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Sustainable Polyesteramides and Copolyamides: Insights into the Copolymerization Behavior of Terpene-Based Lactams

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Sustainable lactams, which are derived from terpenes, are used for the synthesis of different novel copolymers via ring-opening polymerization. Different conditions are tested and the incorporation of the different monomers into the polymers is elucidated. This gives access to a variety of new polymer structures and their application range is thus remarkably extended.

1. Introduction

Polyamides (PAs) are very important polymers for a wide range of applications.[1] After establishing in the 1930s with Nylon 66 and Nylon 6 (Perlon), their importance has been continuously growing. This fact relies on their versatility and their excellent thermal and mechanical properties, which result from, for example, amide groups and hydrogen bonding between polymer chains. While Nylon 66 is synthesized via polycondensation of adipic acid and hexamethylenediamine, Nylon 6 is made via ring-opening polymerization (ROP) of ε-caprolactam (CLa, **Scheme 1**A). Meanwhile, also many biobased polyamides have been developed that are derived from, for example, vegetable oils, carbohydrates, or terpenes,[2,3] which is in the general context of utilizing renewable and also structurally significant feedstock for polymer synthesis.[4–8] Due to their abundance and functionalities, and also their structural diversity, especially terpenes have gained a lot of attention for these approaches.[9–20] An example for this are PAs from L-menthone and from β-pinene, which have been investigated in our group, and which are obtained via the corresponding lactams via ROP, in analogy to the established Nylon 6 synthesis (Scheme 1B,C).[2–4,21–23] In addition to sustainability, interesting structural features (side groups and stereocenters) are thus introduced into the polymers, resulting in ordered microstructures and interesting properties.[2–4] Polyesters (PEs) have also a great importance and find utilizations as mass plastics, but also in the biomedicine field due to their good mechanical properties, biodegradability and biocompatibility. Among them, polycaprolactone (PCLo), synthesized also via ROP (in this case of ε-caprolactone), is one of the most important PEs (Scheme 1D).

Polyesteramides (PEAs) can combine the biodegradability and biocompatibility of PEs with the excellent thermal and mechanical properties of polyamides, and they have thus attracted much awareness.[24–26] In addition to, for example, many amino-acid based PEAs, also the copolymerization of lactones and lactams (e.g., CLo and CLa) to random or block copolymers has been investigated (Scheme 1E).[27–29]

Biopolymers are defined as polymers that are biobased, biogenic or biodegradable.[30–33] The utilization of renewable feedstock for the synthesis of sustainable polymers and materials has been gaining strong impact within the past decades for two main reasons: it enables independency from fossil oil, and it provides access(es) to new structures that cannot be obtained so easily via fossil-based pathways.[3,9–20] This can apply for natural polymers (e.g., cellulose) as well as for molecular building blocks. As mentioned above, terpenes belong to the most interesting building blocks here.[9–20]

Biomaterials are defined as materials with usage in medicine for therapeutic, diagnostic or regenerative functions.[34–36] Among those, polymeric materials find many applications in, for example, drug delivery, tissue engineering, or as implants.[37–45] Though this definition is thus independent from the term 'Biopolymers', there is a large overlap, and many biopolymers find applications also as biomaterials (e.g., polylactide for sutures, or nanocellulose as matrix for 3D cell culture). It is known that

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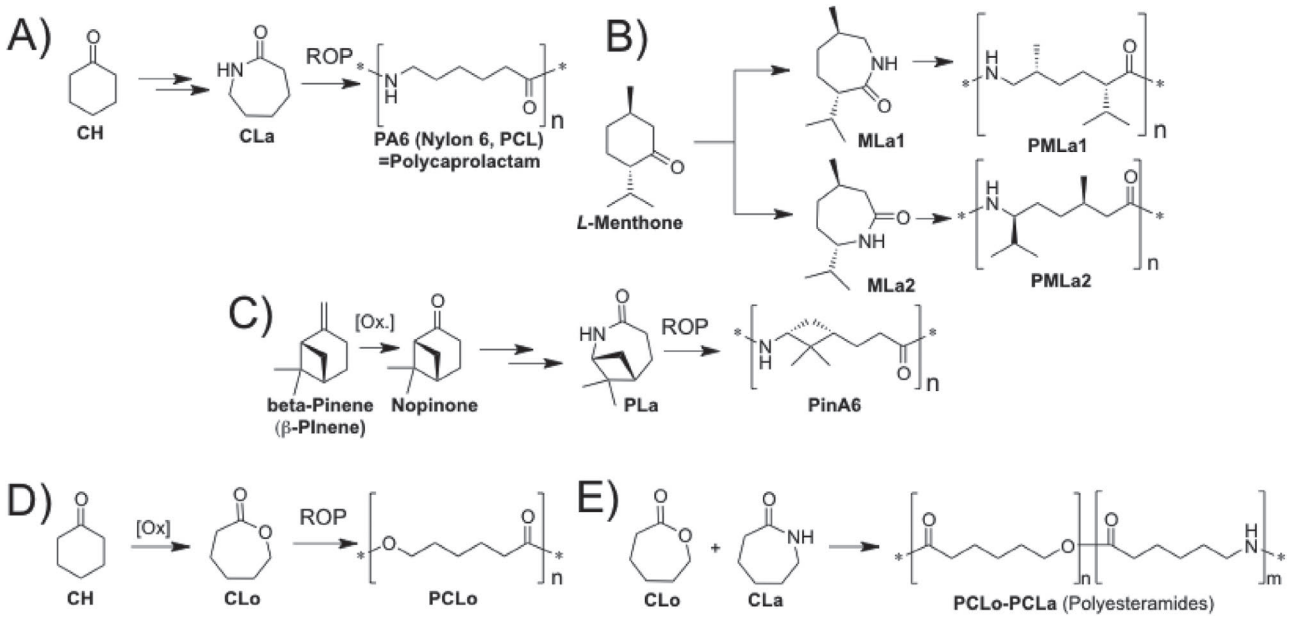


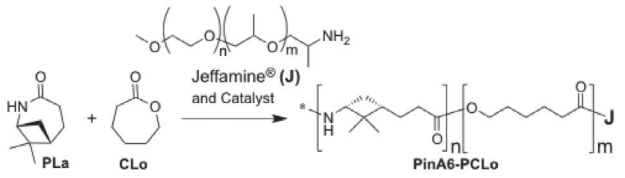
Scheme 1. A) Polyamide 6 (PA6, Nylon 6); B,C) Terpene-based PAs; D) Synthesis of polycaprolactone (PCLo); E) Polyesteramides via copolymerization of CLo and CLa.

many inherent material properties (nanotopography, stiffness, molecular flexibility, chemical functionality, degradability (and resulting byproducts), cell adhesivity and binding affinity) are very important for cell-material interactions and can influence cell behavior (adhesion, proliferation, clustering, ...), for example, by mimicking the biological extracellular matrix.[34,35,46,47]

2. Results amd Discussion

In this whole context, we investigated in this study the preparation and analysis of new terpene-based polyamide-polyester copolymers and copolyamides, as well as their properties. Aim of this study was thus the preparation of sustainable copolymers of several renewable lactams and/or lactones by means of different catalysts and initiators, as well as their analysis, which is the key novelty herein. This procedure remarkably extends the number, diversity, functionality and application fields of accessible terpene-based polymers. In comparison to other synthetic polymers for biomedical applications[48] (especially chemically or physically crosslinked polymer networks),[49,50] the outstanding advantages of polyesteramides are mainly the tunability of nearly all of their properties via their versatile monomer compositions as well as via their amide bond/ester bond ratios.

As it has turned out in some previous homo-polymerization studies[2–4] that the pinene-based lactam PLa polymerizes easier than MLa, we focused first on this lactam for the copolymerization with CLo (**Scheme 2**).[51] For the synthesis of these polyesteramides, Jeffamine (J) was used as (amino-)initiator to start the ring-opening of the cyclic monomers. It influences the polymerizations via an effective nucleophilic reaction with the cyclic monomers, followed by their ring-opening. Furthermore, it enables tunable hydrophilicity of the polymers and NMR end-group analysis of the polymer via integration of the signals.



Scheme 2. Copolymerization of PLa and CLo by means of Jeffamine.

We choose $SnOct_2$ as the main catalyst, which is also known from the effective homopolymerization of CLo due to its peculiarities—an effective coordination to the ester bond and prosperous solubility properties—and which afforded the best results herein, especially for longer polymerization times (24 h). Some experiments were also performed with the catalysts n-$Bu_2SnLaurate_2$ and with H_3PO_2, inspired by the previously described CLa/CLo copolymerization.[10] Different monomer ratios and conditions were applied and compared for the (random and block) copolymerization of the cyclic monomers (**Table 1** (only selected results are shown for space reasons) and Table S1, Supporting Information), and polymer analysis was performed by means of nuclear magnetic resonance (NMR) spectroscopy, gel permeation chromatography (GPC), thermogravimetric analysis and dynamic scanning calorimetry. Furthermore, homopolymers and block-copolymers were also synthesized. Some of these (co)polymers were shown to have defined glass transition temperatures (T_g; between –71.5 and +79.1 °C), dependent on the incorporated monomer ratios (Tables S1 and S2, Supporting Information). For the PEs, a clear melting point is much more obvious (due to their semicrystallinity) than for the mainly amorphous PEAs (Supporting Information). The polymers are stable, with decomposition temperatures above 325 °C (Supporting Information). It can also be seen that—as expected—CLo is incorporated a bit easier into the polymer than PLa due to its higher polymerizeability, as calculated from the ^{1}H NMR spectra. Various copolymers with good molecular weight could be obtained.

Table 1. Copolymerization (random) of PLa and CLo by means of the catalyst/initiator system $SnOct_2$/Jeffamine (J) or H_3PO_2: selected results.

Catalyst [mol%]	PLa: CLo [%]	[M/J]	Conditions[a)]	M_w/M_n	PA/PE[b)]
$SnOct_2$ (0.5)	Only PL	50	24 h, 250 °C	3091/2589[c)]	PinA6
$SnOct_2$ (0.25)	70:30	25	24 h, 250 °C	4815/3355	57/43
$SnOct_2$ (0.25)	70:30	50	24 h, 250 °C	4426/3131	65/35
$SnOct_2$ (0.5)	70:30	25	24 h, 250 °C	5272/3601	56/44
$SnOct_2$ (0.5)	70:30	50	24 h, 250 °C	4563/3266	59/41
$SnOct_2$ (0.25)	50:50	50	24 h, 250 °C	4179/3187	67/33
$SnOct_2$ (0.5)	50:50	25	24 h, 250 °C	4827/3189	19/81
$SnOct_2$ (0.25)	30:70	25	24 h, 250 °C	5224/3667	35/65
$SnOct_2$ (0.5)	30:70	25	24 h, 250 °C	6786/4399	14/86
$SnOct_2$ (0.5)	Only CLo	25	24 h, 250 °C	8983/5439	PCLo
nBu_2Sn $Laurate_2$	50:50	0.5	24 h, 250 °C	6820/4054	19/81
H_3PO_2 (0.25)	50:50	10	1 h, 250 °C	10 140/7840	86/14
H_3PO_2 (0.25)	50:50	10	2 h, 250 °C	15 520/10 500	83/17
H_3PO_2 (0.25)	50:50	10	8 h, 250 °C	16 500/11 200	71/29
H_3PO_2 (0.25)	50:50	10	8 h, 200 °C	9340/7200	86/14

[a)]also other times, temperatures etc. were tested; [b)]as calculated from ^{1}H-NMR-spectra; [c)]here exact, later rounded values.

The different T_gs (Supporting Information) show a clear correlation also to polymer length and composition, as for different polymers the amorphous regions are significantly altered, and higher polymer length lead to more semicrystallinity and (higher) melting points and/or T_g values. Generally, crystallinity is only partially present, but increases with increasing lactam ratio, and—therefore—there is a difference for random and block polymer structures. Remarkably, heating together with $SnOct_2$ oligomerizes also pinene lactam (PLa) alone, which is—to the best of our knowledge—new for lactam polymerization, that is normally performed via anionic or cationic methods. Applying no catalyst resulted—if any—only in little formation of short oligomers. Determination of the incorporated lactam/lactone ratios was done via ^{1}H-NMR spectroscopy by means of the integrations of characteristic signals of the polyamide and—respectively—the polyester moieties (**Figure 1** and Figures S1–S16, Supporting Information—possible only in these spectra where the decisive signals are not affected by too much signal overlap).

In another series, polymerizations were performed with the menthone-based regioisomeric lactams MLa1 and MLa2

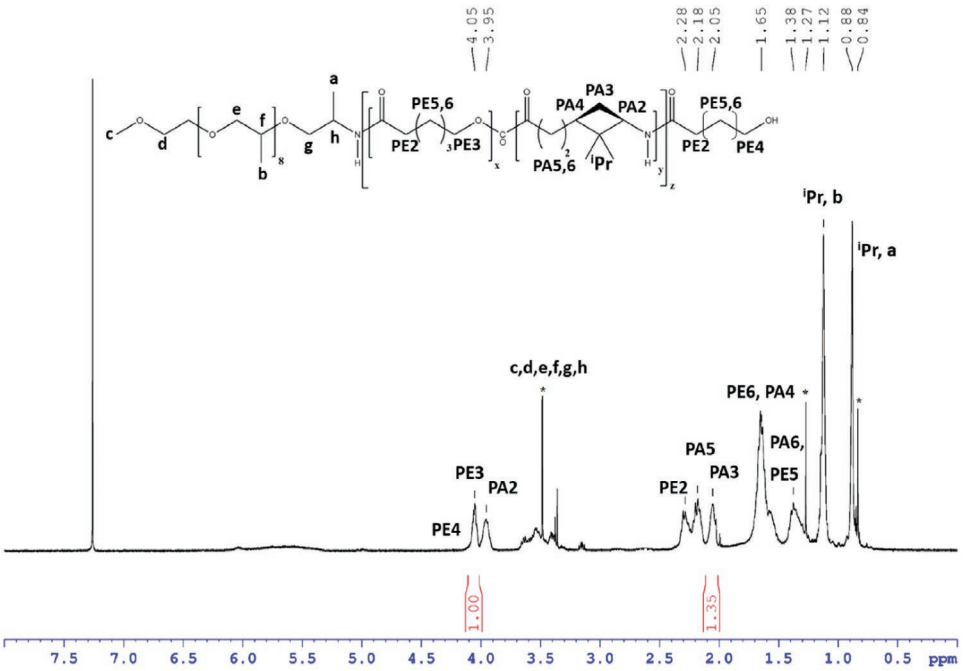
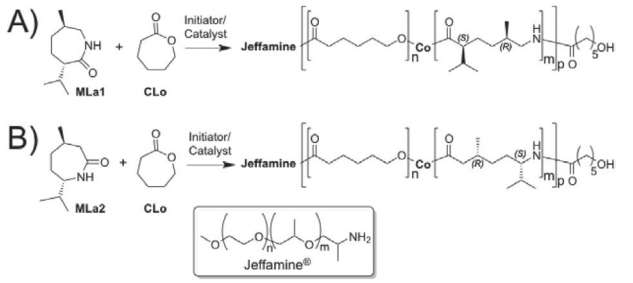
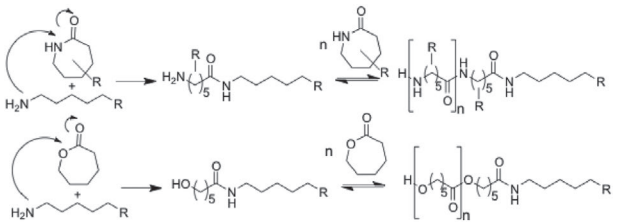


Figure 1. ^{1}H-NMR spectrum of a copolymer PinA6-PCLo (Table 1, entry 2).



Scheme 3. Copolymerizations of terpene-based lactams MLa1 and MLa2 with CLo. ("Co" means random copolymer).



Scheme 4. Aminolytic polymerization of lactams/lactones.

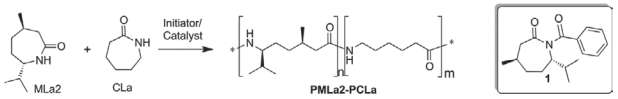
(which is easier available than MLa1[3]) and again CLo as the lactone (**Scheme 3**). Also here, the integration of the NMR signals afforded the incorporated lactam/lactone rations in the polymers.

Due to its easier availability, MLa2 is even more interesting for the copolymerization with lactones. Several conditions were tested, and copolymers with good MW (up to $\approx 1.3 \times 10^4$) were obtained, purified by washing or precipitation and analyzed by, for example, NMR and GPC as described above (**Table 2** and Supporting Information). In addition, copolymerizations of CLa and CLo (above, Scheme 1E) and also homopolymerizations of the monomers were performed for comparison (Supporting Information). Interestingly, polymerization also occurs without initiator, but—as expected—with less efficiency; this fact can be attributed to the mechanism as described, where—in addition to the aminolytic ring-opening (**Scheme 4**)—hydrolytic opening (for example, aqueous H_3PO_2) and/or polycondensation reactions can occur. For MLa1, H_3PO_2 was found to be the most effective catalyst with similar efficiency as for MLa2 (Table S3, Supporting Information). Therefore, also a polylactone formation can occur, followed by the lactam polymerization, which can lead to block copolymers, but also to broader molar mass distributions.

For the copolymerizations of menthone-derived lactams (MLa) and ε-caprolactam (CLa), similar tendencies were observed for the monomer incorporation, and—as expected—the lactams show different reactivity. Different polymerization series were performed to evaluate various conditions. Here—among several catalysts—NaH was found to work out best. This copolymerization was also performed in sealed vials and resulted in a variety of interesting copolyamides (**Scheme 5**).

When using vials that are not pre-heated and without benzoylated co-initiator (1), barely polymers where formed, while the application of the co-initiator yielded oligomers in small amounts (argon, NaH 60% in oil). As expected, the best results were obtained under argon (adding the compound in glovebox) with preheated vials, pure/washed NaH and with co-initiator (1). Table S4, Supporting Information summarizes some of the most representative results of these copolymerizations. For these copolyamides, yield could first be determined roughly from GPC/SEC data—later, selected samples were purified and further analyzed, for example, by means of GPC and resonance (NMR, selected samples; **Figure 2**). Also here, the ratio of the incorporated monomers was calculated from characteristic signals in the ^{1}H-NMR spectrum. Homopolymerizations were also performed for comparison (Table S4, Supporting Information), and the procedure could be improved with regards to yield and efficiency compared to previous homopolymerization studies.[4] XRD experiments show that these copolymers are semicrystalline with a remarkably degree of crystallinity (Supporting Information).

In general, the further modification of suchlike polymers by, for example, the introduction of hydrophilic PEG (PEGylation) or additional functionalities is important for



Scheme 5. Copolymerization of the terpene-based lactam MLa2 with CLa.

Table 2. Copolymerization (random) of MLa2 and CLo: selected results.

	Initiator	Conditions	M_n/M_w kDa [$\times 10^3$ g mol^{-1}]	PDI	Yield [%]	Comments
1	–	4 h, 250 °C	3.6/6.5	1.8	42	Plus by-products
2	$SnOct_2$	4 h, 250 °C	4.5/9.3	2.1	15	PE/PA[a)] 3:2
3	$SnOct_2$	4 h, 150 °C	6.3/9.6	1.5	88	n.d.
4	$SnOct_2$	4 h, 200 °C	7.8/9.6 (+x)[b)]	1.2	99	Plus by-products
5	H_3PO_2	1 h, 250 °C	8.3/11.0	1.3	35	PE/PA 6:1
6	H_3PO_2	2 h, 250 °C	4.2/13.1	3.0	35	6:1
7	H_3PO_2	4 h, 250 °C	5.9/8.1	1.4	45	7:2
8	H_3PO_2	7 h, 250 °C	6.8/8.8	1.3	75	7:2

[a)]Determined from NMR; [b)]plus by-products in GPC.[51]

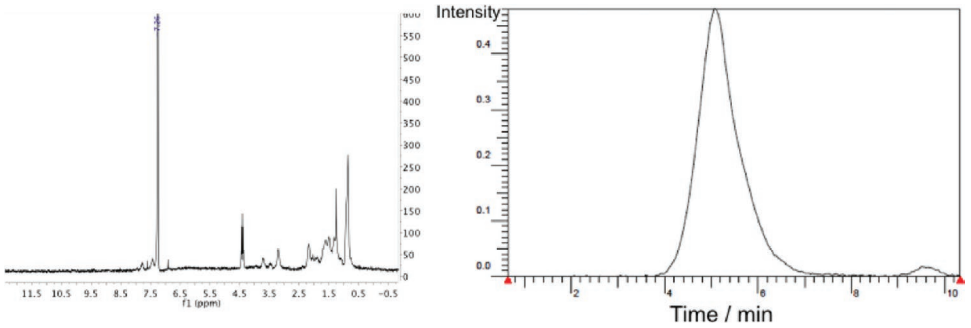


Figure 2. ^{1}H-NMR spectrum (left) and GPC elugram (right) of a copolymer PMLa2-PCLa.[51] Reprinted with permission from DECHEMA e. V..

(bio)medical applications. Therefore, PEGylation was investigated herein in brief, and some blends with PEG were prepared with polyamide PinA6, which were solvent-casted into well plates. In comparison to a recently described solvent casting technique,[18] slower casting leads to surfaces with much better regularity (Supporting Information). Then, HaCat cells were seeded onto them, incubated for a certain time (1 and 2 days) and then investigated via, for example, light microscopy and viability assays (e.g., with MTT, a tetrazolium salt (dye) which is metabolized to the corresponding formazan compound only by living cells; hence, absorption directly correlates with cell viability). Interestingly, cell attachment and viability on the PinA6/PEG blends are very good, get better with increasing PEG content and can also be influenced via surface composition and roughness (**Figure 3** and Figure S96, Supporting Information). The relation between cell movement and clustering and surface properties shows qualitatively that a higher PEG-mediated hydrophilicity leads to enhanced cell clusters.

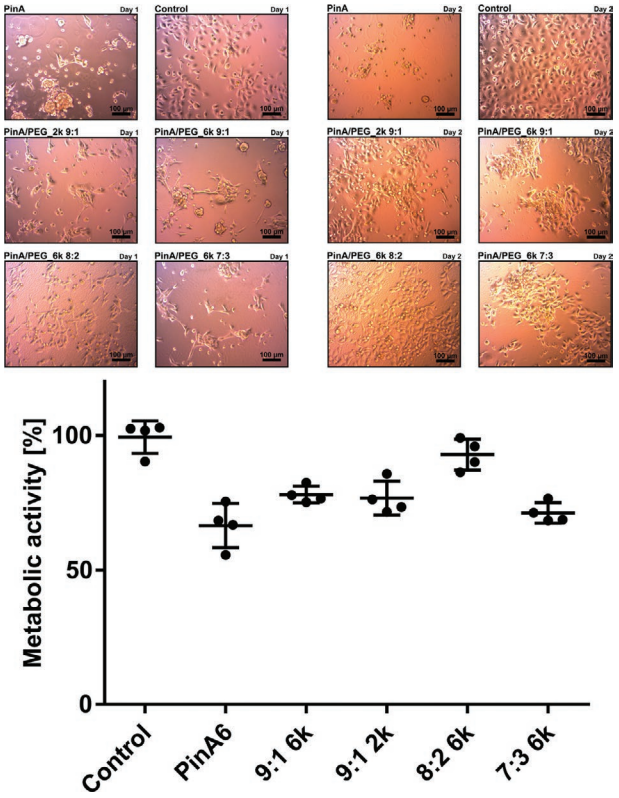


Figure 3. Cell attachment after 1 day and after 2 days (above, left, and right) as well as viability tests (below) of HaCat cells on different PinA6/PEG surfaces (blends). For further figures see Supporting Information.

Investigation of cell attachment on, for example, the menthone-based copolymers require different solvent casting techniques, and it was recognized in initial tests that these have completely different surface structures with different effects on cells (Supporting Information). Detailed elucidations of particularly those interactions would be beyond the scope of this communication and are thus topic of ongoing investigations.

As an idea for explaining cell adhesion and clustering, the surface structures especially with regards to roughness and furrows are decisive factors, due to their direct effects on specific cell receptors, which is also in agreement with previous studies.[35,37] Cells tend to adhere better on rough surfaces. The strong dependence of adhesion on PEG-content here is a new finding, and also clustering is promoted by additional PEG.

In general, the nanotopography of many of these polymer surfaces shows a rough, sometimes wavy structure in scanning electron microscopy (SEM, REM), with correlations, for example, to their stiffness. Also lines of different widths can be observed. This is dependent on the exact composition and the preparation procedure, for example, the solvent or the evaporation time during preparation by solvent casting (**Figure 4**; also see Supporting Information).

For the testing of mechanical properties, several specimens of some of the solid polymers could be produced, that show strength, but also a brittle behavior (Supporting Information). For instance, a tension (σ) of 12.3 MPa was measured for one of these samples together with an elongation of only about 1%. The different molecular weight obtained by different preparation conditions affect the mechanical properties of the polymers as shown in the Supporting Information, and additional relations are currently under investigations. Of course, suchlike values show that these specific copolyamides are stiff compared to mechanically heterogeneous bio tissues (e.g., the Young's modulus of skin could cover the range 0.01–102 MPa, and the tensile modulus of tendon to bone can cover about 0.45–20 GPa[52–54]) and their versatile functions.[55,56] therefore, applications as, for example, loadable components are more obvious in this case. However, especially as blends they are also very suitable for cell culturing, for example, due to their excellent biocompatibility as well as the tunable hydrophilicity and cell adhesivity of their versatile surfaces (see also introduction).

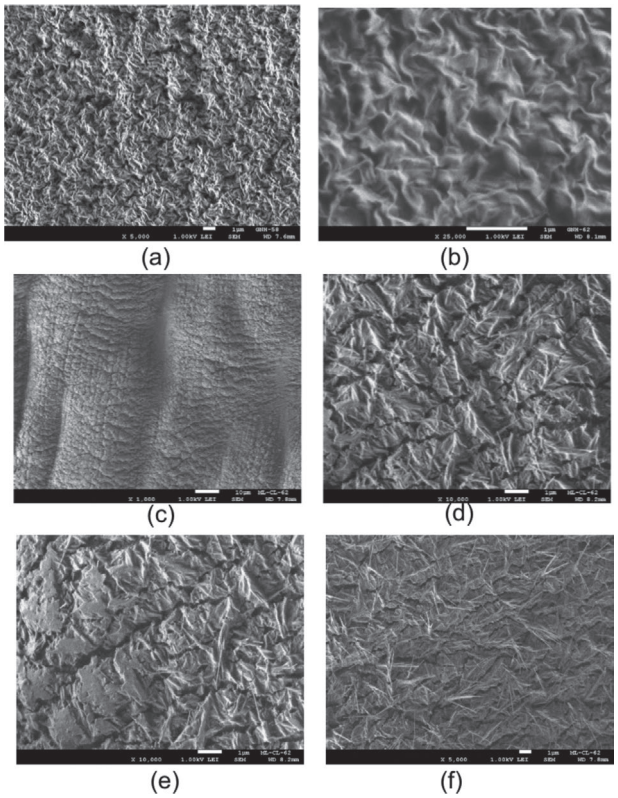


Figure 4. SEM images of different structures present on neat (co)polyamide surfaces at different scales (also see Supporting Information): PinA6: a) overview rough surface; b) furrows of different sizes; PMLa-PCLa c) overview, d) dominant polymer structures, e) flattened shape, and f) other remaining residues for comparison. Scale bars: white bars right below.

Additional toughening or also plasticizing could be achieved via, for example, additional blending or with softeners, which is beyond the scope of this study and thus topic of ongoing investigations. For a preliminary correlation of thermal and mechanical properties, higher T_g and T_m values, for example, lead to better stability.

3. Conclusion

To conclude, in this study, we have successfully prepared and analyzed a series of novel biopolymers based on different terpene-derived lactams. These investigated cyclic monomers can be used for the synthesis of different copolymers and are incorporated into the polymer chains with different efficiency and ratios. In comparison to previous studies on homopolymerizations, also polymerization yields and quantities could be remarkably improved. Due to the variety of building blocks and possible reactions as described above, a polymer library to solve a series of problems and requirements can be established.[57–59] For lactam/lactone copolymerizations, the Sn-catalysts mediated polymerization is most efficient, while for lactam (co)polymerization the anionic polymerization by means of NaH works out best here. Also temperatures and time play important roles for the results of these reactions with regards to molecular weights and yields. A further expansion of these approaches is ongoing: for instance, more than two monomer types and additional end groups could enhance the functionalities of these polymers. Due to several prosperous properties, some of the polymers can also be applied as surfaces for directed cell-material interactions. For this, we have also performed several cell tests and showed the suitability of these biomaterials for the convenient regulation of cell adhesion, clustering and growth. Further suchlike studies, also with other polymer scaffolds like, for example, fibers, are ongoing, as well as additional investigations of the mechanical properties and the biodegradability. For instance, an additional introduction of stimuli-responsiveness into such copolymers, which can already be accomplished by means of polyethylene glycol, could establish detecting and sensing applications, and also a transfer to drug delivery systems is imaginable. This will also give further insights into the life cycles of these polymers.

4. Experimental Section

All experimental details are explained in the Supporting Information.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cell-material interactions, polyesteramides, ring-opening polymerization, sustainable polymers, terpenes

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[1] K. Marchildon, *Macromol. React. Eng.* **2011**, *5*, 22.
[2] M. Winnacker, J. Sag, *Chem. Commun.* **2018**, *54*, 841.
[3] M. Winnacker, B. Rieger, *Macromol. Rapid Commun.* **2016**, *37*, 1391.
[4] a) M. Winnacker, M. Neumeier, X. Zhang, C. M. Papadakis, B. Rieger, *Macromol. Rapid Commun.* **2016**, *37*, 851; b) M. Winnacker, S. Vagin, V. Auer, B. Rieger, *Macromol. Chem. Phys.* **2014**, *215*, 1654.
[5] D. H. Lamparelli, V. Paradiso, F. Della Monica, A. Proto, S. Guerra, L. Giannini, C. Capacchione, *Macromolecules* **2020**, *53*, 1665.
[6] a) A. Gandini, T. M. Lacerda, A. J. F. Carvalho, E. Trovatti, *Chem. Rev.* **2016**, *116*, 1637; b) M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem., Int. Ed.* **2002**, *41*, 414.

[7] S. A. Miller, *ACS Macro Lett.* **2013**, *2*, 550.
[8] R. A. Sheldon, *Green Chem.* **2014**, *16*, 950.
[9] K. Yao, C. Tang, *Macromolecules* **2013**, *46*, 1689.
[10] W. Farhat, A. Stamm, M. Robert-Monpate, A. Biundo, P.-O. Syrén, *Z. Naturforsch., C: J. Biosci.* **2019**, *74*, 91.
[11] O. Hauenstein, S. Agarwal, A. Greiner, *Nat. Commun.* **2016**, *7*, 11862.
[12] D. Dakshinamoorthy, A. K. Weinstock, K. Damodaran, D. F. Iwig, R. T. Mathers, *ChemSusChem* **2014**, *7*, 2923.
[13] P. N. Stockmann, D. van Opdenbosch, A. Poethig, D. L. Pastoetter, M. Hoehenberger, S. Lessig, J. Raab, M. Woelbing, C. Falcke, M. Winnacker, C. Zollfrank, H. Strittmatter, V. Sieber, *Nat. Commun.* **2020**, *11*, 509.
[14] a) P. N. Stockmann, D. L. Pastoetter, M. Woelbing, C. Falcke, M. Winnacker, H. Strittmatter, V. Sieber, *Macromol. Rapid Commun.* **2019**, *40*, 1800903; b) C. Falcke, H. Strittmatter, M. Woelbing, V. Sieber, DE *102014221061 A1*, **2016**.
[15] M. R. Thomsett, T. E. Storr, O. R. Monaghan, R. A. Stockman, S. M. Howdle, *Green Mater.* **2016**, *4*, 115.
[16] M. Naddeo, A. Buonerba, E. Luciano, A. Grassi, A. Proto, C. Capacchione, *Polymer* **2017**, *131*, 151.
[17] F. Auriemma, C. De Rosa, M. R. Di Caprio, R. Di Girolamo, W. Chadwick Ellis, G. W. Coates, *Angew. Chem., Int. Ed.* **2015**, *54*, 1215.
[18] a) M. Winnacker, A. Tischner, M. Neumeier, B. Rieger, *RSC Adv.* **2015**, *5*, 77699; b) M. Winnacker, B. Rieger, *ChemSusChem* **2015**, *8*, 2455.
[19] a) M. Winnacker, *Angew. Chem., Int. Ed.* **2018**, *57*, 14362; b) J. Zhao, H. Schlaad, *Adv. Polym. Sci.* **2013**, *253*, 151.
[20] Y. Zhu, C. Romain, C. K. Williams, *Nature* **2016**, *540*, 354.
[21] a) H. K. Hall, Jr., *J. Org. Chem.* **1963**, *28*, 3213; b) H. K. Hall, Jr., M. K. Brandt, R. M. Mason, *J. Am. Chem. Soc.* **1958**, *80*, 6420.
[22] M. J. Figueira, J. M. Blanco, O. Caamanõ, F. Fernández, X. García-Mera, C. López, G. Andrei, R. Snoeck, E. Padalko, J. Neyts, J. Balzarini, E. De Clercq, *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 348.
[23] a) W. H. Carothers, G. J. Berchet, *J. Am. Chem. Soc.* **1930**, *52*, 5289; b) M. Imoto, H. Sakurai, T. Kono, *J. Polym. Sci.* **1961**, *50*, 467.
[24] K. Ghosal, M. S. Latha, S. Thomas, *Eur. Polym. J.* **2014**, *60*, 58.
[25] A. C. Fonseca, M. H. Gil, P. N. Simões, *Prog. Polym. Sci.* **2014**, *39*, 1291.
[26] P. Garg, D. Klee, H. Keul, M. Möller, *Macromol. Mater. Eng.* **2009**, *294*, 679.
[27] M. Winnacker, B. Rieger, *Polym. Chem.* **2016**, *7*, 7039.
[28] D. Newman, E. Laredo, A. Bello, P. Dubois, *Macromolecules* **2014**, *47*, 2471.
[29] G. Deshayes, C. Delcourt, I. Verbruggen, L. Trouillet-Fonti, F. Touraud, E. Fleury, P. Degée, M. Destarac, R. Willem, P. Dubois, *Macromol. Chem. Phys.* **2009**, *210*, 1033.
[30] R. Mülhaupt, *Macromol. Chem. Phys.* **2013**, *214*, 159.
[31] A. Llevot, P.-K. Dannecker, M. von Czapiewski, L. C. Over, Z. Söyler, M. A. R. Meier, *Chem. - Eur. J.* **2016**, *22*, 11510.
[32] M. A. Hillmyer, W. B. Tolman, *Acc. Chem. Res.* **2014**, *47*, 2390.
[33] P. T. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301.
[34] W. L. Murphy, T. C. McDevitt, A. J. Engler, *Nat. Mater.* **2014**, *13*, 547.
[35] R. Langer, *Nat. Mater.* **2009**, *8*, 444.
[36] L. Liverani, N. Raffel, A. Fattahi, A. Preis, I. Hoffmann, A. R. Boccaccini, M. W. Beckmann, R. Dittrich, *Sci. Rep.* **2019**, *9*, 1150.
[37] A. J. T. Teo, A. Mishra, I. Park, Y.-J. Kim, W.-T. Park, Y.-J. Yoon, *ACS Biomater. Sci. Eng.* **2016**, *2*, 454.
[38] a) T. M. Reineke, *ACS Macro Lett.* **2016**, *5*, 14; b) P. H. Seeberger, T. Carell, *Curr. Opin. Chem. Biol.* **2003**, *7*, 715.
[39] M. Winnacker, B. Rieger, *Polym. Int.* **2017**, *66*, 497.
[40] M. Winnacker, A. J. G. Beringer, T. F. Gronauer, H. H. Güngör, L. Reinschlüssel, B. Rieger, S. A. Sieber, *Macromol. Rapid Commun.* **2019**, *40*, 1900091.
[41] M. Winnacker, *Biomater. Sci.* **2017**, *5*, 1230.
[42] V. Dave, A. Gupta, P. Singh, C. Gupta, V. Sadhu, K. R. Reddy, *Nano-Struct. Nano-Objects* **2019**, *18*, 100288.
[43] H. Manisha, P. D. Priya Swetha, Y.-B. Shim, K. Sudhakara Prasad, *Nano-Struct. Nano-Objects* **2019**, *20*, 100391.
[44] R. Hindumathi, M. Jagannatham, P. Haridoss, C. P. Sharma, *Nano-Struct. Nano-Objects* **2018**, *13*, 30;
[45] K. Nagase, T. Okano, H. Kanazawa, *Nano-Struct. Nano-Objects* **2018**, *16*, 9.
[46] R. Augustine, P. Dan, A. Sosnik, N. Kalarikkal, N. Tran, B. Vincent, S. Thomas, P. Menu, D. Rouxel, *Nano Res.* **2017**, *10*, 3358.
[47] J. Thomas, S. Thomas, J. Jose, N. Kalarikkal, *Recent Trends in Nanomedicine and Tissue Engineering*, River Publishers, Denmark **2017**.
[48] J. L. Guo, Y. Seon Kim, A. G Mikos, *Biomacromolecules* **2019**, *20*, 2904.
[49] Y. S. Zhang, A. Khademhosseini, *Science* **2017**, *356*, eaaf3627.
[50] Y. Ma, M. Lin, G. Huang, Y. Li, S. Wang, G. Bai, T. Jian Lu, F. Xu, *Adv. Mater.* **2018**, *30*, 1705911.
[51] See also the report to the funding agency: M. Winnacker, DECHEMA-Report, Max-Buchner-Forschungsstipendium, **2019**.
[52] F. Xu, T. Wen, T. J. Lu, K. A. Seffen, *J. Mech. Behav. Biomed. Mater.* **2008**, *1*, 172.
[53] K. Franze, P. A. Janmey, J. Guck, *Annu. Rev. Biomed. Eng.* **2013**, *15*, 227.
[54] L. Rossetti, L. A. Kuntz, E. Kunold, J. Schock, K. W. Müller, H. Grabmayr, J. Stolberg-Stolberg, F. Pfeiffer, S. A. Sieber, R. Burgkart, A. R. Bausch, *Nat. Mater.* **2017**, *16*, 664.
[55] A. J. Engler, S. Sen, H. L. Sweeney, D. E. Discher, *Cell* **2006**, *126*, 677.
[56] a) J. K. Leach, J. Whitehead, *ACS Biomater. Sci. Eng.* **2018**, *4*, 1115; b) G. Huang, F. Li, X. Zhao, Y. Ma, Y. Li, M. Lin, G. Jin, T. J. Lu, G. M. Genin, F. Xu, *Chem. Rev.* **2017**, *117*, 12764.
[57] S. R. Ghaemi, B. Delalat, S. Gronthos, M. R. Alexander, D. A. Winkler, A. L. Hook, N. H. Voelcker, *ACS Appl. Mater. Interfaces* **2018**, *10*, 38739.
[58] K. Li, V. Kardelis, A. Adronov, *J. Polym. Sci., Part A: Polym. Chem.* **2018**, *56*, 2053.
[59] P. Zhang, D. Gao, K. An, Q. Shen, C. Wang, Y. Zhang, X. Pan, X. Chen, Y. Lyv, C. Cui, T. Liang, X. Duan, J. Liu, T. Yang, X. Hu, J.-J. Zhu, F. Xu, W. Tan, *Nat. Chem.* **2020**, *12*, 381.