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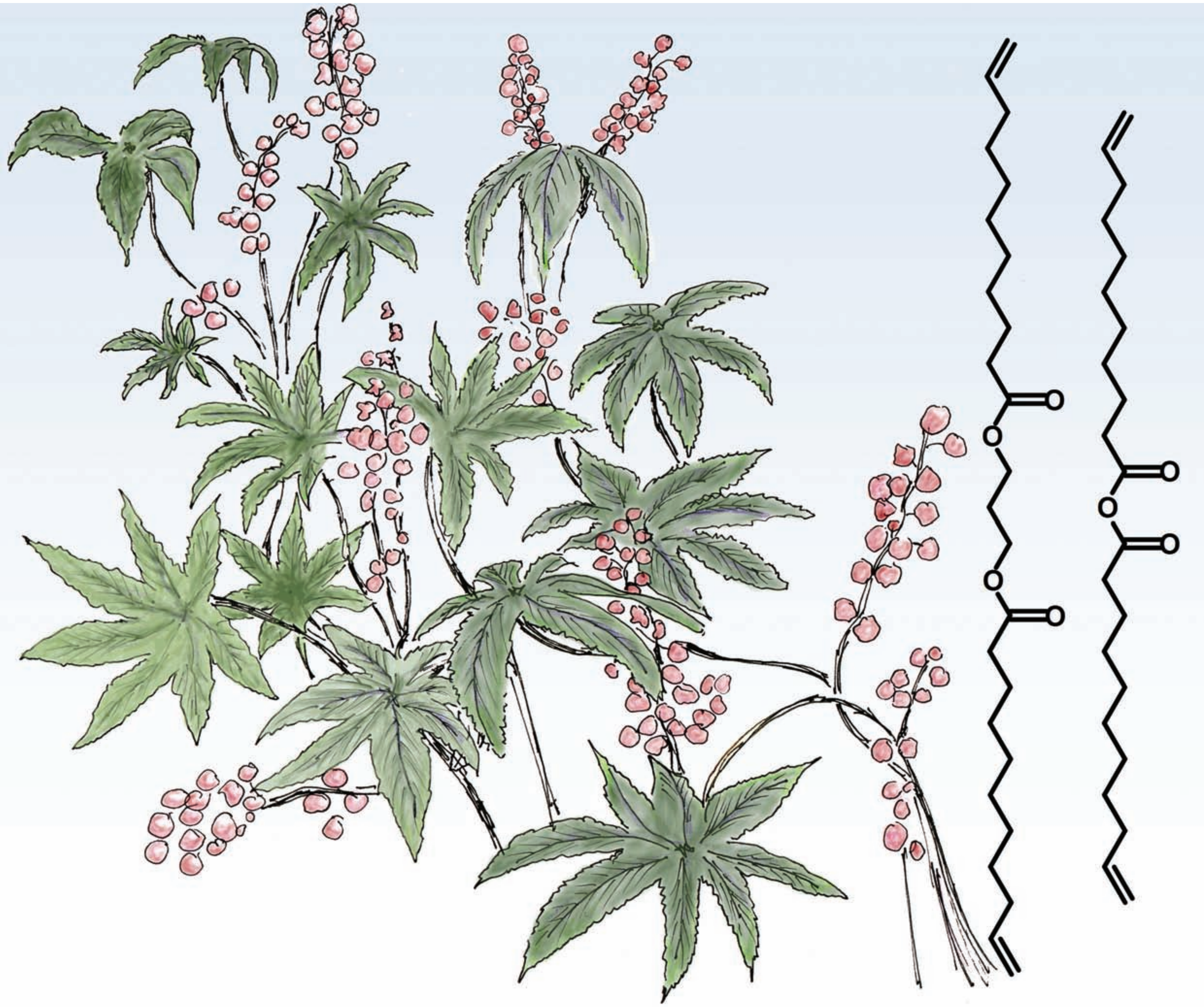

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PAPER

Thiol-ene *vs.* ADMET: a complementary approach to fatty acid-based biodegradable polymers

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The increasing need for biodegradable polymers in medical applications, attempts to use renewable resources instead of fossil resources for material synthesis, and highly efficient polymerization methods that meet the requirements of green chemistry draw attention to fatty acid-based biodegradable polymers. In the present study, we have prepared a set of anhydride and ester functional biodegradable polymers from undec-10-enoic acid *via* ADMET polymerization reactions and/or thiol-ene click reactions. The efficiency of these polymerization methods and the thermal, as well as hydrolytic, stability properties of the polymers were evaluated and compared to each other. The results reveal that the polymers exhibit melting points in the range 44–58 °C, which is higher than physiological temperature, and that polyanhydrides degrade considerably faster in solution than structurally similar polyesters.

Introduction

Recent advances in medical applications have revealed a high demand for polymeric systems that fulfil a number of requirements, such as biodegradability and biocompatibility. Such systems are widely used in temporary implants and drug delivery systems.[1] The use of fatty acids as building blocks for such polymers introduces flexibility, low melting temperatures, hydrophobicity and pliability.[2] Moreover, biocompatibility and the substitution of fossil resources with respect to environmental aspects are additional advantages of fatty acids in the synthesis of biopolymers. The term biopolymers is used in different aspects in material science. Cellulose, starch and other carbohydrate-based polymers, as well as proteins, are examples of biopolymers by means of their origin, *i.e.* they are bio-derived. On the other hand, polymers such as poly(methyl methacrylate) and others that exhibit biocompatibility, but are not bio-derived, are also referred to as biopolymers, owing to their bio-applications. In any case, biodegradability is a structure-dependent property and is not necessarily related to the above-mentioned classifications. On the other hand, on the basis of chemical linkages, biopolymers are classified as polyesters, polyorthoesters, polyanhydrides, polyamides and polyphosphazines.[3] The two major classes of those materials are polyesters and polyanhydrides, which undergo bulk and surface erosion degradation, respectively.[2] Polylactides and poly(lactide-*co*-glycolide)s, the most frequently studied members of this biopolymer family, have been used commercially for half a century. Their degradation, likewise to other polyesters, is classified as bulk degradation with random hydrolytic scission of the polymer chain.[3] For the retention of mechanical properties during the degradation process and for having more regular degradation rates[2] that avoid acid bursting and its inflammatory consequences, the surface erosion mechanism and therefore polyanhydrides seem to be preferable for at least some applications. Typical fatty acid-based polyanhydride syntheses, widely studied by Domb *et al.*, involve condensation reactions that need high temperatures and a vacuum in order to force the reaction towards polymerization, multiple steps and/or solvents.[4–7]

While trying to find highly reliable, selective and fast synthetic methods, Sharpless *et al.*[8] mentioned that reactions that form new C–C bonds should be left to nature due to their modest thermodynamic driving force. Therefore, the term ‘click chemistry’ was introduced for reactions that form heteroatom linkages in an efficient manner. Since then, this term has been used widely for copper-catalyzed Huisgen cycloadditions of azides to acetylenes, which usually need to be attached by an additional reaction step at the desired site of reaction. On the other hand, the thiol-ene addition reaction, though it has been known for more than a century,[9] was not considered to be a click reaction before 2008, when Hawker and co-workers successfully utilized thiol-ene chemistry to synthesize fourth-generation polythioether dendrimers in the absence of solvent and metal catalysts.[10] However, it should be noted that the kinetics of this reaction strongly depends on the structure of the thiol[11] and olefin compounds. It was shown, for instance, that 1-hexene is

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8-times more reactive than *trans*-2-hexene and 18-times more than *trans*-3-hexene.[12] These results are especially important for applications to unsaturated fatty acids and derivatives, which naturally contain double bonds along their main chain. For instance, in our previous report,[11] we showed that the application of thiol-ene chemistry for the functionalization of terminal double bond-containing fatty acids does not need any initiator and/or a high temperature to proceed efficiently.

On the contrary to leaving C–C bond-forming reactions to nature, recent developments in olefin metathesis, especially in acyclic diene metathesis (ADMET), have revealed the great potential of olefin metathesis as a polymerization method for fatty acid-derived α,ω-diene monomers.[13] Especially after the quantitative polymerization of 1,5-hexadiene and 1,9-decadiene with Lewis acid-free catalysts,[14,15] ADMET polymerization has advanced in correlation with the development of a set of metathesis catalysts with highly improved activity and functional group tolerance, very recently reviewed by Meier *et al.*[16] Although this highly efficient catalytic polymerization method can suffer olefin isomerization side reactions, preventing the synthesis of defined polymeric structures, the use of quinone-type compounds was shown to suppress this isomerization to a large extent.[17,18] Nevertheless, even very small amounts of heavy metal catalyst residue within the polymer might be accompanied by biocompatibility issues, especially for medical applications. In addition, since the ADMET reaction itself releases an ethylene molecule for each new C=C double bond formation, the atom efficiency of the overall polymerization is another minor drawback of this method, although it should be possible to recover the ethylene on an industrial scale.

In the present study, we report new complementary synthetic approaches to fatty acid-derived biodegradable polymers and discuss the efficiency of these methods, considering environmental as well as application issues. Thus, fatty acid derived α,ω-dienes with ester and anhydride linkages were polymerized *via* ADMET and thiol-ene click chemistry. Furthermore, the thermal properties and solution stabilities of the synthesized polymers were studied and compared in order to gain an insight into their application possibilities.

Experimental

Materials. 10-Undecenoic acid (Aldrich, 98%), 1,3-propanediol (Aldrich, 99%), *p*-toluenesulfonic acid monohydrate (Aldrich, >98,5%), ethyl vinyl ether (Aldrich, 99%), sulfuric acid (Fluka, 95-97%), *p*-benzoquinone (98%, Fluka), bis(2-mercaptoethyl) ether (Aldrich, 95%), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(*iso*-propoxy)-5-(*N*,*N*-dimethyl aminosulfonyl)phenyl]methyleneruthenium(II) dichloride (Zahn-1B), thionyl chloride (Aldrich, >99%), 2,2′-azobis(2-methylpropionitrile) (AIBN, Aldrich, 98%) and Novozyme 435 (Sigma, ≥10 000 U g^{-1}) were used as received. All solvents and triethylamine (Aldrich, >99%) were freshly distilled over calcium hydride prior to use.

Methyl 10-undecenoate and undec-10-enoyl chloride were prepared by esterification with methanol and by chlorination with thionyl chloride, respectively, from the corresponding 10-undecenoic acid according to standard laboratory procedures. Synthesis of the ester-functional monomer, 1,3-propylene diundec-10-enoate (**2**) and depolymerization reactions were performed as described in earlier reports.[18]

General methods. Thin layer chromatography (TLC) was performed on silica gel TLC-cards (layer thickness 0.20 mm, Fluka). Compounds were visualized by permanganate reagent. For column chromatography, silica gel 60 (0.035–0.070 mm, Fluka) was used.

Polymerization optimization reactions were carried out using a Radleys 12-plus parallel reaction station.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE DPX spectrometer operating at 300 and 500 MHz. Chemical shifts (δ) are reported in parts per million relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm). The relaxation time was set to 5 s for the analyses of the polymers.

Electron spray ionization mass spectra (ESI-MS) were recorded on a Micromass Q-TOF$_{micro}$ instrument.

GC-MS (EI) chromatograms were recorded using a Varian 431 GC instrument with a capillary column FactorFour™ VF-5 ms (30 m × 0.25 mm × 0.25 μm) and a Varian 210 ion trap mass detector. Scans were performed from 40 to 650 m/z at rate of 1.0 scan s^{-1}. The oven temperature program was: initial temperature 95 °C, hold for 1 min, ramp at 15 °C min^{-1} to 200 °C, hold for 2 min, ramp at 15 °C min^{-1} to 325 °C, hold for 5 min. The injector transfer line temperature was set to 250 °C. Measurements were performed in split–split mode (split ratio 50 : 1) using helium as the carrier gas (flow rate 1.0 ml min^{-1}).

Polymer molecular weights were determined using an SEC System LC-20 A from Shimadzu equipped with a SIL-20A auto sampler, PL gel 5 mm MIXED-D column (Polymer Laboratories, 300 mm × 7.5 mm, 100 Å, 1000 Å, 10000 Å) and a RID-10A refractive index detector in THF (flow rate 1 mL min^{-1}) at 50 °C. All determinations of molar mass were performed relative to PMMA standards (Polymer Standards Service, M_p 1100–981.000 Da).

Differential scanning calorimetry (DSC) experiments were carried out under a nitrogen atmosphere at a heating rate of 10 °C min^{-1} with a DSC821e (Mettler Toledo) calorimeter up to a temperature of 150 °C using a sample mass of approximately 5 mg. The melting temperature, T_m, was recorded as the peak of the endotherm on the second heating scan, unless annealing was used as a pre-treatment.

Determination of the degree of isomerization for ADMET-derived polymers. The respective polymer (30 mg), excess methanol (4 mL) and concentrated sulfuric acid (5 drops) were refluxed at 85 °C overnight. At the end of the reaction, the excess methanol was removed *in vacuo*. Then, the residue was dissolved in dichloromethane and filtered over a small plug of basic aluminium oxide. Subsequently, the samples were analyzed by GC-MS and the degree of isomerization (DI) calculated using the following equation:

$$\text{DI} = 100 - (\text{integration of the non-isomerized product/integration of the total products}) \times 100$$

Undec-10-enoic anhydride (1). A solution of 10-undecenoic acid (5.87 g, 31.85 mmol) and triethylamine (3,79 g, 37.43 mmol) was placed into a flash-dried reflux setup equipped with a

Table 1 Performed ADMET polymerizations of monomer **2**

Entry	Monomer/mmol	**4**/mmol	**Zhan-1B**/mmol	***p*-BQ**/mmol	$M_{n\,(1\,h)}$/g mol^{-1} [a]	$M_{n\,(1\,h)}$/g mol^{-1} [b]	PDI	DI[c]
1	1.07	0.00	0.01	0.00	15950	—	1.67	64
2	1.05	0.00	0.01	0.02	18500	32750	1.61	12
3	1.05	0.01	0.01	0.02	17900	n.a.	1.58	7
4	1.06	0.02	0.01	0.02	17300	n.a.	1.57	12
5	1.06	0.04	0.01	0.02	15100	n.a.	1.65	4
6	1.07	0.07	0.01	0.02	8050	19050	1.92	7
7	1.08	0.16	0.01	0.02	5450	6389	2.02	—

[a] GPC calculation results after a 1 h reaction time. [b] ^{1}H-NMR calculation results. [c] GCMS calculation results of hydrolyzed polymers (see Experimental section).

dropping funnel. Undec-10-enoyl chloride (6.52 g, 32.16 mmol) in 50 mL of CH_2Cl_2 was added to the reaction mixture drop-wise while stirring and refluxing for 2 h. Then, the reaction mixture was cooled down, the solvent removed *in vacuo* and the residue collected with hexane, and quickly filtered from a small plug of Na_2SO_4 to remove the by-product, the triethylammonium chloride salt. The filtrate was concentrated *in vacuo* and the unreacted acid chloride, if any, was removed by reduced pressure at 120 °C. The remaining product was a light-brown liquid with a quantitative yield. δ_H (300 MHz, $CDCl_3$, Me_4Si): 5.82 (tdd, J = 16.91, 10.16, 6.66 Hz, 2H, vinylic), 5.06–4.89 (m, 4H, vinylic), 2.45 (t, J = 7.43 Hz, 4H, $-CH_2(C{=}O)O-$), 2.05 (q, J = 6.86 Hz, 4H, allylic), 1.73–1.60 (m, 4H, aliphatic), 1.36 (m, 20H, aliphatic). δ_C (300 MHz, $CDCl_3$, Me_4Si): 170.0 ($C{=}O$), 139.5 ($H_2C{=}CH-$), 114.5 ($H_2C{=}CH-$), 35.7 ($C{=}O{-}CH_2-$), 34.1 ($H_2C{=}HC{-}CH_2-$), 29.4 ($-CH_2-$ aliphatic), 24.6 ($-CH_2-$ aliphatic). MS (ESI-positive, CH_2Cl_2): m/z = 373.29 ($[M + Na]^+$, calc. 373.27).

Polymerization reactions

General procedure for ADMET polymerizations. Into a flash-dried three-necked flask were introduced the diene monomer(s) (in the case of copolymers 1 : 1 equiv.), methyl 10-undecenoate (when used, see Table 1), *p*-benzoquinone (when used, **BQ**, 0.02 equiv.) and Zahn-1B (0.01 equiv.) and stirred mechanically (500 rpm) at 80 °C for 1 h under a 100 (±20) mbar continuous vacuum. The reaction was quenched with ethyl vinyl ether (**EVE**, 50 equiv., considering the catalyst amount) in THF and precipitated into the corresponding solvent.

Polyanhydride via *ADMET (**P1**).* The polymer was precipitated into hexane (74.8%). δ_H (500 MHz, $CDCl_3$, Me_4Si): 5.54–5.29 (m, vinylic), 3.68 (s, ester), 2.46 (t, J = 7.5 Hz, $(C{=}O)OC{=}O{-}CH_2-$), 2.10–1.89 (m, allylic), 1.68 (m, aliphatic), 1.48–1.15 (m, aliphatic).

Polyester via *ADMET (**P2**).* The polymer was precipitated into methanol (82.4%). δ_H (500 MHz, $CDCl_3$, Me_4Si): 5.51–5.25 (m, vinylic), 4.16 (t, J = 6.3 Hz, ester), 3.68 (s, methyl ester), 2.30 (t, J = 7.6 Hz, $OC{=}O{-}CH_2-$), 1.97 (m, allylic), 1.61 (m, aliphatic), 1.44–1.06 (m, aliphatic).

Poly(anhydride-co-*ester)* via *ADMET (**P5**).* The polymer was precipitated into methanol (73.6%). δ_H (300 MHz, $CDCl_3$, Me_4Si): 5.58–5.23 (m, vinylic), 4.15 (t, J = 6.3 Hz, ester), 2.46 (t, J = 7.4 Hz, $-CH_2{-}(C{=}O)OC{=}O-$), 2.31 (t, J = 7.5 Hz, $OC{=}O{-}CH_2-$), 2.12–1.89 (m, allylic), 1.77–1.47 (m, aliphatic), 1.48–1.13 (m, aliphatic).

General procedure for thiol-ene polymerization. Into a dry reaction vessel were introduced the diene monomer(s) (0.5 equiv., in case of copolymer 0.25 : 0.25 equiv.), di(2-mercaptoethyl) ether (**3**, 0.5 equiv.) and AIBN (0.025 equiv.), and stirred magnetically (500 rpm) for 5 min at RT, and then at 80 °C for 2 h with continuous nitrogen purging. The reaction mixture was dissolved in THF and precipitated into the corresponding solvent.

Polyanhydride via *thiol-ene (**P3**).* The polymer was precipitated into hexane (70.4%). δ_H (300 MHz, $CDCl_3$, Me_4Si): 3.64 (m, $-CH_2{-}O{-}CH_2-$), 3.10 (t, J = 6.5 Hz, $-CH_2{-}SC{=}O-$), 2.72 (t, J = 7 Hz, $-S{-}CH_2-$), 2.56 (t, $-CH_2{-}S-$), 2.46 (t, J = 7.4 Hz, $-CH_2{-}C{=}O{-}OC{=}O{-}CH_2-$), 2.36 (t, 3H, $-CH_2{-}COOH$), 2.11–1.99 (m, 1H), 1.75–1.47 (m, aliphatic), 1.46–1.21 (m, aliphatic).

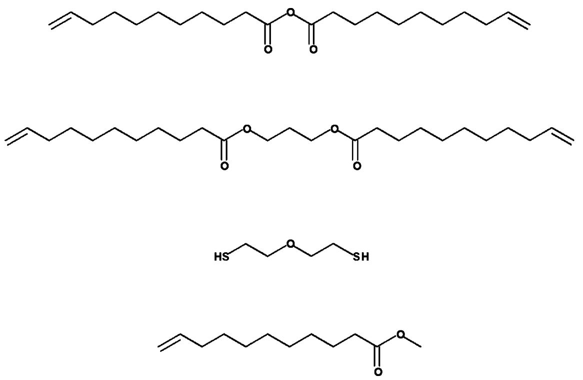
Polyester via *thiol-ene (**P4**).* The polymer was precipitated into methanol (85.0%). δ_H (300 MHz, $CDCl_3$, Me_4Si): 4.12 (t, J = 6.7 Hz, ester), 3.63 (t, J = 7 Hz, $-CH_2{-}O{-}CH_2-$), 2.74 (t, J = 7 Hz, $-S{-}CH_2-$), 2.54 (t, $-CH_2{-}S-$), 1.78–1.52 (m, aliphatic), 1.45–1.17 (m, aliphatic).

Poly(anhydride-co-*ester)* via *thiol-ene (**P6**).* The polymer was precipitated into methanol (70.4%). δ_H (300 MHz, $CDCl_3$, Me_4Si): 4.16 (t, J = 6.3 Hz, ester), 3.64 (t, J = 7 Hz, $-CH_2{-}O{-}CH_2-$), 2.71 (t, J = 7 Hz, $-S{-}CH_2-$), 2.56 (t, $-CH_2{-}S-$), 2.46 (t, J = 7.4 Hz, $-(C{=}O)OC{=}O-$), 2.31 (t, J = 7.5 Hz, $OC{=}O{-}CH_2-$), 2.08–1.91 (m, allylic), 1.78–1.50 (m, aliphatic), 1.33 (m, aliphatic).

Results and discussion

We started our investigations by synthesizing anhydride-functional monomer **1** from 10-undecenoic acid and the corresponding acid chloride. A number of methods in the literature deal with the synthesis of anhydrides. Typically, anhydride synthesis is carried out using carboxylic acids and a dehydrating agent such as dicyclohexylcarbodiimide,[19] carbodimidazole, phosgene, diphosgene or methoxyacetylene.[20] However, these methods produce a mixture of symmetric and mixed anhydrides, which require challenging purification methods in order to gather pure symmetric anhydrides. The condensation of carboxylic acids with acetic anhydride in the presence of heterogeneous coordination catalysts[21] also requires high reaction temperatures, a vacuum and long reaction times. On the other hand, the condensation of a carboxylic acid and an acid chloride in the presence of an acid scavenger (*e.g.* triethylamine or pyridine) results in an almost complete conversion into symmetric anhydrides by much milder conditions, although a negligible amount of free acid is always present in the reaction mixture.[22,23] Therefore, we performed the synthesis of anhydride functional α,ω-diene monomer **1** from 10-undecenoic acid and undec-10-enoyl chloride with triethylamine as the acid scavenger. It should be noted that water-free conditions are essential, especially concerning the solvents, in order to prevent product hydrolysis. The ^{1}H-NMR spectrum of **1** proved its structure, with a shift of the triplet stemming from the α-H at 2.35 ppm to 2.45 ppm, indicating an anhydride functionality. Nonetheless, a very small amount of free acid was always observed in the NMR spectrum, resulting from the high reactivity of anhydride groups towards water (vapor).

The aim of this report is the synthesis of some biodegradable polymers with ester and anhydride functionalities from fatty acid-derived monomers (Scheme 1). Two synthetic approaches, thiol-ene and ADMET polymerization, are applied and compared. The diester functional monomer **2** has already been ADMET-polymerized by our group. The reaction conditions, catalyst screening and isomerization tendencies were previously discussed.[18] In the present report, we use this monomer, as well as our new anhydride functional monomer **1**, in order to establish and compare the efficiency of ADMET and thiol-ene polymerization reactions for biodegradable polymer synthesis. According to our previous study, the best conditions to polymerize **2**, *e.g.* the lowest isomerization together with the highest molecular weight, was obtained with the use of 1 mol% **Zahn-1B** catalyst together with 2 mol% benzoquinone at 80 °C.



1

2

3

4

Scheme 1 The investigated ene and thiol monomers, as well as chain-stopper **4**.

In the present study, we used these optimized conditions, but instead of a continuous nitrogen purge, we applied a continuous vacuum (~100 mbar) in order to remove the ethylene more efficiently and obtain higher molecular weight polymers. Additionally, we used methyl 10-undecenoate (**4**) as a chain-stopper to see if it were possible to synthesize telomers with ester end-groups. Moreover, these telechelic polymers would be very useful for the determination of absolute molecular weights by NMR. A set of experiments was performed with **2** in order to find the optimum amount of methyl 10-undecenoate for the aforementioned purpose, and to check the effect on the resulting molecular weight. We observed that the addition of **BQ** to the reaction resulted in higher molecular weights, slightly lower PDI values of the polymer and much lower levels of isomerization side reactions (compare Table 1). Moreover, a decrease in molecular weight with increasing amount of **4** was observed, as expected. The inclusion of higher amounts of **4** (entries 6 and 7, Table 1) lowered the molecular weights to around 8000 and 5450 Da, with PDI values of 1.92 and 2.02. As already mentioned, the aim was to produce polymers with complete end-group functionalization. Thus, we investigated these polymers by ^{1}H-NMR in order to establish the end-capping efficiency.

As can be clearly seen from the Fig. 1, an increase in the amount of **4** is accompanied by an increase in the intensity of the peak at 3.6 ppm, corresponding to the methyl ester functionality. With the use of 7 mmol of **4** (Table 1, entry 6), no terminal double bond peaks, which appear at δ 5.0 and 5.7, were observed, indicating the complete capping of all the end groups by **4**. Typical side reactions of ADMET polymerization are olefin isomerization resulting from ruthenium hydride species that are formed *in situ* during the reaction.[16] First, we started by studying the isomerization suppression effect of **BQ** by setting up ADMET polymerizations of **2** with and without **BQ** under vacuum. The ADMET polymerization in the absence of **BQ** resulted in a quite high level of isomerization (64%; Table 1, entry 1), while the use of only 2 mmol of **BQ** (Table 1, entry 5) resulted in almost 5-times less isomerization. Having the reaction conditions in hand, we also studied the ADMET polymerization of anhydride functional monomer **1**. Since the anhydride functionality is extremely susceptible to hydrolysis, the monomer should be freshly prepared, and the solvent used to terminate the reaction and precipitate the polymer must be freshly distilled over CaH_2. For instance, it was possible to store **1** in the refrigerator under an inert atmosphere without anhydride hydrolysis for only a few weeks. Moreover, a faster decrease of molecular weight was observed when technical grade THF was introduced into the reaction mixture in order to terminate the polymerization reaction. GPC calculations showed that the ADMET-derived polyanhydride polymer **P1** has an M_n of 9000 g mol^{-1} and a PDI of 1.97 (see Table 2). Moreover, ^{1}H-NMR analysis revealed that the optimized conditions also led to completely end-capped telechelic polymers, as shown in Fig. 2. Thus, we had two structurally very similar polymers in hand (**P1** and **P2**) that only differed by their connectivity (*i.e.* ester *vs.* anhydride), which would be very useful for comparative stability studies, as will be discussed later.

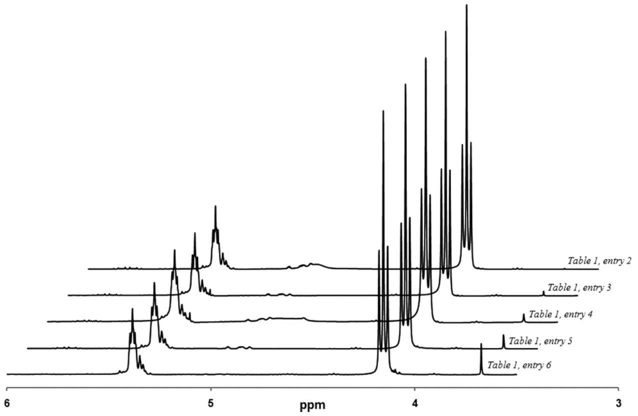


Fig. 1 ^{1}H-NMR spectra of polyesters derived from **2** and prepared *via* ADMET using different amounts of **4** as the chainstopper.

Table 2 Summary of the properties if the investigated polymers

Polymer	Monomers	Polymerization method	M_n/g mol^{-1a}	PDI	T_m/°C
P1	**1** (**4**^{b})	ADMET	9000	1.97	57.7
P2	**2** (**4**^{b})	ADMET	8300	1.90	45.2^c
P3	**1** and **3** (1 : 1 equiv.)	Thiol-ene	5400	2.29	—
P4	**2** and **3** (1 : 1 equiv.)	Thiol-ene	11850	2.00	43.8
P5	**1** and **2** (1 : 1 equiv.)	ADMET	7400	1.84	44.8
P6	**1**, **2** and **3** (0.5 : 0.5 : 1 equiv.)	Thiol-ene	6650	2.01	—

^{a} GPC calculation results. ^{b} **4** was used as chain stopper in amount of 6.5 mol% per diene monomer. ^{c} Annealed at 37 °C.

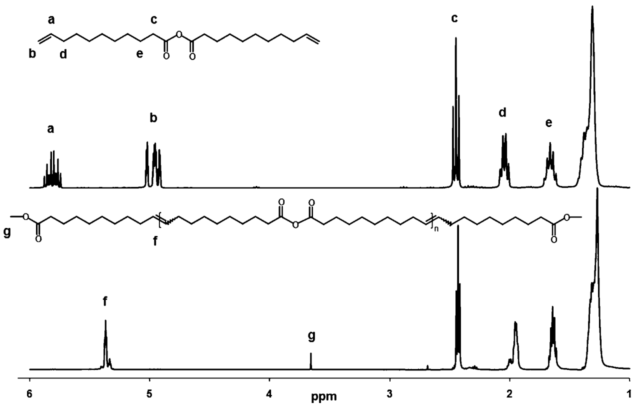


Fig. 2 ^{1}H-NMR spectra of **1** (top) and its derived polymer *via* ADMET **P1** (bottom).

On the other hand, thiol-ene click reactions are presently used very broadly in polymer science.[10] Since monomers **1** and **2** are also perfectly suited to be polymerized *via* thiol-ene click chemistry with a dithiol, this route was investigated as an alternative and compared with ADMET polymerization. Although low temperatures are favorable for thiol-ene additions, when it comes to polymerizations, the reaction temperature should be elevated to avoid crystallization of the polymer during polymerization. Therefore, we increased the reaction temperature to 80 °C and carried out the polymerization reaction of **1** without initiator. GPC analysis showed that even after 6 h, only some oligomers had been formed. However, we observed an extraordinary improvement by the use of a radical initiator. Only 2.5 mol% AIBN was sufficient in order to obtain almost complete conversion of the monomer after 1 h; the polymerization was completed within 2 h under these conditions. Therefore, these conditions were used for all further experiments. GPC analyses thus showed that fatty acid-based polyesters with high molecular weights could also be synthesized *via* thiol-ene polymerization (compare in Fig. 3).

However, thiol-ene click polymerization was less suitable for the polymerization of **1**. The high reactivity of the anhydride functionalities towards nucleophiles, in this case thiol groups, caused the scission of either the monomer or polymer backbone *via* thioester formation, resulting in a molecular weight decrease. ^{1}H-NMR analysis (Fig. 4) confirmed the expected structure of these polymers. In addition to the expected signals of the polymer backbone, the ^{1}H NMR of **P3** also showed two triplets at δ 3.1 and 2.4, which were assigned to thioesters and free carboxylic acids, respectively. These signals confirm the nucleophilic attack of a thiol group at an anhydride carbonyl group, preventing further polymer chain growth and limiting the obtainable molecular weight.

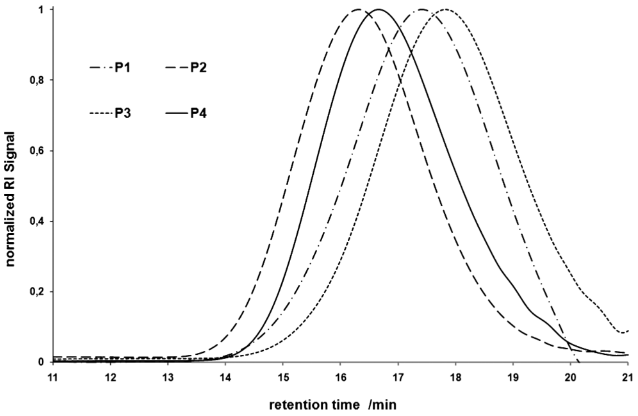


Fig. 3 GPC of the polyesters and polyanhydrides prepared *via* ADMET and thiol-ene chemistry.

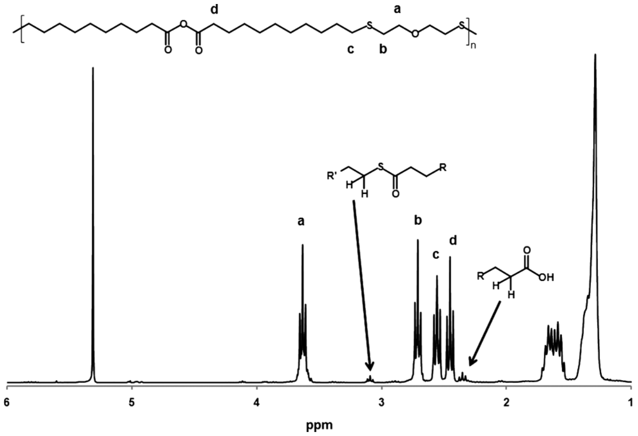


Fig. 4 ^{1}H-NMR spectrum of **P3** (the peak at δ 5.3 stems from CH_2Cl_2 solvent).

In addition, we also prepared random copolymers of **1** and **2**. Since we already have the optimized conditions in hand, we used both ADMET and thiol-ene polymerization methods; the results are summarized in Table 2. The thermal properties of the polymers with similar molecular weights were also analyzed by DSC. All analyses were carried out under a nitrogen atmosphere with a 10 °C min^{-1} heating rate (Fig. 5). All the polymers showed single melting points, while **P2** exhibited two endotherms. In our previous report, a similar behavior was observed for aliphatic polyesters bearing thio-ethers,[11] and annealing was shown to be an efficient technique to obtain a single endotherm. If

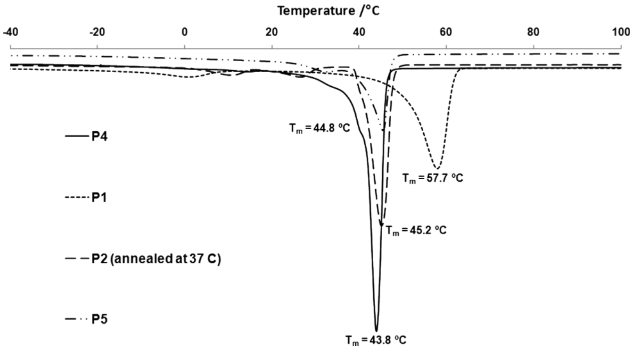


Fig. 5 DSC thermograms of the investigated polymers.

the polymer was heated within the calorimeter to a pre-fixed temperature and left for a sufficiently long time for the polymeric chains to rearrange, a single melting point was detected. In the present case, we applied annealing for 2 h at 37 °C for **P2**, resulting in a single melting point, which was then detected at 44 °C. Both the ADMET and thiol-ene products of monomer **2** exhibited similar melting temperatures, *i.e.* 44.7 and 43.8 °C, respectively, indicating that it is not the choice of polymerization method but the structure of the monomer that has the most pronounced effect on the thermal properties of the polymer derived from this diene monomer. Only **P1** showed a somewhat higher T_m, which might be attributed to a better packing ability of the anhydride functionality present on the main chain.

Polymer stability assay

We compared the stabilities of the polyanhydride and polyester polymers that were synthesized in the present study in order to gain the first information on possible medical applications. Since thiol-ene polymerization does not seem to tolerate the anhydride functionality as efficiently as the ester functionality for the reasons discussed above, we used the polymers that were prepared *via* ADMET polymerization in order to establish their stabilities. Moreover, **P1** and **P2** showed similar molecular weights and were both fully end-capped with **4**. These features are important for our comparative study in order to avoid the influence of any other parameters on the degradation, except for the ester and anhydride functional groups. We set three different conditions, namely only solvent (*i.e.* THF) as reference, acidic solution (H_2SO_4 in THF) and heterogeneous enzymatic conditions (Novozyme 435 in THF) at 37 °C. At each time interval, a sample was taken from the reaction mixture and immediately analyzed by GPC (after dilution). The percentage of the monomer was calculated from the percentage area of the thus-obtained chromatogram.

The stability of a polymer towards degradation strongly depends on the chemical structure, namely the functional groups present along the backbone and their reactivity. In the present study, since the monomers and the molecular weights of the polymers used are very similar, the observed reactivity of the polymers can be directly correlated to the functional groups that they bear. In the present study, we thus directly compared polyesters and polyanhydrides, two typical classes of polymers that are known to degrade *via* bulk and surface erosion, respectively. For drug delivery applications, the surface erosion degradation mechanism is often preferred, since it ensures a regular delivery of the loaded drug. In our study, we clearly observed that the anhydride functional polymer was much less stable than the ester functional polymer, promising fast degradation in both acidic and enzymatic conditions (compare Fig. 6 and Fig. 7).

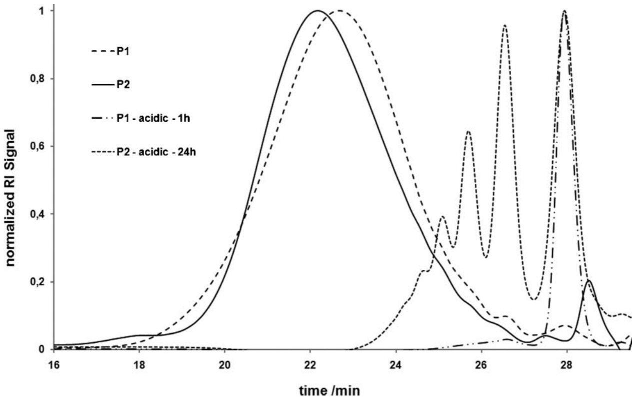


Fig. 6 Degradation of anhydride and ester functional polymers with time under acidic conditions monitored by GPC.

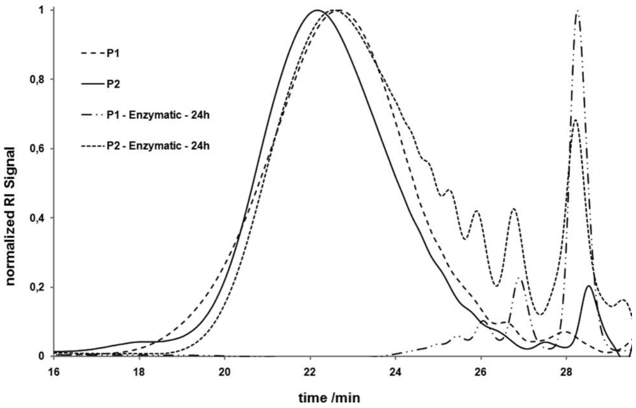


Fig. 7 Degradation rate of anhydride and ester functional polymers under enzymatic conditions.

It is important to note that both polymers were stable in our control experiment (pure THF solution, see Fig. 8), allowing us to correlate the observed degradation under enzymatic and acidic conditions to the connectivity of these polymers. The fastest degradation was observed under acidic conditions, as expected. While the anhydride functional polymer degraded almost completely into the monomer within 1 h, the ester functional polymer degraded much more slowly, and even after 24 h contained only around 35% monomer (Fig. 6 and Fig. 8). On the other hand, under enzymatic conditions, both polymers exhibited slower degradation rates (Fig. 7 and Fig. 8), but the polyanhydride still degraded faster than the polyester. The anhydride polymer degraded to around 65% monomer whilst the ester functional polymer degraded to only around 10% monomer. All of these results are summarized in Fig. 8 and agree well with the literature.

For applications requiring a combination of polyanhydride and polyester-type hydrolysis, *e.g.* faster than polyester but slower than polyanhydride, random copolymers of **1** and **2**

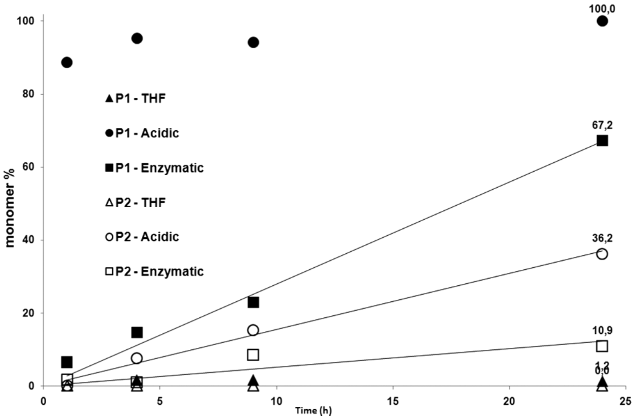


Fig. 8 Monomer percentages in the homopolymer stability assay.

might be a solution. Therefore, we also investigated the solution stability of our copolymer **P5**, and directly compared it to **P1** and **P2**. Fig. 9 shows the comparison of the monomer percentages of the copolymer and the homopolymers under enzymatic conditions. It is obvious that **P1** converts into its monomer faster than **P2**, and after 24 h **P1** has degraded almost completely while **P2** has degraded to only 50% monomer. This result agrees well with the theory and our previous results. Most importantly, the monomer percentage (and therefore the degradation) of copolymer **P5** stays between that of **P1** and **P2**, revealing that it is possible to tune the degradation of these biopolymers by copolymerization.

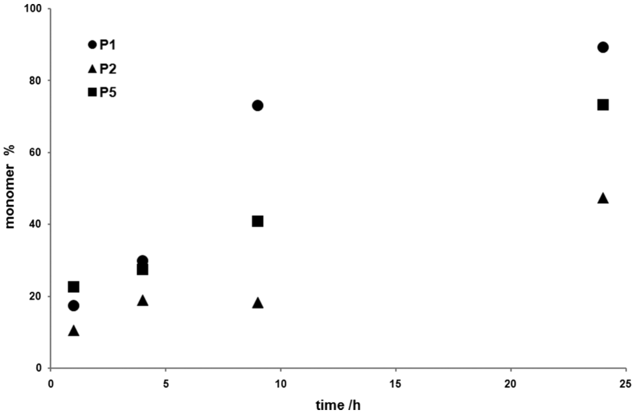


Fig. 9 Stability comparison of copolymer **P5** with homopolymers **P1** and **P2**.

Conclusion

In this study, we aimed to establish two complementary synthetic approaches to biodegradable polymers from a renewable platform chemical using thiol-ene addition reactions and ADMET polymerizations. The synthesized polymers could be used to substitute some of the biomedically-useful polymers usually produced from petroleum-originated monomers. Additionally, thiol-ene and ADMET polymerization were studied and compared to each other. Finally, so as to guide their possible applications, the synthesized polymers were successfully characterized in order to establish their thermal behavior and stability. Within this contribution, we can conclude that ADMET polymerization can tolerate both ester and anhydride functionalities but thiol-ene addition reactions, although being an efficient and environmentally benign tool, cannot tolerate the anhydride functionality very well, while the synthesis of polyesters *via* thiol-ene polymerization was more effective, giving rise to high molecular weight polymers.

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