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Biogenic polymeric materials from lignocellulosic biomass-derivable 4-pentenoic acid and isosorbide for potential biomedical applications

Daniel A. Döpping,^{a,b} Johann Kern,^c Nicole Rotter,^c Audrey Llevot,^d Hatice Mutlu^c *

^aInstitute for Chemical Technology and Polymer Chemistry (ITCP), Karlsruhe Institute of Technology (KIT), Engesserstr.18, D-73131, Karlsruhe, Germany

^bSoft Matter Synthesis Laboratory (SML), Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, D-76344, Eggenstein-Leopoldshafen, Germany

^cDepartment of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty Mannheim of University Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany

^dCNRS, Bordeaux INP, LCPO, UMR 5629, University of Bordeaux, F-33600 Pessac, France

^eInstitut de Science des Matériaux de Mulhouse (IS2M), UMR 7361 CNRS/Université de Haute Alsace (UHA), 15 rue Jean Starcky, Mulhouse Cedex, 68057 France

KEYWORDS lignocellulosic biomass, isosorbide, 4-pentenoic acid, metathesis polymers

ABSTRACT The increasing substitution of petroleum-based polymers by materials of biogenic origin is an important step towards the desired circular economy. In fact, research in this area is not only leading to CO₂-neutral polymers but is also enabling the development of completely new materials with cell compatibility. Thus, using the toolbox of lignocellulosic biomass derivatives (in particularly, isosorbide and 4-pentenoic acid; the latter being less explored and recognized in the field of synthetic polymer chemistry), acyclic diene metathesis polymerization has been explored for the synthesis of the biogenic polymer derivative. Upon characterizing the chemical structure of the 100% "biomass-derived" polyester derivative by nuclear magnetic resonance (NMR), size exclusion chromatography (SEC) and attenuated total reflectance infrared (ATR-IR)

spectroscopy, the thermal properties of the biogenic polymer were investigated by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). While the DSC studies indicated that the polymer was in the amorphous state with a glass transition temperature (T_g) value of 17 °C, the mechanical properties and cell compatibility of the functional novel polyester derivative were also evaluated by dynamic mechanical analysis (DMA) and cytotoxicity test. By assessing the cytotoxicity of the functional novel polyesters, we were able to reflect the benefit of employing isosorbide and 4-pentenoic acid as building blocks for materials with prospective biomedical applications (namely as novel cartilage materials).

Introduction

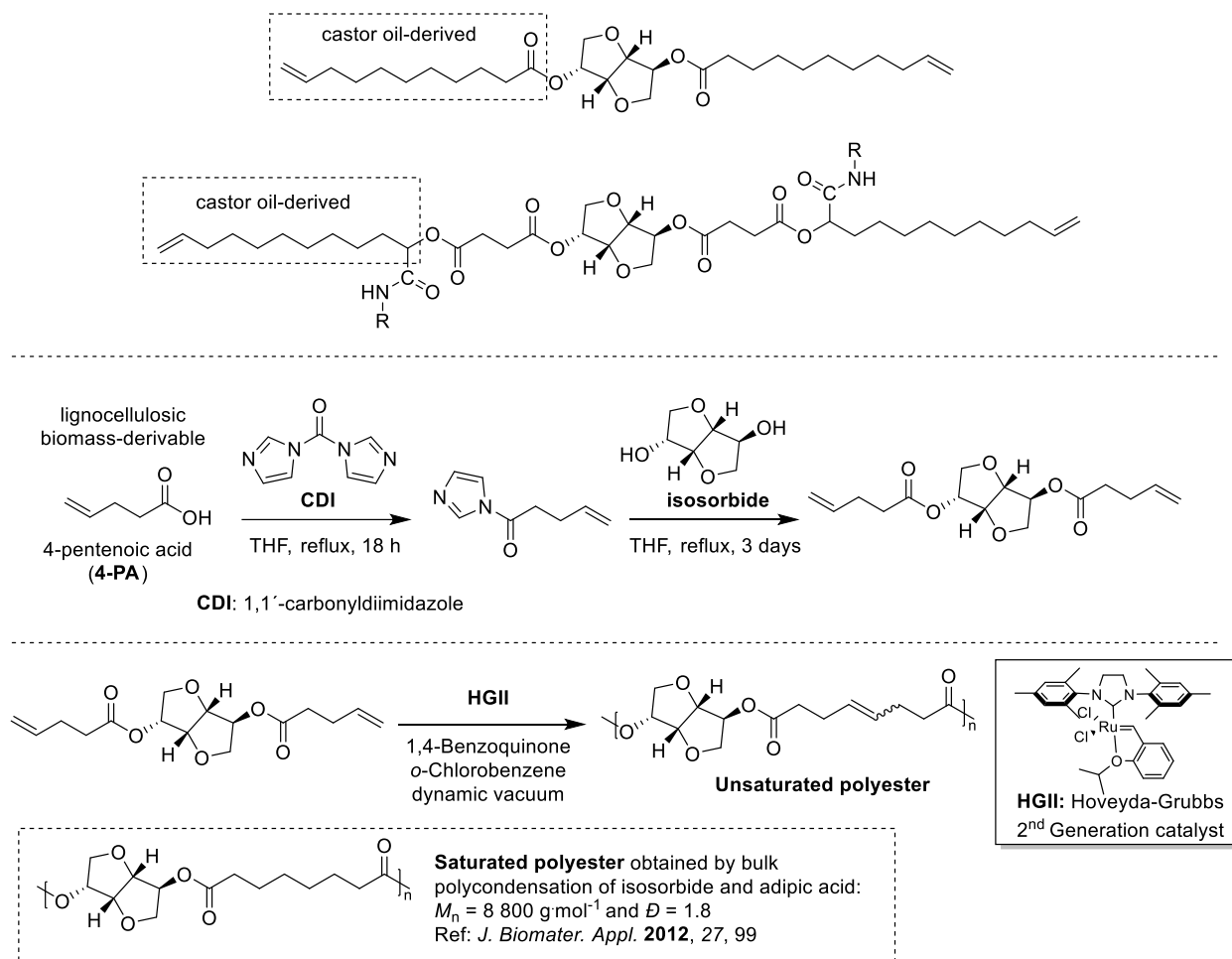
Polymeric materials are crucial for human life and find various applications in fields ranging from packaging to biomedical applications as a result of their low price and excellent performance, therefore, there is a great interest to incorporate renewable resources into monomers and polymers in order to reduce the use of petroleum-based materials, comply with legal and societal standards, and to develop advanced polymeric materials with emergent properties towards a desired circular economy.^{1,2,3} Not surprisingly, although being a niche area, the bulk production volume of renewable-derived polymers ended up at 3.8 % Mt (million tons) in 2019, corresponding to 1% of the output volume of fossil-based polymers.⁴ Bio-derived polymers have the potential to mitigate carbon footprints by 42%, and as recently reported by Venkatachalam et al. their production also consumes 65% less energy compared to the conventional traditional petroleum-based polymers.⁵ Although this significant progress in the field of fully bio-based polymer materials, the urgent need to combat world hunger is exacerbating food insecurity. Consequently, the search for renewable, low-cost, non-edible raw materials endures a tendency for the development of more sustainable

polymer synthesis. Current research highlights the potential of lignocellulose as the most sustainable and crucially non-edible of all renewable biomass resources. Lignocellulose is one of the most abundant non-food biomass resources on the Earth and is mainly composed of cellulose (30–50 wt%), hemicellulose (20–40 wt%) and lignin (15–25 wt%). Thus, there is huge interest on the transformation of lignocellulose into platform chemicals as alternative monomers, and their respective use as building blocks for novel polymeric materials.⁶ At present, isosorbide, a bicyclic stiff diol, is one of the most unique platform chemicals derived from lignocellulose, with enormous potential for use in a wide range of products that shape our daily lives.⁷ Crucially, isosorbide, a 1,4:3,6-dianhydrohexitol, which has been recognized as a direct replacement for rigid diols like bisphenol A, is a potential platform for polymers with tunable T_g values.^{[8][9][10]} Among the broad synthetic toolbox,^{11,12,13,14} noteworthy Nomura and coworkers reported on the synthesis of sustainably derived polymer¹⁵ from isosorbide undecenoate, derived from coupling isosorbide with a castor oil derivative via the unconventional polycondensation reaction, the acyclic diene metathesis (ADMET)¹⁶ polymerization (**Scheme 1A**). Undoubtedly, ADMET polymerization has been recognized as a widely used method in the synthesis of advanced functional polymers.^{17,18,19,20,21,22}

Another intriguing lignocellulose-derived platform molecules is γ -valerolactone (GVL),^{23,24} which in turn can be efficiently transformed into 4-pentenoic acid (4-PA). 4-PA, despite its unique cheese-like odor, has been widely employed as a chemical intermediate in the synthesis of various end-use industries, such as pharmaceuticals, cosmetics, and agrochemicals. Rationally, 4-PA has attracted the attention of polymer chemists due to its unique chemical structure (as contains double bond at the one termini and carboxylic group ($-\text{COOH}$) at the other one). On the one hand, the terminal carboxyl group has been modified to produce anhydrides and epoxides, thus, to deliver

polyanhydrides^{25,26,,27,28,29,30,31,32,33,34} and CO₂-based polycarbonates originating from lignocellulose, respectively.³⁵ On the other hand, the visible light induced thiol–ene click modification of terminal double bond paved the way to synthesize a new biomass-derived dicarboxylic acid which could be further polymerized to deliver novel polyamide derivatives.³⁶ Nonetheless these advances and its commercial availability, 4-PA has remained an under-utilized lignocellulose derivative with great potential in polymer chemistry. It is anticipated that replacement of the undecenoate moiety by 4-PA units in isosorbide undecenoate monomer will deliver ADMET polymers (**Scheme 1B-C**) with distinctive properties compared to the previously reported derivatives which exhibited semi-crystalline behavior T_g of $-10\text{ }^\circ\text{C}$ and melting point (T_m) of $38\text{ }^\circ\text{C}$).¹⁵ In fact, a literature survey reveals that the length of the aliphatic chain is a key parameter in determining structural and thermal properties of polyester derivatives.^{37,38} Crucially, it has been also reported that polyesters with reasonably short aliphatic chains can be utilized as degradable polymers for biomedical applications.³⁹ It has been also emphasized that along the biodegradability of linear polyesters, the mechanical properties can be clearly improved by incorporating rigid units like biobased carbohydrates (i.e., isosorbide derivatives) due to their ability to add stiffness to a polymer backbone.⁴⁰ For instance, Park and colleagues⁴¹ have synthesized biocompatible polyesters by bulk polycondensation of isosorbide and short chain length aliphatic diacid derivatives, such as succinic acid, adipic acid (**Scheme 1C**, the dashed-border rectangle), or sebacic acid. As alternative to the saturated analogue polyester derived from isosorbide and adipic acid, the unsaturated polymers derived from isosorbide and 4-PA were synthesized via acyclic diene metathesis (ADMET) polymerization. Details of the synthetic procedures are reported, as well as the finding of notable and potentially useful differences in thermal and mechanical properties compared to the previously undecenoate-derived polymers. As

isosorbide decorated polyesters are frequently employed in biomedical applications (by virtue of their biodegradability and cell compatibility),⁴² the cytotoxicity of the functional novel polyesters was assessed.



Scheme 1 Schematic representation of: (A) previously reported castor-oil derived monomers applicable in acyclic diene metathesis (ADMET) polymerization;^{11,12,15} (B) the synthesis of a new tailor-made α,ω -diene functionalized monomer **M1** from biomass-derivable 4-pentenoic acid and isosorbide; and (C) its subsequent polymerization via ADMET chemistry to afford unsaturated polyester derivative polymer **P1**. For comparison reasons, the saturated analogue of P1 (synthesized by the bulk polycondensation of isosorbide and adipic acid in the presence of slightly toxic titanium tetraisopropoxide)⁴¹ is shown within the dashed-border rectangle.

Results and Discussion

Synthesis of the novel monomer and the respective polymerization via Acyclic Diene Metathesis (ADMET) chemistry

In the seminal work of Meier et al., 1,1'-carbonyldiimidazole (CDI) was used as an eco-friendly acylation agent to synthesize α,ω -diene functionalized isosorbide ADMET-monomers derived from isosorbide and 10-undecenoic acid.¹⁴ Indeed, CDI has been recognized as a safe and versatile acyl transfer agent,⁴³ which is easy to handle, compared to the commonly employed toxic isocyanates, (tri)phosgene, or chloroformates, thus aligns with the principle "*Designing Safer Chemicals*" (4th Principle of the 12 Principles of Green Chemistry).⁴⁴ As CDI is easily accessible in kilogram quantities,⁴⁵ it was successfully employed in the synthesis of monomers^{46,47} and polymers.^{43,48} Accordingly, the previously reported procedure was adopted by substituting 10-undecenoic acid with 4-pentenoic acid (for synthesis details compare Section C1 in the supporting Information). The only crucial difference was that the crude product was purified via high performance liquid chromatography (HPLC) to yield the targeted monomer in yields which varied between 82% and 65% depending on the scale (4.0 versus 10.0 gram) of the synthesis. Although, the direct scaling of experimental parameters, such as reagent volume, did not translate to the corresponding product yields for the large scale (i.e., 10.0 gram scale), the successful synthesis of the monomer was confirmed via detailed NMR characterization (refer to **Figure 1A** (grey color line) and **Figure S1** within Section C1 in the Supporting Information). In other words, the ¹H NMR spectrum of the 100% renewable monomer, **M1**, depicted characteristic resonances at δ 5.87-5.74 ppm (m, 2H) and δ 5.11-4.95 ppm (m, 4H) ascribed to olefinic protons (a and b) in terminal position (**Figure 1A** (grey color line)); moreover, the magnetic resonance at δ 5.24-5.11 (m, 2H), δ 4.82 (t, J=5.0 Hz, 1H), δ 4.46 (d, J=4.6 Hz, 1H), and δ 4.00-3.74 (m, 4H) ppm were assigned to

the protons of isosorbide core. In similar manner, the corresponding resonances ascribed to the carbons arising from the terminal olefin group were observed at δ 136.4 ppm ($-\underline{\text{C}}=\text{C}$) and δ 115.9 ppm ($-\text{C}=\underline{\text{C}}$) in **Figure S1**. Subsequently, ADMET polymerization conditions similar to those previously reported by Mutlu et al.¹⁷ were tested (1.0 mol percent/double bond of Hoveyda-Grubbs second generation catalyst (HGII, shown in **Scheme 1C**) by varying the solvent (i.e., *o*-dichlorobenzene) concentration in the range of 0.6 -1.0 M at 65 °C; polymerization details are presented within Section C2 in the Supporting Information). HGII was the choice of catalyst due to its high stability to air and moisture, while maintaining functional group tolerance in addition to high activity.⁴⁹ Further, 1,4-benzoquinone was employed to prevent the most known side reaction of the ADMET polymerization (i.e., olefin isomerization induced by ruthenium-hydride species).⁵⁰ Dynamic vacuum (from 200 to 8 mbar, pressure gradually reduced over reaction time) was applied in order to drive the equilibrium toward the formation of polymer by removing the side-product of ADMET polymerization, i.e., ethylene. The first attempt of ADMET polymerization was performed on a half-gram scale monomer in 1.0 M *o*-dichlorobenzene with a rapid gradual pressure reduction from 200 mbar to 8 mbar within 1 h. After total reaction time of 4 h, the polymer **P1-1** (blue color line in **Figure 1B**) with number average apparent molecular weight (M_n obtained via size exclusion chromatography (SEC) measurement in THF as eluent (PMMA standard) shown in **Figure 1**) of 5 850 g·mol⁻¹ and dispersity (D) value of 1.6 (corresponding to degree of polymerization (DP_n) of 21) was isolated in 48% yield upon precipitation in ice-cold methanol. The dispersity was slightly lower than the expected dispersity D of 2 for step-growth polymerizations. It is postulated that this deviation might be due to the work-up, as previous experiments showed that oligomers and short chains of isosorbide derived polymers dissolve in methanol.⁵¹ Hence, the precipitation in ice-cold methanol could remove lower

molecular weight polymer chains and therefore shift the dispersity D towards a lower value. A follow-up attempt on a half-gram scale monomer by utilizing diluted reaction conditions (i.e., 0.6 M) with prolonged reaction time (i.e., 4 h), resulted in polymer **P1-2** with a slightly higher M_n of 9 900 g·mol⁻¹ ($D=1.5$, $DP_n = 36$, black color in **Figure 1B**) in isolated yield of 42%. Increasing the scale of ADMET polymerizations was critical to providing enough material for testing the polymers capability to be employed as cartilage materials. Adequately, performing the ADMET polymerization on an 8-gram scale of the monomer by adopting the conditions for **P1-2** delivered a polymer **P1-3** (green color line in **Figure 1B**) with M_n value in the range of the small-batch polymerization reactions, i.e., M_n of 6 500 g·mol⁻¹ ($D=1.7$, $DP_n = 29$) in isolated yield of 80%. although the increase in viscosity and technical difficulty of stirring magnetically. These unexpected results might be explained by the overall increase of reaction mass in the upscaled reaction setup. As the flask is containing more reaction mixture compared to the previous experiments, the surface area of the mixture decreases. The lower surface-to-volume ratio reduces the amount of solvent evaporating during the reaction which leads to higher monomer/oligomer reactivity and polymer yields as the viscosity is lower compared to the other two preliminary polymerization reactions. Given the potential problems associated with the residual catalyst in the final polymer product, for all polymerization approaches, we have used small organic molecule (i.e., ethyl vinyl ether) that could coordinate to the metal Ru-species arising from the HG-II and modify the solubility of the catalyst, facilitating partitioning of the catalyst into the precipitation solvent. Thus, facilitating removal of residual Ru-species during isolation of the polymer via filtration. Detailed NMR characterisation of the three batches of polymerization has confirmed the identical polymer structure. Magnetic resonances ascribed to the protons of terminal olefins (at δ 5.11-4.95 ppm and δ 5.87-5.74 ppm) disappeared and resonances attributed to protons assigned to

internal olefins (at δ 5.52-5.37 ppm in **Figure 1A**, which depicts the representative NMR spectrum of **P1-2**) were observed, whereas the other resonances arising from the isosorbide core have remained intact. Similarly, the disappearance of resonances arising from the carbon (δ 136.4 (-C=C) and δ 115.9 (-C=C) ppm) in the terminal olefins along with observation of the resonances in the internal olefins at δ 129.7 (-C=C-) was detected in the ^{13}C NMR spectra (**Figure S2** in the Supporting Information). The structure of the polymer was additionally confirmed via the attenuated total reflection (ATR)-mode Fourier transform infrared (ATR-IR) spectroscopy. While the transmittance signals at 1723 cm^{-1} and $1155\text{ -}1090\text{ cm}^{-1}$ corresponding to the vibrational peaks of C=O, and -O-, respectively, as shown in **Figure 1C**, remained intact, the signal at 3071 cm^{-1} arising from the olefinic C-H stretching of the terminal double bond has disappeared, thus demonstrating that the reaction proceeded as expected, retaining the ester bonds, and forming internal double bonds (as it was observed at 1655 cm^{-1}). Noteworthy, the trans stretching band arising from the internal double bond (1655 cm^{-1}) is weak due to lack of change in dipole moment in completely symmetrical structures.

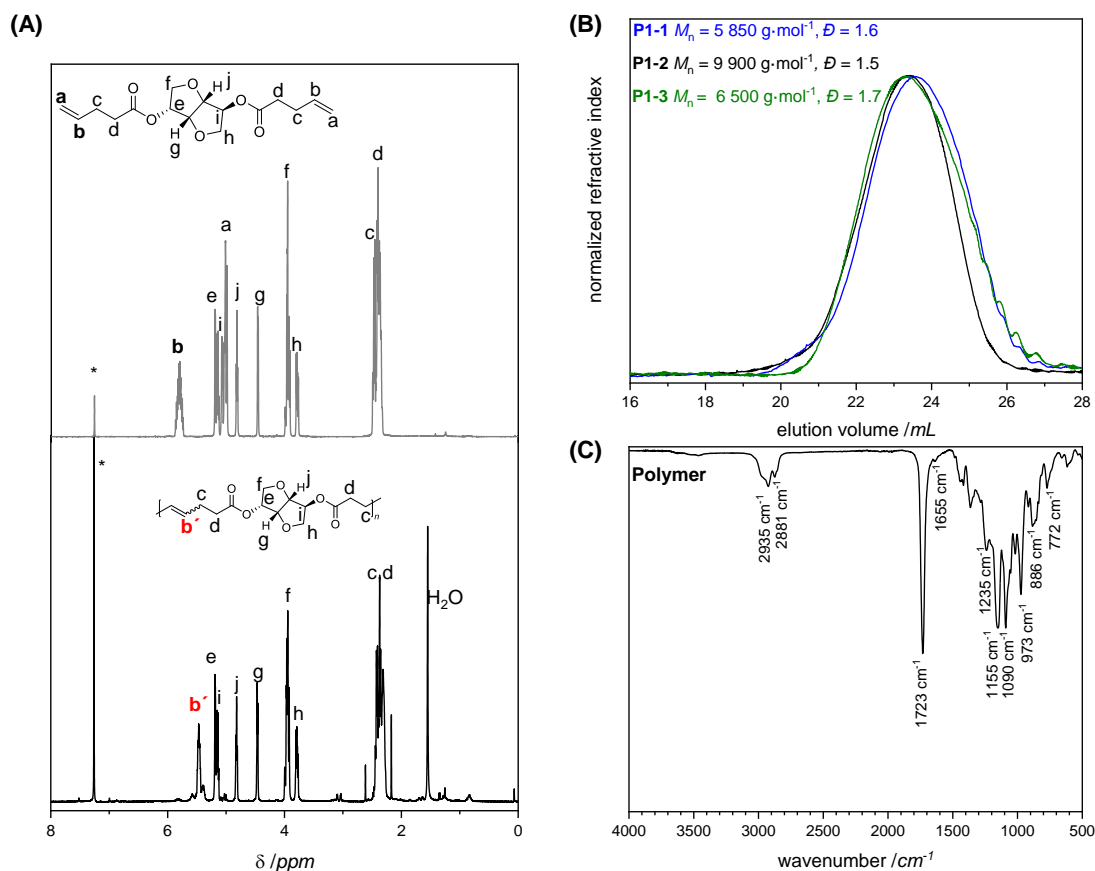


Figure 1 (A) ^1H NMR spectra (up, 400 MHz, CDCl_3 , 298 K) of monomer (grey line) and polymer (bottom, black line); (B) Comparative SEC traces of metathesis polymers obtained under different concentration values (c_{Monomer}) **P1-1** ($M_{n,\text{SEC}} = 5\,850\text{ g}\cdot\text{mol}^{-1}$, $D_{\text{SEC}} = 1.6$, blue line, $c_{\text{Monomer}} = 1.0\text{ M}$) and **P1-2** ($M_{n,\text{SEC}} = 9\,900\text{ g}\cdot\text{mol}^{-1}$, $D_{\text{SEC}} = 1.5$, black line, $c_{\text{Monomer}} = 0.6\text{ M}$), in addition to the 8-gram upscaled polymerization reaction to deliver **P1-3** ($M_{n,\text{SEC}} = 6\,500\text{ g}\cdot\text{mol}^{-1}$, $D_{\text{SEC}} = 1.7$, green line, $c_{\text{Monomer}} = 0.6\text{ M}$), respectively; and (C) ATR-IR trace of **P1-2** (black line).

Thermal and mechanical properties of the polymer

Upon the successful chemical characterization of the obtained polymer, the thermal properties were evaluated by differential scanning calorimetry (DSC) and thermal gravimetric analyses (TGA). The isolated polymers, independent of the polymerization scale, and thus, molecular weights, showed an amorphous morphology with glass transition temperature, T_g , for **P1-2** detected at $17\text{ }^\circ\text{C}$ (**Figure 2A**). The T_g value of the polymer is below the human body temperature,

indicating that the polymer is in a rubbery state and can be potentially employed for biomedical applications.⁴¹ As aforementioned, previous reports indicate that the ADMET polymerization of isosorbide undecenoate yielded semi-crystalline unsaturated aliphatic polyester (i.e., **PIU**) with T_g of $-10\text{ }^\circ\text{C}$ and melting point temperature, T_m , of $38\text{ }^\circ\text{C}$.^{Fehler! Textmarke nicht definiert.}¹⁵ In this work, the absence of crystallinity and the presence of a higher T_g compared to the polymer obtained from isosorbide undecenoate is attributed to the shorter aliphatic chain in between the isosorbide moieties. A similar phenomenon has already been observed in the study of Jannasch *et al.* who reported the synthesis of a series of poly(alkanoyl isosorbide methacrylate)s with pendant linear alkyl chains of different length.⁵² Noteworthy, the polymers synthesized in this work feature similar thermal properties compared to the previously reported functional isosorbide polymers that have been synthesized via a multicomponent polymerization approach (T_g values of $13\text{-}22\text{ }^\circ\text{C}$ were observed)¹¹. Finally, as shown in **Figure 2B**, the polymer displayed reasonable thermostability with $T_{d,5\%}$ of $278\text{ }^\circ\text{C}$ under inert conditions (i.e., nitrogen), which indeed is higher compared to the polyester derived from the adipic acid and isosorbide ($T_{d,5\%}$ of $263\text{ }^\circ\text{C}$ for polymer of $M_n = 8\ 800\text{ gmol}^{-1}$ and $D = 1.8$ shown in Scheme 1C), as the saturated analogue of **P1-2**.⁴¹

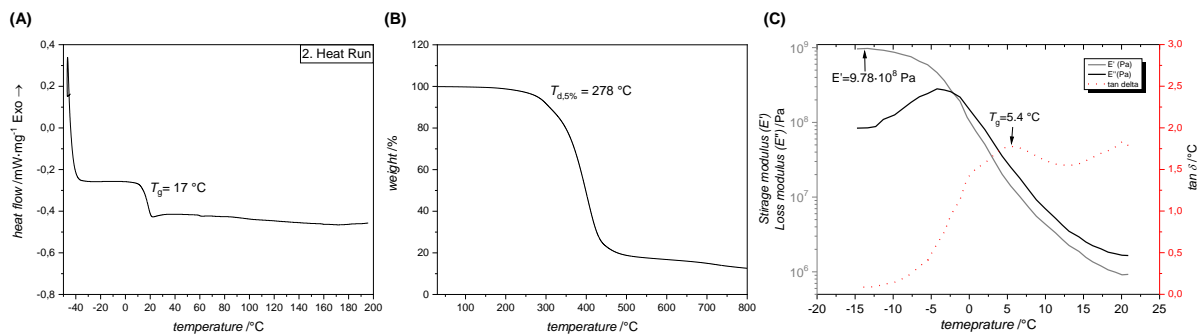


Figure 2 (A) Differential scanning calorimetry (DSC) of polymer **P1-2** (2nd heating cycle); (B) Thermogravimetric analysis (TGA) of **P1-2** from $25\text{-}800\text{ }^\circ\text{C}$ with a heating rate of $10\text{ K}\cdot\text{min}^{-1}$ under nitrogen flow; (C) Dynamic mechanical analysis (DMA) temperature sweep of **P1-2** storage modulus E' (grey), loss modulus E'' (black), and dampening $\tan \delta$ (red).

Dynamic mechanical analysis (DMA) was performed on the polymer and the thermomechanical properties of the sample were determined by a temperature sweep experiment between -15 °C and 20 °C employing a traction set up and using a frequency of 1 Hz and strain amplitude of 5% (**Figure 2C**). The storage modulus E' in the glassy state was around 978 MPa at -10 °C. The polymer lost its higher storage modulus E' as soon as temperatures increased above -10 °C. Indeed, when increasing the temperature, the decrease of the E' value indicated a transition from a glassy state to a rubbery state. The alpha transition temperature T_α of this polymer was determined from the maximum of tan delta at 5.4 °C. The beginning of the rubbery plateau can be observed at 20 °C.

Cell compatibility of polymer

To assess the basic cell compatibility of the novel polymer, three different *in vitro* experiments on primary cells isolated from human cartilage samples were performed. First, in an elution assay, chunks of the polymer were eluted with complete cell culture medium for 24 hours at ambient temperature. The isolated eluate was further diluted in a ratio of 1:10 with complete cell culture medium and subsequently, chondrocytes were cultured for 24 h with the respective diluted eluate. After 24 h, the percentage of surviving cells was determined with a photometric-based viability assay (Alamar Blue Assay). The results obtained were compared to a control sample (cells cultivated with normal complete medium). This elution assay determines if the polymer leaks any cytotoxic leachables into the cell culture medium. Second, in a direct contact measurement, the chondrocytes were added directly onto the polymer for 24 h and the number of surviving cells compared to a control group without added polymer was determined using a microscopical analysis and a viability assay. For the fluorescence microscopic analysis, chondrocytes were

stained with SytoxGreen which stains dead cells green. Lastly, the cell compatibility of the chondrocytes with the polymer was determined by a 3D cell culture experiment. Live chondrocytes in a cell culture medium was observed over 28 days under a microscope to monitor how they interact with chunks of the polymer. A note to the reader: For the experiments with the spheroids, a cell culture time of 28 days was chosen, as chondrocytes require between 14 and 21 days to redifferentiate into mature chondrogenic cells and to fully develop the properties of cells in a cartilage tissue. Indeed, the elution assay for polymer confirmed that the polymer does not have any leachables that affect viability of the chondrocytes as the survival rate of chondrocytes surpasses the untreated control group (**Figure 3A**).

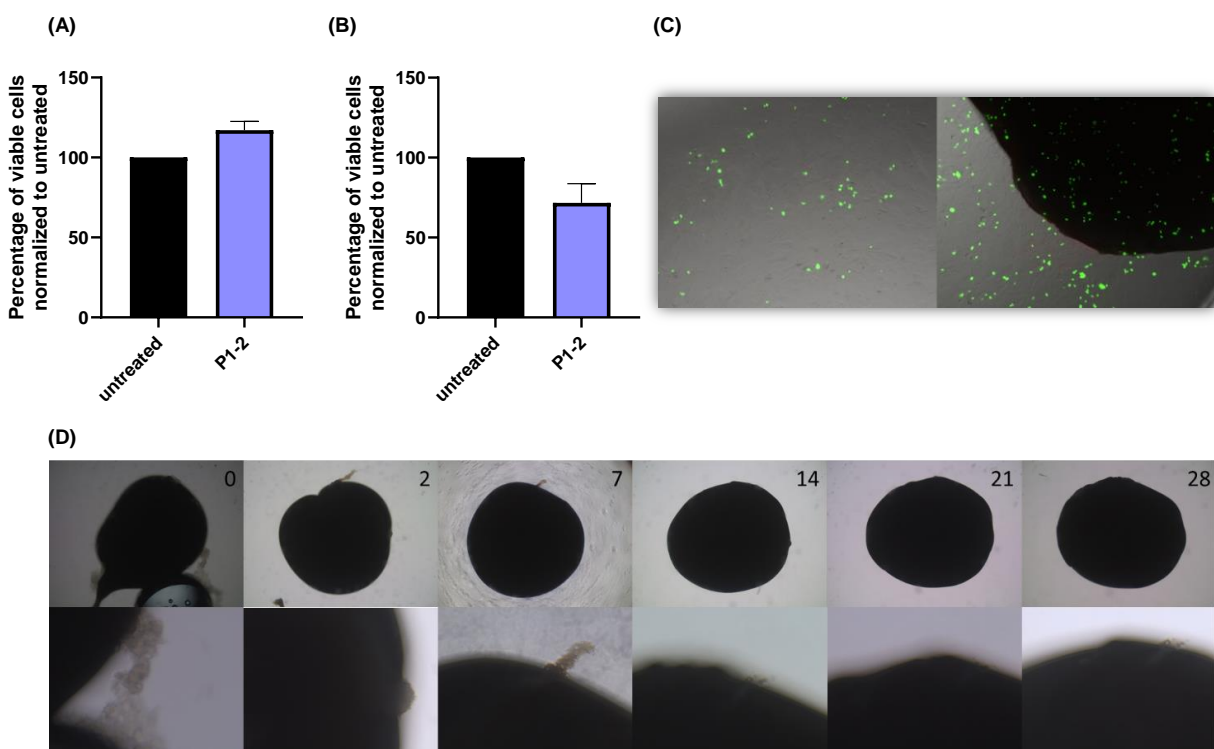


Figure 3 (A) Elution Assay in a dilution of 1:10 of **P1-2** with chondrocytes compared to the untreated control group; (B) Direct Contact measurement of **P1-2** with chondrocytes compared to the untreated control group; (C) Direct Contact measurements depicting the untreated control group (left) and the chondrocytes in contact with the **P1-2** (right). The green spots correspond to dead cells; (D) 3D cell culture experiments of **P1-2** with chondrocytes and a magnification of 25x in the top row and 100x on the bottom row. The number in the top right corner corresponds to the day of the experiment the picture was taken.

In the direct contact measurements, the chondrocyte survivability is 75% compared to the untreated control group (**Figure 3B**). As the threshold for cytotoxic materials defined in DIN EN ISO 10993-5:2009 is a cell viability rate of 70% or lower within 24 h the direct contact measurements show that the novel polymer is marginally above the threshold of cytotoxicity. The microscope pictures depicting the direct contact measurements after 24 h (**Figure 3C**) of the untreated control group and the chondrocytes in contact with polymer indicate a higher mortality rate of cells in contact with the polymer expressed by the significant increase in the number of dead cells (i.e., green spots).

The 3D cell culture experiments of **P1-2** were ambiguous (**Figure 3D**). First, the chondrocytes started to conglomerate at day 2 and it appears, that the newly formed cell spheroid starts to migrate into the **P1-2** at day 7 as no more chondrocytes or parts of spheroids are visible on day 14, 21, and 28. Nonetheless, it implicates that the chondrocytes survive at least until day 7 without their cell membranes dissolving attesting to some cell compatibility of the novel polymers. These results show that this polymer has a limited toxic effect on at least some cells in cell cultures on direct contact. Since the cytotoxicity is not below the 70% specified by DIN for living cells, there is still potential for future clinical application. As we do not yet know what the cause of this limited cytotoxicity is, further investigations are required, e.g., whether modifying the surface of the polymer with more hydrophilic groups would reduce cytotoxicity.

Conclusion

By taking advantage of the toolbox of isosorbide, 4-pentanoic acid and metathesis chemistry, the synthesis of lignocellulosic biomass-derived biogenic polymers was accomplished. The chemical structure of the polymer was characterized in-depth via NMR, SEC and ATR-IR. The 100

%“biomass-derived” carbon polymer was obtained with reasonable molecular weight in acceptable yields. In addition, the thermal properties of the biogenic polymer were investigated via TGA and DSC. Particularly, the DSC studies indicated that the polymer was in the amorphous state, being characterized by T_g value (i.e., 17 °C) below the human body temperature. Last but not at least, the cell compatibility of the novel polymer derivative was evaluated via cytotoxicity test, showing that the polymer was biocompatible with chondrocyte cells in the conditions used in the tests. Still, in order to be able to compare the biogenic properties of the current polymer derivative with any other biogenic polymeric materials derived from cellulose, polysaccharides, and/or collagen, further studies are essential as the cell compatibility of any biogenic polymer is not similar with the current one. In summary, the work described herein highlights the potential utility of isosorbide and 4-pentenoic acid as building blocks for polymers with prospective biomedical application (namely, as novel cartilage materials); and as above mentioned further studies are essential to be able to deliver a reasonable comparison with any other biogenic polymers.

ASSOCIATED CONTENT

Supporting Information. Materials and Characterization, Synthesis protocol, 1D NMR spectra of all small molecules and polymer.

This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*Hatice Mutlu Institut de Science des Matériaux de Mulhouse, UMR 7361 CNRS/Université de Haute Alsace, 15 rue Jean Starcky, Mulhouse Cedex, 68057 France, hatice.mutlu@uha.fr

Present Addresses

†If an author's address is different than the one given in the affiliation line, this information may be included here.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

ADMET, acyclic diene metathesis ADMET

T_g , glass transition temperature
GVL, γ -valerolactone
4-PA, 4-pentenoic acid
–COOH, carboxylic group
 T_m , melting point
CDI, 1,1'-carbonyldiimidazole
HPLC, high performance liquid chromatography
HGII, Hoveyda-Grubbs second generation
 D , dispersity
 M_w , weight average apparent molecular weight
 DP_n , degree of polymerization
FT-IR, Fourier transform infrared
ATR, attenuated total reflection
DMA, Dynamic mechanical analysis
 E' , storage modulus
 T_α , alpha transition temperature

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TOC Figure

