Sequence- and stereo-defined macromolecules – properties and emerging functionalities

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Abstract

Natural macromolecules, such as proteins and nucleic acids, display various complex functionalities in biological systems; these functionalities depend on the macromolecular structure, which is determined by the sequence of monomers and stereochemical factors. Over the past decade, synthetic methods enabling complete control over sequential monomer assembly have been developed; with such precise control over the primary structure of abiotic macromolecules, one can expect to achieve complex functioning, as represented in the case of natural biopolymers. One of the key features in biological processes involves molecule chirality. Therefore, stereochemical considerations form a prerequisite for mimicking biological systems using synthetic polymers. Here, the progress made in the field of stereocontrolled, sequence-defined polymers is summarised. The impact of monomer sequence and stereocontrol on the physicochemical properties of polymers and their emerging functions is discussed, which underlines the importance of macromolecular structure precision. Inspired by the remarkable structures and functionalities of natural biopolymers, chemists have devoted much effort to emulating their features by developing synthetic tools to yield uniform polymers.

In addition to describing synthetic methods leading to stereocontrolled and sequence-defined macromolecules, limitations and problems in their fabrication are highlighted. The review also includes examples showing how sequence and stereocontrol affect the thermal properties and degradation of polymers, which are critical in the engineering and application of polymer materials. The secondary and tertiary structures are responsible for the functions of natural polymers; therefore, the ability of abiotic macromolecules to fold and self-assemble is discussed in detail, with an emphasis on systems beyond polyamides related to protein skeletons. Furthermore, examples of functions that have been displayed by abiotic macromolecules of defined sequence and chirality are presented. The review article focuses on discrete macromolecules built based on abiotic backbones, including oligomers. Polypeptides containing abiotic building blocks are only briefly mentioned as reference examples. In the concluding section, the collected examples are used to elucidate how monomer arrangement and stereocontrol can bring abiotic polymers to a high level of functionality, as manifested by natural macromolecules.

Content

Abbreviations

ATRP	Atom transfer radical polymerization
DP	Degree of polymerization
CDSA	Crystallisation-driven self-assembly
C_n	Conversion of the step n
CuAAC	Copper(I)-catalysed alkyne–azide cycloaddition
DGA	poly(glutaric acid)
DGA-PLA	Diblock copolymers poly(glutaric acid-lactide)
DSC	Differential scanning calorimetry
IEG	Iterative exponential growth
Ins	Insulin
K_a	Association constant
MALDI-TOF	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry
Man	α-D-Mannose
m-THPC	Meta-tetra(hydroxyphenyl)chlorin
m_n	Mass of the product in the step n
m_{ni}	Mass of the product lost in the isolation step n
m_{nth}	Theoretical mass of the obtained product in the step n
OAc	acetyl
OBn	benzyl
PEG	polyethylene glycol
PMMA	Poly(methyl methacrylate)
PLA	Polylactide
RAFT	Reversible addition−fragmentation chain-transfer polymerization
SAXS	Small-angle X-ray scattering

STZ	Streptozotocin
SEC	Size-exclusion chromatography
T_i	Thermal degradation temperature
T_m	Melting point
T_g	Glass transition temperature
WAXD	Wide-angle X-ray diffraction
XRD	X-ray diffraction
Y	Overall yield
Y_n	Stepwise yield

1. Introduction

Sequence-defined polymers are uniform and comprise monomers located in particular positions within the macromolecular chain [1,2]; common examples include natural proteins and nucleic acids. These biological representatives of polymers with defined monomer order exhibit numerous remarkable and complex functionalities, still beyond the reach of their non-biogenic counterparts. The functions of biopolymers are driven by their monomer sequence, referred to as the primary structure. The monomer order determines polymers' physicochemical properties, leading to specific secondary and tertiary structures. Higher-order structures are formed during the folding process, which guides the three-dimensional shape of polymer chains. Simply stated, the shape of macromolecules constitutes the parameter that controls molecular interactions, which is the basis of their notable functionalities, such as selective catalysis, specific recognition, information storage, and complex self-assembly processes, which are responsible for the regulation of multiple events in living organisms. Therefore, controlling the monomer sequence in abiotic polymers has become a research direction in polymer science with increasing attention [3–6]. One can expect that precision in the structure of polymers and the lack of molar mass distribution will allow for the fine programming of

polymer properties and approaching the functionality represented by living matter [7–13]. Such expectations have motivated researchers in the polymer chemistry field to develop synthetic methods to yield discrete macromolecules with a controlled monomer order and to study their sequence–property relationships [3,14,15].

The following question then arises: Is the control of monomer sequences a sufficient condition to mimic the functionalities of biomacromolecules? Considering the structural details of proteins or nucleic acids, one sees that chirality is a property of the biological world. In 1874, Jacobus van't Hoff and Joseph Le Bel recognised that molecules containing a single tetrahedral carbon atom with four different substituents exist in two forms that are mirror images of each other [16]. Their discovery led to the introduction of the term "chirality" in chemistry, which describes a molecule that is non-superimposable on its mirror image [17]. Information on the terminology used in stereochemistry can be found in the article [18]. Stereocontrol is widely observed in biological systems and is critical to the spatial arrangement of atoms, consequently determining biopolymer functionality. Notably, enantiomers possess different properties in a chiral environment yet remain indistinguishable in an achiral environment [19–21]. Sequence control enables the assembly of monomers characterized by opposite steroconfiguration, i.e., R and S, in a defined order, leading to libraries of diastereoisomers with multiple stereocenters in the backbone. In the case of diastereoisomers, one can observe diverse behaviours in a non-chiral environment. Therefore, together with sequence control, stereoregulation is emerging as another dimension of polymer structure control that can tune polymer properties.

This review article aims to elucidate how monomer arrangement and stereocontrol can bring abiotic polymers to a higher level of functionality, as presented in biological polymers, for example. It emphasises the significance of absolute configuration (i.e., chirality) in polymer materials and summarises examples of uniform, sequence-ordered and stereocontrolled macromolecules built on abiotic backbones, including short oligomers. The recent progress

made in synthesising polymers with structural restrictions to discreteness, sequence- and stereocontrol, meeting the criteria of biological structure precision is described. In addition, the impact of stereocontrol on the physicochemical properties and functionalities of polymers is discussed. Further, the ability of abiotic macromolecules to fold and self-assemble, focusing on structures beyond polyamides, is elucidated. Polypeptides containing abiotic building blocks are only briefly mentioned as reference examples.

2. Sequence- and stereocontrol in polymer synthesis

Natural macromolecules, such as proteins and nucleic acids, represent the highest level of structural control among polymers. They are formed as discrete, sequence-defined, and stereocontrolled compounds as a result of biosynthetic processes [22]. The information encoded in DNA is read by protein machinery during the transcription and translation. The four bases of the DNA monomer alphabet are related to the amino acids of the protein by a triplet code – three letters in a gene encode one amino acid. Ribosomes, regarded as macromolecular machines, then facilitate the formation of covalent peptide bonds between the encoded amino acids, leading to a polypeptide chain. Currently, biotechnological methods have progressed beyond the natural building blocks by expanding and reprogramming the genetic code; however, the structures are limited to natural polyamide backbones [23]. Therefore, to fabricate abiotic polymer skeletons, one has to use chemical synthesis methods (Fig. 1).

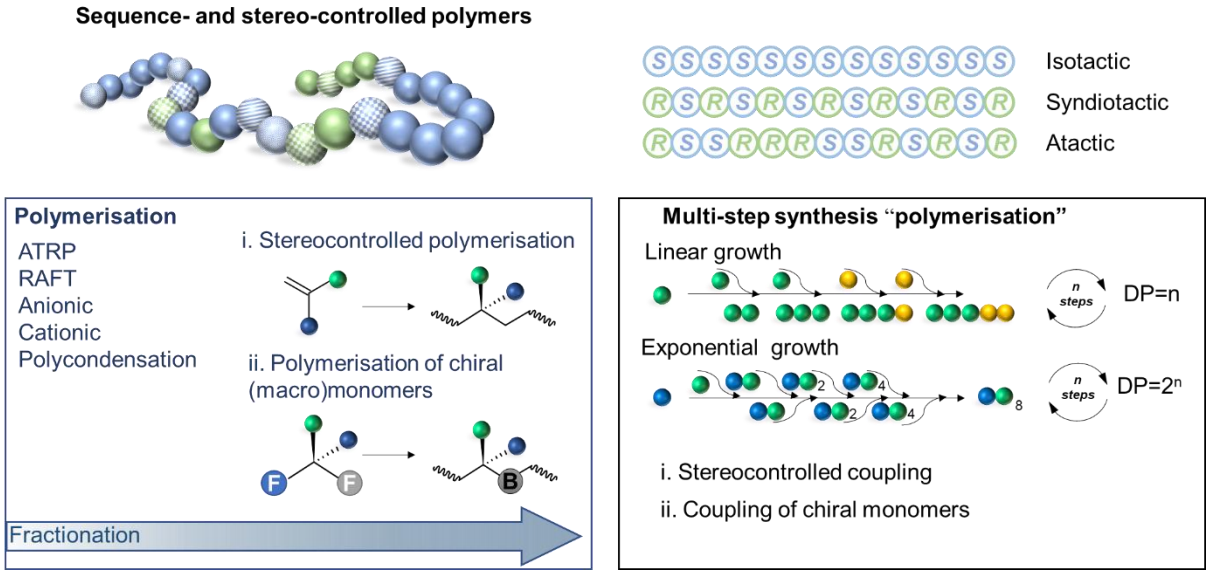

Figure 1. Summary of general synthetic strategies leading to discrete, sequence- and stereodefined polymers. Polymerisation processes lead to polymers characterized by molar mass distribution. Therefore, product isolation via fractionation methods is mandatory. Alternatively, they can be accessed via multistep "polymerisation" using a linear or exponential iterative growth strategy. In both cases, stereocontrol is achieved by stereoselective monomer couplings or the covalent attachments of chiral monomer building blocks.

Generally, the applied synthetic approaches can be classified according to various polymerisation methods [24]: step-growth, chain-growth polymerisation and multistep synthesis, recently defined as multistep growth polymerisation [25]. Depending on the strategy used, multistep synthesis methods can be divided into a synthesis on a solid support, initially developed for peptides [26], and solution synthesis, involving synthesis on soluble polymeric support [27–29] or traditional iterative synthesis. The developed methods can be classified based on the synthetic methodology employed, that is, the protecting group strategy, where difunctional monomers are monoprotected [30], or orthogonal synthesis with chemoselective couplings [31–33] that do not require protection/deprotection steps. Finally, one can carry out classifications based on reactions repeatedly applied in synthesis – that is, cycloaddition [34–37], condensation [38], phosphorylation [39,40], cross-coupling [41], radical addition [42–46],

ring opening [47], light-mediated reactions [48], and thiolactone chemistry [49–51], among other reactions [52–54] – and different polymer families – that is, polytriazoles [55–57], polyesters [38,58], polyphosphates [30,59], polyarylacetylenes [41,60,61], polyurethanes [32,62–64], polythiocarbamates [65], and conjugated oligoheterocycles [66], among other examples [54,67]. However, classifications based on backbone chemistry are not popular due to the complexity of syntheses that often involve several reactions working together, yielding polymers with more than one functional group in the chain, which complicates their nomenclature.

2.1. Polymerisation methods

Despite significant achievements in controlled polymerisation methods, the resulting polymers are not uniform and consist of a mixture of macromolecules [68–74]. Thanks to the progress in polymerisation techniques, control over monomer sequences was significantly improved. [24,75–81]. The literature includes multiple examples of alternating [82–86], multi-block [80,87–92], periodic [93–97], and aperiodic [98–101] copolymers demonstrating sequence control. Usually, control over the monomer order is achieved by monomer reactivity differences [100,102], switchable catalysis [87,88], and controlled monomer addition [42]. Alternatively, one can use sequence-defined macromonomers during the polymerisation process [93]. This strategy is characterised by significant sequence control but is restricted to the amplification of macromonomer sequences.

Discrete macromolecules can be produced using polymerisation methods, yet the polymer product must be purified – this can be achieved by fractionation using an adjusted chromatography technique [103–110]. The main advantage of this method is a relatively simple synthetic protocol compared with multistep synthesis. Using standard automated flash chromatography systems, one can purify multiple grams of the product in one run, though the restriction involves the limited molar mass of the polymers. With the extension of the chain

length, separation becomes increasingly difficult. Hence, this methodology is relevant in oligomer production. Notably, the polymerisation of sequence-defined macromonomers, followed by fractionation, yields discrete, sequence-defined oligomers [103].

To fulfil stereocontrol criteria, one needs to aim for stereospecific polymerisation methods [111–119]. For example, multistereoblock isotactic–atactic polypropylene can be obtained via stereomodulated living Ziegler–Natta polymerisation [120]. The ring-opening polymerisation of different enantiomerically pure monomers catalysed by syndiospecific yttrium catalysts yields sequence-controlled poly(β-hydroxyalkanoate) [121]. Further, accessible catalysts enable the sequential polymerisation of lactide [122,123], styrene [124], methyl methacrylate [125], and 2-vinylpyridine [126], leading to tailor-made stereoblock copolymers. Nevertheless, achieving more sophisticated sequences with multiple monomers is not trivial and cannot be controlled with such polymerisation processes. Discrete, stereocontrolled polymers can be fabricated via the fractionation of polymers obtained in stereocontrolled polymerisation processes [127–130]. For instance, supercritical fluid chromatographic separation [131] or column chromatography [132] have been used to separate discrete, isotactic and syndiotactic poly(methyl methacrylate)s. However, this method proves irrelevant for discrete block-length copolymers differing in stereochemistry.

2.2. Multistep synthesis

Initially developed for synthesising peptides and oligonucleotides [133,134], multistep synthesis remains the most common approach for preparing sequence-defined polymers. [24,25,35,53,54,75,135–137]. Sequence-defined oligopeptides became accessible by the introduction of solid-phase synthesis by Merrifield et al. [26] This method was extended to sequence-defined polymer segments, including mixed segments with chiral amino acids [138], adapting the term “precision polymers” to the particular field of functional species [139]. Subsequently, solution synthesis methods were developed. Iterative coupling of monomers

enables high sequence complexity with numerous monomer building blocks and topology control [140–142]. In the polymer chemistry filed, dendrimer synthesis can be regarded as one of early examples of non-linear sequence-defined polymers [143–147].

In multistep processes, however, one should note that stepwise yield is a parameter that limits the polymer chain length because the overall yield drops significantly with the increase in the number of steps (Fig. 2). Typically, multistep processes require purification between reactions, which can cause additional product losses and further reductions in the overall yield. Even if the conversion of monomer couplings is very high, the synthetic process might prove inefficient due to losses sustained in the isolation steps. Therefore, minimising the number of synthetic steps via, for example, chemoselective monomer couplings that do not require protection/deprotection steps [32–35,148,149], multicomponent reactions [150–153], or one-pot multistep synthesis [154–156] is beneficial. In the case of the synthesis of stereocontrolled macromolecules, we must take into account the enantiomeric purity of the monomers used. In most syntheses, both enantiomers of the monomer will participate in the coupling reaction reducing the enantiomeric purity of the final product. Therefore, the overall yield will be reduced.

Alternatively to classical solution synthesis, one can perform the process on a soluble [28,41] or solid [26,157–162] polymer support to facilitate the purification between the steps. Yet, the support often hinders coupling reactions, thus demanding a large excess of reagents and solvents and consuming vast amounts of organic solvents for resin washing [163]. Such disadvantages limit the synthetic scale and lead to sustainability challenges that generally exclude these methods from practical use, though they are widely used on a laboratory scale [164]. The cost of solid-phase synthesis can be accepted if the product is of significantly high commercial value, as in the case of valuable pharmaceutical products, for example. One of the significant advantages of solid-phase synthesis involves the simple automation of the process,

resulting in the facile fabrication of many sequence libraries with minimal labour effort [30,51,165,166]. For instance, the availability of methods allowing one to obtain a large number of sequences easily is crucial in developing technologies for storing data in polymers [30,151,165,167,168].

To facilitate solution-phase, multistep synthesis, sophisticated purification methods, such as molecular sieving [169], fluorous solid-phase extraction [170], and the boronate-tag assisted solution-phase strategy [171], have been developed. However, due to their specific character dedicated to certain chemical structures, these have not gained widespread popularity.

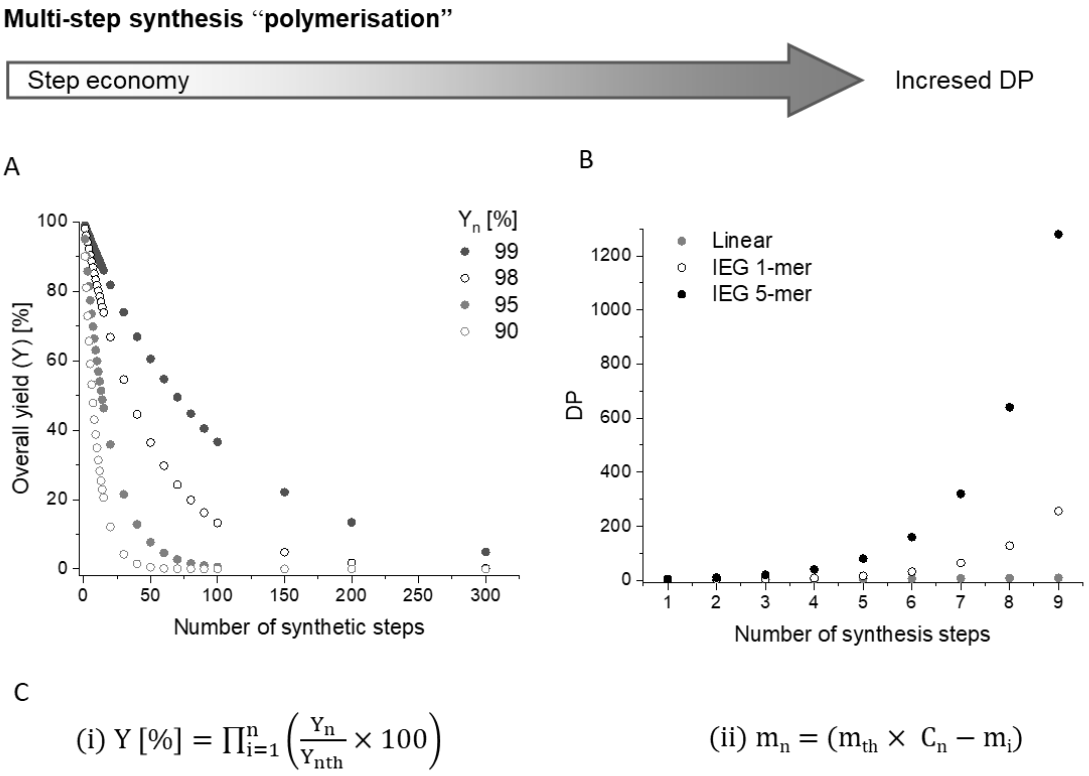

Figure 2. Principles of multistep synthesis. (A) Decrease of overall yield with an increase in the number of synthetic steps for various stepwise yields: 99, 98, 95, and 90%. (B) Increase in the molar mass with the number of steps, assuming a 100% stepwise yield, depending on the strategy used: linear growth, iterative exponential growth starting from monomer, and iterative exponential growth starting from one-pot fabricated 5-mer. (C) Formulas for the calculation of

overall yield (Y) in multistep synthesis, where n is the number of steps; Y_n is the actual yield of step n; m_n is the mass of the product in the step n; m_{nth} is the theoretical mass of the obtained product in the step n, assuming a quantitative yield; C_n is the conversion of the step n; and m_{ni} is the mass of product lost in the isolation step n.

An iterative exponential growth (IEG) strategy seems the most efficient for reaching high-molar-mass polymers with a controlled monomer order [38,172–174]. The concept minimises the number of synthetic steps by coupling oligomeric building blocks (Figure 2B). Step economy results in synthesising sequentially defined polymers of significantly higher molar mass than typical multistep synthesis in solution [175–177]. For example, the IEG of thiol–maleimide coupling combined with orthogonal maleimide and thiol deprotection have been applied to synthesise discrete macromolecules with molecular weights up to 27.4 kDa (128-mer) [176]. Another example of IEG involves the esterification reactions leading to poly(phenyllactic-*co*-lactic acid) with a molar mass of 38 kDa (256-mer) [177]. The IEG concept, matched with flow chemistry, allows for the large-scale production of sequence-defined polymers, as demonstrated for oligotriazole synthesis [178]. Flow-IEG can provide a practical means to generate unimolecular polymers in multigram with the potential to scale up into kilogram quantities. The method opens up possibilities for the commercial exploitation of sequence-defined polymers.

Stereocontrol can be achieved in iterative polymer synthesis by implementing stereoselective reactions [179–181] or using chiral building blocks [58,154,156,174,179,182–189]. Iterative monomer assembly enables the customisation of each stereocenter as needed, resulting in a diverse array of stereoblock architectures, including di-, tri-, and tetrablocks, that are uniform across all polymer chains. For example, stereocontrolled oligopropionates with various sequences of stereocenters can be formed by the reagent-controlled homologation of boronic esters [180]. The process is based on the stereocontrol of the insertion of α-lithioethyl

tri-isopropylbenzoate into carbon–boron bonds. Every monomer coupling generates a new boronic ester for further chain extension with stereochemically defined methyl side groups (Fig. 3), and the process can be easily automated [190]. Experimental and computational analyses showed that in both the solid state and solution, the isomers adopted various conformations depending on the pattern of stereocenters.

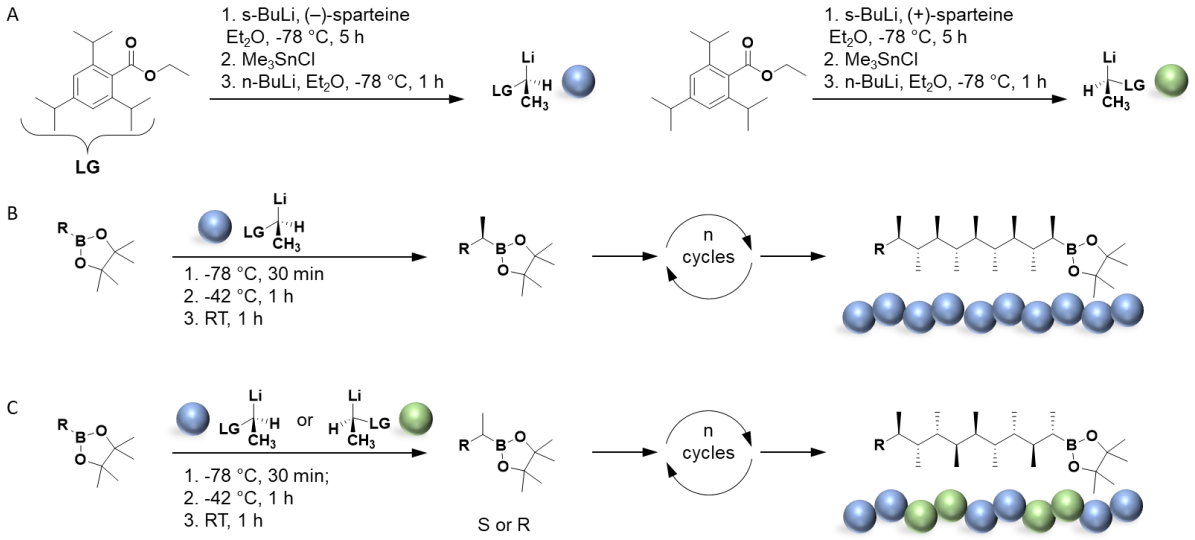

Figure 3. (A) Stereoselective synthesis of the monomers. Iterative assembly-line synthesis of stereocontrolled oligopropionates: (B) isotactic isomer, and (C) heterotactic isomer (based on reported work from [180]).

Discrete, stereospecific oligomers can be prepared through sequential photoinduced RAFT single-unit monomer insertion [181]. Two types of cyclic monomers, indene and N-substituted maleimide, were incorporated into RAFT agents one unit at a time in an alternative manner. The insertion of cyclic monomers into RAFT agents led to the trans configuration due to steric hindrance from the repeating monomer units.

The stereocontrol of sequence-defined polymers is typically achieved by using chiral building blocks [154,156,174,182–189]. Polymers are obtained via solution [179,188] or solid-support [191–193] synthesis, which can be automated to facilitate the process [189]. Due to solubility limitations, synthesising stereocontrolled polymers is usually more demanding than

preparing achiral macromolecules. Therefore, obtaining high-molar-mass polymers is very challenging. Similar to the case in producing sequence-defined polymers, step-economical IEG is the most effective approach here. An early example involves the synthesis of discrete (L)-lactide oligomers from a dimer to a 64-mer via an exponential growth strategy [174]. The synthetic process can be automated using continuous flow chemistry, as demonstrated for sequence-defined poly(L-lactic-*co*-glycolic acid)s up to 64-mer in length [175]. The facile production of polymers makes it feasible to use them for information encoding, storing 64 bits per chain. Further, the IEG of chiral monomers that are orthogonally functionalised/deprotected has been used in the generation of sequence-defined polytriazoles with controlled stereoconfiguration [178,179]. The copper(I)-catalysed alkyne–azide cycloaddition (CuAAC) "click" reaction was used to couple monomers up to a chain length of 32-mer. The methodology was developed into IEG+, where a new side-chain functional group is readily installed via the deprotection of acetyl (OAc) and benzyl (OBn) groups or via the utilisation of thiol−ene addition to incorporate an extensive library of functional groups.

As indicated in a recent report, stereocontrolled poly(thioetheramide)s are accessed via a Michael addition combined with acid-orthogonal deprotection between Trt-thiol and Boc-amino groups using enantiopure serines as the starting material (Fig. 4) [188]. The reported method has demonstrated absolute control over chain lengths up to 32-mer, stereostructure, sequence order, and side-chain functionality.

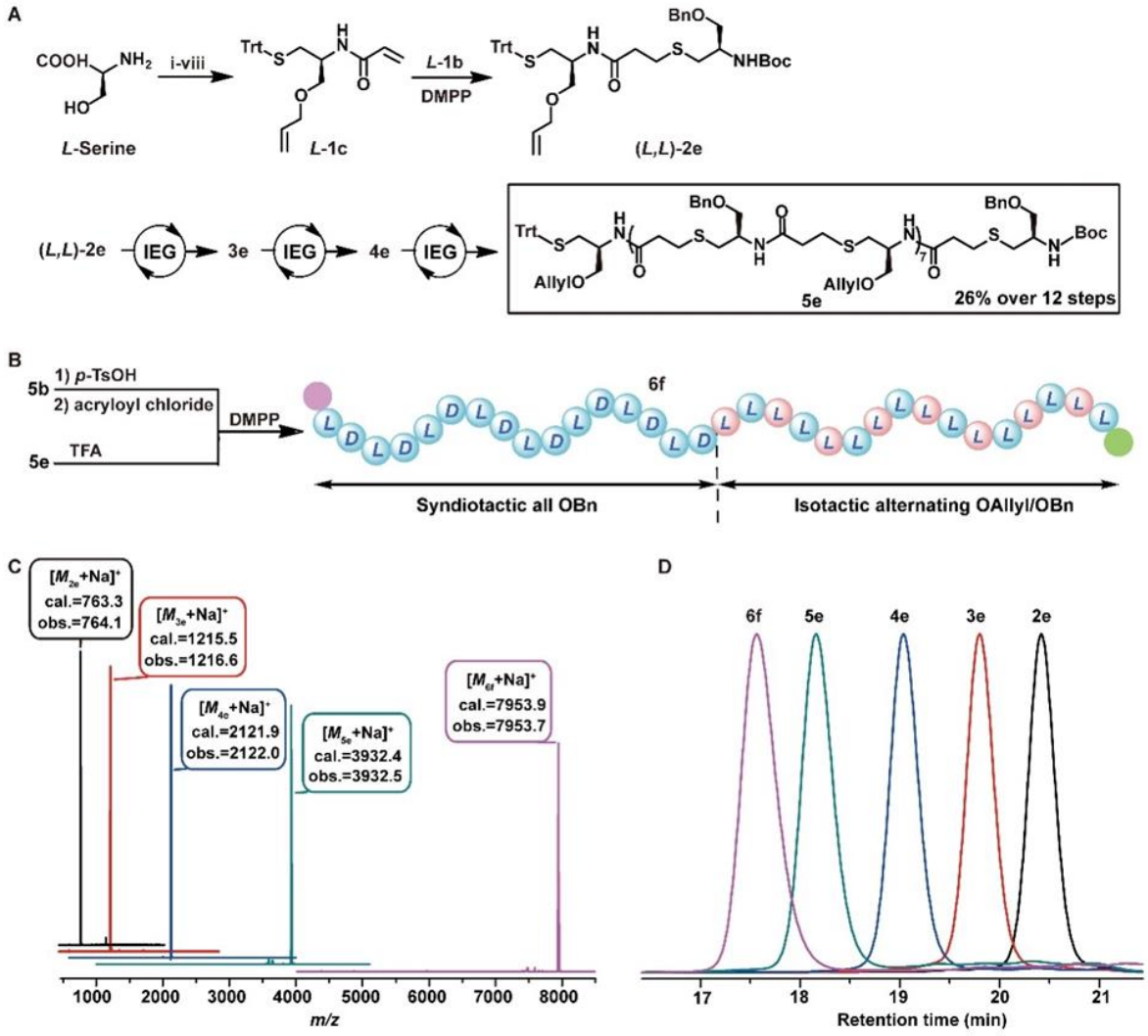

Figure 4. (A) The synthesis scheme of sequence and stereocontrolled poly(thioetheramide)s from dimers (L,L)-2e to 16-mer 5e via acid-orthogonal deprotection and IEG.375 B) General scheme for the synthesis of the stereo- and sequence-defined poly(thioetheramide) 6f from syndiotactic all-OBn hexadecamer 5b and isotactic alternating OAllyl/OBn hexadecamer 5e. C) MALDI-TOF mass spectra of polymers 2e, 3e, 4e, 5e and 6f and D) SEC traces of uniform polymer 6f and other products 2–5e. [188], Copyright 2022. Reproduced with permission from John Wiley & Sons Inc.

3. Influence of stereocontrol on physicochemical polymer properties

The phenomenon of stereocontrol is widely encountered with respect to biopolymers, playing a significant role in shaping their properties and governing their performance. Synthetic, precision polymers are expected to adhere to the same principles observed in their biological counterparts. Primary advancements in polymer stereochemistry were initially observed for widespread plastic materials called vinyl polymers [194,195]. In the late 1940s, despite limited analytical tools, researchers observed that depending on the polymerisation conditions, the X-ray diagram that was associated with the spatial isomerism of vinyl polymer changes [194]. The stereocontrol improved organization of substituent spatial orientation in macromolecule chains, enhancing the polymer crystallinity. Among the early accomplishments in this field is the production of isotactic polymers, such as polypropylene, polystyrene, and poly(methyl methacrylate) [196–198]. Crystalline polymers possess higher melting points, increased densities, reduced solubilities and show remarkable alterations of mechanical properties than their corresponding amorphous counterparts.[199] These properties depend on the sequence of stereocenters in the chain, which affects their spatial alignment and chain mobility [115,120,200–203]. Therefore, subtle differences in polymer chain dynamics governed by stereocenter patterns play significant roles in determining the polymer's physical and mechanical properties, e.g., the tensile and elongation features reflecting the elastomeric character of the material [120]. The effect of stereocontrol is highly noticeable when considering microscale morphology of polymers [174,204]. Stereoconfiguration affects intramolecular interactions that guide bulk and solution self-assembly processes [186,205]. Another feature of stereocontrolled polymers characterised by chirality is optical activity, resulting in the rotation of plane-polarised light. The characteristic Cotton effect depends on

the sequence of stereocenters [188]. The physical properties, controlled by stereoconfiguration aspects, have implications for polymer functionality, which is mainly related to the polymers' secondary and tertiary structures (determining their shape). Folding ability is a characteristic of biotic macromolecules and a prerequisite to inheriting complex functionalities. Hence, stereocontrol is emerging as an invaluable tool for mimicking and modulating complex features of biological systems.

3.1. Thermal properties

The thermal characteristics of polymer materials are one of the major indicators of their properties, ranging from glassy to rubbery states, and allow one to classify their application [206,207]. The characteristic parameters are the glass transition temperature (T_g), which is a property of the amorphous region of the polymer; and the melting point (T_m), characterising the crystalline area. In addition to the chemical structure related to the polymer composition, subtle variables can modulate T_g and T_m [208]. The parameters can be tuned by monomer sequence [95,209,210] and stereocontrol, involving, for example, the length [174,211], number [154], and order [188] of stereocenters. They can also be modulated by other types of structural isomerism [212]. In general, increased symmetry and the inclusion of chain-stiffening units increase T_m and T_g values.

The introduction of chiral building blocks into polymer chains reduces chain mobility and increases T_m. For example, increasing the number of chiral monomers in discrete oligourethane structures shifts T_g and T_m towards higher values (Fig. 5) [154].

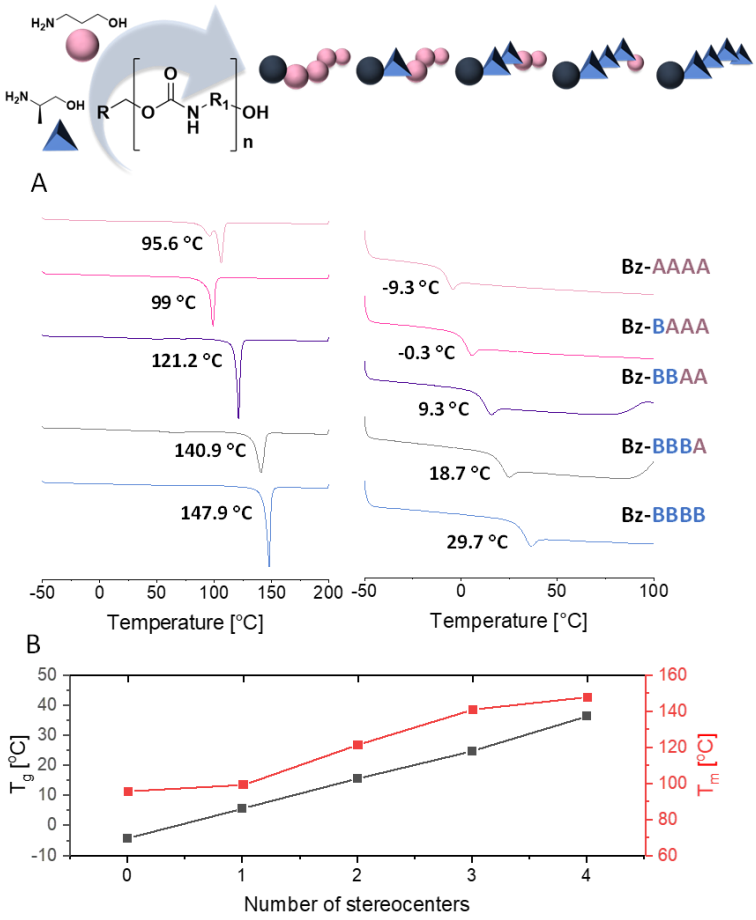

Figure 5. Differential scanning calorimetry (DSC) curves of model oligourethanes of the same molar mass and length with an increasing number of stereocenters. (A) Thermograms of oligourethanes presenting first and second heating cycle at 10 ºC/min. (B) The chiral monomers increase the T_g and T_m values; the T_g values were determined from the second heating cycle, and the T_m values were calculated from the first heating cycle. [154], Copyright 2022. Adapted with permission from Royal Society of Chemistry.

Discrete, stereocontrolled polymers display length-related thermal behaviour: with increasing polymer chain length, T_m and T_g shift towards higher values due to decreased chain mobility [174,211,213]. For example, poly(L-lactide) with various chain lengths from DP = 16–64 shows a shift in T_m values from 92 ºC to 164 ºC [174].

Further, the thermal characteristics of discrete polymers are affected by their stereoconfiguration, though the trend of these changes is not completely clear. Typically, an

increase in regularity in the sequence of stereocenters raises the melting and glass transition temperatures [188,204,214,215]. For instance, isotactic, uniform poly(thioetheramide) L_{32} is a semicrystalline material with a T_m value of 111 °C (Fig. 6) [188]. The stereoblock polymer of L_{16}-b-D_{16} exhibits a T_m of 116 °C, which is ~5 °C higher than the isotactic polymer. In contrast, the syndiotactic polymer $(L\text{-}D)_{16}$ has a melting peak at 122 °C, significantly higher than that of the isotactic polymer. Moreover, each semicrystalline diastereoisomer displays characteristic spectral patterns in the wide-angle X-ray diffraction (WAXD) analyses meaning various packing of the chains in the crystalline phase.

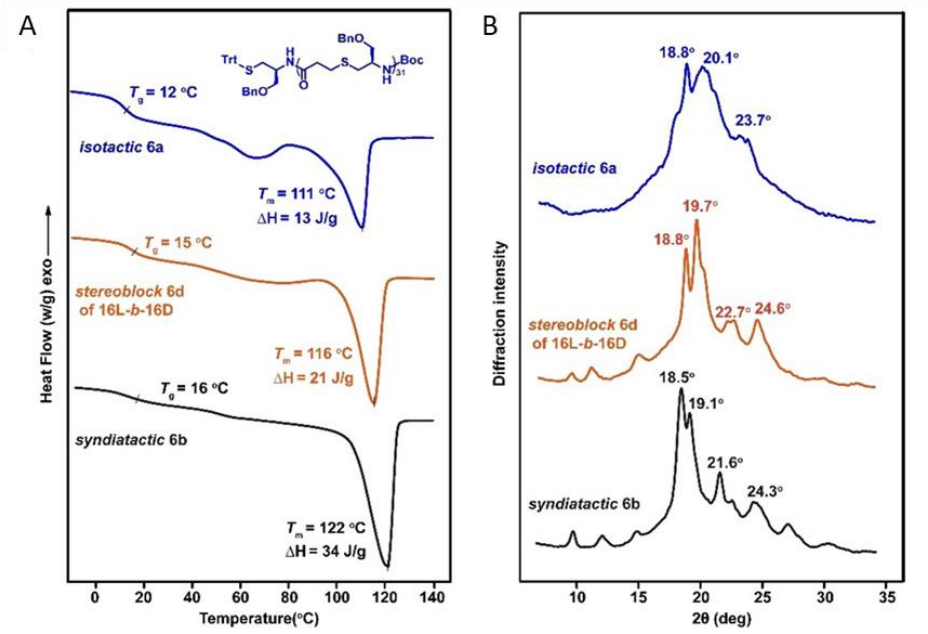

Figure 6. Effect of the sequence of stereocenters on thermal properties and crystallinity of discrete poly(thioetheramide). (A) DSC thermographs and (B) WAXD profiles of isotactic L_{32} (6a), stereoblock L_{16}-b-D_{16} (6d), and syndiotactic $(L\text{-}D)_{16}$ 6b poly(thioetheramide). [188], Copyright 2022. Reproduced with permission from John Wiley & Sons Inc.

3.2. Degradation

Polymer degradation became one of the critical characteristics to assess the duration of material performance and its disposal after its lifetime. Several factors, such as the chemical structure, polymer chain length, and crystallinity, can affect polymer decomposition [211].

Consequently, factors affecting crystallinity, such as the monomer sequence, its regularity, and the stereochemistry, can influence polymer stability [86,216–220].

An important parameter usually determined together with the analysis of T_g and T_m is the thermal degradation temperature (T_i) by thermogravimetric analysis. A study of the decomposition temperature of stereocontrolled lactide oligomers revealed an increase in their thermal stability with increasing molecular weight. The extension of the oligomer length from a 2-mer, which begins to decompose at 100 ºC, to an 8-mer results in shift of decomposition temperature to 250 ºC [174]. The decomposition profile of 8-mer is very similar to that of the commercial, high-molecular-weight polylactide material, meaning that the effect is pronounced in oligomeric molar weight range.

The sequence of chiral centres has an impact on thermal degradation. The thermal stabilities of isotactic and syndiotactic polylactide and their blend were similar, indicating that the effects of tacticity or blending on thermal stability are barely visible [221,222]. However, these differences become more evident when analysing the long-term thermal degradation process at elevated temperatures [223].

The influence of sterocontrol is significant in the case of degradation via external factors, such as hydrolytic or biodegradation. In general, the hydrolytic degradation rate decreases with increasing polymer stereoregularity [101,224]. It is connected to the crystallinity of the material that hinders the penetration of material by water molecules, thus slowing down the decomposition. Notably, polylactide (PLA) copolymers are more prone to hydrolysis than PLA polyblends of opposite stereoconfiguration with an exact ratio of L- to D-monomers. The difference is caused by stereocomplexation between mirror-image isomers, stabilising the PLA structure [225]. Stereocomplexation, similar to crystallization, hinders the water access to ester bonds, preventing hydrolysis. More on the stereocomplexation phenomenon will be described in the following section.

Studies have found that stereocontrol plays a significant role in determining swelling and erosion, as reflected in the degradation rate. For example, poly(lactide-glycolide) copolymers with similar monomer ratios swelled less and displayed a more gradual mass loss with decreased L-L linkages. The significant sequence-dependent swelling behaviour suggests that osmotic pressure, driven by the differential accumulation of degradation products, plays an important role here [217].

3.3. Folding

Natural proteins display outstanding functionalities due to their precisely regulated three-dimensional form. The folding of biological macromolecules is driven by the information encoded in the monomer sequence, leading to various distributions of the α-helix or β-sheet typical conformations [226]. This information is directed by the monomer properties, such as their stereoisomerism, geometry, charge, polarisability, magnetic dipoles, and hydrophilic/hydrophobic balance, instructing the formation of origami-like structures. Based on the principles guiding the three-dimensional structures of biopolymers, foldamers have been developed [227]. They are sequence-specific oligomers, similar to peptides and oligonucleotides, that fold into well-defined structures [13,228–235]. The backbone scaffolds range from stiff oligoaromatic architectures to flexible amide-based peptidomimetic motifs [236–240]. The folding of stiff aromatic structures relies on restricting possible conformations by their rigidity and strong directional interactions, leading to easily-predictable systems. The shape of flexible motifs is guided by torsions with distinct angle preferences induced by the demand for directional bonds [241,242]. Recently, methodologies towards forming tertiary and quaternary structures based on cooperativity between folded motifs are emerging in the continued development of the field, involving, for example, helix dimers, β-sheet bends, eight-helix bundle and foldaxenes [243–247]. Although the field of foldamers is very broad, there are only a few examples of abiotic foldamer families beyond amide-based skeletons, such as

oligoureas [248,249], oligoimides [250], oligo(triazole)s [185,187,251], and aromatic conjugated oligomers with restricted molecular motions [212,252,253]. The vast majority of synthetic polymer structures, which are now available as uniform macromolecules with an ordered sequence, have not been explored in that term.

Scholars have assumed that the classical polymers in solution form random coils that do not refer to one specific shape but that are a statistical distribution of conformations for all the chains in a population [254]. However, the history of helical polymers dates back to the 1950s, when Natta discovered highly isotactic polypropylene, which possesses a helical structure in its crystalline state [196]. More recently, studies have demonstrated that the conformation of short oligopropionates strongly depends on the sequence of stereocenters in the backbone and can modulate their shape [180,255]. Furthermore, over the years, several examples of synthetic polymers that adopt a helical conformation have been discovered and developed, with examples including polyamides, poly(isocyanates), poly(methacrylates), polysilanes, and poly(acetylenes) [256–262]. These are characterised by specific helix inversion barriers that determine their structural stability.

Stereocontrolled polymers, such as poly(methyl methacrylate) [198,263–265] and poly(L-lactide) [266–268], can form stereocomplexes characterised by increased stability compared to single-helix systems [269–273]. The formation of stereocomplexes is affected by several factors: stereocontrol, monomer sequence, chain length, and molecular weight distribution [274–278]. Among the mentioned factors, the length of the polymer and stereochemistry are determinants for the structure of the formed complexes. For example, poly(methyl methacrylate) (PMMA) stereocomplexs if chains reach the critical lengths (Fig. 7) [132]. Depending on the sequence of stereocenters the minimum degree of polymerisation that can form stereocomplexes differs, i.e., 15 units for *it*-PMMA and 20 units in *st*-PMMA. Further, the length of the assembling polymers affects complex stability and crystallisation (Fig. 7C).

Interestingly, PMMA stereocomplexes display selective recognition between stereocontrolled polymer chains mimicking DNA strand displacement [279,280]. PMMA have a preference to form helical strands between chains of similar molar masses that drive the selectivity of complexation. The dynamic behaviours in synthetic polymeric systems can be programmed using polymer building blocks of different molar masses.

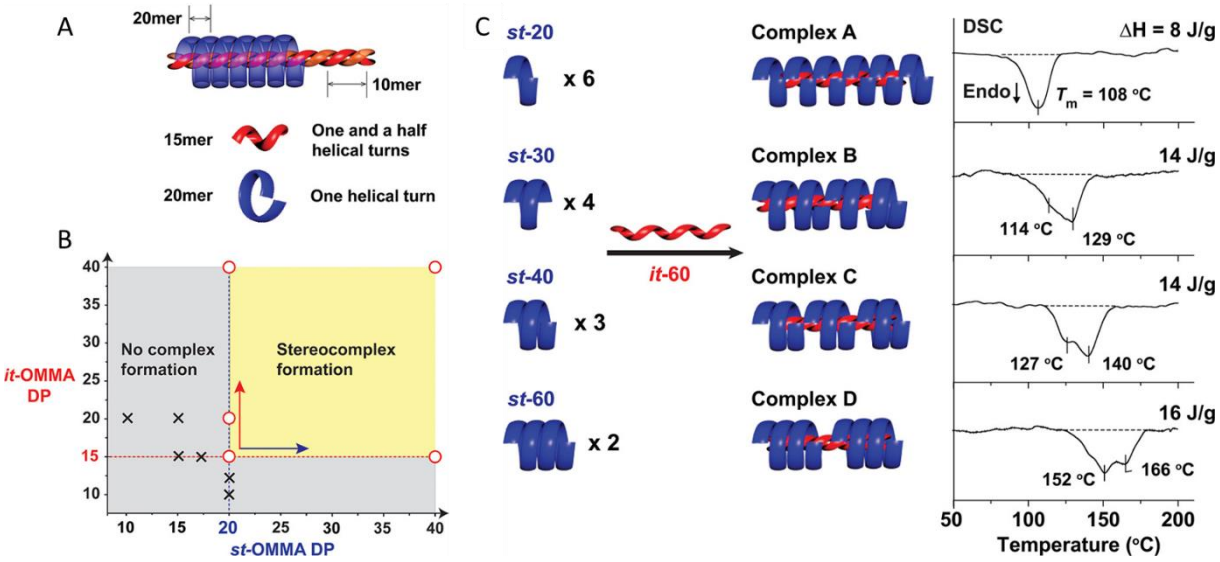

Figure 7. (A) Schematic illustration of the minimal chain length of stereoregular PMMA forming helices. (B) Diagram illustrating the chain length requirements for *it*- and *st*-PMMAs to form the triple-helix stereocomplex, as determined by X-ray diffraction (XRD) and DSC. Circles (○) and crosses (×) indicate the observation of complexation and lack thereof, respectively. (C) Schematic illustration of a series of helical "isomers" with the same total helical length, prepared from *it*-60 with *st*-20, *st*-30, *st*-40, and *st*-60 samples, involving an *it*-/*st*- molar ratio of 1:2. [132], Copyright 2018. Adapted with permission from American Chemical Society.

The effect of stereocontrol has been widely studied for single-chain peptide folding and their self-assembly [281–287]; however, it is still immature in polymer science. A few examples

show the effect of tacticity on single-chain folding [288–291]. Yet, due to the broad conformation freedom of polymer chains, structures display a wide range of conformations.

3.4. Self-assembly

All living organisms are formed through self-assembly, which constitutes the fundament of bioprocesses organising disordered components [292,293]. Cells, the basic structural units of life forms, self-organise to form functional tissues and organs. Polymer self-assembly refers to the process where macromolecules form an organised structure or pattern due to specific, local interactions among the chain elements. Typically, the process involves non-covalent interactions, such as van der Waals forces, hydrogen bonds, π–π stacking, and electrostatic interactions, that keep the assembled objects together. The self-assembly of polymers can be distinguished as a bulk assembly process that determines the material morphology [294–296] or aggregation in solution [297,298]. The latter is often driven by crystallisation that induces the separation of macromolecules or their fragments from the solvent, directing the chains towards self-organisation [260]. Crystallisation can also act as a force for the microphase separation of different polymer blocks [299].

The simplest example of sequence-controlled polymers that self-assemble are block copolymers, which consist of at least two chemically distinct monomers [205,300–304]. The assemblies of these materials are determined by the chemical structure of the polymer and exhibit notable features at the nanometre scale depending on the monomer sequence, which determines the block numbers, lengths, and dispersity [294,305–310]. The monomer order affects microphase separation, resulting in various morphologies ranging from spherical, lamellar, cylindrical, gyroidal, and cubic to modulated hexagonal forms [311,312], with shapes that promote energy efficiency, minimise surface area, and maximise symmetry [313,314]. The block lengths in copolymers determine the hydrophobic–hydrophilic balance. Therefore, even discrete changes in the polymerization degree strongly affect the materials' morphology and

crystallinity [315–321]. With the increasing complexity of the primary structure, sequence-defined synthetic polymers can attain highly sophisticated hierarchical structures [322,323]. Stereocontrol, which influences polymer chain mobility, crystallisation, and the secondary structure, as described earlier, is emerging as an unexplored tool to regulate the resultant self-organised systems. A high level of structural complexity is critical for creating functional materials that can mimic and even outperform their natural counterparts.

Access to uniform co-oligomers/polymers with defined sequences and stereochemical arrangements have led to new perspectives for systematic studies of discrete systems. Understanding the significance of the exact lengths, sequence order (while preserving the same composition), and stereochemistry in copolymer self-assembly processes is attracting considerable attention with the aim to improve control over the material properties and reveal principles of biological system assembly. Subtle modifications can influence the free energy landscape, leading to different phase structures, lattice dimensions, and phase stabilities [324].

The elimination of molar mass dispersity leads to improved uniformity of the morphology of the polymer material. The dispersity of polymers significantly influences microphase segregation, as revealed in a study of block copolymers with an amorphous oligodimethylsiloxane block and a crystalline oligo-L-lactic acid or oligomethylene block [325]. The microseparation of discrete copolymers results in lamellar structures with improved uniformity in the domain spacing compared to analogues characterised by the molar mass distribution of the crystalline block.

The regularity of the monomer sequence significantly influences the ability of copolymers to crystallise, affecting their bulk organisation. Typically, during crystallisation, polymer chains assemble into lamellar structures, and the regular positioning of comonomer defects creates uniform segments of crystallisable units in the polymer chain that are consistent in length [318].

The material morphology of stereocontrolled polymers depends on the degree of polymerisation [326]. For example, upon analysing poly(L-lactic acid)s of various chain lengths from16- to 64-mer, it was found that the chains exhibited different lamellar structures [174]. The lamellar thickness was almost identical to the theoretical molecular sizes of polymers in the case of the 16- and 32-mers. Notably, the lamellar width in the 64-mer polymer was approximately half of its expected molecular length. This observation indicated that the chains of the highest length are folded in the crystal structure.

The bulk polymer assembly of uniform, stereocontrolled polymers can be tuned by the chemical structure of the side chains. For example, amphiphilic isotactic polytriazoles composed of hydrophobic decane and hydrophilic triethylene glycol or thioglycerol side chains, which determined the various domains, were segregated into the alteration of hexagonal cylindrical morphologies [327]. The side chain structure controlled the dimensions of the cylinders. Due to the flexibility of the backbone, the observed polymer segregation was driven by an amorphous assembly process.

Another factor critical for the self-assembly behaviour is the conformational asymmetry of block copolymers. Studies of copolymers formed from lactide and γ-alkyl-α-hydroxy glutaric acid with various alkyl side chain lengths have revealed the diversity of the synthesised structures, which depends on the size of alkyl substituents and blocks distribution [317]. Copolymers are organised into unusual Frank–Kasper σ or A15 and quasicrystalline phases. The enhancement of conformational asymmetry via the elongation of the alkyls results in the expansion of the spherical packing region, leading to complex morphologies.

The controlled doping of discrete copolymers with uniform homopolymers is a relatively simple approach for obtaining rare morphologies. A recent study has demonstrated that blending a polymer into a block poly(lactide-dimethylsiloxane) is an effective method to regulate the formation of complex microphases [328]. The precise tuning of the polylactide

homopolymer chain length and content leads to various spherical packings, including σ, A15, C15, and C14 phases.

Scholars have started exploiting the effect of stereochemical arrangements to control the organisation of polymers. The stereoconfiguration of polymers significantly impacts the chain conformation, leading to diverse lattice parameters and chain packing behaviours [186,329]. For example, amphiphilic block polytriazole with glycidyl propargyl ether and tri(ethylene)glycol side chains (DP=32) with different arrangements of stereocenters L_{16}/L_{16}, D_{16}/L_{16}, $(DL)_8/L_{16}$ and $(DL)_8/(DL)_8$ assembles into diverse morphologies [186]. X-ray scattering analyses and theoretical studies have revealed that stereochemistry modulates the phase behaviour of stereodistinct polylactides in a broad range of structures, i.e. lamellar, gyroid, and hexagonal. Comparing polymers of the same length and composition demonstrates the pure contribution of stereoconfiguration to packing behaviours.

In another study, a series of discrete diblock copolymers poly(glutaric acid-lactide) (DGA-PLA) with identical chain lengths and diverse stereosequences of PLA block was investigated [329]. High polymer crystallinity favours the crystallisation-driven self-assembly mechanism. The stereochemistry profoundly influenced the lattice dimensions and the order-to-disorder transition temperature. The precise chemical structure decoupled the intertwined variables, explicitly revealing the essence and detailed contribution of stereospecyficity parameter. Performed analyses have indicated that the pattern of stereocenters guides the material morphology, resulting in a rich collection of ordered structures, including the rare Frank–Kasper A15 and σ phases (Figure 9) [307]. The above-mentioned examples demonstrate that the stereochemical sequence, without the involvement of changes to the polymer chemical structure, can regulate polymer self-assembly, which can serve as a tool for rational structural engineering.

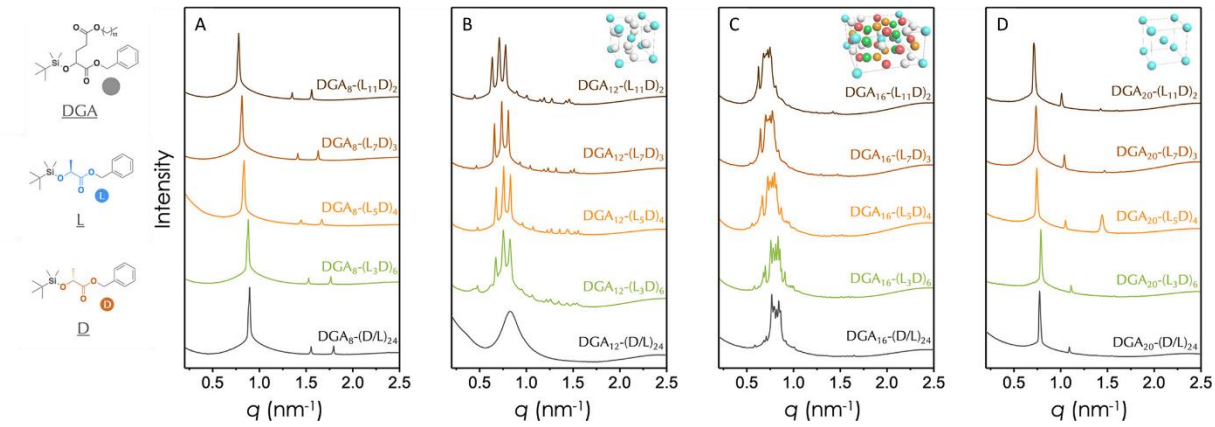

Figure 9. Chemical structures of the DGA, L-LA, and D-LA monomers. Small-angle X-ray scattering (SAXS) profiles of a discrete block copolymer with various lengths of DGA block (A) n = 8, (B) n = 12, (C) n = 16, and (D) n = 20, and different sequences of stereocenters PLA block. The meso counterparts (black line) have the same composition as LD block, but a random distribution of L- and D-monomers was adopted for comparison. [329], Copyright 2022. Adapted with permission from American Chemical Society.

Block copolymers can self-organise into various structures in selected solvents, offering great promise for constructing delivery vehicles and complex nanoscale assemblies [330]. The solution self-assembly of copolymers depends on multiple factors that influence the balance between intra- and intermolecular interactions, which can be finely tuned by controlling the composition, the position of the monomers, and the length. For example, amphiphilic peptoid block copolymers can form spherical micelles with strictly tailored radii and aggregation numbers [331]. Further, sequence control can be used to regulate the organisation of the complex coacervates [332], which are formed by separating oppositely charged polyelectrolytes into dense and dilute phases, known as the coacervate and supernatant, respectively [333]. A study of sequence-defined polypeptides with different arrangements of ionic lysine and glutamic acid residues indicated that charge patterns significantly impact the associations of the chains [334]. In addition, demonstrated examples unveiled the potential of sequence control in the regulation of self-assemblies.

Stereoregularity impacts the behaviour of discrete polymers in solution. As revealed in a study of discrete block copolymers built with stereocontrolled poly(lactic acid) attached to poly(ethylene glycol), manipulating the number and sequence of enantiomeric lactic acid units in the blocks resulted in various nanostructures (Figure 8) [335]. The self-assembly of the homostereoblocks PLA and poly(ethylene glycol) leads to planar nanostructures with unilamellar crystalline cores composed of polylactide. If the stereoblock is formed by D- and L-monomers, the process can be influenced by stereocomplexation. As evidenced by DSC (DLAn)-(LLA)n stereoblocks were folded by intramolecular stereocomplexation, driving the assembly process to form planar nanostructures. The number of repeating domines (DLAn) and (LLAn) regulates the thickness of the formed assemblies.

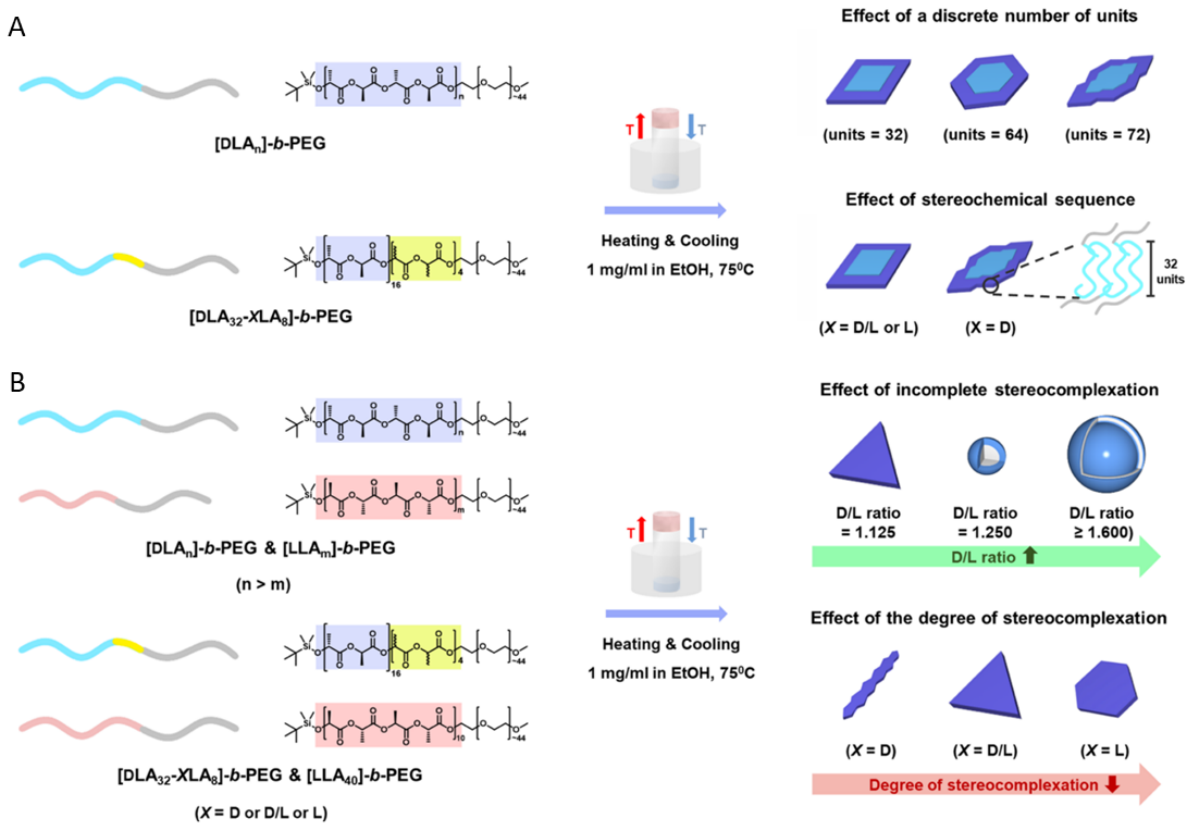

Figure 8. Schematic representation of the formation of various nanostructures through crystallization-driven self-assembly (CDSA). (A) Stereoblock copolymers with a discrete number of repeating units and stereochemical sequence of PLA blocks and resulting 2D nanostructures. (A) CDSA of pairs of block copolymers having a mismatch in the size and

stereochemical sequence of PLA blocks and assembled structures. [335], Copyright 2021. Reproduced with permission from the American Chemical Society.

Studies of uniform oligotriazoles with homogenous and alternated sequences of stereocenters have revealed that the gelation process leads to diverse assemblies with various fibre sizes and network patterns [336]. The arrangement of stereocenters affects the crystallisation of polymers and their packing behaviour, leading to different solubilities in organic solvents. Notably, the importance of stereocontrol in modulating self-organisation in solutions continues to gain popularity, and more examples are expected in future studies.

4. Functions and applications

Sequence-defined natural polymers, such as proteins and nucleic acids, display a wide range of complex functionalities, such as catalysis with perfect stereoselectivity, selective recognition in the presence of interfering analytes, information storage, and the creation of self-assembly systems with a broad range of properties. They are responsible for the regulation of multiple processes in living organisms. Recent progress in the area of sequence-defined polymers has revealed that abiotic macromolecules can mimic the functions of biopolymers. For example, non-biogenic polymers can store information similarly to natural DNA [10,337]. The encoded data can be edited by a light trigger [338], mirroring the concept of gene editing technology [339,340]. The information can be read using instrumental [341,342] or biotechnological methods [343,344] that enable polymer sequencing [345,346]. The stereocontrol of the polymer backbone is particularly important when mimicking protein functions, of which the two main ones – the catalytic and receptor functions – drive the bioactivity of proteins. The sequence of stereocenters significantly impacts folding, which determines the mentioned functionalities.

4.1. Catalysis

Enzymes are proteins with remarkable catalytic performance that accelerate biochemical transformations required for controlling multiple bioprocesses [347]. The sequence of amino acids and stereocontrolled protein structure guide the folding process and the formation of catalytic pockets for reactions with distinct specificity. Catalytic activity is also represented in DNA where the chirality of the deoxyribose sugar governs the stereochemistry of the double helical structure to ensure supramolecular interaction among the complementary nucleobases [348]. Progress has been made in the development of artificial enzymes in the field of biotechnology [349], and new-to-nature elements have been incorporated into biopolymer structures to expand the scope of enzymatic reactions [350]. Enzymes containing diverse metal cofactors, organocatalytic groups, and non-canonical building blocks have demonstrated how protein structures could be optimised to harness the reactivity of non-proteinogenic elements [351–355]. Further, artificial enzymes have been developing in the field of synthetic polymers through molecular imprinting technology [356], topology control [357,358], helical polymer synthesis [359], and supramolecular self-assembly [360–365] that led to macromolecules with good catalytic properties in organic solvents. However, polymers characterised by molar mass and structure distribution do not form discrete shapes. Therefore, their catalytic selectivity is restricted compared to natural enzymes. Hence, the natural continuation of the development of catalysts based on synthetic polymers follows the use of discrete macromolecules with a defined sequence of units and stereoconfiguration.

As specificity and selectivity in catalysis are highly conformation dependent, foldamers of controlled secondary structures have attracted considerable attention [366–368]. The efficiency and selectivity of catalysis depend on the monomer order and composition, tuning the distance between catalytic points [369,370]. Foldamers usually comprise oligoamide peptide derivatives composed of non-natural amino acid building blocks, and they have been used as catalysts for

various reactions, such as the activation of RNase S [371], macrocycle formation [372], crossed aldol reactions [369], the enantioselective oxidation of alcohols [373], etc [366–368]. Another structurally similar group of oligomers explored in catalysis includes the peptoids [374,375], which are peptide derivatives with N-substituted amide bonds [376–378]. The advantage of using nonbiological oligoamides is that the reaction can be performed in a broad range of environments, including organic solvents.

Stereocontrol is critical for enantioselective transformations as the transfer of chiral information from a folded scaffold can lead to products of defined stereochemistry [373,379]. Based on their inherent modularity, sequence-defined polymers based on abiotic backbones show significant potential for devising highly efficient catalysts for asymmetric catalytic reactions. Despite the considerable interest in exploring non-biogenic sequence-defined polymers in catalysis, scholars have not examined them extensively in developing specific catalysts, and the literature includes only a few examples of the utilisation of abiotic sequence-defined macromolecules [380,381]. For instance, helical oligourea foldamers have been used in the catalysis of enantioselective C–C bond formation, displaying up to 99% ee [382].

The effect of the monomer sequence is significant in the case of cooperative catalysts engaging several functional groups in the reaction. The distance between catalytic units can be adjusted by favourable positioning in the chain, resulting in increased reaction efficiency [383–385]. For example, short synthetic oligotriazoles with a sequence of catalytic functional groups spatially arranged by dense surface grafting display an improvement of up to fivefold in the selective oxidation of alcohols compared to a “mismatched” sequence or free oligomers [386].

One reason hindering the prevalence of polymers in catalysis is the difficulty of rational sequence design and the associated synthetic effort. The number of combinations of different sequences is practically unlimited, with a massive library of building blocks. Therefore, it is essential to develop alternative research methods, such as computational means, to preselect

structures and reduce the labor consumption. For example, using molecular dynamics simulations allows for the selection of sequences with the expected catalytic activity [387]. As indicated in [387], tuning the primary structures of oligotriazoles is crucial for ensuring cooperative interactions between the catalytic units and, thus, reaching higher catalytic activities. The developed approach can assist in establishing structure–property relationships, leading to the rational design of sequence-defined catalytic oligomers via computational chemistry calculations.

4.2. Binding and recognition

Next to catalysis, selective recognition is an essential feature of biological polymers. The interactions between molecules require an adequate binding strength and cavity to show selectivity. Stereocontrol is a significant factor considering the spatial arrangement of functional groups and the affinity of the elements responsible for capturing the target ligands.

Receptor-like functionality can be introduced into abiotic polymers by inserting capture groups, such as sugar ligands know from its binding affinity to lectins [388–392] or peptide motifs. [393–395] The addition of peptide segments to precision polymers with drug-directed specificity enables the hosting and transporting of the drug, offering means to achieve advanced formulation additives where chirality coins complexation behaviour. Glycopolymers obtained from the polymerisation of sequence-defined glycomacromonomers bearing one to five α-D-Mannose (Man) ligands can bind lectins, as demonstrated for the model Concanavalin A. In addition, increasing the number of sugar moieties enhanced the binding affinity of the polymer. Notably, the binding of glycopolymers to lectins can be also increased using nonglycosidic motifs. Incorporating sulfonated or sulfated groups led to greater interactions with galectin-3 than glycosylated structures. An in vitro wound scratch assay demonstrated that sulfonated and sulfated nonglycosidic motifs caused a delay of nearly 20% in wound closure in the studied galectin-3 positive MCF 7 breast cancer cell line [396].

The stereochemistry of glycopolymers influences the binding activity with human lectins. Kinetic evaluations of surface plasmon resonance results have revealed that depending on their stereoconfiguration, glycosylated polytriazoles bind to lectins with different association constants [391]. Stereohomogeneous R and S macromolecules bind more strongly to MBL lectins than the respective racemic polymers by two orders of magnitude. The R polymer provides the preferred configuration for binding MBL, whereas DC-SIGN, DEC-205, and CLEC10A prefer to bind to the S polymer. Despite the predominating impact of multivalency in the polymer backbone, stereocontrol has emerged as an effective method to differentiate between lectins, leading to increased selectivity in interactions.

Studies have revealed that synthetic macromolecules with abiotic backbones and peptidic side groups can successfully mimic the binding affinity of biomolecules. For example, the screening of linear and cyclic oligocarbamate libraries has led to the discovery of high-affinity ligands for integrin GPIIb/IIIa [397]. Other examples are oligourea and oligocarbamate, two TAR RNA-binding peptidomimetics that inhibit transcriptional activation by the Tat protein in human cells. Peptidomimetics can target specific RNA structures, providing novel molecules that can be used to control cellular processes involving in vivo protein–RNA interactions [398].

Non-biogenic oligomers can bind nonbiological ligands [399] or metal ions [400], and the binding between molecules occurs according to the principles of supramolecular bond formation [401–403]. Further, the stereocenter sequence can influence the interactions between molecules [399]. For example, oligourethanes with phenyl substituents can bind bisphenol A. Due to the planarity of the resonance-stabilised urethane bond [404], changes in the stereochemical arrangement lead to diverse oligomer conformations that affect the binding of the ligand (Fig. 10).

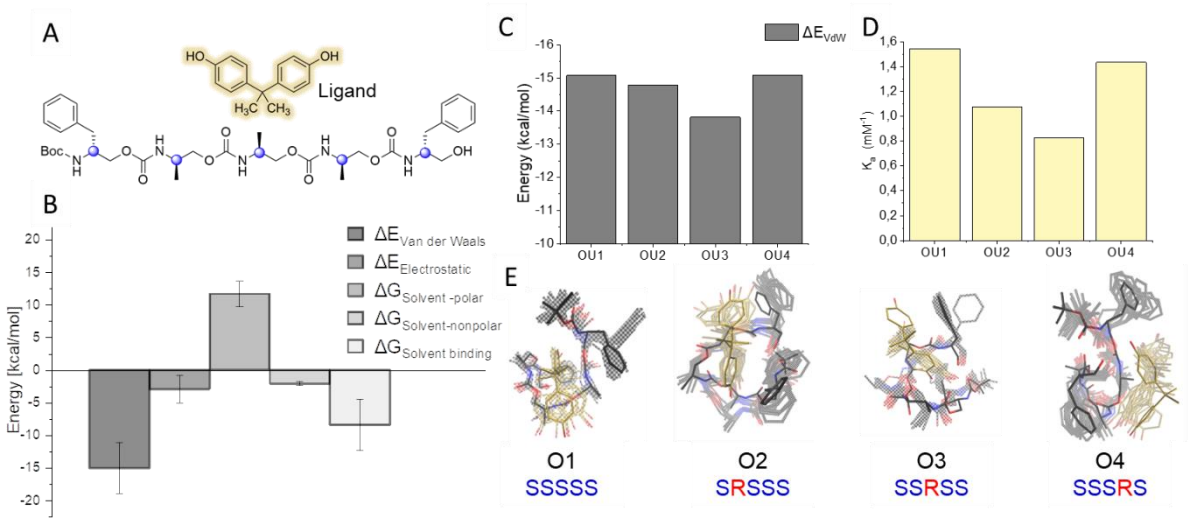

Figure 10. (A) Chemical structure of the oligourethane O3 (SSRSS) and bisphenol A ligand. (B) Binding energy components revealed from molecular dynamics simulations. (C) Comparison of van der Waals energy component for different diastereoisomers (O1–O4) complexed with bisphenol A. (D) Comparison of association constant (K_a) values for different diastereoisomer (O1–O4) complexes determined based on fluorescence quenching during bisphenol A titrations (oligomer 6.8 μM, ligand 1-11 mM). (E) Simulated structures of oligourethane–bisphenol A complexes [399].

Inducing the polymer–ligand binding function is not very problematic because it can be achieved by introducing capture moieties or considering the rational design of supramolecular interactions. However, reaching the high selectivity levels as present in biological systems is notably challenging due to the vast number of possible sequence combinations and the large library of building blocks. Generating multiple variable structures, coupled with the lack of knowledge of sequence–structure relationships, makes rational design beyond reach. Therefore, developing solutions that allow for searching an ample sequence space is essential.

One approach involves constructing sequence libraries, which are then screened to select macromolecules with desirable properties that are widely used in biological studies [405–409]. This method is gaining its popularity in studies of sequence-defined polymers consisting of non-natural elements [410]. On the other hand, one can use computational methods for in silico

structure preselection [399]. Current developments in information technology have opened up new possibilities regarding the screening of abiotic macromolecules for desired functionalities [411]. Further, machine learning technologies enable the enlargement of the sequence space of the investigated library, which can be extended beyond the practical limit.

For example, studies of sequence-defined polymers highly functionalised with nucleic acids have demonstrated that the library of screened structures can be enlarged from $\leq\sim10^{15}$ to 10^{22} by combining in vivo methodologies and machine learning. This approach has been used to explore regions of sequence space unrelated to experimentally derived variants and promote the discovery of sequences with potent affinities for a small target molecule (daunomycin) [412].

4.3. Bioactivity

Living organisms comprise stereocontrolled objects that create a chiral environment. Depending on their stereoconfiguration, enantiomers of small organic molecules display various biological effects [413]. For example, (S,S)-(+)-ethambutol is used to treat tuberculosis, whereas the (R,R)-(–)-enantiomer is harmful and causes blindness. Thalidomide, a popular drug prescribed for morning sickness in the past, when was dosed as a racemate and damaged unborn children when taken in early pregnancy due to the substantial teratogenic effect of S-thalidomide. Therefore, efforts to manipulate polymer stereochemistry are expected to lead to distinct interactions with chiral biomolecules and influencing their biological properties [414,415]. Yet, the significance of absolute stereoconfiguration remains largely unexplored in the field of biomedical polymer applications, leaving many questions unanswered.

The stereocontrol and conformational rigidity of polymers affect interactions with living matter. For example, depending on their rigidity, chiral bottlebrush copolymers composed of two enantiomeric pairs of stereocontrolled oligotriazole macromonomers display various cell interactions [415]. Conformationally flexible polymers show significant differences in cytotoxicity, cell uptake, blood pharmacokinetics, and liver clearance depending on their

stereoconfiguration, while their comparably rigid mirror images show no differences. Notably, the considerable effect of stereocontrol on in vitro and in vivo biological properties is only observed for the flexible structures. The distances between triazole groups, controlled by the number of atoms between each repeating unit, are shown to lead to significant differences in conformational flexibility and biological properties, providing a versatile platform for one to use the stereochemistry of synthetic, non-natural polymers to impact their biofunction.

Biological activity can be translated to abiotic backbones using site-chain functionalities originating from natural stereocontroled biopolymers [184,191,416–418]. Polymers built from peptidomimetic building blocks can retain the same functions as the original peptide sequence and display similar sensitivity to single monomer mutations or exchanges. Significant sequence dependency is evident with regard to drug payload capacities and drug release kinetics, allowing for the fine-tuning of drug transporter properties according to therapeutic requirements [416]. These can even surpass the parent peptide properties by achieving higher payload capacities and a more favourable kinetic profile of drug release [417]. For example, the peptide QFFLFFQ is able to accommodate the photosensitiser meta-tetra(hydroxyphenyl)chlorin (m-THPC) and can be converted into abiotic polymer backbones based on oligo(N-substituted acrylamide)s and oligo(2-substituted α-hydroxy acid)s, retaining the characteristics of the original peptide. The corresponding PEG-oligoester conjugates mimic the properties of the parent peptide-PEG drug solubiliser with 40% higher payloads. The translation strategy might guide the design of precision polymers to achieve the advanced functions originating from sequence-specific interactions in biological systems [184].

Backbone modifications can serve as an excellent tool for developing pseudopeptides with improved biological function [419]. Arginine-rich peptides display excellent membrane penetration properties [420–422]; however, having consecutive arginine residues can increase susceptibility to proteolytic degradation and hinder membrane interactions, ultimately affecting

its bioavailability. These limitations can be overcome by replacing the amide backbone with abiotic carbamate [193]. Modifications incorporated into biologically active peptides often improve the metabolic stability of the peptide backbone [423]. Hydrolytic enzymes do not recognise non-natural structural elements. Therefore, replacing amide bonds in peptides with carbamate bonds can enhance their stability. For instance, carbamate-based pseudopeptides corresponding to the antimicrobial sequence show an extended half-life in serum compared with the original peptide [423]. Increased resistance to degradation results in improved antimicrobial activity against test bacteria and fungi. The incorporation of backbone modifications has been analysed using circular dichroism spectra and chromatography to reveal the impact of the structure helicity and hydrophobicity on activity. The results indicated that the alpha-helical structure was the most crucial factor in antimicrobial activity, while hydrophobicity had a notable effect on the pseudopeptide stability. Interestingly, with the knowledge of structure–activity relationships, backbone modifications can be programmed for developing bioactive molecules from membrane-active antimicrobial peptides.

Further, pseudopeptide modification by non-natural elements, such as 6-aminohexanoic acid-based spacer moieties, improves the flexibility and hydrophobicity and ensures the optimal spacing of polar guanidinium groups [424]. Enhancing fundamental properties increases the transfection efficiency compared to the capability of the amide counterpart. Carbamate–plasmid DNA complexes primarily utilise lipid raft-dependent cellular entry pathways compared to other possibilities. Therefore, hydrophobic modification facilitates their increased transfer in the lipid-raft-rich milieu of the skin. This example illustrates the effect of rationalised oligomer design, despite the complex characteristics of biological systems.

4.4. Bioconjugation

The conjugation of non-biogenic polymers with biologically active molecules has been used to improve the properties of therapeutics, such as their stability, pharmacokinetics, and

biodistribution [393,425–431]. However, applying classical polymers characterised by molar mass distribution presents significant restrictions. The heterogeneity of the resulting bioconjugates may lead to manufacturing variabilities, poorly controlled physiological performance, and limited ability to optimise structure−property relationships. Among synthetic polymers, poly(ethylene glycol), or PEG, is the most widely explored in bioconjugations [105,432–439]. Its growing popularity has led to its high commercial availability in discrete form, with defined end functional groups. However, the immunogenicity of PEG is a critical concern, as reported in a recent review [440], underscoring the need to explore alternative polymers as potential substitutes for PEG [440–442]. Therefore, sequence-defined polymers are emerging as alternatives for drug conjugation [443–446].

The therapeutic effect of drugs is affected by the stereoconfiguration of polymer bioconjugates. For example, studies on a diabetic mouse model revealed that the lowering glucose performance of insulin-oligotriazole conjugates depended on their stereocenter configuration and composition [447]. Specific insulin conjugates have demonstrated quicker-acting or more enduring effects than commercial insulin derivatives and PEGylated insulin (Fig. 11). Stereocontrol regulates the molecular details of synthetic polymers that impact the functions of their biopolymer conjugates. It demonstrates new possibilities for optimising the properties of synthetic polymers, such as therapeutic performance and drug stability.

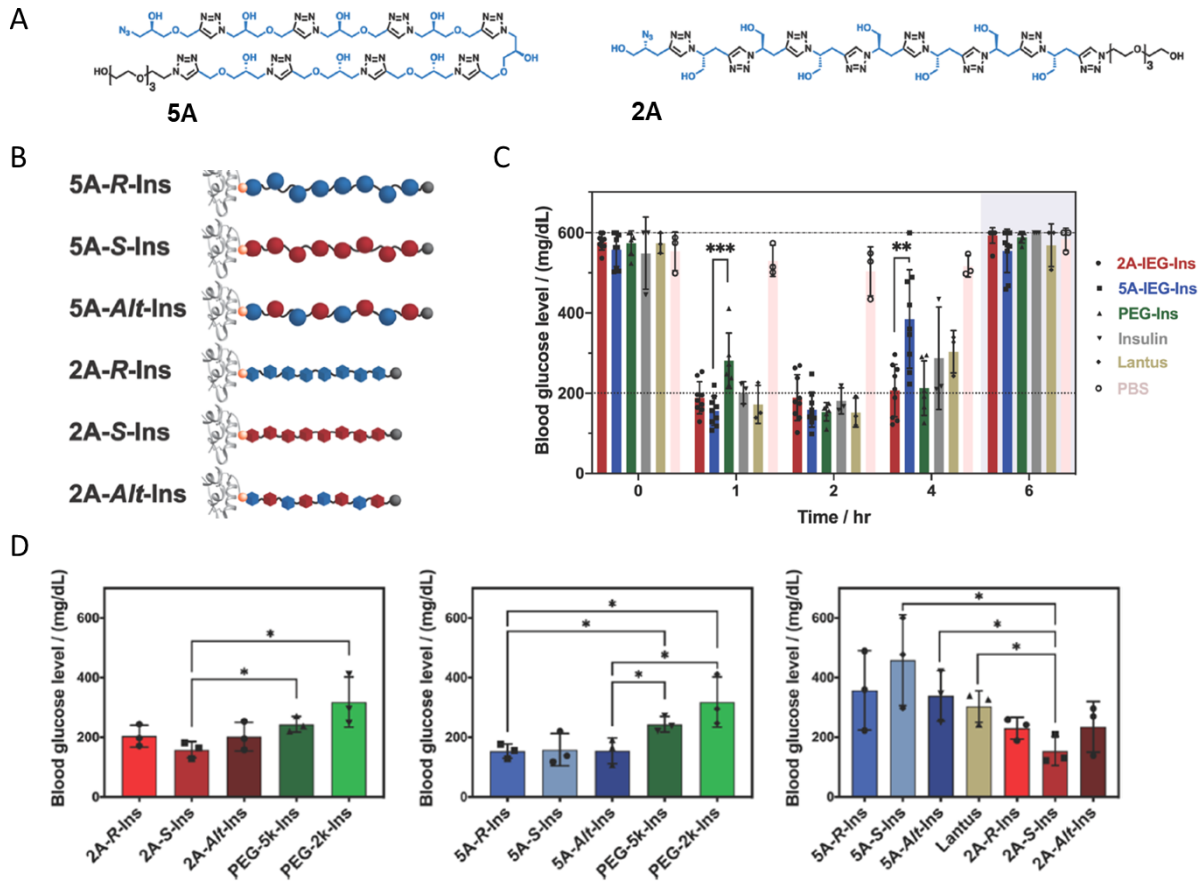

Figure 11. (A) Structures of water-soluble polytriazoles 5A and 2A synthesised in this work. (B) Library of investigated polytraizole sequences of different stereoconfiguration. Two different backbones, 2A and 5A, were leveraged to tune the backbone rigidity, while the absolute configurations of each molecule were defined by the monomers employed in the IEG synthesis. (C) Blood glucose levels versus time for polymers grouped by composition (e.g., "2A-IEG-Ins" presents the average for 2A-R-Ins, 2A-S-Ins, and 2A-Alt-Ins combined, similarly for 5A-IEG-Ins and PEG-Ins), showing the overall differences in activity compared to commercial Lantus and insulin alone. (Food was provided after the 4 h data point.) (D) In vivo blood glucose studies in STZ-induced diabetic C56BL/6J mice (n = 3 mice per treatment group). The blood glucose levels are plotted against time for the polymers, which are grouped by composition (e.g., "2A-IEG-Ins" presents the average for 2A-R-Ins, 2A-S-Ins, and 2A-Alt-Ins combined; the case is similar for 5A-IEG-Ins and PEG-Ins), showing the overall differences

in activity compared to commercial Lantus and insulin alone. [447], Copyright 2022. Adapted with permission from American Chemical Society.

5. Conclusions and outlook

Combined with sequence control, stereocontrol is emerging as a novel tool for regulating macromolecular properties and functionalities (Figure 12). Discrete, chiral polymers with defined monomer orders are accessible using various approaches. Among the methods described, multistep synthesis allows for the most precise level of structural control, providing access to macromolecules with biological features. In contrast, polymerisation methods are currently still limited in meeting the rigorous criteria of structural control that prevails in biological systems. Specific polymers can be accessed via early solid-phase synthetic methods developed for peptides and oligonucleotides or solution synthesis, which is increasing in popularity. The most significant advantage of solid-phase synthesis is the associated facile automatisation, making it feasible to synthesise numerous sequences parallelly. Access to libraries of different polymer sequences is essential for academic studies of sequence–property relationships and some applications, e.g., for data storage. Step economy solutions, such as one-pot multistep synthesis, multicomponent reactions, and iterative exponential growth, are prospective directions in further developing the solution synthesis approach. Reducing the number of steps increases the overall yield and promotes a greener process compared to traditional methodologies. This reasoning has led to continued progress in synthesising sequence-defined polymers and delivering longer polymers with higher molar masses and larger-scale synthesis than was possible in the previous decade. However, reported methods require further development and optimisation for practical application. There is no single synthetic strategy that can serve as the optimal one for all purposes and future applications. Therefore, it is essential to develop both automated solid-phase synthetic methods yielding a

vast number of sequences and scalable, practical approaches in line with sustainable development.

Multiple parameters can be modified to regulate macromolecule properties, including the chemical structure, average molar mass, copolymer composition, tacticity, and dispersity. These factors have been considered since the advent of the field of polymer chemistry. With the development of precision polymer synthetic methods, the possibilities to influence polymer structures have become more subtle, involving the discreetness of the polymer chain length, the monomer sequence, and the recently emerging sequence of stereocenters. Scholars are shifting away from employing average parameters, such as the average molar mass, copolymer composition, and overall tacticity, towards tuning parameters with the highest level of precision, that is, the exact chain length; the order of monomers while preserving the same composition; and stereospecificity. In general, the effect of these changes varies depending on the molar mass of the polymer. Short oligomers are very sensitive to each modification or chain extension. However, with elongation, the effects caused by fine structural changes are increasingly less pronounced. Most research in the emerging field of sequence-defined polymers has been conducted for model oligomers, allowing the sequence–property relationship to be clearly captured. The investigated polymers are generally characterised by a degree of polymerisation from 4–64 units, and whether these constitute macromolecules or oligomeric systems is debatable. Thus far, the molar mass cutoff between the polymer and the oligomer has not been clearly determined. According to IUPAC molecule can be regarded as a synthetic polymer if adding one or few units has a negligible effect on the properties [448]. It should perhaps be investigated to know the chain length limit at which it is feasible to observe property changes caused by nuanced structural differences, such as the monomer sequence, addition of a single monomer unit or mutation of stereocenters.

Although the influence of relative stereoconfiguration on polymer characteristics has been recognised for many years, as demonstrated for polypropylene, the significance of absolute configuration remains largely unexplored. Combined with sequence control, the stereoregulation of polymers is just gaining its popularity. Considering the collected examples, stereocontrol has the potential to be employed in programming the properties and functions of polymers. It may be unsurprising because sequence-defined biopolymers, such as proteins, are stereocontrolled, and their chirality dictates their role and performance in living organisms. Stereoregularity reduces the mobility of polymer chains, which is reflected in increased glass transition temperatures and susceptibility to crystallisation. Consequences are the notable effect of stereocontrol on polymer folding and induced self-assembly. Precise stereochemical modifications lead to various sophisticated morphologies and even rarely occurring examples. A subtle variation in the arrangement of stereocenters is sufficient to interrupt the free energy landscape, resulting in distinct phase structures, lattice dimensions, and phase stabilities. It should be underlined that there exists no restriction to produce only polymer enantiomers. With structural control at the monomeric level, one can create a wide range of possible diastereoisomers characterised by unique sequences of stereocenters, which display various properties in an achiral environment.

Programming complex functions in abiotic macromolecules are not trivial, mainly if we aim for specific interactions. The broad range of synthetic monomers and backbones makes very difficult to predict the desired sequence-function relation. So far, the design of biofunctions has usually been done using established interactions of biological systems. Typically, non-natural macromolecules are formed by modification of natural biopolymers by introducing synthetic motifs. Those modifications can lead to significant improvement of native features. However, to induce specific functions in synthetic polymers, one must reach for effective tools. Quickly developing information technologies with empowering artificial intelligence are powerful

methods that can accelerate the development of the polymer chemistry field. Machine learning has become an invaluable tool to reveal secrets hidden in biological macromolecules [449,450], yet still gaining popularity in polymer science [451–453]. Those methods are increasingly applied to find patterns in data to predict properties of previously unseen but similar structures. Yet, at present, the potential of computational methods in polymer design is far from being efficiently exploited. Automatization of experiments is needed to generate high-quality, big data sets for prediction model training. Effective use of machine learning will catalyze the development of sequence-and stereocontrolled polymers by enabling the programming of their functions, as it is happening in biology.

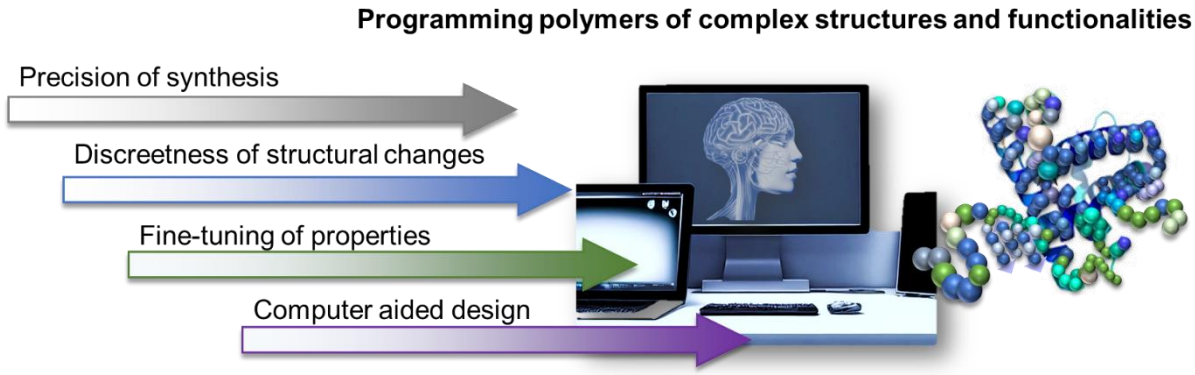

Figure 12. The combination of precise polymer chemistry, which allows finely controlling the properties and the power of machine learning technology, is an emerging direction to induce complex functions into abiotic macromolecules.

Acknowledgements

The author is highly grateful to Polish National Science Centre grants: No. 2018/31/D/ST5/01365, No 2021/43/I/ST4/01294, No. 2021/42/E/ST4/00010, National Centre for Research and Development project No. LIDER/27/0148/L-12/20/NCBR/2021 and Łukasiewicz Centre grant No. 4/Ł-PORT/CŁ/2021 for received financial support to conduct research in the field of sequence-defined polymers.

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