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Hydroxyproline-derived biomimetic and biodegradable polymers

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ABSTRACT

4-hydroxy-L-proline (Hyp) is a ubiquitous amino acid naturally-occurred in proteins such as collagens. Owing to the easy accessibility and unique structural features, Hyp can be exploited as an interesting building block for the design of novel biomimetic and biodegradable polymers with fascinating materials properties and biological applications. This review highlights recent progresses regarding Hyp-derived polymers and oligomers including polypeptides, polyesters, polythioesters, γ-peptides, and oligourethanes, with an emphasis on the structural design and synthesis. Perspective and future directions are briefly summarized at the end of review.

1. Introduction

It has been 100 years since Staudinger published the 1920 heroic article "Über Polymerisation" [1], which marked the foundation of polymer science. During the past century, polymer science has made a unparalleled impact to the advance of modern society and welfare of human being [2]. Synthetic polymers such as plastics, elastomers, and fibers have now become indispensable in every facets of modern society, ranging from commodities applications in food industry, clothing, housing, and farming, to high-performance functional materials for automobiles, cell phones, aerospaceplane, and biomedicines. However, the production of synthetic polymers such as plastics constitutes ~6% fossil fuel consumption annually now and is projected to soar to 20% by 2050, accelerating the depletion of the finite natural sources [3]. On the other hand, and perhaps more concerning, many of these polymers are designed with incredible durability and can last without degradation for thousands of years, if not longer [4,5]. The everlasting (micro)plastic wastes have posed growing environmental pollution [4], endangered wild animals, and threatened the health of human beings. It was estimated that the overall carbon dioxide (CO_2) emission due to the production, handling, and incineration of plastics reached ~860 million tonnes in 2019, constituting ~2.4% global total carbon emission [6]. As the public awareness of the plastics crisis growing continuously, there is an enormous need for more sustainable approaches toward environmentally benign polymeric materials [7–12].

Fascinatingly, Mother Nature has been doing this job in an exceptional fashion. Biopolymers such as polysaccharides, nucleic acids, proteins, lignin, natural rubber, and polyhydroxyalkanoates (PHAs) have been efficiently synthesized in extra high molar mass (M_n) and/or sequence precision. It is intriguing, thus, for synthetic polymers to mimic the structure, characters, and even biological functions of their natural counterparts. For example, amino acids, the building block of proteins, have been widely used to make *N*-carboxyanhydride (NCA) [13] monomers for the production of synthetic polypeptides, a.k.a. poly (amino acid)s. Historically, synthetic polypeptides such as poly (γ-methyl L-glutamate) have been used to validate the α-helix model, which was firstly proposed by Linus Pauling in 1950s [14–17]. Till now, the ring-opening polymerization (ROP) of NCA has been the most powerful method for making synthetic polypeptides in high M_n and large volume. The versatility of the chemistry can be exemplified by the modular tunability of the side groups, which expands the repertoires of such biomimetic polymers to an entirely new horizon. These achievements have been comprehensively summarized and discussed in excellent reviews recently [18–27].

Apart from polypeptides, amino acids can also be used to build up other novel degradable polymers, thanks to their multifunctionality, chiral configuration, easy accessibility, and excellent biocompatibility [28]. (Scheme 1). For instance, Tao and Wang et al. reported a novel approach for the synthesis of ε-poly-L-lysine from the ROP of a novel lysine-derived caprolactam [29–31]. The polymers hold great potential for medical and cosmetic applications. By using condensation polymerization of amino acid derivatives, Becker prepared various poly (ester urea)s with adjustable thermal properties and interesting shape memory behaviors applicable for biomedicines [32–34]. Moreover, Li

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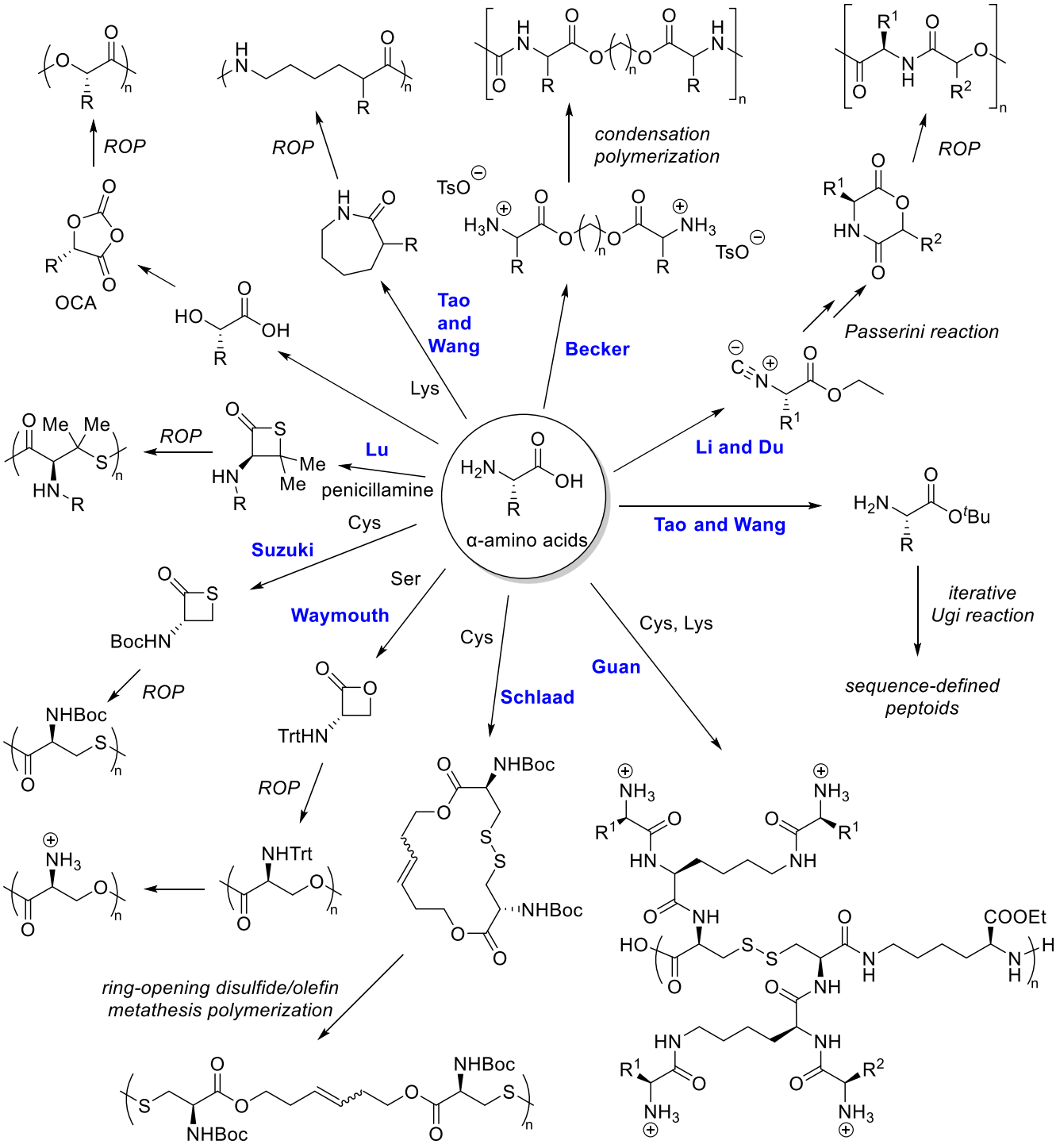
[35,36] and Tao [37,38] utilized efficient multicomponent Passerini and Ugi reactions to construct polydepsipeptides, sequence-defined poly (ester-amide-ester) and peptoids from amino acid starting materials. Dendritic and hyperbranched poly-L-lysine have been generated for drug and gene delivery [39,40]. Guan et al. prepared cationic polymers containing degradable disulfide in the backbone and cationic dendrons in the side chain from various amino acids such as lysine and cysteine [41]. These polymers were found superb delivery vehicles for oligonucleotide therapeutics such as siRNA. Similarly, Schlaad et al. incorporated disulfide into polymer backbone via entropy-driven ring-opening olefin/disulfide metathesis polymerization of cysteine-based macrocycles [42–44], providing new methodology for the preparation of amino acid-based (degradable) polydisulfides. Waymouth and Wender et al. developed an organocatalytic ROP strategy for *N*-trityl-L-serine lactone monomer (β-lactone) [45]. The resulting poly(serine esters) could be used as transporters for mRNA delivery. Suzuki prepared a β-thiolactone from *N*-Boc-L-cysteine (N^{Boc}-CysTL) for polythioester (PTE) synthesis [46]. The polymer showed interesting dynamic properties derived from the thioester bonds in the backbone. Lu et al. recently prepared various β-thiolactones (N^{R}-PenTL) from a naturally occurring amino acid D-penicillamine and successfully realized their controlled ROP, affording PTEs with variable side groups, high M_n, and

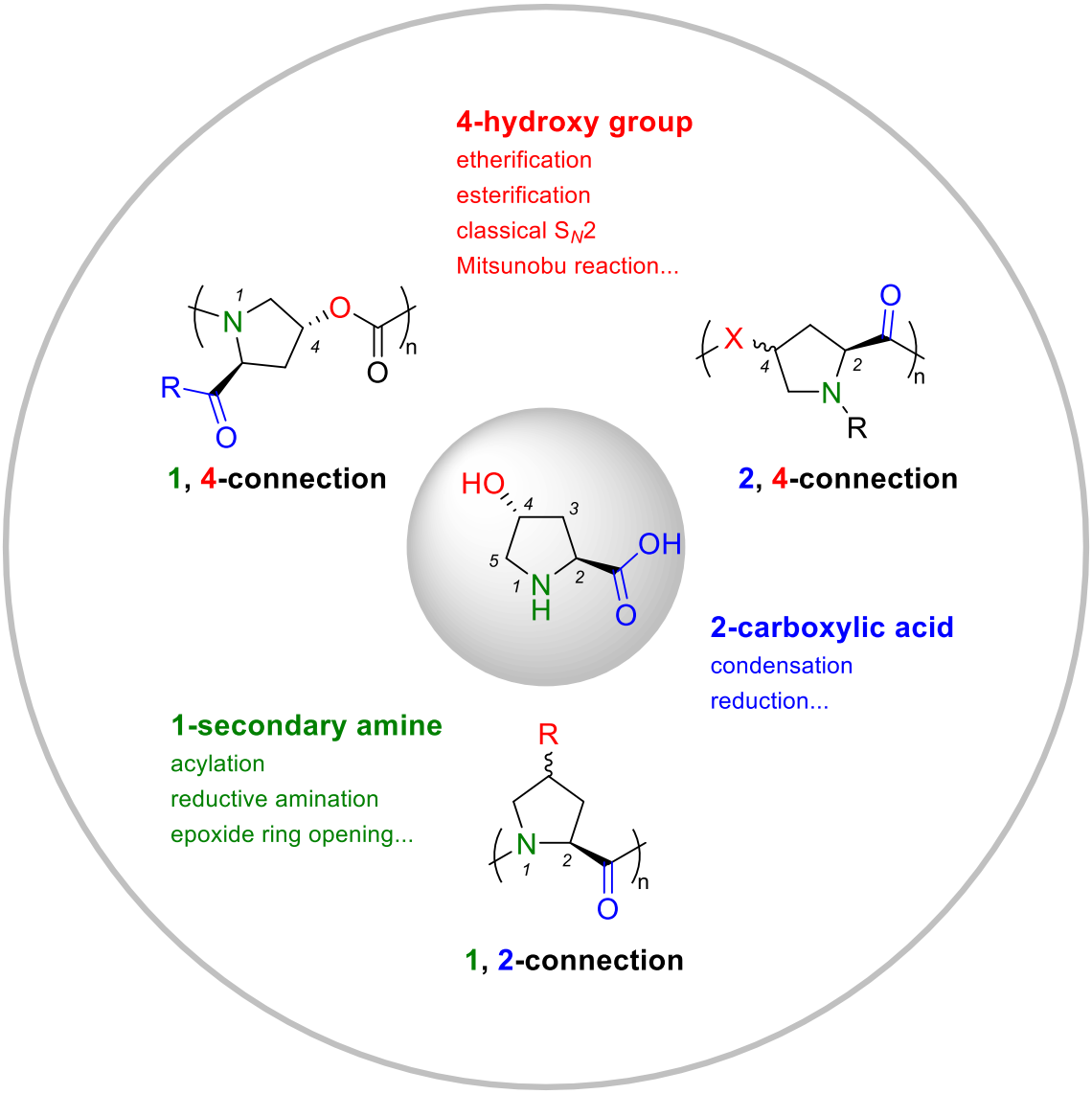


Scheme 1. Selected examples of various amino acid-based degradable polymers.

low dispersity (*Đ*) [47]. More excitingly, the penicillamine-based PTEs can be completely depolymerized in a controlled unzipping fashion to yield pure monomers, offering an appealing platform for recyclable plastics and self-immolative biomaterials. Amino acids have also been converted to *O*-carboxyanhydride (OCA) for the synthesis of semi-crystalline aliphatic polyesters [48–53]. Rather than exhausting all works in literation [54–56], which is certainly beyond the scope of this paper, here, we would like to focus on novel polymers made from an ubiquitous amino acid, 4-hydroxy L-proline (Hyp) (see Scheme 2).

2. HYP as building block for polymer synthesis

L-Proline (Pro) is special in that it is the only proteogenic amino acid bearing a cyclic pyrrolidine and a secondary amine. Taking advantage of these structural features, many Pro-based agents such as the Jørgensen catalyst [57,58] and the Corey–Bakshi–Shibata reagent [59] have been developed for asymmetric catalysis. The available ϕ torsion angle of Pro in protein was restricted in the range of the $-65° \pm 25°$. This restriction in conformation and the absence of hydrogen bonding make Pro preferentially observed in motifs such as turns, collagen triple helix, or polyproline helices [60–63]. Hyp, usually formed through post-translational modification of Pro, is prevailing in proteins and constitutes ~6–9% of the total amino acid contents of collagen [64,65]. Many biochemical studies have revealed that the introduction of Hyp helps stabilizing the triple helix of collagen. From a synthetic point of view, the additional 4-hydroxy group renders Hyp a much more versatile building block for polymer synthesis as compared with Pro. For example, Hyp has two chiral centers on the pyrrolidine ring, which can offer stereoregular polymers with a nonaromatic ring embedded in the backbone. This type of structural character is relatively rare and can give special properties complementary to regular polymers. Moreover, with the triple functionalities of Hyp, one can select either two of the three functional groups for monomer connection, and in the meantime exploit the last one for side chain functionalization (Scheme 2). Furthermore, the *trans*-hydroxyl group can be readily converted to other functionalities such as *cis*-hydroxyl, *cis*-thiol, *cis*-azide, *cis*-amine, and many others, creating numerous opportunities in making new types of polymers. In the following discussion, we will summarize recent advances of Hyp-based biomimetic polymers, which can be classified by the way Hyp polymerizes via its functional groups and positions. Of note, polymers attaching Hyp as side groups fall out of the scope of this review and will not be discussed here.



Scheme 2. Construction of biomimetic polymers via different connection ways of Hyp.

3. Polymers via 1,2-connenction of HYP

The 1,2-connection of HYP can give rise to functionalized polyproline. Polyproline has been known to exhibit two different helical conformations, namely polyproline I (PPI) and polyproline II (PPII) helices in which all the peptide bonds adopting *cis*- and *trans*- isomers, respectively [61–63]. The water-soluble PPII helix is more extended and can be found in aqueous or acetic acid solutions, whereas the PPI helix is more compacted and typically seen in relatively hydrophobic solvents such as aliphatic alcohols. The two conformations can be differentiated by their distinguished circular dichroism (CD) patterns: the PPI helix has a characteristic strong positive band at 214–215 nm and a weak negative band at 231–232 nm, whereas the PPII helix has a strong negative band at 202–206 nm and a positive band at 225–229 nm [66]. Notably, although PPII helix is named after polyproline and the presence of proline can give high propensity of PPII conformation, proline is not necessarily mandatory for many PPII helieces seen in native proteins. Overall, although not as abundant as α-helix and β-sheet, the PPII helix is actually found in ~2% of residues in protein data bank (PDB), comparable to the frequency of 3_{10}-helix [67].

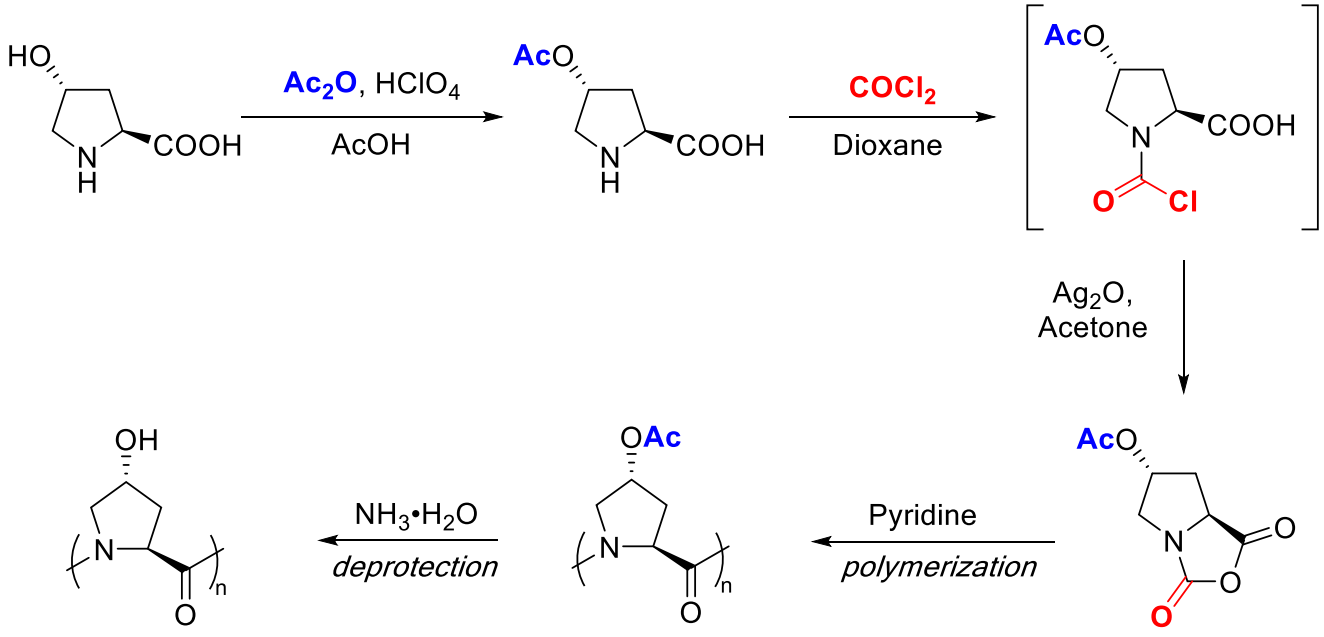
In 1958, Katchalski et al. reported the synthesis of Hyp-based functionalized polyproline for the first time (Scheme 3) [68]. They selectively acylated the hydroxyl group of Hyp under strong acidic condition to give *O*-acetyl-L-hydroxyproline. After passing phosgene through the suspension of intermediate, the target NCA monomer was obtained with the treatment of silver oxide in acetone. The polymerization of NCA was executed in pyridine, affording poly(*O*-acetyl hydroxyproline). Subsequent deacetylation in ammonium hydroxide yielded poly(Hyp) with a reported M_n of ~5.8 kg/mol. In 2014, Gkikas et al. protected the 4-hydroxyl group of Hyp with a benzyl group and synthesized the corresponding NCA (Fig. 1) [69]. Using the Hyp-based NCA monomer, they reported a series of novel rod-rod diblock copolypeptides poly(γ-benzyl-L-glutamate)-*block*-poly(benzyl-L-hydroxyproline) (PBLG-*b*-PBLHyP). The block copolymer was shown to self-assemble into zigzag lamellar structures with unusually large periodicity, which was likely driven by the microphase separation of the two domains adopting standard α-helix for PBLG and polyproline helix for PBLHyp, respectively.

Thanks to the characteristic rigidity and well-defined secondary structure of PPII helix, oligoprolines, made by solid phase peptide synthesis (SPPS) [70], were often used as molecular rulers in biology and material sciences. The use of Hyp as alternatives to Pro in SPPS can create oligo-Hyp containing alterable side groups and in the meantime retaining the special scaffold of polyproline [71–73]. In 2005, Chmielewski et al. designed a series of *O*-functionalized oligo-Hyp as cell-penetrating agents via SPPS (Fig. 2) [74]. The idea was to use the modified 4-hydroxy group of Hyp mimicking the side group of canonical amino acids. For example, the introduction of an isobutyl group from the 4-hydroxyl could be considered as a proline-based mimic of leucine. Similarly, functionalization of the 4-hydroxyl group with a terminal amino or a guanidinium group led to proline-based mimics of lysine or arginine, respectively. The sequences of the oligomer were carefully designed to arrange hydrophobic pendent groups on one face of the PPII threefold helix and the cationic groups on the other two, endowing the polyproline scaffold with facial amphiphilicity. It was demonstrated that both the amphiphilicity and the PPII scaffold played key roles for the enhanced cell translocation.

4. Polymers via 2, 4-connenction of HYP

The 2,4-connection of HYP is a versatile way of creating new type of polymers. As mentioned earlier, the *trans*-4-hydroxy group can be facilely converted to various new functional groups including *cis*-4-azido, hydroxyl, mercapto, or amino groups via classical SN2 or Mitsunobu reaction. The 2-carboxylic acid can undergo either condensation reactions or be reduced to hydroxymethylene group for polymer linkage. Thus, the scope of polymers can be broadly expanded by different combinations of the functional groups installed at the 2- and 4- positions. Another appealing feature of the 2, 4-connection is that it allows fine tuning of material properties via stereochemistry regulation (e.g. *trans* versus *cis*) thanks to the well-defined chirality of both positions.

Owing to the biodegradability, low toxicity, and good mechanical properties, bioderived aliphatic polyesters such as polylactide (PLA) [75–77] and PHA have long been considered excellent candidates replacing petroleum-based commodity polymers [78–80]. However, most polyesters currently being studied are difficult to derivatize and the backbones are usually acyclic. It would be interesting to incorporate cyclic motifs fusing or imbedding to the polymer scaffolds. This notion was best exemplified by the elegant work from Chen et al.: by fusing a *trans*-six-membered ring to the nonstrained γ-butyrolactone, the resulting polyesters showed significantly increased glass transition



Scheme 3. Preparation of poly(4-hydroxy L-proline) via ROP of Hyp-derived NCA.

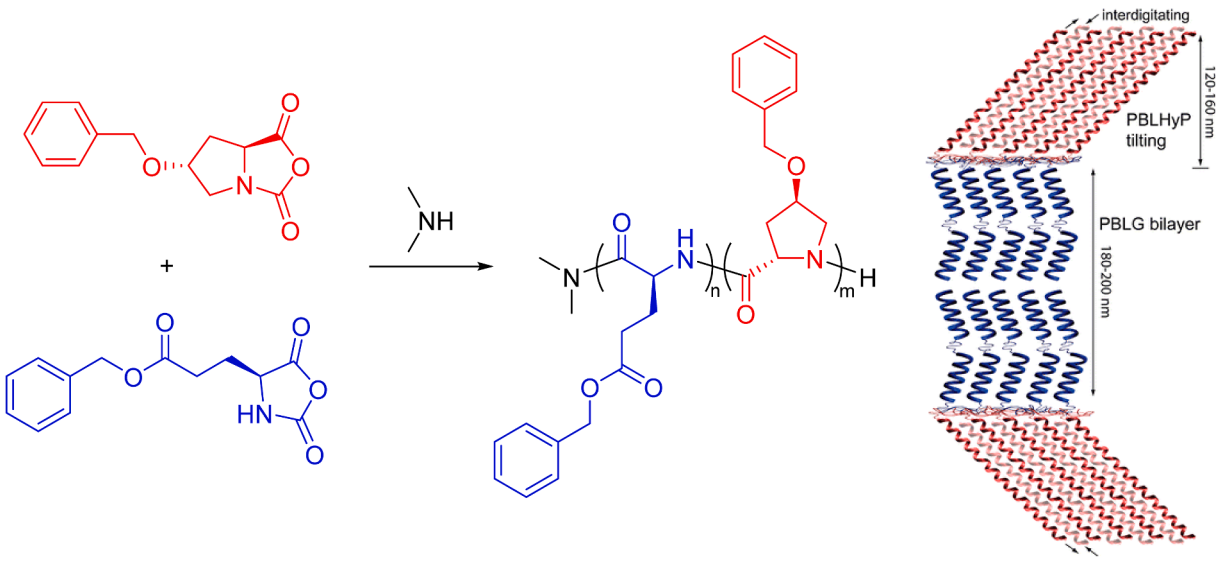


Fig. 1. Synthesis and cartoon illustration of the self-assembled structure of poly(γ-benzyl-L-glutamate)-*block*-poly(benzyl-L-hydroxyproline) [69]. Copyright ACS Publications.

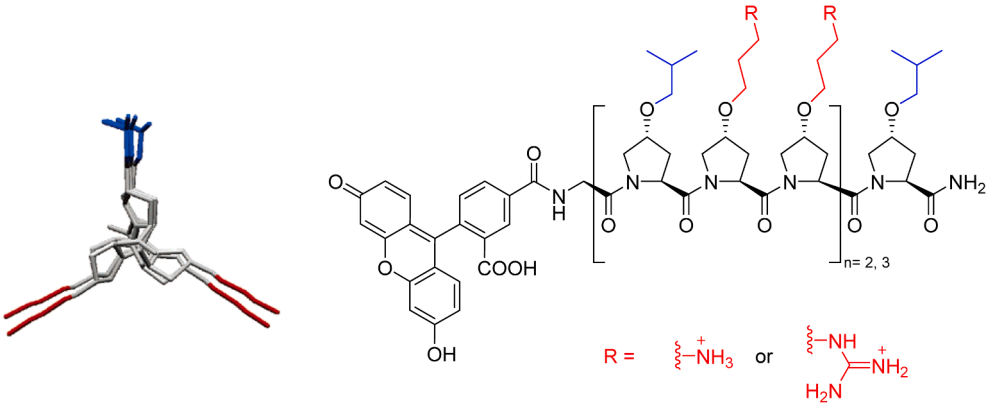


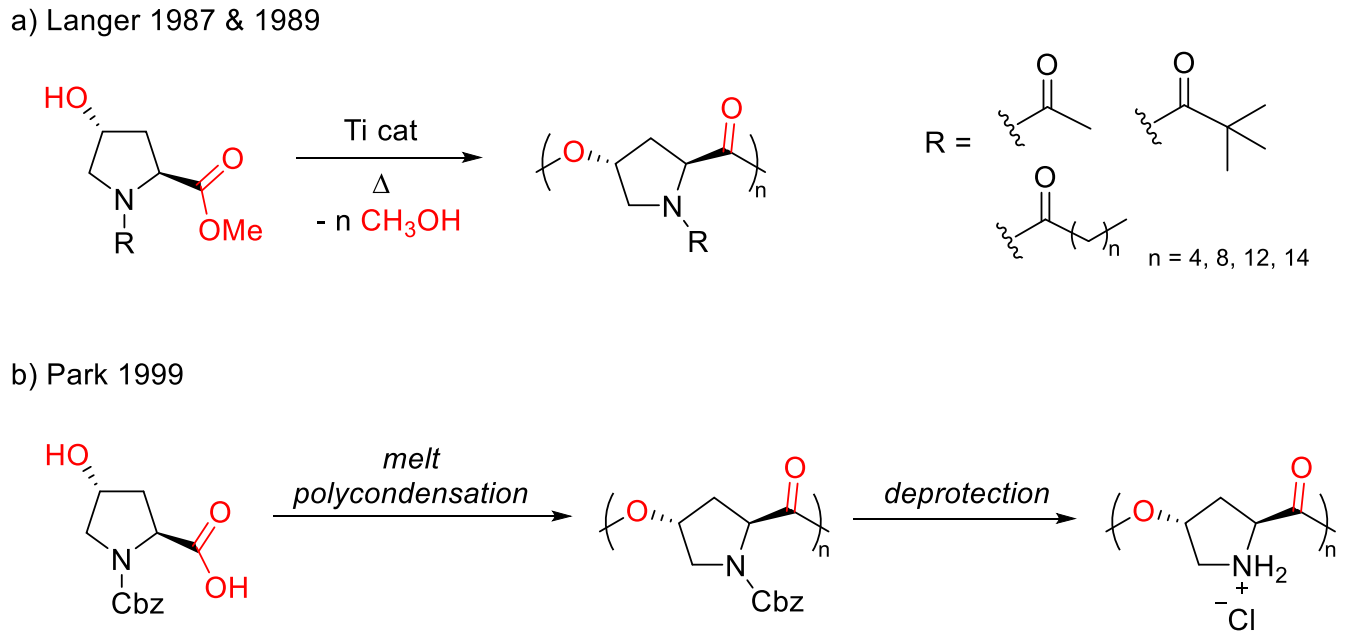
Fig. 2. Amphiphilic PPII helix and sequence of *O*-functionalized oligo-Hyp [74]. Copyright ACS Publications.

temperature (T_g), melting temperature (T_m), decomposition temperature (T_d), and greatly enhanced mechanical properties, as compared to the pristine poly(γ-butyrolactone) [81]. From this point of view, Hyp is an ideal starting material for the synthesis of polyesters with nonaromatic ring and well-defined stereochemistry.

The most straightforward approach of making a Hyp-based polyester is the direct condensation (e.g. esterification or transesterification) between the 2-carboxylic acid/ester and the *trans*-4-hydroxyl group. Due to the poor solubility of Hyp in most organic solvents [74] and the higher reactivity of the amine relative to the hydroxyl, the secondary amine of Hyp was usually protected in the form of amide or urethane bond bearing various alkyl or aromatic groups [82]. The condensation between carboxylic acid and hydroxyl group usually requires strong Lewis or Brønsted acid catalysts. In 1987 and 1989, Langer et al. investigated the melt polymerization of various *N*-acylated Hyp methyl esters (Scheme 4a) via metal catalyst-mediated transesterification [83,84]. The catalysts had profound effects on the degree of polymerization (DP) and *Đ*. Among those rigorously tested main group metal Lewis acids such as Al, as well as the transition metals including Ti, Pb, and Zn, Ti-catalysts yielded the highest weight-averaged molecular weight (M_w) of polymer. This was possibly a result of the more electropositive metal center of Ti over other screened metal ions. Even though, the optimized condition for titanium isopropoxide catalyst was still relatively harsh, 180 °C for 20–24 h with a catalyst loading of 1 mol %. Polymers with M_w greater than 40,000 g/mol can be obtained with generally broad *Đ*s. The polymerizability and material properties varied upon different pendant groups of the monomers: those with a longer pendant acyl group seemed to give a higher DP and a lower T_g. More careful thermal and mechanical characterization of the materials, however, were not reported and it is unclear whether there was any epimerization under such extreme polymerization conditions.

In 1999, Park et al. utilized *N*-Cbz protected Hyp for direct melting condensation polymerization at 180 °C for 5 days to produce poly(4-hydroxy-*N*-cbz-L-proline ester) (PHCP ester) (Scheme 4b), with a *Đ* of 1.7 and an average DP less than 40 [85]. After the deprotection of *N*-Cbz, the obtained cationic polyester, namely poly(*trans*-4-hydroxy-L-proline ester) (PHPE), displayed a faster degradation speed at the beginning. This is likely because the charged amine increased the hydrophilicity of the polymer and thus facilitated the influx of water for faster ester hydrolysis. However, the complete degradation needed 3 months to give pure Hyp at pH 7.0 and 37 °C. It was proposed that some of the ester bonds in PHPE were attacked by its own amine groups to form amide bonds. Interestingly, the cationic polymer PHPE formed a stable complex with DNA in aqueous solution by means of electrostatic interaction and was explored as a potential biodegradable carrier for gene delivery.

In 2003, Lee and Yang carried out $Sn(Oct)_2$-mediated copolymerization of *N*-Cbz Hyp with cyclic carbonates (Scheme 5a) [86]. The reaction was conducted in melt state at 140 °C for 30 h with a screened



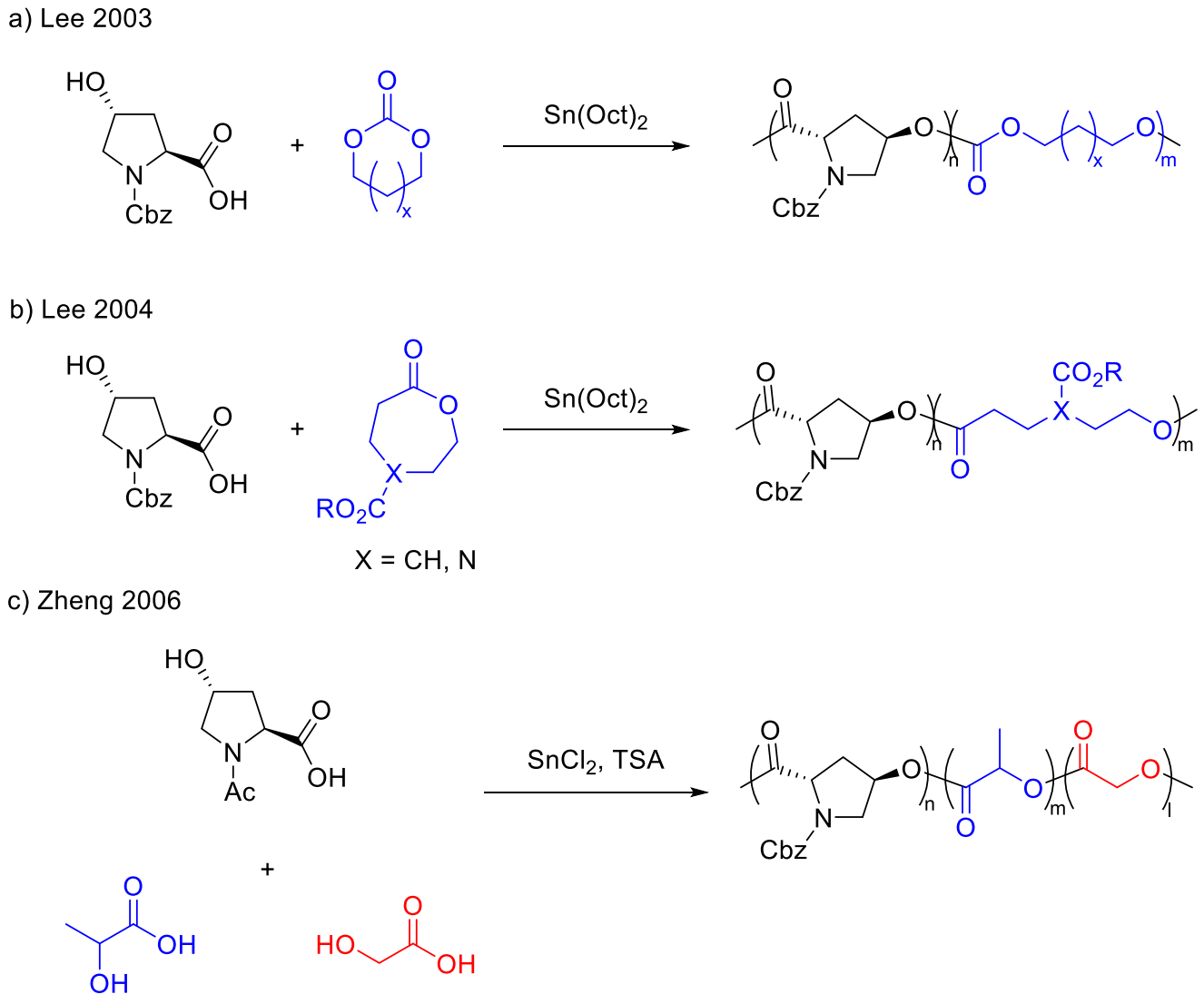
Scheme 4. Melt polycondensation for the synthesis of *trans*-Hyp-based polyesters [83–85].

catalyst loading of 1.5 wt%. The composition and T_g of the copolymer were adjustable by varying the feeding ratio of the two monomers. Copolymerization of Hyp derivatives with cyclic esters such as functional ε-caprolactones were also studied in 2004 (Scheme 5b) [87]. After the deprotection of pendant *N*-Cbz, the resultant cationic copolymers exhibited excellent degradability under physiological conditions, similar to previously synthesized PHPE. Moreover, Zheng synthesized a novel biodegradable polymer poly(lactic acid–*co*-glycolic acid-*co*-hydroxyproline ester) (Scheme 5c), via catalysts such as Tin and TSA [88].

Recently, Lu and Chen et al. developed a Hyp-based lactone platform generating stereoregular aliphatic polyesters via controlled ROP (Fig. 3) [89]. Specifically, they utilized Mitsunobu reaction to convert the *trans*-4-hydroxyl of HYP into various bicyclic lactones (N^R-PL). The amino group was used as a chemical handle introducing various side chains including short and long alkyl groups, hydrophilic oligo(ethylene glycol), modifiable double bond, and aromatic groups. Living polymerization was achieved at room temperature using benzyl alcohol as initiator and DBU as catalyst. Quantitative conversion can be achieved for the highly strained bicyclic monomer. The method gave *cis*-poly(Hyp ester) (PN^R-PE) with M_ns up to 97.5 kg/mol, $Đ$s usually below 1.10, and well-defined terminal groups on both ends (Fig. 3). Based on detailed hydrolysis and NMR experiments, they concluded that there was no epimerization during the polymerization. The side chain structure significantly impacted the thermal stability and crystalline structure of PN^R-PE. One of the polymers bearing a long dodecyl side chain (PN^{C12}-PE) gave a T_m and T_d (5% weight loss) at 202 and 300 °C, respectively. The polymer can be hot processed into transparent films, which exhibited a modulus of 143 MPa at 20 °C and a 6.1% elongation at break. Another polymer PN^{EG3}-PE showed excellent water solubility for the tethered EG_3 side chain, and was amenable to site-specific protein conjugation via highly efficient native chemical ligation when terminally functionalized with a reactive phenyl thioester. The well-controlled ROP, coupled with the tunability on the side group, underscored vast potential of this platform in generating functional aliphatic polyesters with preserved tacticity.

Following a similar strategy, the Lu group also developed various bicyclic thiolactones (N^R-ProTL) [90]. The monomers were facilely synthesized via a three-steps-in-one-pot fashion using *N*-protected Hyp as the starting material (Fig. 4), a procedure that had been used in industry at a more than 1000 kg scale. The monomers were highly polymerizable due to the reactive nature of thioester and the strained ring. Fast (20 min to a few hour) and first-order ROP kinetic was observed with benzyl mercaptane as initiator and triethylamine (TEA) as catalyst. A stronger base such as DBU further accelerated the reaction reaching equilibrium within seconds. Previously, chemical production of high M_n polythioesters had been difficult due to inter- and intra- chain transfer originated from uncontrollable transthioesterification [46,91–94]. However, using this novel monomer platform, they obtained well-defined polythioesters PN^R-ProTE with M_ns up to 226 kg/mol and narrow $Đ$s below 1.15. The well-controlled nature of the ROP was attributable to the low electrophilicity of the thioester linkages in the PN^R-ProTE backbone, which minimized the undesirable trans-thioesterification. The low reactivity of the prolyl thioester was partially due to the steric hindrance of the pro-pro junction, and also in part owing to the n-π* orbital overlap between the side chain urethane carbonyl and the backbone thioester carbonyl [95]. Most interestingly, the Hyp-derived thiolactone N^R-ProTL turned out to have a significant lower ring strain compared to the analogous bicyclic lactone N^R-PL (Fig. 3). X-ray diffraction of the two types of monomer revealed substantially longer C-S bonds (178 and 182 pm) in N^R-ProTL and shorter C-O bonds (135 and 147 pm) in N^R-PL. According to the Van't Hoff plot drawn from the ROP of N^R-ProTL at various temperatures, the ΔH_p^o and ΔG_p^o were measured to be −3.7 and −0.86 kcal/mol, respectively. As a result, the backward depolymerization of PN^R-ProTE into its original monomer N^R-ProTL could be easily realized by adding basic catalyst to the diluted polymer solution at a modestly elevated temperature (Fig. 4). This unique chemistry therefore enabled the complete and highly efficient recycling of monomers with low energy input, establishing a closed loop of monomer-polymer-monomer economy. This platform could facilitate the manufacture of high-value functional materials, self-immolative polymers, sustainable plastics with immense potentials for biomedical and/or optical/photochemical applications.

Royo et al. developed a new family of foldamers based on Hyp derivatives [96]. Specifically, *cis*-4-amino-L-proline was conveniently prepared from Hyp with a chiral reversion at the 4-OH position (Fig. 5). Using this new derivative of Hyp as building block, they were able to connect the *cis*-4-amine and the 2-carboxylic acid in the form of amide bond via SPPS, yielding γ-peptide hexamers. The secondary amine on the pyrrolidine ring was initially protected by *N*-Boc and subsequently converted to either *N*-Acyl or *N*-Alkyl substitutions. CD spectroscopy and



Scheme 5. Copolymerization of Hyp derivatives with cyclic carbonates (a) [86], lactones (b) [87], and lactic (glycolic) acid (c) [89].

NOE NMR experiments implied the *cis*-Hyp-derived γ-peptide adopted a turn-like folded secondary structure in both TFE and aqueous solutions. It was believed that such a stable secondary structure was in part owing to the rigid prolyl scaffold because analogous linear γ-peptides controls were unable to maintain their folding structures in aqueous solutions.

With this foundation in hand, Royo next prepared several Hyp-derived γ-peptide bearing various cationic side groups on the prolyl secondary amine [97]. They evaluated the cell-penetrating performances of the γ-peptides and concluded that the materials could be advantageous in terms of lower toxicity and improved protease resistance as compared with the well-known cell-penetrating peptide TAT. In another contribution, Giralt et al. presented a set of novel polyproline dendrimers using *cis*-4-amino-L-proline as a branching point from the polyproline backbone, which allowed minimal distortion to the conformation of the original polyproline type I/II helices [98]. These dendritic polyprolines were found to be actively internalized by rat kidney cells.

5. Polymers via 1,4-connenction of HYP

The synthesis of polymers based on 1,4-connection of Hyp has not been realized yet, however, sequence-defined oligomers connected via urethane bond has been reported In 2016. Briefly, Anderson group prepared a number of trimer and hexamer oligocarbamates via stepwise synthesis in solution [99]. The carboxylic acid was amidated for the introduction of various side groups, and the prolyl amine was connected with the 4-hydroxyl group using carbonyldiimidazole as a coupling reagent (Scheme 6). Purification was realized using a perfluorocarbon handle at the terminal of the oligomer, which allowed facile column chromatography using fluorous silica. Bioconjugation of the oligomer to siRNA was reported in the study.

6. Outlook and perspectives

This review summarizes recent progresses of exploiting amino acids, with an emphasis on Hyp, as the major building block for the synthesis of biomimetic and biodegradable polymers. These designer polymers have demonstrated fascinating physicochemical characters that can be explored for a broad scope of materials purposes and biological applications. Despite the current advances, the applications of these polymers are mostly in infancy stages and many interesting questions remain unanswered. Here, we would like to point out a few promising future directions from the angle of synthesis, materials property, and bio-applications, respectively.

Although several new backbones have been successfully constructed from Hyp, the category of accessible polymers are still relatively rare. To further expand the diversity and facilitate controlled polymerization, it will rely on both clever molecular design of the monomer structure and

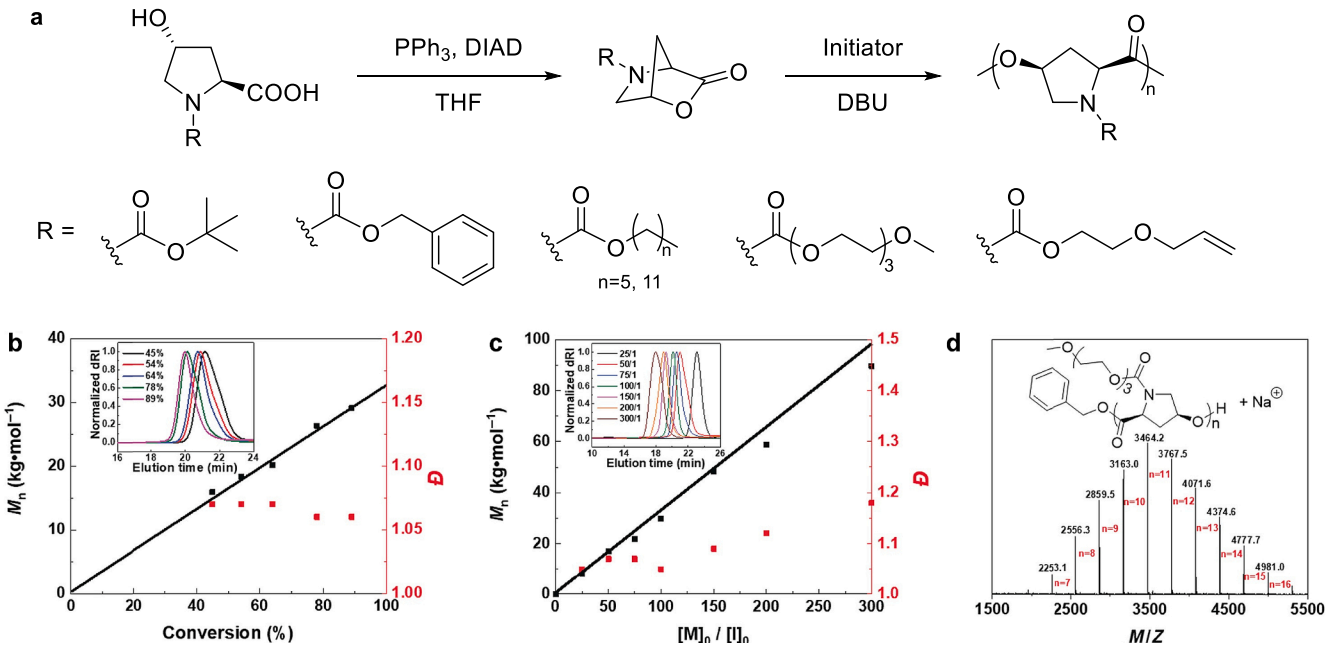


Fig. 3. Ring-opening polymerization of Hyp-based lactones [89]. (a) The synthesis of cyclic monomers and corresponding polymerization catalyzed by DBU. (b) The plots of M_n and $Đ$ as a function of monomer conversion. (c) The plots of M_n and $Đ$ as a function of feeding $[M]_0/[I]_0$ ratio. (d) MALDI-TOF mass spectrum. Copyright CCS Publications.

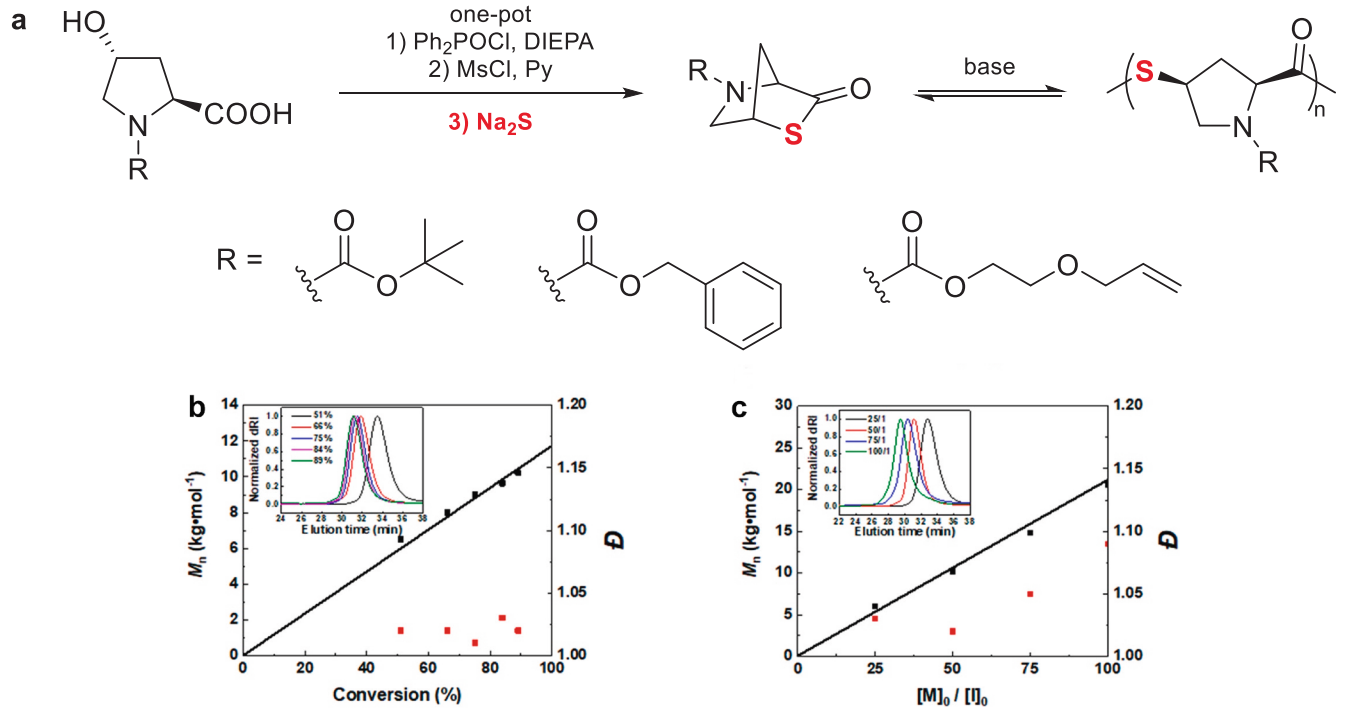


Fig. 4. (a)Ring-opening polymerization of Hyp-based thiolactones and the reversible ring-closing depolymerization. (b) Plots of M_n and $Đ$ as a function of monomer conversion (c) Plots of M_n and $Đ$ as a function of the $[M]_0/[I]_0$ ratio [90]. Copyright ACS Publications.

the implementation of novel organic transformation methodologies. Efficient functionalization and modification of Hyp, particularly on the pyrrolidine ring, are highly desirable. As far as polymerization methods are concerned, common step-growth condensation polymerizations are handy and easy to scale up, but these methods usually need fairly strong conditions and afford materials (e.g. *trans*-type polyesters PHPE) with poorly controlled M_n. On the other hand, solid phase synthesis can provide discrete molecular weight and precision sequences but is limited in scalability and low M_n of products (e.g. γ-peptide and urethane). As such, new Hyp-derived cyclic monomers and catalytic systems that can facilitate controlled ROP and affording high M_n are at the core of the chemistry design.

For materials property, the most exploitable feature of Hyp-based polymer is the rigid aliphatic pyrrolidine ring and the high propensity of forming well-defined PPII helix, both are relatively difficult to access from other existing monomers. Future researches can take advantage of

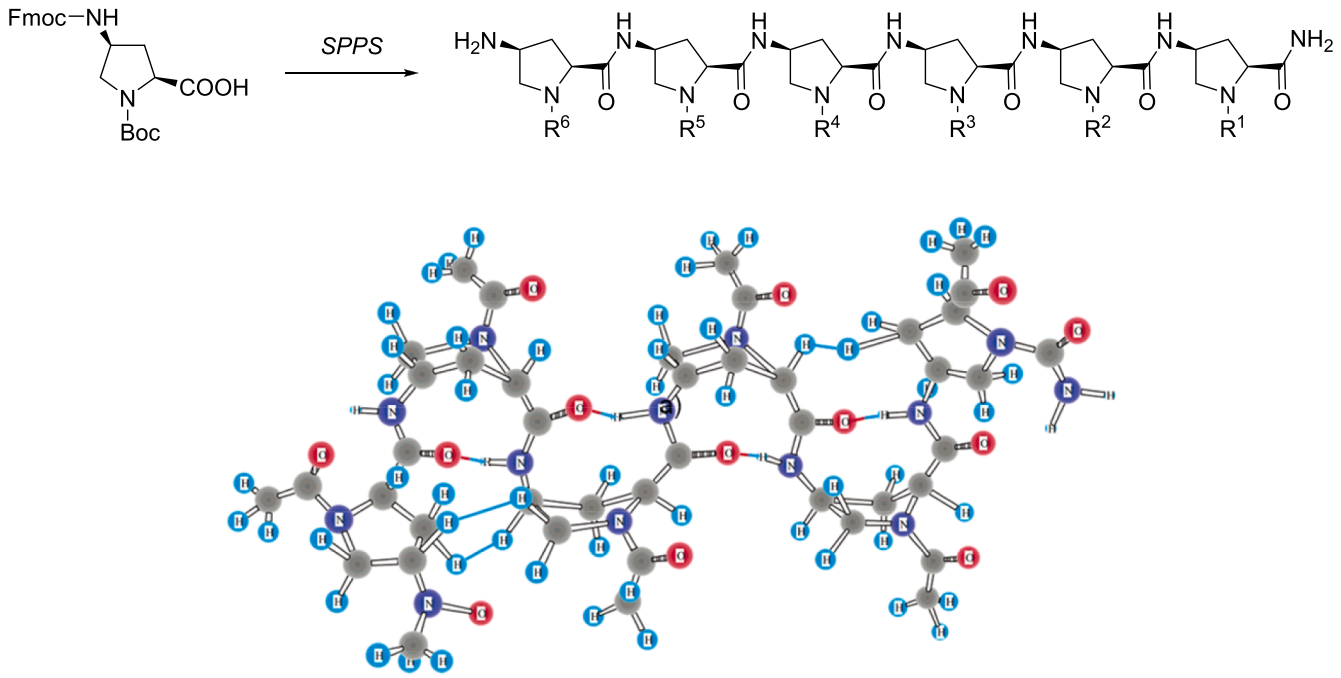
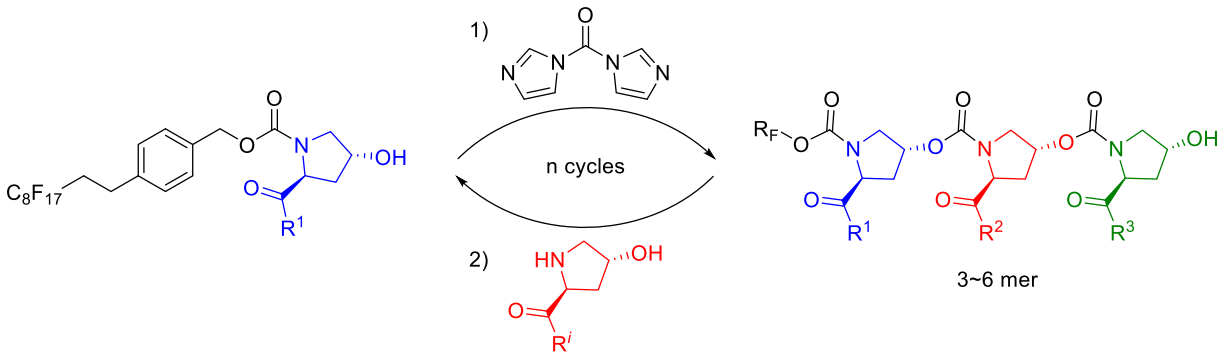


Fig. 5. Synthesis of Hyp-based γ-peptide hexamers (top) and the proposed folded structure (bottom) [96]. Copyright ACS Publications.



Scheme 6. Stepwise synthesis of sequence-defined Hyp-based oligourethanes.

these structural characters preparing degradable High T_g polymers, high modulus materials, foldamers, hard domain for thermoplastic elastomers, or shape-memory materials. Another interesting question along this direction is how different would the material properties be for the analogous polymers built upon two stereo isomers, namely the *trans*-2,4 and *cis*-2,4 connections. Furthermore, as a family of rod-like polymers, the intramolecular folding and hierarchical self-assembly behavior are also worth careful investigation. The poor solubility of these polymers due to the rigid skeleton, however, needs to be taken into account during the molecular design.

As biomimetic polymers, the Hyp-based polymers can be readily applied for a diverse range of biological and biomedical applications. Previous studies have pointed out some promising directions including drug carriers, absorbable implants, and cell-membrane penetrating materials. These preliminary results lay a solid foundation for future works. For example, by altering side groups, one can easily design new Hyp-derived materials as degradable alternatives to PEG for drug and protein conjugation [89], or for antimicrobial purposes. Moreover, other interesting applications of these polymers include macromolecular asymmetric catalysis and chiral separation by taking advantage of the chiral stereochemistry of Hyp and/or the higher-ordered PPII helix [100,101]. Overall, we expect a stream of exciting studies conveying not only de novo molecular design, but also functional applications of Hyp-based biomimetic polymers in the near future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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