potential application as antimicrobial coatings.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Synthesis and Evaluation of Antimicrobial Polyurethane Coatings based on Undecylenic Acid

Cristina Lluch[a], Braulio Esteve-Zarzoso[b], Albert Bordons[b], Gerard Lligadas[a], Joan C Ronda[a], Marina Galià[a], Virginia Cádiz[a]

[a] Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel.lí Domingo s/n, Tarragona 43007, Catalonia, Spain. [b] Departament de Bioquímica i Biotecnologia, Facultat d'Enologia, Universitat Rovira i Virgili, C/ Marcel.lí Domingo s/n, Tarragona 43007, Catalonia, Spain.

* To whom correspondence should be addressed: gerard.lligadas@urv.cat

Abstract:

In the present study we have prepared plant oil-derived surface-modifiable polyurethane coatings. Polyols synthesis was carried out taking advantage of thiol-yne photopolymerization of alkynic fatty acid derivatives. The prepared methyl ester-containing polyurethane coatings allowed surface modification treatment to enhance their hydrophilicity and antimicrobial properties through the following two steps: (1) grafting poly(propylene glycol) monoamine (Jeffamine M-600) via aminolysis and (2) Jeffamine layer complexation with iodine. The antimicrobial activity of the iodine containing polyurethanes has been demonstrated by their capacity to inhibit the growth of *Staphilococcus aureus* and *Candida albicans* in agar media.

Introduction

The development of polymeric systems for biomedical applications is currently an active area of research.[1-3] The incorporation of polymer-based materials in the manufacture of medical devices from short-term store and filtration equipment to long-term implants have been widely used to save lives and to restore quality for many people. However, the infections of microorganisms in physiological environments are serious issues associated with their use, often leading to the failure of the medical device.[4-6] Device-related infections start with the adhesion of microorganisms cells to the biomaterials surfaces. Thus medical industry has prompted a strong interest in coatings that applied on the surface of biomedical device provide antimicrobial performance.[7,8]

Due to their biocompatibility and excellent performance as coating materials for various surfaces, polyurethanes (PUs) have been considered to prepare antimicrobial materials with diverse final biomedical and non-biomedical applications.[9-15]Both biocide release and contact-kill approaches have been investigated. Nowadays, PUs are mainly prepared from petroleum-based raw materials; however, many scientific and industrial attempts have been started to replace them with those based on renewable resources. The main achievement in this regard is devoted to the preparation of polyols from vegetable oils as widely available, inexpensive, biocompatible and biodegradable feedstock.[16-18]There are some reports regarding the preparation of plant oil-based antimicrobial PUs.[19-20]In the biomedical area, triglycerides and derived fatty acids are attractive as building blocks in linear and crosslinked polymers due to inherent biodegradability, limited toxicity, and existence of modifiable functional groups. Although little has been studied about potential biomedical applications of such biobased PUs,[21-26] their intrinsic hydrophobicity is envisioned to be a major drawback in high demanding applications.

Hydrophobic surfaces have been shown to be more quickly populated by free-swimming bacteria than hydrophilic surfaces.[8] Although most microorganisms have a charged outer surface, they also contain hydrophobic patches and these may be involved in the adhesion to the hydrophobic surface of a medical implant. In reality, however, the adhesion of microorganisms is almost always dependent on formation of a protein layer

on the surface, possibly exposing high-affinity adhesion sites. The proteins are present in the tissues of the patient and adsorb very rapidly upon implantation. Especially with blood contacting the surface, proteins like albumin, fibrinogen and fibronectin promptly adsorb onto the surface. This means that when designing and antimicrobial surface, the adhesion of proteins to the surface is an important parameter that has to be taken into account. One of the commonly applied strategies to prevent protein adhesion on biomaterials and improve the hemocompatibility without detrimentally affecting the bulk physical and mechanical properties of the initial material is to create non-fouling surface with a hydrophilic layer based on for example poly(ethylene glycol),[27,28] heparin,[29,30] phospholipid polymer,[31,32] natural materials (gelatin, collagen, chitosan), or alginate.[33-36] Moreover, hydrophilic surfaces are also beneficial for cell attachment and cell growth in tissue engineering applications.

In the search of biobased functional polyols for PU technology our group recently applied thiol-ene and thiol-yne click chemistry couplings to 10-undecenoic acid (UD) and its alkyne derivative, 10-undecynoic acid (UDY).[37,38] UD is a C11 fatty acid derivative with a terminal C-C double bond, which can be obtained by heating ricinoleic acid, the major component of castor oil, under vacuum pyrolysis. Here, we apply thiol-yne step-growth polymerization to undecenyl alcohol/methyl undecynoate mixtures to afford a novel set of methyl ester-containing biobased polyols (PL). The obtained polyols have been used for the synthesis of surface-modifiable PU coatings. In this work we also study the possibility of preparing plant-derived PUs with enhanced surface hydrophilicity coupled with antimicrobial property through the following two steps: (1) The PU surface hydrophilicity was increased by grafting poly(propylene glycol) monoamine (Jeffamine M-600) onto the methyl ester-containing PU coating via aminolysis and subsequently (2) the more hydrophilic PU surface terminated by Jeffamine layer was complexed with iodine, one of the most used antiseptics in biomedical settings with low cost and high efficacy, through the formation of a charge-transfer complex. The antimicrobial activity of the copolymers has been evaluated by determining their capacity to inhibit colony growth of different microorganisms.

Experimental Section

Materials. The following chemicals were purchased from Aldrich and used as received: 10-undecenoic acid (98%), 2,2-dimethoxy-2-phenylacetophenone (DMPA) (99%), 3,6-dioxa-1,8-octane-dithiol (95%), tin (II) 2-ethylhexanoate, 4,4′-methylenebis(phenylisocyanate) (MDI) and iodine (≥ 99.99%). Tetrahydrofuran (THF) was distilled from sodium immediately before use. O-(2-Aminopropyl)-O′-(2-methoxyethyl)polypropylene glycol 600 (Jeffamine M-600) was purchased from Fluka. Methyl 10-Undecynoate (UDYM) and 10-undecynol (UDYO) were prepared following the methodology described previously.[37] *Pseudomonas aeruginosa* CECT 110 (*P. aeruginosa*), *Staphylococcus aureus* CECT 239 (*S. aureus*) and *Candida albicans* CECT 1392 (*C. albicans*) were obtained from Colección Española de Cultivos Tipo (CECT), Valencia, Spain.

Instrumentation. NMR spectra were recorded on Varian VNMRS400. The samples were dissolved in deuterated chloroform, and ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature with tetramethylsilane (TMS) as an internal standard. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurements were performed with a Voyager DE-RP mass spectrometer (Applied Biosystems, Framingham, MA) equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol was used as a matrix, and silver trifluoroacetate was used as a cationization agent. In a vial, 25 mg of the matrix was dissolved in 1 mL of THF. Separate solutions of polymer (10 mg/mL in THF) and salt (2 mg/mL in dionized H_2O) were prepared. The solution for MALDI-TOF analysis was obtained by mixing the matrix, polymer, and salt solution in a 5/1/1 volumetric ratio. Then 0.5 μL portions of the mixture were deposited onto 10 wells of the sample plate and dried in air at room temperature. Size exclusion chromatography (SEC) analysis was carried out with an Agilent 1200 series system equipped with an Agilent 1100 series refractive-index detector. THF was used as an eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained with polystyrene standards. Differential Scanning Calorimetry (DSC) measurements were carried out with a Mettler DSC822e thermal

analyser with N_2 as the purge gas. 6-12 mg samples were used for DSC analysis. Polyol samples were heated from -20 to 150ºC with a heating rate of 20ºC/min, cooled down to -90ºC with a cooling rate of -20ºC/min, and then heated again to 150ºC at the same heating rate. Tg values were obtained from the second heating curves. For analyzing polyurethanes, samples were heated from -80 to 240ºC with a heating rate of 20ºC/min. Thermal stability studies were carried out with a Mettler TGA/SDTA851e/LF/1100 with N_2 as the purge gas at a scanning rate of 10ºC/min. Ultraviolet (UV) light irradiation of the samples for thiol-yne photopolymerization was carried out with two 9W bench lamps which emit around 365 nm wavelength. The IR spectra were recorded on a Bomem Michelson MB 100 FTIR spectrophotometer with a resolution of 4 cm^{-1} in the absorbance mode. An attenuated total reflection (ATR) accessory with thermal control and a diamond crystal (Golden Gate heated single reflection diamond ATR, Specac-Teknokroma) was used to determine FTIR spectra. The contact angle of deionized water against polymer surfaces was measured by the water drop method (3μL) at 25°C, using the OCA15EC contact angle setup (Neurtek Instruments). Tensile tests were performed with an Instron Dynamometer (model 5942, USA) on films of 5 cm length (distance between the grips of about 30 mm) and 500 mm width at a crosshead rate of 10 mm/min and at room temperature.

Preparation of Polyols

Polyols were prepared by the following general procedure described for PL(50/50). A 25 mL flask was charged with 0.17 g (1 mmol) of UDYO, 0.18 g (1 mmol) of MUDY, 20 mg of DMPA (0.09 mmol) and 0.34 mL (2 mmol) of 3,6-dioxa-1,8-octandithiol. The reaction was carried out at room temperature by irradiation with two UV lamps (365 nm) during 1h. The completion of the reaction was confirmed by ^{1}H NMR analysis. The synthesized polyols were used to prepare various PU coating formulations without further purification.

^{1}H NMR [$CDCl_3$]/(TMS), δ, ppm): 3.60 (s, 6H, -OCH_3), 3.57 (m, 18H, -CH_2-O-; -CH_2OH), 2.82 (dd, 2H, -S-CH_2-), 2.62-2.72 (m, 12H, -S-CH_2-, -S-CH-), 2.24 (t, 2H, -$COCH_2$), 1.71-1.23 (m, 30H, -CH_2-).

Preparation of PU Coatings

The prepared polyols were dissolved, immediately after synthesis, in anhydrous THF (50% solution) under argon atmosphere. The homogeneous solution was heated at 55°C and added to a 50% solution of MDI in THF (55 ºC) under argon atmosphere. The solution was homogenized and casted over silanized glass preheated at 50°C. The PU was cured at 50 °C overnight and at 110 °C for 2 hours. For determining the gel content of PU, samples were weighted accurately and extracted by THF in a Soxhlet extractor for 24h. The insoluble part was dried at 70ºC and weighted. The gel content was defined as follows:

Gel content (%) = $(W_d/W_i) \times 100$

Where W_d is the weight of dried sample after extraction and W_i is the initial weight of the sample.

Two Step Surface Modification of PU(25/75) Coating

PU(25/75) films of 1 x 0.5 cm were washed with water/ethanol (50% v/v) to clean dirt, with large amount of water and then dried at room temperature under reduced pressure for 12h. Then, films were aminolysed immersing them in a 4M Jeffamine M-600/iPropanol solution for 3h at 37ºC. After this, the modified samples were repeatedly rinsed with a large quantity of distilled water to remove free amine for 24h and finally dried under reduced pressure at 30ºC for 12h.

The aminolysed films were then immersed in a iodine/ethanol solution (1.58 g/L or 3.16 g/L) at room temperature for 3h. Then, the iodine treated films were thoroughly washed with n-heptane, which is known to be a good solvent for the adsorbed iodine.[39] The PU(25/75)-iodine complex discs were air dried, conditioned in a desiccator for 24h at room temperature and weighted.

The percent iodine content was calculated according to the following equation:

$I_2\% = (W_2 - W_1)/W_1 \times 100$

where W_1 and W_2 were the weights of the PU films before and after iodine binding, respectively.

Microbial Incubation

Gram positive bacterium *S. aureus* and Gram negative bacterium *P. aeruginosa* were grown in sterilized TSB (Tryptone Soya Broth) at 37ºC overnight and yeast *C. albicans* was cultivated in sterilized YPD (Yeast extract-Peptone-Dextrose) broth at 28ºC overnight. Then the microbial suspensions were diluted in sterilized water.

Antimicrobial Activity Measurements of PU Coatings

Antimicrobial performance of the PU coatings was studied according to agar diffusion test. Briefly, 100 µL of microbial growth (with a concentration of ca. 10^6 colony forming units (CFU)/ml) and the PU disks (d=5 mm), previously sterilized by UV irradiation, were placed on the agar plate and incubated for 24h at 28ºC (*C. albicans*) or 37ºC (*P. aeruginosa* and *S. aureus*) After that, the bacterial growth inhibition halos around the of samples were observed and their diameters were measured. Each test was repeated two times obtaining reproducible results.

Bacterial Testing of inhibition kinetics curve

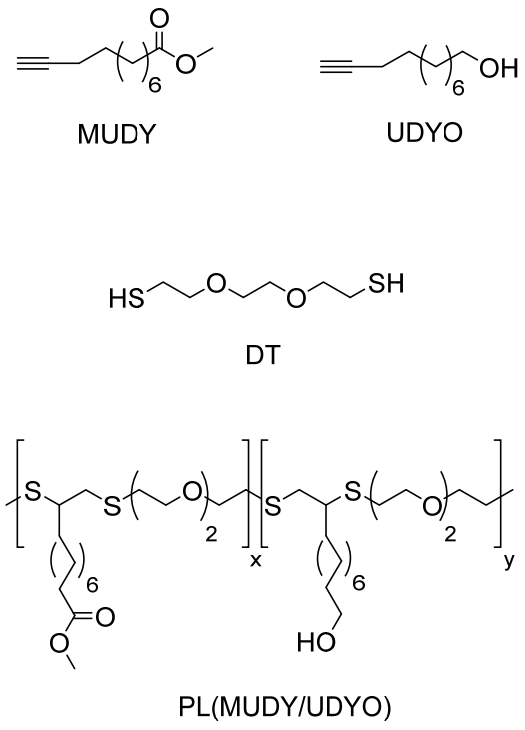
To examine the kinetics of the bacteria growth in presence of the PU, 50 mg of PU were immersed in 3.5 mL of culture media (TSB or YPD) with 100 µL of bacterial medium (with a concentration of ca. 10^6 colony forming units (CFU/mL). The incubation was performed at 28ºC or 37ºC during 9h. Pure microorganisms media (10^6 CFU/mL) were also incubated and served as controls. The optical density (OD) of the medium at 600 nm was measured by a UV-vis spectrophotometer and the values represented versus time.

Results and Discussion

Synthesis and Characterization of Methyl Ester-Containing Polyols

As described previously,[40] alkyne-derivatized fatty acids can be obtained in acceptable yields from the corresponding unsaturated fatty acids by bromination and subsequent dehydrobromination using well-established procedures.[41] In this study, 10-undecynoic acid (UDY) was prepared from 10-undecenoic acid, a major product of castor oil pyrolisis, and used as starting material for the preparation of both fatty acid-derived

polyol building blocks: methyl 10-undecynoate (MUDY) and 10-undecynol (UDYO) (Scheme 1).



Scheme 1. Chemical structure of MUDY, UDYO, DT and polyols PL(MUDY/UDYO).

Photoinitiated thiol-yne step-growth polymerization was used to homopolymerize both alkyne-derivatized fatty acid using 3,6-dioxa-1,8-octane-dithiol (DT, Scheme 1). The radical-mediated photopolymerization of thiols to fatty acid alkynes has been also described recently.[42] As with the thiol-ene coupling, the thiol-yne addition, in general proceeds rapidly under a variety of experimental conditions selectively yielding the mono- or bis-addition products.[43] In the case of the double addition products formed under radical conditions, the reaction of two equivalents of thiol with an alkyne is itself a two-step process. The first step involves the addition of thiol to the C≡C triple bond to yield an intermediate vinyl thioether that subsequently undergoes a second, formally thiol-ene reaction with an additional thiol, yielding the 1,2 double-addition product as the sole product in quantitative yield.

Initially, the photoinitiated thiol-yne homopolymerization of MUDY and UDYO was carried out to determine optimum reaction conditions to ensure complete alkyne conversion. Reactions were carried out at room temperature using 1/1 C≡C/DT molar ratio under UV-light with/without DMPA as photoinitiator. The reaction was monitored by ^{1}H NMR analysis. The disappearance of the signal associated to the triple bond (1.92 ppm) and the appearance of new signals associated to thioether linkages (2.7-2.9 ppm) was used to prove the successful polymerization. As expected, photopolymerization in the absence of DMPA proceeded only to low conversion. On the other hand, 4.3 mol-% of DMPA was enough to achieve complete conversion of both MUDY and UDYO only in 1h. SEC analysis of the obtained polymers revealed the presence of a mixture of oligomers with molecular weight at around 10.000 Da and polydispersity index slightly higher than 2. To gain insight about the structure of the obtained polymers, PL(MUDY/DT) was analyzed by MALDI-TOF-MS (Figure 1a). Two principal series of peaks can be observed. Series A (■) have an interval between peaks of 378 Da which correspond to the molar mass of the repeating unit of the polymer. This series present the peaks at m/z ((182.3 + 196.2)n + Ag^{+}; n(2)=865, n(3)= 1243, n(4)= 1621, n(5)= 2000,...), which could correspond to a brush-like structure with a SH and vinyl sulphide end-groups or to the cyclic structure. The other major series of peaks, series B (▲) at m/z ((182.3+196.2)n +182.3 + Ag^{+}; n(2)=1045, n(3)=1423, n(4)=1801, n(5)=2180,...) also shows a peak-to-peak increment of 378.3 Da but matches with a brush-like structure with two SH moieties at the chain ends.

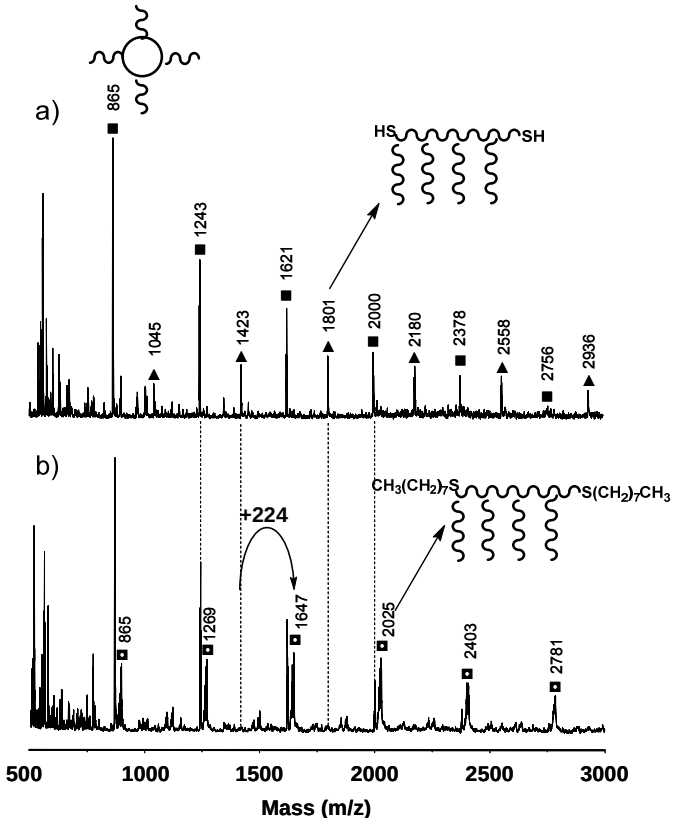


Figure 1. MALDI-TOF spectra of PL(MUDY/DT) (a) before and (b) after thiol-ene reaction with an excess of 1-octene in the presence of DMPA as a photoinitiator under UV light.

To confirm the nature of series A and B, an end-group modification experiment was carried out via photoinitiated thiol-ene coupling at the polymer chain end. Thus, free SH end groups of PL(MUDY/DT) were end-capped with 1-octene in the presence of DMPA as photoinitiator and UV irradiation. As can be seen in Figure 1b, after end-capping, series B (▲) completely vanished and at the same time appeared 224 units above (series ◘) the previous distribution. This value corresponds to two times the molar mass of 1-octene (112). This observation confirms that series B corresponds to a brush-like structure with two terminal SH moieties. On the other hand, the main series of peaks A were unaffected under thiol-ene coupling conditions. This observation confirms unequivocally that series A corresponds to cyclic structures with no SH moieties.[44] These results indicate that PL(MUDY/DT) and PL(UDYO/DT) are a mixture of cyclic and brush-like oligomers, and explain the quite low values obtained for these polymers (~10.000 Da).

In the search of novel biobased functional polyols for PU technology, the feasibility of the thiol-yne photopolymerization of MUDY and UDYO prompted us to further carry out the copolymerization of both monomers. UDYO was copolymerized with different amounts of MUDY under the above mentioned conditions to obtain polyols with different hydroxyl content values and pendant methyl ester functionalities. Scheme 1 shows the general structure of the prepared polyols PL(MUDY/UDYO), and Table 1 summarizes the polyol compositions and properties.

Table 1. Composition, hydroxyl content, molecular weight and thermal properties of the synthesized polyols.

Polyol Code	UDYO [a]	MUDY [a]	DT [a]	mmolOH/g polyol[b]	M_n^{SEC} (g/mol)[c]	T_m (°C)[d]
PL(100/0)	1	0	1	2.78	10165	-53
PL(75/25)	0.75	0.25	1	2.04	10400	-54
PL(50/50)	0.5	0.5	1	1.34	12900	-58
PL(25/75)	0.25	0.75	1	0.66	8470	-60

[a] Molar percentage in the feed; [b] Calculated from the UDYO composition in the feed; [c] Determined by SEC using polystyrene standards; [d] Determined by DSC (20ºC/min).

As expected molecular weight of the synthesized polyols was at around 10.000 Da regardless the monomer composition in the feed. The chemical structure of the prepared polyols was evaluated by ^{1}H NMR and FTIR spectroscopy. Figure 2 shows the ^{1}H NMR spectrum of PL(50/50).

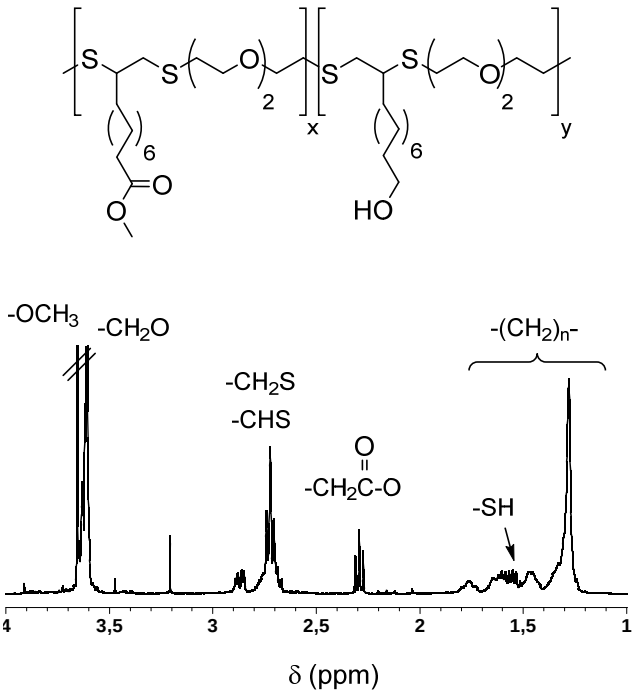


Figure 2. ^{1}H NMR spectrum of polyol PL(50/50)

The signals of the newly formed thioether linkages appeared at 2.7-2.9 ppm. As well, the peaks of methylol and methyl ester moieties appeared overlapped with CH_2-O signals at 3.7 ppm. According to Figure 2, the peaks of signal associated to the triple bond (1.92 ppm) disappeared completely, which showed fully consumption of triple bond during the thiol-yne reaction. The same conclusion can be derived from FTIR spectrum, since no signal was observed at 2200 cm^{-1} (C≡C stretching). Moreover, the peaks due to the stretching vibration of O-H and carbonyl ester groups were detected at 3400 cm^{-1} and 1742 cm^{-1}. Thermal behavior of synthesized polyols was investigated by DSC. All polyols exhibited similar thermal behavior, showing a Tg at around -55ºC. For formulation of the final PUs, the hydroxyl content value of the prepared polyols was calculated based on the UDYO amount on the feed.

Synthesis and Characterization of PU Coatings

The above synthesized polyols were used to prepare various formulations of PU networks without further purification. PU coatings were prepared via reaction of the polyols with slight excess of MDI diisocyanate (isocyanate index 1.02) at 50ºC for 12h. To ensure complete curing of PUs, the samples were postcured at 110ºC for 2h. FTIR spectroscopy was utilized for the evaluation of PUs chemical structure. Carefully observation of the carbonyl stretching vibration region reveals differences among the prepared PUs (Figure 3).

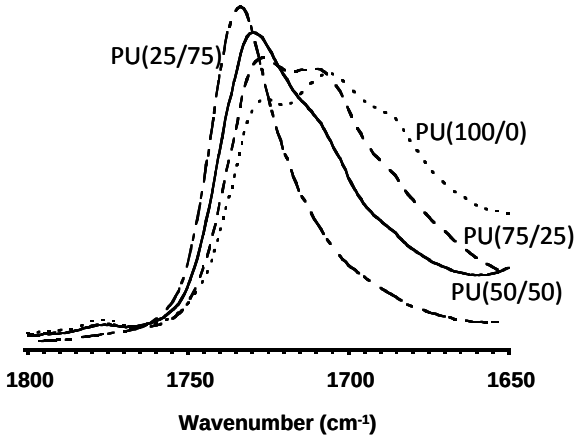


Figure 3. A section of FTIR spectra of PL(MUDY/UDYO)–derived PUs.

PU(25/75) shows a non-symmetrical broad band located at 1735 cm^{-1} with overlapped urethane/methyl ester carbonyl stretching vibrations. On the other hand, PUs with lower (PU(50/50), PU(75/25)) or no methyl ester content (PU(100/0)) showed two peaks at 1725 cm^{-1} and 1710 cm^{-1}, attributable to free and hydrogen bonded C=O urethane groups, respectively. As expected, the intensity of the band attributed to the bonded urethane groups, increases with an increase of PU urethane content indicating a higher degree of association. All PUs show a band related to the combination of N-H deformation and C-N stretching vibrations at 1533 cm^{-1} and 1233 cm^{-1}, respectively. Moreover, the stretching vibration of urethane N-H groups was detected as a broad peak centered at 3350 cm^{-1}. The absence of peak of isocyanate groups at 2270 cm^{-1} in the FTIR spectra

together with the obtained high gel content (>98%) of cured PU samples (see Table 2) confirmed complete reaction of active groups in the final networks.

Thermal, Mechanical, and Surface Hydrophilicity Properties of PU Coatings

Thermal transitions of prepared PUs were analyzed by DSC and values are listed in Table 2. The prepared materials are completely amorphous and display a glass transition temperature (T_g) between -50 to 30°C. According to Table 2, T_g value of PUs decrease as the hydroxyl content values of the parent polyol decreases. This is in accordance with a lower degree of crosslinking and poorer chain packing due to the presence of dangling methyl ester-terminated chains. Initial modulus, tensile strength, and elongation at break were obtained from stress-strain curves at 25ºC of PU samples in order to evaluate their tensile properties. Tensile strengths of all PU samples fell in the range of 1-8 MPa, except for the PU(100/0), which displayed about three times higher strength. Two factors affected the tensile strength: the crosslinking density of samples and the physical state of the material at the test temperature. Because the Tg of all samples except the PU(100/0) was below the testing temperature, they were tested in the rubbery state, which resulted in somewhat lower strengths and moduli and high elongations at break.

Table 2. Thermal, tensile and surface hydrophilicity properties of the synthesized PU coatings.

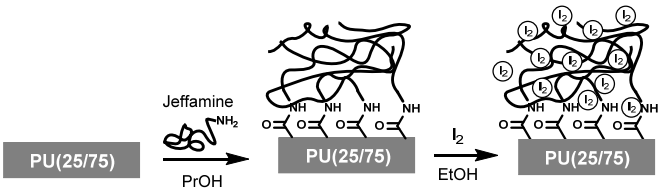
PU Code	T_g (ºC)[a]	$T_{5\%}$ (ºC)[b]	T_{max} (ºC)[b]	Modulus (MPa)	Stress (MPa)	Strain (%)	Contact angle (θ)	Gel Content (%)
PU(100/0)	32	300	346/467	10	23	72	73	98
PU(75/25)	2	307	347/470	7	7	64	80	96
PU(50/50)	-21	307	344/467	3	3	32	90	97
PU(25/75)	-47	309	342/463	1	1	51	91	98

[a] Determined by DSC (20ºC/min); [b] Determined by TGA under nitrogen atmosphere.

The thermal stability of the PUs was studied by TGA in a nitrogen atmosphere and the obtained data are also listed in Table 2. The TGA curves are almost identical for all the PUs and the differences in the thermal stability appear to be small. The derivative curves reveal that more than one process occurs during thermal degradation: the main loss around 340°C is related to the decomposition of urethane and the polyol itself. This decomposition process is follow by another around 460°C which is attributed to C-C chain scission. The weight loss in the first degradation stage increases as the hydroxyl content decreases. The surface hydrophilicity of prepared PUs was measured by evaluation of their static contact angle with distilled water. The surface of all samples was considered hydrophobic, since their water contact angle values were in the range of 70-90º.

Modification of PU surface via Aminolysis with Jeffamine M-600 and Iodine Complexation

The surface modification of polyester-type PUs and polyesters via aminolysis is a well-known procedure.[45-47] Recently, we have reported that methyl esters-containing thermoplastic PUs films based on fatty acids can be surface functionalized to improve cell-adhesive properties via aminolysis and further ionically immobilization of chondroitin sulfate.[23] In the present study, the above synthesized methyl-containing PU coatings also possess the capability to form covalent bonds with amines. Thus, PU(25/75) was selected to test a two step procedure to enhance its surface hydrophilicity and impart antimicrobial property. As seen in Scheme 2, PU(25/75) surface was first modified via aminolysis with poly(propylene glycol) monoamine (Jeffamine M-600) that was further complexed with iodine, one of the most used antiseptics in biomedical settings with low cost and high efficacy.



Scheme 2. Schematic illustration for the two steps surface modification of PU(75/25) with Jeffamine M-600 and iodine.

Aminolysis was carried out under mild conditions (37ºC) without catalyst by immersing the PU film in a 4M Jeffamine/^{i}Propanol solution for 3h. As can be seen in Figure 4, PU surface become significantly more hydrophilic after Jeffamine aminolysis treatment with the increase of inmmersion time and reached a plateau after 12h. Water contact angle value decreased from 91º to 65º in 24h.

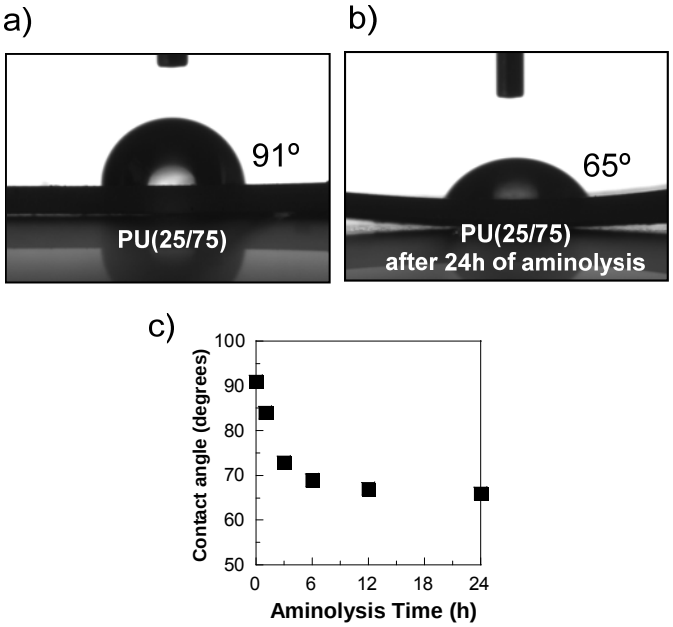


Figure 4. Contact angle images for PU(25/75) (a) before and (b) after 24h aminolysis treatment with Jeffamine/^{i}Propanol solution. (c) Contact angle evolution with aminolysis time treatment for PU(25/75).

Figure 5a and b shows the SEM micrographs of the (a) untreated and (b) aminolyzed PU coating for 3h. No significant variation on the surface morphology was observed after aminolysis treatment and both surfaces maintained a homogeneous morphology. ATR-FTIR spectroscopy also supported the occurrence of a chemical reaction at the PU surface, showing the appearance of strong C-O-C stretching vibration band at 1100 cm^{-1} due to the polyether Jeffamine chain. In addition, an increase in the intensity of the C-H stretching and bending vibration bands at 2920 cm^{-1} and 2850 cm^{-1} respectively was observed compared to the spectrum of the control PU.

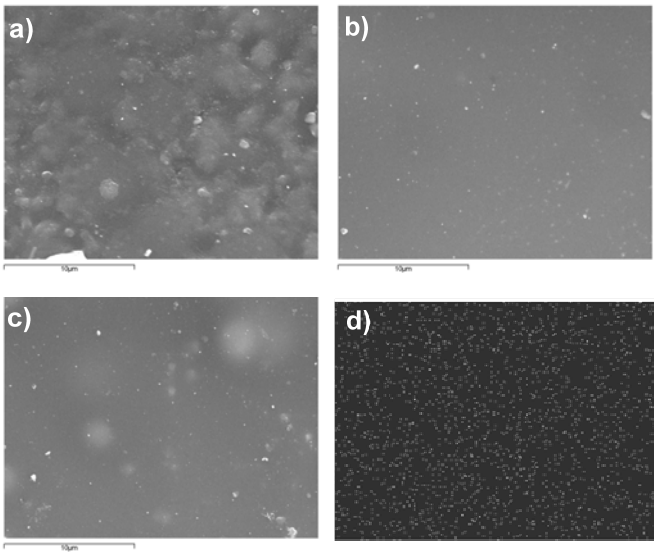


Figure 5. SEM micrographs of (a) PU(25/75) control, (b) after 3h aminolysis treatment with Jeffamine/iPropanol solution, and (c) after 3h immersion in a iodine/ethanol solution. Micrograph (d) corresponds to iodine Ka X-ray map of the PU(25/75) after aminolysis and iodine treatments.

In the second step, the PU surface terminated by Jeffamine layer was complexed with iodine, using different iodine/ethanol solutions for 3h. Immersion in a 1.58 g I_2/L solution produced a PU with 2 wt-% I_2, whereas using a solution of 3.16 g I_2/L produced a PU with higher iodine content (2.8 wt-% I_2). The yellow unmodified PU film turned dark purple after 60 min immersion in two different iodine/ethanol solutions. The color was not removed by repeating washing with heptane, suggesting strong iodine bonding. As can be seen in Figure 5c, PU surface after iodine complexation also maintained a regular and homogeneous morphology. Iodine charge-transfer complex formation was confirmed by SEM/EDX analysis. The EDX analysis showed that the intensity of the iodine Kz peak at 4 keV was essentially independent of the analyzed area, consistent with the homogeneity of the surface. As can be seen in Figure 3d, X-ray mapping confirmed a uniform distribution of iodine on PU surface.

XPS analysis was used to study both surface modification treatments and was consistent with the previous observations (Figure 6). In the XPS of control PU surface, the C1s peak consisted of three components at about 286, 288, and 291 eV which may be assigned to

the presence of aliphatic C-H and C-C bonds, C-O and C-N bonds and COOR groups, respectively (Figure 6a). In the C1s spectrum of the PU surface terminated by Jeffamine layer, compared to that of unmodified PU, signal at 286.6 eV assignable to –C-O-C- from Jeffamine[48] significantly increase after aminolysis treatment indicating the effective grafting of Jeffamine on PU surface (Figure 6b). PU surface containing complex-bound iodide was also investigated by XPS (Figure 6c). The presence of the I_{3d} peak ($I_{3d5/2}$ at 618.5 eV and $I_{3d3/2}$ at 631.1 eV proved the formation of iodine complexes in the surface layer of modified PU. Moreover, the splitting of the peaks in the I_{3d} region confirmed the formation of I_3^- species.[49]

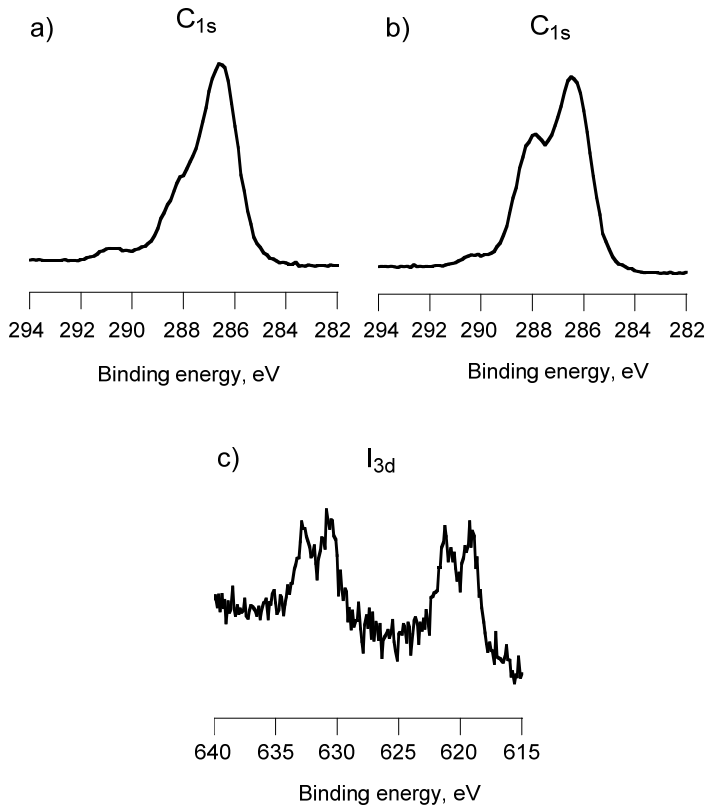


Figure 6. C1s spectra for (a) PU(25/75) control and (b) after 3h aminolysis treatment with Jeffamine/iPropanol solution. (c) I3d spectrum of PU(25/75) after aminolysis and iodine treatments.

Antimicrobial activity of surface modified PU

The antimicrobial activities of the iodine-containing PU(25/75) and controls were evaluated by Kirby Bauer technique (Figure 7). After 24h incubation, iodine-containing

PU(25/75) clearly showed activity against Gram positive bacteria *S. aureus* (37ºC) and also in yeast *C. albicans* (28ºC), but no activity was observed against Gram negative bacteria *P. aeruginosa* (37ºC), under the conditions studied. Moreover, the zone of inhibition (ZI) was larger by increasing iodine content. The zones of inhibition for high and low iodine content were 7.0 and 4.0 mm in *S. aureus* and 1.7 and 0.2 in *C. albicans*. As a controls, PU(25/75) and aminolyzed PU(25/75) showed no inhibition effect. Therefore, it can be concluded that the antimicrobial activities were mainly ascribed to the presence of iodine complex on the surface of the PUs.

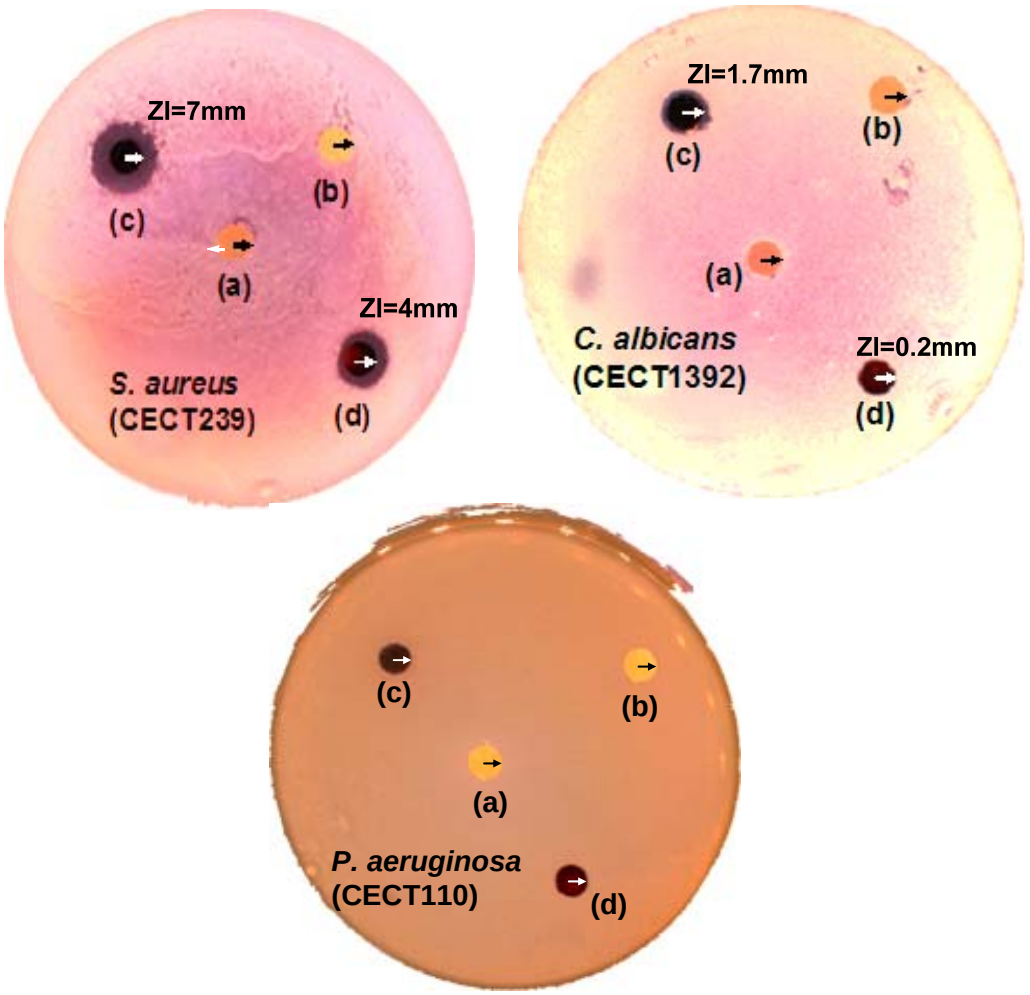


Figure 7. Antimicrobial test results for *S. aureus*, *C. albicans* and *P. aeruginosa* after 24h incubation. (a) PU(25/75) control, (b) PU(25/75) after 3h aminolysis treatment with Jeffamine/^{i}Propanol solution and PU(25/75) after aminolysis and iodine treatments containing (c) 2.8 wt-% I_2 and (d) 2 wt-% I_2.

The antibacterial activity of the iodine containing PUs was further investigated by growth time course *S. aureus* and *C. albicans* in liquid medium in the presence and absence of the polymeric coating. As can be seen in Figure 8a, both iodine containing PUs inhibited growth of *S. aureus* but this bacterium was able to overcome this inhibitory effect by the end of the 9 h incubation period. After 9 h incubation the culture containing PU film had achieved the same level of growth as the control. These observations show remarkable differences in the nature of the antimicrobial activity when compared to results obtained using agar diffusion method (Figure 7). In fact, innumerous factors may influence the difference in the antimicrobial activity observed when using the two techniques. On the other hand, PUs displayed very low activity towards *C. albicans* in the disc diffusion assay although inhibition of its growth was clearly evident in the assay of bacterial growth in liquid media (Figure 8b).

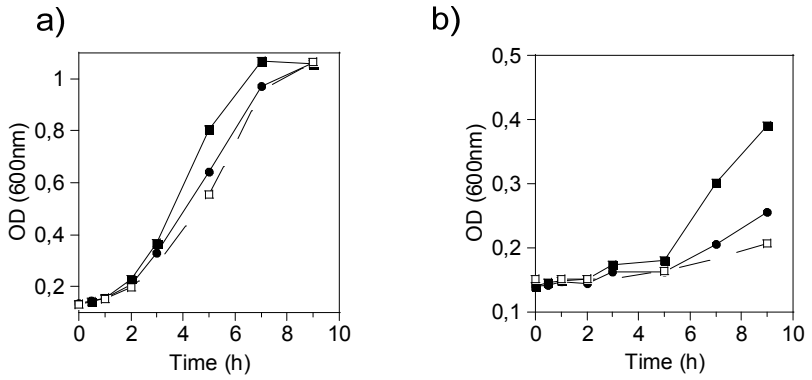


Figure 8. (a) Inhibition of *S. aureus* (a) and *C. albicans* (b) growth for PU(25/75) containing 2.8(□) and 2 (●) wt-% I_2. Control *S. aureus* (a) and *C. albicans* (b) values without PU are also represented (■).

Conclusions

Thiol-yne step-growth polymerization of undecenyl alcohol/methyl undecynoate mixtures has afforded a novel set of methyl ester-containing biobased polyols which have been used in the preparation of polyurethane networks. The surface hydrophilicity of the PUs has been modified via aminolysis with poly(propylene glycol) monoamine (Jeffamine M-600). The amine layer has been subsequently complex to iodine, endowing the PUs with antimicrobial activity against *S. aureus* and *C. albicans.* Hence, it can be concluded that aminolysis-I_2 complexation represents an efficient strategy for preparation of tailored antimicrobial coatings based on fatty acid PUs. Thus, the prepared PUs can have great interest for variety of applications, including medical devices, protective clothing, antimicrobial filters and bandages.

Acknowledgment. Financial support by the MICINN (Ministerio de Ciencia e Innovacion) (MAT2011-24823) is gratefully acknowledged. R. Barriga and D. González from Instron are greatfully acknowledged for the tensile properties measurements.

[1] G. Rakhorst, R. Ploeg, Eds., *Biomaterials in Modern Medicine The Groningen Perspective,* World Scientific Publishing Co. Pte. Ltd. Singapore 2008.

[2] R. Ravichandran, S. Sundarrajan, J. R. Venugopal, S. Mukherjee, S. Ramakrishna, *Macromol. Biosc*. **2012**, 12, 286.

[3] M. Elsabahy, K. L. Wooley *Chem. Soc. Rev*. **2012**, 41, 2545.

[4] L. G. Harris, R. G. Richards, *Injury* **2006**, 37(2 Suppl. 1), S3.

[5] R. O. Darouiche, *N. Eng. J. Med.* **2004**, 350, 1422.

[6] J. W. Costerton, P. S. Stewart, E. P. Greenberg, *Science* **1999**, 284, 1318.

[7] K. Vasilev, J. Cook, H. J. Griesser, *Expert Rev. Med. Devices* **2009**, 6, 553.

[8] F. Siedenbiedel, J. C. Tiller, *Polymers* **2012**, 4, 46.

[9] D. Park, A. M. Larson, A. M. Klibanov, Y. Wang, *Appl. Biochem. Biotechnol*. **2013**, 169, 1134.

[10] M. B. Yagci, S. Bolca, J. P. A. Heuts, W. Ming, G. de With, *Prog. Org. Coat.* **2011**, 72, 305.

[11] N. Fong, L. A. Poole-Warren, A. Simmons, *J. Biomed. Mat. Res. Part B* **2013**, *101B*, 310.

[12] J. Luo, Y. Deng, Y. Sun, *J. Bioact. Comp. Polym*. **2010**, 25, 185.

[13] K. T. Tan, S. K. Obendorf, *J. Membr. Sci*. **2007**, 289, 199.

[14] U. Makal, L. Wood, D. E. Ohman, K. J. Wynne, *Biomaterials* **2006**, 27, 1316.

[15] J. A. Grapski, S. L. Cooper, *Biomaterials* **2001**, 22, 2239.

[16] M. Desroches, M. Escouvois, R. Auvergne, S. Caillol, B. Boutevin, *Polym. Rev.* **2012**, 52, 38.

[17] P. Pfister, Y. Xia, R.C. Larock, *ChemSusChem*. **2011**, 4, 703.

[18] G. Lligadas, J.C. Ronda, M. Galià, V. Cádiz, *Biomacromolecules* **2010**, 11, 2825.

[19] H. Bakhshi, H. Yaganeh, S. Mehdipour-Ataei, *J. Biomed. Mater. Res. A* **2013**, 101, 1599.

[20] H. Bakhshi, H. Yeganeh, S. Mehdipour-Ataei, M. A. Shokrgozar, A. Yari, S. N. Saeedi-Eslami, *Mat. Sci. Eng.* **2013**, 33, 153.

[21] S. Miao, P. Wang, Z. Su, Y. Liu, S. Zhang, *Eur. J. Lipid Sci. Technol*. **2012**, 114, 1165.

[22] B, Das, P. Chattopadhyay, M. Mandal, B. Voit, N. Karak, *Macromol. Biosci*. **2013**, 13, 126.

[23] R. J. González-Paz, G. Lligadas, Juan C. Ronda, M. Galià, A. M. Ferreira, F. Boccafoschi, G. Ciardelli, V. Cádiz, *Macromol. Biosci*. **2012**, 12, 1697.

[24] R. J. González-Paz, A. M. Ferreira, C. Mattu, F. Boccafoschi, G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, G. Ciardelli, *React. Funct. Polym.* **2013**, 73, 690.

[25] R. J. González-Paz, G. Lligadas, J. C. Ronda, M. Galià, A. M. Ferreira, F. Boccafoschi, G. Ciardelli, V. Cádiz, *J. Biomed. Mater. Res. Part A* **2013**, 101A, 1036.

[26] C. Lluch, G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *Macromol. Biosci*. **2013**, *13*, 614.

[27] H. W. Kim, C. W. Chung, Y. H. Rhee, *Int. J. Biol. Macromol.* **2005**, 35, 47.

[28] Y. J. Du, J. L. Brash, G. M. Clung, L. R. Berry, P. Klement, A. K. C. Chan, *J. Biomed. Mater. Res. A* **2007**, 80, 216.

[29] J. Andersson, J. Sanchez, K. Nilsson, G. Elgue, B. Nilsson, R. Larsson, *J. Biomed. Mater. Res. A* **2007**, 67, 458.

[30] Q. Lu, S. J. Zhang, K. Hu, Q. L. Feng, C. B. Cao, F. Z. Cui, *Biomaterials* **2007**, 28, 2306.

[31] A. Korematsu, Y. Takemoto, T. Nakaya, H. Inoue, *Biomaterials* **2002**, 23, 263.

[32] T. Furuzono, K. Ishihara, N. Nakabayashi, Y. Tamada, *Biomaterials* **2000**, 21, 327.

[33] H. Suh, Y. S. Hwang, J. E. Lee, C. D. Han, J. C. Park, *Biomaterials* **2001**, 22, 219.

[34] H. G. Zhu, J. Ji, R. Y. Lin, C. Gao, L. Feng, J. Shen, *Biomaterials* **2002**, 23, 3141.

[35] Z. Ding, J. N. Chen, S. Y. Gao, J. B. Chang, J. F. Zhang, E. T. Kang, *Biomaterials* **2004**, 25, 1059.

[36] W. C. Lin, C. H. Tseng, M. C. Yang, *Macromol. Biosci.* **2005**, 5, 1013.

[37] R. J. González-Paz, G. Lligadas, M. Galià, M. Galià, J. C. Ronda, V. Cádiz, *Polym. Chem.* **2012**, 3, 2471.

[38] G. Lligadas *Macromol. Chem. Phys.* **2013**, 214, 415.

[39] N. A. Mazumdar, R. Vardarajan, H. Singh, *J. Macromol. Sci. Pure Appl. Chem.* **1996**, 33A:353.

[40] G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *Biomacromolecules* **2007**, 8, 1858.

[41] *Vogel's Textbook of Practical Organic Chemistry*, ed. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, Longman Scientific & Technical, Harlow, 5th edn, 1989.

[42] O. Türünç, M. A. Meier, *J. Polym. Sci. Part A: Polym. Chem*. **2012,** 50, 1689–1695.

[43] R. J. González-Paz, G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *J. Renewable Materials*, **2013**, 1, 3.

[44] E. I. Troyansky, R. F. Ismagilov, E. N. Korneeva, S. Pogosyan, G. I. Nikishin, *Mendeleev Commun*. **1995**, 5, 18.

[45] Y. Zhu, C. Gao, T. He, J. Shen, *Biomaterials* **2004**, 25, 423.

[46] Y. Zhu, C. Gao, X. Liu, T. He, J. Shen, *Tissue Eng.* **2004**, 10, 53.

[47] Y. Zhu, Z. Mao, H. Shi, C. Gao, *Sci. China Chem.* **2012**, 55, 2419.

[48] Y. Q. Wang, Y. L. Su, X. L. Ma, Q. Sun, Z. Y. Jiang *J. Membr. Sci.* **2006**, 283, 440.

[49] Y. Wang, A. J. Easteal, *J. Appl. Polym. Sci*. **1999**, 71, 1303.

[50] A. W. Bauer, D. M. Perry, W. M. M, Kirby, *Arch. Intern. Med*. **1959**, 104, 208.

Chapter 4

Rapid Approach to Biobased Telechelics through Two One-Pot Thiol-Ene Click Reactions

In this chapter the potential of thiol-ene Click Chemistry as polymerization and post-polymerization tool of monomers and polymers based on undecylenic acid will be studied.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Rapid Approach to Biobased Telechelics through Two One-Pot Thiol-Ene Click Reactions

Cristina Lluch, Joan C Ronda, Marina Galià, Gerard Lligadas, Virginia Cádiz*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili,

C/ Marcel.lí Domingo s/n, 43007 Tarragona, Spain

* To whom correspondence should be addressed: gerard.lligadas@urv.cat

Abstract:

The application of environmentally-friendly thiol-ene chemistry to the preparation of biobased telechelics is presented in this work. This methodology is based on two one-pot photoinitiated thiol-ene click processes: step-growth polymerization using a 3,6-dioxa-1,8-octanedithiol and end-groups postpolymerization modification with three functional thiols: 2-mercaptoethanol, 3-mercaptopropionic acid and 3-mercaptopropyltrimethoxysilane. We applied this approach to a potentially 100% biomass-derived monomer, allyl ester of 10-undecenoic acid (UDA). To show the generality and scope of this methodology, a series of well-defined telechelics with molecular weight ranging from 1000-3000 g/mol and hydroxyl, carboxyl, or trimethoxysilyl groups at the polymer terminus were prepared. An exhaustive ^{1}H NMR and MALDI-TOF MS analyses demonstrates the highly end-group fidelity of this methodology being an interesting procedure for the accelerated preparation of telechelics derived from divinyl monomers. UDA-based telechelic diol prepared using this methodology was reacted with 4,4′-methylenebis(phenylisocyanate) and 1,3-propanediol as the chain extender to obtain multiblock poly(ester urethane).

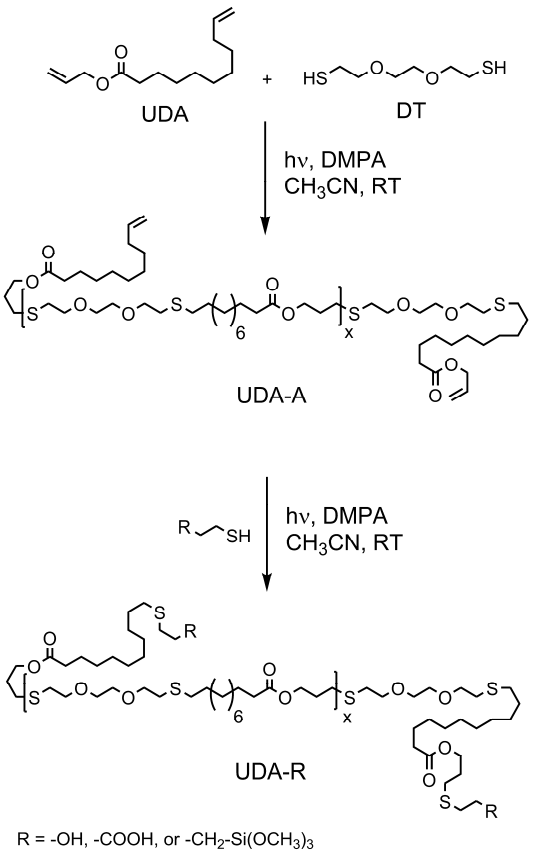
Introduction

Ongoing use of petroleum for chemical feedstocks is not sustainable and is encouraging chemists to reorient their research toward designing safer processes and chemicals from renewable feedstock with an increased awareness of environmental and industrial impact. Recent consensus in the scientific community is that in the long run, renewable resources such as plant oils, carbohydrates and starch are the only workable and viable solutions to replace oil and coal as basic feedstock.[1] Vegetable oils are already one of the most important renewable resources for the chemical industry due to universal availability, low price and wide variety of possibilities for chemical transformations.[2]

The contribution of chemical industry to sustainable development not only involves the use of renewable raw materials but also the application of environmentally friendly and high efficient processes. In this line, chemical couplings defined as click chemistry reactions,[3] have emerged as green methodologies and have opened new perspectives for the synthesis and modification of polymeric materials with targeted properties.[4] Besides the classical and popular Cu-catalyzed azide-alkyne click reaction, a variety of other click-type reactions has recently been employed to prepare polymeric materials.[4,5] Thiol-involved couplings, such as thiol-ene/yne,[6] thio-bromo,[7] pyridyl disulfide/thiol,[8] maleimide/thiol,[9] enone/thiol[10] and para-fluorine/thiol[11] are excellent examples of click reactions and have recently emerged as a valuable tool for chemists, showing an impressive versatility and clear potential in polymer and materials synthesis.[12] Concerning thiol-ene coupling, some studies have already focused on the synthesis of linear oligomers and polymers through step-growth polymerization of diolefins with dithiols,[13] as well as the end groups modification of RAFT-generated polymers[14] and alkene[15] and maleimide[16]-functionalized linear polymers.

Over the past several years there has been an increasing interest in new synthetic methods for the preparation of well-defined polymers with controlled chain-end functional groups.[17] These end-functional polymers, as exemplified by telechelic polymers, possess reactive functional groups at both chain ends, which have been used

as precursors of block copolymers, agents capable of modifying the thermal and mechanical properties of condensation polymers, in the formation of polymeric networks, and as compatibilizers of polymer blends.[18] A major problem for the preparation of telechelic polymers and particularly for the transformation of end-groups is the incompleteness of reactions. In this context, it is necessary to develop synthetic methodologies involving reactions with high efficiency. The aim of the present work was to develop an efficient and versatile "one-pot" method for the accelerated preparation of well-defined telechelics via two sequential thiol-ene click processes: step-growth photopolymerization and end-groups postpolymerization modification (Scheme 1).



Scheme 1. Synthetic Procedure for Rapid Approach to Telechelics through Two Consecutive Thiol-ene Click Reactions.

We applied this methodology to a potentially 100% biomass-derived monomer: allyl ester of 10-undecenoic acid (UDA). UDA and a dithiol were "clicked" to prepare alkene-functionalized linear polymers with variable molecular weight by thiol-ene click step-growth polymerization. Thereafter, the modification at the polymer terminus has been done using a consecutive thiol-ene click coupling with three different commercially available functional thiols. 2-Mercaptoethanol and 3-mercaptopropionic acid were chosen for its ability to add primary hydroxyl and carboxylic acid functionalities in lieu of double bond, and therefore were used in the preparation of biobased telechelic diols and diacids. Similarly, 3-mercaptopropyltrimethoxysilane contains the trimethoxysilane group that can allow forming crosslinked networks via acid/base catalyzed condensation reactions. This methodology provides a fast, efficient and green approach towards novel biobased telechelic macromonomers with a variety of functionalities.

Experimental Section

Materials. The following chemicals were purchased from Aldrich and used as received: acetonitrile, allyl acetate, 10-undecenoic acid (98%), allyl alcohol (>98%), 2,2-dimethoxy-2-phenylacetophenone (DMPA) (99%), 3,6-dioxa-1,8-octane-dithiol (95%), 2-mercaptoethanol, 3-mercaptopropionic acid, 3-mercaptopropyltrimethoxysilane, 3-chloroperbenzoic acid, trifluoroacetic anhydride, 1,4-butanediol, tin (II) 2-ethylhexanoate and 4,4′-methylenebis(phenylisocyanate) (MDI). N.N-dimethylformamide (DMF) was dried with CaH_2 for 24h and freshly distilled before use.

Instrumentation. NMR spectra were recorded on Varian VNMRS400. The samples were dissolved in deuterated chloroform, and ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature with TMS as an internal standard. ESI MS were run on an Agilent 1100 Series LC/MSD instrument. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurements were performed with a Voyager DE-RP mass spectrometer (Applied Biosystems, Framingham, MA) equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol was used as a matrix, and potassium trifluoroacetate was used as a cationization agent. In a vial, 25 mg of the

matrix was dissolved in 1 mL of THF. Separate solutions of polymer (10 mg/mL in THF) and salt (2 mg/mL in dionized H_2O) were prepared. The solution for MALDI-TOF analysis was obtained by mixing the matrix, polymer, and salt solution in a 5/1/1 volumetric ratio. Then 0.5 µL portions of the mixture were deposited onto 10 wells of the sample plate and dried in air at room temperature. Size exclusion chromatography (SEC) analysis was carried out with an Agilent 1200 series system equipped with an Agilent 1100 series refractive-index detector. THF was used as an eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained with polystyrene standards. Differential Scanning Calorimetry (DSC) measurements were carried out with a Mettler DSC822e thermal analyser with N_2 as the purge gas. 6-12 mg samples were used for DSC analysis. Telechelic diol samples were heated from -20 to 150ºC with a heating rate of 20ºC/min, cooled down to -90ºC with a cooling rate of -20ºC/min, and then heated again to 150ºC at the same heating rate. T_g and T_m values were obtained from the second heating curves. For analyzing polyurethanes, samples were heated from -90 to 200ºC with a heating rate of 20ºC/min. Thermal stability studies were carried out with a Mettler TGA/SDTA851e/LF/1100 with N_2 as the purge gas at a scanning rate of 10ºC/min. Ultraviolet (UV) light irradiation of the samples for thiol-ene photopolymerization was carried out with two 9W bench lamps which emit around 365 nm wavelength.

Synthesis of Allyl 10-Undecenoate

To a 250-mL round-bottom flask, 40 g (0.213 mol) of 10-undecenoic acid, an excess of allyl alcohol 53 mL (0.778 mol), and p-toluensulphonic acid as a catalyst were added, and the mixture was refluxed and magnetically stirred for 8h. Once the reaction was completed, the mixture was washed with ether and 10% sodium bicarbonate solution, dried over anhydrous magnesium sulphate and filtered. The solvent was evaporated off under reduced pressure. Finally, the product was distilled under vacuum (bp 110ºC at 0.45 mmHg) to afford pure allyl 10-undecenoate as viscous oil, in a 80 % yield.

^{1}H NMR ($CDCl_3$/tetramethylsilane (TMS), δ(ppm)): 5.88 (m, -CH=C), 5.78 (m, C=CH-), 5.33-5.21 (dd, C=CH_2), 5.00-4.90 (dd, CH_2=C), 4.56 (d, -OCH_2), 2.32 (t, -CH_2-CO-), 2.01 (m, CH-C$\underline{H_2}$-), 1.62 (m, -CH_2-), 1.33-1.28 (m, -CH_2-, 10 H).

^{13}C NMR ($CDCl_3$, δ(ppm)): 173.45 (s), 139.12 (d), 132.41 (d), 118.04 (t), 114.20 (t), 64.93 (t), 34.28 (t), 33.83 (t), 29.32 (t), 29.24 (t), 29.16 (t), 29.09 (t), 28.93 (t), 24.98 (t).
MS (ESI-positive, CH_2Cl_2): m/z=247.2 ($[M+Na]^+$, calc. 247.2).

Thiol-Ene Coupling of Allyl 10-Undecenoate with 2-Mercaptoethanol

In a 25 mL flask 1.0 g (4.46 mmol) of allyl 10-undecenoate (UDA) reacted with 0.44 mL (6.24 mmol) of mercaptoethanol. The radical initiator was added in the proportion 0,3% mol init./mol C=C. The amount of acetonitrile necessary to dissolve the UDA and photoinitiator was added. The reaction was carried out at room temperature, without deoxygenation, by irradiation with two UV-lamps (λ=365 nm). After few minutes a white solid precipitated. The completion of the reaction was confirmed by ^{1}H NMR by the completely disappearance of the double bond signals that appear in the region of 5-6 ppm. The mixture was crystallized from ether, filtered, washed with cold ether and hexanes, and dried under vacuum (yield 98%).

^{1}H NMR [$CDCl_3$/tetramethylsilane (TMS), δ, ppm): 4.15 (C(O)-O-CH_2), 3.71 (CH_2-OH), 2.71 ($C\underline{H}_2$ -CH_2-OH), 2.58 (CH_2-S), 2.50 (S-CH_2), 2.28 (CH_2CO), 1.91 (CH_2-), 1.58 (CH_2), 1.37-1.26 (CH_2, 12 H).
^{13}C NMR ($CDCl_3$, δ(ppm)): 173.96 (s), 62.79 (t), 60.40 (t), 60.28 (t), 35.43 (t), 35.40 (t), 34.40 (t), 31.73 (t), 29.84 (t), 29.51 (t), 29.45 (t), 29.32 (t), 29.26 (t), 29.22 (t), 28.94 (t), 28.91 (t), 28.23 (t), 25.06 (t).
MS (ESI-positive, CH_2Cl_2): m/z=403.2 ($[M+Na]^+$, calc. 403.2).

Competitive Addition of Allyl Acetate and Methyl 10-Undecenoate towards 2-Mercaptoethanol. General Procedure

Acetonitrile solution containing a definite amount of allyl acetate (0.4 mL, 3.70 mmol), methyl 10-undecenoate (1mL, 4.40 mmol), and 2,2-dimethoxy-2-phenylacetophenone (13mg, 0.05 mmol) was placed in a reaction tube sealed with Teflon-lined silicone rubber septa with stirring. After stirring for 2 min, the reaction tube was irradiated at λ=365 nm and the required amount of 2-mercaptoethanol (0.25 mL, 3.60 mmol) was injected. The reaction mixture was irradiated for 1 h and the quantities of unreacted allyl acetate

and methyl 10-undecenoate were immediately determined by ^{1}H NMR. In absence of significant side reactions, the reactivity ratio, k_2/k_1, was calculated from the initial and final concentrations of the two reacting olefins. ^{1}H NMR signals used for determining final concentration were 5.00-4.90 ppm (dd, CH_2=C) and 3.62 ppm (s, OCH_3) for methyl 10-undecenoate and 4.56 (d, -OCH_2) and 4.55 ppm (s, S-CH_2) for allyl acetate.

General Procedure for the Synthesis of Telechelics through Two One-Pot Thiol-Ene Click Couplings.

The general procedure is described for UDA-OH1 preparation: 5.87 g of UDA (0.026 mol), 2.5 mL of DT (0.015 mol) and 41.5 mg of DMPA (0,3% mol init/mol C=C) were charged to a 50-mL round-bottom flask. The reaction mixture was irradiated for 2 hours at λ=365 nm. An excess of 2.1 mL of 2-mercaptoethanol (0.03 mol) and 17.0 mg of DMPA were added to react with oligomer chain ends and the mixture was irradiated for an additional hour. The crude product was diluted with dichloromethane, washed with distilled water to eliminate the excess of mercaptoethanol, dried over anhydrous magnesium sulphate and filtered. The solvent was evaporated off under reduced pressure to afford UDA-OH1 as white waxy solid, in 92 % yield.

UDA-OH

^{1}H NMR ($CDCl_3$/tetramethylsilane (TMS), δ(ppm)): 4.13 (m, C(O)-O-CH_2-), 3.71 (t, -CH_2-OH), 3.61 (m, -CH_2-O), 2.70 (m, C$\underline{H}_2$-CH_2-OH), 2.57 (m, -CH_2-S), 2.52 (t, S-CH_2-), 2.27 (t, CH_2-CO), 1.89 (m, CH_2), 1.57 (m, CH_2), 1.39-1.25 (m, CH_2).

UDA-COOH

^{1}H NMR ($CDCl_3$/tetramethylsilane (TMS), δ(ppm)): 4.13 (m, C(O)-O-CH_2-), 3.64 (m, -CH_2-O), 2.80 (t, -C$\underline{H}_2$-CH_2-COOH), 2.71 (m, -CH_2-COOH, S-CH_2-), 2.62 (t, CH_2-S), 2.53 (t, S-CH_2), 2.29 (t, CH_2-CO), 1.92 (m, -CH_2-), 1.64-1.24 (m, CH_2).

UDA-Si

^{1}H NMR ($CDCl_3$/tetramethylsilane (TMS), δ(ppm)): 4.10 (m, C(O)-O-CH_2-), 3.59 (m, -CH_2-O), 3.51 (s, -Si(OCH_3)$_3$), 2.66 (m, -CH_2-S), 2.56 (t, S-CH_2), 2.48 (t, S-CH_2), 2.24 (t, CH_2-CO), 1.86 (m, -CH_2-), 1.53 (m, -CH_2-), 1.40-1.22 (m, CH_2), 0.7 (m, CH_2-Si).

Preparation of Thermoplastic Poly(ester urethane)s with Hydroxyl-terminated Oligomer 3 (UDA-OH3)

To a dry 50 mL round-bottom flask were charged 5 mL of DMF, 0.70 g of hydroxyl-terminated oligomer UDA-OH3 (M_n^{NMR} = 3100), 0.75 g of MDI, and 16 mg of tin (II) 2-ethylhexanoate. The flask was immersed into a 65 ºC preheated silicone oil bath with a magnetically stirred. After 1 h polymerization a solution of 0.25g of 1,4-butanediol in DMF (4 mL) was added. The reaction was continued at 65 ºC for another 2 h. After reaction, the mixture was poured into methanol (50 mL) and polymer was precipitated. After drying in vacuum oven for 24h at 60 ºC, 1.5 g (88 % yield) of poly(ester urethane) was obtained.

Results and Discussion

Synthesis of Allyl 10-Undecenoate (UDA) from Renewable Feedstock

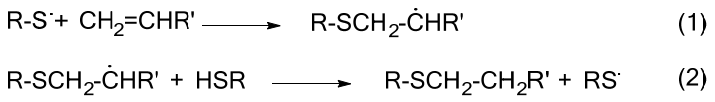
Recently, the interest in biomass has increased because is an abundant and readily available feedstock that has great potential as a renewable source of chemical intermediates. In line with our concern with the valorization of renewable resources for the development of green polymers,[19] we selected allyl 10-undecenoate (UDA) as starting monomer. The synthesis of allyl ester of 10-undecenoic acid was carried out by refluxing 10-undecenoic acid, which is the major product of castor oil pyrolysis, with an excess of allyl alcohol together with 2% p-toluenesulfonic acid for 6-8h. The ^{1}H NMR spectra of the product corresponded to the expected structure. The five allyl protons resonate at 5.88, 5.27, and 4.56 ppm whereas the three protons of the other vinyl group resonate at 5.78 and 4.95 ppm. Their resonance intensity ratios were in excellent agreement with their proton number ratios. Although allyl alcohol is a large-scale industrial chemical, presently produced from propene, it is worth mentioning here that

UDA is potentially a 100% biomass derived monomer. Allyl alcohol can be easily obtained from glycerol, the main byproduct in the triglyceride transterification process for biodiesel manufacture.[20] Alternatively, synthetic procedures for allyl esters starting from fatty acids and glycerol are also available in the literature.[21]

Reactivity of Allyl 10-Undecenoate towards Thiol Addition

It is well known that terminal alkenes react very rapidly with thiols, achieving complete conversions in few minutes.[22] To evaluate the reactivity of UDA towards photoinitiated radical addition, 2-mercaptoethanol (ME) was used as a model thiol. Coupling was carried out at room temperature for 1h in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator. The reaction was conducted with slight excess of thiol (1.2 equiv relative to double bond) in acetonitrile. Complete C=C conversion was determined by ^{1}H NMR after 5 min. The model compound was isolated by crystallization with diethyl ether and the main structure was confirmed by ^{1}H and ^{13}C NMR. NMR analysis revealed that the radical addition of thiol was 100% anti-Markovnikov.

The thiol-ene coupling mechanism has been extensively studied and is known to follow a radical mechanism, in which the addition of a thiyl radical to a double bond is followed by chain transfer to thiol.[23]



UDA is a divinyl monomer with two different vinylic functionalities. It is logical that the chemical structure of an alkene can significantly affect its reactivity in thiol-ene reactions because of differences in the steric strain and ene susceptibility to thiyl attack and subsequent hydrogen abstraction. A series of competitive reaction experiments were designed to determine the relative reactivity of two UDA end groups towards thiol addition (ME). Two model monofunctional monomers were used to mimic UDA structure:

allyl acetate (AA, M_1) and methyl 10-undecenoate (UDM, M_2). If we use these two monomers, then their relative reactivity would be described by

$$\log (M_{2,0}/M_2)/ \log (M_{1,0}/M_1) = k_2/k_1 \quad (3)$$

where k_1 and k_2 are the rate constants for competitive addition reaction (eq. 1) of M_1 (AA) and M_2 (UDM) towards thiyl radicals, respectively and $M_{1,0}$ (and $M_{2,0}$) and M_1 (and M_2) the initial and final concentrations.

The relative reactivity of UDM to AA (k_2/k_1) has been determined by means of Eq. 3 (Table 1). Although there are good reasons to believe that reaction (1) may be reversible,[24] the addition of thiyl radicals to 1-substituted olefins is generally rapid and irreversible.[25] If a reverse reaction of Eq. 1 occurs to a great extent, k_2/k_1 values obtained from Eq. 3 should vary with the concentration of thiol. In the competitive reaction of UDM and AA towards ME, we have confirmed that the reverse reaction does not take place, namely in Table 1 the k_2/k_1 values show no significant variation with the concentration change of ME. Moreover k_2/k_1 values indicates that UDM is 1.84 times more reactive than AA towards thiol-ene coupling. Presumably this is due to an increase in the propensity for the elimination reaction in AA resulting from the highest insertion product energy due to the presence of an electron-withdrawing group that destabilize the radical intermediate. Extrapolating these results to UDA, it can be seen that allylic and vinylic chain ends exhibit different reactivity towards thiol addition.

Table 1. Relative Reactivities (k_2/k_1) of Photoinitiated Radical Addition Reaction of Methyl 10-Undecenoate (UDM) to Allyl Acetate (AA) towards 2-Mercaptoethanol (ME) in acetonitrile.

$[UDM]_0$ (mol/l)	$[AA]_0$ (mol/l)	$\frac{[UDM]_0}{[AA]_0}$	$[ME]_0$ (mol/l)	k_2/k_1
1.77	0.73	2.42	1.81	1.73
2.07	1.72	1.20	1.66	1.83
2.06	1.91	1.08	1.03	1.86
1.52	1.42	1.07	0.81	1.74
1.73	2.26	0.77	1.71	1.90
0.9	1.72	0.52	2.11	1.99

Synthesis of Telechelic Diols via Two Consecutive Thiol-Ene Click Couplings Preparation of Alkenyl-terminated Oligomers

In the previous section, model studies provided insight into how UDA reacts during thiol-ene coupling. To extend this investigation to more complex architecture, thiol-ene polyaddition of UDA with a dithiol was investigated. UDA and 3,6-dioxa-1,8-octanedithiol (DT) were coupled by thiol-ene click step-growth photopolymerization in the presence of DMPA (Scheme 1). To ensure the production of alkenyl-terminated oligomers (UDA-A) and target average degree of polymerization, a precisely controlled imbalance of both reactants (excess of UDA over DT) was used. The molar ratio between UDA and DT was varied to target oligomers with theoretical number-average molecular weight values (M_n^{th}) of 1000 (UDA-A1, UDA/DT = 1.712), 2000 (UDA-A2, UDA/DT = 1.259) and 3000 (UDA-A3, UDA/DT = 1.158) g/mol. UDA/DT molar ratios were theoretically determined using the Carothers equation.[26]

The photopolymerization was monitored by ^{1}H NMR analysis of a sample of the reaction mixture at different reaction times. The progress of the polymerization was indicated by the appearance of new NMR signals (2.52 and 2.57 ppm) due to CH_2 protons corresponding to the thioether linkages from the thiol-ene polymerization which were absent at the beginning of the polymerization. The signals areas for these two signals increased as the polymerization progressed whereas the areas of the signals due to C=C

double bonds decreased. Further, the SEC analysis of the reaction mixture after 2 h verified that polymerization reaction occurred due to the total consumption of thiol. Alkenyl-terminated UDA oligomers (UDA-A) showed molecular weight distribution typical for polycondensation polymers. Low molecular weight species were observed as separate peaks while higher molecular weight species merged into a single peak. Molecular weight distribution was close to 2.0. Solvent was removed under reduced pressure and UDA-A oligomers were analyzed by ^{1}H NMR. Figure 1 shows the ^{1}H NMR spectrum of oligomers UDA-A1, UDA-A2, and UDA-A3.

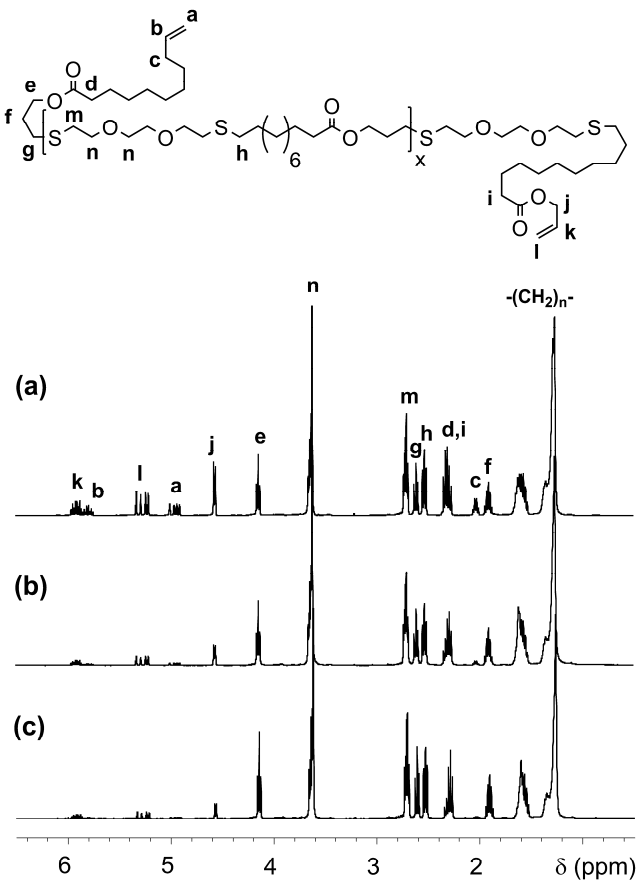


Figure 1. 400 MHz ^{1}H-NMR spectra ($CDCl_3$) of alkenyl-terminated UDA oligomers obtained by photoinitiated thiol-ene click step-growth polymerization with dithiol DT: (a) UDA-A1 (UDA/DT = 1.712; M_n^{NMR} = 895) , (b) UDA-A2 (UDA/DT = 1.259; M_n^{NMR} = 2060), and (c) UDA-A3 (UDA/DT = 1.158; M_n^{NMR} = 2970).

Resonances between 4.8 and 6.0 ppm correspond to vinyl chain ends. As expected, the signal intensities of the end groups from oligomers prepared with UDA/DT molar ratios closer to 1 are smaller in relation to the integrals of the repeating units. Moreover, in agreement with results presented above (UDA allylic group are less reactive towards radical addition than the other vinyl group), thiol-ene polyaddition of UDA with a dithiol produces allylic-rich vinyl-terminated oligomers (approximately 65% of the chain ends are allylic). For each oligomer, the M_n was determined by ^{1}H NMR spectroscopy from the ratio of the signal intensities of the repeating units and the end-groups. The M_n values obtained by this method (894, 2060, and 2970 g/mol) are in good agreement with the theoretical predictions from the monomer ratios determined using the Carothers equation, thus demonstrating the efficiency of this polyaddition process.

MALDI-TOF was performed on UDA-A oligomers to further investigate the efficiency of thiol-ene click chemistry step-growth polymerization step. Dihydroxybenzoic acid, dithranol, *trans*-3-indole acrylic acid, and sinapinic acid were examined as matrices. The use of dithranol and potassium as a cationization agent gave the best results in the analysis of these polymers. Hence, dithranol/K^+ was chosen as the matrix/cationization agent pair for all of our samples. Figure 2 shows the MALDI-TOF spectrum of oligomer UDA-A3 (M_n^{NMR} = 2970).

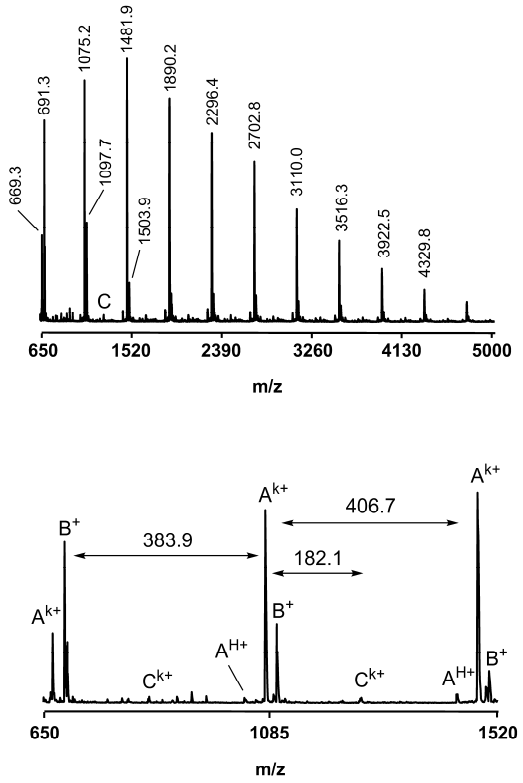
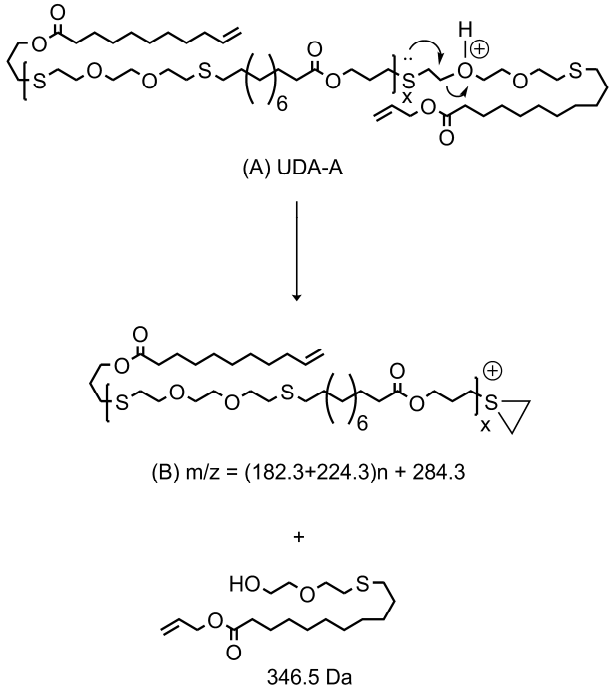


Figure 2. MALDI-TOF MS spectrum of alkenyl-terminated oligomer UDA-A3 (M_n^{NMR} = 2970) obtained by photoinitiated thiol-ene click step-growth polymerization with dithiol DT (UDA/DT = 1.158).

One main set of peaks was observed with a peak-to-peak mass increment of 406 Da (labeled A). This mass increment corresponds to the molar mass of the repeating unit. This series correspond to expected alkenyl-terminated UDA-A oligomers. The general chemical structure of these oligomers is also presented in Scheme 1. Two additional series of ions, labeled B and C, were present predominantly in the low mass range. With the exception of some ions from B series at low mass range, these series had significantly lower abundance (especially for series C) than series A. Series C, with a mass difference of 182 to series A, can be explained by the formation of macrocycles. Such cyclizations were also observed in step-growth polymerizations involving Cu-catalyzed azide-alkyne click reactions.[27] On the other hand series B peak intensity decreases with increasing m/z value and therefore are probably formed by fragmentation of alkenyl-terminated oligomers (series A).

With the aim of investigating the origin of series B, we examined sample preparation method to see the effects of cationization salts. Three sample preparation methods were examined having used (a) dithranol as matrix without adding any salts, (b) dithranol with sodium chloride solution, and (c) dithranol with a silver trifluoroacetate solution. Following all trials, we found that salt plays an effective role in the cationization of series A. The signals of alkenyl-terminated oligomers series A carrying a sodium and silver ion could be detected for method (b) and (c), respectively. Concerning series B, we found that such salts play no effective roles in the cationization process. In fact, when no cationization agent was used (method a) MALDI-TOF spectrum of UDA-A3 showed only series B^+. These results suggest that the predominant cationization mechanism for series B cannot be attributed to added salt solutions but rather are cationic species. According to these observations, our hypothesis is that series B is formed by fragmentation of main series A through inductive charge-site catalyzed cleavage of $–CH_2-O-CH_2-$ ether bonds (Scheme 2).



Scheme 2. Suggested Fragmentation Pathway of Alkenyl-terminated UDA Oligomers during MALDI-TOF Analysis.

Different charge-initiated decompositions of ether bonds of PEG oligomers were previously observed and studied by Lattimer during MS analysis.[28] In our case, we attribute the enhanced abundance of this ether cleavage product to anchimeric assistance from the neighboring sulfur center with a lone pair of electrons (Scheme 2). The incipient ionic product released from this decomposition is an episulfonium ion. This could explain why series B were detected in our MALDI spectra even without cationization agent.

The mild conditions used in the thiol-ene photopolymerization step endorse our hypothesis that fragmentation takes place during the MALDI-TOF analysis. This was confirmed by an additional experiment consisting on oxidation of thioether linkages of UDA-A3 to sulfone units using 3-chloroperbenzoic acid in dichloromethane at room temperature. If this fragmentation of main series A (Scheme 2) is promoted by sulphur centres with a lone pair of electrons and is taking place during MALDI-TOF analysis, oxidation of thioether linkages to sulfone should suppress it. Figure 3 illustrates a section of the ^{1}H NMR and MALDI-TOF spectra of oligomers UDA-A3 before and after oxidation process.

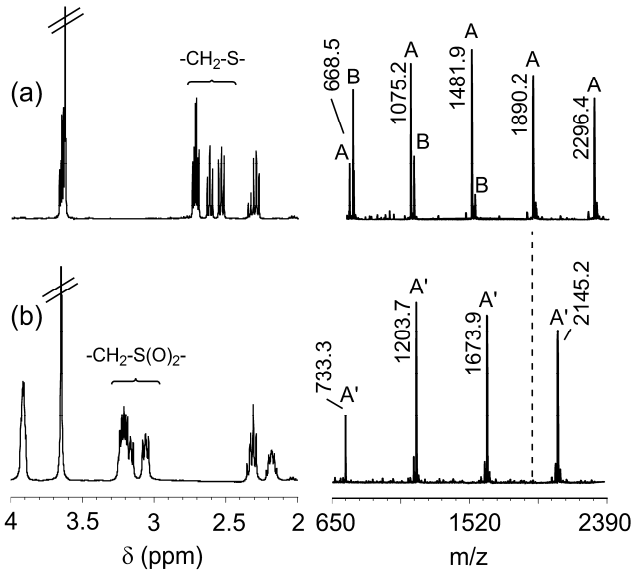


Figure 3. Expanded 400 MHz ^{1}H-NMR ($CDCl_3$) and MALDI-TOF MS spectra of alkenyl-terminated UDA oligomer UDA-A3 (a) before and (b) after oxidation with 3-chloroperbenzoic acid.

The α-methylene protons of the sulphur atoms were observed between 2.5-2.8 ppm and 3.0-3.3 ppm before and after oxidation, respectively. MALDI-TOF analysis shows that after oxidation, series A corresponding to sulphide containing oligomers completely shifted to higher m/z as series A′ (every peak shifted n times the molar mass difference between –S- and $–S(O)_2-$, where n is the number of sulphur atoms present in each chain). Delightfully it can be seen that oxidation of sulphur centers eliminates series B and therefore corroborates our hypothesis. These results demonstrate that under the reported conditions, thiol-ene coupling is an effective method of step-growth polymerization of divinyl monomers leading to further clickable polymers with well-defined structure.

Chain-ends Modification

The synthesis of end functionalized polymers presents a number of challenges with efficiency being the foremost. Recently, Hawker and co-workers have elegantly demonstrated the potential of thiol-ene coupling reaction in the functionalization of single end-group functionalized PS, PMMA, and PEG.[15a] The high efficiency showed by thiol-ene click coupling makes it a promising candidate as a telechelic terminus functionalization tool. The series of three above described oligomers UDA-A with molecular weight ranging from 1000-3000 g/mol were functionalized at both the chain ends through a second thiol−ene coupling without isolation and purification of the alkene-terminated precursors. In this case, 2-mercaptoethanol (ME) was selected as a functional thiol (R = OH in Scheme 1) to give a series of telechelic diols (UDA-OH, Scheme 1). Telechelic diols are important precursors for polycondensation polymers such as polyesters, polyurethanes and silicones, and can also be used to introduce photocrosslinkable functionalities into polymer systems.[18,29] Thiol-ene coupling at both oligomer alkene chain ends groups was achieved by reaction with ME at room temperature under UV light. Quantitative conversion to primary alcohol chain ends was confirmed by MALDI-TOF. Figure 4 shows the expanded MALDI-TOF spectra before and after thiol-ene coupling at the oligomer UDA-A2 chain-ends leading to UDA-OH2.

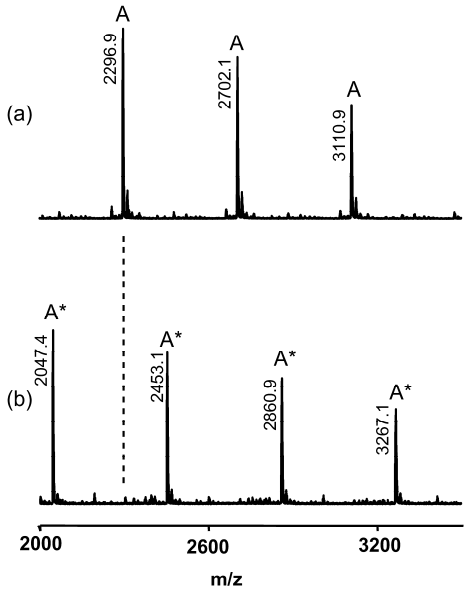


Figure 4. Expanded MALDI-TOF MS spectra of (a) alkenyl-terminated oligomer UDA-A3 (M_n^{NMR} = 2970) and (b) the corresponding dihydroxy derivative UDA-OH3 obtained by photoinitiated thiol-ene click with ME.

It can be seen that after end-groups transformation, peak distribution corresponding to the alkene terminated chains (series A) completely disappears and a new distribution (series A*) appears ~157 mass units above the former series. This value corresponds to two times the molar mass of ME confirming the click joining of two ME at both polymer terminus.

The exact detection of the molar masses of the telechelics is an important prerequisite for the application of telechelics as starting materials in a subsequent synthesis, e.g. in a polyaddition reaction. M_n of the biobased diols were determined by two different methods: ^{1}H NMR spectroscopy and SEC (Table 2).

Table 2. Molecular Weight and Thermal Properties of UDA-based Telechelic Diols (UDA-OH).

				DSC[c]							TGA[d]
UDA-OH	M_n^{NMR} (g/mol)[a]	M_n^{SEC} (g/mol)[b]	Yield (%)	T_g (ºC)	T_m^1 (ºC)	ΔH_f^1 (J/g)	T_c (ºC)	ΔH_c (J/g)	T_m^2 (ºC)	ΔH_f^2 (J/g)	$T_{5\%}$ (ºC)
1	960	1900	92	-60	-2	11	7	10	31	48	318
2	2065	3590	98	-57	-1	13	2	26	28	51	330
3	3100	4230	97	-54	-1	21	3	27	28	51	331

[a] Calculated from ^{1}H NMR spectrum of samples derivatized with trifluoroacetic anhydride; [b] Value determined with polystyrene as standard in THF; [c] Data obtained from the second DSC scan (20ºC/min); [d] N_2 was used as the purgue gas (10ºC/min).

First, an end-capping reaction of the hydroxyl groups with trifluoroacetic anhydride was performed to indentify the signals related to the end-groups of the macro-diols. Figure 5 shows the ^{1}H NMR spectra of UDA-OH2 as well as its bistrifluoroacetylated derivative in $CDCl_3$, ranging from 2.0 ppm to 5.0 ppm.

Small signal neighboring intense peak at 3.6 ppm disappears after the endcapping reaction. Therefore, this can be assigned to the methylene groups adjacent to the hydroxyl groups. A new signal at approximately 4.5 ppm is assigned to the methylene group adjacent to the newly formed trifluoroacetylated chain ends.

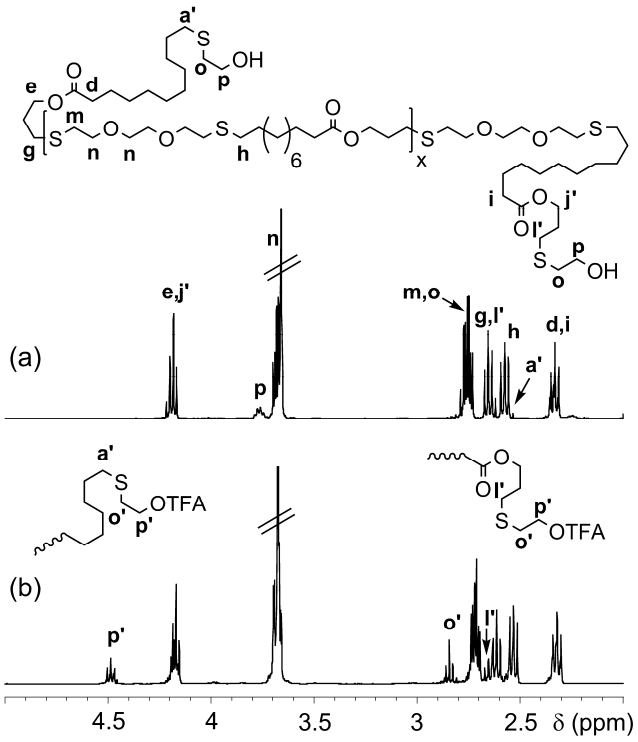


Figure 5. Expanded 400 MHz ^{1}H-NMR spectra ($CDCl_3$) of (a) telechelic diol UDA-OH2 and (b) the corresponding bistrifluoroacetylated derivative.

M_n of the telechelics was determined from the ratio of the signal intensities of the repeating units and the end groups. For the three macrodiols synthesized, M_n determined by ^{1}H NMR were about 960, 2060, and 3050 g/mol. The SEC results for these three telechelic diols indicated a M_n of 1900, 3600, and 4700. However, systematically high M_n values were observed by SEC, due to the use of polystyrene standards, which differ structurally from the telechelic polymers. Therefore, the M_n obtained by ^{1}H NMR results to be more accurate, although the SEC results are useful for providing information about the molecular weight distribution. Molecular weight distribution for these telechelics was close to 2.0. However it has to be considered that a conventional precipitation step at the end of the synthetic procedure reduces M_w/M_n to values close to 1.3.

Key thermal properties of these telechelic diol were investigated by differential scanning calorimetry (DSC) (Figure 6, Table 2).

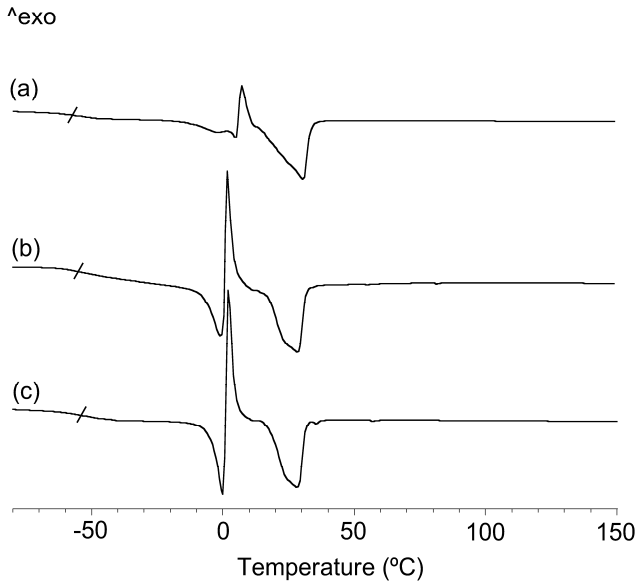


Figure 6. Second scan DSC traces (20ºC/min) of UDA-based telechelic diols obtained by two consecutive thiol-ene couplings: (a) UDA-OH1 (M_n^{NMR} = 960) , (b) UDA-OH2 (M_n^{NMR} = 2060), and (c) UDA-OH3 (M_n^{NMR} = 3100).

All the synthesized macrodiols, isolated as waxy white solids, were semicrystalline, exhibiting glass transition temperatures (T_g's) at around -55ºC, two melting endotherms and a cold crystallization peak. As shown in Figure 6 and Table 2, T_g, T_m^1, T_m^2 and the heat of fusions (H_f) do not significantly increase with increasing molecular weight, as expected due to the effect of molecular weight on the thermal transitions of linear semicrystalline polymers. However, it must be pointed out that crystallinity of a polymer is also affected by interchain bonding. In this case, the lower the molecular weight of the telechelic diol the higher concentration of hydroxyl groups. The low T_g values illustrate how well these telechelic diols could serve in the preparation of segmented copolymers. Moreover, UDA-based telechelic diols prepared using UDA/DT molar ratio closer to 1, T_m^2 achieved values close to 40ºC and therefore these materials could have application in the field of block copolymers with shape memory effect at body temperature.

Concerning thermal stability, prepared biobased telechelic oligomeric diols showed to be thermally stable above 300ºC.

Other Telechelics via Two Consecutive Thiol-Ene Click Couplings

For the first time it has been demonstrated that telechelic diols with different molecular weight can be easily obtained through "one-pot" methodology involving two consecutive thiol-ene couplings. To show the generality and scope of this methodology, it has been extended to the preparation of other UDA-based telechelics by using 3-mercaptopropionic acid (MPA) and 3-mercaptopropyltrimethoxysilane (MPS) as monofunctional thiols. MPA and MPS were chosen for its ability to add carboxyl and trimethoxysilane moieties in lieu of double bond.

Following the general procedure described above, clickable UDA-based oligomer (synthesized using UDA/DT molar ratio = 1.3), was functionalized at the chain ends with MPA and MPS leading to telechelics UDA-COOH and UDA-Si, respectively. ^{1}H NMR was used to monitor the disappearance of the protons associated with the double bonds, and the appearance of proton signals corresponding to the thioether product. The end group modification with both thiols was found to be quantitative in few minutes. Purification of the products was done in this case by simple precipitation techniques. Figure 7 shows the ^{1}H NMR spectrum of UDA-based telechelic with trimethoxysilyl end groups (UDA-Si).

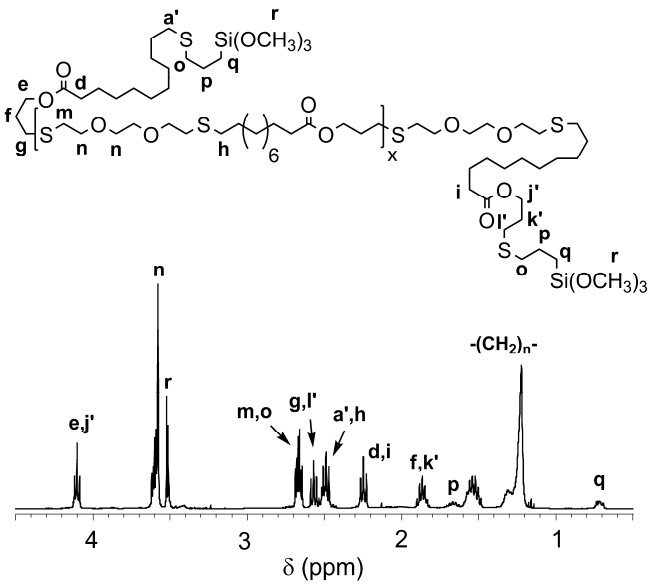


Figure 7. 400 MHz ^{1}H-NMR spectra ($CDCl_3$) of UDA-based telechelic with trimethoxysilane end groups (UDA-Si).

This telechelic polymer can further allow forming crosslinked networks via acid/base catalyzed condensation reactions. These successful examples open up a way to prepare a palette of telechelic polymers based on UDA or other biobased[13a,13c,30] or non-biobased divinyl monomers.[13b]

Thermoplastic Poly(ester urethane)s from Biobased Macrodiols

The suitability of the synthesized telechelics as components for the synthesis of multiblock copolymers was demonstrated by the incorporation of a telechelic macrodiol (M_n^{NMR} = 3100) as soft segment in poly(ester urethane)s using an aromatic diisocyanate, 4,4'-methylenebis(phenylisocyanate) (MDI), and 1,4-butanediol (BD) as a chain extender. The two-step polyurethane synthetic method resulted in a thermoplastic segmented polyurethane with a low-temperature T_g and a melting point at -45ºC and -9ºC, respectively. The T_g and T_m of the PU correlated well with the thermal properties of their corresponding prepolymer. A second T_g with a midpoint of approximately 55ºC and a broad melting endotherm at 190ºC corresponding to BD-MDI domains support a phase separated morphology.[31] We are currently studying additional UDA diols based polyurethanes in terms of thermal, mechanical, biodegradation, and

cytotoxicity properties. Results of ongoing research in our laboratories along these directions will be reported in due course.

Conclusions

In summary, by taking advantage of the recent advances in click chemistry we describe for the first time a general methodology for the rapid preparation of telechelics by using a two "one pot" thiol-ene click couplings and applied it to a monomer from renewable feedstock. A detailed ^{1}H NMR, SEC, MALDI-TOF MS analyses of the whole process demonstrated the highly efficiency and end-group fidelity of this accelerated methodology. The simplicity, mild reaction conditions, short reaction times, high yields and easy work-up make it an interesting procedure for the preparation of different kinds of telechelics based on divinyl monomers that might be applied in the future for the tailoring of polymer structure and properties. Moreover these results envision that thiol-ene click chemistry is a promising route for designing novel bio-inspired monomers and shaping structural and functional polymers.

Acknowledgment. Financial support by the MICINN (Ministerio de Ciencia e Innovacion) (MAT2008-01412) is gratefully acknowledged.

[1] Gandini, A. *Macromolecules* **2008**, 41, 9491-9504.

[2] Biermann, U.; Friedt, W.; Lang, S.; Luhs, W.; Machmuller, G.; Metzger, J. O. *Angew. Chem. Int. Ed.* **2000**, 39, 2206-2224.

[3] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, 40, 2004-2021.

[4] Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2010**, 43, 1-13.

[5] (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, 43, 3928-3932; (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, 108, 2952–3015; (c) Iha, R. K.; Wooley, K. L.; Nystrom, A. M.; Burke, D. J.; Kade M. J.; Hawker, C. J. *Chem. Rev.*, **2009**, 109, 5620–5686.

[6] (a) Yu, B.; Chan, J. W.; Hoyle, C. E.; Lowe, A. B. *J. Polym. Sci. Part A: Polym. Chem.* **2009**, 47, 3544-3557; (b) Hensarling, R. M.; Doughty, V. A.; Chan, J. W.; Patton, D. L. *J. Am. Chem. Soc.* **2009**, 131, 14673-14675; (c) Chen, G.; Kumar, J.; Gregory, A.; Stenzel, M. H. *Chem. Commun.*, **2009**, 41, 6291-6293; (d) Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int.* Ed. **2010**, 49, 1540-1573.

[7] (a) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. *J. Polym. Sci. Part A: Polym. Chem.* **2009**, 47, 3931-3939; (b) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. *J. Polym. Sci. Part A: Polym. Chem.* **2009**, 47, 3940-3948; (c) Xu, J.; Tao, L.; Boyer, C.; Lowe, A. B.; Davis, T. P. *Macromolecules* **2010**, 43, 20-24.

[8] Vazquez-Dorbatt, V.; Tolstyka, Z. P.; Chang, C. W.; Maynard, H. D. *Biomacromolecules* **2009**, 10, 2207-2212.

[9] Pounder, R. J.; Stanford, M. J.; Brooks, P.; Richards, S. P.; Dove, A. P. *Chem. Commun.* **2008**, 5158-5160.

[10] Witczak, Z. J.; Lorchak, D.; Nguyen, N. *Carbohydr. Res.* **2007**, 342, 1929-1933.

[11] Becer, C. R.; Babiuch, K.; Pilz, D.; Hornig, S.; Heinze, T.; Gottschaldt, M.; Schubert, U. S. *Macromolecules* **2009**, 42, 2387-2394.

[12] Kade, M. J.; Burke, D. J.; Hawker, C. J. *J. Polym. Sci. Part A: Polym. Chem*. **2010**, 48, 743-750.

[13] (a) Koyama, E.; Sanda, F.; Endo, T. *Macromolecules* **1998**, 31, 1495-1500; (b) Shin, J.; Matsushima, H.; Chan, J. W.; Hoyle, C. E. *Macromolecules* **2009**, 42, 3294-3301; (c) Acosta, R.; Garcia, A. E.; Martinez M. G.; Berlanga, M. L. *Carbohydrate Polym*. **2009**, 78, 282-286.

[14] Boyer , C.; Granville, A.; Davis, T. P.; Bulmus, V. *J. Polym. Sci. Part A: Polym. Chem*. **2009**, 47, 3773-3794.

[15] (a) Campos, L. M.; Killops, K. L.; Sakai, R.; Paulusse, J. M. J.; Damiron, D.; Drockenmuller, E. ; Messmore, B. W. ; Hawker, C. J. *Macromolecules* **2008**, 31, 7063-7070; (b) Gress, A.; Volkel, A.; Schlaad, H. *Macromolecules* **2007**, 40, 7928-7933.

[16] (a) Stanford, M. J.; Dove, A. P. *Macromolecules* **2009**, 42, 141-147; (b) Li, M.; De, P.; Gondi, S. R.; Summerlin, B. S. J. *J. Polym. Sci. Part A: Polym. Chem*. **2008**, 46, 5093-510 ; (c) Tolstyka, Z. P. ; Kopping, J. T. ; Maynard, H. D. *Macromolecules* **2008**, 41, 599-606.

[17] Percec, V. *Chem. Rev*. **2009**, 109, 4961-4962.

[18] (a) Boutevin, B.; David, G.; Boyer, C. *Adv. Polym. Sci*. **2007**, 206, 31-135; (b) Goethals, E. J. Telechelic Polymers: Synthesis and Applications; CRC Press: Boca Raton, FL, 1989.

[19] (a) Montero de Espinosa, L.; Ronda, J. C.; Galià, M.; Cádiz, V. *J. Polym. Sci. Part A: Polym. Chem*. **2008**, 46, 6843-6850; (b) Sacristán, M.; Ronda, J. C.; Galià, M.; Cádiz, V. *Biomacromolecules* **2009**, 10, 2678-2685 ; (c) Lligadas, G.; Ronda, J. C.; Galià, M.; Biermann, U. ; Metzger, J. O. *J. Polym. Sci. Part A: Polym. Chem*. **2006**, 44, 634-645.

[20] Arceo, E.; Marsden, P.; Bergman, R. G.; Ellman, J. A. *Chem. Commun.* **2009**, 23, 3357-3359.

[21] Eras, J.; Escribà, M.; Villorbina, G.; Oromí-Farrús, M.; Balcells, M.; Canela, R. *Tetrahedron* **2009**, 65, 4866-4870.

[22] Roper T. M., Guymon, C. A.; Jönsson, E. S.; Hoyle, C. E. *J. Polym. Sci. Part A: Polym. Chem*. **2004**, 42, 6283-6298.

[23] Jacobine, A. F. Thiol-ene Photopolymerization in Radiation Curing, in Polymer Science and Technology; Vol. 3 Fouassier, J. P. and Rabek J. F. (Eds.), Chapman and Hall, London , 1993.

[24] Griesbaun, K. *Angew. Chem. Int. Ed*. **1970**, 9, 273-287.

[25] Walling, C.; Helmreich, W. *J. Am. Chem. Soc*. **1958**, 81, 1144-1148.

[26] Hocking, M. B. Handbook of Chemical Technology and Pollution Control, 3th ed.; Academic Press: San Diego (CA), 2005.

[27] Binauld, S.; Boisson, F.; Hamaide, T.; Pascault, J. P. ; Drockenmuller, E. ; Fleury, E. *J. Polym. Sci. Part A: Polym. Chem*. **2008**, 46, 5506-5517.

[28] Lattimer, R. P. *J. Am. Soc. Mass Spectrom*. **1992**, 3, 225-234.

[29] (a) Ozturk, G.; Long, T. E. *J. Polym. Sci. Part A: Polym. Chem*. **2009**, 47, 5437-5447; (b) Chan-Park, M. B.; Zhu, A. P.; Shen, J. Y.; Fan, A. L. *Macromol. Biosci*. **2004**, 4, 665-673; (c) Pierce, B. F.; Brown, A. H.; Sheares, V. V. *Macromolecules* **2008**, 41, 3866-3873.

[30] (a) Fokou, P. A.; Meier, M. A. R. *J. Am. Chem. Soc*. **2009**, 131, 1664-1665; (b) Montero de Espinosa, L.; Ronda, J. C.; Galià, M.; Cádiz, V.; Meier, M. A. R. *J. Polym. Sci. Part A: Polym. Chem*. **2009**, 47, 5760-5771.

[31] Xu, Y.; Petrovic, Z.; Das, S.; Wilkes, G. L. *Polymer* **2008**, 49, 4248-4258.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Chapter 5

Thermoplastic Polyurethanes from Undecylenic Acid-based Soft Segments: Structural Features and Release Properties

In this chapter the oligomeric polyols prepared in the previous chapter will be used as soft segments in the synthesis of segmented thermoplastic polyurethanes with potential application as drug delivery carriers.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Thermoplastic Polyurethanes from Undecylenic Acid-based Soft Segments: Structural Features and Release Properties

Cristina Lluch, Gerard Lligadas, Joan C Ronda, Marina Galià, Virginia Cádiz*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili,

C/ Marcel.lí Domingo s/n, 43007 Tarragona, Spain

* To whom correspondence should be addressed: gerard.lligadas@urv.cat

Abstract:

A set of thermoplastic polyurethanes were synthesized combining undecylenic acid-derived telechelic diols as soft segments and 1,4-butanediol/4,4´-methylenebis(phenylisocyanate) as hard segment. These polymers were fully chemically and physically characterized by means of NMR, FTIR, SEC, DSC, TGA, tensile tester and contact angle measurements. The obtained results revealed that both molecular weight of the diol and the hard segment content greatly influence the physical and mechanical properties of these polymers. In addition, given the potential use of these materials for biomedical applications, hydrolytic degradation, biocompatibility using human fibroblast cell line, and performance as drug delivery carriers have been evaluated.

Keywords: renewable resources, drug delivery systems, polyurethanes, biocompatibility

Introduction

The synthesis of polymeric materials based on renewable resources has become an important research topic, due to the widespread commitment to promote sustainable development. Plant oils in particular, have a long-term use as raw materials for polymer synthesis, owing to their economic and environmental advantages, such as availability, price, biodegradability and low toxicity.[1] Nevertheless, the use of bioresources must be intimately linked to the application of green technologies in order to implement sustainability to higher levels. In this context, the use of plant oils and derivatives, together with the application of click chemistry processes could be considered a prominent eco-friendly combination.[2]

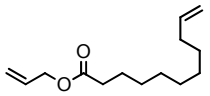
Vegetable oils are one of the most important platform chemicals for biobased polyols and derived polyurethanes (PUs) synthesis.[3] Most of these natural oils need to be functionalized with hydroxyl groups to be used as polyols. Thus, carbon-carbon double bonds and carbonyl groups present in these structures have been modified by several approaches to obtain polyols. Nowadays, there is a significant presence of PUs derived from vegetable oils which have found application in practically all fields, from automotive industry to biomedicine. The biobased PU manufacturing is dominated by thermosets and even though they generally show excellent mechanical properties and thermal stability, they cannot compete with the environmental benefits of the linear counterparts. Thus, the recyclability of linear PUs adds a high sustainability value to this technology, motivating an emergence of research interest in the last few years.[4]

Among linear PUs, segmented polyurethanes (sPUs) are the most attractive due to their superior properties and performance, influenced by their inherent biphasic structure. sPUs are block copolymers with alternating soft and hard blocks that separate into microphases. Hard segments (HS), made up of a diisocyanate and a chain extender, play the role of physical cross-links and act as high modulus fillers whereas the soft segment (SS), consisting in an oligomeric diol, provides extensibility to the material. The molecular weight of the diol and the concentration of SS and HS are the main

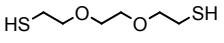
parameters that control the distribution of the two blocks in domains and consequently the final properties of the PU.

The synthesis of oligomeric diols based on plant oils, to be used as soft segments in block copolymers, is a barely explored field. These PU components have been prepared from polycondensation of fatty acids-derived dicarboxylic acids with an excess of a diol, under metal catalytic conditions at high temperature. Petrovic et al.[5] prepared ricinoleic acid-based soft segments bearing carbon dangling chains, via polycondensation of methyl ricinoleate with diethylene glycol. The prepared oligomers were used in the synthesis of sPUs showing wide range of mechanical properties. More recently, Narine et al.[6] prepared oligomeric polyesterdiols of molecular weights close to 1000 g/mol by polycondensation of azelaic acid and 1,9-nonanediol, both derived from vegetable oil feedstock, to be used as biobased PU precursors. Our group recently reported the preparation of well-defined telechelic oligodiols from undecylenic acid, a castor oil derivative, via two sequential thiol-ene couplings (TECs): step-growth photopolymerization and polymer end-groups modification with 2-mercaptoethanol.[7] Thiol-ene chemistry shows many of the features of click chemistry such as chemoselectivity, versatility, and the absence of metal catalysts and its potential has been widely exploited in many research areas.[8] In this sense, thiol-ene as well as thiol-yne chemistry provided an efficient and green approach towards novel plant derived diols and polyols avoiding the use of metal catalysts under the harsh conditions.[9]

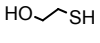
The purpose of this study was to synthesize biobased sPUs using the previously synthesized telechelic diols as SS (UDA-OH, Scheme 1) and 1,4-butanediol (BD)/4,4'-methylenebis(phenylisocyanate) (MDI) as the HS. The molecular weight of the diol as well as the SS/HS balance influence will be studied in terms of mechanical and thermal properties of the final polymers. Also, the potential of these PUs in the controlled release of hydrophobic drugs using rhodamine B as model compound will be addressed.



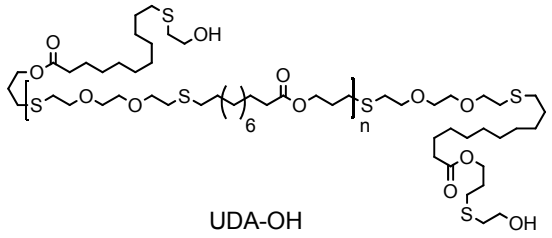
UDA



DT



ME



UDA-OH

UDA-OH	Mn^{NMR} (g/mol)	Mn^{SEC} (g/mol)
1	960	1900
3	3100	4230

Scheme 1

Experimental Section

Materials. Oligomeric diols (UDA-OH) based on undecylenic acid were synthesized as previously described.[7] The following chemicals were purchased from Aldrich and used as received: 1,4-butanediol, tin (II) 2-ethylhexanoate, Rhodamine B (Merck) and 4,4′-methylenebis(phenylisocyanate) (MDI). N,N-dimethylformamide (DMF) was dried with CaH_2 for 24h and freshly distilled before use.

Instrumentation. Ultraviolet (UV) light irradiation of the samples for thiol-ene photopolymerization was carried out with two 9W bench lamps which emit around 365 nm wavelength. NMR spectra were recorded on Varian VNMRS400. The samples were dissolved in deuterated DMF, and ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature with TMS as an internal standard. Size exclusion chromatography (SEC)

analysis was carried out with an Agilent 1200 series system equipped with a Shimadzu RID 6A series refractive-index detector. DMF/ LiBr (0.05M) was used as an eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained with polystyrene standards. Differential Scanning Calorimetry (DSC) measurements were carried out with a Mettler DSC822e thermal analyser with N_2 as the purge gas. 6-12 mg samples were used for DSC analysis. Telechelic diol samples were heated from -20 to 150ºC with a heating rate of 20ºC/min, cooled down to -90ºC with a cooling rate of -20ºC/min, and then heated again to 150ºC at the same heating rate. T_g and T_m values were obtained from the second heating curves. For analyzing polyurethanes, samples were heated from -80 to 240ºC with a heating rate of 20ºC/min. Thermal stability studies were carried out with a Mettler TGA/SDTA851e/LF/1100 with N_2 as the purge gas at a scanning rate of 10ºC/min. WAXD measurements were made using a Siemens D5000 diffractometer (Bragg-Brentano parafocusing geometry and vertical Θ-Θ goniometer) fitted with a curved graphite diffracted-beam monochromator, incident- and diffracted-beam Soller slits, a 0.06° receiving slit, and a scintillation counter as a detector. The angular 2Θ diffraction range was between 1° and 40°. Samples were dusted onto a low background Si(510) sample holder. The data were collected with an angular step of 0.05° at 3 s per step. Cu KR radiation was obtained from a copper X-ray tube operated at 40 kV and 30 mA. The IR spectra were recorded on a Bomem Michelson MB 100 FTIR spectrophotometer with a resolution of 4 cm^{-1} in the absorbance mode. An attenuated total reflection (ATR) accessory with thermal control and a diamond crystal (Golden Gate heated single reflection diamond ATR, Specac-Teknokroma) was used to determine FTIR spectra. The contact angle of deionized water against polymer surfaces was measured by the water drop method (3μL) at 25°C, using the OCA15EC contact angle setup (Neurtek Instruments). Tensile tests were performed with an Instron Dynamometer (model 5965, USA) on films of 5 cm length (distance between the grips of about 30 mm) and 500 mm width at a crosshead rate of 10 mm/min and at room temperature.

Preparation of Thermoplastic Polyurethanes

The polymers were prepared using the following methodology. In the preparation of sPU3-59, a dry 50 mL round-bottom flask was charged with 5 mL of DMF, 0.70 g of UDA-OH3 M_n^{NMR} = 3100 g/mol, 0.75 g of MDI, and 16 mg of tin (II) 2-ethylhexanoate. The flask was immersed into a 65 ºC preheated silicone oil bath with a magnetic stirrer. After 1 h polymerization a solution of 0.25g of 1,4-butanediol in DMF (4 mL) was added. The reaction was continued at 65 ºC for another 2 h. After reaction, the mixture was precipitated twice into methanol (50 mL). After drying in vacuum oven for 24h at 60 ºC, 1.5 g (88 % yield) of poly(ester urethane) was obtained. The polymer was dissolved in DMF (20% w/v), cast into film and evaporated at 50°C overnight.

Cytotoxicity assay

To evaluate cell viability of both monomers and PU, MTT assays were performed. The culture medium was Dubelcco's modified eagle medium (DMEM), rich in glucose, modified with 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (Sigma, Steinheim, Germany) and supplemented with 10% fetal bovine serum, 200 mM L-glutamine, 100 units/mL penicillin, and 100 μg/mL streptomycin.

UDA-OH3 was dissolved in DMSO in a weight ratio of 4:1. The mixture was dispersed in the serum-free medium (DMEM FCS-free) in order to obtain 0.1 wt % mixture solution containing 0.080 wt % of UDA-OH3 and 0.020 wt % of DMSO. This solution was successively diluted with serum-free medium. Human fibroblasts were seeded at a density of 10 x 10^4 cells/mL in complete medium in a sterile 96-well culture plate and incubated to confluency. After 24 h of incubation the medium was replaced with the corresponding dilution and incubated at 37 °C in humidified air with 5% CO_2 for 24 h. A solution of MTT was prepared in warm PBS (0.5 mg/mL), and the plates were incubated at 37 °C for 4 h. Excess medium and MTT were removed, and dimethylsulfoxide (DMSO) was added to all wells in order to dissolve the MTT taken up by the cells. The solution was mixed for 10 min, and the absorbance was measured with a Biotek ELX808IU detector using a test wavelength of 570 nm and a reference wavelength of 630 nm. The relative cell viability (RCV) was calculated from the following equation:

$RCV\ (\%) = 100 \times (OD_S - OD_B)/OD_C$

where OD_S, OD_B and OD_C are the optical densities of formazan production for the sample, blank (medium without cells) and control (DMSO in free serum supplemented DMEM), respectively. A dose-response curve of relative cell viability was plotted to delineate the concentrations of the monomer that depressed MTT-formazan production by 50% (IC50 value). The same experiment was applied to DMSO to demonstrate that its use during the study has no effect on the results obtained and resulted in no apparent toxicity of the DMSO itself.

To determine the cytotoxicity of the PUs, polymer films and thermanox disks (TMX) as negative control, were set up in 5 mL of (DMEM FCS-free), and incubated at 37°C for 1, 2 and 7 days and the extracts were removed to be used as the incubation medium. Human fibroblast cells were seeded at a density of $10x10^4$ cells in a 100 μL of growth media and incubated for 24h in 5% CO_2 at 37°C. The medium was replaced by the corresponding polymer eluted extracts and incubated at 37°C in a humidified air with 5% CO_2 for 24h. Finally, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution was added to the culture medium and further incubated for 3h. The media was discarded and DMSO was added to dissolve the formazan crystals. Optical absorbance was measured at 570 nm to determine the amount of viable cells. Results were normalized with respect to a negative control (TMX=100%) and statistically tested with ANOVA ($p<0.05$).

Hydrolytic degradation

Hydrolytic degradation of some of the polymers was evaluated by immersing square sample films (10 x 10 mm) into glass bottles containing 100 mL of phosphate buffer solution (pH 7.4 at 37ºC). Polymer samples were withdrawn at different time intervals, dried at 50°C under vacuum and weighted. The hydrolytic degradation was studied by monitoring the mass loss. Mass loss was defined as follows:

mass loss (%) = $(M_0 - M_t)/M_0$ x 100,

where M_0 represents the weight of the dry sample before degradation and Mt represents the weight of the dry sample after degradation at different time intervals.

Drug Release of Rhodamine B from Polyurethane Films

Rhodamine B (5 wt.-%) was dissolved in DMF together with the polyurethane and solvent cast onto glass petri dishes. Drug release studies were conducted placing 10x10 mm polymer films in 100 mL phosphate buffer (pH=7.4) at 37ºC. At each time point, the specimen was keep out from the incubation solution. Rhodamine B concentration in the solution was determined by UV detection at a wavelength of 550 nm. The concentration was determined from a standard curve by measuring the absorption at 550 nm of pure rhodamine B at concentrations ranging from 0.2-15 ppm.

Results and Discussion

Polyurethane Synthesis and Characterization

We previously reported the preparation of well-defined telechelic diols (UDA-OH) of molecular weight ranging from 1000 to 3000 g/mol, using a potentially 100% biomass-derived monomer, allyl ester of undecylenic acid (UDA).[7] Undecylenic acid is a castor oil derivative whereas allyl alcohol is available from glycerol, the main byproduct in triglyceride transesterification. This methodology is based on two one-pot photoinitiated TECs: step-growth polymerization of UDA using 3,6-dioxa-1,8-octanedithiol (DT) and oligomer end-groups modification with 2-mercaptoethanol (ME). The chemical structures of UDA, DT, ME and oligomeric diols UDA-OH are shown in Scheme 1.

Two of the above mentioned UDA-based macrodiols with molecular weight, determined by ^{1}H NMR, of 960 g/mol (UDA-OH1) and 3100 g/mol (UDA-OH3) were used in the preparation of sPUs. Non-segmented PUs were also prepared as model soft segment blocks in segmented structures. In non-segmented formulations, the corresponding oligodiol UDA-OH was reacted with MDI in DMF, whereas in segmented systems the prepolymer technique was applied as follows; UDA-OH was reacted first with an excess of diisocyanate and the subsequent chain extension was carried out by reaction with the equivalent amount of BD. Designation, molar ratio and HS content of the synthesized PUs are summarized in Table 1. SS concentration was taken to be the weight percentage of macrodiol component, whereas MDI plus chain extender was considered as HS. The final polymers were purified properly by reprecipitation, vacuum dried and then analyzed.

Table 1. SPUs composition (1mmol UDA-OH), molecular weight, solubility and contact angle values

PU	BD (mmol)	MDI (mmol)	HS (%)	Yield (%)	SEC[a]		Solubility[b]			Contact angle
					M_n^{GPC} (g/mol)	Mw/Mn	THF	DMF	$CHCl_3$	
PU1	-	1	-	93	28438	1.53	+	+	+	81
sPU1-30	0.54	1.54	30	94	36482	1.45	-	+	-	85
sPU1-56	3.03	4.03	56	96	75677	1.50	-	+	-	90
PU3	-	1	-	92	48517	1.62	+	+	+	85
sPU3-37	4.27	5.27	37	96	45970	1.49	-	+	-	86
sPU3-59	11.45	12.45	59	88	46363	1.52	-	+	-	93

[a] Values obtained in DMF/LiBr (0.05M) using polystyrene standards; [b] Solubility at 25 °C: + soluble, - insoluble

The chemical structures of the prepared PUs were assessed by NMR and FTIR spectroscopies. ^{1}H and ^{13}C NMR spectra were in full concordance with the chemical structures of the synthesized PUs, showing the characteristic signals of urethane bonds at 9.60 ppm (-NH) and 4.25 ppm (-$\underline{CH_2}$COONH-). As can be seen in Figure 1A, characteristic urethane linkages FTIR absorption bands were also detected at 3200-3500 cm^{-1} (N-H stretching vibration), 1637-1730 cm^{-1} (C=O stretching vibration), 1533 cm^{-1} (N-H deformation), 1309 cm^{-1} (-OCONH stretching vibration), and 1233 cm^{-1} (C-N stretching vibrations). All the PUs were obtained as white products with molecular weights ranging from 30.000 to 75.000 g/mol. The solubility of the sPUs resulted to be limited to DMF, whereas non-segmented PUs were soluble in a wide range of solvents. The yield, solubility and molecular weight data of the resulting polymers are also collected in Table 1.

FTIR is commonly used to study the hydrogen bonding properties of the sPUs.[10] Hydrogen bonding between functional groups together with the chemical composition and sequence length of HS and SS closely affects the phase separation morphology of sPUs.[11] Thus, the analysis of the carbonyl region of the FTIR spectra could provide valuable information in understanding the extent of microphase separation in the synthesized PUs. FTIR spectra for PU1 and PU3 series (PU1, sPU1-30, sPU1-56, PU3, sPU3-37, sPU3-59) are shown in Figure 1B and 1C, respectively.

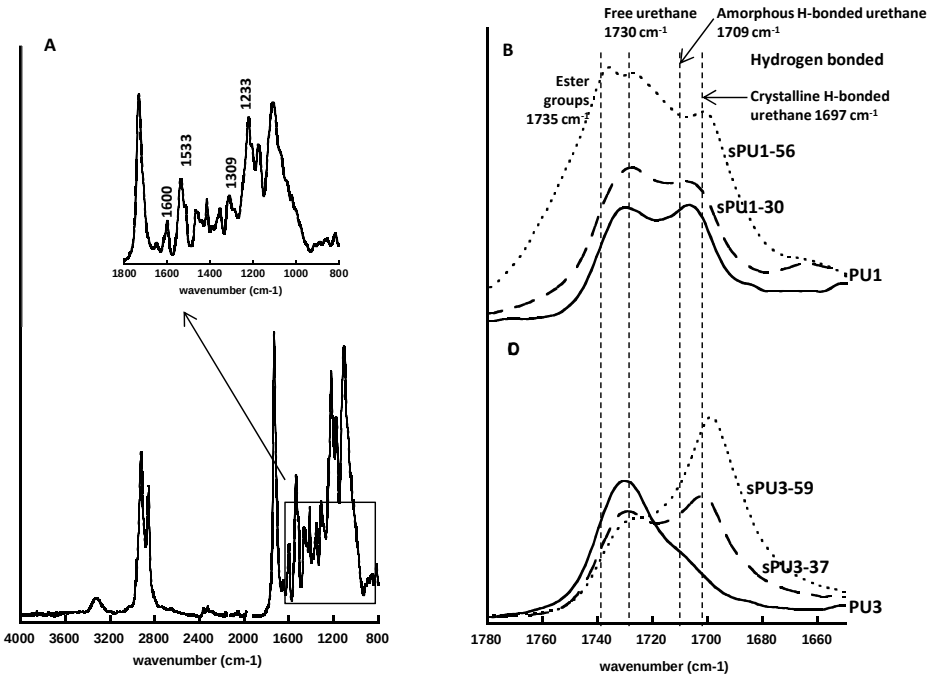


Figure 1. FTIR spectra of (A) PU3; (B) PU1 series; (C) PU3 series.

All the spectra show a band located at 1730 cm^{-1} corresponding to C=O stretching vibration of urethane carbonyl groups in which, in some cases, is embedded the band at 1735 cm^{-1} ascribed to the ester groups of the oligodiol UDA-OH. It is also known, that at a lower frequency (1697-1709 cm^{-1}) appear the bands associated to hydrogen bonded carbonyl groups.[12] Moreover, two distinctive bands can be differentiated in this region associated to ordered (1697 cm^{-1}) and disordered (1709 cm^{-1}) hydrogen bonded domains.[13]

For sPU3 systems, the intensity of the band attributed to hydrogen bonded urethane groups increases with increasing HS content. As expected, higher urethane content leads to higher hydrogen bonding possibilities, contributing to the formation of interconnected HS domains. sPU1 systems do not show the same trend and the intensity of the band attributed to the hydrogen bonded urethanes is very similar in both sPU1-30 and sPU1-56. This phenomenon could be attributed to phase mixing of the hard/soft domains.

The wide angle X-ray diffraction (WAXD) of all synthesized PUs showed essentially the same pattern, presenting a broad halo centered al 2 Θ =19º indicating amorphous or very little crystallized systems. Nevertheless, DSC analysis of synthesized PUs revealed significant differences and it was used to determine the phase separation extent between HS and SS in each system. The DSC curves of sPU1 and sPU3 series are shown in Figure 2A and B, respectively. The values of thermal transitions obtained for the studied PUs are summarized in Table 2. Non-segmented PUs showed a glass transition temperature (Tg) at around -40ºC, and no effect of the molecular weight was observed. In sPUs, phase separation takes place due to thermodynamic incompatibility between HS and SS. The Tg of the SS (Tg^{ss}) values reveal the relative purity of the soft domain and can be used as a measure of the SS and HS phase mixing extent.[14] The degree of miscibility between HS and SS depends on their respective lengths and each other affinity, mainly through the ability to establish hydrogen bonding interactions, which strongly depend on segments chemical composition, and also on the HS content.[15] Tg^{ss} is raised when HS is dissolved in the soft phase, so decreasing phase separation degree.

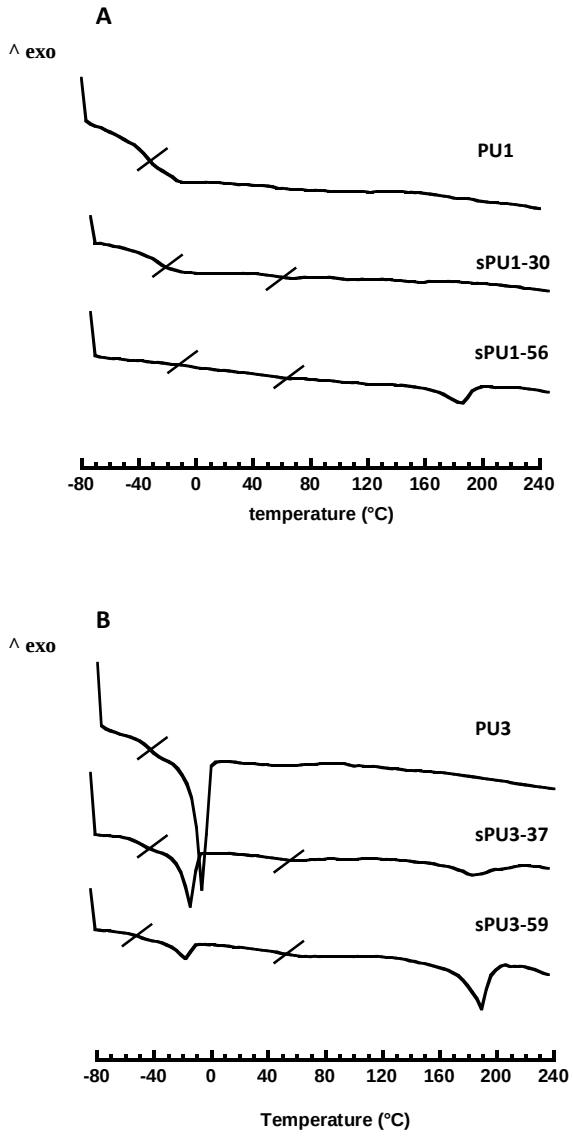


Figure 2. DSC thermograms of (A) PU1 series; (B) PU3 series.

For sPUs, based on UDA-OH1, higher Tg^{ss} values were obtained compared to the non-segmented formulation. Tg^{ss} increases slightly with HS content, suggesting that certain amount of HS is present in the soft phase, resulting in a decrease of the overall degree of phase separation. On the other hand, PUs based on UDA-OH3, showed a Tg^{ss} at about -45ºC, regardless the HS content, indicating lower phase mixing. Otherwise, a low temperature endotherm due to the SS melting Tm^{ss}, appears only for sPU3 and is not observed for UDA-

OH1 derived systems. Melting enthalphy was dependent of the percentage of HS and decreases as HS content increases.

Tg corresponding to the HS (Tg^{HS}) was observed at approximately 50-60ºC for all the synthesized sPUs. For all series, as HS content increases, Tg^{HS} increases, due to the restricted mobility of the large hydrogen bonded connected hard domains.

Table 2. Thermal and mechanical properties of the prepared sPUs.

PU	DSC						Tensile properties	
	Tg^{SS} (°C)	Tm^{SS} (°C)	ΔHf (J/g)	Tg^{HS} (°C)	Tm^{HS} (°C)	ΔHf (J/g)	σ^a (MPa)	ε^b (%)
PU-1	-36	-	-	-	-	-	2.4	221.6
sPU1-30	-29	-	-	49	-	-	0.8	63.4
sPU1-56	-20	-	-	54	178	11.3	15.5	230
PU3	-44	-6	32.2	-	-	-	1.0	140.1
sPU3-37	-45	-9	12.6	50	187	7.0	5.7	207.5
sPU3-59	-49	-13	4.9	56	193	20.9	10.3	36.9

[a] stress at break; [b] strain at break

Although DSC curves of segmented polyurethane systems are not clear enough to unequivocally locate Tg^{HS}, these values were corroborated by thermodynamomechanical measurements. Also, for high HS contents an endotherm Tm^{HS} can be observed, due to the formation of larger crystalline structures.[14-16] This endothermic peak appears in sPU3 series even at lower HS content (sPU3-37). Indeed, the formation of better ordered crystalline domains in sPU3 series is in agreement with the FTIR results. An accurate analysis of Figure 1B and C shows that for all sPU3, the hydrogen bonded urethane band increases with HS content and appears at 1697 cm^{-1}, as described for ordered

crystalline domains. In contrast, for PU1 series, only sPU1-56 shows crystalline domains (1697 cm^{-1}), whereas sPU1-30 shows a band centered at 1709 cm^{-1}, indicating amorphous hydrogen bonded domains, which is interpreted as an increased miscibility of the SS/HS. Finally, it must be remarked that DSC and FTIR have confirmed better microphase separation for higher molecular weight diols (UDA-OH3) and higher HS content (60%).

Table 3. Thermal stability data for SPU and parent UDA-OH from TGA measurements using N_2 as purge gas.

	TGA				
PU	**$T_{5\%}$[a] (°C)**	**T_1 max[b] (°C)**	**W_1[c] (%)**	**T_2 max[d] (°C)**	**W_2[e] (%)**
UDA-OH1	318	-	-	374	100
PU1	302	300	2	365	67
sPU1-30	278	301	6	366	60
sPU1-56	275	304	13	367	57
UDA-OH3	331	-	-	372	100
PU3	330	287	3	375	84
sPU3-37	281	288	11	375	59
sPU3-59	267	294	18	374	53

[a] Temperature corresponding to 5% weight loss; [b] Temperature of the first maximum of the derivative plot; [c] Weight loss of the first degradation stage; [d] Temperature of the second maximum of the derivative plot; [e] Weight loss of the second degradation stage.

The mechanical properties of PU1 and PU3 series were examined by tensile tests at 25ºC and the results are given in Table 2. Tensile tests showed that PUs with higher HS content had higher modulus and larger linear portion at the beginning of the stress-strain curve relative to non-segmented systems. For PU3 series, tensile stress at break increases as a function of increasing HS content. However, the elongation at break decreases from 37 to 59% HS, implying that optimum HS content or degree of phase

separation exists for optimum elongation. In 59% HS, the high degree of crystallinity in the hard phase, could act as shear stress contractor at the narrow soft/crystalline hard interphase, giving rise to poor tensile properties and resulting in a weaker structure. Indeed, hard segment crystallinity degree is critical in mechanical properties.[16] sPU1-56 displayed the highest tensile stress and elongation at break, probably due to the optimum crystalline degree and greater degree of chain entanglements, provided by its higher molecular weight.

Thermal and Hydrolytic Degradation

The degradation profiles of the synthesized PUs were evaluated thermally and hydrolytically. Figure 3 shows the thermal degradation behavior of PU3 series and parent UDA-OH3 diol. Thermal stability data for all systems are collected in Table 3. PUs are known to be relatively thermally unstable materials and normally the first stage of degradation is related to urethane bond decomposition. Generally, three mechanisms of decomposition of urethane bonds have been proposed and reactions may proceed simultaneously: dissociation to isocyanate and alcohol, formation of primary amine and olefin and formation of secondary amine and carbon dioxide. In the second stage the degradation corresponding to the soft segment occurs. Furthermore, it is possible to observe a third weight loss stage associated with other segments of the remaining structure or might be due to a probable C-C bond cleavage.[17] Thermal stability of PUs depends strongly on urethane groups per unit volume. It can be seen that $T_{5\%}$ of UDA-OH oligodiols degradation is higher than the corresponding PU systems, according to the mechanism of the first degradation step. Due to the influence of urethane bonds, when the molecular weight of the diol increases, $T_{5\%}$ decreases. As it can be observed from Table 3, the $T_{5\%}$ of the parent diol and derived PUs decreases as HS content increases suggesting that the starting point of degradation takes place predominantly within HS. The mass loss of the first degradation step around 300°C (W_1) increases as the HS content does, according to the above mentioned decomposition mechanism.[18]

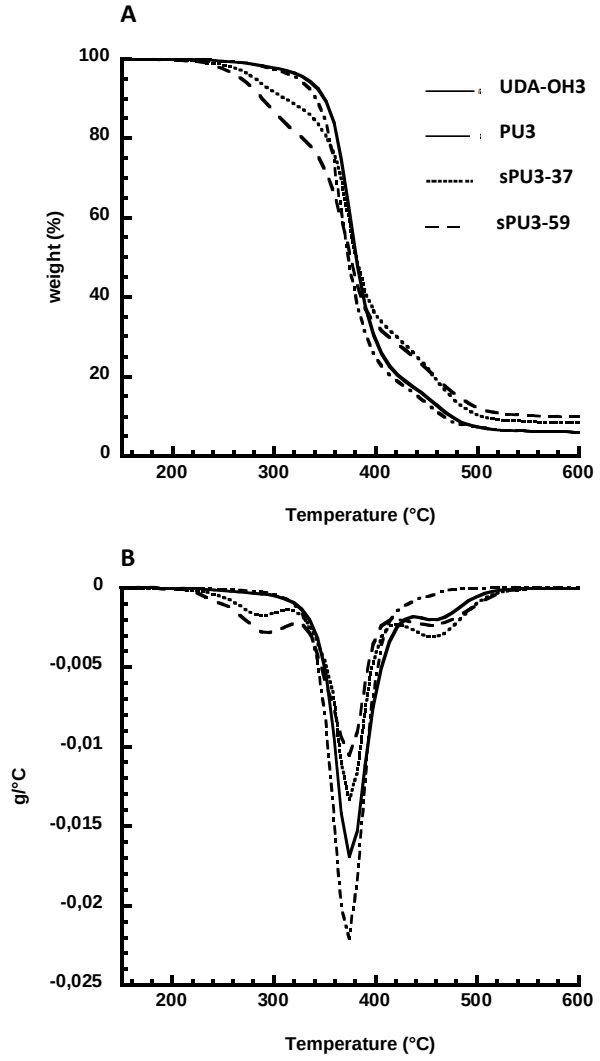


Figure 3. TGA traces of sPU3 series: (A) weight loss curves; (B) first derivative curves.

Around 370 ºC another decomposition peak, corresponding to soft segment decomposition ($T_{2\ max}$) can be observed. $T_{2\ max}$ is very similar for all PUs, regardless of their HS content and a decrease of mass loss (W2) during the second stage is observed for PUs with higher HS content. At a considerably higher temperature (ca. 460 ºC) another decomposition peak is observed, which is related with the above explained third degradation stage.

Hydrolytic degradation of these PUs was also studied. Samples were placed in a phosphate buffer solution at 37 and 60ºC for 6 months. No significant weight loss of the

polymer films were detected over the studied period. The most obvious reason for the hydrolytic stability of the polymers is their hydrophobicity, which prevents any water from penetration into the materials to initiate degradation. To evaluate the hydrophobicity of the polymers, water contact angle measurements were carried out. The contact angle values for the prepared PUs are collected in Table 1. These values slightly increase as the HS content increases, showing that PUs with high content of soft segment present lower hydrophobicity than PUs with high HS content. The effect of the UDA-OH molecular weight on the contact angle values does not show any clear trend.

Polyurethanes Cytotoxicity and *In vitro* Drug release studies

Since fatty acids are natural body components, the hypothesis that could be good candidates for the preparation of biocompatible polymers is generally accepted. Nevertheless, the study of the cytotoxicity of diols and PUs is essential to gain insight into their suitability for biomedical use. One of the most common assays for testing cellular viability is the MTT assay based on the reductive cleavage of the yellow tetrazolium dye to purple formazan, by the succinic dehydrogenase present in intact mitochondria. This conversion only occurs in living cells and consequently a decrease in metabolic activity offers an earlier indicator of cell death. Cytotoxicity against human fibroblasts of undecylenic acid-based diols was studied using UDA-OH3 as a representative diol. The UDA-OH3 dose response curve exhibits the typical sigmoidal form associated with cell viability assays. The IC50 was calculated to be 0.36 mg/mL under the conditions tested. The toxicity dose response behavior demonstrates the significant cell viability characteristics of these biobased telechelic diols. Measurements on DMSO were carried out to demonstrate that its use during the study has no effect on the results obtained and resulted in no apparent toxicity of the DMSO itself.

To test the cytotoxicity of PU3 and sPU3-59, the extraction medium from each PU sample after 1, 2 and 7 days was used to culture human fibroblasts for 24h at 37ºC. The extraction procedures were performed to simulate clinical conditions to evaluate the presence and release of toxic leachables without affecting the chemical or mechanical properties of the PU matrix. The results from MTT assay of the mentioned PUs are shown in Figure 4A.

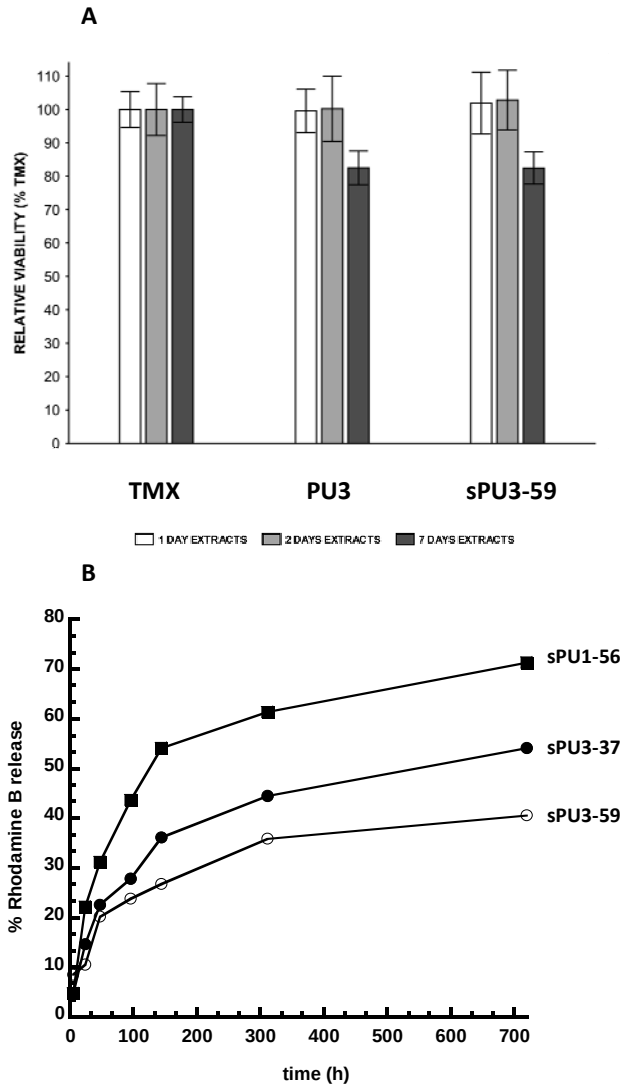


Figure 4. (A) MTT assay for PU3 and sPU3-59. Statistical analysis (n=12) for each polymer was performed with respect to TMX; (B) Drug release profiles of the prepared sPUs.

In order to ascertain the potential of these sPUs in the controlled release of hydrophobic drugs, a hydrophobic model dye, Rhodamine B, was incorporated into the PU films by solvent casting. The diffusion of the entrapped drug through the polymeric matrix to an aqueous solution was studied. Surface properties and crystallinity of the polymer greatly influence the drug release rate, as they control water penetration.[19] In our systems drug diffusion must be also discussed in terms of microphase morphology of the sPUs. The representative drug release profile of the studied sPUs is shown in Figure 4B. As it can

be observed, for the same concentration of hard segment (sPU1-56 and sPU3-59), a more sustained release is obtained for the more crystalline formulation due to the difficulty to water penetration.[20] Polymer matrices with higher content of hard segment (sPU3-59) lead to a more sustained release compared to the lower hard segment content matrix (sPU3-37). Larger interchain hydrogen bonds of the urethane functionalities lead to the reduced mobility of the segmented units, forming a rigid and impermeable barrier.[21] Faster release rates were observed for the systems sPU1-56 probably due to a more uniform distribution of the drug throughout the polymer matrix, as the result of poorer phase segregation.[22] As explained, the drug release rate of these polyurethanes is affected by the contact angles and the composition and morphology of these polyurethanes.

Conclusions

Thermoplastic sPUs have been prepared using oligodiols based on undecylenic acid, as renewable feedstock. The molecular weight of the telechelic diols as well as the SS/HS ratio showed to be determinant for microphase separation. sPUs based on macrodiol of Mn around 3000 g/mol (sPU3 series) show a clear phase segregated morphology, evidenced by a comprehensive analysis of FTIR and DSC. In contrast, the use of lower molecular weight soft segments (sPU1 series) results in a significant mixing of soft/hard domains. Nevertheless, the disordered morphology of sPU1 series does not cause a detrimental impact on the mechanical properties of the material. sPUs with higher HS content (56-59%) show better microphase separation mainly due to higher hydrogen bond interactions upon increasing urethane proportion. The biocompatibility properties and the diffusion-controlled drug release profiles of these PUs make them to be considered well-suited as sustained delivery carriers of hydrophobic drugs.

Acknowledgment. Financial support by the MICINN (Ministerio de Ciencia e Innovacion, MAT2011-24823) is gratefully acknowledged. We thank J. Parra for cytotoxicity assays.

[1] J.C. Ronda, G. Lligadas, M. Galià, V. Cádiz, *Eur. J. Lipid Sci. Technol*. 2011, 113, 46; Y. Xia, R.C. Larock, Green Chem. **2010**, 12, 1893.

[2] O. Türünç, M. A. R. Meier, *Eur. J. Lipid Sci. Technol*. **2012** (DOI: 10.1002/ejlt.201200148).

[3] M. Desroches, M. Escouvois, R. Auvergne, S. Caillol, B. Boutevin, *Polym. Rev*. **2012**, 52, 38; D.P. Pfister, Y. Xia, R.C. Larock, *ChemSusChem*. **2011**, 4, 703; G. Lligadas, J.C. Ronda, M. Galià, V. Cádiz, *Biomacromolecules* **2010**, 11, 2825; Z. S. Petrovic, Polym. Rev. **2008**, 48, 109.

[4] R.J. González-Paz , G. Lligadas, J.C. Ronda, M. Galià, V. Cádiz. *Polym. Chem.* ***2012***, 3, 2471; D.V. Palaskar, A. Boyer, E. Cloutet, J. Le Meins, B. Gadenne, C. Alfos, C. Farcet, H. Cramail, *J. Polym. Sci., Part A: Polym. Chem*. **2012**, 50, 1766; M. Desroches, S. Caillol, R. Auvergne, B. Boutevin, *Eur. J. Lipid Sci. Technol*. **2012**, 114, 84; C. Bueno-Ferrer, E. Hablot, F. Perrin-Sarazin, M.C. Garrigós, A. Jiménez, L. Averous, *Macromol. Mater. Eng*. **2012**, 297, 777; A.S More, L. Maisonneuve, T. Lebarbé, B. Gadenne, C. Alfos, H. Cramail, *Eur. J. Lipid Sci. Technol.* **2012** (DOI: 10.1002/ejlt.201200172); L. Hojabri, X. Kong, S.S. Narine, *Biomacromolecules* **2010**, 11, 911; L. Hojabri, X. Kong, S.S. Narine, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, 48, 3302; D.V Palaskar, A. Boyer, E. Cloutet, C. Alfos, H. Cramail, *Biomacromolecules* **2010**, 11, 1202.

[5] Y. Xu, Z. Petrovic, S. Das, G.L. Wilkes, *Polymer* **2008**, 49, 4248.

[6] L. Hojabri, J. Jose, A. Lopes Leao, L. Bouzidi, S. S. Narine, *Polymer* **2012**, 53, 3762.

[7] C. Lluch, J.C. Ronda, M. Galià, G. Lligadas, V. Cádiz, *Biomacromolecules* **2010**, 11, 1646.

[8] C.E. Hoyle, A.B. Lowe, *Chem. Soc. Rev*. **2010**, 39, 4, 1355; A.B. Lowe, *Polym. Chem*. **2010**, 1, 17.

[9] Lligadas, G. *Macromol. Chem. Phys*. DOI: 10.1002/macp.201200582

[10] M.A. Hood, B. Wang, J.M. Sands, J.J. La Scala, F.L. Beyer, C.Y. Li, *Polymer* **2010**, 51, 191; L. Rueda-Larraz, B. Fernandez d´Arlas, A. Tercjak, A Ribes, I. Mondragon, A. Eceiza, *Eur. Polym. J.* **2009**, 45, 2096.

[11] R. Hernandez, J. Weksler, A. Padsalgikar, T. Choi, E. Angelo, J. S. Lin, L.C. Xu, C. A. Siedlecki, J. Runt, *Macromolecules* **2008**, 41, 9767.

[12] F. Yen, J. Hong, *Macromolecules* **1997**, 30, 7927.

[13] S. K. Pollack, D. Y. Shen, S. L Hsu, Q. Wang, H. D. Stidham, *Macromolecules* **1989**, 22, 551.

[14] A. Saralegui, L. Rueda, B. Fernández-D'Arlas, I. Mondragon, A. Eceiza, M.A. Corcuera, *Polym. Int*. **2012** (DOI: 10.1002/pi.4330).

[15] M.A. Corcuera, L. Rueda, A. Saralegui, M.D. Martín, B. Fernández-D'Arlas, I. Mondragon, A. Eceiza, *J. Appl. Polym. Sci*. **2011**, 122, 6, 3677.

[16] D.J. Martin, G.F. Meijs, G.M. Renwick, P.A. Gunatillake, S.J. McCarthy, *J. Appl. Polym. Sci*. **1996**, 60, 4, 557.

[17] S. V. Levchik, E. D. Weil, *Polym Int*. **2004**, 53, 1585.

[18] C. Bueno-Ferrer, E. Hablot, M. Garrigós, S. Bocchini, L. Averous, A. Jiménez, *Polym. Degrad. Stab.* **2012**, 97, 1964.

[19] F. Quaglia, M.C Vignola, G. De Rosa, M.I. La Rotonda, G. Maglio, R. Palumbo, J. *Control. Release* **2002**, 83, 263.

[20] F. Barbato, M. A La Rotonda, G. Maglio, R. Palumbo, F. Quaglia, Biomaterials **2011**, 22, 1371; T. T. Reddy, M. Hadano, A. Takahara, *Macromol. Symp*. **2006**, 242, 241.

[21] A. Wolinska-Grabczyk. *J. Membr. Sci*. **2006**, 282, 225.

[22] D. Sarkar, J. Yang, S. T. Lopina, *J. Appl. Polym. Sci*. **2008**, 108, 2345.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Chapter 6

Versatile and Efficient Post-Polymerization Modifications of a Functional Polyester from castor oil

This chapter deals with the study of different efficient post-polymerization modifications on a functional polyester based on castor oil. The polymer will be modified with specific moieties to render it with new potential applications.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Versatile and Efficient Post-Polymerization Modifications of a Functional Polyester from castor oil

Cristina Lluch, Gerard Lligadas, Joan C Ronda, Marina Galià, Virginia Cádiz*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili,

C/ Marcel.lí Domingo s/n, 43007 Tarragona, Spain

* To whom correspondence should be addressed: marina.galia@urv.cat

Abstract:

This work reports versatile and efficient post-functionalization of an aliphatic functional polyester. The functional polyester is prepared by enzymatic polycondensation of dimethyl 2,8-dibromosebacate and 1,10-decanediol, both derived from castor oil. The alkyl halide functionalities of these polyesters have shown to react with thiols, amines and carboxylic acids under mild and efficient conditions obtaining multifunctional graft polymers and copolymers.

Introduction

Aliphatic polyesters, including poly(ε-caprolactone), poly(glycolic acid) and poly(lactic acid), are well-known materials that have been extensively used as industrial plastics as well as medical devices. Given their general biocompatibility and biodegradability, they continue to receive significant attention.[1] However, the hydrophobic and semicrystalline properties and the inherent lack of reactive chemical handles for the incorporation of functionalities of common natural and synthetic aliphatic polyesters, introduces limitations and reduces the broad applicability of these materials. To widen the versatility of the polymers, special efforts have been devoted to the functionalization of the polyester backbone. [2] Numerous examples of chain-end functionalized aliphatic polyesters have been reported, prepared most commonly by the use of functional nucleophiles to initiate ring-opening lactone polymerization. However, pendant functionalization provides a unique opportunity to alter physical and chemical properties by distributing functionality along polymer backbone. This imparts a structural homogeneity that can assume considerable importance for example in the degradability behavior, where the properties of the degradation products are critically important. Strategies have emerged that employ a variety of routes and chemistries for the pendant functionalization of synthetic polyesters via copolymerization with specialty monomers, post-polymerization modification or a combination of the two strategies. The improved functional group tolerance of living/controlled polymerization techniques when compared with conventional polymerization techniques allowed the preparation of well-defined polymers bearing a wide variety of functional groups that can be quantitatively and selectively modified using relatively mild conditions without any side reactions.[3] The application of click chemistry to aliphatic polyesters is particularly valuable, given the sensitivity of the polyester backbone to the conditions required for many organic transformations and couplings. Many examples of incorporation of double bonds,[4] triple bonds,[5] thiols[6] and azides[7] onto polyesters backbone, amenable to react under the well known click reactions conditions, have been described.

Renewable resources are of strong interest in materials research[8] and fatty acids are highly valuable platform chemicals for the development of sustainable alternatives to

depleting fossil oil reserves.[9] There are two major pathways to prepare polymers from fatty acids. The first one involves the use of the original functional groups to prepare polymers by various polymerization techniques and the second route is the chemical functionalization of the fatty acids before polymerization. Most of the conversions of fatty acids towards renewable monomers have been reported for the low reactivity carbon-carbon double bond of the aliphatic chain, to be replaced with new functional groups, which are then readily polymerized.[10-11] Among the different reactive positions of fatty acids derivatives, the α-halocarbonyl positions offers the possibility of rapid and quantitative nucleophilic displacement. The synthesis of halogenated polyesters based on renewable resources has been described due to the synthetic possibilities they offer. Thus, ε-caprolactones substituted mainly in the α and γ positions with pendant halogen groups have been prepared and further ring-opened polymerized by aluminium or tin alkoxides, into functionalized aliphatic polyesters.[12] Polycondensation of bromosuccinic or 2-bromoadipic acid and diols using scandium catalysts at room temperature has been also described. [13, 14] The substitution of the pendant halogen groups by azide is one of the most widely employed strategies for the post-polymerization modification of these functional groups via click chemistry.[15]

Enzymatic polymerization of polyesters has been regarded as an environmentally friendly synthetic process due to its special features: high catalytic activity, mild reaction conditions and high selectivity. [16] This catalytic system is an attractive alternative when the polymer bear labile functional groups and also when the polymers are targeted to biomedical applications, as no toxic metal catalysts are used.

Here, we describe an approach to functionalized aliphatic polyesters by enzymatic polymerization of two monomers derived from castor oil: dimethyl 2,8-dibromosebacate (DMBS) and 1,10-decanediol (DCD)**.** To take advantage of the α-brominated polyesters reactivity, we studied the nucleophilic substitution of the alkyl bromide functions with thiols, amines and carboxylic acids.

Experimental Section

Materials. Chemicals and solvents were used, unless otherwise noted, as received. Sebacic acid (95%), thionyl chloride (97%) and diphenyl ether (99%) were purchased from Fluka. The following chemicals were purchased from Sigma-Aldrich: 1,10-decanediol (DCD) (99%), triethylamine (99%), bromine (99%), lipase acrylic resin from *Candida Antarctica* (specific activity 5000 U/g)*),* 2-mercaptoethanol (99%), 3-mercaptopropionic acid (99%), 2-aminoethanol (98%), glycolic acid (99%), propionic acid (99.5%), poly-(N-isopropylacrylamide)-carboxylic acid terminated (Mn: 2000 g/mol) (NIPAAm COOH) and potassium fluoride (KF) (99%). Diphenyl ether (DPE) was dried under molecular sieves before use. Lipase was dried under vacuum for 24h before use.

Instrumentation. NMR spectra were recorded on Varian VNMRS400. The samples were dissolved in deuterated solvent, and ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature with tetramethylsilane (TMS) as internal standard. Kinetic studies were carried out by dissolving the reactants in DMF-d_7. Size exclusion chromatography (SEC) analysis was carried out with different systems using as solvents THF or DMF/LiBr (0.05M) at a flow rate of 1.0 mL/min. THF soluble polymers were analyzed with an Agilent 1200 series system equipped with an Agilent 1100 series refractive-index detector. SEC analysis of DMF soluble polymers was carried out with an Agilent 1200 series system equipped with a Shimadzu RID 6A series refractive-index detector. The calibration curves for SEC analysis were obtained with polystyrene standards.

Synthesis of dimethyl 2,8-dibromosebacate (DMBS)

To a 250-mL round-bottom flask fitted with a reflux condenser and $CaCl_2$ tube, 18 mL (234.86 mmol) of thionyl chloride were added and heated to 80°C. Then 20 g (93.94 mmol) of sebacic acid were added in portions and reacted for 2 hours. Bromine (12.03 mL, 234.86 mmol) was added dropwise during 6 hours. Finally, the flask was cooled down and the solution was added dropwise to 500 mL of cold methanol. The solution was stirred overnight at room temperature. Then, chloroform was added to the mixture and it was washed with aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ and dried over

anhydrous magnesium sulphate. The product was obtained as a clear oil and purified by vacuum distillation (180°C, 0.45 mm Hg, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$/TMS , δ): 4.22 (t, 2H, -CH-Br), 3.76 (s, 6H, -OCH_3,), 1.90-2.00 (m, 4H, CHBr-$\underline{CH_2}$), 1.52-1.25 (m, 8H, -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$/TMS, δ): 170.26 (s, C=O), 52.89 (q, CH_3-O), 45.58 (d, -CHBr), 34.74 (t, -CH_2-CHBr), 28.44 (t, -CH_2), 27.01 (t, -CH_2).

Nucleophilic substitutions on DMBS (Scheme 1)

Thiols as nucleophiles

In a round-bottom flask, 0.111 g (0.28 mmol) of DMBS and 0.044 mL (0.62 mmol) of 2-mercaptoethanol **(1)** (1.1 mol SH/ mol Br) were dissolved in DMF (10% w/v) and 0.09 mL of triethylamine (1 mol NEt_3/mol SH) was added dropwise at room temperature. The reaction was followed by ^{1}H NMR. Data for the substitution products using different nucleophiles:

2-mercaptoethanol **(1)**. ^{1}H NMR (400 MHz, $CDCl_3$/TMS , δ): 3.76 (s, 6H,-OCH_3), 3.73 (t, 4H, -CH_2-OH), 3.30 (t, 2H,-CH-S-), 2.74-2.96 (m, 4H,-S-CH_2-), 1.62-1.90 (m, 4H,-CH_2-), 1.28-1.42 (m, 8H,-CH_2-).

3-mercaptopropionic acid **(2)**. ^{1}H NMR (400 MHz, $CDCl_3$/TMS , δ): 3.71 (s, 6H,-OCH_3), 3.24 (t, 4H, -CH-S), 2.83 (m, 4H,-S-CH_2-), 2.63 (m, 4H,-CH_2COOH), 1.80 (m, 2H,-CH_2-), 1.60 (m, 2H,-CH_2-), 1.40-1.20 (m, 8H,-CH_2-).

Amines as nucleophiles

In a round-bottom flask, 0.117 g (0.30 mmol) of DMBS and 0.040 mL (0.66 mmol) of 2-aminoethanol **(3)** (1.1 mol NH_2/ mol Br) were dissolved in DMF (10% w/v) and 0.18 mL of triethylamine (2 mol NEt_3/mol SH) were added dropwise at 30ºC. The reaction was followed by ^{1}H NMR. Data for the substitution products using different nucleophiles:

2-aminoethanol **(3)**. ^{1}H NMR (400 MHz, $CDCl_3$/TMS, δ): 3.73 (s, 6H, -OCH_3), 3.63 (t, 4H, CH_2-OH), 3.27 (t, 2H, CH-NH-), 2.61-2.92 (m, 4H, -NH-CH_2-), 1.63 (m, 4H, -CH_2-), 1.28-1.42 (m, 8H, -CH_2-).

Carboxylic acids as nucleophiles

In a round-bottom flask, 0.1 g (0.26 mmol) of DMBS, 0.048 g (0.62 mmol) of glycolic acid (1.2 mol COOH/ mol Br) and 0.073 g of KF (2 mol KF/mol COOH) were dissolved in DMF (10% w/v) and stirred at 30ºC. The reaction was followed by ^{1}H NMR. Data for the substitution products using different nucleophiles:

glycolic acid **(4)**. ^{1}H NMR (400 MHz, $CDCl_3$/TMS, δ): 5.07 (t, 2H, -CHOCO-), 4.28 (s, 4H, -CH-OH), 3.76 (s, 6H, -OCH_3), 1.85 (m, 4H, -CH_2-), 1.30-1.44 (m, 8H, -CH_2-).

propionic acid **(5)**. ^{1}H NMR (400 MHz, $CDCl_3$/TMS, δ): 4.98 (t, 2H, -CHOCO-), 3.75 (s, 6H, -OCH_3), 2.43 (q, 4H, -CH_2-CH_3), 1.82 (m, 4H, -CH_2-), 1.30-1.44 (m, 8H, -CH_2-), 1.10 (t, 6H, -CH_3).

General procedure for the synthesis of polyesters

In a 25 mL round bottom flask, 7.5 g (19.3 mmol) of DMBS and 3.37 g (19.3 mmol) of 1,10-decanediol were added in presence of 1.5 g of lipase (20% w/w DMBS) and 10% w/v of diphenylether. The reaction mixture was magnetically stirred at 90°C under vacuum for 96 hours. The viscous polymer was dissolved in chloroform and the lipase was removed by filtration. Finally, the polymer was precipitated in methanol and dried at 40°C overnight to obtain a polymer oil (83%). In order to prepare polyesters of different molecular weights, stoichiometric imbalances of DMBS/DCD were used, obtaining polyesters with 30KDa (1:1), 17KDa (1:1.01) and 9KDa (1:1.02).

^{1}H NMR (400 MHz, $CDCl_3$/TMS , δ): 4.20 (m, 6H, -CH-Br + -$COOCH_2$), 2.00 (m, 4H, CHBr-$\underline{CH_2}$), 1.62 (m, 4H, -$OCH_2\underline{CH_2}$-), 1.52-1.25 (m, 24H,-CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$/TMS, δ): 170.13 (s, C=O), 66.23 (t, CH_2-CO), 46.33 (d, -CHBr), 34.99 (t, -CH_2CHBr), 29.36-25.97 (t, -CH_2).

Nucleophilic substitutions on the functionalized polyesters

In a round-bottom flask, 0.17 g (0.33 mmol) of the bromo-functionalized polyester (PE-Br) and 0.05 mL (0.72 mmol) of 2-mercaptoethanol **(1)** (1.1 mol SH/ mol Br) were dissolved in DMF (10% w/v) and 0.10 mL (0.72 mmol) of triethylamine (1 mol NEt_3/mol SH) was added dropwise at room temperature. At the end of the reaction, the salt formed was filtrated and the polymer was precipitated in cold diethyl ether.

^{1}H NMR (400 MHz, $CDCl_3$/TMS ,δ) for modified polymers using different nucleophiles:

(1): 4.20 (t, 4H, -$COOCH_2$), 3.74 (t, 4H, -CH_2OH), 3.30 (t, 2H, CH-S-), 2.90-2.70 (m, 4H, S-CH_2-), 1.85 (m, 4H, -$OCH_2\underline{CH_2}$-), 1.62-1.20 (m, 24H,-CH_2-).

(3): 4.20 (m, 4H, -$COOCH_2$), 3.68 (m, 4H, -CH_2-OH), 3.30 (t, 2H, CH-NH-), 2.80-2.60 (m, 4H, -NH-CH_2-), 1.70-1.30 (m, 28H, -CH_2-).

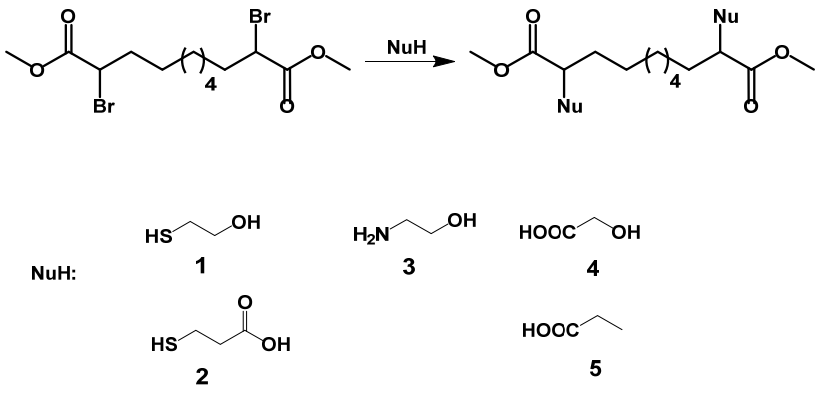
(5): 4.95 (t, 2H, -CHOCO-), 4.20 (m, 4H,-$COOCH_2$), 2.35 (m, 4H,-CH_2CH_3), 1.70 (m, 4H, -$OCH_2\underline{CH_2}$-), 1.60 (m, 4H, -CH2), 1.42-1.23 (m, 20H,-CH_2-), 1.15 (m, 6H, -CH_3).

N-isopropylacrylamide-COOH terminated as nucleophile. ^{1}H NMR (400 MHz, DMF-d_7/TMS , δ): 5.05 (m, 2H, CO-CH-OCO), 4.20 (m, 4H, -$COOCH_2$), 4.10-3.90 (m, 27H, CHNH), 2.80 (t, 4H, -CH_2S), 2.63 (t, 4H, -CH_2COO-), 2.20-2.05 (m, 27H, CHCONH), 1.90-1.08 (m, -CH_2+ -CH_3).

Results and Discussion

Synthesis of DMBS and nucleophilic substitutions

Sebacic acid was α-brominated by conventional bromination of the corresponding acyl chloride and further esterified to afford DMBS, which contains electrophilic centers prone to react with nucleophiles (Scheme 1). The thiol-halogen reaction is generally performed by reacting thiol and bromide employing mild organic bases such as trialkylamines. It shows high efficiency, very mild conditions and easy removal of byproduct by washing with water, being touted as a click reaction.[17,18]



Scheme 1. Nucleophilic substitutions on DMBS.

First of all, we studied the reactivity of DMBS towards thiols using 2-mercaptoethanol as a model compound. The progress of the reaction was followed by ^{1}H NMR ($CDCl_3$) through the disappearance of CH-Br signal at 4.2 ppm and the appearance of the corresponding CH-S moiety signal at 3.3 ppm. When the equimolar amount of thiol was added to a DMBS solution in DMF (10% w/w) at room temperature, no reaction takes place. However, when a base such as triethylamine is added in equimolar ratio complete substitution of Br is observed in 24h. Thus, as expected, it is necessary to generate the thiolate anion which is more nucleophile than the thiol and promotes the substitution. Moreover, triethylamine captures displaced HBr, forming the salt, which is easily removed. The addition of small excess of thiol (1.1 or 1.2 mol SH/1 mol Br), notably accelerates the substitution reaction, being completed in 7 and 3 hours, respectively (Figure 1). Thus, it is demonstrated the feasibility of the nucleophilic substitution of the alkyl bromides with a thiol containing a hydroxyl functional group. Similarly, functionalization of DMBS with 3-mercaptopropionic acid allows incorporation of acid groups onto the model monomer which can further react.

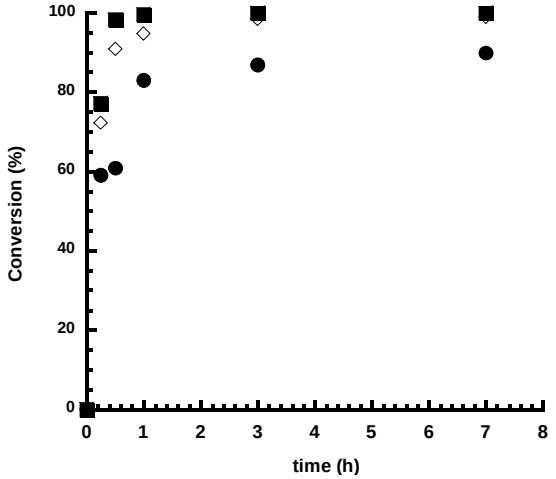


Figure 1. Nucleophilic substitution of DMBS with 2-mercaptoethanol in different SH/Br molar ratio: 1:1 (●), 1.1:1 (◊) and 1.2:1 (■).

Sequential functionalization reaction was explored as a general strategy that could be developed to produce a library of materials bearing multiple funcionalities from a parent polymeric substrate. The reaction was performed by sequentially adding 2-mercaptopropionic acid and 3-mercaptoethanol to DMBS and the attachment of both moieties was examined by ^{1}H NMR spectroscopy (DMF-d_7). In an NMR tube were added DMBS (0.23 mmol), 3-mercaptopropionic acid (0.23 mmol), NEt_3 (0.23 mmol) and 1.5 mL of DMF-d_7. As can be observed in Figure 2, the intensity signal of CH-Br at 4.9 ppm (**b**) decreases and the new signal at 3.8 ppm (**b'**) attributable to the CH-S linkage appear. The quantification of substitution corroborates the expected 50% modification degree. After 24h the reaction was finished and 0.23 mmol of 2-mercaptoethanol and 0.23 mmol of NEt_3 were added to the NMR tube. Then, further decrease in the CH-Br signal was observed correlating with the growth of the CH-S signal, until total disappearance of CH-Br signal in 48h. These results indicate that the sequential reaction allow the substitution with thiols containing different functional groups and yield the product in agreement with the stoichiometry of reactants.

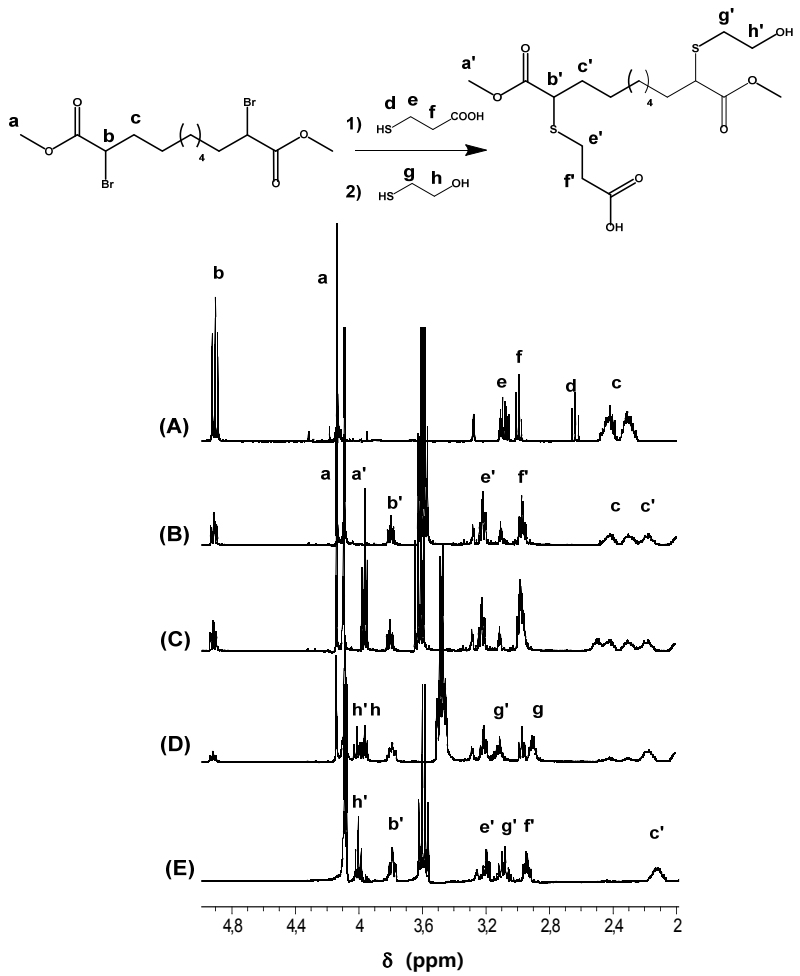


Figure 2. ^{1}H NMR spectra of sequential nucleophilic substitution of DMBS with **2** and **1**: (A) DMBS and **2** at t=0; (B) t=24h; (C) Addition of **1**; (D) t=40h; (E) Reaction product after 48h.

Amines have also been previously shown to be good nucleophiles in the substitution of halogens. The halogen polymer end groups have been transformed into other functionalities by means of nucleophilic displacement reactions with amines.[19] Moreover, the bromine pendant groups of poly(γ-bromo-ε-caprolactone) were substituted by pyridine as nucleophile.[20]

We performed the reaction of DMBS and 2-aminoethanol in equimolar ratio at 30ºC using DMF as solvent. The progress of the reaction was followed by ^{1}H NMR spectroscopy through the disappearance of CH-Br signal at 4.2 ppm and the appearance

of the corresponding CH-N moiety signal at 3.27 ppm. After 24 h, the conversion was around 60% and the reaction did not progressed to higher conversions (Figure 3). By addition of NEt_3 in equimolar ratio to the primary amine, a conversion of 85% after 48h was reached. Nevertheless, the addition of an excess of NEt_3 was necessary to get higher conversions (95%) in 48h.

Although primary amines are good nucleophiles to promote bromo-substitution, the addition of NEt_3 is necessary to capture the released HBr and to avoid the protonation of the amine and the deactivation of its nucleophicity.

In order to accelerate the reaction, we studied the addition of an excess of 2-aminoethanol (1.1 and 1.2 mol NH_2/ 1 mol Br) and NEt_3 (2 mol NEt_3/1 mol NH_2) to DMBS, obtaining high conversions (94 and 97%, respectively) after 24h.

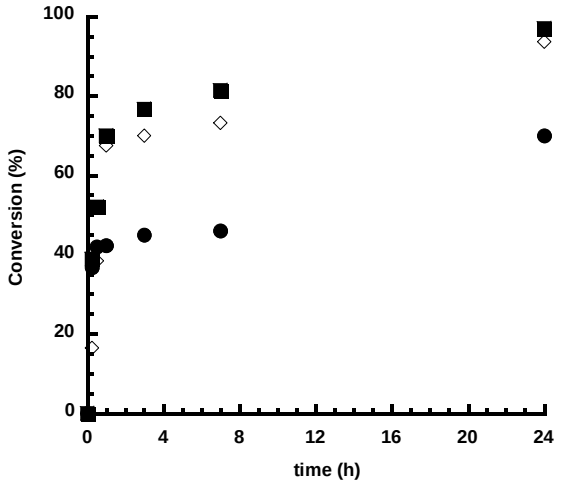


Figure 3. Nucleophilic substitution of DMBS with amines in different NH_2/Br molar ratio: 2-aminoethanol (1:1) (●), 2-aminoethanol (1.1:1) and 2 mol NEt_3/1 mol NH_2 (◊), 2-aminoethanol (1.2:1) and 2 mol NEt_3/1 mol NH_2 (■).

Besides thiols and amines, carboxylic acids can also efficiently react with alkyl halides. In particular, the alkylation of carboxylic acids with alkyl halides in presence of KF has shown to be feasible.[21] In this case a salt is also formed with the displaced bromine. Thus, we studied the reaction of DMBS with different carboxylic acids in presence of KF. The progress of the reaction was followed by ^1H NMR spectroscopy through the

disappearance of CH-Br signal at 4.2 ppm and the appearance of the corresponding CH-OOC moiety signal at 5.07 ppm. First, we attempted reaction of DMBS and glycolic acid in presence of KF, using equimolar ratio of reagents but substitution proceed only to 35% conversion (Figure 4). The use of an excess of glycolic acid (1.2 mol COOH/1 mol Br) and KF (2 mol KF/ 1 mol COOH) drive the esterification of DMBS to higher conversions, achieving 80 and 95% conversion after 24 and 48h, respectively. The low reactivity of glycolic acid can be ascribed to the presence of the hydroxylic group in the α position that diminishes the carboxylic acid nucleophilicity. In fact, the reaction of DMBS with propionic acid (1.2 mol COOH/1 mol Br) and KF (2 mol KF/ 1 mol COOH) yield fast and quantitative substitution of bromine in 7h.

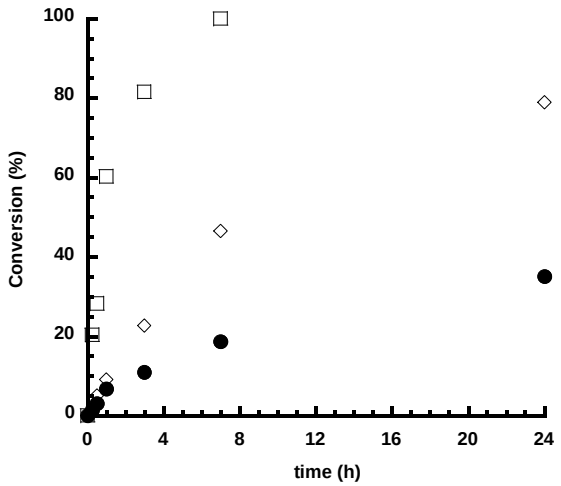


Figure 4. Nucleophilic substitution of DMBS with carboxylic acids in different COOH/Br molar ratio: glycolic acid (1:1) and 1 mol KF/1 mol COOH (●), glycolic acid (1.2:1) and 2 mol KF/1 mol COOH (◊), propionic acid (1.2:1) and 2 mol KF/1 mol COOH (□).

Enzymatic polymerization of DMBS

Enzymatic polymerization of castor oil derivatives DMBS and DCD was carried out in presence of Novozyme 435 under vacuum at 90ºC, both in bulk and DPE as solvent. The progress of the polymerization was monitored through the evolution of molecular weight distribution obtained by GPC analysis. The GPC trace for the control reaction in absence of Novozyme 435 verifies that chain growth occurs due to enzyme catalysis.

Figure 5 shows the results obtained using different catalyst loadings with and without solvent. The results are consistent with the retention of a substantial fraction of the original enzymatic activity through-out the 96 h polymerization. The polymerization takes place relatively faster and higher Mn are obtained when catalyst concentration increases, both in bulk and solution conditions. Moreover, significant differences can be found for a given catalyst concentration in bulk or DPE solution, being the increase in molecular weight slower for the former and reaching lower molecular weights. This result is likely due to greater constraints on chain diffusion for bulk polymerizations. It may also be that the enzyme has enhanced activity for polymerization when the reaction is conducted in DPE than in bulk. No significant differences on polydispersities values are observed being all around 1.6.

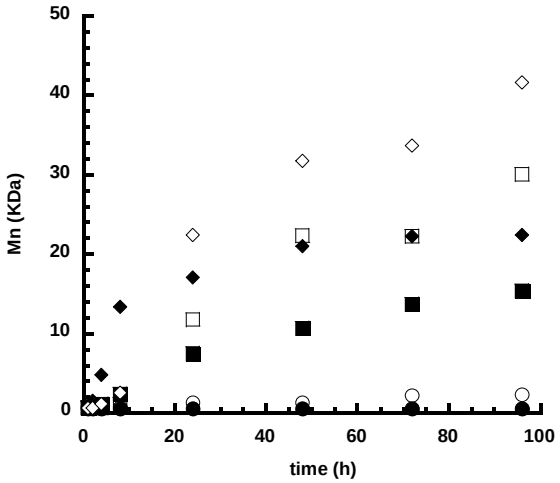


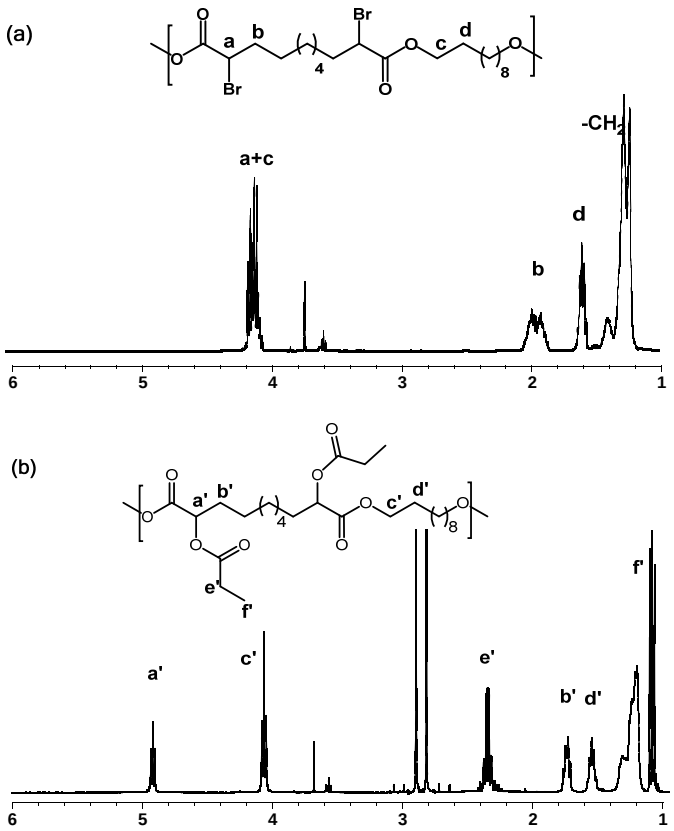
Figure 5. Mn vs. polymerization time for the polymerization of DMBS and DCD using different catalysts concentration (% w/w Novozyme/DMBS). Open symbols for solution polymerization and solid symbols for bulk polymerization. (○ 10%, □ 20%, ◊ 40%).

Polymers were characterized by ^{1}H NMR spectroscopy. Figure 6a shows a representative spectrum of the polymer with Mn=9 KDa. Signals at 4.2 ppm corresponding to CH-Br (**a**) and $COOCH_2$ **(c)** moieties were observed as well as the expected chain signals.

Post-polymerization modification of functionalized polyesters

The synthesized polyesters bear on their main chain bromine functionalities which are expected to be easily functionalized with different functional groups (thiols, amines and carboxylic acids) according the successful modifications on the model DMBS. Thus, reaction of PE-Br (Mn=9KDa) with mercaptoethanol was first studied using slight excess of thiol (1.2 mol SH/1 mol Br) at room temperature. The progress of the reaction was followed by ^{1}H NMR ($CDCl_3$) through the disappearance of CH-Br signal at 4.2 ppm and the appearance of the corresponding CH-S moiety signal at 3.3 ppm. In this case, complete functionalization of the polymer was observed after 3h (Figure 7). Similarly, modification of PE-Br (Mn=30KDa) with 2-mercaptoethanol is also complete in 3h.

PE-Br was also modified with 2-aminoethanol (1.2 mol NH_2/1 mol Br) and NEt_3 (2 mol NEt_3/1mol NH_2) at 30ºC reaching high conversions (>96%) after 24h.



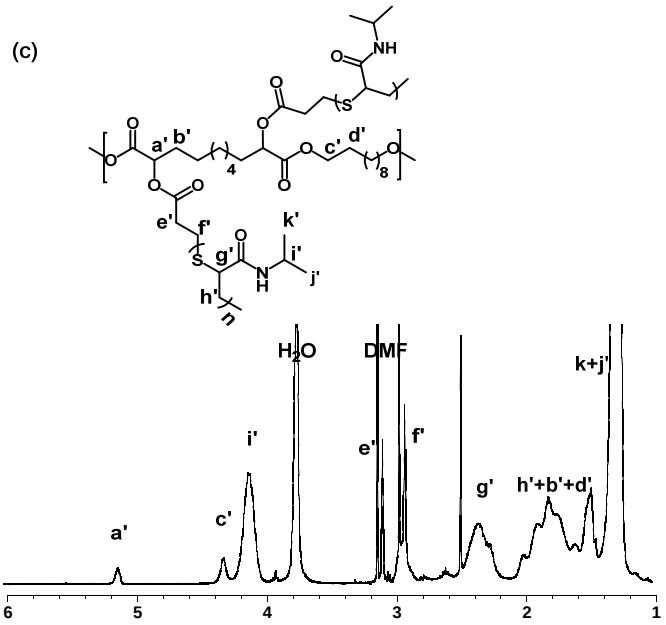


Figure 6. ^{1}H NMR spectra of a) PE-Br polyester (Mn=9KDa); (b) PE-Br modified with propionic acid; (c) PE-Br modified with NIPAAm-COOH.

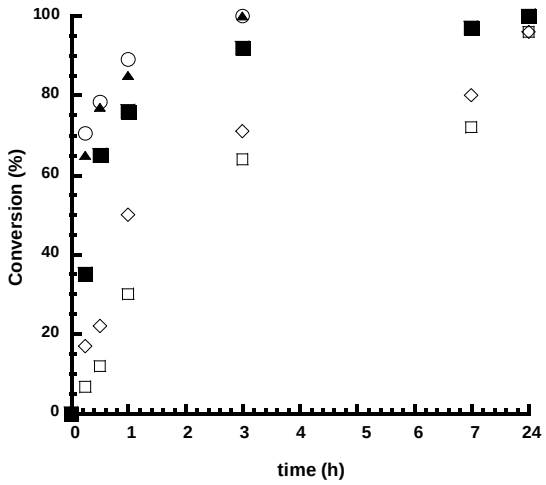


Figure 7. Nucleophilic substitution of PE-Br (Mn=9KDa) with different nucleophiles in 1.2: 1 NuH: Br molar ratio: 2-mercaptoethanol (Mn: 9KDa)(○), 2-mercaptoethanol (Mn: 30KDa)(▲), 2-aminoethanol (□), propionic acid (■) and poly(N-isopropylacrylamide)(◊).

Modification of the PE-Br with carboxylic acids was studied using propionic acid (1.2 mol COOH/1 mol Br) and KF (2 mol KF/1 mol COOH). The progress of the reaction was followed by ^{1}H NMR spectroscopy through the disappearance of CH-Br signal at 4.2 ppm and the appearance of the corresponding CH-OCO- moiety signal at 5.2 ppm (Figure 6b). High degree of modification (>98%) was observed after 7h at 30ºC.

In this study, we have demonstrated that the Br- functionalities on the main chain of the polyester can efficiently react with different small moieties to introduce new functionalities on the polymer backbone. The pendant functionalities on the polymers are usually used to graft polymeric chains via a grafting from or onto approach. As a proof of concept, we studied the coupling of a small molecular weight polymer, NIPAAm-COOH terminated (Mn=2000) onto the PE-Br backbone. Thus, both polymers reacted under optimized conditions (1.2 mol COOH/ 1 mol Br/ 2.4 mol KF) in DMF at 30ºC. The reaction was followed by ^{1}H NMR spectroscopy (Figure 6c). The integration ratio of the signals **a'** and **c'** indicate a high modification degree of the PE-Br (97%) after 24h.

Moreover, the grafting of NIPAAm moieties onto the PE main chain would lead to a substantial increase on its molecular weight. Thus, SEC measurements before and after polymer modification were assessed. As expected, a considerable shift of molecular weight after polymer modification was observed, with a molar mass value (56500 g/mol). in agreement to the expected value for a 96% degree of modification (Figure 8), further demonstrating the successful grafting of the polymer under these conditions.

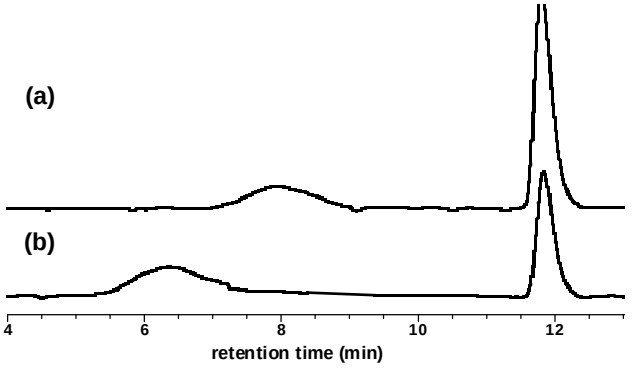


Figure 8. SEC measurements of: a) PE-Br and b) PE-Br modified with NIPAAm-COOH.

The incorporation of thermo-sensitive NIPAAm moieties onto the polymer backbone have endowed the polymer with new properties and thus, new potential applications, which are under investigation.

Thus, PE-Br have been demonstrated to be easily functionalized both with small molecules but also polymers using different efficient coupling reactions which give access to a wide spectra of polymers with different functionalities and applications from a unique PE structure.

Conclusions

In this work, we have synthesized castor-oil derived functional aliphatic polyesters via enzymatic polymerization. The introduced bromine functionalities onto the backbone of the polyester have been further modified with different amines, thiols and carboxylic acids. Thiols have shown to be more reactive with alkylbromides compared to the carboxylic acid and amines. Nevertheless, in all cases high modification degrees are obtained under fast and mild reaction conditions.

Acknowledgment. Financial support by the MICINN (Ministerio de Ciencia e Innovacion, MAT2011-24823) is gratefully acknowledged.

[1] H. Seyednejad, A. H. Ghassemi, C. F. Van Nostrum, T. Vermonden, W. E. Hennink, *J. Control. Release* **2011**, *152*, 168-176.

[2] C. K. Williams, *Chem. Soc. Rev.* **2007**, *36*, 1573–1580.

[3] A. S. Goldman, M. Glassner, A. J. Inglis, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2013**, *34*, 810-849.

[4] Z. Ates, P. D. Thornton, A. Heise, *Polym. Chem.* **2011**, *2*, 309-312; V. Darcos, S. Antoniacomi, C. Paniagua, J. Coudane, *Polym. Chem.* **2012**, *3*, 362-368

[5] B. Parrish, R. B. Breitenkamp, T. Emrick, *J. Am. Chem. Soc.* **2005**, *127*, 7404-7410; L. Billiet, D. Fournier, F. Du Prez. *J. Polym. Sci. Part A Polym. Chem.* **2008**, *46*, 6552–6564.

[6] M. Kato, K. Toshima, S. Matsumura, *Biomacromolecules* **2009**, *10*, 366-373.

[7] T. Naolou, K. Busse, J. Kressler, *Biomacromolecules* **2010**, *11*, 3660-3667.

[8] P. N. R. Vennestrom, C. M. Osmundsen, C. H. Christensen, E. Taarning, *Angew. Chem. Int. Ed.* **2011**, *50*, 10502-10509.

[9] K. Yao, C. Tang, *Macromolecules* **2013**, *46*, 1689-1712.

[10] O. Türünç, M. A. R. Meier, *Eur. J. Lipid Sci. Technol.* **2013**, *115*, 41-54.

[11] G. Lligadas, J. C. Ronda, M. Galià, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 2111-2124.

[12] P. Lecomte, R. Riva, C. Jérôme, R. Jérôme, *Macromol. Rapid Commun.* **2008**, *29*, 982–997.

[13] A. Takasu, Y. Iio, T. Mimura, T. Hirabayashi, *Polym. J.* **2005**, *37*, 946-953.

[14] C. Hahn, H. Keul, M. Möller, *Macromol. Symp.* **2010**, *296*, 366-370.

[15] R. Riva, S. Schmeits, F. Stoffelbach, C. Jerome, R. Jerome, P. Lecomte. *Chem. Commun.* **2005,** 5334-5336; N. Xu, R. wang, F.S. Du, Z.C. Li, *J. Polym. Sci. Part A: Polym. Chem.* **2009**, *47*, 3583-3594.

[16] S. Kobayashi, *Macromol. Rapid Comm.*, **2009**, *30*, 237-266; R. A. Gross, M. Ganesh, W. Lu, *Trends in Biotechnology*, **2010**, *28*, 435–443; Y. Yu, D. Wu, C. Liu, Z. Zhao, Y. Yang, Q. Li, *Process Biochemistry*, **2012**, *47*, 1027-1036.

[17] C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355-1387.

[18] L-T. T. Nguyen, M. T. Gokmen, F. Du Prez, *Polym. Chem*. DOI: 10.1039/C3PY00743J.

[19] V. Coeesens, T. Pintauer, K. Matyjaszewski, *Prog. Polym. Sci*. **2001**, *26*, 337-377; H. Zhang, X. Jiang, R. Van der Linde, *Polymer*, **2004**, *5*, 1455-1466; J. Li, Z. Sun, Y. Zhen, Q. Ren, Q. Yu, Y. Cui, M. Yamagishi, Y. Ikeda, *J. Polym. Res*. **2010**, *17*, 551-556.

[20] B. Vroman, M. Mazza, M.R. Fernandez, R. Jerome, V. Préat, *J. Control. Release* **2007**, *118*, 136-144.

[21] J. H. Clark, J. M. Miller, *J. Am. Chem. Soc.* **1977**, 99, *2*, 498-504; J. Li, Y. Maekawa, T. Yamaki, M. Yoshida, *Macromol. Chem. Phys*. **2002**, *203*, 2470-2474.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Chapter 7

Conclusions

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

In the course of this thesis, different chemical strategies based on Click chemistry reactions have been developed to obtain new monomers and polymers based on fatty acids as renewable resources. The conclusions of this work are stated below:

- Thiol-ene Click reactions provide a successful functionalization of terminal and internal carbon-carbon double bonds of undecylenic and oleic acids, allowing the straightforward preparation of monomers.

  Following this approach, fast acting polyanhydride drug delivery carriers can be obtained from polycarboxylic acid monomers based on castor and sunflower oils.

- Two one-pot thiol-ene Click reactions approach has proven to be successful to obtain well-defined telechelics from allyl ester of undecylenic acid.

  Sustained segmented polyurethane delivery carriers of hydrophobic drugs can be obtained from telechelic diols based on undecylenic acid.

- Thiol-yne Click reaction is an efficient photopolymerization method to oligomerize undecynoic acid derivatives.

  Antimicrobial coatings with enhanced surface hydrophilicity can be obtained from methyl ester containing castor oil-based polyurethanes, via surface aminolysis and iodine complexation.

- Nucleophilic substitutions on bromine containing castor oil-derived polyesters based on sebacid acid and 1,10-decanediol allow straightforward post-polymerization modification with the highest efficiency observed when using thiols as nucleophiles.

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014

Appendix A: List of abbreviations

AIBN	2,2′-azobis(2-methylpropionitrile)
ATR	Attenuated total reflection
ATRP	Atom transfer radical polymerization
BD	1, 4-Butanediol
BDT	1, 4-Butanedithiol
C. albicans	*Candida albicans* CECT 1392
CFU	Colony Forming Units
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
$CDCl_3$	Deuterated chloroform
DA	Diels – Alder reaction
DBTDL	Dibutyltin dilaurate
DCD	1,10-decanediol
DMAc	Dimethylacetamide
DMBS	Dimethyl 2,8-dibromosebacate
DMF	N,N′-dimethylformamide
DMPA	2,2-dimethoxy-2-phenylacetophenone
DMSO	Dimethyl sulfoxide
DPE	Diphenyl ether
DSC	Differential scanning calorimetry
DT	3,6-dioxa-1,8-octane-dithiol
Equiv	Equivalents
EDX	Energy-dispersive X-ray spectroscopy
ESI MS	Electrospray ionization mass spectrometry
FTIR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography couple with mass spectrometry
GPC	Gel permeation chromatography
ΔHm	Melting enthalpy
HDA	Hetero Diels Alder
HMDI	Hexamethylene diisocyanate
HS	Hard segment
IC50	Half maximal inhibitory concentration
IR	Infrared

IPDI	Isophorone diisocyanate
Jeffamine M-600	O-(2-Aminopropyl)-O′-(2-methoxyethyl)polypropylene glycol 500
MALDI-TOF-MS	Matrix – assisted laser desorption / ionization time – of – flight mass spectrometry
MDI	Methylene diphenyl diisocyanate
ME	2-mercaptoethanol
MTGLY	Methyl thioglycolate
MDI	4,4′-methylene-bis(phenylisocyanate)
M_n	Number average molecular weight
M_w	Weight average molecular weight
Me_2PPh	Dimethylphenylphosphine
MPA	3-mercaptopropionic acid
MPS	3-mercaptopropyltrimethoxysilane
MTGLY	Methyl thioglycolate
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MUDY	Methyl 10-undecynoate
MS	Mass spectrometry
NIPAAm COOH	Poly-(N-isopropylacrylamide)-carboxylic acid terminated
NMR	Nuclear Magnetic Resonace Spectrometry
NEt_3	Triethylamine
OD	Optical density
OLA	Oleic acid
OLM	Methyl oleate
OLS	9,10-(2-carboxyethylthio)octadecanoic acid
PA	Polyanhydride
PE-Br	Bromo-functionalized polyester
PDI	Polydispersity index (M_w/M_n)
P. aeruginosa	*Pseudomonas aeruginosa* CECT 110
PL	Polyol
PLA	Polylactide
PMDETA	N,N,N′,N′′,N′′-Pentamethyldiethylenetriamine (PMDETA)
PU	Polyurethane
RAFT	Reversible addition-fragmentation chain transfer
RID	Refractive-index detector
RT	Room temperature
SEC	Size exclusion chromatography

SEM	Scanning electron microscopy
sPU	Segmented polyurethane
S. aureus	*Staphylococcus aureus* CECT 239
SS	Soft segment
TBD	Triazabicyclodecene
TEC	thiol-ene coupling
$T_{5\%}$ loss	Temperature of 5 % loss
Tg	Glass-transition temperature
TGA	Thermogravimetric analysis
TGLY	1-thioglycerol
THF	Tetrahydrofuran
T_m	Melting temperature
Tmax	Temperature of maximum weight loss
TMPTA	Trimethylolpropane tri-3-mercaptopropionate
TMS	Tetramethylsilane
TSB	Tryptone Soya Broth
UD	Undecylenic acid // 10-undecenoic acid
UDA	Allyl 10-undecenoate
UDO	10-undecenol
UDM	Methyl-10-undecenoate
UDS	11-(2-Carboxyethylthio)undecanoic Acid
UDTG	Undecylenic acid triglyceride
UDTGS	11-(2-carboxyethylthio)-undecanoic triglyceride
UDY	10-undecynoic acid
UDYO	10-undecynol
UV	Ultraviolet
WAXD	Wide-angle X-ray diffraction
XPS	X-ray photoelectron spectroscopy
YPD	Yeast extract-Peptone-Dextrose

UNIVERSITAT ROVIRA I VIRGILI
CLICK AND CLICK-TYPE CHEMISTRIES IN CASTOR AND SUNFLOWER OIL-BASED MONOMERS AND POLYMERS
Cristina Lluch Porres
Dipòsit Legal: T.182-2014