Technische Universität München
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Novel β-Pinene- and Limonene-Based Biopolymers: Their Synthesis, Characterization, and Tailoring to Potential Applications in Biomedicine

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“Muss ja…” – Tim & Lukas

“The road and the tale have both been long, would you not say so? The trip has been long and the cost has been high...but no great thing was easily attained. A long tale, like a tall Tower, must be built a stone at a time.”

Stephen King – The Dark Tower

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List of Publications

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M. M. Kleybolte, L. Zainer, J. Y. Liu, P. N. Stockmann, M. Winnacker, (+)-Limonene-Lactam: Synthesis of a Sustainable Monomer for Ring-Opening Polymerization to Novel, Biobased Polyamides, *Macromol. Rapid Commun.,* **2022**, 43, 2200185. (DOI:10.1002/marc.202200185)

M. M. Kleybolte, M. Winnacker, From Forest to Future: Synthesis of Sustainable High Molecular Weight Polyamides Using and Investigating the AROP of *β*-Pinene Lactam, *Macromol. Rapid Commun.,* **2024**, 45, 2300524. (DOI:10.1002/marc.202300524)

Submitted Publications

M. M. Kleybolte, C. P. Vogt, M. Winnacker, High Precision Tuning of Limonene Polyamide via Side-Chain Functionalization for Specialized Applications, **2024**, *submitted.*

Publications exceeding this work

D.H. Lamparelli, **M. M. Kleybolte**, M. Winnacker, C. Capacchione, Sustainable Myrcene-Based Elastomers via a Convenient Anionic Polymerization, *Polymers,* **2021**, 13, 838. (DOI:10.3390/polym13050838)

F. Niknam, V. Capaccio, **M. Kleybolte**, D. H. Lamparelli, M. Winnacker, G. Fiorani, C. Capacchione, [OSSO]-Type Chromium(III) Complexes for the Reaction of CO_2 with Epoxides, *ChemPlusChem,* **2022**, 87, e202200038. (DOI:10.1002/cplu.202200038)

Conference Contributions

M. M. Kleybolte, M. Winnacker, Sustainable terpene-based polyamides and their co-polymers as potential biocompatible high performance polymers, ACS Spring 2022, American Chemical Society, **2022**, San Diego, *oral presentation*.

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M. M. Kleybolte, M. Winnacker, Combining sustainability, biocompatibility, and tunability in terpene-based polyesteramides for medical application, validated by cell tests, 9th International Conference on Mechanics of Biomaterials and Tissues, Elsevier, **2023**, Hawaii

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I. Abstract

Polyamides (PAs) are an important class of polymers due to their exceptional mechanical properties, thermal stability, and chemical resistance. However, conventional PAs prepared from fossil-based feedstocks face limitations in terms of structural diversity and sustainable production. Fossil resources are finite, and their extraction and processing contribute to various environmental problems. Furthermore, there is a growing need for innovative materials for specialty applications to meet the needs of modern society, especially in the field of biomedicine. Biomaterials, i.e. bio-PAs and their co-polymers, derived from renewable biomass, offer a sustainable solution by addressing environmental concerns and introducing unique structures for tailored properties.

This work explores the synthesis and strategic design of bio-based materials derived from renewable terpene monomers. The overarching objective is to develop a comprehensive framework encompassing the establishment of efficient monomer synthesis, the polymerization of sustainable bio-PAs, and the adaptation of polymer properties through copolymerization and strategic functionalization. Particular emphasis is placed on investigating potential biomedical applications.

The research begins by identifying the terpenes, limonene, and β-pinene as abundant and structurally advantageous starting materials for lactam modification and subsequent polymerization. Efficient synthesis routes for their respective lactams are established and optimized, meeting industrial scalability and applicability. The unique structural features of these monomers, such as the bicyclic nature of β-pinene and the exo-cyclic double bond in limonene, hold the promise to impart stability or functionalizability into the resulting polymers. Anionic ring-opening polymerization (AROP) is employed for the controlled synthesis of high molecular weight limonene polyamide (**LiPA**) and β-pinene polyamide (**PiPA**). Challenges posed by steric hindrance and side reactions are addressed through the judicious selection of initiators and activators. Upscaling to gram quantities is achieved, enabling thorough material characterization and processing. The resulting **PiPA**s exhibit excellent thermal stability, good mechanical properties, and transparent appearance, while **LiPA**s possess not only good thermal stability but also functionalizability, rendering both PAs promising for high-performance/bio-applications.

To combine the strengths of PAs, e.g. high thermal and mechanical stability, and the strengths of polyesters, e.g. biocompatibility, ring-opening copolymerization (ROCOP) of β-pinene lactam and ε-caprolactone is investigated, yielding polyesteramides (PEAs) with tunable properties, such as solubility and brittleness, and high thermal stability.
Recognizing the potential of **LiPA** for biomedical applications, thiol-ene click chemistry is employed to introduce various functional groups, including alkyl, ester, and sulfonate moieties. This strategic modification enables the tuning of glass transition temperature, solubility, hydrophilicity, and even the formation of amphiphilic micelles for potential drug delivery applications. The high tolerance of the thiol-ene reaction towards diverse functional groups opens avenues for future incorporation of bioactive moieties, such as cell-binding motifs for tissue engineering.

While the findings are highly promising, further investigations are necessary to address challenges like poor solubility, processability, and evaluating specific biomedical applications through cell tests. Nevertheless, this thesis contributes significantly to the field of sustainable materials science by introducing novel monomers, polymers, and a versatile functionalization approach, ultimately paving the way for innovative and environmentally conscious solutions in biomedicine and beyond.

II. Zusammenfassung

Polyamide (PAs) sind aufgrund ihrer außergewöhnlichen mechanischen Eigenschaften, ihrer thermischen Stabilität und ihrer chemischen Beständigkeit eine wichtige Polymerklasse. Konventionelle PAs, die aus Erdöl hergestellt werden, stoßen jedoch bezüglich ihrer strukturellen Vielfalt und nachhaltigen Produktion, an ihre Grenzen. Fossile Ressourcen sind nicht nur endlich, sondern ihre Gewinnung und Verarbeitung tragen zu verschiedenen Umweltproblemen bei. Darüber hinaus besteht ein wachsender Bedarf an innovativen Materialien. speziell für die Bedürfnisse und Probleme einer modernen Gesellschaft, insbesondere im Bereich der Biomedizin. Biomaterialien, d. h. Bio-PAs und ihre Co-Polymere, die aus erneuerbarer Biomasse gewonnen werden, bieten eine nachhaltige Lösung, indem sie Umweltprobleme umgehen und besondere Strukturen für anpassbare Eigenschaften einführen können.

Diese Arbeit befasst sich mit der Synthese und dem strategischen Design von biobasierten Materialien, die aus erneuerbaren Terpenmonomeren gewonnen werden. Das übergeordnete Ziel ist die Entwicklung eines umfassenden Konzepts, das die Etablierung einer effizienten Monomersynthese, die Polymerisation von nachhaltigen Bio-PAs und die Anpassung der Polymereigenschaften durch Copolymerisation und strategische Funktionalisierung umschließt. Besonderes Augenmerk wird dabei auf die Untersuchung potenzieller biomedizinischer Anwendungen gelegt.

Der Anfang der Forschung stellt die Identifizierung der Terpene, Limonen und β-Pinen als reichlich vorhandene und strukturell vorteilhafte Ausgangsstoffe für die Lactam-Modifikation und anschließende Polymerisation, dar. Effiziente Syntheserouten für die jeweiligen Lactame werden etabliert und für eine industrielle Skalierbarkeit und Anwendbarkeit optimiert. Die einzigartigen strukturellen Merkmale dieser Monomere, wie die bicyclische Natur von β-Pinen und die exo-cyclische Doppelbindung in Limonen, versprechen Stabilität oder Funktionalisierbarkeit für die resultierenden Polymeren.

Für die kontrollierte Synthese von hochmolekularem Limonenpolyamid (**LiPA**) und β-Pinenpolyamid (**PiPA**) wird vorzugsweise die anionische Ringöffnungspolymerisation (AROP) eingesetzt. Die Herausforderungen durch sterische Hindernisse und Nebenreaktionen werden durch die sorgfältige Auswahl von Initiatoren und Aktivatoren bewältigt und ein Upscaling auf Grammmengen erreicht, was eine gründliche Materialcharakterisierung und Verarbeitung ermöglicht. Die resultierenden **PiPA**s zeichnen sich durch eine ausgezeichnete thermische

Stabilität, gute mechanische Eigenschaften und ein transparentes Aussehen aus, während **LiPA**s nicht nur eine gute thermische Stabilität aufweisen, sondern auch funktionalisierbar sind, was beide PAs vielversprechend für Hochleistungs-/Bioanwendungen macht.

Um die Stärken von PAs, z. B. hohe thermische und mechanische Stabilität, mit den Stärken von Polyestern, z. B. Biokompatibilität, zu kombinieren, wird die Ringöffnungscopolymerisation (ROCOP) von β-Pinenlactam und ε-Caprolacton für die Synthese von Polyesteramiden (PEAs) mit einstellbaren Eigenschaften wie Löslichkeit und Sprödigkeit sowie hoher thermischer Stabilität untersucht und eingesetzt. Angesichts des Potenzials von **LiPA** für biomedizinische Anwendungen wird die Thiol-En-Click-Chemie eingesetzt, um verschiedene funktionelle Gruppen wie Alkyl-, Ester- und Sulfonatgruppen einzuführen. Diese strategische Modifikation ermöglicht die Einstellung der Glasübergangstemperatur, der Löslichkeit, der Hydrophilie und sogar die Bildung von amphiphilen Mizellen für potenzielle pharmazeutische Anwendungen. Die hohe Toleranz der Thiol-En-Reaktion gegenüber verschiedenen funktionellen Gruppen eröffnet die Möglichkeit einer Funktionalisierung mit bioaktiven Komponenten, wie z. B. zellbindenden Motiven für das Tissue Engineering.

Obwohl die genannten Ergebnisse vielversprechend sind, sind weitere Untersuchungen erforderlich, um Probleme wie schlechte Löslichkeit und Verarbeitbarkeit zu lösen und spezifische biomedizinische Anwendungen durch Zelltests zu evaluieren und zu ermöglichen. Dennoch leistet diese Arbeit durch die Einführung neuer Monomere, Polymere und einen vielseitigen Funktionalisierungsansatz einen wichtigen Beitrag zum Bereich der nachhaltigen Materialwissenschaften und ebnet letztlich den Weg für innovative und umweltbewusste Lösungen in vielen Bereichen, wie in der Biomedizin.

1. Introduction – The Rise of Biopolyamides

The History of Polyamides – A Pioneering Polymer Class That Shaped Our World

In the ever-evolving landscape of polymer science, few polymers have left an indelible mark quite like the class of polyamides (PAs). From the groundbreaking discovery of Nylon 66 by Carothers (DuPont) in 1935 [1], these remarkable materials have woven themselves into the fabric of modern life. PAs have found extensive utility across diverse sectors, including textiles, automotive manufacturing, packaging, and medicine, earning global recognition and widespread use. Their exceptional mechanical strength, high degradation temperatures, and high resistance to a broad spectrum of chemicals, including organic solvents, acids, and bases, stem from very strong hydrogen bonding among the amide groups (-CONH-), rendering them ideal for applications requiring durability and resilience. Furthermore, the popularity of conventional synthetic PAs is underscored by their low-cost mass production. Crude oil-derived monomers, such as ε-caprolactam for Nylon 6, enable the production of cheap materials for everyday – and often single – use.[2]

The Limitations of Fossil-Based Polymers: Sustainability and Structural Novelty

Despite their wide-ranging success, conventional synthetic PAs face an uncertain future due to their reliance on fossil resources and environmental impact. One pressing concern is the sustainability and long-term availability of crude oil-based starting materials. Fossil resources are finite, and their extraction and processing contribute to greenhouse gas emissions and other environmental issues. Additionally, the price volatility of crude oil can significantly impact the cost of PA production. Moreover, common homo-PAs such as nylon-6 and nylon-6,6 are not readily biodegradable in natural environments, thereby posing substantial disposal challenges and exacerbating the accumulation of plastic waste in landfills and oceans.[2,3]

Beyond these environmental and economic considerations, the most significant challenge with fossil-based polymers lies in their limited access to structurally diverse monomers. This limitation arises from the inherent properties of petrochemical feedstocks and established polymerization techniques, making the introduction of structural novelty synthetically complex and economically challenging. Yet, the growing demand for materials tailored to modern needs in tandem with technological advancements necessitates materials with unique structural properties and functionalities.[4] Especially in the field of biomedicine, structural novelty for developing advanced materials inherits a critical role. Polymers with specific molecular architectures, functional groups, or stereochemical features can interact with biological systems in unique ways, enabling targeted drug delivery, improved biocompatibility, or tailored

biodegradation profiles. Moreover, stimuli-responsiveness, self-healing capabilities, or specific optical and electronic properties can only be achieved through the introduction of functional (side-)groups. The pursuit of novel polymers is further fueled by the imperative for sustainable and environmentally friendly materials. Unique polymer structures derived from renewable resources or designed for efficient biodegradation hold promise in mitigating the environmental impact associated with synthetic PAs.[3,5–7]

From Nature to An Innovative, Divers And Sustainable Polymer Future

As the world awakens to the pressing need for sustainable solutions, a new class of polymers is emerging from nature itself – The **Biopolyamides (Bio-PAs)**. Bio-PAs possess at least one of the following defining characteristics: Bio-based origin, biocompatibility, and biodegradability. Bio-based PAs present a promising solution to the issues faced by crude oil-based PAs, offering unique structural properties and improved sustainability. They inherit their unique structural features from nature, enabling the design of materials with tailored properties for specialized applications and reducing the dependence on fossil fuels. Furthermore, the diverse range of biomass sources provides opportunities for introducing structural novelty and tailoring properties to meet the demands for specialized applications.[3–8]

Bio-based PAs can be divided into two groups: **PAs derived directly from nature** and **PAs polymerized from nature-based monomers**. Although polymers directly sourced from nature possess inherent benefits such as cost-effectiveness, the fundamental structure of these polymers cannot be easily changed once isolated. Polymers from nature-based monomers, however, are versatile due to the possibility of modifying monomers prior to polymerization. This flexibility allows for fine-tuning of the polymer's properties to suit specific applications. Different polymerization processes/conditions enable control over various polymer properties, e.g. chain length and crystallization.[7,8]

In summary, amid growing demands for specialized applications and sustainable materials, bio-PAs synthesized from nature-derived monomers have emerged as a promising solution. They combine structural novelty, sustainability, and other properties like biodegradability and biocompatibility. While current production volumes of bio-based and PAs remain relatively low compared to conventional commodity plastics, significant growth is anticipated in the coming years. With the advancement of bio-PAs, the forthcoming era of polymer chemistry will herald a sustainable polymer future – a future woven from nature itself, intertwining structural innovation and sustainability for specialty (bio-) applications.[8,9]

2. Ring-Opening Polymerization As Convenient Method for the Synthesis of Terpene-Based Aliphatic Bio-Polyamides and Their Copolymers

The subsequent chapter furnishes a comprehensive theoretical background concerning the hypothesis that Ring-Opening Polymerization (ROP) serves as a convenient method for synthesizing terpene-based aliphatic bio-PAs and their copolymers. This chapter aims to summarize the general understanding and definition within the field of sustainable bio-PAs, alongside providing an overview of their historical development and current state of the art. Prior to exploring the range of suitable bio-based monomers, it is essential to elucidate the general preparation methods of PAs and define the material class biopolymers. Following a detailed illustration of the synthesis of relevant bio-based monomers, the resulting types of biomaterials will be presented. Finally, their potential application fields will be discussed.

2.1. Biopolyamides – Definition and State of the Art

As the worldwide demand for novel, structurally complex, and sustainable materials with unique properties increases, biopolymers – in this context, bio-PAs – could hold the solution to these challenges. To understand the motivation and objectives of this thesis, the material class “Biopolymers” must be defined first.[2–4,6–9]

Biopolymers possess at least one of the following defining characteristics:

- **Bio-based**: Polymers derived or synthesized from sustainable resources, such as plants or microorganisms, reducing the dependence on non-renewable fossil fuels.

- **Biocompatibility**: Polymers that are non-toxic and can interact favorably with biological systems, making them suitable for biomedical applications.

- **Biodegradability:** Capacity of the material to undergo degradation by microorganisms, such as bacteria or fungi, into smaller molecular components or biomass, thereby reducing their environmental impact.

Bio-based PAs themselves can be again divided into two groups:

- **Bio-PAs derived directly from nature:** These bio-PAs are obtained directly from natural sources, such as silk, wool, or plant-based proteins. Examples include silk fibroin and plant-based PAs like those found in wheat gluten or soy proteins.

- **Bio-PAs polymerized from nature-based monomers**: These bio-PAs are synthesized from monomers derived from renewable biomass sources, such as plant oils, carbohydrates, or terpenes. Examples include PAs based on sebacic acid (derived from castor oil), PAs from diacids obtained from fermentation processes, and PAs derived from terpene-based lactams.

2.2. The History of Nylon-Type Polyamides – Nylon 6,6 vs Nylon 6

Aliphatic PAs can be produced using different methods, yet two main routes have been established: Polycondensation and ROP. The first synthetic PA – Nylon 66 - was prepared by Wallace H. Carothers in 1935 *via* polycondensation of adipic acid and hexamethylenediamine.[1] This PA possesses high mechanical strength, thermal stability, and favorable solution resistance, revolutionizing the polymer and plastic manufacturing industries. Polycondensation proceeds *via* a step-growth mechanism, whereby the molecular weight increases gradually as the reaction progresses. While polycondensation is considered a straightforward method, it has drawbacks such as the requirement for high temperatures, thus temperature-stable monomers, difficulty in achieving high molecular weights, and the formation of condensation products like water, which need to be removed (see **Figure 1, A**).[2]

An alternative synthesis method for PAs is the ROP of lactams. Nylon 6, first prepared by Paul Schlack (IG Farben) in 1938, is similar to nylon 66, consisting of a 5-methylene spacer between the amide linkages (see **Figure 1, B**).[10] Nylon 6 can be easily prepared *via* ROP of ε-caprolactam. Initially, the industry employed water-catalyzed ROP at high temperatures (240–280 °C).[10] However, due to the lack of reproducibility, other methods were sought. Anionic AROP), with strong bases as initiators and acylated lactams as activators, afforded higher rates and better control over the reaction. The ROP of lactams usually proceeds *via* a chain growth mechanism. Using anionic ROP (AROP) as an example, the lactams are initiated by strong non-nucleophilic bases such as alkali metal hydrides. These bases abstract a proton from the lactam monomer to form a lactamate anion. This anion then attacks an activator

(sometimes called a co-initiator) molecule, typically an N-acyl lactam derivative such as an N-benzoyl caprolactam, producing the first anionic propagating species.[2] ROP has several advantages compared to polycondensation, including the ability to achieve high molecular weights and the absence of volatile byproducts. Additionally, another substance class can be used for polymerization. The development of improved initiators and activators AROP rendered a robust and controlled method for synthesizing various PAs.

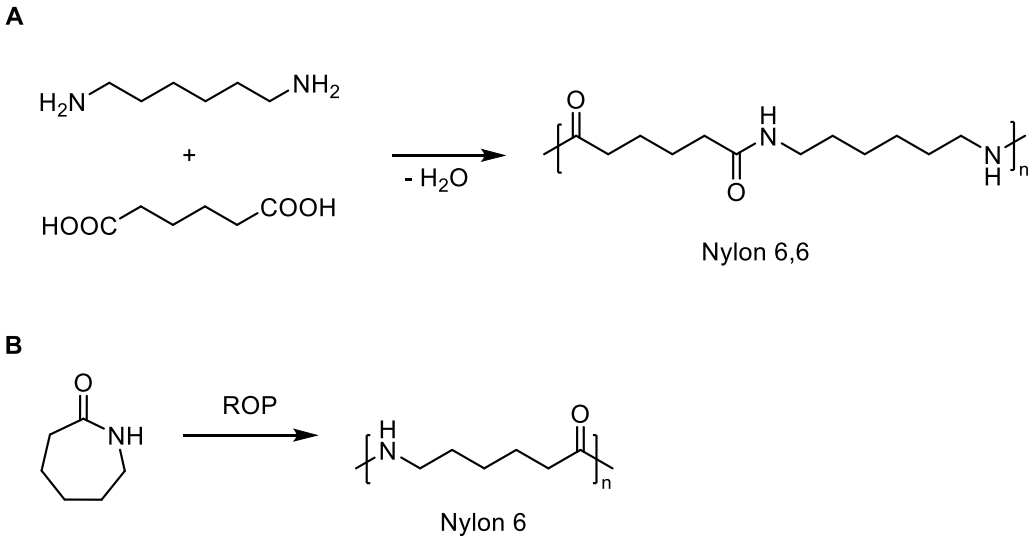


Figure 1: The two established main routes for the preparation of PAs using Nylon 6,6 and Nylon 6 as examples: polycondensation and ROP.

After these discoveries, additional PAs have been commercialized, e.g., Nylon 12 *via* ROP of laurolactam. Anyhow, until today, the Nylon 6 product segment accounts for more than 50 % of the global revenue for nylon polymers, estimated at over 30 billion US dollars.[11] Which makes Nylon 6 the most widely produced and commercially significant PAs worldwide.[12]

2.3. Scope of Sustainable Monomers in Ring-Opening Polymerization

2.3.1. General Considerations

Lactams are used as monomers to prepare PAs *via* ROP. The most prominent and historically first example is the ε-caprolactam (**3**), which is utilized for the synthesis of Nylon 6. The synthesis of **3** follows an established synthetic pathway, starting with the corresponding ketone (**1**). It is estimated that approximately 90% of the global production of **3** is derived from cyclohexanone (**1**). The conversion of **1** to **3** involves two steps: firstly, **1** undergoes oximation, and subsequently, the oxime (**2**) undergoes a *Beckmann rearrangement*, a reaction discovered by Ernst Beckmann in 1886.[13] This sequence of reactions facilitates the relatively facile synthesis of **3**, as illustrated in **Figure 2**.

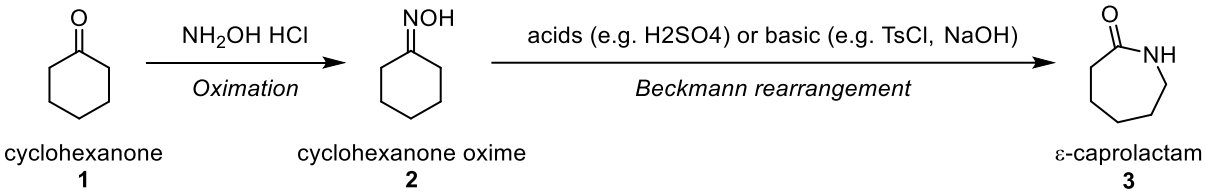


Figure 2: The established synthesis route for the preparation ε-caprolactam (**3**) *via* oximation and Beckmann rearrangement of cyclohexanone (**1**).

It is important to note that the ROP can be applied for a diverse range of lactam monomers, encompassing β-lactams derivates with four ring-atoms to the larger laurolactams derivates containing thirteen ring-atoms (see **Figure 3**). As an example, nylon 3 polymers from β-lactams – also known as β-peptides – have been extensively studied regarding their biomedical applications.[14] However, the ring size and structural properties of the lactam monomers exert a significant influence on the polymerization conditions and the resulting PA characteristics.[2,15,16] A comprehensive discussion on the impact of lactam ring size and structural features on the polymerization behavior will be presented in the subsequent chapter.

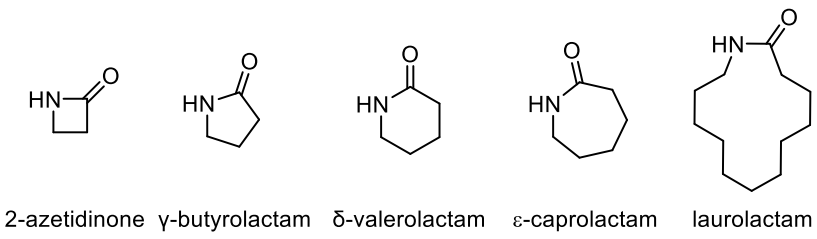


Figure 3: Various lactams with different ring sizes for ROP.

2.3.2. Polymerizability of Lactams

The ability of lactams to undergo ROP is called *polymerizability*. When talking about polymerizability, we have in mind both the thermodynamic feasibility and a suitable reaction path to convert the cyclic monomer into a linear polymer. However, the term *polymerizability* is sometimes used as a synonym for both the rate of polymerization and the thermodynamic instability of the lactam.[2,15,16]

Thermodynamic polymerizability is related to the Gibbs energy change (ΔG_p) for the polymerization reaction. A negative ΔG_p indicates that lactam polymerization is thermodynamically feasible. Generally speaking, ΔG_p decreases for lactams with ≥7 ring atoms being negative and thus favoring polymerization. However, a negative ΔG_p is a necessary but not sufficient condition for polymerization to occur, as kinetic factors also play a role.[15,17]

Kinetic polymerizability refers to the ease or difficulty of transforming a cyclic lactam into a linear polymer chain under specific conditions. It depends on factors like the initiation mechanism (anionic, cationic, or hydrolytic), ring strain, substitution, nucleophilicity, and electrophilicity.[2,18] The correlation between these parameters is complex, and kinetic polymerizability can vary significantly depending on the conditions. Substituents on the lactam ring can affect the kinetic polymerizability, but their effects are not well understood and can be contradictory. However, since the rate-determining step of polymerization is very sensitive to steric effects in the vicinity of the amide group, we can make the general assumption that a steric-demanding lactam tends to be harder to polymerize.[18]

In summary, both thermodynamic and kinetic factors influence the overall polymerizability of lactams, with ring size being a key determinant of thermodynamic feasibility and various structural and mechanistic factors affecting the kinetic aspects.[15,16]

Ring strain and substituents are, in both cases, important criteria for evaluating the polymerizability of lactams. The higher the ring strain and the less sterically hindered, the higher the polymerizability. The magnitude of each type of strain depends on the ring size, substitution, and nature of ring atoms. For all lactams ring-strain increases with inhibition or reduction of amide group resonance. Smaller rings (3-4 members) have high strain due to bond angle distortion, whereas 5-membered rings have strain from bond opposition/eclipsed conformations. Medium rings (7-, 8- membered) have strain from non-bonded interactions, bond opposition, and restricted amide resonance, and very large rings avoid strain by adopting extended conformations.[15,18,19]

While 7-membered cyclic monomers exhibit moderate polymerizability and necessitate relatively high temperatures for polymerization, they remain the most extensively investigated and polymerized monomers in the field.[2] The PAs derived from these monomers are highly sought after, yet there is an increasing demand to render these PAs sustainable and tailor them for specialized applications.[15]

In the subsequent chapter, we will explore renewable starting materials for the synthesis of 7-membered lactams, addressing the need for novel and sustainable PAs with special properties.

2.3.3. Terpenes: Bio-based Monomers for the Preparation of Bio-Polyamides

Nature provides a rich array of monomers with diverse chemical structures and functionalities, offering exciting avenues for tailoring polymer properties through strategic modification.[20] Terpenes – a class of naturally occurring compounds – stand out as a promising sustainable feedstock for PA synthesis due to their unique structural features and widespread availability. One of the key advantages of cyclic terpenes is their ability to be readily converted into lactams, which can then undergo ROP to yield PAs with unique properties. This approach is analogous to the well-established synthesis of Nylon 6 from **3**, starting with cyclohexanone **1** (**Figure 2**). Although, for most terpenes, the monomer synthesis route to their lactams, described in chapter *102.3.1 General Considerations* can be applied, but adjustments are necessary due to their different structure.[13,21–26]

In recent years, several cyclic terpenes have already been modified into their lactam, usually for subsequent ROP (see **Figure 4**).[2,27] However, the synthesis of terpene lactams dates back to 1893, when O. Wallach pioneered the synthesis of β-pinene lactam (**11**) using the then recently discovered Beckmann rearrangement.[13,22,25] Terpene-based lactams have been synthesized not only for polymerization but also for various other applications, such as bioactive probes in medical research or as precursors in organic chemistry.[23] β-pinene (**5**) was probably the first terpene to be converted into its lactam, which was subsequently polymerized (or rather oligomerized) by H. Hall in 1963, however, without further characterization.[24] Following this discovery, terpenes like α-pinene[28], (-)-menthone[29] (**6**), 3-carene (**8**)[27,28], and camphor (**9**)[9,22,30] have also been modified to their respective lactams and subsequently synthesized to their PAs.[9,13,22,25–27,29]

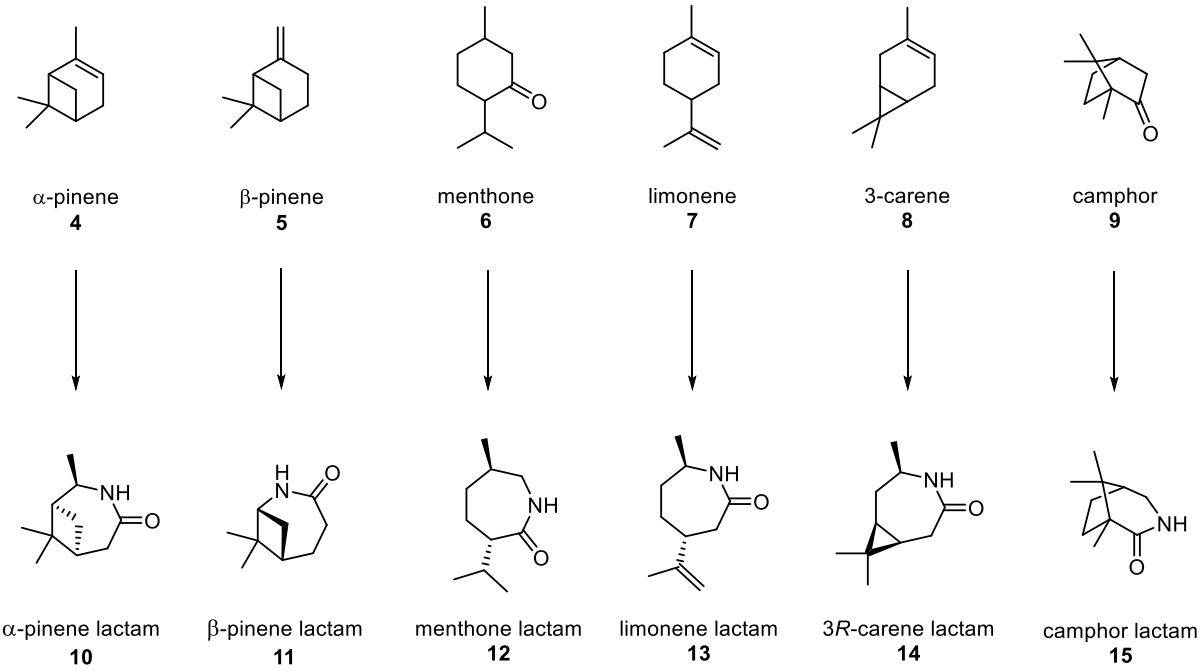


Figure 4: Most prominent cyclic terpenes and their respective lactams.

2.4. Mechanism and Characteristics of the Ring-Opening Polymerization of Lactams

Nylon 66 revolutionized industries with its unique properties like low thermal and electrical conductivity, lightweight, and solvent/corrosion resistance. Its early applications ranged from hair combs to ship propellers to stockings. Structurally similar to nylon 66, nylon 6 was easier to prepare through ROP of ε-caprolactam (**3**), initially using water catalysis at high temperatures.[10] Improvements in AROP in the 1960s, including acylated **3** or acylating agents as activators, enabled higher polymerization rates and low residual monomer content.[2]

In the following, the most common ways of ROP are presented and shortly discussed regarding their feasibility, pros, and cons. Russo and Casazza can be addressed for more detailed insights as they released 2012 one of the most detailed and impressive reviews on lactam ROP so far.[16] To illustrate the shown reaction mechanism in this work, we will use lactam **3** as a model compound.

For a general understanding of the different mechanisms and ROP conditions, the nucleophilicity of different lactam species is beforehand necessary (see **Figure 5**).[16]

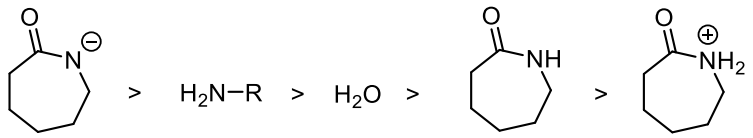


Figure 5: Order of nucleophilic reactivity of the model compound 3 and its derivates.

2.4.1. Hydrolytic and Catalytic Ring-Opening Polymerization

Hydrolytic ROP was the first ROP used for PA preparation and is an important industrial process for producing PAs like nylon-12. The mechanism and kinetics of water-initiated polymerization have been extensively studied and are well-established.[16]

The hydrolytic ROP proceeds through a combination of stepwise addition and condensation reactions governed by three main equilibrium reactions:

At high temperatures, the lactam (here **3**) undergoes hydrolysis to form an ω-amino acid (**3-aa**), which acts as the initiator. This endothermic reaction is favored by increasing temperature. The amine-terminated and acid-terminated chains undergo condensation to form amide linkages, contributing to chain growth. However, the presence of water negatively impacts the entropy, thus hindering the attainment of high molar masses. For a successful polymerization, water must be removed, shifting the reaction towards the PA. Lactam monomers can undergo

subsequent stepwise addition to either amine or carboxyl end groups, known as aminolytic and acidolytic polyreactions, respectively. The aminolytic reaction is the predominant pathway and can be catalyzed by carboxyl groups (see **Figure 6**).[16,16,31]

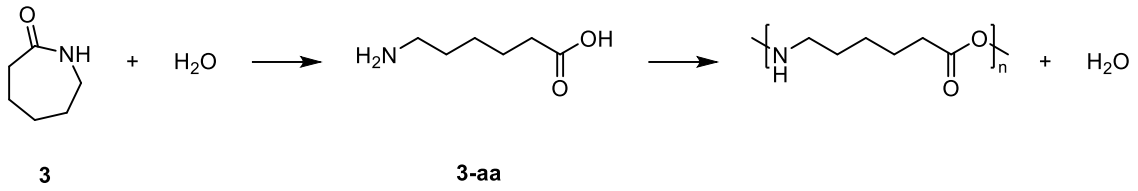


Figure 6: Hydrolytic ROP using the model compound **3**.

While the hydrolytic ROP offers advantages, it also comes with some drawbacks. The presence of water, for example, hinders the attainment of high molar masses. Therefore, water must be effectively removed in the final steps to achieve the desired molecular weights. Depending on the stability of the lactams, the hydrolytic ROP requires high temperatures (240–300 °C), limiting the range of more complex monomers that can be utilized. Additionally, the formation of cyclic oligomers, especially of the cyclic dimer, impacts the polymerization process and the properties of the resulting PA.[16,16,31,32] Despite these drawbacks, the hydrolytic ROP method still remains an important industrial process for producing PAs, owing to its simplicity.[16,31]

2.4.2. Cationic Ring-Opening Polymerization

The cationic polymerization of unsubstituted lactams was extensively studied between the late 1960s and late 1980s, primarily for mechanistic purposes, as it had very limited practical applications at the time. Currently, cationic ROP (CROP) is considered industrially unimportant among the various lactam polymerization processes and has been largely abandoned. While not as widely employed as anionic polymerization, CROP offers access to N-substituted lactam polymers that are otherwise difficult to obtain. The CROP mechanism can be rather complex as it is highly dependent on both the initiating system/mechanism and the lactam substitution. The general mechanism can be divided into three stages: initiation, propagation, and termination.[16,16,33]

Initiation

Among the various mechanisms, the polymerization initiated by protic inorganic acids, such as hydrogen chloride, is the most frequently used and, therefore, also the one described here. The polymerization begins with the protonation of the lactam (here **3**) by a proton donor, resulting in an electrophilic center. As two potential sites of protonation exist in unsubstituted amides, it is important to note that protonation occurs preferentially at the less basic oxygen atom due to the higher resonance stability of this protonated lactam species compared to when the nitrogen atom is protonated. The neutral lactam (strongest nucleophile) then attacks the protonated lactam, yielding the aminoacyl lactam cation as an ammonium salt **3b** or an amidine species **3c** *via* a tetrahedron intermediate (**3a**) (see **Figure 7**).[16,16,33,34]

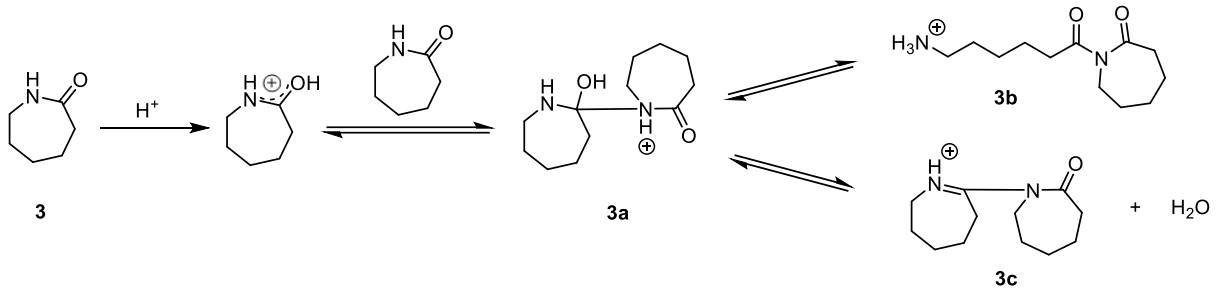


Figure 7: Initiation mechanism of cationic ROP using **3** as a model compound. The tetrahedral intermediate (**3a**) indicates a two-way reaction (**3b** and **3c**).

Propagation

Due to two active sites in **3b**, namely the N-acyl lactam group and the ammonium ion, the propagation involves two mechanisms: chain growth by acylation and by aminolysis.[16,33,34]

Chain Growth by Acylation

The ammonium cation **3b** participates in an equilibrium reaction, regenerating the protonated lactam and a neutral molecule with an amine end group (**3d**). Since the neutral amine group is the strongest nucleophile (see **Figure 5**), it is immediately acylated by the lactam cation, incorporating another monomer unit (**3b+1**) and propagating the chain growth by acylation (see **Figure 8**).[16,16,33]

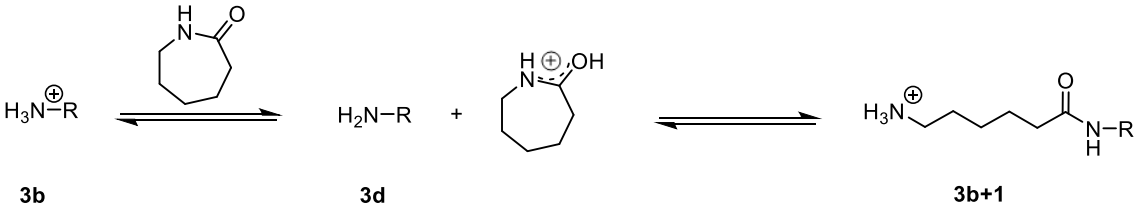


Figure 8: Propagation *via* acylation mechanism using **3** as a model compound.

Considering that the attack of **3d** to the lactam cation also results in a tetrahedral intermediate, not only **3b+1** is possible but also the formation of another amidine species, analogous to **Figure 7**.[16]

Chain Growth by Aminolysis

In this mechanism, the terminal N-acyl lactam moiety in the already formed PA molecule (**3d+n**) reacts with the terminal amine group of another polymer chain (**3b+m**) after undergoing the same equilibrium reaction described in **Figure 8**. This results in linking the two polymer chains together through aminolysis. This reaction can occur at either the endo- or exocyclic carbonyl of the terminal acyl lactam, leading to two possible intermediates, **3e** or **3f** (see **Figure 9**).[16,16,34]

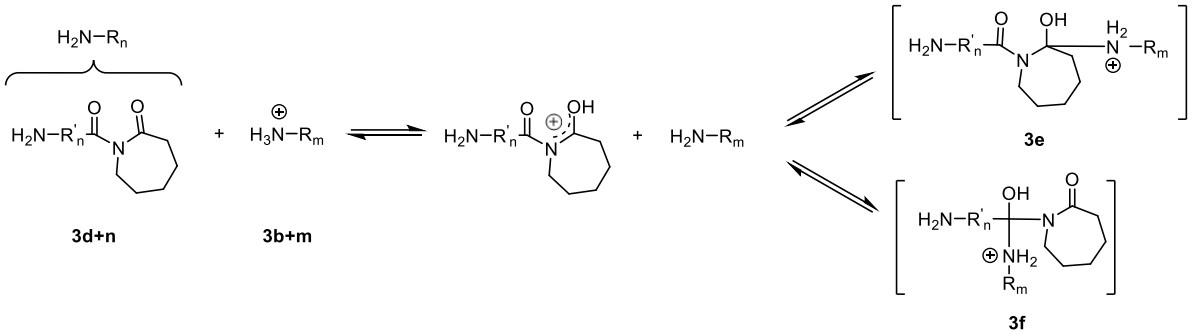


Figure 9: Propagation *via* aminolysis mechanism to the two possible intermediates **3e** and **3f**.

Intermediates **3e** and **3f** can – analogous to **Figure 7** – undergo each two pathways, resulting in a total of four possible outcomes. Both intermediates can form an amidine species (**$3e_1$, $3f_1$**) or promote further chain propagation by cleavage of the hemiaminal bond, resulting in **$3e_2$** and **$3f_2$** (see **Figure 10**).[16,33]

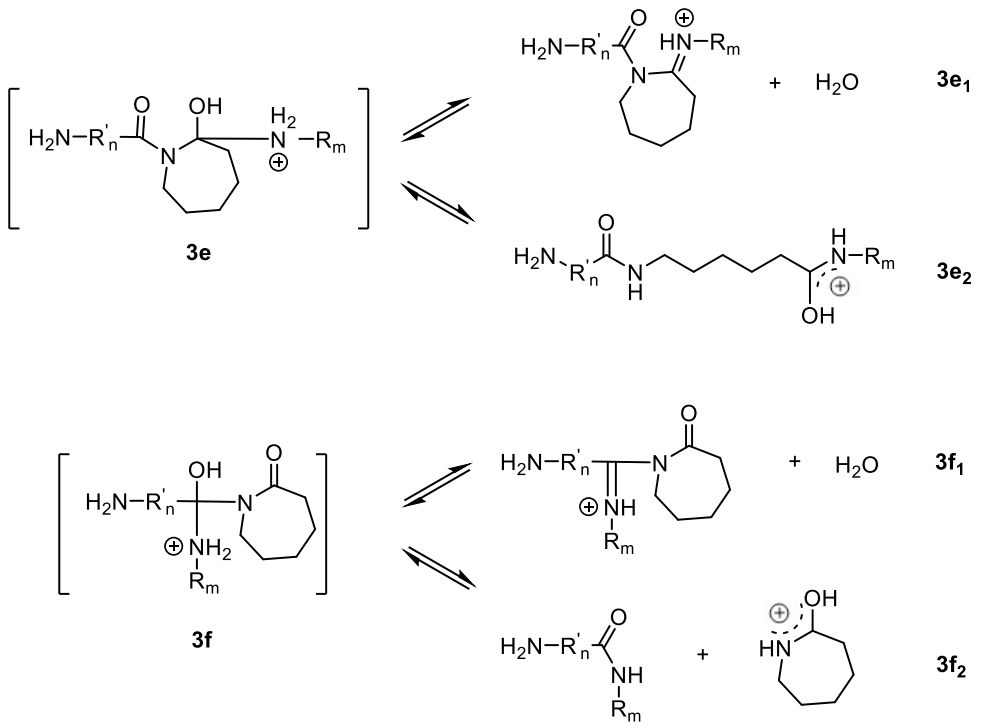


Figure 10: Propagation *via* aminolysis mechanism starting from the two intermediates **3e** and **3f**.

Termination

Despite the high reaction rates, cationic polymerizations often stop at relatively low conversions and low molar masses with high polydispersity due to side reactions that deactivate the active species. The formed amidine groups, for example, are highly basic and can neutralize the acidic initiator and deprotonate the lactam cations, reducing the formation of new propagation centers and stopping the chain growth. The water generated during this amidine formation, however, can lead to hydrolytic reactions with acylated lactams and acylated amidine structures, yielding a carboxylic end group, which again promotes the propagation step but also favors backbiting processes. This illustrates how complex and, in most cases, uncontrolled CROP is.[16,33]

2.4.3. Anionic Ring-Opening Polymerization

The AROP of lactams has undergone significant developments since its early discovery. Especially the ability to polymerize a greater monomer scope in a feasible manner increased the popularity and interest in this method.[35] The polymerization mechanism involving chain growth *via* amide anions was established over the years, leading to comprehensive reviews by notable authors like Šebenda[15,36], Sekiguchi[37], Reimschuessel[38], Hashimoto[18], Russo and Casazza[16].[2,16,18,38]

In general, the AROP of lactams consists of the initiation (usually the *in-situ* generation of the lactamate), charge transfer, propagation, and termination. We can differentiate between an 'activated polymerization' and a 'non-activated polymerization', using an activator/co-initiator or none, respectively. Literature often uses various terms interchangeably, leading to confusion. Here, initiators refer to the compounds capable of starting the discussed polymerization process. Activators or co-initiators are species that act as sources of non-ionic growth centers, enabling polymerization under more favorable conditions (higher rates and lower temperatures).[16]

<u>Initiation</u>

The initiation starts with the generation of a lactam anion, also known as a lactamate. This is achieved by abstracting a proton from the lactam monomer using a strong base, referred to as the initiator, such as an alkali metal. Subsequently, the lactamate reacts with either the monomer (R = H, non-activated AROP) or the activator molecule (R = activation species, activated AROP) through a ring-opening transamidation reaction. This reaction forms the N-acyl lactam structure **3g**, a process known as the disproportionation reaction. The rate of this disproportionation reaction depends on various factors, including the counter ion, reaction medium, lactam ring size, substituents, and the structure of the resulting monomeric unit.[16] The N-acyl lactams formed during the reaction are highly reactive towards the lactam anion. However, their buildup is slow, leading to an initial induction period characterized by a low polymerization rate. To eliminate this induction period and enable AROP to occur at much lower temperatures, an N-acyl lactam (R = activating species) can be added as an activator from the start.[2,16] Regardless of the approach (activated or non-activated AROP), the amine anion **3g** is highly reactive and rapidly undergoes proton exchange with a lactam molecule. This proton exchange yields an imide dimer (**3h**) and regenerates a lactam anion (see **Figure 11**).[2,16,18]

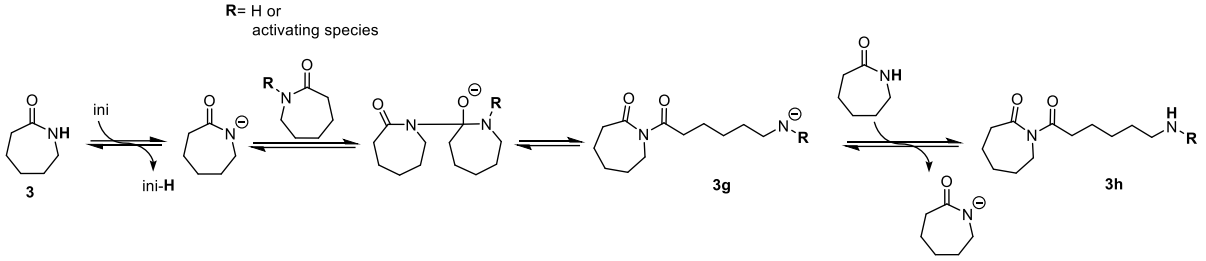


Figure 11: Initiation in AROP using lactam **3** as a model compound. The initiation consists of proton abstraction, formation of a tetrahedral dimer-intermediate, a disproportionation reaction forming **3g**, and a proton exchange between a lactam and **3g** to the imide dimer **3h** and a lactamate.

The initiator's ability to produce the lactam anion is crucial for initiating the polymerization process. In general, the choice of initiator and reaction conditions (temperature, co-initiators) depends on the specific lactam monomer and the desired polymer properties, such as molecular weight and dispersity.[2,23] In the following part of this section, we will elucidate the most common and suitable initiators:

Alkali Metals and Alkali Metal Hydrides

Alkali metals or alkali metal hydrides (e.g., sodium, potassium, sodium hydride) can initiate the AROP of lactams by *in situ* generation of lactamates. These initiators have been used for the polymerization of various lactams, including ε-caprolactam, laurolactam, and terpene-based lactams e.g. menthol-based ε-lactams. Huge advantages are the low costs, the easy handling, and the ability to quench remaining traces of water.[2,18,20,27,29]

Phosphazene Bases

Phosphazene bases, such as *t*-BuP_4, initiate AROP similar to hydrides and offer advantages like moisture tolerance and milder reaction conditions compared to alkali metal-based initiators. The polymerization mechanism is highly responsive to the addition of co-initiators such as acylated caprolactam. *t*-BuP_4 has been used for the polymerization of ε-caprolactam, α-amino-ε-caprolactam, and unsubstituted β-lactams, with varying degrees of control over molecular weight and dispersity.[39,40]

N-Heterocyclic Carbenes (NHCs)

NHCs are organo-catalysts that can initiate the AROP of lactams. The basicity of the generated carbene, influenced by factors like ring size and substituent groups, plays a crucial role in the polymerization efficiency. NHC-catalyzed polymerizations can be conducted without the need for co-initiators and may exhibit "chain multiplication" behavior, leading to lower molecular weights at higher monomer conversions.[2,41]

Propagation and Termination

The lactamate attacks the electrophilic carbonyl group of **3h**, causing ring-opening and the formation of a new anionic center. This process continues *via* proton exchange with another monomer to the respective lactamate and the formation of **3h+1**, **3h+2**, etc.[16,42]

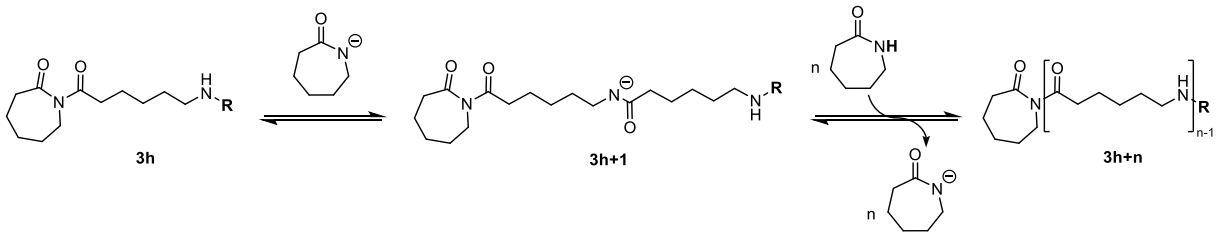


Figure 12: Propagation mechanism in AROP using lactam **3** as a model compound.

The propagation step in AROP of lactams is a complex and multifaceted process that has been the subject of extensive research and debate within the scientific community. While the exact mechanism is not yet fully understood, the main influences could be identified. The mechanism is mainly influenced by the nature of the counter ions, temperature, and solvent polarity. Several mechanisms have been proposed to especially elucidate the role of counter ions and their interactions with the growing polymer chain. The nature of the counter ion is a crucial factor in determining the degree of dissociation of the lactamates, which directly impacts the propagation process.[42,43]

The polymerization can be terminated by introducing a quenching agent that reacts with the anionic chain end or by allowing the anionic species to undergo side reactions or elimination processes, e.g. water at room temperature.[2,16,18]

Side Reactions

Side reactions are a common occurrence in AROP of lactams due to the high reactivity of the species involved. They become increasingly prevalent when operating at elevated temperatures and extended polymerization times. The strongly basic conditions inherent to this polymerization type promote polymer branching and the formation of troublesome β-keto compounds. The primary side reactions that can occur during AROP are transamidation, Clasen-type condensation, and depolymerization. Understanding these side reactions is crucial for achieving controlled polymerization and well-defined polymer architectures.[2,18,39,42]

Transamidation and Condensation

Transamidation and condensation reactions involve the exchange of groups between the growing polymer chain end and another molecule. Possible side reactions and their mechanism are portrayed in **Figure 13**, using **3h+n** from **Figure 12** as model PA.

One of the most notable side reactions is the formation of carbanions. The hydrogen atoms in the α-position relative to the imide group carbonyls in **3h+n** have comparable acidity to those in amide groups. Consequently, in the presence of a strong base (e.g., lactamate), carbanions can form, which in turn can undergo Claisen-type condensation reactions. C-acylation reactions on the exo- and endocyclic carbonyls of the N-acyl lactams form side products like β-ketoimides and, subsequently, β-ketoamides (see **Figure 13** a) and b)). The rates of these C-acylation reactions are often comparable to or even exceed the rate of propagation itself. Once formed, these β-keto compounds are far from idle bystanders. They can participate in a myriad of secondary reactions, including branching or crosslinking, further complicating the polymer architecture.

Transamidation, on the other side (depicted in **Figure 13** c), d), e), and f)) results in chain transfer yielding either longer chains (c)) or branched PAs (d)). This side reaction also participates in subsequent reactions (e) and f)), complicating the polymerization and polymer structure.[15,16,18]

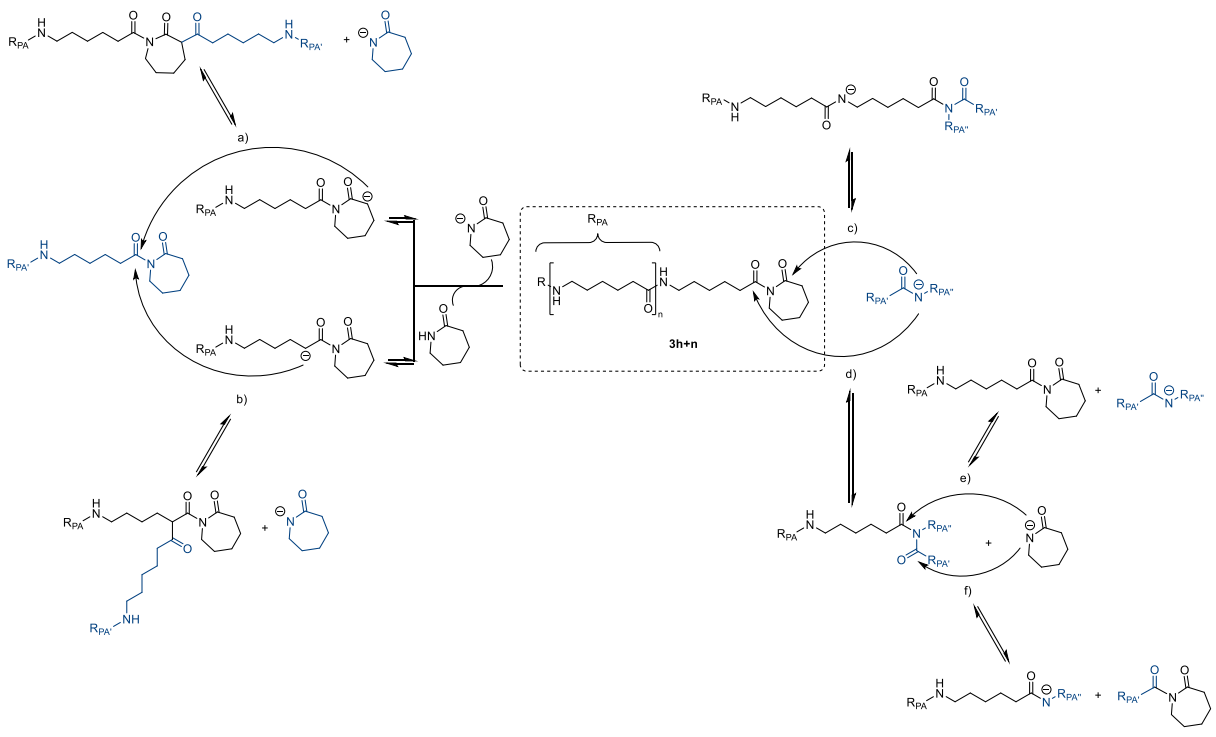


Figure 13: Modell transamidation reactions to demonstrate possible side reactions typically in AROP.

Depolymerization

Depolymerization can occur during AROP, particularly at elevated temperatures or in the presence of protic impurities (**Figure 13** e) and f)). Additionally, β-ketoamides – formed e.g. during Claisen-type condensation (**Figure 13** c)) and subsequent ring-opening – can undergo thermal or base-catalyzed decomposition, yielding ketones and isocyanates.[16]

Suppressing Side Reactions

These reactions can lead to a broadening of the molecular weight distribution and loss of control over the polymerization process. Suppressing these side reactions is crucial for achieving living AROP and obtaining well-defined PAs with controlled molecular weights and architectures. While it is challenging to completely eliminate side reactions, adopting fast, low-temperature polymerization conditions can significantly limit their formation. Other strategies to mitigate side reactions include the use of lactam monomers with minimal active hydrogens and high ring strain and minimizing the presence of protic impurities and moisture, which can initiate side reactions.[16]

Kinetics

AROP has been extensively studied in academic research, contributing to a deeper understanding of polymerization kinetics, reaction mechanisms, and structure-property relationships. Duda and Kowalski contributed with their review on “Thermodynamics and Kinetics of Ring-Opening Polymerization” to the mechanistic understanding of AROP.[17]

Besides being chain growth polymerization, AROP is often considered a living-type polymerization where the active anionic centers remain reactive throughout the polymerization, enabling chain growth without termination or irreversible chain transfer. Additionally, fast and quantitative initiation ensures all polymer chains start growing simultaneously. When plotting a living-type AROP, one can observe a linear decrease of monomer concentration with time, indicating a constant concentration of active species, creating a linear semi-logarithmic kinetic plot. The number-average molar mass also increases linearly with monomer conversion, indicating the absence of termination or chain transfer.[17,18]

By fulfilling these aspects, living-type AROP enables excellent control over the polymerization process, resulting in well-defined polymer architectures with predetermined molar masses and narrow polydispersity.[17]

Advantages of Anionic Ring-Opening Polymerization

AROP stands out as the fastest method for the preparation of PAs, with a relatively low activation energy. The anionic mechanism involves a more reactive nucleophilic attack on the lactam ring compared to the CROP, leading to faster propagation rates and higher conversions. AROP is also considered the most suitable polymerization method for structurally complex lactams, e.g. nature-derived lactams. Bulk polymerizations can occur below or above the polymer's melting point, with the lower limit being the lactam's melting temperature and the solubility limit of the polymer in the molten monomer. This allows for milder reaction conditions, while cationic ROP often requires harsher conditions, such as high temperatures or the use of strong acids as initiators, which can lead to side reactions or degradation.[14,16–18,31,33,34,42–44]

AROP allows for the synthesis of high molecular weight PAs with narrow molecular weight distributions and controlled polymer properties due to the living nature of the polymerization. Unlike hydrolytic polymerization, which generates water as a byproduct, AROP proceeds without the formation of any side products. This simplifies the purification process and avoids potential side reactions that can lead to branching or crosslinking.[2,14,15,17,18,36,42–44]

In summary, the living nature, fast kinetics, mild conditions, versatility in monomer selection, and ability to control polymerization renders AROP the preferred method for the synthesis of high-performance PAs from lactams compared to hydrolytic and cationic ROP techniques.

2.5. Anionic Ring-Opening Polymerization of Terpene-Based Lactams: A Gateway to Divers Materials

The AROP of lactams has emerged as a versatile synthetic route to access a wide range of PAs. This powerful technique not only enables the synthesis of homo-PAs but also facilitates the preparation of copolymers and functionalized PAs, offering a rich playground for polymer chemists.

2.5.1. Homo-Polyamides

Homo-PAs, derived from the AROP of lactams, have gained significant attention due to their potential for sustainability and unique properties. Among these, terpene-based PAs stand out as promising candidates for various applications. Terpene-based materials exhibit remarkable properties that make them attractive for diverse applications. Their inherent rigidity and crystallinity contribute to excellent mechanical strength and thermal stability, while their hydrophobic nature imparts resistance to moisture and solvents, which in return also means insolubility in most solvents and difficult processability. The incorporation of terpene moieties can introduce unique functionalities, such as antimicrobial or antioxidant properties, expanding the potential applications of these polymers.[2,9,21,27–29]

2.5.2. Copolymers: Tailoring Properties through Molecular Architecture

The AROP of lactams also enables the synthesis of copolymers, which offer a powerful means to fine-tune the properties of the resulting materials. The two main categories important here are block copolymers and random (statistical) copolymers, depending on the arranged monomers, e.g. Monomer A and Monomer B, as apparent in **Figure 14**.[2]

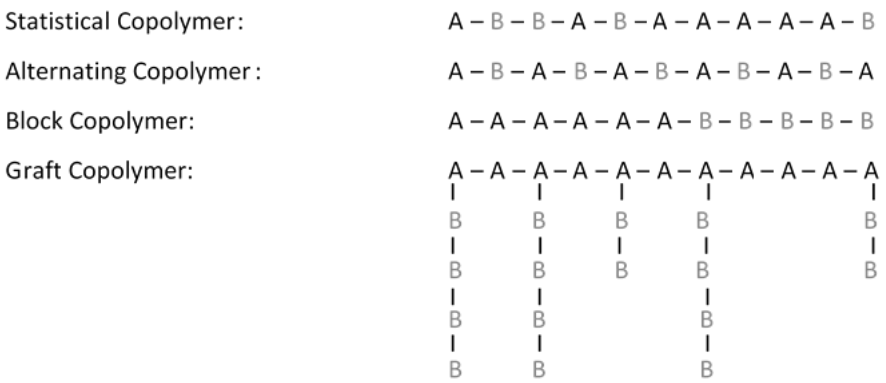


Figure 14: Different types of copolymers. A and B symbolize two different monomers.

Block Copolymers vs. Statistical Copolymers

Block copolymers are characterized by strictly separated monomer bocks (see **Figure 14**). If the monomers inherit very different properties (e.g., regarding hydrophilicity), this molecular architecture results in phase separation and microphase separation, leading to unique morphologies and properties. Block copolymers can exhibit self-assembly behavior, forming nanostructures such as micelles, vesicles, or cylindrical structures, making them attractive for applications in drug delivery, nanoreactors, and templating.[2,45–47]

In contrast, statistical copolymers feature a random distribution of different monomers along the polymer chain. This random arrangement can lead to a combination of properties from the individual monomers, enabling the fine-tuning of physical and chemical characteristics. Random copolymers often exhibit improved solubility, processability, and compatibility compared to their homopolymer counterparts. [2,45,48]

Polyesteramides

Polyesteramides (PEAs) serve as an excellent example of copolymers accessible *via* AROP (see **Figure 15**). PEAs combine the properties of polyesters and PAs, resulting in materials with enhanced thermal stability, mechanical strength, and chemical resistance combined with the biocompatibility and biodegradability of polyesters. By carefully controlling the monomer feed ratio and sequence distribution, PEAs can be tailored for specific applications, such as engineering plastics, coatings, or biomedical devices.[46,48,49]

Related to this, the functionalization of polyester amides is also very interesting, as it offers the possibility of linking pharmacologically active compounds and obtaining biodegradable elastomers. These might be able to avoid the deficits of typical cross-linked aliphatic polyesters, such as rapid degradation when implanted or the limited number of chemical units for chemical modification.[50] In view of these promising multiple property profiles, it is expected that the use of PEA as a high-performance or specialty material will play a major role in specific applications such as biomaterials in the (bio)medical field in the future.[46,48]

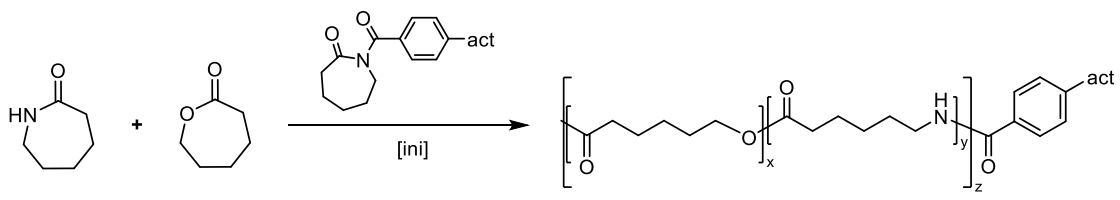


Figure 15: An illustrated approach for the preparation of polyesteramides using the model compounds ε-caprolactam and ε-caprolactone.

2.5.3. Side-Chain Functionalization

In addition to copolymerization, the AROP of lactams offers opportunities for side-chain functionalization, further broadening the versatility of PAs. One notable example is the synthesis of allyl PAs, which feature pendant allyl groups along the polymer backbone. Allyl PAs possess reactive side chains that can undergo various post-polymerization modifications, such as thiol-ene click reactions, epoxidation, or hydrosilylation. These modifications enable the introduction of diverse functional groups, including fluorescent labels, bioactive moieties, or stimuli-responsive units. Consequently, allyl PAs find applications in areas such as biomedical materials, sensors, and stimuli-responsive systems.[45,51]

2.6. Polyamides and Their Copolymers in Biomedicine – A Promising Future

2.6.1. Polyamides in Biomedicine

PAs have garnered significant attention in the biomedical field due to their remarkable properties, including mechanical strength, chemical resistance, and biocompatibility. These exceptional characteristics have paved the way for numerous applications, making PAs invaluable materials in various biomedical domains.

One of the major applications of PAs in biomedicine is their use as suture materials for wound closure and surgical procedures. Their high tensile strength, knot-tying ability, and resistance to degradation make them well-suited for this purpose. Also, nylon catheters –used, e.g., for drainage and drug delivery– are very popular due to their flexibility, chemical resistance, and durability, especially when in contact with body fluids. PAs composites also found applications in biomedicine. In the fabrication of dentures, for example, as reinforcing fibers in denture base resins. Additionally, PAs are employed in the production of other prosthetics, contributing to their strength and reliability. PA composites have also been explored for use in bone formation scaffolds. The addition of PA nanofillers can improve the mechanical attributes of composite materials and show potential for promoting cell growth, rendering them suitable for bone tissue engineering. Last but not least, recent studies have shown that PA materials, such as nylon, exhibit low microbial contamination and bacterial transmission compared to other polymers. This property makes PAs attractive for applications where infection prevention is crucial, such as in medical devices, implants, and wound dressings.

In summary, nylons have proven to be valuable biomaterials in various biomedical applications, ranging from sutures and catheters to tissue engineering scaffolds and antimicrobial devices. Their biocompatibility, mechanical properties, and versatility in processing make them attractive candidates for continued research and development in the field of biomedicine. As our understanding of these materials deepens, we can expect to witness further advancements and innovative applications that contribute to improving healthcare and enhancing patient outcomes.[2,5,20,48,52]

2.6.2. Polyesteramides in Biomedicine

PEAs combine, to some extent, the desirable properties of polyesters and PAs, making them attractive biomaterials for various biomedical applications. These versatile materials can be designed to be biodegradable, rendering them suitable for implantable devices that degrade over time and are eventually absorbed by the body. This property is particularly advantageous for applications such as resorbable sutures and drug delivery systems. It is crucial, however, to ensure that the degradation products are non-toxic and do not exhibit undesirable bioactivities.

PEAs can be functionalized with antimicrobial agents, such as silver nanoparticles or antibiotics, to prevent bacterial infections associated with implants or medical devices. However, on their own, they already exhibit excellent biocompatibility, making them suitable for applications that involve direct contact with biological tissues.[48] While PEAs are relatively new biomaterials, ongoing research is exploring their potential in various biomedical fields, such as orthopedics, cardiovascular applications, and wound healing. The ability to fine-tune their properties and incorporate bioactive molecules makes PEAs promising candidates for the development of advanced biomedical devices and therapies.[5,20,46,48,49]

2.6.3. Amphiphilic Materials And Their Potential In Controlled Drug Delivery

To understand the design approaches of polymers toward potential drug delivery, the concept of polymeric micelles has to be explained: Polymeric micelles are self-assembled nanostructures formed by amphiphilic block copolymers in an aqueous environment. The formation of polymeric micelles is driven by the hydrophobic effect, where the hydrophobic polymer blocks associate to minimize their exposure to water, forming a core surrounded by a hydrophilic shell (see **Figure 16**).[47,53] The hydrophobic core of polymeric micelles can encapsulate poorly water-soluble drugs, improving their solubility and bioavailability. The hydrophilic shell provides colloidal stability and can be functionalized with targeting ligands or stealth moieties (e.g., polyethylene glycol) to prolong circulation time and enhance targeted delivery.[53,54]

For amphiphilic polymers to form stable micelles, the following criteria must be met:

- **Amphiphilicity:** The polymer must possess both hydrophilic and hydrophobic segments. The hydrophobic block should have a sufficient length to drive micellization, while the hydrophilic block provides colloidal stability in aqueous media.[47,53]
- **Molecular weight and composition:** The molecular weight and ratio of the hydrophilic to hydrophobic blocks influence the micelle size, shape, and stability. Generally, higher molecular weights and longer hydrophobic blocks favor micelle formation.[53,54]
- **Concentration:** The polymer concentration must be above the CMC, which is the minimum concentration required for micelle formation.[47,53]

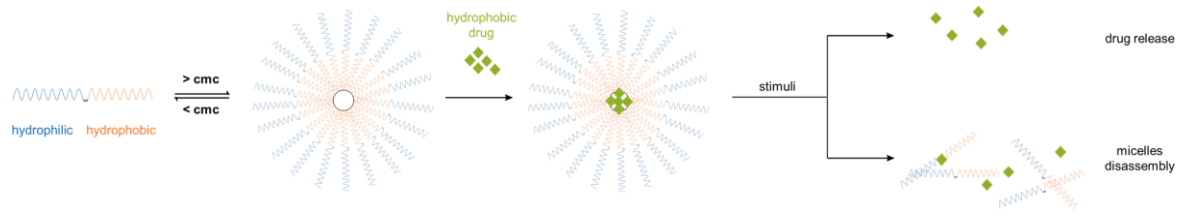


Figure 16: Micelle formation, subsequent drug loading, and stimuli-induced drug release or micelle disassembly.

Amphiphilic PA copolymers have emerged as a promising class of materials for drug delivery applications, owing to their remarkable ability to deliver therapeutic agents by improving their solubility and bioavailability, a critical challenge in the field of drug delivery.[2]. One approach to harness the potential of these copolymers involves the synthesis of amphiphilic block copolymers containing PA segments. For instance, block copolymers of nylon-3 with poly(ethylene glycol) (PEG) can self-assemble into micelles with a hydrophobic PA core and a hydrophilic PEG shell. Alternatively, researchers have explored the preparation of random or statistical copolymers of hydrophilic and hydrophobic lactam monomers. The resulting amphiphilic PAs can self-assemble into nanoparticles or polymersomes depending on their block's architecture.[2,9,27–29,45,46,48]

In summary, the unique amphiphilic nature of PA copolymers, combined with their structural diversity and biocompatibility, positions them as promising candidates for developing advanced drug delivery systems. Their ability to self-assemble into nanostructures, encapsulate therapeutic agents, and be tailored for specific applications through chemical modifications makes them a versatile platform for addressing the challenges of efficient and targeted drug delivery.

3. Objective

Our generation is struggling with the consequences of climate change, exploitation of resources, and earth pollution. Additionally, polymers and monomers derived from crude oil are reaching their limits regarding their structural complexity and possible applications. However, the worldwide demand for specialized materials is growing. Biomedicine and other areas like aerospace and the automobile industry need high-performance polymers and/ or "bioactive" materials. Nature-based material engineering offers a promising avenue for addressing both our pressing needs and our environmental concerns. Bio-based, non-food-based monomers hold the potential to unlock a realm of sustainable polymers while simultaneously introducing complex and hard-to-synthesize properties into the material. With this motivation in mind, the project plan of this thesis was relatively clear from the get-go of my research:

> *The establishment of a comprehensive framework for the synthesis of sustainable monomers, the preparation of their respective PAs, and the strategic design of their properties through co-polymerization, functionalization, and blending techniques. A particular emphasis was placed on exploring potential biomedical applications.*

In order to achieve this goal, all projects have been designed with the following workflow, encompassing three distinct phases, in mind (see **Figure 17**):

1. Establishment of a Renewable Monomer Pool
2. Polymerization of the Sustainable Terpene-Based Monomers
3. Property Analysis and Evaluation for Biomedical Applications

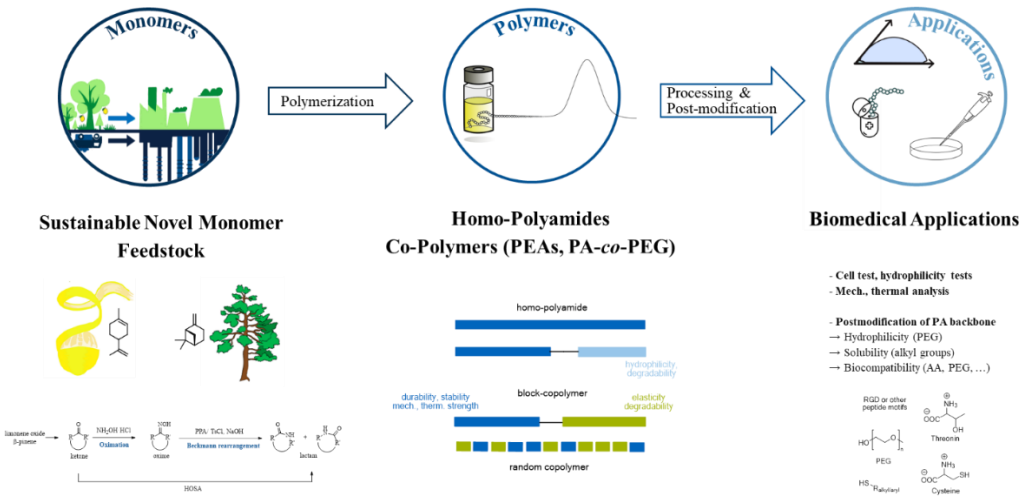


Figure 17: Project aim and planned workflow, divided into three different phases.

3.1. Establishment of a Renewable Monomer Pool

The first phase of this project was dedicated to identifying and synthesizing a new "sustainable" terpene-based monomer pool.
Thinking about all suitable cyclic terpenes for lactam modification, the selection of suitable monomers is akin to searching for a needle in a haystack. However, when evaluating the terpenes in terms of their structural properties and their natural abundance, it quickly becomes clear which two terpenes are the focus of this research. If we remember **Figure 4** we notice that bicyclic terpenes, such as pinenes, offer structural advantages as a means of introducing strength into the polymer. This also applies to terpenes with a functional group, such as limonene with an exo-cyclic double bond, which could enable functionalizability.

Among the terpene family, pinenes are the most abundant ones and can be relatively easily isolated from non-edible plant parts, such as wood processing (turpentine oil). Of the pinene isomers, β-pinene (**5)** is particularly attractive as a monomer due to its exo-cyclic double bond, which can be efficiently oxidized to the ketone (nopinone) and subsequently converted to the corresponding lactam **11**. In contrast, α-pinene (**4)** possesses an internal trisubstituted carbon-carbon double bond, rendering it challenging to modify and polymerize due to steric hindrance. Another promising candidate is limonene (**7)**, an abundant cyclic terpene extracted from citrus peels. The unique structure of **7**, featuring both an intra-cyclic and an exo-cyclic double bond, makes it an ideal starting material for the lactam modification and subsequent polymerization while maintaining the exo-cyclic double bond. Their abundance and their special structures render **5** and **7** very (if not the most) promising starting materials for the preparation of sustainable PAs with special properties and are thus the focus of this work.[8,9,27–29,48]

Starting from **5** and **7**, their lactams are synthesized *via* oximation and Beckmann rearrangement. These terpenes-based lactams enable ROP to their PAs, in accordance to previous studies (see **Figure 18**).[9,27–29,48]

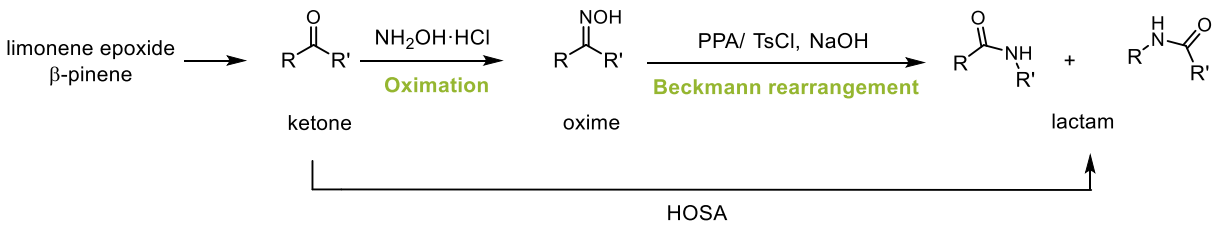


Figure 18: General monomer synthesis starting from limonene and β-pinene.

3.2. Polymerization of the Sustainable Terpene-Based Monomers – Their Analysis and Evaluation Regarding Biomedical Applications

Building upon the foundation laid in the first phase, my research endeavor delved into the realm of polymerization. Upscaling the polymerization process aimed to facilitate the production of processable, sustainable PAs, enabling the assessment of industrial-scale feasibility and opening doors to material modification.

The synthesis of copolymers, particularly PEAs, emerged as a focal point, as well as the functionalization of the PAs. Both approaches aim to achieve diverse properties tailored to specific applications. Moreover, the incorporation of polyethylene glycol (PEG) into the materials held the promise of imparting biocompatibility and anti-fouling properties, rendering them highly suitable for medical devices, drug delivery systems, and tissue engineering scaffolds. The disparity in polarity and solubility between PEG and PA segments could enable the self-assembly of copolymers into micelles in aqueous environments, unlocking new avenues for exploration.

As the prepared materials were intended for biomedical applications, their thermal and mechanical properties were analyzed. Hot-pressing techniques were employed to process the resulting materials, enabling the evaluation of mechanical strength, which is a crucial indicator of performance and applicability in various applications. By assessing factors such as stiffness, mechanical strength, solvent resilience, thermal stability, and biomedical behavior, insights are gained into the potential uses of these sustainable polymers.

3.3. Significance and Contribution

This thesis represents a contribution to the growing field of sustainable materials science, introducing novel monomers and polymers derived from renewable resources. Furthermore, the exploration of biomedical applications holds the promise of yielding advancements in biomedicine, ultimately improving healthcare technologies and, thus, patient outcomes.

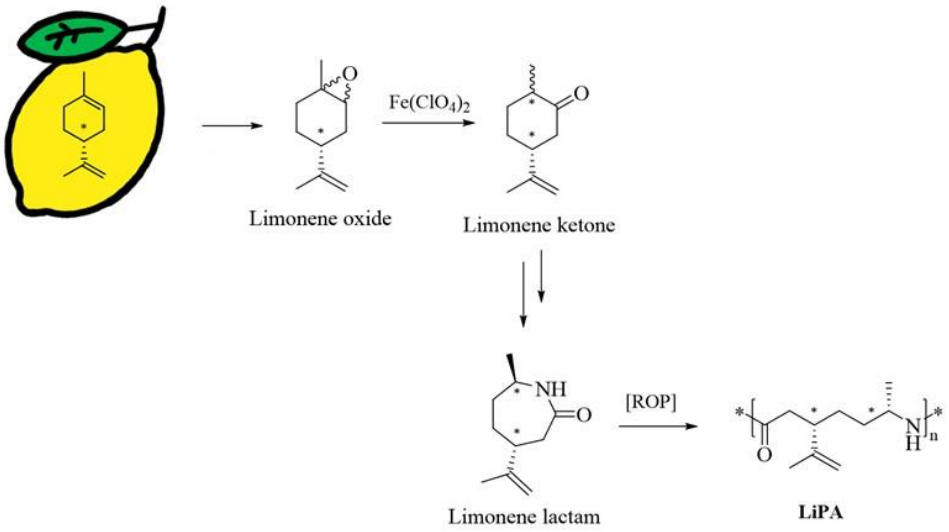
Through a systematic and interdisciplinary approach, this thesis endeavors to bridge the gap between sustainable polymer synthesis, novel specialty materials, and biomedical applications, paving the way for innovative and environmentally conscious solutions in the field of materials science.

4. Projects

4.1. Preparation and Analysis of Sustainable Homopolyamides Prepared from Terpene-Based Lactams

4.1.1. (+)-Limonene-Lactam: Synthesis of a Sustainable Monomer for Ring-Opening Polymerization to Novel, Biobased Polyamides

Bibliographic Data



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Content

Bio-based materials are gaining significant interest as sustainable replacements for conventional petroleum-based materials. Terpenes, such as limonene, offer unique structural features for high-performance applications. In this project limonene lactam, a novel bio-based building block derived from limonene epoxide, was synthesized, and its subsequent ROP to sustainable PAs was established. In the beginning, the focus of this work lies on the investigation of a synthesis route to limonene lactam, the reaction route optimized/simplified for industrial applicability and sustainability.

By evaluating the monomer synthesis route according to the principles of green chemistry, it was demonstrated that the reaction pathway meets most “green chemistry”-criteria defined by Tang et al.[55], including waste reduction, use of low-toxic substances, catalytic reagents, and simple reaction steps without high temperatures or pressures. Subsequently, the in-bulk ROP of limonene lactam to **LiPAs** was investigated. The successful synthesis of PAs with over 100 monomer units was confirmed by nuclear magnetic resonance (NMR) spectroscopy and gel permeation chromatography (GPC). Thermal properties were analyzed using differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA), which revealed promising thermal characteristics and the potential for further functionalization *via* the intact double bond.

This study demonstrates the potential of limonene as a bio-based monomer for ROP to sustainable PAs. The synthesis and polymerization of limonene lactam pose challenges due to its stereocenters and an isopropylene side group. Nevertheless, these structural elements also enable the preparation of novel polymers with distinctive properties, including functionalizability.

Author Contribution: Magdalena M. Kleybolte, Paul N. Stockmann, and Malte Winnacker conceived the work and designed the project. Laura Zainer performed the initial experiments. Magdalena M. Kleybolte performed the characterizations. X-ray experiments and structure determination *via* X-ray and related manuscript/supplementary sections were conducted by Jin Y. Liu. Magdalena M. Kleybolte and Malte Winnacker wrote the manuscript and the supplementary information.

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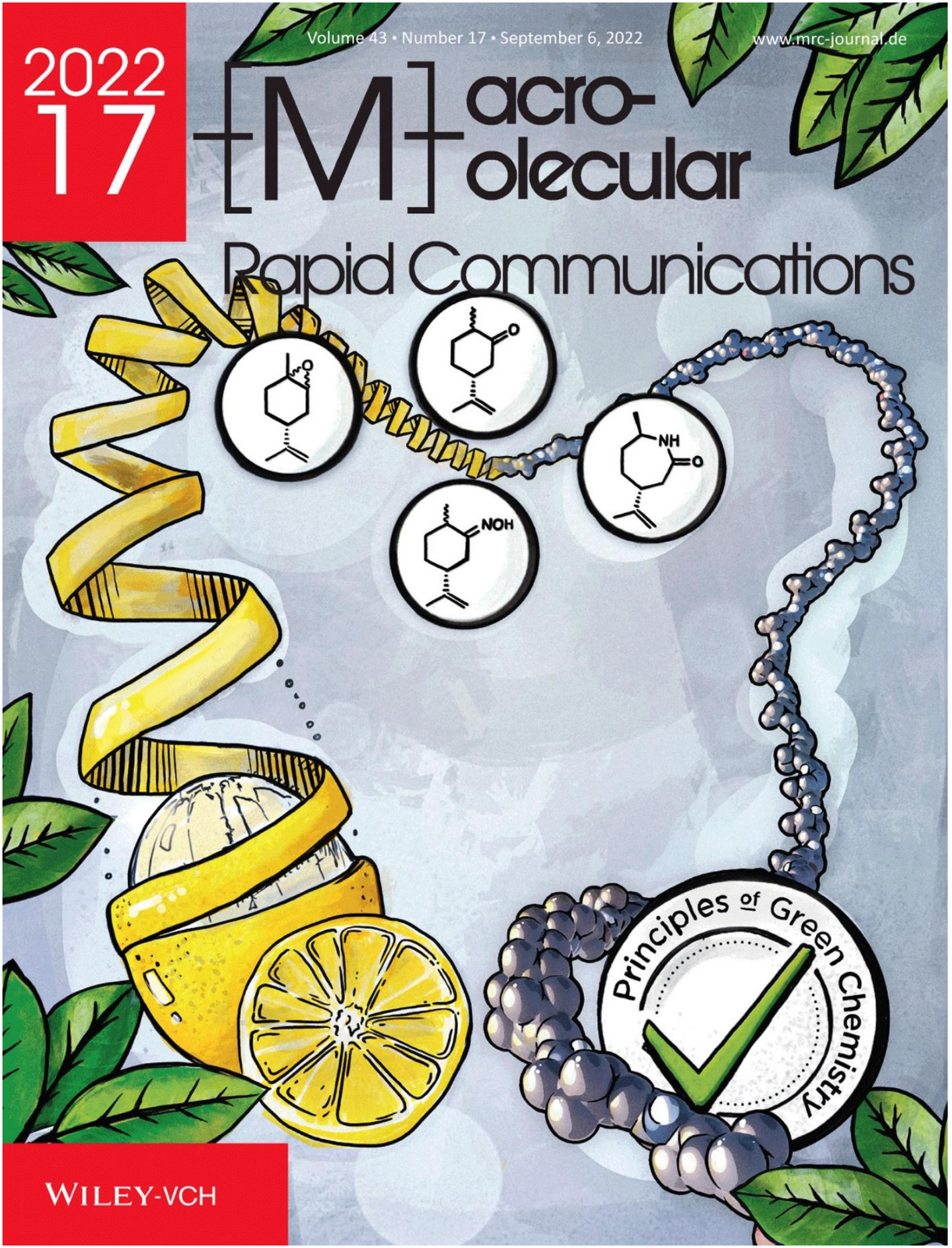

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RESEARCH ARTICLE

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(+)-Limonene-Lactam: Synthesis of a Sustainable Monomer for Ring-Opening Polymerization to Novel, Biobased Polyamides

Magdalena M. Kleybolte, Laura Zainer, Jin Y. Liu, Paul N. Stockmann, and Malte Winnacker**

In this work, the synthesis of limonene lactam starting from limonene epoxide and its subsequent ring-opening polymerization (ROP) to novel polyamides is presented. Sustainable, biobased materials are gaining interest as replacements of conventional, petroleum-based materials, and even more important, as high-performance materials for new applications. Terpenes—structurally advanced biobased compounds—are therefore of great interest. In this research, limonene lactam, a novel biobased monomer for preparing sustainable polyamides via ROP, can be synthesized. Limonene lactam possesses an isopropylene and a methyl side group, thus stereocenters posing special challenges and requirements for synthesis, analysis and polymerization. However, these difficult-to-synthesize structural elements can generate novel polymers with unique properties, e.g., functionalizability. In this work, a sustainable monomer synthesis is established, and simplified to industrial needs. For the sterically demanding in-bulk ROP to limonene polyamides, various initiators and conditions are tested. Polyamides with more than 100 monomer units are successfully synthesized and confirmed via nuclear magnetic resonance (NMR) spectroscopy and gel permeations chromatography (GPC). Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are used to analyze its thermal properties. In summary, a sustainable monomer synthesis is established, and promising polyamides with intact double bond and interesting thermal properties are achieved.

1. Introduction and Theory

Green Chemistry aims to reduce or eliminate the use or generation of hazardous substances in the development, production and application of chemical products.[1,2] Therefore, one of the most important criteria of green chemistry is the utilization of renewable starting materials.[3] This objective poses major challenges since renewable biobased compounds can suffer from high production costs and different performance that we are not used from conventional petroleum-based materials. To fully exploit the potential of natural compounds, it is therefore important to make them superior to fossil-based resources.[4,5,6,7] Polymer chemistry can achieve this goal by using biobased monomers with unique, hard-to-synthesize chemical structures, suitable for subsequent polymerization.[8] This so-called "monomer approach" distinguishes from the "polymer approach," where natural polymers (e.g., cellulose, natural rubber) are directly accessed. Even if the polymer approach appears to be more straightforward, the monomer approach offers more possibilities to tune the polymers

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as needed, since the monomers themselves or the polymerization can be modified. Also, with successful incorporation of the biobased monomers, the already mentioned hard-to-synthesize properties are also incorporated into the polymers. This use of biobased monomers will not only establish a future-oriented and sustainable polymer industry, but they also give access to special thermal, mechanical and chemical properties, rendering them suitable for further functionalization or modification. This clearly differentiates them from conventional petrochemical polymers.[9]

In this context, terpenes are very important building blocks for the synthesis of biobased polymers.[10,11] Most of them are abundant and derived from non-edible parts of plants, therefore generally considered as "green" and "sustainable." There are over 80 000 terpenoid structures, of which many have the desired stereocenters or functional groups, making this class of natural compounds to be a "gold mine" for polymer and materials chemistry.[12,13,14] A classification can be made into acyclic, monocyclic, bicyclic and polycyclic terpenes, as well as into the number of isoprene (C5) structural units.[15] Accordingly, many different terpene-based polymers have already been described, e.g., different polyolefin/hydrocarbon polymers[16] and polyesters.[17] Modification of the terpenes expand the pool of available compounds.[18]

Limonene—one of the most common cyclic terpenes—is extracted from, e.g., citrus peels with over 70 000 t/a.[19] Although this already shows a high availability, the amount is expected to rise with an increasing utilization, thus increasing demand for limonene, which can be promoted by a variety of functionalization strategies.[20] Limonene is present in the stereoisomers (R)-(+) and (S)-(−) and has both, an intracyclic and an exocyclic double bond, suitable for further modifications. The utilization and functionalization of limonene is therefore a highly researched topic, and remarkable progress regarding limonene-based polymers like polycarbonates,[21,22,23] polyurethanes and polyamides,[24] and polyesters[25] have already been made.[26,27]

Especially polyamides (PAs) are a very important polymer class with a wide range of applications from consumer goods to high-performance polymers in the technical or biomedical field.[28] PAs are characterized by a good property range: They show favorable mechanical properties even at high temperatures and good chemical resistance. On top of that they show a low gas permeability, high toughness, tensile strength, and impact resistances. These properties render polyamides indispensable for everyday and also high-performance applications. Some biobased polyamides (i.e., PA 410, PA 610) are already produced in remarkable quantities for high-performance engineering thermoplastics and for fibers.[29]

Accordingly, terpene-based PAs are very promising "green" alternatives to petroleum-based polyamides. In addition, the formation of novel polyamides that address new or unsolved needs/problems is possible. In the cases of cyclic terpenes, PAs are produced by modifying the cyclic molecules to lactams and subsequent ring-opening polymerization (ROP).[30] Examples for already modified terpenes to lactams for PA-synthesis are (−)-Menthone[31,32,33], β-Pinene[34,35,36], Camphor and 3-Carene.[37,38] Also, co-polymers such as polyesteramides have been synthesized from these building blocks.[39]

In this work, we have developed a simple monomer synthesis route to limonene lactam for subsequent ring-opening polymerization to produce PA as a potential high-performance biopolymer. For this purpose, starting from commercially available (+)-limonene epoxide (*cis/trans*-diastereomeric mixture) **1**—which can be easily obtained from limonene by oxidation—the corresponding ketone **2** was formed using different Lewis-acids in a Meinwald rearrangement. Oximation of **2** yielded limonene oxime **3** which was transformed in limonene lactam **4** via Beckmann rearrangement. The resulting ϵ-lactam of limonene was subsequently polymerized by ring-opening polymerization (ROP) to Limonene-Polyamide (**LiPA**) (**Scheme 1**). Regarding the ROP to **LiPA** various initiators/catalysts were investigated. With this work, we aim to introduce an optimized, facile, and "green"[d] monomer synthesis route starting from limonene and to demonstrate the potential of these building blocks with respect to the formation of biobased polyamides.

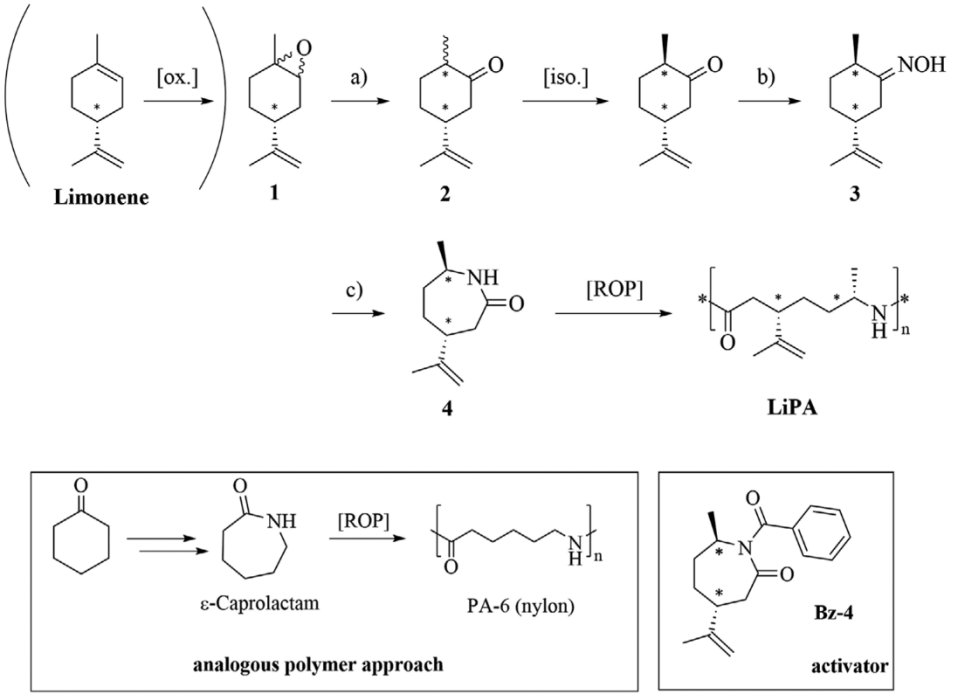
2. Results and Discussion

2.1. Synthesis of the Monomer Limonene Lactam

To obtain limonene ketone **2**, a Meinwald rearrangement of the commercially available *cis-trans* mixture (+)-limonene oxide **1** is necessary. In general, several catalysts can be considered for a Meinwald rearrangement.[40] We tested four different candidates: $ZnBr_2$, $Fe(ClO_4)_2$, $Zn(OTf)_2$, and $Zn(ClO_4)_2$.

$Zn(OTf)_2$ and $Zn(ClO_4)_2$ are not suitable, since $Zn(ClO_4)_2$, shows low conversion and yield for the Meinwald reaction despite relative high amounts of catalyst, while $Zn(OTf)_2$ shows high conversions and passable yields in a short period of time but also many side reactions. The remaining catalysts $ZnBr_2$ and $Fe(ClO_4)_2$ show hardly any difference in terms of conversion (>99%) and yield (>90%), but differ significantly in reaction time (19 and 4 h) and catalyst amounts (50 and 0.5 mol%). Regarding a more sustainable, "greener" and convenient synthesis, the method with $Fe(ClO_4)_2$ is therefore preferable due to catalytic amounts (0.5 mol %) of catalyst and short reaction time of 4 h at 60 °C or 6 h at 40 °C. In addition, the down-stream of the reaction catalyzed by $Fe(ClO_4)_2$ is much easier since distillation directly from the reaction mixture is possible (0.025 mbar, oil bath temperature: 60 °C, thermometer temperature: 33 °C). Particularly important is the complete dissolution of the catalyst in the reaction mixture, which means in this case that $Fe(ClO_4)_2$ has to be pre-solved in EtOAc, since the catalysis is homogeneous. We were also able to upscale the reaction to 40 g yielding over 96%. The dependencies of catalyst concentration, time and temperature are shown in Table S1 (Supporting Information). With these reaction conditions, the process design is simplified for future industrial use but also renders the reaction cheaper and "greener" compared to other possibilities mentioned for Meinwald rearrangements.

Although we found that an high isomer ratio (as close as possible to isomeric purity) is important for subsequent reaction, isomerization of **2** is not necessary due to the enhanced stereoselectivity of the reaction with $Fe(ClO_4)_2$ in cyclohexane (analyzed via GC) and adjusted oximation reaction. Oxime **3** is formed by the addition of hydroxylamine hydrochloride and sodium acetate in ethanol and water. Stirring the mixture over night at room



Scheme 1. Synthesis of limonene lactam **4** and its polyamide LiPA from limonene oxide **1** via ketone **2** and oxime **3**. a) $ZnBr_2$, EtOAc or $Fe(ClO_4)_2$, cy-Hex; b) NH_2OH*HCl, NaOAc, EtOH:H_2O; c) NaOH, TsCl in MeCN or TFA, $AlCl_3$; d) ROP with NaH, NHCs, DPP, H_3PO_4, P_4-tBu or HCl. Box: Established synthesis of Nylon from ϵ-caprolactam, and benzoylated LiLa (**Bz-4**) functioning as activator.

Table 1. Catalyst screening for the formation of limonene lactam **4** starting from **3**. Yields were determined either via ^{1}H-NMR or GC-MS (*). T = temperature, t = time, o.n. = overnight, M = molar, PPA = Polyphosphoric acid.

Entry	m_{Oxim}[g]	Catalyst	Eq_{cat}	Solvent	t [h]	T [°C]	Yield [%]
1	1	–	–	PPA	4	120	–
2	1	–	–	H_2SO_4	3	85	–
3		$AlCl_3$	0.1	MeCN	4	75	traces*
4	1	TFA	1	MeCN	4	75	traces*
5	1	$Fe(ClO_4)_2$	0.1	MeCN	2	85	–
6	1	TsCl	1.05	MeCN/ 2M NaOH	*o.n.*	0-r.t.	94
7	5.5	TsCl	1.05	MeCN/ 2M NaOH	*o.n.*	5-r.t.	>90*
8	10.5	TsCl	1.05	MeCN/ 2M NaOH	*o.n.*	0-r.t.	>99*
9	40	TsCl	1.05	MeCN/ 2M NaOH	*o.n.*	0-r.t.	81

temperature yielded over 90% of **3**, as white crystals. In addition to solvent reduction (8 mL g^{-1} of each solvent 1:1), we were able to lower the reaction time to 6 h once temperatures of 60 °C were applied and to introduce environmentally friendly solvents.

The last step of the monomer synthesis is the Beckmann rearrangement of **3** to lactam **4**. For this reaction, we tested different reagents and conditions, obtaining the best results with TsCl in basic medium (**Table 1**). Although Lewis-acid-catalyzed rearrangements are also possible, they show difficulties in purification as well as significantly poorer yields and an increased number of side reactions. Additionally, for the rearrangement with tosyl chloride an upscale up to 40 g was possible with yields above 80%. For a simple isolation of the product 100% conversion of the oxime is necessary. If a total conversion is not achieved, the reaction mixture can "re-react" with TsCl without damaging the already formed product. We could purify the resulting monomer up to 99.99% (confirmed by GC analysis) via crystallization in n-hexane and subsequent sublimation. GC-MS, IR spectroscopy, NMR and X-ray crystallographic measurements confirmed the intact lactam monomers with an double bond and allow a precise structure elucidation (see **Figures 1–3**).

In principle, there are two stereoisomers respectively for the ketone, the oxime, and the lactam. In the case of **2** we can observe two isomers via GC-MS and ^{1}H-NMR (see Figure S1, Supporting Information). However, the conversion of the ketone **2** to limonene oxime (**3**) and LiLa (**4**) is stereospecific (see Figure 2, see Figures S5–S8, Supporting Information). From literature it is well known that the Beckmann rearrangement for ketoximes is stereospecific. Exceptions can sometimes be created by choosing specific solvents and reaction conditions. However, we expect that the bulky side groups of **4** enhance stereoselectivity, since the migrating group aligns anti-periplanar to the leaving group at the nitrogen.[41] For the stereo-information of **4**, we performed a NOESY experiment (see Figure S8, Supporting Information) and recorded its crystal structure via X-ray shown in Figure 2. ^{1}H-/^{13}C-NMR, COSY, and NOESY indicate that only one stereo-configuration for **4**—either a *SS*- or *RR*-configuration—occurs. The crystal structure not only verifies this finding but also specifies the stereo-information to a *RR*-configuration. Via crystal structure we could also observe a boat-chair conformation as most stable conformation like already suspected in NOESY.[42] Following this finding the methyl and *iso*-propyl group are

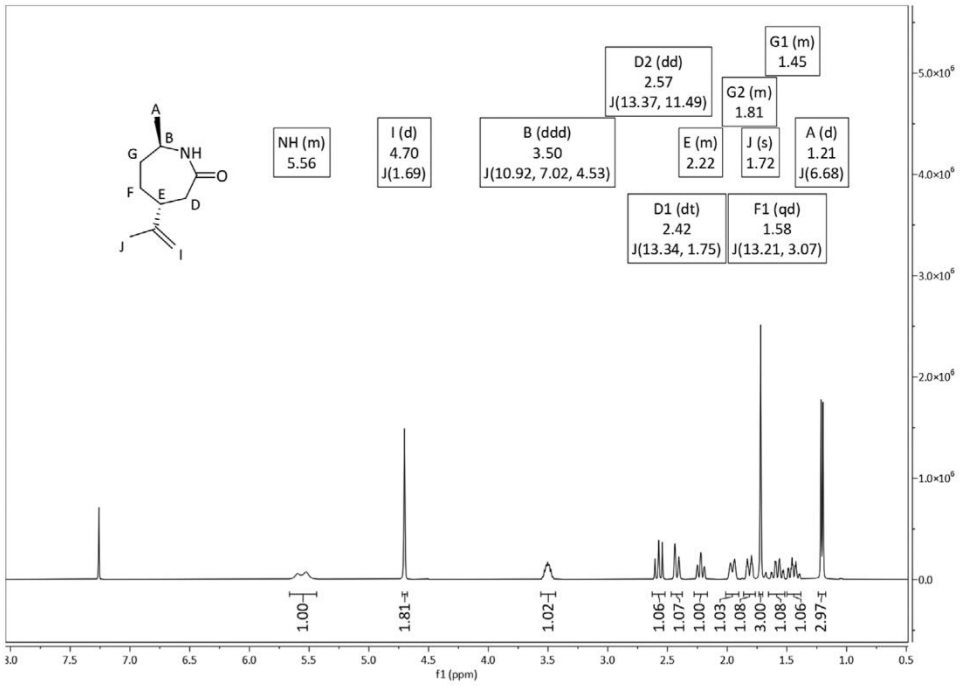


Figure 1. ^{1}H-NMR spectrum of limonene ϵ-lactam 4. Signal of the double bond (H_I) is found at 4.7 ppm while H_B at 3.5 ppm indicates the proton next to NHCO.

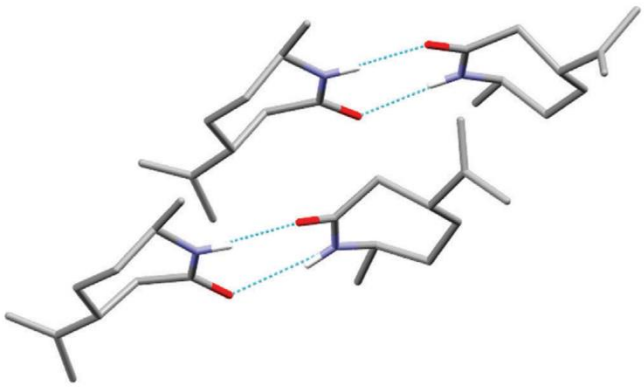


Figure 2. Crystal structure of **4**. Methyl and iso-propyl group show equatorial arrangement.

arranged equatorial. These structural properties are likely to hinder the attack of acids, bases, carben, or other initiators. Additionally, ring-opening itself is more difficult, since the to-be-opened C–N bonds arrange themselves facing each other due to hydrogen bonding (see Figure 2: blue lines).

2.2. Polymerization of Limonene Lactam to LiPA

Formation of the new limonene polyamide LiPA is achieved by ring-opening polymerization through different mechanisms. For this purpose, we tested different catalysts. Typical acids such as HCl and H_2PO_3, diphenyl phosphate (DPP) as acidic organocatalyst or Lewis acids like $AlCl_3$ can initiate cationic ROP via positively charged reaction sites. When aqueous acids such as aq. HCl are used, hydrolytic polymerization occurs in addition to the cationic mechanism. We also investigated anionic ROPs by testing bases, like triazabicyclodecene (TBD), NaH and P_4-tBu, as well as carbenes, i.e., IMes and iPr. As an activator for the anionic ROP, **4** was benzoylated (**Bz-4**). Such activators can facilitate the nucleophilic attack of deprotonated lactams at the amide bonds, thus promoting anionic chain propagation. Since **4** is a novel ROP monomer, we performed polymerizations at common temperatures for in bulk ROPs: 150, 200, 250 °C. In the following, the most successful catalysts are reported for the respective temperatures see **Table 2**. More detailed data can be found in Table S4 (Supporting Information).

Table 2. Catalyst/initiator screening for the polymerization of 0.2 g limonene lactam 4 at different temperatures for 24 h in bulk.

Entry	Initiator	$n_{activator}$ [mol%]	T [°C]	M_n [g mol^{-1}]	M_w [g mol^{-1}]	PDI
1	NaH	10	200	4400	6100	1.4
2	IMes	–	200	9100	9700	1.1
3	P_4-tBu	10	200	4700	5800	1.2
4	NaH	10	150	4800	5900	1.2
5	IMes	–	150	7300	8000	1.1
6	P_4-tBu	10	150	3900	4700	1.2
7	HCl	–	250	8400	22 000	2.6

The polymers were purified by solving or suspending them in chloroform and subsequent precipitation in n-hexane, followed by a washing step with hot n-hexane, EtOAc and filtration. According to the more detailed Tables S4 and S5 (Supporting Information), it becomes apparent that 200 °C is the preferred

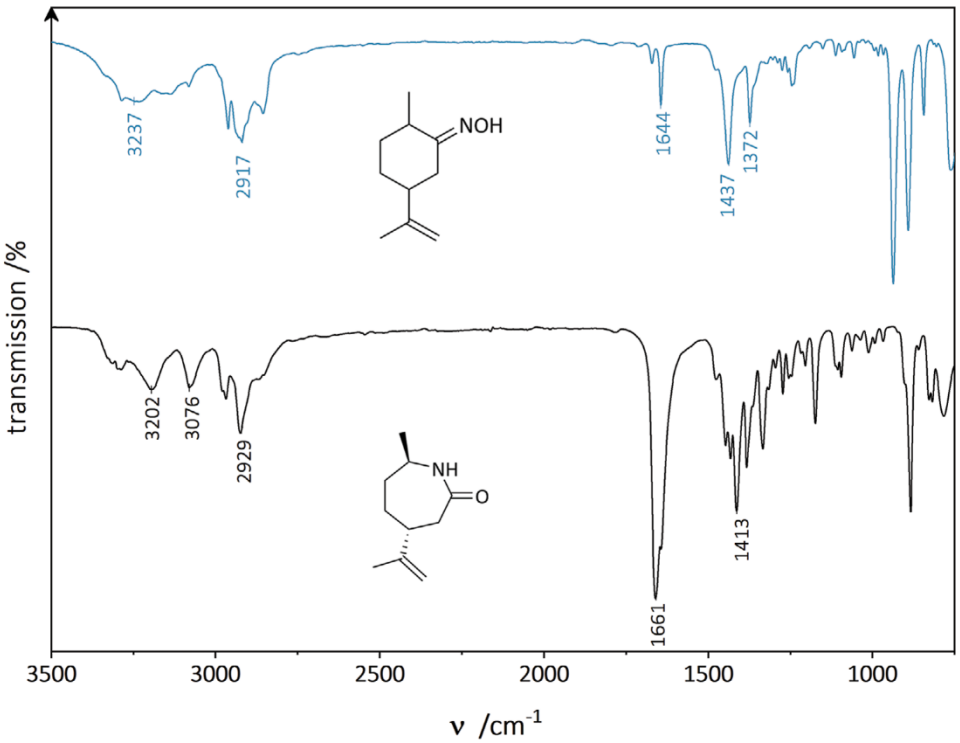


Figure 3. IR-spectrum of limonene oxime **3** and ϵ-lactam **4** in comparison. C=C vibrations at 1644 cm^{-1} (In the case of lactam this vibration overlaps with the CO vibration).

temperature for ROP of **4**. In particular IMes, P_4-tBu and NaH achieve at this temperature good results with molecular weights up to 9700 g mol^{-1} (58 monomer units). Polymerizations with the commonly used HCl or H_3PO_2 at 150 or 200 °C did not give sufficient results.[43,44] However, in the case of 250 °C HCl yielded LiPA with M_w = 22000 g mol^{-1} (131 monomer units) but with a high PDI. This will be investigated to a greater extent in the future, but we can already anticipate that this is most likely due to uncontrolled polymerization when using aqueous acids. It is important to note that with the use of acids, heat, and water, amino acid formation is likely to occur, rendering a termination of the polymerization possible, but also polycondensation. In general, we observed that a monomer purity below 99.9% achieve uncontrolled ring openings with very high PDIs. Since IMes, P_4-tBu and NaH achieved the best results at 200 °C, NaH was further investigated due to its easy handling, cheapness and commonness as living anionic ROP-initiator. We were able to observe a deterioration of the molar masses in relation to increasing time which raises the question of whether our polymer is experiencing depolymerization or chain multiplication (see **Table 3**). As an additional explanatory approach, we examined the anionic ROP at different times (see Figure S14, Supporting Information). Since decreasing molecular weight but increasing yield after 3 h can be observed, a chain multiplication is likely. This effect occurs when the sterically demanding lactam opens to a linear, sterically less demanding, polymer. This is followed by the attack of activated monomer on amide functionalities, resulting in a chain split. Chain multiplication lowers the molecular weight and increases the number of polymeric chains.[45] This question and ROP using different initiator systems and/or organocatalysts will be further investigated and constitutes the main focus of our research on terpene-based polyamides in the future.

Table 3. Time screening for the anionic polymerization of limonene lactam **4** (0.2 g) with NaH at 200 °C with different initiator amounts.

Entry	$n_{catalyst}$ [mol%]	$n_{activator}$ [mol%]	t [h]	M_n [g mol^{-1}]	M_w [g mol^{-1}]	PDI
1	10	10	12	5700	7400	1.3
2	5	5	12	5200	6900	1.3
3	5	0.5	12	3000	5600	1.8
4	10	10	24	4400	6100	1.4
5	5	5	60	1600	3800	2.4

Regarding the thermal properties (measured by TGA and DSC), we found relatively high T_gs up to 100 °C, T_ds up to 423 °C, and no detectable T_m. In general, PA chains form hydrogen bonds among each other, causing high decomposition and melting temperature, even though the polymer chains are not very long. Hexafluoroisopropanol (HFIP) has the ability to prevent this bonding, making it possible to analyze the single polymer molecules via GPC.[46] For a detailed insight, the section "2.4 Thermal Analysis" in the Supporting Information can be consulted.

The lack of a T_m could be caused by problems with a dense parallel arrangement of the chains when larger side groups, i.e., high steric demand, are present. Generally, the larger the side groups, the poorer can be the crystallization of the polymer. To the best of our knowledge, terpene-based amorphous polyamides were first observed in carene polyamide. Amorphousness,

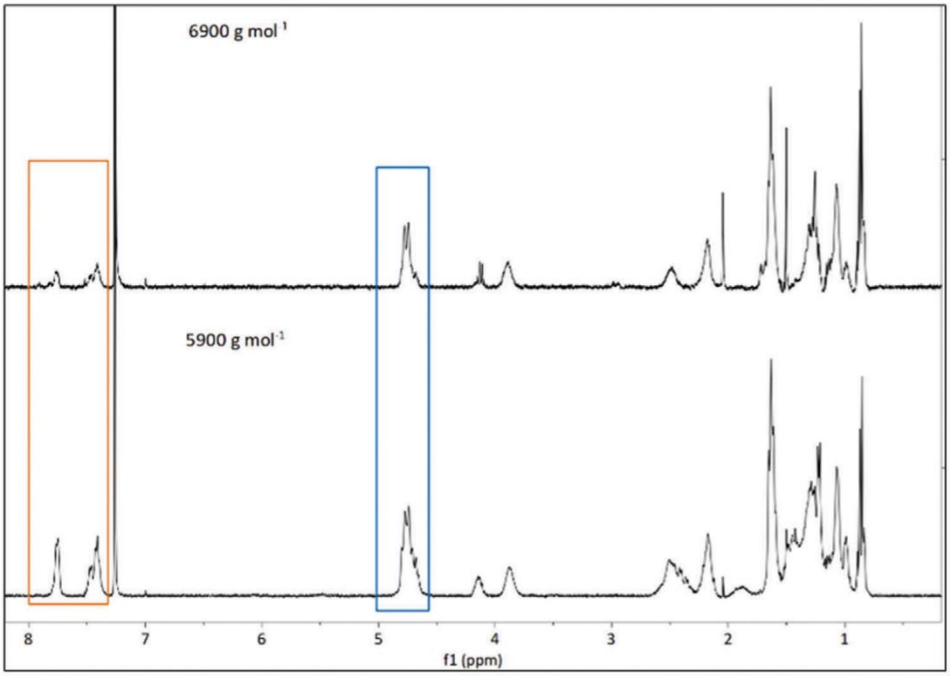


Figure 4. ^{1}H-NMR spectrum of LiPA with different molecular masses (5900, 6900 g mol^{-1}) polymerized via anionic ring-opening polymerization. Signal of the double bond is found at 4.7 ppm (blue) while the aromatic signals from activator **Bz-4** are found at 7.3–7.75 ppm (orange).

microcrystallinity, or a significantly longer crystallization time were reported by Stockmann et al. [37] and is consistent with our observations. This finding will be further investigated.

The polymer was not only analyzed in respect of its thermal properties, but also by means of NMR (see **Figure 4**) and IR (see Figure S10, Supporting Information). This allowed us to determine whether the polymer has an intact double bond, which was the case (blue box). A more accurate peak assignment without the observed overlap, especially regarding the polymer backbone, for example –CH_2–, can be made when longer LiPAs with small PDIs are produced.

3. Conclusions

In this study we could clearly demonstrate the potential of limonene as a biobased monomer for the ring-opening polymerization to sustainable polyamides. We have successfully synthesized the monomer limonene ϵ-lactam **4** possessing two chiral centers and a functionalizable iso-propylene group. We were also able to simplify the reaction significantly, especially regarding purification, rendering the synthesis route more attractive for industry and future applications.

By evaluating monomer synthesis according to the principles of green chemistry (*PRODUCTIVELY*) by Tang et al.,[47] we can consider the reaction route to limonene lactam as an important step toward green monomer synthesis since it meets most of the following criteria/principles:

By optimizing ketone and oxime formation, we not only reduce waste (*P*) but also improve the E-factor (*E*), establish the use of low toxic substances (*L*), like ethanol instead of methanol and in the case of ketone formation $FeClO_4$ instead of $ZnBr_2$ which also ticks the box for using catalytic reagents (*C*). All reaction steps are relatively simple (*Y*) to perform and down-stream (*U*) without additional derivation steps (*O*) and high temperatures and pressures (*T*). This signifies not only that our reaction meets the definition of green chemistry by Tang et al.[47] but also show the possibility of an easy upscale and therefore industrially application.

For the ring-opening polymerization, we have investigated different conditions and catalysts with NaH, IMes, and P_4-tBu as most promising catalysts/initiators for subsequent studies. The polymerization of **4** to oligomers and medium chain polymers over 80 chain units were successfully proven by GPC and NMR. However, we found the polymerization of limonene lactam restricted by its sterically hindered structure and possible cyclic polymer formation. For the future, especially anionic ROP with different activator systems should be investigated. We will also focus on the potential of organocatalysts like carbenes to obtain the desired biobased polymers and materials with good mechanical and physical properties. For this purpose, we will also consider lactam polymerizations in solution which seems to be promising after first attempts in THF. Copolymerizations with other lactams to, e.g., PA-co-PAs, and with lactones[48] to PEAs are under further investigation also with regards to kinetics and the different monomer reactivities. Incorporated double bonds of **4** enable functionalization of the resulting PA, leading to its tunability. Since terpene-based Polyamides seem to be very promising regarding biocompatibility[35] further work will also address the investigation of the biocompatibility of limonene-based (co-)polymers and blends/ composites, and their effects on living cells with regards to different (bio-)medical applications.

4. Experimental Section

Materials: All chemicals were purchased at *Sigma Aldrich* and used as received except HFIP, which was purchased from *Carbolution* Chemicals GmbH.

If not stated otherwise, the reactions were carried out on air at atm.

(5R)-2-Methyl-5-(prop-1-en-2-yl)Cyclohexan-1-One (2): Cis and trans mixture of (+)-limonene oxide (**1**) (1.0 eq.) was dissolved in cyclohexane (3 mL $g^{-1}{}_1$). A solution of $Fe(ClO_4)_2 \bullet H_2O$ (358 mg, 1.31 mmol, 0.5 mol%) in EtOAc (4 mL) was added. The reaction mixture was stirred for 4 h, cooled to room temperature and organic solvent removed under reduced pressure. The yielded brown oil contained 96% of **2** (analyzed via NMR) which was directly distilled from the crude mixture.

(5R)-2-Methyl-5-(prop-1-en-2-yl)Cyclohexan-1-One Oxime (3): **2** (60 g, 394.12 mmol, 1 eq.) was dissolved in a mixture of water (8 mL g^{-1}) and EtOH (8 mL g^{-1}) before NaOAc (48.50 g, 591.18 mmol, 1.5 eq.) and $NH_2OH \bullet HCl$ (30.13 g, 433.53 mmol, 1.1 eq.) were added. The reaction mixture was stirred at room temperature overnight. Subsequently 150 mL water were added, and the mixture extracted with cyclohexane (4 × 200 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution (1 × 200 mL), sat. aq. NaCl solution (1 × 200 mL) and dried over Na_2SO_4. Organic solvents were removed under reduced pressure to yield crude **3** as white crystals, which was purified by crystallization in n-hexane to yield colorless crystals (55.37 g, 331.06 mmol, 84%).

(4R)-7-Methyl-4-(prop-1-en-2-yl)Azepan-2-One (4): In a round bottom flask **3** (10 g, 59.8 mmol, 1.0 eq.) was dissolved in MeCN (80 mL) and cooled to 0 °C, followed by dropwise addition over 30 min of 2 M NaOH solution (92 mL, 3.1 eq.). The reaction mixture was stirred at 0 °C for 1.5 h. Subsequently, TsCl (11.9 g, 62.8 mmol, 1.05 eq.) was slowly added over 30 min. Afterward, the reaction mixture was stirred for 3 h at 0 °C and then allowed to warm up to room temperature overnight. The phases were extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution (1 × 100 mL), sat. aq. NaCl solution (1 × 100 mL) and dried over Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was crystallized from n-hexane and sublimated (70 °C at 0.04 mbar) to yield **4** (9.37 g, 56.0 mmol, 94%) as colorless crystals.

(4R)-1-Benzoyl-7-Methyl-4-(prop-1-en-2-yl)Azepan-2-One (Bz-LiLa): 25 mL 2-Methyl-THF (21.25 g, 8.2 eq) were cooled in an ice bath and NaH (540 mg, 15.5 mmol, 2.60 eq.) was added under inert conditions. After 10 min **4** (1.00 g, 6.0 mmol, 1.00 eq) was added portion-wise within 5 min. After stirring for 2 h, benzoyl chloride (1.00 mL, 7.80 mmol, 1.30 eq.) was slowly given to the mixture. The mixture was allowed to reach room temperature and was stirred for 12 h before 20 g ice was slowly added. After extraction with cyclohexane (3 × 100 mL), the combined organic phases were washed with NaOH (2.0 M, 2 × 100 mL), with sat. aq. $NaHCO_3$ solution (1 × 100 mL) and sat. aq. NaCl solution (1 × 100 mL) and dried using Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 cyclohexane: EtOAc, Rf: 0.3) to yield **Bz-LiLa** (0.85 g, 3.30 mmol, 75%) as white crystals.

Polymerization: Specific quantities of 4, Bz-LiLa and catalyst/initiator were added to a crimp neck vial under argon atmosphere. The vial was sealed and placed in a heating block for 12, 24, or 60 h time at a given temperature. Subsequently, the vial was cooled to room temperature and opened. The obtained product was dissolved/suspended in chloroform (1 mL) and precipitated in n-hexane (20 mL). After centrifugation (4300 rpm, room temperature, 4 min) the product was washed with hot n-hexane (5 mL) and EtOAc (1 mL), filtered and dried in vacuo. The obtained LiPAs were analyzed via GPC, NMR, DSC and TGA.

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.

Author Contributions

M.M.K., P.N.S., and M.W. conceived the work and designed the project. M.M.K. and L.Z. performed the synthetic experiments and M.M.K. performed the characterizations. X-ray experiments and structure determination via X-ray and related manuscript/supplementary sections were conducted by J.Y.L. M.M.K. and M.W. wrote the manuscript and the supplementary information.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords

limonene, polyamides, ring-opening polymerizations (ROP), sustainable polymers, terpenes

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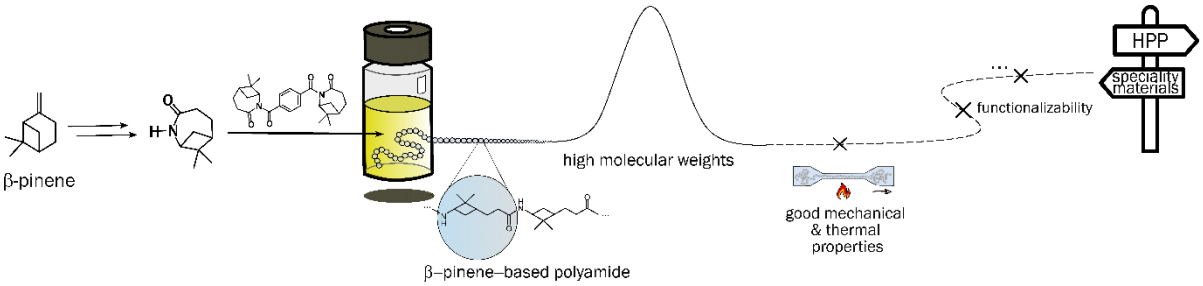
4.1.2. From Forest to Future: Synthesis of Sustainable High Molecular Weight Polyamides Using and Investigating the AROP of β-Pinene Lactam

Bibliographic Data



Title:	From Forest to Future: Synthesis of Sustainable High Molecular Weight Polyamides Using and Investigating the AROP of β-Pinene Lactam
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DOI:	10.1002/marc.202300524
Authors:	Magdalena M. Kleybolte, Malte Winnacker

Content

Nature-derived monomers can introduce unique structures into PAs, imparting distinct polymer properties. β-pinene, an abundant terpene in nature with a presumed stability-giving bicyclic structure, is therefore highly promising.

This work presents a simple approach for the AROP of β-pinene lactam, both in bulk and in solution, for the preparation of β-pinene PAs (**PiPA**). The study began with an investigation into the suitability of different initiators. NaH was found to be the most successful initiator for in-bulk polymerization, achieving a degree of polymerization (DP) of about 322. For solution-AROP, iPrMgCl·LiCl was successfully used for the first time, achieving DPs up to about 163. Both in-bulk and solution AROP were controllable in terms of polydispersity index and

molecular weight. However, solution AROP also offers the advantage of combining purification and processing, which is applicable in, e.g., fiber spinning.

All resulting PAs exhibited high molecular weights suitable for further processing. Indeed, it was possible to hot press the obtained PAs into uniform specimens, also enabling the analysis of their dynamic mechanical properties. As these bio-PAs offer good mechanical properties, high thermal stability (T_ds up to 440 °C), and a transparent appearance, they are highly promising for high-performance or specialty applications. However, challenges such as poor solubility, hydrophobic properties, or high processing temperatures need to be addressed.

In the end, this paper gives an overview of the potential application fields of this biomaterial and underlines the promising features of the high molecular weight **PiPA**.

Author contributions: The conceptual contribution was made by M. M. Kleybolte and M. Winnacker. Initial test reactions were executed by M. M. Kleybolte. M. M. Kleybolte planned, performed, and analyzed the experiments/ synthetic steps in this work. M. M. Kleybolte wrote the manuscript.

RESEARCH ARTICLE

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From Forest to Future: Synthesis of Sustainable High Molecular Weight Polyamides Using and Investigating the AROP of β-Pinene Lactam

*Magdalena M. Kleybolte and Malte Winnacker**

Polyamides (PA) are among the most essential and versatile polymers due to their outstanding characteristics, for example, high chemical resistance and temperature stability. Furthermore, nature-derived monomers can introduce hard-to-synthesize structures into the PAs for unique polymer properties. Pinene, as one of the most abundant terpenes in nature and its presumable stability-giving bicyclic structure, is therefore highly promising. This work presents simple anionic ring-opening polymerizations of β-pinene lactam (AROP) in-bulk and in solution. PAs with high molecular weights, suitable for further processing, are produced. Their good mechanical, thermal (T_ds up to 440 °C), and transparent appearance render them promising high-performance biomaterials. In the following, the suitability of different initiators is discussed. Thereby, it is found that NaH is the most successful for in-bulk polymerization, with a degree of polymerization (DP) of about 322. For solution-AROP, *i*PrMgCl·LiCl is successfully used for the first time, achieving DPs up to about 163. The obtained PAs are also hot-pressed, and the dynamic mechanical properties are analyzed.

1. Introduction

Synthetic polymers are nowadays indispensable. They are not only replacing expensive natural materials such as silk and metal, but also have superior properties regarding thermal and mechanical stability, weight, and production costs. In 1935, the first polyamide (PA) Nylon was synthesized by Carothers and Hill.[1] Since then, PAs have been particularly in the spotlight by playing an essential role in various fields of application. Their diverse set of properties, for example, temperature stability, solvent resistance, and superior mechanical properties, allow them to replace heavy or high-resistance materials and also to be used, for example, for multipurpose fibers. Especially the success of existing high-performance PAs has fueled the demand for new materials in fields such as lightweight construction, the automotive industry, and electronics.[2]

Biopolymers as well as bio-PAs, can meet many of these demands and open the doors to novel fields of application, such as biomedicine. This is because their bio-based monomers often have structural properties that are otherwise difficult to synthesize, for example, functionalizable olefin moieties and chirality.[3–8] Furthermore, using bio-based monomers not only paves the way for a sustainable polymer future but also renders their production independent from non-renewable raw materials.[9–13]

In this context, terpenes and terpenoids are important as they not only pose an abundant and renewable monomer feedstock but also show unique structural properties.[14–19] To preserve these functionalities, for example, double bonds, cyclic terpenes can be modified to their lactams as suitable monomers for anionic ring-opening polymerization (AROP).[3,20,21] This procedure is analogous to the established Nylon-6 (Perlon) synthesis from cyclohexanone via ϵ-caprolactam[3,20,22]

The most common terpenes in nature are pinenes, which can be relatively easily isolated from non-edible plant parts, for example, wood processing (turpentine oil). Among all pinene isomers, β-pinene is the easiest to modify to its lactam, as it exhibits an exocyclic double bond. This double bond can be oxidized efficiently to the ketone (nopinone), which is converted to its oxime and lactam, respectively. β-Pinene is therefore an attractive monomer for sustainable PAs.[23,24] Additionally, it is assumed that the bicyclic structure introduces high mechanical and thermal stability into the PA. In 2017, our group successfully "polymerized" β-pinene lactam for the first time, yielding rather oligomers than polymers.[3] In the following years, the monomer synthesis was further optimized in our laboratories, and the co-polymerization of β-pinene lactam with ϵ-caprolactone to polyesteramides was studied.[23,25,26] However, we were particularly interested in

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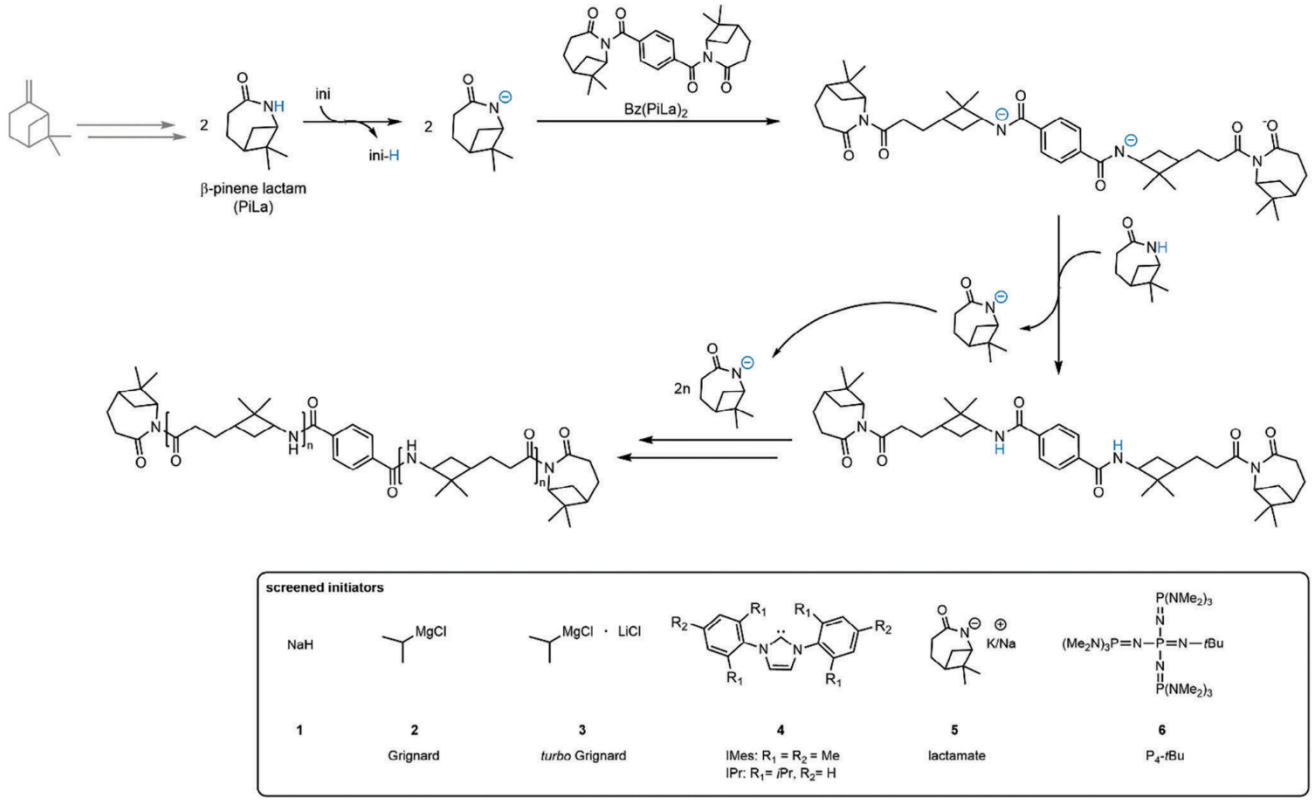

Scheme 1. General mechanism of the anionic ring-opening polymerization of β-pinene lactam (derived from β-pinene) with *N,N′*-terephthaloylbis(pinene lactam) as the activator. Showing six different initiators: NaH (1), Grignard *i*PrMgCl (2), turbo-Grignard *i*PrMgCl·LiCl (3), the carbenes IMes and IPr (4), pinene lactamate (5), the sterically hindered super-base P_4-*t*Bu (6).

bio-polymers, which are able to enter the high-performance field of application. Accordingly, it became obvious that we would need to increase the molar mass of the β-pinene oligomers significantly. Therefore, we want to shine light onto the preparation of high molecular weight β-pinene-PAs. Further, this work aims to prove that β-pinene-based PAs are materials with high mechanical and thermal stability caused by the bicycle.

In this work, we compare and evaluate different initiators for the anionic ring-opening polymerization of β-pinene lactam (PiLa) regarding their efficiency and suitability for high molecular weight PAs. We were also able to establish a solution-polymerization as an alternative to the commonly used in-bulk polymerization. Especially polymerization kinetics will be discussed in this context. Since we aim for processable PAs, we upscaled the polymerization and processed the resulting PA via hot-pressing. Furthermore, the synthesized PA specimens were analyzed regarding their dynamic mechanical properties.

2. Results and Discussion

AROP is the most commonly used method for polymerizing lactams.[27] As an initiator, AROP requires a strong but less nucleophilic base.[3] In our case, particular emphasis is placed on entirely removable or at least non cell-toxic initiators for a possible biomedical application of the obtained biopolymers. Therefore, the hydride NaH (1), *i*PrMgCl (2), the turbo-Grignard *i*PrMgCl·LiCl (3), the carbenes IMes (4) and IPr (5), and the isolated lactamate salt (6) were chosen as initiators.

The sole use of strong bases as initiators is only possible to a limited extent since this would result in high polymerization temperatures and relatively slow reaction rates; side reactions would therefore be unavoidable. Moreover, only the more reactive lactams, such as ϵ-caprolactam, readily polymerize in non-activated reaction conditions. The less reactive lactams are much harder to polymerize because the formation of the imide dimer is less favored. These limitations can be circumvented if the imide is generated beforehand by the reaction of the lactam with an acylating agent and used as an activator, often referred to as a co-initiator.

As illustrated in **Scheme 1**, the propagation step in the AROP of lactams is composed of the nucleophilic attack of the lactamate anion to the acyl lactam-type activator ($Bz(PiLa)_2$) and the following proton transfer from another lactam monomer molecule to the resulting amidate anion. Therefore, it can be concluded that the AROP depends on the activator's ring-opening ability and the lactamate's nucleophilicity.[28,29] Here, the bifunctional *N,N′*-terephthaloylbis(pinene lactam) ($Bz(PiLa)_2$) with two possible chain starts was chosen as the standard activator. Bz-PiLa, Jeffamine M600, and benzyl alcohol were also briefly tested as commonly used activators, especially in preparing related polyesters and polyesteramides.

We chose conventional in-bulk polymerization for the initial testing and evaluation of the various initiators listed in Scheme 1. This way, we tried to circumvent the solvent's influence, thus

Table 1. 1 mol% NaH and/or 1 mol% lactamate initiated ROP of 0.2 g PiLa at 170 °C for 4.5 h in-bulk with $Bz(PiLa)_2$ as the activator. In all cases we achieved full conversion and quantitative yields.

Entry	ini	5	n(act)/[mol%]	M_n/[kg mol^{-1}]	M_{theo}/[kg mol^{-1}]	PDI
1	1	–	0.3	15.6	51.1	2.5
2	1	K+	0.3	27	51.1	8.6
3	1	Na+	0.3	28.9	51.1	9.9
4	—	K+	0.25	22	61.3	7.8
5	—	Na+	0.3	18.3	51.1	7

solubility of the monomer, and a temperature limitation. Also, in-bulk is often industrially favored and, therefore, of great interest.[30] The temperatures were screened between 120–200 °C. 200 °C was chosen as the upper limit as we observed an uncontrolled auto-ring–opening above this temperature. In reverse, we observed no or nearly no conversion with temperatures below 120 °C. In previous studies, we have already found that 150–170 °C is a good temperature range for in-bulk homo-polymerization of limonene-, menthone-, and carene-derived lactams, proofing the observed temperature range for β-pinene lactam.[20,21,31]

However, besides the mentioned advantages of in-bulk polymerization, disadvantages like bad heat-transfer and diffusion limitations render the AROP uncontrolled. In contrast, solution polymerization is able to introduce new processing methods, workups, and control over the polymerization and gives access to other initiators.

2.1. In-Bulk AROP

Since NaH is a commonly used initiator in the AROP of lactams, we first analyzed the system NaH with $Bz(PiLa)_2$ as activator. In all in-bulk polymerizations we were able to prepare transparent PA with high yields and full conversion. However, in the first tests, we observed relatively broad polydispersity indices (PDI) (up to 10) especially with a longer polymerization time (>7 h). In this context, high PDIs are one of the major drawbacks and especially problematic regarding control, processing, and mechanical properties.

According to Hashimoto et al.[28], high PDIs can also be explained by the relationship between initiation (k_i) and propagation (k_p) rate constant k_i/k_p. Generally, a low PDI of PAs can be caused by the high value of k_i/k_p, whereas one reason for a high PDI can be a low value of k_i/k_p.[28] Since β-pinene lactam is more sterically hindered than in the case of, for example, ϵ-caprolactam, and its bicyclic structure favors a ring-opening due to ring strain, we already expected comparatively high PDIs. However, the values depicted in **Table 1** exceed this expectation by far higher PDIs. Kaalber et al.[32] state that viscosity and, thus, diffusion of the reaction mixture play a vital role in the nature of the polymerization kinetics. In our case, we noticed a significant viscosity increase up to the solidification of the sample during the in-bulk polymerization, which very likely causes a diffusion limitation. Additionally, heat transfer is significantly hindered due to the increase in viscosity, causing a temperature increase, which can lead to an "overshooting" of the polymerization. These assumptions were all validated by the results depicted in Table 1 and Figure S2, Supporting Information.

Based on these results we wanted a better insight into the polymerization behavior of β-pinene lactam. Instead of an in situ lactamate generation with NaH or KO*t*Bu via proton abstraction, we isolated this lactamate (5) and used it in comparison. Since k_i for 5 is greater than for NaH, we expected a PDI reduction. When the performance of NaH and 5 are compared, however, we observed higher molecular weights but also broader PDIs (see Table 1) for the lactamate. Apparently, the polymerization rates and thus viscosity increase so fast that their negative impact on the PDI overrules the positive aspect of the increasing k_i/k_p ratios.

Kinetic measurements for in-bulk polymerizations are especially challenging since it is difficult to draw aliquots due to possible quenching reactions and high viscosity. Nevertheless, for a first approximation of the kinetics, we prepared samples with NaH as initiator that were as identical as possible and extracted them from the heating block (170 °C) at different times (see section 3.1.1 in the Supporting Information). In general, the AROP of lactams is considered a quasi-living polymerization.[29,33] Because of the disadvantageous properties of in-bulk polymerization, the living character could not be observed here. Nevertheless, we were able to observe a controllable polymerization when activator and initiator concentrations were varied (see section 3.1.2. in the Supporting Information). As expected, the molar mass increases with initiator concentration and decreases with activator concentration due to the increasing number of chain starts. We found that long polymerization times either have no or even a disadvantageous effect on the chain length and PDI caused by the gel-effect/ diffusion limitation common for in-bulk polymerizations (see Figure S3, Supporting Information).

To overcome the broad PDIs, we choose Grignard and turbo-Grignard reagents as alternative initiators. This assumption was based on the fact that $k_{i,\,Grignard}$ is larger compared to $k_{i,\,NaH}$ and that probably fewer side reactions take place.[34]

In 2006, Knochel and co-workers succeeded in developing the mixed lithium and magnesium amide bases $R_1R_2NMgCl{\cdot}LiCl$ by reacting *i*PrMgCl·LiCl with the corresponding secondary amines.[35] Here we assume that an in situ Mg/Li-amide ($R_1R_2NMgCl{\cdot}LiCl$) base is formed via metalation of β-pinene lactam. Subsequently, this amide base initiates the AROP, as shown in Scheme 1.[34]

In this work, turbo-Grignard was—to the best of our knowledge—used for the first time as an AROP initiator of lactams. Even though we observed significant lower molar masses for turbo-Grignard–initiated AROPs (degree of polymerization up to 80) than those of NaH-initiated PAs (DP up to 322), it is evident that this initiator is advantageous regarding the PDIs (see **Table 2**). We will find this advantage again later in the solution polymerization. In addition, the decomposition and by-products of the initiator do not appear to have any known cytotoxic effects and, thus, do not appear to interfere with a potential biomedical application.

Finally, carbenes were screened as a promising initiator group. Although carbenes such as IMes and IPr are currently considered suitable for AROP, they were less effective than the other initiators in our case (see Table S3, Supporting Information).[36] They exhibited low yields and low molecular weights (degree of

Table 2. turbo-Grignard (*i*PrMgCl·LiCl) 1.3 M in THF initiated AROP of 0.2 g PiLa at 170 °C in-bulk with $Bz(PiLa)_2$ as activator.

Entry	*n*(ini)/ [mol%]	*n*(act)/ [mol%]	*t*/ [h]	M_n/ [kg mol^{-1}]	M_{theo}/ [kg mol^{-1}]	*Y*/ [%]	PDI
1	0.5	0.1	4.5	3.4	153.2	52	1.8
2	0.5	0.3	4.5	12	51.1	73	1.7
3	2	0.3	4.5	8.3	51.1	83	1.5
4	5	1	4	11.3	15.3	93	2.6
5[1)]	5	1	6	12.3	15.3	n.d.	3.9
6	11	1	4.5	14.5	15.3	98	1.8

[1)] Stirred for 4 h at 170 °C, 1 h at 180 °C, and 1 h at 190 °C

polymerization up to 25), and a brittle and black appearance of the polymers. However, as they are reported to be good initiators for ROPs and can tolerate oxygen and moisture when paired with Li- or Mg-salt, they will be investigated more in the future.

Even though in-bulk AROPs have, in general, several advantages, such as being a straightforward method for producing transparent PAs in quantitative yields that can easily be upscaled, we also observe several challenges and difficulties mentioned above.

2.2. Solution AROP

To suppress possible side reactions and broad PDIs, mild and controlled conditions are favorable. Solution polymerization usually prevents an abrupt increase in viscosity, guarantees a homogeneous mixed solution and thus allows a stable heat transfer and a more controlled polymerization reaction. Since the AROP of lactams requires somewhat high reaction temperatures, frequently used solvents, such as toluene and tetrahydrofuran, are not suitable. Additionally, lactams and their PAs have polar amide bonds with strong hydrogen bonding, so that their polymerization rate is strongly affected by (the changes in) the permittivity of the reaction mixture during the polymerization.[28]

Suitable solvents for AROP of pinene lactam are either DMSO (bp. 189 °C) or NMP (bp. 202 °C). The latter was used preferably in previous ROP studies for PAs, for example, by Cywar et al.[37] When we look at NMP and DMSO, both solvents perform similarly, although NMP seems to be slightly better. Differences are also not apparent costly wise and regarding the handling. However, DMSO stands out from NMP due to its safety profile. DMSO is non-toxic by all exposure routes, biodegradable and safe. Therefore, DMSO should be considered the more suitable solvent. Especially since we are aiming in the long run for biomedical applications.

Starting with initiator screening we adopted the polymerization conditions, that is, 0.4 mL solvent, from Cywar et al. (see **Table 3**).[37] Generally, we obtained—as expected—lower yields and molecular weights with similar reaction times also used for in-bulk polymerization. This can be explained by the lower concentration, and thus a lower chance to "meet," thus reacting with each other. Since a quasi-living AROP can take place when using a solvent, the yield and molecular weight are directly proportional to the polymerization time.[22]

Table 3. Solution AROP of 0.2 g PiLa with different initiators (NaH (1), Grignard (*i*PrMgCl) 2 M in THF (2), turbo-Grignard (*i*PrMgCl·LiCl) 1.3 M in THF (3), lactamate (5), P_4tBu (6)) in 0.4 mL NMP (entry 1–5) or 0.4 mL DMSO (entry 6–8) and $Bz(PiLa)_2$ as activator.

Entry	ini	*n*(ini)/ [mol%]	*n*(act)/ [mol%]	*t*/ [h]	*T*/ [°C]	*Y*/ [%]	M_n/ [kg mol^{-1}]	PDI
1	1	2	0.5	5	120	38	18	3.3
2	1	2	0.3	4	120	17	8.2	1.9
3	5	2	0.3	4	120	13	5.7	1.6
4	6	2	0.3	4	120	23	9.7	2.4
5	3	3	1	5	150	62	9.4	2.4
6	1	2	0.5	4	170	30	5.8	2.6
7	2	2	0.3	7	120	93	8.8	1.4
8	3	2	0.3	7	120	51	6.5	1.3

However, another advantage is the controlled polymerization termination with formic acid addition, which leads to a gel-like reaction mixture and easy purification by single precipitation in acetone. This purification method is very promising for fiber spinning, which renders processing facile and effective. But not only the processing and the work-up are significant advantages of solvent polymerization, but also the already mentioned more controlled reaction since we observed an increase in yield with increasing activator and initiator concentration. In Table 3, selected results are presented. If we compare the efficiency of the different initiators, it becomes apparent that 2 and 3 are the most efficient ones. However, also P_4tBu seems to be a very promising candidate.[38]

In contrast to in-bulk polymerizations, the kinetics measurement of solution polymerizations is much easier to conduct. In this work, we polymerized in a small scale using high-temperature NMR (HT-NMR) to analyze the reaction kinetics. For this purpose, the polymerization in deuterated DMSO is heated in a J. Young NMR tube to 140 °C—the upper-temperature limit of the instrument—and a ^{1}H-NMR is measured every 30 min to 1 h.

The conversion of the polymer is calculated by comparing the integrals of the polymer and lactam signals (see Supporting Information section 3.1.3.). This method for kinetic measurements is a rather convenient one, however, it is important to keep in mind that no stirring, that is, homogeneous mixing and heat transfer, can be guaranteed. **Figure 1** shows the conversion versus time of the best initiators for the in-solution AROP of *β*-pinene: Grignard reagent 2 and turbo-Grignard reagent 3. 3 was able to achieve an almost complete conversion after ≈9 h while 2 shows not only a lower polymerization rate (see Figure S4, Supporting Information) but also a conversion limitation of around 60%.

It has been reported that AROP can be supported by simple Li-salts addition.[39] It can therefore assumed that the usage of turbo-Grignard reagents is also beneficial for AROP.[34,35] Hermann et al. give recent insights into the enhanced reactivity of turbo-Grignard reagents via their different transition states. They postulate a barrier lowering effect of the incorporated lithium chloride influencing reactivity and, thus conversion.[40] We assume that a turbo-Hauser base formation can take place when *i*PrMgCl·LiCl is used.[35]

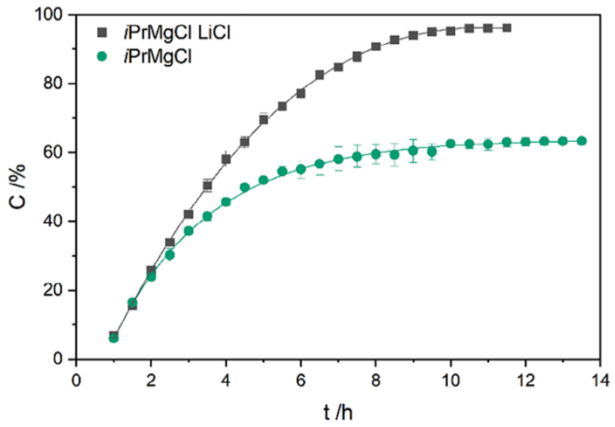

Figure 1. Kinetics of the HT-NMR measurements of the AROP with Grignard 2 and turbo-Grignard 3 as initiators at 140 °C in DMSO-d6. Every data point was measured at least three times to ensure reproducibility.

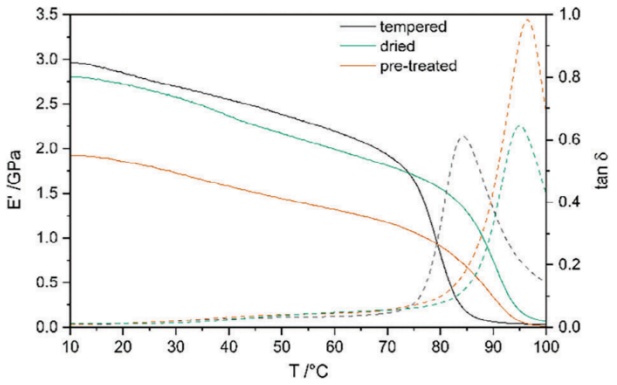

Figure 2. Influence of tempering and moisture for β-pinene PA analyzed via DMA measurements.

Summarized we introduced a successful in-solution polymerization of β-pinene lactam, which renders various processing and purification steps more straightforward. In addition, we were able to get a better analytical insight into the β-pinene-based PAs and were able to conduct in situ kinetic measurements of the AROP. HT-NMRs for the kinetic calculations can be found in the Supporting Information (see Figure S5, Supporting Information).

Comparing the kinetics of in-bulk polymerization and solvent polymerization, we should note that the methods of determining the kinetics are fundamentally different. Apart from this aspect, we can see that in-bulk polymerization is much faster but also much more uncontrolled. We need higher temperatures and harsh purification methods for the in-bulk polymerization whereas for solution polymerization higher reaction times, solvents and initiator concentration is required. All in all, both polymerization methods feature their own advantages and disadvantages and should be selected according to the following processing methods and applications.

2.3. Thermal Properties of β-Pinene Polyamide

Regarding the thermal properties (measured with TGA and DSC), we found very high T_gs up to 195 °C, T_ds up to 440 °C, and no detectable T_m. Especially the T_ds indicate a very temperature-stable PA. For a detailed insight, sections 4.3 and 4.4 in the Supporting Information can be consulted.

The lack of a T_m could be due to problems of forming dense parallel arrangements of the chains when larger and/or more complex side groups are present. In general, the larger the side groups, the worse the polymer can crystallize. Terpene-based amorphous PAs were also observed in carene PA: Amorphousness, micro-crystallinity, or a significantly longer crystallization time were reported by Stockmann et al.[33] and are consistent with our observations. Surprisingly, no formation of a T_m, and thus crystallization, was generated even after various processing methods such as milling, hot-pressing, solvent casting, or repeated heating and subsequent slow cooling.

2.4. Dynamic Mechanical Properties of β-Pinene Polyamide by Means of Hot-Pressed Specimen

The usual processing of polymers and plastics, including nylons, is melting and subsequent processing of the polymers by various techniques such as extrusion, molding, fiber spinning, and pressing. In our case we yielded amorphous PAs without a T_m which is usually necessary for the standard processing method melt pressing. Therefore, only hot-pressing at elevated temperatures was possible. For this reason, we used the determined thermal properties of β-pinene PA and prepared test specimens by hot-pressing and analyzed their dynamic mechanical properties via DMA. Through milling, washing, drying, and hot-pressing our PA, we obtained various transparent specimens (for more detailed information and pictures, see Supporting Information section 1.3 and Figure S1, Supporting Information).

If we compare both DSC and DMA analyses, we directly notice that the T_gs differ significantly and are considerably lower in the case of the DMA values. In general, we can attribute the reduction of the T_g to three main reasons. First, hot-pressing of the polymer granulate leads to increasing PDIs since the needed temperature is with 200 °C relatively high. To validate this hypothesis, we measured GPC for the milled and washed polyamide followed by GPC measurement of the hot-pressed specimen. We observed a decrease in chain length (from 8.9 to 7.69 kg mol^{-1}) and an increased PDI (from 4.3 to 5.8). Not only can the high temperature simply degrade the polymer, but also the terminal lactams can open and react at higher temperatures (see **Figure 2**). Self-polymerization and transamidation was already observed in former studies at 200 °C.[23] The second reason for the T_g differences in DSC and DMA measurements could be rooted in DMA-sample preparation after hot-pressing. Generally speaking, the hydrogen bonds between the polymer chains cause the high T_g. At the same time, however, the ability to form hydrogen bonds and the high polarity also cause the high moisture absorption of the PAs. Depending on the moisture uptake during sample preparation, different T_gs are therefore observed (see Figure 2). In addition, we produced the specimens by fusion molding and did not mill the specimen out of a polymer block obtained by cast molding. Uneven edges and surface defects like air inclusion can also contribute to lower T_gs and is very likely.

Last but not least large differences are often found in T_gs values determined by different methods due to the temperature range of the transition area and due to the fact that they reflect various aspects (mechanical or purely thermal) of the same process.[41]

In Figure 2, we can see, as mentioned above, the influence of temperature treatment and moisture content on the dynamic mechanical properties of pinene PA. Although the $T_{g,DMA}$ differs greatly from the $T_{g,DSC}$ intrinsic tendencies can be observed. First, the polymer specimen was stored under air for 2 days before the DMA measurements (pre-treated, orange). After measurement, we dried the sample overnight in a vacuum (dried, green) or tempered the specimen at 200 °C (tempered, black) for subsequent analysis. Based on this experiment, we can conclude that moisture has a negative effect on the dynamic-mechanical properties of the PA , as the storage modulus (E') deteriorates by almost one third. Tempering, on the other hand, improves the stiffness of the polymer up to 3 GPa (E') but lowers the T_g significantly.

We can conclude that the thermal and mechanical properties can be improved by modifying the preparation method, that is, milling out of a polymer block and tempering. The obtained results, however, already indicate a highly stable PA with possible applications for specialty and high-performance materials.

3. Conclusion and Outlook

In this study, we have developed and optimized simple AROP techniques for the bio-based β-pinene–lactam. By using AROP, we can prepare transparent bio-PAs with high molecular weights and conversion, which are suitable for further processing and applications. Both in-bulk and solution AROP can be controlled regarding PDI and molecular weight. Solution AROP, however, could also combine purification and processing, which would render this polymerization route favorable. The resulting PAs were characterized by their thermal and dynamic mechanical properties. Their excellent characteristics make them a promising bio-PA for high-performance or specialty materials for, for example, biomedicine.

We were able to extend previous work conducted in the field of terpene-based homo.PA in various aspects. First, when comparing the efficiency of other initiators in PA preparation with emphasis on subsequent biomedical applications, we concluded that NaH and the turbo-Grignard *i*PrMgCl·LiCl are the most suitable initiators. The solvent polymerization enabled the investigation of its kinetics up to a quantitative conversion. We were additionally able to study our otherwise hard-to analyze homo-PAs. Turbo-Grignard reagents, used for the first time for AROPs, seem to be promising alternatives, especially for reducing the PDIs for in-bulk polymerization and in terms of solution polymerization. Although their role still needs to be further investigated, we can already see the advantages over conventional used initiators, for example the ability to fully convert β-pinene lactam to its PA with nearly no side reactions. Second, to evaluate whether the proposed polymerization can be applied in industry, we analyzed the mechanical and thermal properties of the resulting PAs. In all polymerization approaches we were able to produce transparent polymer films. Both the thermal and mechanical properties were very good with T_ds up to 440 °C. Also, hot-pressing was possible, and fiber spinning seems very promising when polymerizing in solution.

In the end, this paper should give an overview of the possible application fields of this biomaterial and underline the promising features of the high molecular weight β-pinene-based PAs.

Polymeric biomaterials are widely used in biomedicine. They are not only easy to manufacture, flexible, and biocompatible but also possess a wide—often tunable—range of mechanical, chemical, and thermal properties.[42] β-Pinene-based PA could introduce a high level of stability and durability into a biomaterial. However, β-pinene-based PAs have some challenges regarding processability and biocompatibility, for example, bad solubility, hydrophobic properties, or high processing temperatures. In the future, we will move beyond the homo-PA by studying copolymerization with other bio-based lactams, particularly limonene lactam. We hope this will allow us to overcome the already mentioned problems and introduce functionalizability into the PA.

4. Experimental Section

For the polymerization, the reagents were always added under an argon atmosphere in crimp vials and sealed with the corresponding air-tight high-temperature crimp lids. Syringes, needles, and spatulas were prior heated to 130 °C overnight before being transferred into the glovebox.

In-bulk Polymerization: β-Pinene lactam, activator, and initiator(s) were weighted in a glovebox in a crimp vial equipped with a stirring bar. The vial was closed with a flaring tool in the glove box, "sealed" with parafilm and placed in a pre-heated aluminum heating block outside the glovebox. After the reaction time, the samples were abruptly cooled to room temperature and immediately exposed to air. Since the polymer was insoluble in conventional solvents, they were cut into little pieces, sonicated in ethyl acetate over 4 h, and soaked in ethyl acetate overnight. After drying the samples in vacuo, they were analyzed via GPC, DSC, TGA, and IR.

Solvent Polymerization: β-Pinene lactam, activator, and initiator(s) were weighted in a glovebox in a crimp vial equipped with a stirring bar. The solvent was added via syringe into the crimp vial, which was subsequently closed with a flaring tool in the glove box and "sealed" with parafilm. The samples were placed in a pre-heated aluminum heating block outside the glovebox. After the reaction time, the vials were abruptly cooled to room temperature and immediately exposed to air, and 1 mL TFAA was added. After the polymer solvent mixture was completely dissolved, the polymer mixture was slowly participated in acetone by using a syringe. The resulting white polymer fibers were washed three times with acetone, dried, and analyzed via GPC, TGA, DSC, and IR.

Hot-Pressing of DMA Specimen: The purified polymer was milled and again washed with EtOAc and dried. The mold for hot-pressing was filled with the obtained white polymer powder and placed in the preheated hot press (200–210 °C). After the sample was heated for 3 min, 150 bar was applied and heated for another 5 min. The cooled sample was then removed from the mold and polished. The transparent specimen was then analyzed to determine its mechanical properties.

Supporting Information

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

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords

anionic ring-opening polymerization, β-pinene–based polyamide, biopolyamide, dynamic mechanical analysis, solution polymerization

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4.2. Co-Polymers: β-Pinene-Derived Polyesteramides and Their Blends: Advances in Their Upscaling, Processing, and Characterization

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Content

Polyesteramides (PEAs) can combine the excellent thermal and mechanical properties of PAs with the biocompatibility and biodegradability of polyesters. Moreover, the nature of co-polymers allows for the properties to be tuned depending on the percentage of PA or polyester incorporated into the PEA. This project focuses on the synthesis and characterization of terpene-based PEAs derived from β-pinene and ε-caprolactone.

The initial focus of this research was on optimizing the synthesis of the monomer β-pinene lactam from β-pinene. The oxidation of β-pinene to nopinone, the first step in the synthesis of β-pinene lactam, was made more sustainable and efficient using H_2SO_4 as a catalyst. A variety of catalysts and co-reagents were evaluated for the Beckmann rearrangement, with the reaction using tosyl chloride emerging as the most promising. This approach offers several advantages, including easier purification and greater scalability, making it a promising candidate for potential industrial applications.

After the successful monomer synthesis, the preparation of PEAs was investigated. A variety of initiators (here also called catalysts) were tested, with $Sn(Oct)_2$ and $Sn(Lau)_2$ proving to be the most promising for the ROCOP of β-pinene lactam and ε-caprolactone. The chain lengths of the β-pinene-based PEAs were remarkably increased from 6 kg mol^{-1} to more than 25 kg mol^{-1} by fine-tuning the polymerization. The resulting PEAs exhibited melting temperatures around 55 °C and decomposition temperatures of 354 °C or higher, demonstrating their high thermal stability.

For potential biomedical applications, blends of PEA with polyethylene glycol (PEG) were successfully prepared, yielding a more hydrophilic material. The mechanical properties of the blends were also improved compared to the brittle PA alone, as the processing of the polymer blends into test specimens was possible.

The study highlights the great potential of β-pinene-based polymers as high-performance polymers (HPPs). The findings contribute to the development of sustainable and efficient methods for producing terpene-based PEAs, paving the way for a more sustainable polymer industry.

Author contributions: The conceptual contribution was made by M. M. Kleybolte and M. Winnacker. M. M. Kleybolte planned and performed the experiments/ synthetic steps in this work. M. M. Kleybolte collected, analyzed, and interpreted the results. M. M. Kleybolte and M. Winnacker wrote the manuscript. M. M. Kleybolte wrote the supporting information.

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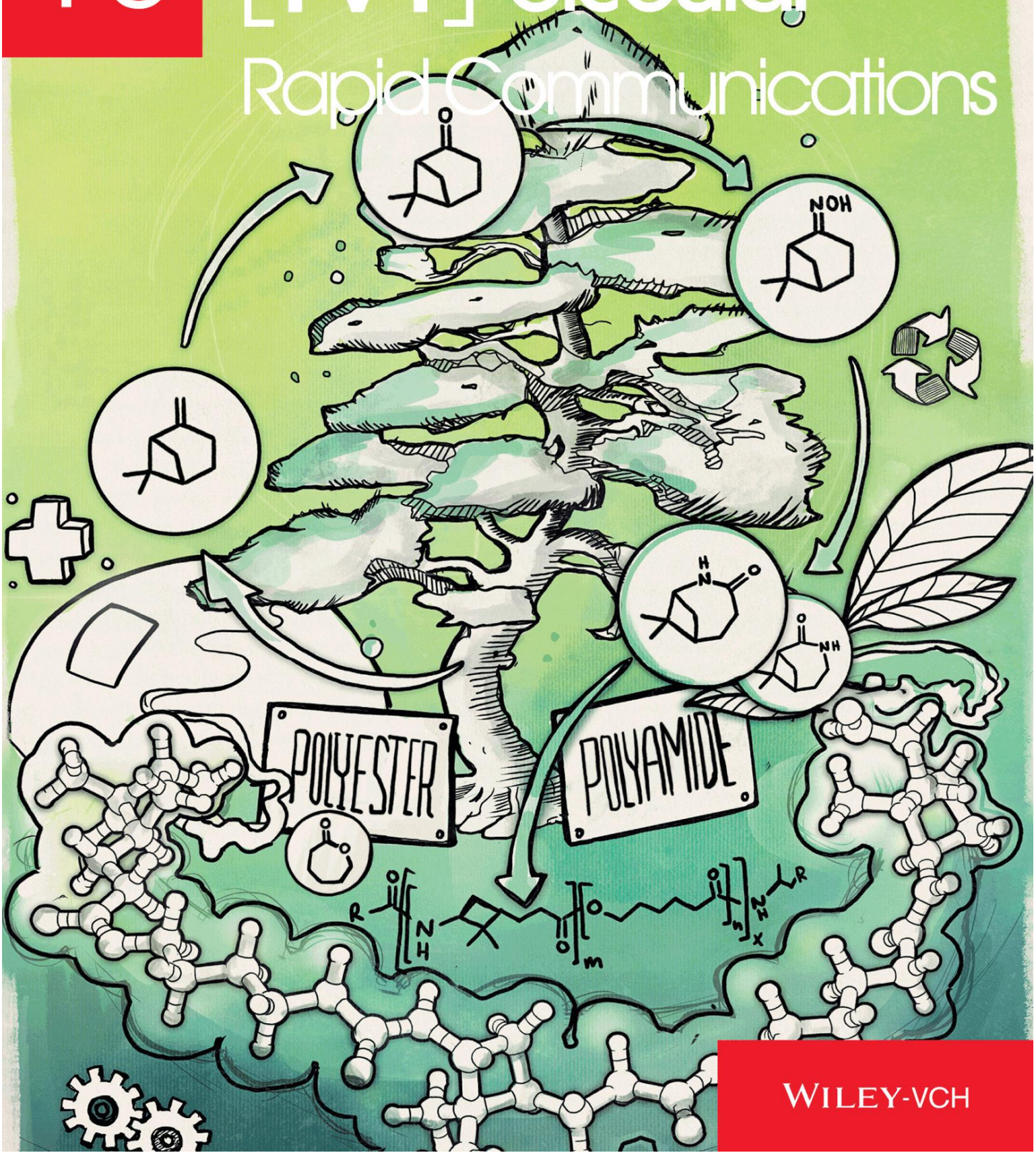

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β-Pinene-Derived Polyesteramides and Their Blends: Advances in Their Upscaling, Processing, and Characterization

*Magdalena Maria Kleybolte and Malte Winnacker**

Terpene-based polyesteramides (PEAs) are sustainable and have a variety of favorable properties, making them suitable for a wide range of applications and for contribution to a much more sustainable polymer industry. This work focuses on the synthesis of the lactam from β-pinene and its copolymerization with ϵ-caprolactone. An important step in synthesizing β-pinene lactam is the oxidation of β-pinene to nopinone. To make the established oxidative cleavage more sustainable and efficient, the required amounts of Al_2O_3 and $KMnO_4$ are significantly reduced by using H_2SO_4 as a catalyst. For the Beckmann rearrangement various catalysts and co-reagents are screened. Among these, the reaction with tosyl chloride is found the most favorable. Subsequently, the chain lengths of the β-pinene-based PEAs are remarkably increased from 6000 g mol^{-1} to more than 25 100 g mol^{-1} by fine-tuning reaction time, temperature, and decreasing catalyst and initiator concentrations. Also, different catalysts for polymerization are tested. The resulting material shows melting temperatures of ≈55 °C and decomposition temperatures of 354 °C or higher. Processing via melt pressing or casting turned out to be quite difficult due to the polymer's brittleness. Furthermore, regarding biomedical applications, blends of PEA with polyethylene glycol were successfully prepared, yielding a more hydrophilic material.

1. Introduction

Due to their diverse properties and cost-efficient mass production, plastics are almost irreplaceable in daily life and find a wide variety of applications. However, due to their durability and resistance to physiological influences, conventional polymers for mass plastics are often not able to degrade, resulting in many environmental challenges. Also, many of these polymers are processed in a costly, wasteful manner. The majority of polymers are still based on fossil resources, but depletion of the oil reserves due to the increasing energy demand is challenging us to find other monomer feedstocks.[1,2]

Biopolymers have the high potential of replacing conventional plastics by more sustainable materials.[3–5] In addition to natural functional polymers,[6] biopolymers are defined as such if they are either produced from biobased raw materials and/or if they are biodegradable.[7–11] Biobased materials are produced from renewable biogenic sources, for example, biomass. Biodegradability by itself describes the ideally complete degradation of a material by natural microorganisms to carbon dioxide, water, ammonia, or other metabolic products.[12,13]

The advantage of biobased materials is that—in addition to their sustainability, where their production etc. also have to be considered—new or complex molecules can be obtained relatively easily from nature, which cannot be obtained so easily via fossil-based synthetic pathways. Typically, it is challenging to synthesize molecules with special structural properties such as chirality. By using natural molecules, molecules that are difficult to synthesize can be sourced even in high quantities and in stereospecific forms. A differentiation can be made between a polymer approach, where natural polymers (e.g., polysaccharides) are utilized, and a monomer approach, where small molecules (e.g., carboxylic acids, terpenes, ...) are used for polymerization, either directly or upon further modification, is possible.[14–17]

For the synthesis of sustainable polymers, abundant natural materials, especially from non-edible plant parts, are preferable. Since terpenes obtained from many plants, like turpentine oil which is extracted from wood production in large quantity, they are particularly well suited as starting materials. The family of terpenes has a diverse range of structural properties with favorable, difficult-to-synthesize properties such as chirality or side groups.[18–20] For this reason, terpene-based polymers are a main

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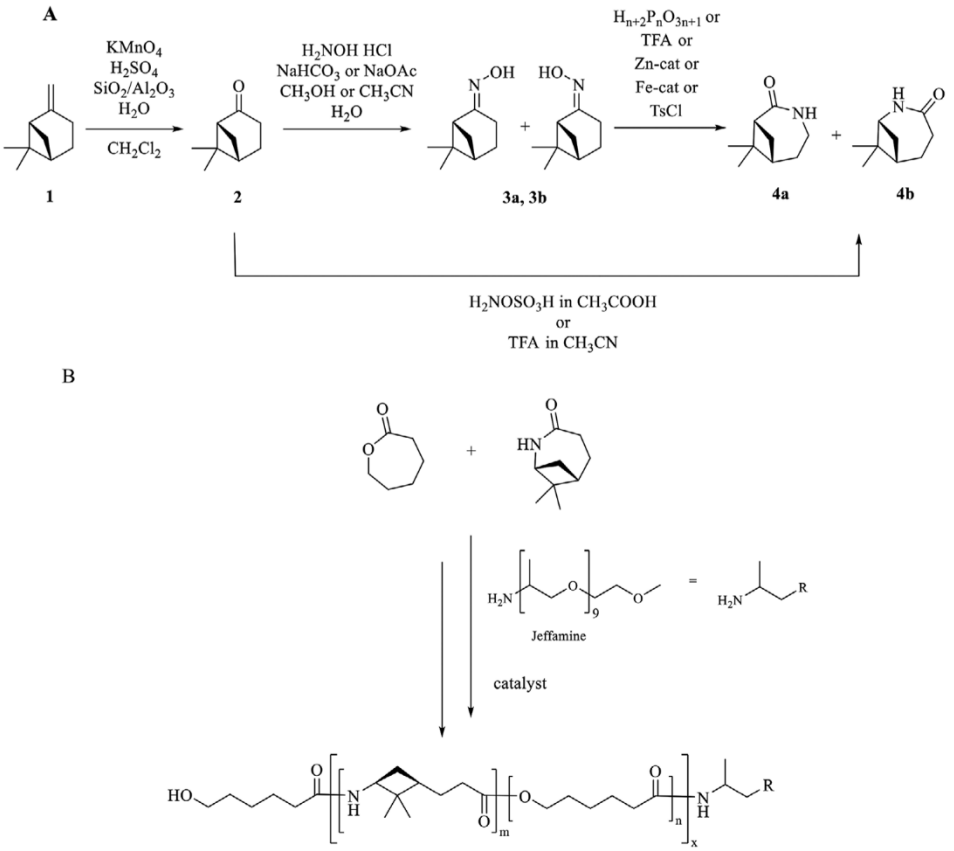

Figure 1. A) Overview of different synthesis routes of the lactams **4a**, **4b** and B) its polymerization.

aim in modern polymer chemistry, since they are not only non-food-based, sustainable, environmentally friendly but also have a wide range of structures and property profiles.[21–28]

Polyesteramides (PEAs) are very important polymers which can also combine the stiffness and excellent thermal and mechanical properties of polyamides with the biocompatibility and biodegradability of polyesters.[29–31] Moreover, because they are copolymers, it is possible to tune these properties in a variety of ways. Thus, terpene-based PEAs are prominent examples for biobased and biodegradable polymers and have been investigated in this study.

Pinenes are the main constituents of turpentine oil and have chiral centers, making them a particularly promising starting material. Although β-pinene occurs less frequently than α-pinenes, their exocyclic double bond is located more favorably for further synthesis. This work is therefore focused on β-pinene-based polyesteramides. To obtain such polyesteramides or polyamides, cyclic terpenoid ketones are converted to their corresponding lactams, which are then polymerized.[32]

β-Pinene-lactam-based polyesteramides have the potential to cover many important applications, and they could contribute to a more sustainable and "greener" polymer economy. Cost-effective, reliable procedures of their production are essential for this purpose. This study aims to investigate and significantly improve the synthesis of β-pinene-based polyesteramides and their terpene monomer. Further optimizing and analyzing the synthesis of β-pinene lactam as well as its copolymerization with ϵ-caprolactone represents an important progress toward a better understanding of the synthesis methods of these sustainable polymers.

2. Results and Discussion

2.1. Monomer Synthesis

The first step of synthesizing β-pinene lactam is the oxidation of β-pinene (**1**) to nopinone (**2**). For the further reaction to the lactams (**4a**, **4b**), two reaction routes are possible: the two-step reaction in which two regioisomeric oximes (**3a**, **3b**) are formed as intermediate products, and the one-step reaction with trifluoroacetic acid (TFA) or hydroxylamine-*O*-sulfonic acid (HOSA).[33–35] The corresponding overall reactions are depicted in **Figure 1**A. The lactam is then polymerized with ϵ-caprolactone by means of Sn-, Zn- or P-catalyst to the pinene-based polyesteramide (Figure 1B).

2.1.1. Nopinone Synthesis

The oxidation of β-pinene to nopinone (**2**) is a decisive step for this procedure that has fundamental significance also for further upscaling and possible industrial applications. In this study, this reaction is based on an experimental procedure described by Lee

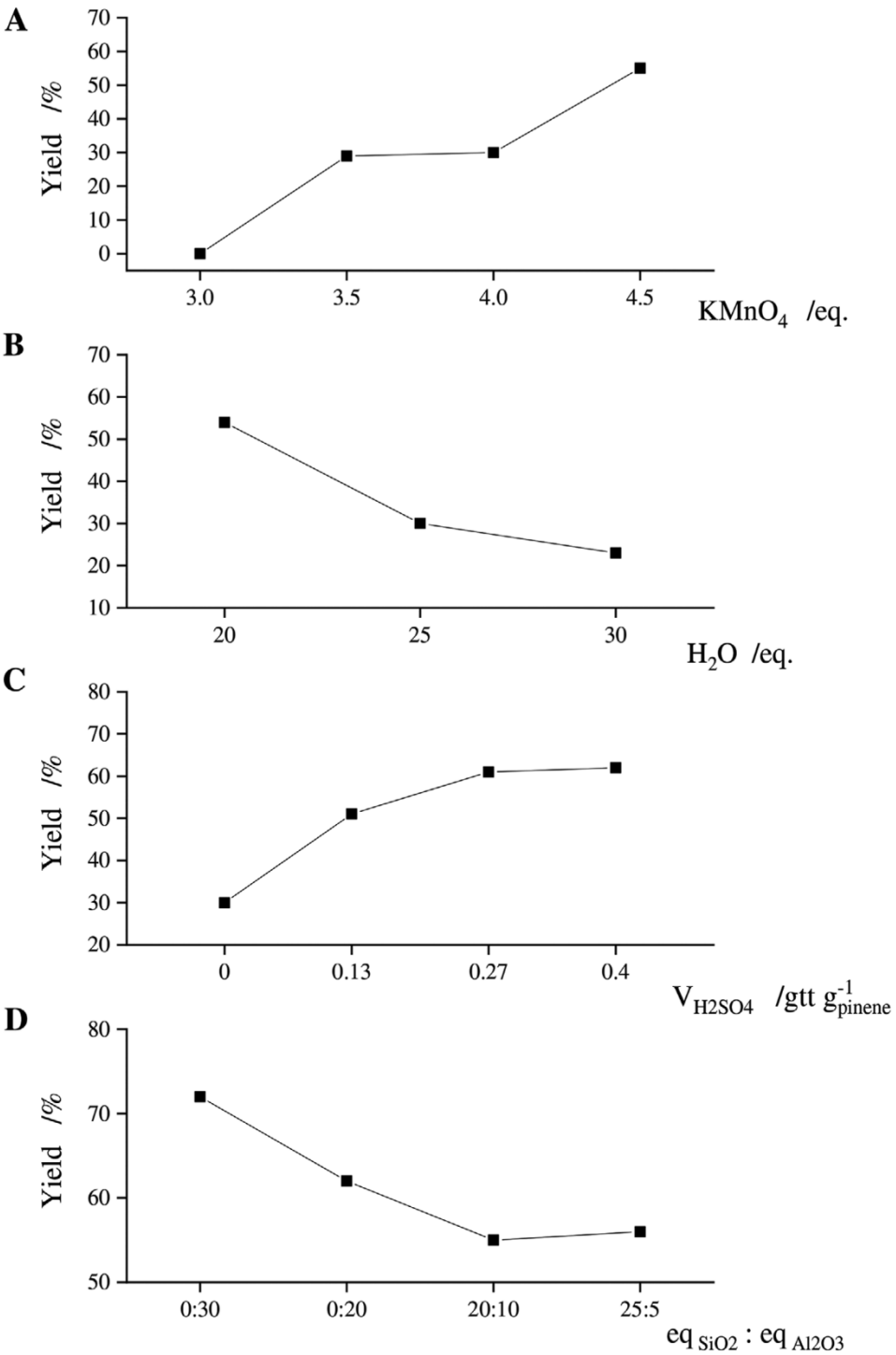

Figure 2. Trends and dependencies of the nopinone (oxidized β-pinene) synthesis. A) The higher the amount of $KMnO_4$ the higher the yield. B) With increasing V(H_2O) yield decreases. C) With increasing H_2SO_4 amount yield increases, where a limit occurs and D) with higher Al_2O_3 amounts higher yields were observed.

et al. using $KMnO_4$ as oxidant.[31] This initially cumbersome reaction requires large amounts of solvent, support (Al_2O_3), oxidant, and purification via column chromatography. Herein, the oxidation reaction was remarkably optimized with respect to reaction time, reaction equivalents, and purification method. For these further improvements, sulfuric acid was added as a catalyst, with the amount of H_2SO_4 having the greatest influence on the obtained yield (see **Figure 2**C). The yield increases with increasing acid amount, although no major improvement is apparent at a volume content higher than 0.27 gtt per 1 g β-pinene.

Table 1. Reaction conditions and results of selected tested catalysts.

Entry	m_{Oxime} [g]	Catalyst	$Eq_{catalyst}$	Solvent	$V_{solvent}$ [mL]	*t* [h]	*T* [°C]	Yield [%]
1	6	PPA	[a]	–	–	6.5	125	55
2	7	PPA	[b]	–	–	7	125	63
3	2	TFA	2.6	MeCN	26	5	80	traces[d], oligomers
4	2	$Zn(ClO_4)_2$ $6H_2O$	0.01	MeCN	26	6	80	traces[d]
5	2	$Zn(OTf)_2$	0.01	MeCN	26	6	80	traces[d]
6	2	$Zn(OTf)_2$	0.01	MeCN	26	4	85	traces[d]
7	2	$Fe(OTf)_2$	0.01	MeCN	26	4	85	–
8	2	$Fe(ClO_4)_2$ H_2O	0.01	MeCN	26	4.5	85	traces[d], oligomers
9	7.8	TsCl	1.05	MeCN/ 2 M NaOH	40/72	25	<20	31
10	5	TsCl	1.05	MeCN/ 2 M NaOH	20/46	24	<20	44
11	5	TsCl	1.05	MeCN/ 2 M NaOH	20/46	26	<20	59
12	1	citric acid	3	hexane	20	7	80	–
13	1	citric acid	0.3	–[c]	–	1.5	160	–

Temperature, (*T*); time, (*t*); volume, (*V*); acetonitrile, (MeCN); [a] 288 mL; [b] 144 mL; [c] inert atmosphere; [d] analyzed with ^{1}H-NMR.

In addition, adsorbent Al_2O_3 could partly be replaced by SiO_2 and the initially 30 eq. of Al_2O_3 were reduced to 10 eq. of each SiO_2 and Al_2O_3. Also, 4.9 eq. of $KMnO_4$ were reduced to 4 eq. An acid catalyzed upscale to 15 g was successfully established with yields of up to 62% and to 20 g with yields up to 30%. Furthermore, the complex purification step by column chromatography was replaced by convenient vacuum distillation ($T_{overhead}$: 52 °C, $T_{oil\ bath}$: 60 °C, *p*: 0.02 mbar). Although these oxidation reagents by themselves are not really green, their strong quantity reduction compared to previous procedures[21,36] make this synthesis much more easy and environmentally friendly. General trends and dependencies are shown in Figure 2 and resulted by a combination in the optimized nopinone synthesis. More detailed data can be found in the Supporting Information in Table S1, Supporting Information.

2.1.2. Lactam Synthesis

Two-Step Approach: The desired oxime (**3a**, **3b**) was first synthesized via the classical approach by converting nopinone (**2**) with hydroxylamine hydrochloride and sodium hydrogen carbonate for 6–7 h at 65–70 °C in $MeOH/H_2O$.[37] The yields increased at longer reaction time and increasing solvent-oxime ratio up to 90%. An upscale was also successful: 25 g could be converted to **3a** and **3b** with yields as high as 92%. Alternatively, **2** was converted overnight at room temperature with $NH_2OH{\cdot}HCl$ and sodium acetate in $MeCN/H_2O$ or $MeOH/H_2O$ with yields up to 97% (see Table S2, Supporting Information). Following the paper by P. Stockmann et al. this mild synthesis route *o.n.* is more suitable for an industrial application.[23] Both isomers of the oxime were used in an unpurified state to synthesize the lactams **4a**, **4b** by Beckmann rearrangement, although the oxime was obtained nearly regioselective (^{1}H-NMR and IR-spectra is shown in the Supporting Information).

For the Beckmann rearrangement several catalysts and co-reagents were tested. **Table 1** shows the different catalysts/chemicals and their corresponding yields.[38] Although polyphosphoric acid (PPA) achieves higher yields, the alternative with tosyl chloride (TsCl) in 2 M NaOH (aq.) is preferable, since it is not only well suited for upscaling but also for industrial applicability as demonstrated by Stockmann et al. In addition, PPA is difficult to handle and due to the additional step of quenching also not very convenient.[23]

Generally, the selectivity of lactam as compared to side products was rather low, yields up to 63% were achieved. However, a selective synthesis between the lactams **4a** and **4b** was observed since lactam **4a** was obtained >98–100% in all cases. Regarding entries **5** and **6**, not only the selectivity but also the conversion was low, since more than 50% of the oxime remained unreacted. In case of entries **3** and **8**, not only **4a** was detected but also oligomers, which points to the high potential of these catalysts. For citric acid (entries **12**, **13**), surprisingly a complete conversion back to nopinone (**2**) was observed. Conventionally, the lactam is purified by column chromatography. Herein, this procedure could be replaced by recrystallization in hexane and subsequent sublimation (*T*: 70 °C, *p*: 0.03 mbar), rendering it much more suitable for industrial applications.

TFA-/HOSA-Route: HOSA and TFA[39] were explored as a potentially more efficient and less cumbersome single-step alternative to the two-step method. However, the HOSA route was more complicated and had a lower yield than the two-step method, while the TFA route only yielded traces of lactam **4a** and oxime **3a**, **3b** (see Table S4, Supporting Information).

In the case of the HOSA route, **2** is completely converted, indicating that the poor yield is due to the multiple favored side reactions. The already low selectivity, which was observed for the previous route, is therefore aggravated by condensing its two steps into one. In addition, if product was present (confirmed by ^{1}H-NMR) it could not be properly isolated even though the purification method was adjusted several times. This calls to question simple reaction screenings by NMR or GC-MS, which do not subsequently attempt to isolate the product. All in all, the two-step lactam synthesis via oxime and subsequent Beckmann rearrangement with TsCl has worked best here and has the highest potential for industrial applications.

2.2. Polymerization of the Monomers to β-Pinene-Based Polyesteramides

β-pinene-based polyesteramides were synthesized using catalytic ring-opening copolymerization (ROCOP) in bulk. Different tin, zinc, and phosphorus catalysts were used for the copolymerization: tin(II)-2-ethylhexanoate ($Sn(Oct)_2$), dibutyltin(II) dilaurate ($Sn(Lau)_2$), -which are known from neat lactone polymerizations-diethylzinc ($ZnEt_2$) and diphenyl phosphate (DPP). In addition to different reaction times and temperatures, different concentrations and catalyst-initiator ratios were tested. In order to obtain the PEAs, the two monomers β-pinene lactam and ϵ-caprolactone were copolymerized by adding the catalyst and initiator under inert conditions at given temperatures and times. The polymerizations with both $ZnEt_2$ and DPP resulted in polyesters with less than 1% polyamide content. They therefore indicate that they are well suited for ring-opening polymerization (ROP) for lactones, but not suitable for lactams.

The ROCOPs with $Sn(Oct)_2$ and $Sn(Lau)_2$ were initially carried out under certain conditions which were previously used in a study about PEAs that can form bioactive surfaces.[40] In the course of further improvements, reducing the catalyst concentration from 0.25 mol% to 0.05 mmol% and increasing the concentration ratio of monomer Jeffamine-M600 from 20 to 700, led to substantially higher molar masses (entries **6–9** and **2–5**) and higher yields (entry **b0-2**). Further increase in the concentration ratio of Jeffamine did not achieve additional improvements and the yield decreased again for ratios higher than 700 (entries **2–5**, **20–26**).

In general, it is important to mention that chain length and polymer yield was significantly increased with respect to the previously described procedure.[36] It should be noted that the standard crimp vial caps were replaced with temperature-stable ones with a PFTE/silicon insert. The best temperatures for the polymerization were determined to be between 200–205 °C. Temperatures of 105 °C and below failed to yield a polymer and temperatures of 250 °C led to short polymer chains and low yields.

After the polymerization parameters were optimized, an upscaling from 0.05 to 1.5 g was performed (entry **20–30**). As expected, chain length and yields decreased with increasing monomer concentration, leading to increase polydispersity indices (PDI). This is probably due to the differences in mixing and heat transfer. Selected polymerizations and their parameters are shown in **Table 2**. A more extensive table can be found in the Supporting Information (Table S5, Supporting Information).

Generally, the interpretations and assignments as previously reported were primarily used as a guide.[36] It is known that it is often challenging to characterize polymers by NMR, since dynamic processes coexist on very different time scales and both structural disorder and dynamic heterogeneity are present.[41] This challenge can also be observed regarding our polymers. In some cases, the assignments of the peaks to the polymers turned out to be quite difficult—due to the increased chain lengths compared to the previous study.[36] As a result, not all polyamide groups are clearly visible, since peaks have merged or are overlapping with the prominent polycaprolactone peaks, since they lie in the similar ppm ranges. Nevertheless, the characteristic polyamide and polyester peaks could be detected in all tested polymers with ^{1}H-NMR and/or IR spectroscopy (see **Figure 3**). In IR, the characteristic amide adsorption bands at wavelengths of 3280 and 1635 cm^{-1} and in ^{1}H-NMR the characteristic methyl groups at 0.88 and 1.14 ppm confirm the presence of polyamide. All detectable integrals of the polyamide were used for comparison with those of the polyester to calculate the incorporated monomer ratios. The highest amide–ester-ratio detected was 29:71.

In addition to chain lengths and monomer incorporations, the thermal and mechanical properties of the polymers were further investigated. First, the thermal properties were measured using TGA and DSC. The decomposition temperature of the measured polymers ranged from 275–557 °C. On average, the materials had decomposition temperatures above 354 °C, which shows their high stability. Melting temperatures were with up to 54 °C close to those of conventional polycaprolactones, and recrystallization temperatures were between 25–37 °C. However, these measurements do additionally show the presence of polyamide, due to wide melting temperature ranges or two different melting temperatures. The melting point tends to increase with increasing molecular weights as expected (**Table 3** and Table S5, Supporting Information).

To assess the material's mechanical properties, the PEAs were processed via melt pressing and casting. Due to the low proportion of polyamides, the material was expected to be elastic and easy to process. However, as soon as the material cooled down and hardened, spherulite structures appeared, demonstrating the PEAs' brittle character (Figure S12, Supporting Information).

2.3. Polyesteramides-Polyethylene Glycol Blends

PEA polymers have the potential to cover many important applications like bioactive materials in regenerative biomedicine. Since the polymers alone can be too hydrophobic for many biomedical purposes, that is, cell adhesion and cell growth,[42] blends with the hydrophilic biocompatible polyethylene glycol (PEG) M6000 were prepared with equal mass fractions.

Contact angle measurements (CAM) were performed for further surface analysis. CAM is an analytical method for determining the hydrophilicity within polymers. With increasing hydrophilicity, the contact angle (Θ_{av}) decreases. Therefore, the water droplet on the polymer surface becomes flatter. According to this analysis, the PEG blends have—as expected—a significantly lower contact angle and thus a higher hydrophilicity than the pure polyester amides (see **Table 4** and Figure S11, Supporting Information). It was also not possible to measure the Young's modulus since the blends were still too brittle despite their high PEG content. It was expected that the PEG content would result in an improvement of the mechanical properties.

2.4. Additional Analysis

Additional analyses such as scanning electron microscope (SEM) and biodegradability studies were performed. Both the fracture sites and the polymer surface of PEA-21 display a lamellar structure, making it a characteristic feature. A layered, flaky structure

Table 2. Reaction conditions and results of selected polymerizations and the resulting polymers. The molar ratio of lactam and lactone in feed was 1:1, except a) with 2:1 and b) 4:1.

Entry	$m_{\beta\text{-PLa}}$ [g]	catalyst	Catalyst [mol%]	[M]/[Jeff] ratio	t [h]	T [°C]	M_w [a)] [g mol^{-1}]	M_n [a)] [g mol^{-1}]	PDI	Yield [%]	PA:PE [b)]
b0	0.05	–	–	50	7	205	5300	2300	2.3	2	2:98
1	0.05	$Sn(Oct)_2$	0.2	50	7	205	1500	900	1.7	8	–
2	0.05	$Sn(Oct)_2$	0.02	50	7	205	7700	4700	1.6	13	13:87
3	0.05	$Sn(Oct)_2$	0.02	500	7	205	7200	4400	1.7	21	7:93
4	0.05	$Sn(Oct)_2$	0.02	600	7	205	8700	5100	1.7	25	6:94
5	0.05	$Sn(Oct)_2$	0.02	700	7	205	9000	5500	1.6	21	3:97
6	0.05	$Sn(Oct)_2$	0.2	900	7	205	1900	1200	1.7	20	–
7	0.05	$Sn(Oct)_2$	0.02	700	7	205	6100	3800	1.6	24	3 : 97
8	0.05	$Sn(Oct)_2$	0.02	700	7	205	8100	4800	1.7	28	–
9	0.05	$Sn(Oct)_2$	0.002	700	7	205	12100	6100	2	31	2:98
10	0.05	$Sn(Oct)_2$	0.002	700	7	205	15700	7100	2.2	23	2:98
11	0.05	$Sn(Lau)_2$	0.2	700	7	205	6400	3600	1.8	22	–
12	0.05	$Sn(Lau)_2$	0.02	700	7	205	16900	7300	2.3	30	6:94
13	0.05	$Sn(Lau)_2$	0.02	900	7	205	14100	6800	2.1	21	4:96
15 [a)]	0.05	$Sn(Oct)_2$	0.2	700	7	205	700	500	1.6	8	- [c)]
16 [b)]	0.05	$Sn(Oct)_2$	0.2	700	7	205	1400	600	2.2	8	- [c)]
			[mmol%]								
17	0.075	$Sn(Oct)_2$	0.2	500	8	205	28300	14300	2	88	–
18	0.075	$Sn(Lau)_2$	0.6	500	8	205	25500	12500	1.8	86	–
19	0.08	$Sn(Lau)_2$	0.03	600	7.5	205	13000	7100	1.8	79	–
20	0.08	$Sn(Oct)_2$	0.06	600	7.5	205	38800	18400	2.1	80	–
21	0.5	$Sn(Oct)_2$	0.1	700	8	205	25100	13600	1.9	13	20:80
22	0.5	$Sn(Lau)_2$	0.05	700	8	205	20300	11100	1.8	25	23:77
23	0.5	$Sn(Oct)_2$	0.1	700	7.5	205	6600	4500	1.5	14	17:83
24	0.5	$Sn(Lau)_2$	0.05	700	7.5	205	7300	4700	1.6	30	20:80
25	1	$Sn(Oct)_2$	0.1	900	7.5	205	10300	6100	1.7	48	29:71
26	1	$Sn(Lau)_2$	0.05	900	7.5	205	20400	9500	2.2	31	4:96
27	1	$Sn(Oct)_2$	0.1	900	7.5	205	10300	8300	2	13	–
28	1	$Sn(Lau)_2$	0.05	900	7.5	205	17800	10200	1.8	16	18:82
29	1.5	$Sn(Oct)_2$	0.2	700	7.5	205	7200	4700	1.5	9	6:94
30	1.5	$Sn(Oct)_2$	0.2	700	7.5	205	34600	11700	2.9	32	4:96

Temperature, (T); time, (t); molecular weight, (M); polydispersity index, (PDI); monomer concentration, [M]; (b0 = blind experiment; [a)] Determined by Gel permeation chromatography/ Size exclusion chromatography (GPC/SEC) and rounded up; [b)] Calculation as accurate as possible. Difficulties due to peak overlap and it has to be considered that there can be different homogeneities in the sample; [c)] not measurable due to high PA content thus solubility difficulties.

can be observed for the PEA-PEG-blend. As expected, its surface is similar to PEA-21, but it seems to be more structured (**Figure 4** and Figure S9, Supporting Information). This indicates a successfully prepared, relatively homogenous blend. Generally, structured surfaces can be observed in both cases. Especially regarding the PEA-PEG blend, these surfaces could be well suited for cell adhesion or similar bio-applications. In terms of biodegradability, the polymers show resistance and a high stability in soil over several weeks/month (Figure S10, Supporting Information); therefore, also experiments for longer times and within other environments are ongoing. In addition, exemplary images of the contact angle measurements (Figure S11, Supporting Information) and images of the test specimen (Figure S12, Supporting Information) are available in the Supporting Information.

3. Conclusion

β-Pinene-based polymers show great potential for different applications, and as a bio-based replacement for conventional plastics, or as HPPs. This work has focused on polyesteramides (PEAs) and their preparation using Sn-, Zn-, and P-based catalyst systems.

The synthesis route starts with the oxidation of β-pinene and proceeds with the formation of its lactam. β-pinene lactam is then copolymerized with ϵ-caprolactone forming PEAs. By searching over possible educt quantities and concentration as well as alternative down-streaming processes, the monomer synthesis reaction was significantly optimized. Compared to the current state of the art, this optimized reaction is much more efficient while requiring a much smaller amount of educts,

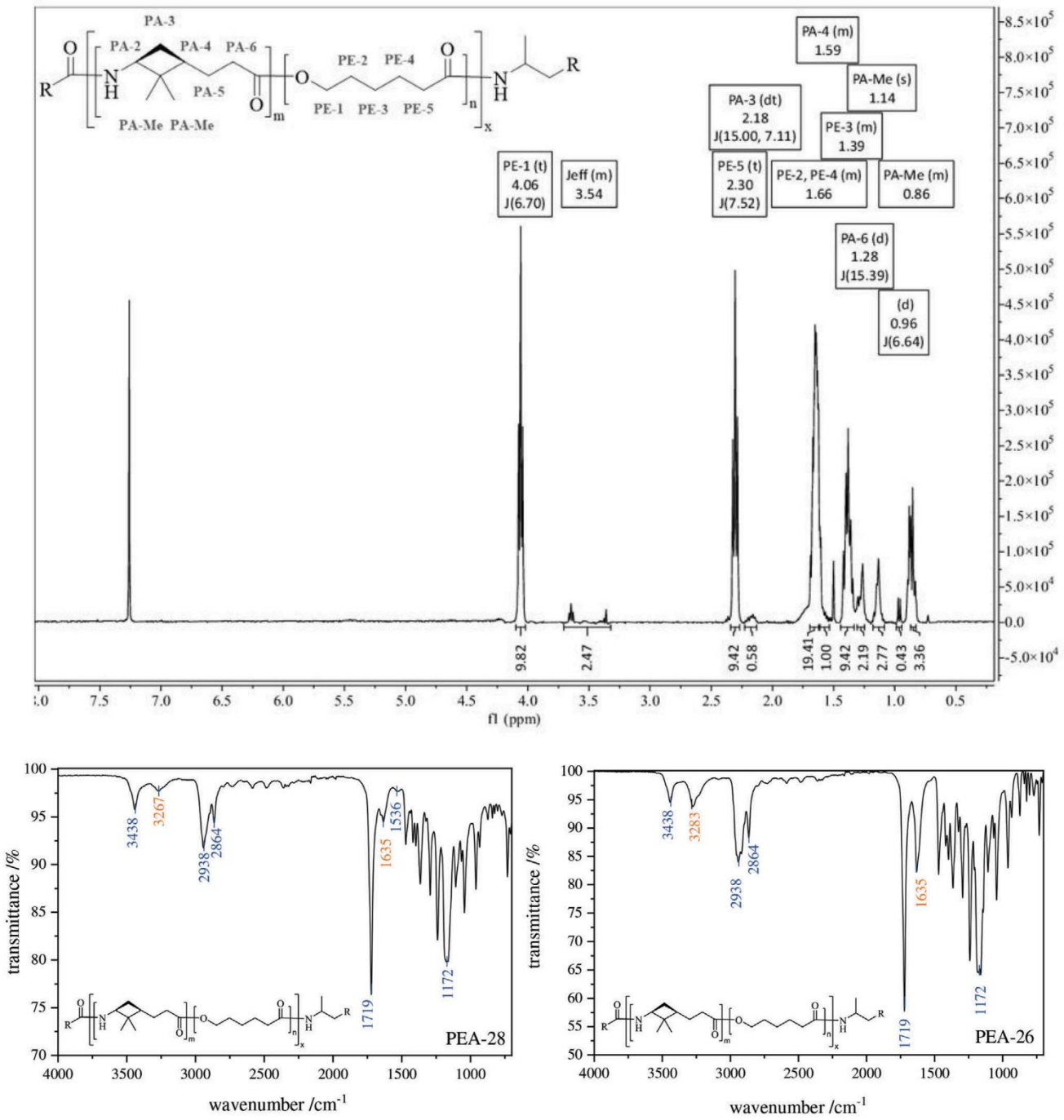

Figure 3. ^{1}H-NMR and IR-spectroscopy measurements (determined PA:PE ratios, left:18:82, right: 4:96) of exemplaric *β*-PLa-*co*-CLo copolymers.

compared to previous procedures. These findings render this production both less costly and much more sustainable. Other, more "green" oxidation procedures are currently under investigation. Also, different reaction pathways for the lactam formation were investigated. The oxime reaction could be optimized in terms of milder reaction conditions. Regarding the Beckmann rearrangement the normally used strong acids like polyphosphoric acid or sulfuric acid could be replaced with tosyl chloride in aq. NaOH. This not only enables an easier purification, but also renders upscaling more feasible, thus moving the reaction one step closer to a potential industrial application. $Sn(Oct)_2$ and $Sn(Lau)_2$ turned out to be the most promising ROCOP catalysts, since the other catalysts favored the ROP of ϵ-caprolactone. Therefore the polymerization of monomers to PEAs using tin catalyst systems was further improved. Besides optimizing temperature as well as catalyst and initiator concentration, replacing

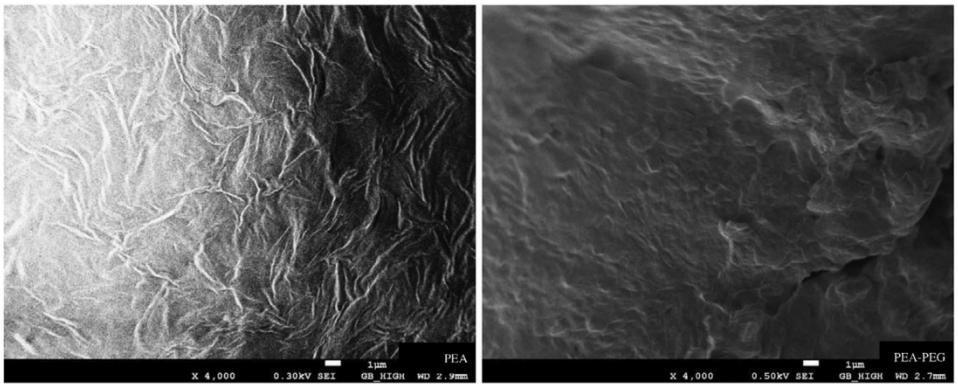

Figure 4. SEM imaging of PEA-21 PEA-PEG-blend.

Table 3. Thermal analytics of selected examples.

Entry	PE:PA	T_m [°C]	T_c [°C]	T_d [°C]
2	13:87	45.9[a)]	24.3	–
3	7:93	47	23.6	–
4	6:94	49.6	28.8	–
5	3 97	49.9	29.5	–
11	–	49.7[a)]	30.2	–
12	6:94	53.9[a)]	36.6	–
13	4:96	53.6[a)]	34.8	–
21	20:80	51.5[a)]	34.3	–
22	23:77	–	–	368.1
23	17:83	42.6	29.1	353.7
24	20:80	43.2	29.5	351.8;557.2
25	29:71	45.9[a)]	31.1	334;525.9
26	4:96	45.3[a)]	33.8	418.2
27	n.p.	44.4[a)]	27.2	177.7;404.6
28	18 :82	38.8[a)]	25.3	167.7;362.7

[a)] broad peak, indicating PA content; [b)] two peaks indicating a high PA content.

Table 4. Contact angle (Θ) measurements of two selected PEA-PEG blends and their PEA.

Polymer	Θ_1	Θ_2	Θ_3	$\Theta_{average}$
PEA-21	91.5	86.5	95	91
PEA-21-PEG	79	72.5	78	76.5
PEA-c21	99.5	91	92	94.2
PEA-c21-PEG	62	62	63	62.3

the standard crimp vial caps with ones with a PTFE/silicone seal led to polymer chain lengths with more than *M*: 25 000 g mol^{-1}. This work shows that the investigated tin catalyst systems are very promising candidates for producing polyesteramides with high molar masses. However, to make the reaction more sustainable, "greener" catalyst systems than tin-based ones will be investigated in the future. High decomposition temperatures demonstrate the stability of these polymers, and melting points close to that of polycaprolactone confirm a relatively high proportion of polyester within these PEA copolymers.

Both thermal and mechanical properties can be further improved with increased chain lengths. They will also further be optimized by changing the ratio between polyamides and polyesters. The materials may be interesting for the biomedical field, and—depending on its properties—they could also find use as a replacement for conventional plastics or an HPP. As the polymer alone is too hydrophobic for most biomedical purposes, for example, cell adhesion and cell growth, blends with PEG were produced, which have an increased hydrophilicity. As a first step in this direction, the mechanical properties of the blends—as compared to the polymer alone—are presumingly improved, since the processing of the polymer-blends to test specimen were possible (Figure S11, Supporting Information). Additional catalysts as well as the synthesis of block copolymers are now under further investigation. Additionally, improving not only the PEA alone, but also PEA blends would likely improve these properties and should therefore a focus of future research. Also, other bio-based polymers for blend production, such as polysaccharides, other terpene-based PEA, polyesters, and polyamides, as well as polyhydroxyalkanoates are possible candidates for further optimizations. In the future, the reactions should further be optimized in order to render the polymers suitable for large-scale applications. The family of *β*-pinene-based polymers should be further explored, with regards to polyesteramides, polyamides, or polymer blends.

This work has thus made further steps in this direction by making the production of *β*-pinene lactam, a structurally significant terpene resource, much more efficient and by improving the subsequent copolymerizations with a lactone, and it has thus further illustrated the great potential of these resulting materials.

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.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

Keywords

β-pinene, polyesteramides, ring opening polymerization, sustainable polymers, terpenes

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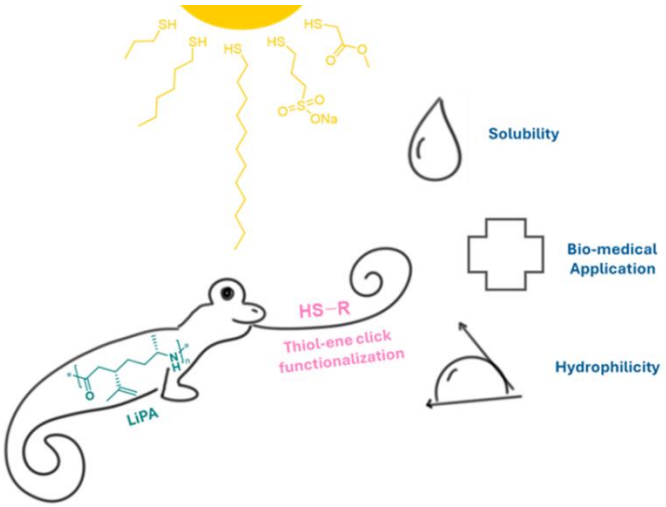
4.3. Functionalization of Limonene Polyamide

Bibliographic Data



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Content

Today, materials must meet increasingly specialized needs. The biomedical field, in particular, requires novel and innovative materials to meet specific criteria for special applications. In this work, the synthesis and functionalization of limonene polyamide (**LiPA**) is investigated as a promising alternative to conventional nylon for biomedical applications.

This project started with the optimization of the AROP of **LiPA**, achieving high molecular weights up to 54 kg mol^{-1} and making upscaling to 3 g possible. However, upscaling resulted in high polydispersity indices (2.7–4.6) due to mixing and heat transfer limitations during in-bulk polymerizations. Subsequently, **LiPA** was successfully modified with various functional groups (alkyl, ester, sulfonate) *via* thiol-ene click reaction, achieving up to 53 % modification. The modifications allowed for the tuning of polymer properties, including glass transition temperature (44–133 °C), solubility, and hydrophilicity. The alkyl modifications increased hydrophobicity and solubility in non-polar solvents, while ester and sulfonate groups improved

solubility in polar solvents, including methanol and even water in the case of the latter modification. All modified **LiPA**s exhibited hydrophilic surfaces ($\theta < 90°$), with alkyl groups increasing hydrophobicity. The sulfonate-modified **LiPA** showed amphiphilic behavior, forming micelles in aqueous solution, demonstrating potential for drug delivery applications.

In summary, this word demonstrated a successful tunability of **LiPA**'s properties through strategic side-chain modifications, paving the way for diverse biomedical applications. Although the findings are highly promising, further investigations are necessary, including the exploration of additional processing methods, the analysis of biocompatibility *via* cell tests, and the evaluation of specific biomedical applications. However, the high tolerance of the thiol-ene reaction towards various functional groups enables the future incorporation of bioactive moieties, such as cell-binding motifs for tissue engineering, which will facilitate the overcoming of the aforementioned challenges.

Author contributions: The conceptual contribution was made by C. P. Vogt, M. M. Kleybolte, and M. Winnacker. C. P. Vogt and M. M. Kleybolte planned and performed the experiments/ synthetic steps in this work. C. P. Vogt and M. M. Kleybolte collected, analyzed, and interpreted the results. M. M. Kleybolte wrote the manuscript and the supporting information.

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High Precision Tuning of Limonene Polyamide *via* Side-Chain Functionalization for Specialized Applications

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Keywords: limonene polyamide, polymer functionalization, terpene, biopolymer, tunable polyamides, micelles

Despite the success of conventional nylons in biomedicine, there is growing demand for specialized materials tailored to modern needs. Tunable and sustainable bio-polyamides (PAs) derived from terpenes offer a promising alternative. This work focuses on limonene polyamide (LiPA) synthesized *via* anionic ring-opening polymerization (AROP) from limonene lactam and its functionalization *via* thiol-ene click reaction. Optimizing the AROP enables the preparation of high molecular weight LiPA up to 54 kg mol^{-1} and its upscaling up to 3 g, rendering the material attractive for further utilization. Subsequent exploration of the side-chain functionalization *via* thiol-ene click chemistry allows for the introduction of diverse functional groups (e.g., alkyl, ester, sulfonate) and finetuning of the polymers' properties. The modifications give control over solubility, processability, hydrophilicity, and glass transition temperature (44–133°C). While alkyl groups increase hydrophobicity, all PAs display hydrophilic surfaces ($\theta < 90°$). Notably, the sulfonate-modified LiPA shows amphiphilic behavior, forming micelles in aqueous solution, demonstrating potential for drug delivery applications. The high tolerance of the thiol-ene reaction towards various functional groups enables future incorporation of bioactive moieties, like cell-binding motifs for tissue engineering.

In summary, this investigation demonstrates the tunability of LiPA's properties through strategic side-chain modifications, paving the way for diverse biomedical applications.

1. Introduction

Since ancient times, polymers have played a role in medical applications, with early instances revolving around natural polyamides (PA) such as wool and silk, particularly used in wound dressings.[1] As scientific understanding advanced, Nylon66 – the first synthetic PA renowned for its exceptional tensile strength, flexibility, and low tissue reactivity – entered the realm of biomedicine. Nylons – a term generally used for synthetic PAs – meet critical needs by producing a variety of medical devices. Nowadays, medicine is no longer imaginable without them.[2] The biocompatible properties of nylons are attributed to the presence of amide groups in their chemical structure, which share structural similarity with natural peptide bonds found in biomolecules. This structural resemblance is thought to contribute to the bio-inert nature of nylons, as they do not elicit significant immune responses or toxicity when introduced into the body.[1,3,4] Sutures made from nylon, particularly monofilament sutures, find extensive use in microsurgery due to their lack of interstices that could harbor bacteria and their minimal tissue irritation. Additionally, nylon-coated medical instruments, resistant to abrasions and chemical wear, endure sterilization processes effectively. Catheters, dental implants, and even drug delivery are also examples of successful PA applications in medicine.[2–6]

Despite the success of nylon, the demand for specialized materials in medical applications continues to grow. However, reliance on crude oil-based polymers, i.e. conventional PAs, poses challenges due to their limited structures, hindering the synthesis of desired functionalities. Moreover, concerns about the environmental impact and future availability of fossil resources prompt a reevaluation of polymer production methods. In response to these challenges, attention turns to sustainable alternatives, particularly biobased PAs tailored to modern biomedical needs. Nature provides a rich array of monomers with diverse chemical structures and functionalities, offering avenues for tailored properties through modification.[4,7–9] Terpenes – abundant and possessing unique structural properties – emerge as a promising feedstock for sustainable PAs. Terpene-based PAs hold the potential to address the evolving needs of specialty medical applications while mitigating environmental concerns associated with fossil-based PAs.[8,10–15] Through controlled polymerization techniques, these bio-based PAs offer a sustainable pathway forward, aligning with the imperative for sustainable, more efficient material solutions in biomedicine.[13,16]

Limonene polyamide (**LiPA**) is a promising bio-based polymer synthesized *via* anionic ring-opening polymerization (AROP) from limonene lactam, established by our group in *2022*.[15]

With its pendant alkene group, **LiPA** presents a platform primed for further functionalization to access special properties crucial in biomedical applications. However, in our group's latest study on **LiPA**, we realized that the polymerization requires optimization regarding its control, the material's properties and upscale.[15]

The objective of this article is to present a comprehensive approach to novel and tunable bio-materials derived from the terpene limonene. This work aims to optimize the AROP of limonene lactam first. With higher molecular weights, the mechanical and thermal properties of **LiPA** should also enhance, rendering the material attractive for application and further utilization. This hypothesis is going to be tested with various analysis methods, e.g. thermal analysis methods for the thermal stability. However, the true goal of this project lies in the exploration of **LiPA**'s side-chain functionalization through thiol-ene click chemistry, introducing diverse functional groups. Through strategic modification, the polymer's solubility, processability, hydrophilicity, and biocompatibility should be tuned, thereby broadening its scope for biomedical utility.

2. Results and Discussion

2.1. Anionic Ring-Opening Polymerization of Limonene Lactam to Limonene Polyamide – Optimization, Upscale and Characterization

In order to fulfill the objective of a tuneable material, it is necessary to first acquire a controlled ring-opening polymerization (ROP), defined molecular weights, reproducible upscale, and sufficient mechanical and thermal properties. In the following section, we suggest an optimized approach toward **LiPA** as a suitable material for processing and potential application with or without subsequent functionalization.

2.1.1. Optimization and Upscaling of the In-Bulk Anionic Ring-Opening Polymerization of Limonene Lactam

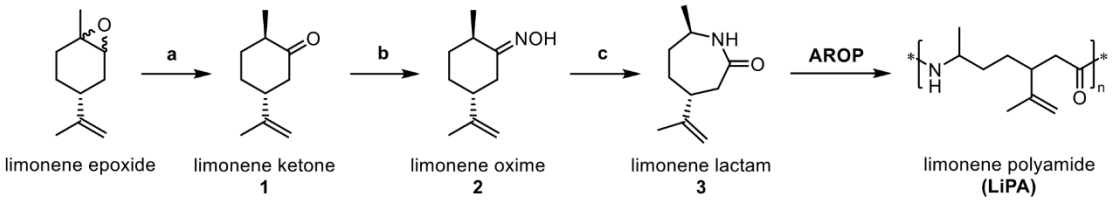


Figure 1. Synthesis route to limonene polyamide (**LiPA**). Limonene epoxide undergoes a *Meinwald* rearrangement (**a**) to the limonene ketone (**1**), which forms an oxime (**2**) *via* oximation (**b**). Subsequent *Beckmann* rearrangement (**c**) yields limonene lactam (**3**), which is polymerized *via* anionic ring-opening polymerization (**AROP**) to limonene polyamide (**LiPA**).

Before we discuss the preparation of **LiPA,** it is necessary to provide a brief outline of the monomer synthesis route. The synthesis of limonene lactam (**3**) from limonene epoxide was carried out following the optimized procedure by Kleybolte et al.[15] (see **Figure 1**). The initial *Meinwald reaction*, oxime formation, and eventually *Beckmann rearrangement* achieved a total yield of up to 84 % (for further details, please refer to the supplementary information). When employed in polymerization reactions, **3** was purified by crystallization and sublimation, with subsequent storage under an argon atmosphere in a glove box.

In the last years, our group has extensively studied the ROP of terpene-based lactams. In the case of α-pinene[14], β-pinene[10,11], 3-carene[8,14], and menthone[12] based lactams, AROP seemed to be the most suitable polymerization method. Following these findings, our group screened different polymerization conditions for **3** and was able to report a successful preparation of **LiPA** in *2022*[15]. The best results were achieved with NaH, P_4-t-Bu, and IMes

as initiators using benzoyl limonene lactam (**4**) as an activator.[15] However, the measured molar masses (M_w) of the polymers did not exceed 10 kg mol^{-1} with low yields, limiting their mechanical and thermal properties. Especially the low yields and bad reproducibility regarding the polydispercity index Đ troubled us the most. The main problem seemed to be the steric hindrance in both lactam and activator, paired with the reaction-prone propylene groups.[15]

To address these problems, we looked especially into the role of activators in AROPs: The general AROP mechanism is divided into initiation, propagation, and termination. The AROP of lactams is usually initiated by strong non-nucleophilic bases like alkali metal alkoxides or hydrides. These bases abstract a proton from the lactam monomer, generating a lactamate anion. This anion then attacks an activator or co-initiator molecule, typically N-acyllactam derivatives like N-acylcaprolactam, generating the first anionic propagating species. The use of activators is crucial as they facilitate the initiation step by providing an electrophilic carbonyl group for the initial nucleophilic attack of the lactamate. The initiation is followed by propagation through successive ring-opening, proton transfer to a lactam monomer, and nucleophilic attack of the lactamate.[2,7,17,18]

We already know that the simple replacement of activator **4** with a diimide-type activator, like **5,** results in significantly better results, as already observed in the case of β-pinene.[10,15] This can be explained by two possible growth centers and the decrease of the +M-effect by the substituted aromatic ring and the increase of resonance stability.[17] However, only when we used **6** a major improvement in polymerization yields and molecular weights were observed. Activator **6** shows compared to **5** reduced steric hindrance, enabling a better conversion *via* faster initiation (see **Figure 2** and **Table 1**).[19]

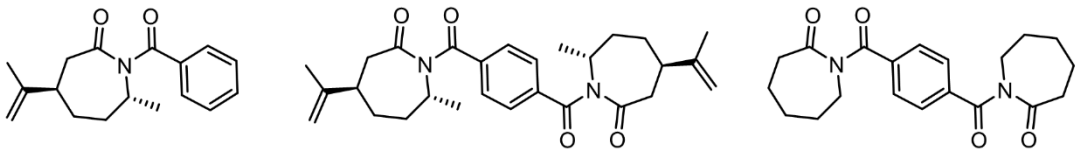


Figure 2. Different tested activators for the AROP of **3**: N-acyl limonene lactam **4**, N,N'-terephthaloylbis (limonene lactam) **5**, N,N'-terephthaloylbis (capro lactam) **6**.

Table 1: Selected anionic ring-opening polymerizations at 170 °C for 16 h using NaH as initiator and screening different activators and concentrations of activator and initiator. Y_{iso}= isolated Yield.

Entry	m(**3**) /g	act	n(act) /mol%	n(NaH) /mol%	Y_{iso} /%	M_n /kg mol^{-1}	M_w /kg mol^{-1}	Đ
1	0.15	**4**	4	10	20	2.3	3.4	1.5
2	0.15	**4**	8	10	30	2.3	3.5	1.6
3	0.15	**6**	2	10	21	8.7	13.6	1.6
4	0.15	**6**	4	10	99	>20	n.d	n.d
5	1	**5**	4	10	45	9	26	2.7
6	1	**6**	4	10	97	11	46	4.3
7	3	**6**	4	10	38	10	27	2.7

Our findings indicate that 10 mol% NaH and 4 mol% activator are the optimal conditions for achieving the best polymerizations and upscaling the batch size (see **Table 1**). We obtained molecular weights up to 27 kg mol^{-1} for 3 g monomer (entry 5) and 54 kg mol^{-1} for 1 g monomer (entry 4). As previously stated, the measured M_w was significantly higher when using $Bz(CaLa)_2$ as an activator (44 kg mol^{-1}, entry 2) than when using $Bz(LiLa)_2$ (26 kg mol^{-1}, entry 1). In addition to higher molecular weights, the Đs increased significantly for all reactions and were typically between 2.7 and 4.6. This is a common problem, as the higher batch size can lead to mixing and heat transfer problems. Applying other polymerization methods, such as solution polymerization, could reduce these limitations. However, when screening solution polymerization as employed for other terpenes, e.g., β-pinene, the AROP of **3** was unsuccessful (see supporting information chapter 1.2.2). We used the up-scaled reaction conditions to prepare **LiPA** for post-modification reactions discussed in the next chapter.

2.2. Functionalization of Limonene Polyamide

2.2.1. *Functionalization via Thiol-ene Click Reaction*

Click chemistry, pioneered by Sharpless, includes notable reactions like the azide-alkyne cycloaddition, the Diels-Alder reaction, and the thiol-ene reaction.[20] Their modularity, high yields, and inoffensive byproducts make them invaluable across fields like chemical biology and drug delivery.[20,21]

The thiol-ene click reaction is an *anti*-Markovnikov addition of thiols to alkenes. It can proceed through radically initiated or base-catalyzed pathways. The radical mechanism begins with a thiyl radical generated by UV light or heat. This radical then adds to the alkene, creating a

carbon radical that abstracts a proton from another thiol, forming the product. Alternatively, the nucleophilic pathway requires activated alkenes with electron-withdrawing groups and proceeds *via* thia-Michael addition.[22–24] Lenardao[25,26], Perin[27], Ranu[28] et. al. described catalyst-free thiol-ene reactions promoted by glycerol or water. These "greener" approaches avoid additional reagents but often lack high conversion or selectivity. [25–28] Thiol-ene click reactions have become indispensable in polymer chemistry due to their excellent yields, rapid rates, and functional group tolerance. They enable controlled post-modifications, introducing diverse functionalities inaccessible through conventional methods and tuning polymers' chemical and physical properties.[22,29]

In order to identify the most optimal conditions for a given reaction, it was necessary to select a suitable thiol model. In this instance, 1-hexane thiol was selected for its moderate size and lack of polar functional groups, which helped us avoid any potential electronic effects that could complicate our analysis.

At the beginning of this post-modification screening, we noticed that limonene polyamide comes with its own challenges that had to be first overcome: One of the major hurdles was the poor solubility of **LiPA** in most common solvents, especially at room temperature, due to the combination of strong hydrogen bonds between the amide units of the polymer backbone and the hydrophobic alkyl side groups.[15] However, we discovered a notable exception in hexafluoroisopropanol (HFIP), which is known for its ability to disrupt hydrogen bonds between amide units.[30] Additionally, we found that **LiPA** exhibited limited solubility in methanol, DMF, and DMSO at elevated temperatures.

In our pursuit of the optimal reaction conditions, we conducted a series of experiments to identify the most effective radical initiation methods, temperatures, solvents, and mixing effects. Through our investigations, we identified two successful systems: Photochemical radical initiation with DMPA in HFIP and thermal radical initiation with AIBN in MeOH at 70 °C. **Table 2** provides a comprehensive overview of our findings. By carefully considering factors such as solvent choice, temperature, and radical initiation methods, we were able to identify two promising protocols that pave the way for further investigations and potential applications.

Table 2: Reaction conditions for the post-modification of 50 mg LiPA with 1-hexane thiol in 5 mL degassed solvent. DB = double bond, C = Conversion.

Entry	Solvent	Radical initiator	T /°C	t /h	C_{DB} /%
1[a)]	THF	AIBN	70	6	-
2	HFIP	DMPA	r.t.	16	55
3[a)]	MeOH	AIBN	70	6	45
4	MeOH	AIBN	70	16	40
5	DMF	AIBN	70	16	-

[a)] Sonication instead of conventional mixing

It becomes evident that the success of the double bond conversion *via* the thiol-ene click reaction is highly reliant on the specific reaction setup. Prior to use, all solvents were degassed *via* freeze-pump-thaw method to prevent the formation of oxygen radicals. As anticipated, the thorough solvation of polymer chains is crucial for the reaction to proceed (smoothly). In THF, for example, where **LiPA** is insoluble even at high temperatures, no conversion was observed (**Table 2**, entry 1). The percentages of modified alkene units were determined *via* ^{1}H-NMR spectroscopy. It should be noted, however, that these values are merely estimates due to the challenges of accurately integrating polymer signals. Further description of the analysis of the NMR spectra is provided in the next section.

After evaluating different solvents, we investigated the impact of the radical initiation method. Photochemically initiated reactions typically occur at room temperature (r.t.) using a UV source (365 nm) and a radical initiator like DMPA.[22,24] Under these conditions, the unmodified polymer initially exhibited limited solubility in HFIP but fully dissolved after reacting overnight, indicating successful modification (**Table 2**, entry 2). When employing thermal initiation with AIBN in MeOH, the polymer exhibited near insolubility at room temperature but slight solubility at 70 °C. Once again, the polymer was completely dissolved after the modification reaction (**Table 2**, entries 3−4). It is worth noting that using HFIP at elevated temperatures was not feasible due to its low boiling point of 58 °C and corrosive nature.[30]

We were able to achieve moderate conversions, between 40% and 55%. This can be partially attributed to solubility challenges and steric effects. We observed that photochemical reactions demonstrated slightly better efficiency compared to thermal initiation. This finding aligns with the comprehensive study by Campos et al.[31] who observed that photochemical initiations

generally resulted in higher conversions than thermal initiations for polymer modification.[31,32] Notably, no reaction occurred when DMF was employed as the solvent, likely due to the fact that DMF can act as a protecting agent for the double bond through a Lewis acid-base interaction mechanism (**Table 2**, entry 5).[33] Although photoinitiation yielded slightly better results, it requires HFIP as a solvent, which poses serious environmental and health risks and is also expensive. To circumvent these concerns, particularly when scaling up the reaction, thermal initiation with a combination of AIBN and methanol was selected for further experiments.

2.2.2. Structural Analysis of the Modified Limonene Polyamide

With the optimized modification conditions established, the next phase of this study delved into a comparative investigation of how various functional groups impact the thermal properties, solubility, processability, and hydrophilicity of the polyamide. As illustrated in **Figure 3**, the research examined three alkyl chains (**7a–c**) with increasing length to elucidate the effects of escalating steric hindrance on polymer characteristics. Moreover, an ester (**7d**) and a sulfonate function (**7e**) were strategically incorporated to enhance hydrophilicity.

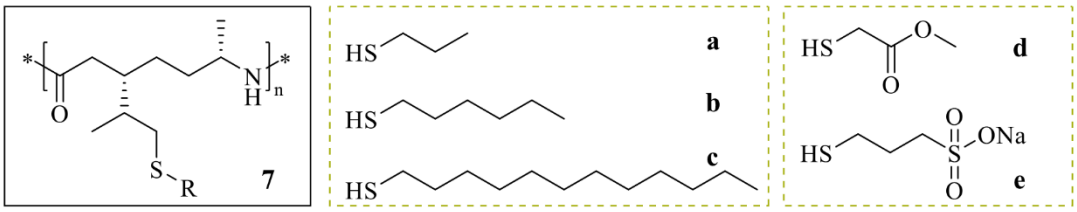


Figure 2. Structures of modified **LiPA** and the thiols used for modification.

The post-modification process was successfully scaled up from 50 mg to 300 mg, demonstrating its potential for practical applications. The successful modification was rigorously validated by ^{1}H-NMR spectroscopy, GPC, and IR analyses, ensuring the reliability and reproducibility of the results.

The alkene conversion was determined by ^{1}H-NMR spectroscopy. The spectra before and after the reaction of **LiPA** with 1-hexane thiol (**7b**) are shown exemplarily in **Figure 4**. Typical for polymers with broad PDIs, the ^{1}H-peaks also appear very broad, making it difficult to assign and integrate them precisely. Therefore, the CH-signal adjacent to the amide bond at 3.66 ppm (**Figure 4**, B) is used as a reference as it neither overlaps with other peaks nor changes during the reaction.[34]

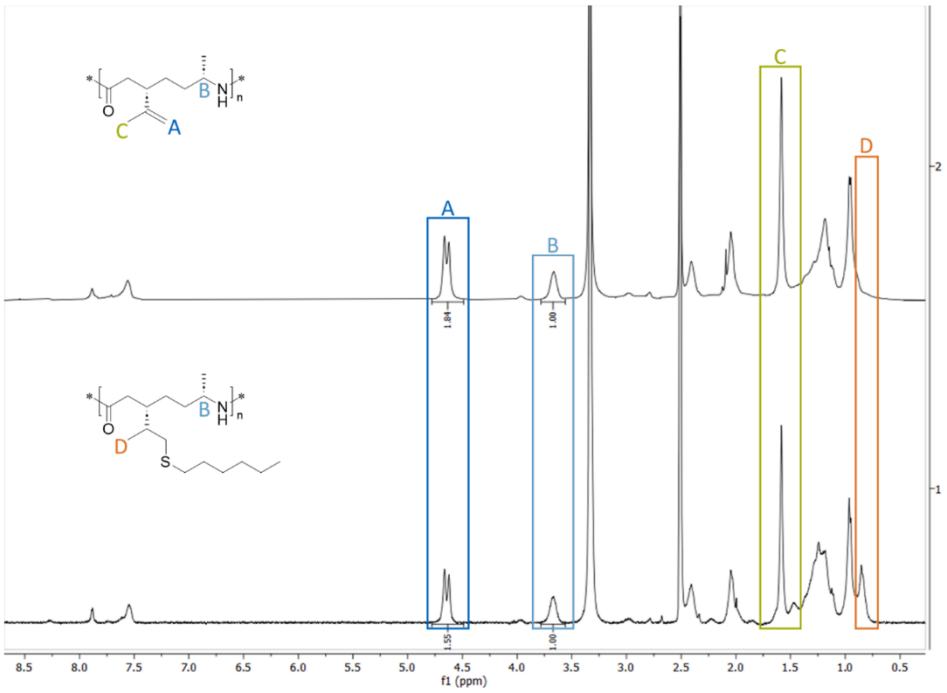


Figure 4: Comparison of the NMR spectra of unmodified and hexyl-modified LiPA (**7b**).

As anticipated, the alkene signal at 4.71 ppm (**Figure 4**, A) decreased for all successful reactions. Furthermore, the singlet at 1.58 ppm (**Figure 4**, C), corresponding to the methyl group next to the alkene unit, shifts to 0.83 ppm (**Figure 4**, D) as the chemical environment drastically changes when the double bond is consumed.[34] Unfortunately, new signals from the thiol modifications appear in the upfield region, making it impossible to assign them due to their overlap with the broad polymer signals. To circumvent this problem, we attempted to modify **LiPA** with an aromatic thiol, namely 4-Bromothiophenol, but this was unsuccessful. This may be due to steric hindrance or electronic effects caused by the bromide.

Furthermore, we employed infrared spectroscopy, as depicted in **Figure 5**, to investigate and compare the modified polymers. The C–S stretching frequencies of sulfides (ν=750–650 cm^{-1}) would indicate a successful modification. However, they are typically relatively weak, particularly for higher molecular weight sulfides.[35] As anticipated, we encountered this issue when analyzing the IR spectra of the modified polymers. Although we were able to detect a small signal at ν=730 cm^{-1} for some modifications, the intensity was too low to prove a successful modification. However, for the alkyl-modified PAs **7a–c**, the presence of sulfide alkyl chains becomes evident with increasing intensity of the signals between

ν=2950−2850 cm^{-1}. For the ester and sulfonate modifications (**7d** and **7e**), we observed new signals caused by the C–O vibrations (ν=1250 cm^{-1}) and S–O vibration (ν=1180 cm^{-1}), respectively. The absence of signals between ν=2600−2550 cm^{-1} indicates the absence of S–H stretching vibrations and, thus, thiols.[35] This implies that no free thiol is present in the polymer, and all new observed signals originate from covalently bound units. In conclusion, these results demonstrate the successful modification of **LiPA** with different thiols.

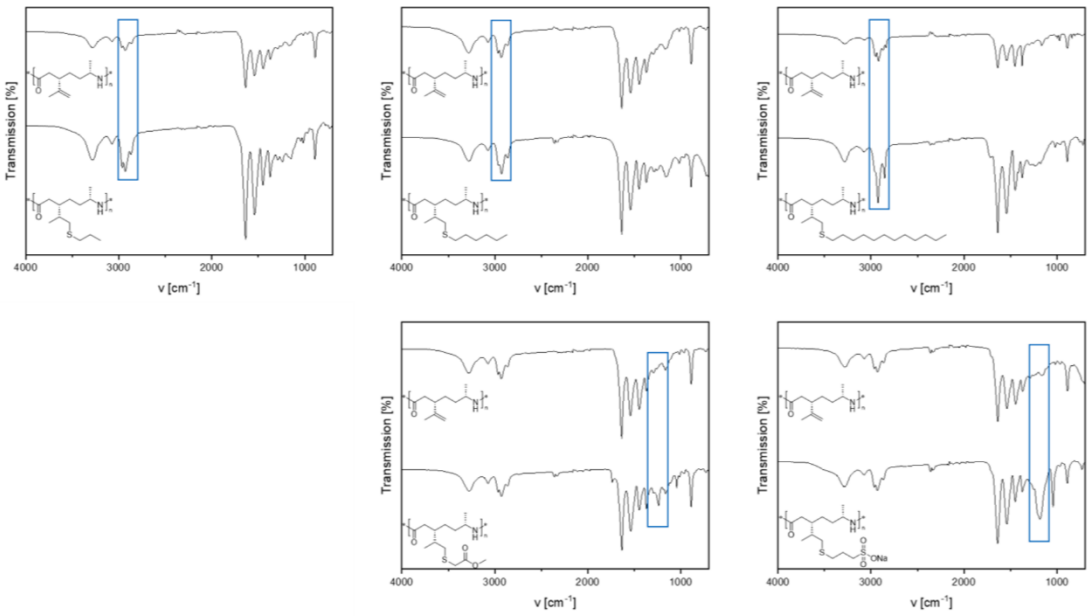


Figure 5: Comparison of the IR spectra of unmodified (top) and thiol-ene-modified LiPA (bottom). The blue boxes highlight the bands originating from the modifications.

The combination of these analytical methods clearly demonstrates the successful modification of LiPA. We were able to show that functionalization was not only possible with "simple" alkyl modifications but also with polar groups such as esters or sulfonate salts. This broad substrate scope enables the possibility of modifying LiPA with bioactive groups such as peptides or with antimicrobial groups, paving the way for biomedical applications. The following chapter will discuss the impact of the modifications on the polymers' thermal properties, processability, solubility, and hydrophilicity.[36]

2.2.3. Tuneability of the Thermal Properties of Limonene Polyamide

The polymers' decomposition temperature (T_d) is a crucial characteristic needed to determine their potential applications. Prior to this work, our group found that homo-LiPA exhibits high decomposition temperatures of up to 400 °C.[15] The findings here are consistent with those in

the literature, as the onset temperatures of unmodified **LiPA** (measured by TGA) ranged between 330−340 °C (see SI **Figure S9**). After modification, the T_d increased slightly for most samples, except **7e** (see **Table 3**). Since we only observed one weight loss with increasing temperature during TGA measurement, we suggest that the thioether moiety and the various functional groups remain stable at high temperatures, facilitating processing and enabling high-temperature applications.

DSC measurements indicate an amorphous material with no detectable melting point in the case of unmodified **LiPA**. This finding did not turn out as something new as we already argued in previous work that the bulky side groups can hinder crystallization.[15] After modification, the PAs remained amorphous and did not exhibit a melting point when DSC analysis was conducted between −25 and 200 °C (see SI **Figure S9**). Another important polymer property is the glass transition temperature (T_g).[37] We found that the glass transition temperature highly depends on the chosen functional group (**Table 3**). Alkyl modifications were assumed to decrease the T_g by disrupting the hydrogen bonding between the amide groups, thereby increasing chain flexibility.[34] Indeed, we saw a decrease in T_g ranging between 44 °C and 105 °C, whereas longer alkyl chains resulted in a stronger deviation (see SI **Figure S9**). In contrast, introducing highly polar sulfonate groups, and thus strong interactions between the sulfonate groups, increased the T_g to 133 °C.

These results demonstrate that T_g is highly dependent on the modification and can be specifically tuned by selecting different functional groups. The high T_d additionally facilitates processing and enables high-temperature applications.

Table 3: Decomposition and glass transition temperatures of **LiPA** and modified polymers **7a–e**.

	LiPA	**7a**	**7b**	**7c**	**7d**	**7e**
T_d	335 °C	375 °C	386 °C	381 °C	384 °C	328 °C
T_g	119 °C	98 °C	105 °C	44 °C	117 °C	133 °C

2.2.4. Tuneability of the Solubility of Limonene Polyamide

The processability of homo-**LiPA** is severely limited due to its poor solubility in most common solvents, rendering techniques like solvent casting nearly impossible. This limitation restricts the range of potential applications, such as coatings or film production. However, we were able to significantly increase the solubility by modifying **LiPA** as shown in **Table 4**, although it should be noted that the comparability of the different modifications is somewhat limited due to the different degrees of functionalization. As anticipated, polymer solubility increased after modification with alkyl chains due to their steric demand, interrupting hydrogen bonding between the amide units. Polymers modified with shorter alkyl-chains, such as **7a** and **7b**, exhibited good solubility in polar solvents, whereas longer alkyl chains shift the solubility towards non-polar solvents, demonstrating that solubility can be precisely tuned by varying the side chain size. By adding functional groups like an ester moiety (**7d**) or a sulfonate group (**7e**), we were able to tune the solubility even more. While **7d** remains insoluble in non-polar solvents and water, **7e** is showing amphiphilic properties, making it soluble in various organic solvents and water, allowing for purification by dialysis.

These findings highlight the versatility of **LiPA** modification, even with low alkene conversions, in tailoring their properties, paving the way for diverse applications that were previously inaccessible due to solubility limitations.

Table 4: Alkene conversions of **LiPA** with different thiol modifications (left) and the resulting solubility of the modified polymers (right). (-): insoluble, (+): soluble, (++): good soluble.

modification	C_{DB} /%	Hexane	$CHCl_3$	MeOH	DMSO	HFIP	H_2O
7a	45	-	+	++	++	+	-
7b	22	-	+	++	++	+	-
7c	55	-	++	+	-	-	-
7d	13	-	+	++	++	+	-
7e	44	-	+	++	+	++	++

2.2.5 Exploring Possible Applications – Processability, Hydrophilicity, and Micelle Formation

The processability of a material plays a vital role when finding/evaluating its potential applications. Here, solvent casting was not only employed as the processing method for further analysis but also as a suitable technique for potential coating applications. Solvent casting with a methanol-chloroform (1:1) mixture was successful for all functionalized polymers except for **LiPA** and **7c**, which needed HFIP as a solvent to yield even polymer films.

In most bio-active applications, materials require a hydrophilic surface to promote cell growth and mitigate the body's rejection response.[7] However, certain medical applications, such as hydrophobic coatings, demand contrasting properties to prevent adhesion or enhance durability. A tunable hydrophilicity would, therefore, enable tailoring the material's properties to meet specific requirements. Contact angle measurement (CAM) provides a valuable tool for examining the hydrophilicity of surfaces. The contact angle (θ) is defined as the angle formed between a liquid and a solid surface, in this case, water and the polymer film. If $\theta < 90°$, the surface is considered hydrophilic, whereas $\theta > 90°$ indicates a hydrophobic material. As surface roughness can major influence the θ, it should be considered when interpreting the results.

All modifications yielded hydrophilic material surfaces ($\theta < 90°$); even in the case of **LiPA**, we observed a contact angle of $\theta = 65°$. Since esters are classified as "hydroneutral" compounds no significant alteration of the hydrophilicity was observed. Our hypothesis that alkyl-functionalization decreases the polarity of the PAs and thus increases the contact angles, while sulfonate-functionalization should show the contrary effect, was validated when measuring CAM. Interestingly, the different alkyl lengths did not substantially influence the hydrophilicity when comparing **7a**, **7b**, and **7c** with functionalizations between 40–50% (θ = 74–77°). However, varying the degrees of functionalization played a crucial role, with higher functionalization percentages leading to lower contact angles: $\theta_{22\%} > \theta_{39\%} > \theta_{50\%} > \theta_{53\%}$. For more details, see the supporting information **Table S2** and **Figure S10**.

7e exhibited amphiphilic properties, which lead in the aqueous phase to self-assembling into micelles. We observed two distinct size maxima at hydrodynamic diameters of 18.4 nm and 152 nm, as revealed by dynamic light scattering (DLS) measurements (see supporting information **Figure S11**). Notably, filtration through PES membranes (0.2 µm pore size) or prolonged settling periods did not influence the micelle diameters, suggesting their stable nature.

The formation of these polymeric micelles holds promising potential for applications in loading-and-release systems, e.g. drug delivery.[5]

With achieving tunable hydrophilicity, combined with good processability *via* solvent casting, these materials are becoming promising candidates for various biomedical applications where tailored surface properties are a necessity. Hydrophilic or hydrophobic molecules, e.g. readily available amino acids, can be considered to actively tune the hydrophilicity further.

3. Conclusion

This project began by successfully scaling up the anionic ring-opening polymerization (AROP) of **3** to **LiPA** to a maximum batch size of 3 g, demonstrating the potential for large-scale polymerizations. Furthermore, we optimized the polymerization conditions, achieving molecular weights up to 54 kg mol^{-1}. However, the upscaling resulted in high polydispersity indices (Đ) between 2.7 and 4.6 due to mixing and heat transfer limitations during the in-bulk polymerizations.

After optimizing the preparation of **LiPA**, we investigated the functionalization *via* thiol-ene click reaction for accessing different applications, particularly in the field of biomedicine. With screening different solvents for the model thiol 1-hexane thiol, we were able to successfully modify **LiPA** in HFIP at room temperature with photocatalytic initiation, as well as in MeOH at 70 °C with thermal initiation, achieving a maximum of 53% modification of alkene units. Subsequently, we investigated the effects of different side-chain modifications on **LiPA**: alkyl modifications with varying lengths, an ester moiety, a sulfonate salt, and an aromatic group. The modification was successful for all groups except the aromatic ring, as confirmed by ^{1}H-NMR and IR. For all modifications, we observed excellent thermal stability with decomposition temperatures above 320 °C and no melting point between –25 and 200 °C, indicating an amorphous polymer.[37] The side chains allowed us to tune the glass transition temperature of the polymers, which ranged between 44 °C and 133 °C.

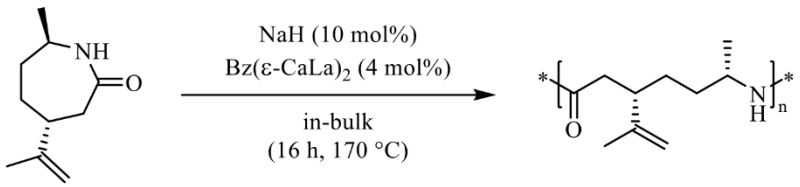
Finally, we studied the solubility, processability, and hydrophilicity of the polymers; as they are crucial for biomedical application. While alkyl functionalizations increased the solubility in non-polar solvents, the ester and sulfonate modifications improved the solubility rather in polar solvents such as MeOH. The improved solubility of modified **LiPA** facilitated processability, and we were able to coat glass slides *via* solvent casting, avoiding toxic solvents like HFIP or DMF. Contact angle measurements (CAM) showed hydrophilic polymer surfaces with contact angles below 90° for all unmodified and modified PAs. Additionally, we could tune the hydrophilicity and behavior in aqueous solution by side-chain selection. While alkyl side chains increased the contact angle, sulfonate-modified **LiPA** exhibited amphiphilic properties and formed micelles with two size maxima at hydrodynamic diameters of 18.4 nm and 152 nm in aqueous solution, as measured by DLS. The formation of these core-shell structures could lead to possible drug delivery applications.

In summary, this work demonstrated the successful tuning of various polymer properties by strategic side-chain functionalization. The attained enhanced solubility opens the doors to a diverse array of processability and, thus, applications. Moreover, with the tuneable hydrophilicity and behavior in the aqueous solution, we are likely able to tune the material in terms of biocompatibility and application area, e.g., drug delivery or medical device coating. The perhaps most intriguing finding is the high tolerance of the thiol-ene modification towards a diverse range of functional groups. This versatility empowers us to introduce bioactive groups, such as cell binding motifs (CBMs), into the polymer structure, facilitating tissue engineering.[36] Although the findings hold great promise, it is important to recognize that this is still early-stage, fundamental research. Further investigations regarding biomedical applications, including finding other ways to process these materials and analysing crucial properties like biocompatibility *via* cell tests, are nessecary.

4. Experimental Section/Methods

All used solvents and chemicals were purchased from Sigma Aldrich or Carbolution and used without further purification. For moisture-sensitive reactions, the solvents were dried with a BSPS-800-purification system from M.Braun GMBH and stored under argon atmosphere and over molecular sieves. HFIP was purchased from Carbolution Chemicals GmbH. Air and moisture-sensitive reactions were performed using standard Schlenk techniques in argon 4.6 atmosphere (99.996 % purity, Westfalen AG) or in LABstar glovebox systems by M.Braun GMBH.

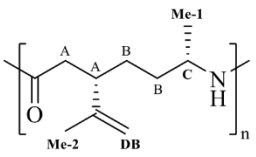
*Polymerization of **3** to limonene polyamide (LiPA)*



3 **LiPA**

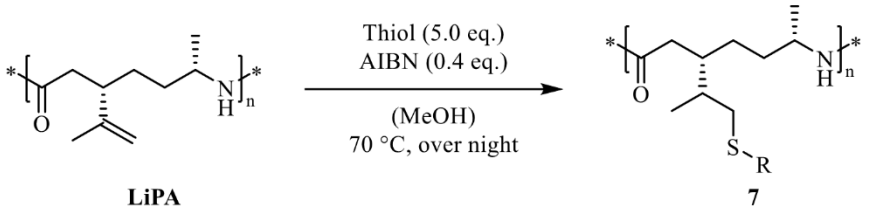
In the glovebox under argon atmosphere, 1.02 g of **3** (6.11 mmol, 1.0 eq.), 14.5 mg NaH (0.61 mmol, 10 mol%), 85.6 mg $Bz(CaLa)_2$ (0.24 mmol, 4 mol%), and a stirring bar were added to a dried crimp neck vial. The vial was sealed, placed in a heating block outside of the glovebox, and stirred at 170 °C for 16 hours. The polymerization was quenched by abrupt cooling to room temperature and by opening the vial with subsequent hexane or acetone addition. The dried polymer was then milled in a cryo-ball-mill, washed with acetone (3 ×50 mL), and dried in a vacuum, yielding 980 mg **LiPA** (5.90 mmol, 97 %) as a beige solid.

LiPA:



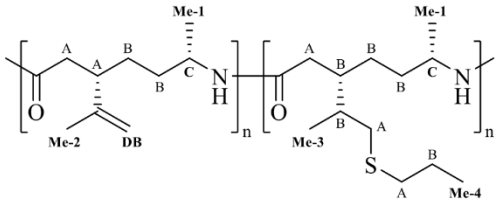
^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.52–7.34 (m, Activator) 4.64 (d, J = 15.1 Hz, DB) 3.79–3.55 (m, C) 3.21–2.58 (m, A) 2.45–1.66 (m, A) 1.58 (s, Me-2) 1.50–1.05 (m, B) 1.03–0.84 (m, Me-1).

Functionalization of limonene polyamide (LiPA)



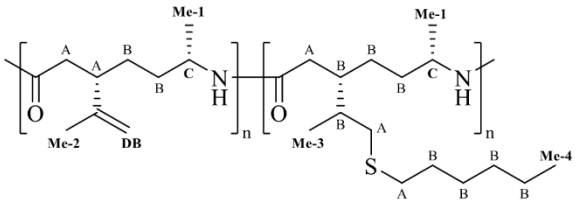
Under argon atmosphere, 1.0 eq. 15, 5.0 eq. thiol, 0.4 eq. AIBN, and GC-MS grade MeOH (10 mg/mL) were added to a pressure Schlenk-flask. The mixture was then degassed with the Freeze-Pump-Thaw method and stirred at 70 °C overnight. After cooling to room temperature, all volatiles were removed in vacuum. Compounds **7a**, **7b**, and **7d** were purified by dissolution in MeOH and precipitation in EtOAc three times. Compound **7c** was purified by dissolution in $CHCl_3$ and precipitation in n-hexane three times. Compound **7e** was dissolved in water and purified by dialysis (dialysis tube, 8 kDa) over three days. All compounds were subsequently dried in vacuum.

7a:



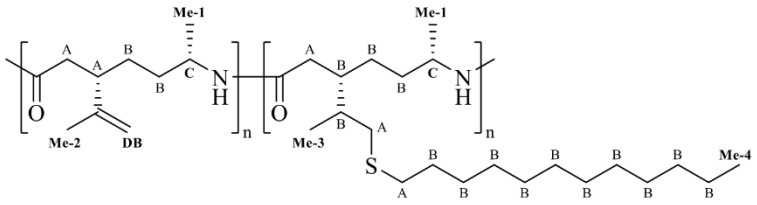
^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.46–7.32 (m, Activator) 4.64 (d, J = 15 Hz, DB) 3.78–3.57 (m, C) 3.16–2.62 (m, A) 2.47–1.70 (m, A) 1.58 (s, Me-2) 1.51–1.06 (m, B) 1.06–0.92 (m, Me-1) 0.92–0.75 (m, Me-3, Me-4).

7b:



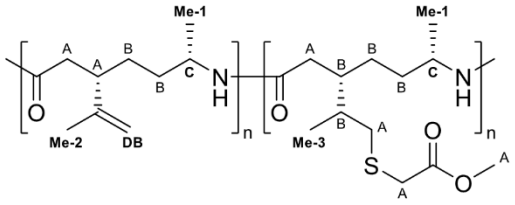
^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.37–7.30 (m, Activator) 4.63 (d, J = 16 Hz, DB) 3.77–3.56 (m, C) 3.14–2.63 (m, A) 2.47–1.68 (m, A) 1.58 (s, Me-2) 1.50–1.03 (m, B) 1.01–0.91 (m, Me-1) 0.89–0.72 (m, Me-3, Me-4).

7c:



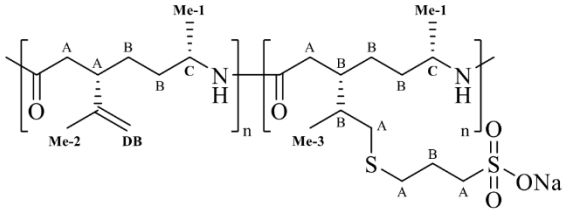
^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.18–7.66 (m, Activator) 4.74 (d, J = 11 Hz, DB) 3.97–3.75 (m, C) 3.33–1.67 (m, A) 1.62 (s, Me-2) 1.57–1.12 (m, B) 1.11–1.02 (m, Me-1) 1.00–0.81 (m, Me-3, Me-4).

7d:



^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.34–7.35 (m, Activator) 4.64 (d, J = 16 Hz, DB) 3.75–3.58 (m, C) 3.14–2.63 (m, A) 2.46–1.71 (m, A) 1.58 (s, Me-2) 1.47–1.05 (m, B) 1.05–0.92 (m, Me-1) 0.92–0.68 (m, Me-3)

7e



^{1}H-NMR (400 MHz, DMSO-d_6, δ [ppm]) = 8.44–7.33 (m, Activator) 4.64 (d, J = 15 Hz, DB) 3.79–3.55 (m, C) 3.17–2.64 (m, A) 2.46–1.68 (m, A) 1.58 (s, Me-2) 1.50–1.07 (m, B) 1.06–0.92 (m, Me-1) 0.08–0.70 (m, Me-3).

Supporting Information ((delete if not applicable))

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

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M.M.K., and M.W. designed the project. C.P.V. and M.M.K. performed the synthetic experiments and characterizations. M.M.K. wrote the manuscript and supplementary information.

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5. Summary and Outlook

This thesis presents a comprehensive framework for the synthesis of sustainable monomers, the preparation of their respective polyamides (PAs) *via* ring-opening polymerization (ROP), and the strategic design of their properties through copolymerization, functionalization, and blending techniques, with a particular emphasis on exploring potential biomedical applications.[56–59]

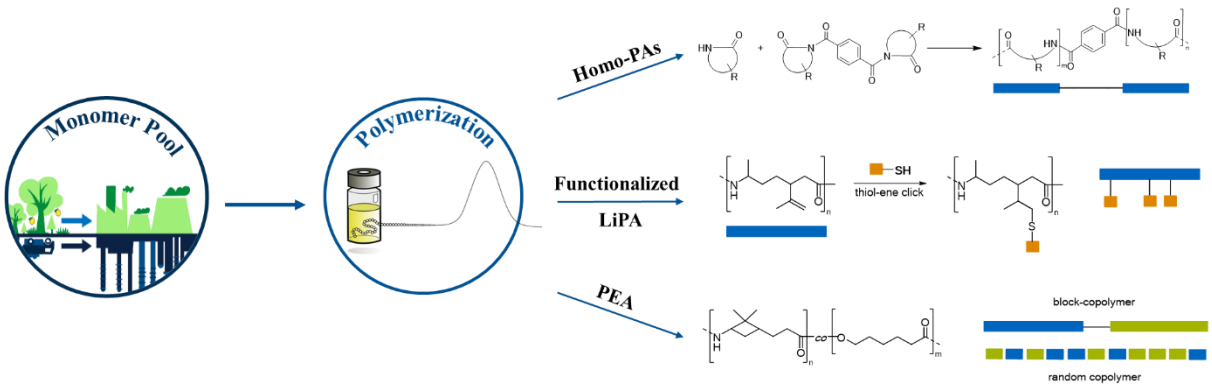

Figure 19: Illustration of the thesis goals and achievements.

5.1. Monomer Synthesis

The terpenes limonene and β-pinene were selected as sustainable monomer feedstocks due to their high abundance in nature. They can be readily isolated from non-edible plant parts such as wood processing (turpentine oil) and citrus peels. The unique structural characteristics of these terpenes render them optimal starting materials for the synthesis of materials with promising properties and functionalities that are otherwise difficult to synthesize. The combination of intra-cyclic and exo-cyclic double bonds in limonene enables lactam synthesis while maintaining and introducing possible functionalizability into the resulting PA. Additionally, the bicyclic structure of β-pinene is presumed to impart stability to the resulting polymers, making it highly promising for high-performance applications.[8,9,27–29,48,56–58]

The synthesis of β-pinene lactam was optimized by using H_2SO_4 as a catalyst for the oxidation of β-pinene to nopinone and evaluating various catalysts and co-reagents for the Beckmann rearrangement, with tosyl chloride and NaOH emerging as the most promising system. The feasibility of purification and the scalability of the reaction render this synthesis route promising for industrial application.[58]

For limonene lactam a synthesis route was established that is both efficient and simple, ensuring industrial applicability and sustainability. The lactam synthesis meets the majority of the "green chemistry" principles outlined by Tang et al.[55], including waste reduction and the use of low-toxic substances.[55,57] However, despite these promising findings, it became apparent that limonene lactam is greatly hindered by its sterically demanding structure. This phenomenon not only impeded the synthesis of the monomer, resulting in lower conversion and selectivity compared to β-pinene lactam but had a similar influence regarding the polymerization process.[57]

5.2. Polymerization and Preparation of Homo-Polyamides

Although cationic and hydrolytic ROP are the oldest approaches for preparing PAs, they are difficult to control and are, therefore, less commonly used for polymerizing lactams. Anionic ROP (AROP), on the other hand, is known to efficiently polymerize lactams due to its controlled nature and ability to produce high molecular weight polymers with narrow polydispersity indices.[1,2,16,17,33]

For limonene polyamide (**LiPA**), AROP was established and subsequently optimized, achieving high molecular weights up to 54 kg mol^{-1} and enabling upscaling to 3 g. However, the upscaling process led to high polydispersity indices due to limitations in mixing and heat transfer during in-bulk polymerizations.[57,59] In our initial investigation, we discovered that the polymerization of limonene lactam is primarily constrained by its sterically hindered structure and side reactions, including transamidation and cyclic polymer formation.[57] By examining the AROP with diverse activator systems, we observed a significant enhancement in chain length and conversion when diimide-type activators were utilized. The successful upscale, leading to larger quantities of **LiPA**, not only allowed for a more thorough analysis of the material but also enabled its further functionalization, tackling challenges like poor solubility and poor processability.[56,57]

In the case of β-pinene polyamide (**PiPA**), both in-bulk and solution AROP were investigated. NaH was found to be the most successful initiator for in-bulk polymerization, achieving a degree of polymerization (DP) of up to 322, while iPrMgCl·LiCl was successfully used for the first time in solution AROP, achieving DPs up to 163. In this study, the kinetics of in-solution AROP were investigated by high-temperature NMR, which led to the conclusion that iPrMgCl·LiCl is a better initiator than iPrMgCl, in addition to findings regarding the, for this system, "optimal" reaction time and concentration. The resulting **PiPA**s exhibited high molecular weights suitable for further processing, good mechanical properties, high thermal stability (up to 440 °C), and a transparent appearance, making them highly promising for high-performance or specialty applications. However, challenges such as poor solubility, high processing temperatures, and thus, poor processing remain to be addressed.[56]

5.3. Preparation of Polyesteramide – Combining The Best of Two Worlds

Polyesteramides (PEA) can combine the excellent thermal and mechanical properties of PAs with the biocompatibility and biodegradability of polyesters, rendering them promising for biomedical applications. Here, we synthesized PEAs from β-pinene lactam and ε-caprolactone. $Sn(Oct)_2$ and $Sn(Lau)_2$ proved to be the most promising initiating systems for ring-opening copolymerization (ROCOP). The chain lengths of the β-pinene-based PEAs significantly increased from 6 kg mol^{-1} to more than 25 kg mol^{-1} by fine-tuning the ROCOP. The resulting PEAs exhibited melting temperatures of around 55 °C and decomposition temperatures of 354 °C or higher, demonstrating their high thermal stability.

Blends of PEA with polyethylene glycol (PEG) were successfully prepared to improve hydrophilicity and mechanical properties for potential biomedical applications, yielding indeed a more hydrophilic and processable material. While these findings illuminate the preparation of sustainable and novel copolymers with promising properties, it is important to note that $Sn(Oct)_2$ and $Sn(Lau)_2$ are generally not suitable for biomedical applications due to their toxicity.[58]

5.4. Functionalization of Limonene Polyamide – Entering New Fields of Application?

Although **LiPA** already exhibited promising properties, the material was mainly limited by its brittleness, poor solubility, and processability. Through strategic modification of **LiPA**'s side chains, the polymer's solubility, processability, hydrophilicity, and biocompatibility were tuned, thereby broadening its scope for biomedical utility.[56]

We were able to successfully modify **LiPA** with various functional groups (alkyl, ester, sulfonate) *via* thiol-ene click reaction, achieving up to 53% modification. The modifications allowed for the tuning of polymer properties, including glass transition temperature (44–133 °C), solubility, and hydrophilicity. The alkyl modifications increased hydrophobicity and solubility in non-polar solvents, while ester and sulfonate groups improved solubility in polar solvents, including methanol and even water in the case of the latter modification. The sulfonate-modified **LiPA** showed amphiphilic behavior, forming micelles in aqueous solution, demonstrating potential for drug delivery applications.[56]

Future work should follow up on these highly promising findings, including the exploration of additional processing methods, the analysis of biocompatibility *via* cell tests, and the evaluation of specific biomedical applications. Nevertheless, the high tolerance of the thiol-ene reaction towards various functional groups enables the future incorporation of bioactive moieties, such as cell-binding motifs for tissue engineering.[56]

5.5. Outlook: A Glance Into the Future

In summary, the projects presented in this thesis established controlled polymerizations for limonene and β-pinene lactams, yielding high molecular weight PAs and overcoming challenges like steric hindrance and side reactions. The optimized AROPs enabled upscaling to gram quantities, facilitating thorough material characterization and paving the way for possible industrial applicability. Combining the strengths of PAs and polyesters, novel PEAs were prepared from β-pinene lactam and ε-caprolactone *via* ROCOP, achieving high thermal stability and tunable properties – a step closer to sustainable, high-performance biomaterials. Through thiol-ene click chemistry, **LiPA** was successfully modified with various functional groups, tuning its solubility, hydrophilicity, and even enabling amphiphilic behavior for potential drug delivery applications.

There are key challenges hindering the widespread application of these promising materials that should be addressed in future work. The polymer functionalization employed in these projects could be one approach, as poor solubility and processability have been major roadblocks to these sustainable materials. Building on the successfully established and versatile thiol-ene click functionalization of **LiPA**, one could think about incorporating other functional groups to impart desired functionalities. Bio-active moieties, like cell-binding motifs, antimicrobial agents, or drug molecules, can be, for example, grafted onto the peptide-like PA backbone, enabling applications like tissue engineering, wound healing, and drug delivery.

Advanced processing techniques could be another solution approach, circumventing the challenge of poor processability caused by, e.g., poor solubility or side-reaction at higher temperatures. Cutting-edge processing techniques like reactive extrusion, electrospinning, and 3D printing are just some examples that could expand the range of potential applications for these renewable materials beyond traditional melt processing.

6. Licenses

All publications used in this work are open-access and do not require any licenses:

- **M. M. Kleybolte**, M. Winnacker, *β*-Pinene-Derived Polyesteramides and Their Blends: Advances in Their Upscaling, Processing, and Characterization, *Macromol. Rapid Commun.,* **2021**, 42, 2100065. (DOI:10.1002/marc.202100065)
- **M. M. Kleybolte**, L. Zainer, J. Y. Liu, P. N. Stockmann, M. Winnacker, (+)-Limonene-Lactam: Synthesis of a Sustainable Monomer for Ring-Opening Polymerization to Novel, Biobased Polyamides, *Macromol. Rapid Commun.,* **2022**, 43, 2200185. (DOI:10.1002/marc.202200185)
- **M. M. Kleybolte**, M. Winnacker, From Forest to Future: Synthesis of Sustainable High Molecular Weight Polyamides Using and Investigating the AROP of *β*-Pinene Lactam, *Macromol. Rapid Commun.,* **2024**, 45, 2300524. (DOI:10.1002/marc.202300524)

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III. Literature

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