Synthesis of Stereocontrolled Polyurethanes with Defined Monomer Order by Step-economy Approach

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ABSTRACT: Polyurethanes are valuable materials in the industrial sector due to their broad scope of various applications. Traditional synthesis methods rely on step-growth polymerization, which inherently lacks precise molecular weight and structure control. Consequently, pursuing a synthetic strategy for stereocontrolled, sequence-defined polyurethanes represent a substantial challenge in soft material design. This study demonstrates an approach to synthesising discrete, stereo-regulated polyurethanes with defined monomer order by combining the one-pot synthesis method with iterative exponential growth. This work presents a methodology to fabricate non-biological polymers with structural precision characteristics for biomacromolecules. By varying the composition of different monomers and gradually increasing the chiral monomer content or altering its position within the polymer chain, we can influence the secondary structures of polyurethanes and consequently their properties and functions. Furthermore, we demonstrated the production of polymers with non-symmetrical sequences, showcasing the feasibility of tailoring polymer chains

to specific requirements and preserving complete sequence control. This synthetic strategy paves the way for the facile fabrication of abiotic polymers that could emulate the characteristics of artificial proteins.

Introduction

Precise sequence, stereoregularity and defined length in biomacromolecules have proven essential in determining their sophisticated biological functions.[1–3] Inspired by remarkable functionalities guided by unique spatial structures of biopolymers, abiotic polymers with precise monomeric sequence and stereo-control have been developed.[4–6] Sequence-defined polymers are formed on abiotic polymer backbones, preserving controlled primary structures – monomer sequence.[7,8] During the last decade, these polymers have been explored in various applications, e.g.,catalysis[9,10], data storage[11–15] anticounterfeiting technologies[16], biomedical applications[17] *etc*. In particular, polymers with controlled stereoregularity, as present in biomacromolecules, have a high potential to dictate properties and functions in synthetic polymers and provide promising alternatives to biopolymers.[4–6]

Recently, methods to synthesise abiotic polymers with precise monomer sequences and defined stereochemistry have been introduced to polymer chemistry.[18] Stepwise iterative strategies based on solid-phase[19–22] and solution-phase[23–26] syntheses involving multi-step protocol have been explored to fabricate well-defined abiotic polymers. While solid-phase synthesis is widely used for biomacromolecule synthesis and holds great potential for the preparation of abiotic analogues, it has many limitations, resulting in a restricted synthesis scale. Moreover, the solid support hinders couplings and thus requires high reagent excess and time, which is unsuitable for extended polymer chain synthesis.[27] Conversely, the solution-phase iterative approach is scalable yet usually

accompanied by purification through chromatography or liquid-phase extraction techniques after each synthesis step.[28] The purification between iterative steps reduces overall yield and restricts the polymer length (Figure 1a).[26] Therefore, the step economy approach by reducing the number of synthetic steps is crucial for producing long polymer chains having defined monomer order.

The solution-phase iterative exponential growth (IEG) has been developed to achieve a high degree of polymerisation for sequence-defined polymers.[29,30] In IEG, the length of the chain and the polymer molar mass grow exponentially with fewer steps than classical methods, leading to well-defined polymers.[31] Despite seeing high potential in the IEG technique, examples of stereocontrolled, sequence-defined polymers with controlled stereoregularity remain scarce due to practical synthesis challenges such as solubility issues and inefficient chemical transformations.[6] Only a few reports presented how to generate simultaneous sequence and stereoregulation in synthetic polymers. For example, Johnson and co-workers[32,33] demonstrated an iterative exponential growth plus (IEG+) strategy for stereo-regulated uniform polytriazoles (32-mers) with side-chain epoxide and alkene functionalisation. Tao and co-workers[34] reported that using acid-orthogonal deprotection strategy, enantiopure serines could be incorporated in iterative synthesis of stereoconfigured and sequence-defined polythioetheramides up to 32-mers. Ding's group[35] and recently by Hashidzume's group[36] prepared sequence-defined oligotriazoles (8-mers) based architecture with stereocontrolled 1,2,3-triazole monomers through metal-free iterative strategy and Copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) reaction, respectively. Kim, Jamison and Du Prez's group employed automated synthetic strategies to fabricate stereocontrolled sequence libraries of oligomers.[25,37,38] Stereoregularity in the IEG strategy is achieved using chiral monomer building blocks. Yet, IEG yields symmetrical sequences and is inappropriate for irregular monomer patterns.

Following the step-economy idea, we proposed a strategy for fabricating sequence and stereocontrolled polyurethanes by combining the developed in our group one-pot synthesis[26,39] with iterative exponential growth (Fig 1b). The reported one-pot approach for synthesising sequence-defined oligourethanes enables overcoming the limitations of solution-phase synthesis. The simplified synthetic procedure eliminates the liquid-phase extraction between iterative activation and coupling steps, allowing high-yielding and scalable synthesis of oligourethanes.

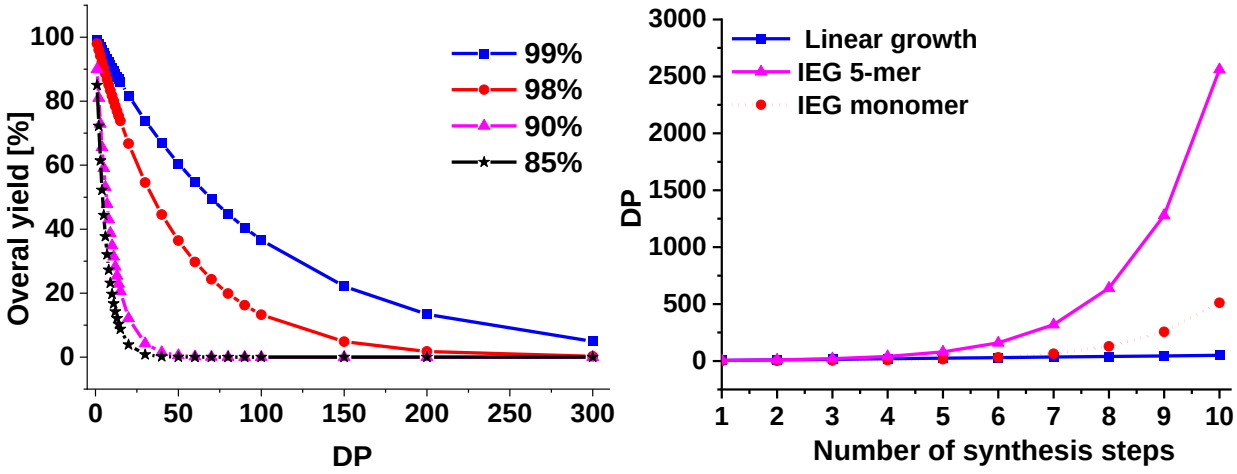

Figure 1. (a) Reduction in the total yield as the number of synthetic steps increases, considering various stepwise yields: 99, 98, 90, 85%. (b) Increase of molar mass with increasing the number of steps, given a 100% stepwise yield based on different synthetic approaches: linear growth, iterative exponential growth initiated from monomers, and iterative exponential growth initiated from one-pot fabricated pentamers.

We assumed that using the one-pot strategy and applying the resulting oligomers into IEG could unlock access to stereocontrolled and sequence-defined polyurethanes. Figure 1 represents a theoretical prediction of an increase in the polymerisation degree depending on the number of synthesis steps using one-pot plus IEG for sequence-defined polymers. Considering the quantitative yield, it is possible to obtain DP = 160 in only 5 steps starting from 5-mer, whereas

starting from monomer leads to DP = 32. A library of five stereospecific, discrete oligomers up to DP = 40 with rich and diverse compositions of chiral and achiral monomeric units is presented to prove the above concept. We investigated the potential of a synthetic approach in the fabrication of oligomers with the irregular arrangement of monomers by combining pentamers in a sequence of reactions. We studied the influence of increasing the chiral monomer component on circular dichroism spectra of polymers.

Results and Discussion

As we reported previously, the sequence-defined pentamer precursors are synthesised by two repetitive reactions in one pot (Figure 2a).[26] In the first step, the hydroxy group of *tert*-butyl (S)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (**Boc-P**) was activated with *N,N′* disuccinimidyl carbonate (DSC) by using pyridine as base leading to unsymmetrical active carbonate. In the second step, the activated alcohol was coupled with amino alcohol chemoselectivity with amine to afford hydroxy-functionalized oligourethane. The activated carbonate and coupling product is formed quantitatively with a common byproduct of *N*-hydroxysuccinimide (NHS) which does not hinder consecutive reactions, therefore purification between each step is unnecessary. Additionally, the byproduct is highly soluble in water and can easily be washed out at the end of sequence formation. The repetition of activation with DSC and coupling with the desired monomer in a one-pot manner led us to construct a library of six sequence-defined oligourethanes up to 5 monomers long (**5a-5f**) at a multigram scale. To induce stereocontrol in the sequences, we used two chiral monomers (S)-2-amino-3-phenylpropan-1-ol (**P**) with aromatic side chain and (S)-2-aminopropan-1-ol (**B**) with methyl side chain. The list of sequences with obtained yields is presented in Table 1. The structures of the obtained products were confirmed by NMR (Figure S8-S31) and LC-MS

analysis (Figure S32-S41). Single liquid/liquid phase extraction at the end of sequence formation was sufficient to produce pentamers with high purity, as confirmed by size exclusion chromatography (SEC) (Figure S2-S7).

Table 1. Sequence-defined oligourethanes synthesis of 5-mers.

No.	Sequence[a]	M_{mi}[b]	m/z[c]	Y[d]	Scale[e]
5a	Boc-PBAAA	655.7460	655.3429	77	14.0
5b	Boc-PBBAA	655.7460	655.3429	78	12.8
5c	Boc-PBBBA	655.7460	655.3429	85	20.7
5d	Boc-PBBBB	655.7460	655.3429	91	29.2
5e	Boc-PAABA	655.7460	655.3429	92	21.6
5f	Boc-PABAA	655.7460	655.3429	90	23.6

[a]Building blocks: 3-Amino-1-propanol (A), (S)-2-Amino-1-propanol (B), (S)-2-Amino-3-phenyl-1-propanol (P); [b]monoistopic molar mass; [c]LC-MS analysis; [d]yields calculated for crude products isolated by extraction in %; [e]weight of obtained product in grams.

To amplify the molar mass of sequence-defined polyurethanes, we combined the developed one-pot protocol with the iterative exponential growth (IEG) (Figure 2b). The prepared library of pentamers synthesised at a large scale possesses a hydroxy group and Boc-protected amine group, which is easily removed by acid treatment. Deprotection of oligourethanes leads to macromonomers, which can be coupled using hydroxy group activation and coupling reactions.

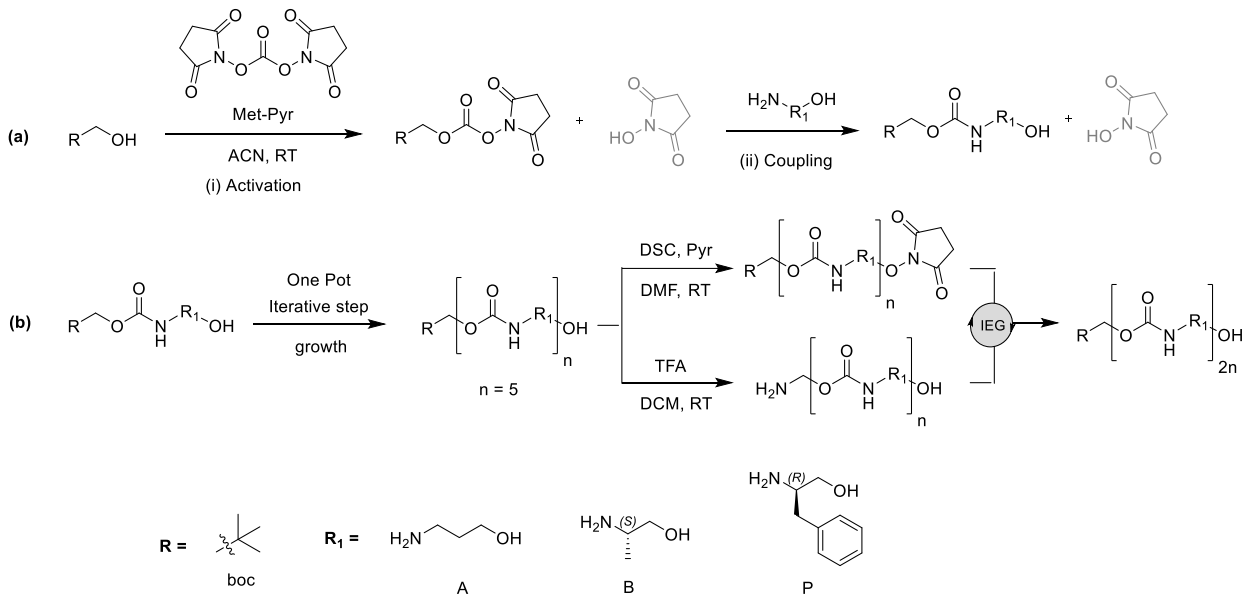

Figure 2. Schematic representation of stereo and sequence-defined polyurethane synthesis in the solution phase. (a) Synthesis involves two general steps (i) Activation of hydroxyl group to form active carbonate, (ii) chemoselective coupling of activated adduct with amino alcohol. (b) One pot iterative step growth synthesis of oligourethanes up to 5-mers followed by iterative exponential growth approach.

The Boc-protected amine group was efficiently deprotected using acidolysis to generate a free amine group, and the resulting amino alcohol was used as a macromonomer in IEG. To ensure quantitative activation of Boc-protected alcohol (5-mer) we used excess of DSC (ranges from 1.5 to 3.0 equiv). Next, the extra DSC was quenched with a drop of water to form NHS byproduct, which does not interfere with the subsequent coupling reaction. Therefore, the resulting activated species was subsequently coupled with a freshly prepared deprotected pentamer to afford a decamer (10-mer) in a one-pot manner. The three steps *i.e.* deprotection, activation and coupling, constitute one IEG cycle to obtain a library of 10-mers (**10a-10e**). The newly generated oligomer possessing Boc and hydroxy group at both ends undergo two more IEG cycles to afford a library of 20-mers

(**20a-20e**) and 40-mers (**40a-40e**) of sequence-defined polyurethanes with varying stereo-configurations. The resulting oligomers at each step do not require purification by column chromatography; instead, simply washing with general solvents such as ethyl acetate, methanol, and water was sufficient to remove the unreacted compounds or byproducts The sequence **40d,** built from 40 chiral monomers, was synthesised on a gram-scale to demonstrate the scalability of the approach. The data suggests that the synthetic methodology can be adopted to synthesise long sequence-defined polyurethanes without cumbersome purification processes. Final products were isolated by extraction and characterised. The list of precise polyurethanes is outlined in Table 2. SEC (Figure S2-S7), NMR (Figure S8-S31) and LC-MS (Figure S32-S41) analyses confirmed the structure and purity of the obtained oligomers. Five examples of stereo-controlled sequence-defined polyurethanes with up to 40 units were constructed with good isolated yields to demonstrate the efficacy of the one-pot plus IEG concept.

Table 2. Sequence-defined polyurethanes synthesis of 40-mers.

No.	Sequence	M_{mi}[a]	m/z[b]	Y[c]	Scale[d]
40a	Boc-(PBAAA)$_8$	4727.1070	4726.2374	85	0.68
40b	Boc-(PBBAA)$_8$	4727.1070	4726.2374	69	0.62
40c	Boc-(PBBBA)$_8$	4727.1070	4726.2374	57	0.31
40d	Boc-(PBBBB)$_8$	4727.1070	4726.2374	45	1.75
40e	Boc-(PAABA)$_8$	4727.1070	4726.2374	71	0.57
40r	Boc-(PABAA-PBBBA-PAABA-PBBBA-PABAA-PBBBA-PAABA-PBBBA)	4727.1070	4726.2374	16	0.31

[a]monoistopic molar mass; [b]LC-MS analysis; [c]yields calculated for crude products isolated by extraction in %; [d]weight of obtained product in grams.

Considering the importance of chiral monomers in sequence-defined polymers, we tried to synthesise elongated oligomers with non-regular sequences comprising arbitrary arrangements of monomers. The scheme depicting asymmetrical oligomer synthesis is shown in Figure S1. We arranged three different pentamers (5c, 5e, 5f) in the defined order. Pentamers **5f** and **5e** were activated with DSC under basic conditions and coupled with deprotected **5c** to afford two decamers **10fc** and **10ec** in 76% and 81% yield, respectively. Treatment of **10fc** with DSC provided activated adduct and Boc-deprotected **10ec** under acidic conditions involving generated new amino alcohol. The coupling reaction between activated **10fc** and deprotected **10ec** led to a 20-mer (**20fcec**) in 82% isolated yield. 40-mer (**40r**) with asymmetrical arrangements of monomers was obtained by subjecting one more three-step IEG cycle with an isolated yield of 16%. This simple strategy for elongated chiral sequence-defined oligomers represents the feasibility of producing sequence-defined polyurethanes with the desired sequence and chain length.

Size exclusion chromatography (SEC) analysis was performed to confirm the subsequent elongation of oligomers by IEG. The recorded chromatograms in Figure 3a and S2-S7 reveal a uniform structure and an increase of polymer length from 5-mers to 40-mers.

Liquid chromatography–mass spectrometry (LC–MS) analyses of all 5-mers and 40-mers were performed to confirm the structures and successful synthetic approach for stereocontrolled sequence-defined oligomers. The obtained spectra are displayed in Figure 3b and S32-S41, which depict high agreement with the theoretical values.

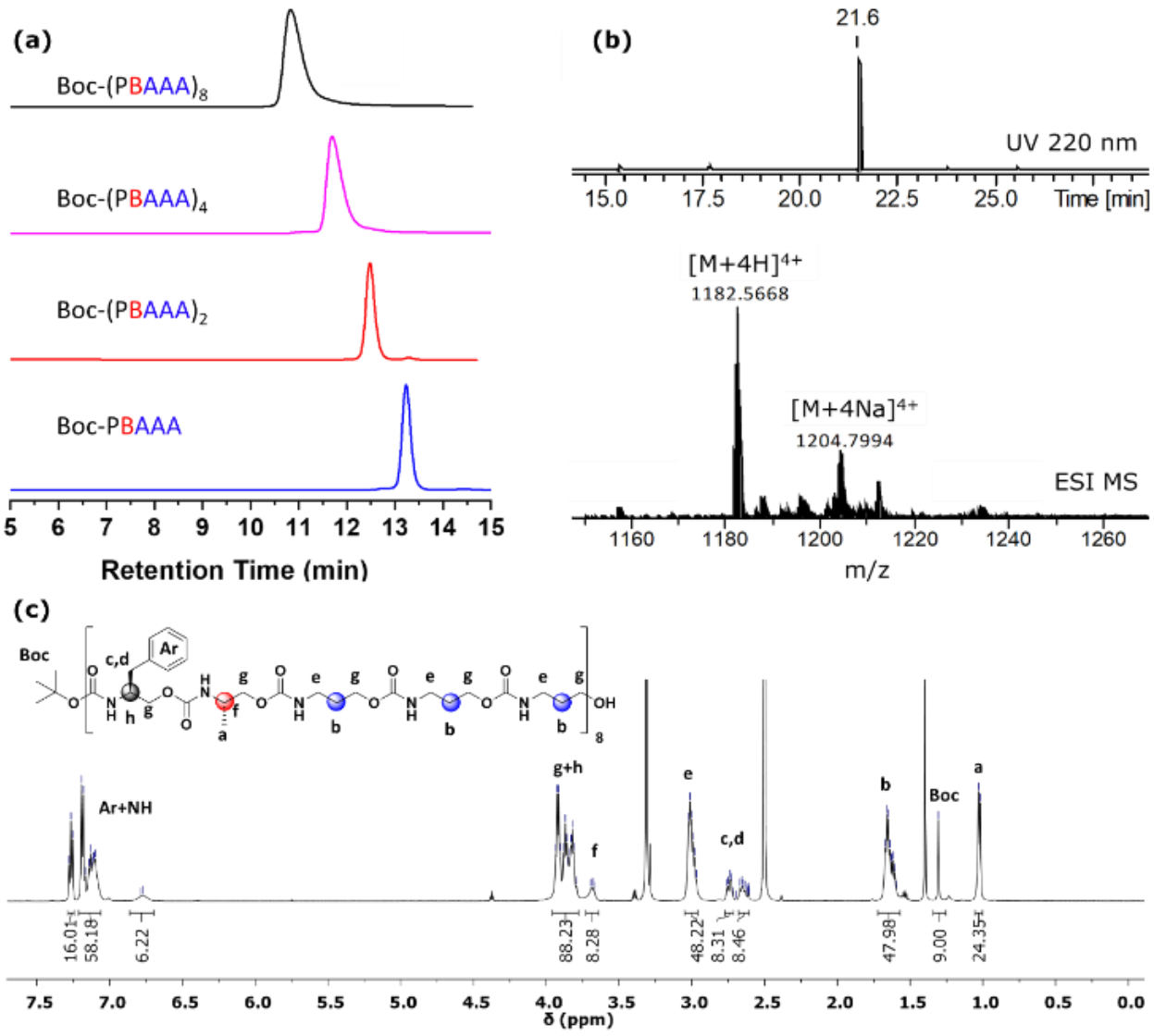

Figure 3. Characterisation of stereo and sequence-defined oligourethanes (a) SEC traces of 5a, 10a, 20a and 40a, (b) LC-MS of 40a, (c) ^{1}H NMR spectrum of 40a.

Oligomers 5-mers and polymers 40-mers were characterised by ^{1}H and ^{13}C NMR. Their corresponding spectra are provided in Figure 3c and S8-S31. All the signals derived from protons associated with each functional group were assigned in the spectra to confirm polymers chemical structures. The distinct peak at 1.31 ppm is attributed to the characteristic Boc group. The sequences comprising aliphatic monomer (**A**) show multiplets at 1.6 ppm and 3.0 ppm and the number of protons depends on the number of monomers loading in the sequences. The signals ranging between

2.49 ppm to 2.76 ppm belongs to diasterotopic protons of methyl group adjacent to phenyl ring. Multiplet signals between 3.5 ppm and 4.0 ppm arise from chiral monomers (**P** and **B**) and the number of protons increases with increasing number of **B** monomer. The signals ranges between 6.62 ppm to 7.28 ppm corresponds to aromatic protons in **P** monomer and amine groups in urethane linkages. In general, the ^{1}H NMR spectra signals coming from polymer backbones represent sequence-characteristic patterns dependent on the number of chiral monomers (Figure 3c).

The synthesised sequence-defined oligomers (40-mers) were further characterised by circular dichroism (CD) spectroscopy to gain insight into their structural properties. The CD analyses indicated different spatial arrangements of sequences depending on the number and position of chiral monomers in the chain. Figure 4. depicts the CD spectra for polyurethanes with increasing number of chiral monomers (40a-d) at 1mM concentration in acetonitrile and water (8:2) as a solvent. The spectra indicated a similar negative Cotton effect with a maximum value of 217 nm. The CD signal increases its intensity with the content of chiral monomer B. For 40d consisting of 40 stereocenters, we can observe a characteristic second band at 213 nm.

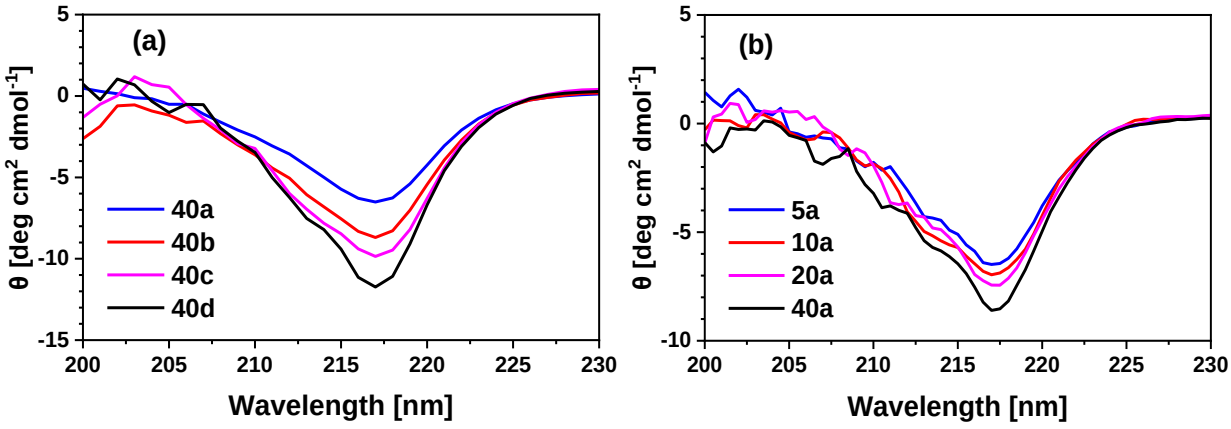

Figure 4. CD measurements between (a) 40a, 40b, 40c, 40d measured in acetonitrile:water (8:2) at 1 mmol concentration and (b) 5a, 10a, 20a, 40a measured in methanol:water (8:2) at 1 mmol concentration.

Furthermore, the intensity of CD signals increases with polymer elongation. In Figure 4b, we can see a change in CD signal for increased polymer length from **5a** to **40a** at the same weight concentration in MeOH/ water mixture. The unique properties in CD spectra may offer potential applications for designing chiroptical macromolecules with variable properties.[35]

Conclusion

In conclusion, combining the one-pot approach with iterative exponential growth (IEG) gives access to stereocontrolled, sequence-defined polyurethanes up to 40 units long. A simple purification technique involving washing with organic solvents such as ethyl acetate, methanol and water was sufficient to remove the byproducts and obtain high-purity polymers. The presented step-economy protocol does not require tedious chromatography purification between steps, leading to the scalable and sustainable protocol for synthesising discrete polymers with defined monomer sequences and stereochemistry. The proposed approach is suitable for polymers with non-symmetrical sequences comprising arbitrary arrangements of monomers with desired chain lengths. Combining different monomers with a gradual increment of chiral monomer loading and its positional change leads to the stabilisation of the polyurethane secondary structure. The presented synthetic strategy opens up the possibility for the fabrication of abiotic polymers with features of artificial proteins.

Associated Content

Supporting Information. The supporting information is available free of charge.

Synthetic procedures, experimental methods and characterisation data (GPC, NMR, LC-MS).

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Author Contributions

RS conceived and designed the study, evaluated data, and supervised all experimental work. AS performed the majority of experimental work on the synthesis and characterisation of polyurethanes. PC synthesised polymer 40b, some of the pentamer precursors and performed LC-MS analyses. VG synthesised polymer 40a and its precursors. RS and AS wrote the manuscript. The authors have approved the final version of the article.

Notes

The authors declare no competing financial interest.

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Abbreviations

DSC, *N,N'*-Disuccinimidyl carbonate; SEC, size exclusion chromatography; NMR, Nuclear magnetic resonance; LC-MS, Liquid chromatography–mass spectrometer; NHS, *N*-hydroxysuccinimide; CD, Circular Dichroism; IEG, iterative exponential growth; A, 3-Amino-1-propanol; B, (S)-2-Amino-1-propanol; P,(S)-2-Amino-3-phenyl-1-propanol.

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