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► **To cite this version:**

Ranajit Barman, Jean-François Lutz. A General Strategy to Access All Stereosequences in a Synthetic Polymer. *Journal of the American Chemical Society*, 2025, 147 (48), pp.44430-44436. <10.1021/jacs.5c15603>. <hal-05406274>

HAL Id: hal-05406274

<https://hal.science/hal-05406274v1>

Submitted on 9 Dec 2025

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A general strategy to access all stereosequences in a synthetic polymer

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Published in *Journal of the American Chemical Society*, 147, 44430-44436 (2025)

<https://pubs.acs.org/doi/abs/10.1021/jacs.5c15603>

Abstract.

The control of main-chain stereocenters in synthetic polymers remains a longstanding challenge, with traditional polymerization methods typically yielding only three types of well-defined stereosequences: isotactic, syndiotactic, and heterotactic. Here, we show that a broader range of stereochemical patterns can be accessed using iterative phosphoramidite chemistry. Two monomers bearing opposite configurations at a carbon stereocenter were synthesized and employed in automated solid-phase synthesis to construct poly(phosphodiester amide)s with defined stereosequence. High coupling efficiencies enabled the generation of polymers with exact chain lengths and primary structures. Comprehensive characterization by high-resolution mass spectrometry, ion-exchange HPLC, NMR spectroscopy, and circular dichroism confirmed the high stereochemical fidelity of the resulting materials. This approach enabled the synthesis of perfectly isotactic and syndiotactic polymers (100% *m* or *r* dyads), surpassing the precision achievable through conventional polymerization. More importantly, the method also facilitated access to non-classical and previously unattainable stereosequences, including periodic, stereomutated, and stereocoded arrangements. For polymers with 20 stereocenters, this methodology allows for the theoretical creation of over one million unique stereosequences. These findings establish a new paradigm in stereocontrolled polymer synthesis, expanding the structural and functional landscape of synthetic macromolecules.

Introduction.

Stereochemistry plays a crucial role in the structure and function of both natural and synthetic polymers.¹ A defining feature of biopolymers - such as nucleic acids (*e.g.*, *d*-DNA), proteins (composed of *L*-amino acids), and polysaccharides - is their homochirality, which is fundamental to life (Figure 1a).² However, nature also employs other stereochemical patterns, such as alternating *D-L* peptides, which exhibit significant antibiotic activity.³ Furthermore, scientists have engineered mirror-image biopolymers, like *l*-DNA,⁴⁻⁵ which open the door to the intriguing possibility of mirror-image life.⁶

The stereochemistry of synthetic polymers has also been extensively studied for decades.⁷⁻⁹ The chirality,¹⁰ optical activity,¹¹ helicity,¹²⁻¹³ complexation¹⁴⁻¹⁶ and self-assembly¹⁷⁻¹⁹ of stereocontrolled polymers have been widely investigated. Despite this progress, controlling the stereochemical arrangement of main-chain units (commonly referred to as tacticity) remains a significant challenge.²⁰ According to recent IUPAC definitions, only a few distinct tactic forms have an official name (Figure 1b): isotactic (characterized by a high proportion of *m* dyads), syndiotactic (predominantly *r* dyads), and heterotactic (alternating *m* and *r* dyads).²¹ Stereoblocks and stereogradients have also been reported.²²⁻²⁵ Apart from those, the only remaining category is that of atactic polymers, which are defined by a random distribution of *m* and *r* dyads.^{21,26} The limited stereocontrol in synthetic polymers arises from two primary factors. First, only a few polymerization methods exhibit stereoselectivity,²⁷ such as coordination polymerization,²⁸ anionic polymerization,²⁹ and, under specific conditions, certain cationic,³⁰ ring-opening³¹⁻³³ or radical³⁴⁻³⁶ polymerizations. Second, synthetic polymers are typically non-uniform (*i.e.*, dispersity $\mathbb{D} > 1$), meaning their macromolecules vary in chain length and primary structure.³⁷ Therefore, a polymer referred to as “isotactic” is not composed exclusively of *m* dyads, but rather contains a predominant proportion; typically exceeding 95%.²¹ In recent years, there have been several attempts to prepare synthetic, stereocontrolled

polymers with uniform structures ($\mathfrak{D} = 1$), using methods such as exponential iterative growth and solid-phase iterative chemistry.³⁸⁻⁴² However, these efforts have mostly been limited to well-established cases, such as isotactic sequences or stereoblock architectures.

In this study, we present a general strategy for achieving absolute control over polymer tacticity (Figure 1c). This method enables the synthesis of uniform polymers with virtually any desired stereosequence. In other words, it not only allows the precise formation of known configurations, such as an entirely isotactic sequence with 100% *m* dyads, but also opens the door to creating a vast range of novel stereosequences that have never been explored or even imagined.

Results and discussion.

Our approach is based on phosphoramidite polymer chemistry (PPC), a solid-phase iterative method⁴³ that involves coupling a P(III) reactive group with a primary alcohol.⁴⁴ Originally developed for oligonucleotide synthesis,⁴⁵ PPC was later adapted for the creation of synthetic and bio-hybrid macromolecules.⁴⁶⁻⁴⁹ One of the key advantages of PPC over other solid-phase iterative chemistries is its ease of automation and its capacity to produce long polymer chains.⁵⁰ However, until now, it has not been applied to the synthesis of perfectly controlled stereosequences. To address this, we first synthesized two phosphoramidite monomers **R** and **S**, in which an asymmetric carbon has opposite configurations (Figure 1c). The compounds were synthesized in three steps starting from commercially available, enantiomerically pure methyl 3-hydroxy-2-methylpropionate (Scheme S1). Initially, the alcohol group was protected with a dimethoxytrityl group.⁵¹ Next, the methyl ester was reacted with ethanolamine to afford the ethanolamide intermediate.⁵² The OH group of this intermediate was then treated with phosphoramidite chloride to produce monomers **R** and **S**.⁵¹ The monomers were characterized using ¹H, ¹³C, and ³¹P NMR spectroscopy (Figures S1-S3), high-resolution mass spectrometry

(HR-MS), and polarimetry. Polarimetric analysis evidenced opposite optical activity for the two monomers. It shall be, however, noted that the stereoconfiguration of the phosphorus(III) atom is not controlled in these monomers. Nevertheless, this does not influence the stereochemistry of the resulting polymers, as the phosphoramidite group is converted into an achiral phosphodiester during PPC. These monomers were subsequently employed in automated solid-phase synthesis on a thymidine-loaded controlled pore glass (CPG) solid support. Table 1 presents the various stereosequences synthesized in this study. At each step of the syntheses, the synthesizer reported very high coupling yields, confirming the compatibility of monomers **R** and **S** with PPC (Table S1 and Figure S4). The synthesized polymers were characterized using HR-MS and high-performance liquid chromatography (HPLC), (Figure 2 and Figures S5–S23). All techniques confirm the formation of uniform polymers, with only minor defects primarily arising from chains missing a single monomer unit; a common occurrence in PPC.⁴⁹ For example, in all recorded HR-MS spectra, the primary series corresponds to various charge states of macromolecules whose molar masses closely match theoretical predictions. This indicates that each step of the solid-phase iterative process functions correctly, resulting in macromolecules with perfectly-defined chain lengths and stereosequences.

To confirm these findings, the polymers were analyzed using circular dichroism (CD) spectroscopy, differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). Homopolymers **P1** and **P2**, composed entirely of the **R** and **S** monomers respectively, exhibited distinct and opposite CD signals (Figure 2d). Although **P1** and **P2** are not exact mirror-image polymers - both contain a D-deoxyribose end group - their CD spectra clearly indicate the formation of perfectly isotactic polymers (*i.e.*, 100% *m* dyads) with opposite chiralities.⁵³ In contrast, the syndiotactic polymer **P3** showed no significant CD signal, consistent with its structure comprising 100% *r* dyads. DSC measurements also revealed that the glass transition temperatures (*T*_g) of **P1** and **P3** differ by approximately 25°C (Figure S24). However, ¹³C NMR

spectroscopy, a standard method for assessing the tacticity of vinyl polymers,⁵⁴⁻⁵⁵ did not reveal any substantial differences between the isotactic **P1** and syndiotactic **P3** samples (Figure S25). This is likely due to the relatively long spacing (seven atoms) between stereocenters in these polymers, which is considerably greater than in vinyl polymers.

In addition to classical isotactic and syndiotactic polymers, several other stereosequences were prepared in this work. Notably, the heterotactic sequence **P4**, previously known but notoriously difficult to obtain,⁵⁶ was readily synthesized using our method. Even more remarkably, entirely novel stereosequences were achieved. For instance, polymers **P5** and **P6** exhibit periodic tacticities with repeat units of $-RSS-$ and $-RSSSS-$, respectively. To the best of our knowledge, such periodic stereosequences have never before been realized in synthetic polymers. Our approach also enables the design of stereoblocks composed of two blocks with opposite configurations; for example, **P7** with symmetric block lengths and **P8** with asymmetric block lengths. Stereoblocks isotactic-*b*-syndiotactic **P9** and isotactic-*b*-heterotactic **P10** were also prepared. In the latter, a longer chain length was targeted to ensure a sufficiently long heterotactic sequence in the second block. More complex architectures were also synthesized, including defined multi-stereoblocks such as **P11**, and stereogradient polymers like **P12**, which features a perfect monomer gradient. Beyond these relatively simple configurations, virtually any desired stereosequence can be programmed. Polymer **P13** exemplifies this capability: it contains a deliberately encoded stereomessage; a form of molecular information storage proposed years ago but never previously achieved.⁵⁷ Site-specific mutations can likewise be introduced. For example, polymers **P14** and **P15** are isotactic chains containing a single stereochemical mutation at position 11 (counting from the thymidine end group), while **P16** and **P17** feature mutations at their terminal positions. These examples are just a sample of what can be achieved with this approach. In fact, for a polymer chain with

20 stereocenters, more than one million unique configurations ($2^{20} = 1,048,576$) are theoretically accessible.

These additional stereosequences were analyzed by CD spectroscopy (Figure 3). Figure 3a compares polymers **P2**, **P5-P6**, **P15** and **P17**, in which all *m* dyads consist exclusively of left-handed monomer **S**. Within this group, the CD signal minimum intensity (circa 214 nm) appears to correlate with the proportion of *m* dyads F_m , following the trend: **P5** (35% of *m*) < **P6** (63%) < **P17** (89%) < **P15** (89%) < **P2** (100%). However, for polymers **P15** and **P17**, which feature discrete stereomutations, the classical F_m expression does not adequately capture the variations in stereochemistry. In this case, the enantiomeric excess (*ee*) of chiral monomer units in the formed polymer, which is more commonly employed for the description of chiral and supramolecular polymers,⁵⁸⁻⁵⁹ likely offers a more accurate interpretation of the observed CD results (inset in Figure 3a). These trends should be interpreted with caution, as CD measurements are susceptible to variability and potential errors. Nevertheless, it suggests that periodic polymers **P5** and **P6** retain detectable chirality, despite containing a significant fraction of *r* dyads. Furthermore, in **P15** and **P17**, the effect of single-site or double-site mutations, leading to two *r* dyads in the sequence, is still detectable in their CD spectra, which approach but do not fully match the one of isotactic polymer **P2**. For polymers **P1**, **P8**, **P9**, **P14** and **P16**, in which *m* dyads contain a majority of right-handed monomer **R**, a similar trend could also be detected at the CD signal maximum intensity (circa 211 nm) (Figure 3b). Stereosequences with mixed *m* dyads composed of either two **R** or two **S** monomers showed no discernible CD signals, as expected from their *ee* values, which are close to or equal to zero. This is exemplified by the spectra of heterotactic **P4**, stereoblocks **P7**, multi-stereoblocks **P11**, stereogradient **P12** and stereocoded **P13** in Figure 3c.

The concept is not limited to the medium-sized model chains discussed above. As noted in the introduction, automated phosphoramidite chemistry enables the synthesis of much longer

chains, with lengths exceeding one hundred repeat units.⁵⁰ Polymers **P10** and **P18-P20** (Table 1) exemplify such extended chains with precisely controlled stereosequences. HPLC analysis (Figure 3d) and CD spectroscopy (Figure S26) confirm that fine control over chain-length and primary structure was maintained throughout these syntheses.

Outlook.

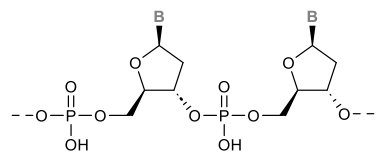
This work demonstrates that perfectly controlled tacticities can be achieved through precision polymer chemistry, with two major implications. First, it establishes that polymers with fully defined stereosequences, in which every stereocenter is precisely positioned along the chain, can now be synthesized. This represents a significant advance beyond traditional tacticity control, which typically governs only a portion of stereocenters. Second, it challenges the conventional classification of polymer stereochemistry into just a few categories (isotactic, syndiotactic, heterotactic, atactic). As shown here, a vast range of previously inaccessible stereosequences can now be realized. For instance, as aforementioned, a polymer with 20 stereocenters (DP20) can theoretically exhibit over a million unique sequences, far exceeding classical textbook expectations. For a polymer with 50 stereocenters (DP50), the number of possible sequences exceeds one quadrillion. Importantly, these newly accessible polymers are not atactic. With the exception of a small fraction of defect chains, all macromolecules produced share the exact same stereosequence, unlike stereoirregular atactic polymers. As of now, there is no term in polymer science to adequately describe this level of stereochemical precision, a limitation that has also been noted in the emerging field of sequence-controlled polymers.⁶⁰ More than sixty years ago, Giulio Natta proposed the term eutactic (from the Greek εὖ, meaning “good”) to describe polymers with fully ordered stereochemical arrangements.⁶¹ Although the term was never officially adopted and eventually faded from use, we propose reviving it to classify the polymers described in this study. While Natta likely envisioned only periodic

sequences, our findings extend the concept to include any precisely-defined stereosequence. Overall, this work opens a new chapter in polymer chemistry. Although not all accessible stereosequences may be functionally useful, they hold promise for inspiring new approaches in the design of informational polymers (*e.g.* stereocoded macromolecules), optically-active polymers, foldamers, ordered polymer materials (*e.g.* crystalline polymers, liquid crystals) and self-assembled materials.⁹

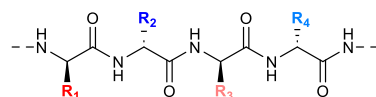
Supporting Information. Full Experimental part. NMR spectra of monomers. HPLC traces and ESI-MS spectra for all polymers. Additional, NMR, DSC and CD figures. This material is available free of charge via the Internet at <http://pubs.acs.org>

Acknowledgements. The authors thank the French National Research Agency (ANR-22-CE93-0009-01) for financial support as well as Cyril Antheaume (ISIS, Strasbourg) for the MS measurements, Laurence Charles (ICR, Marseille) for discussions about MS data, Mélanie Legros (Institut Charles Sadron, Strasbourg) for the DSC measurements and Giulio Ragazzon (ISIS, Strasbourg) for giving access to the CD spectrometer.

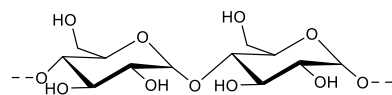
a. Biopolymers



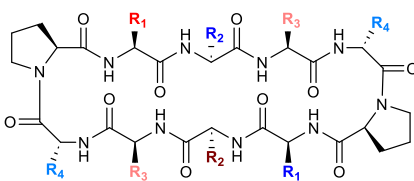
DNA made of *D*-deoxyribose



Protein made of *L*-amino acids



Starch made of *D*-glucose

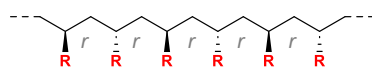


Gramicidin S (*D*-*L* peptide)

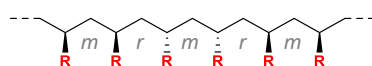
b. Synthetic polymers



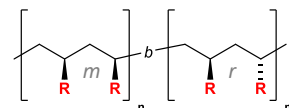
Isotactic polymer



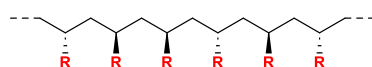
Syndiotactic polymer



Heterotactic polymer



Stereoblocks



Atactic polymer
(random distribution)

c. This work

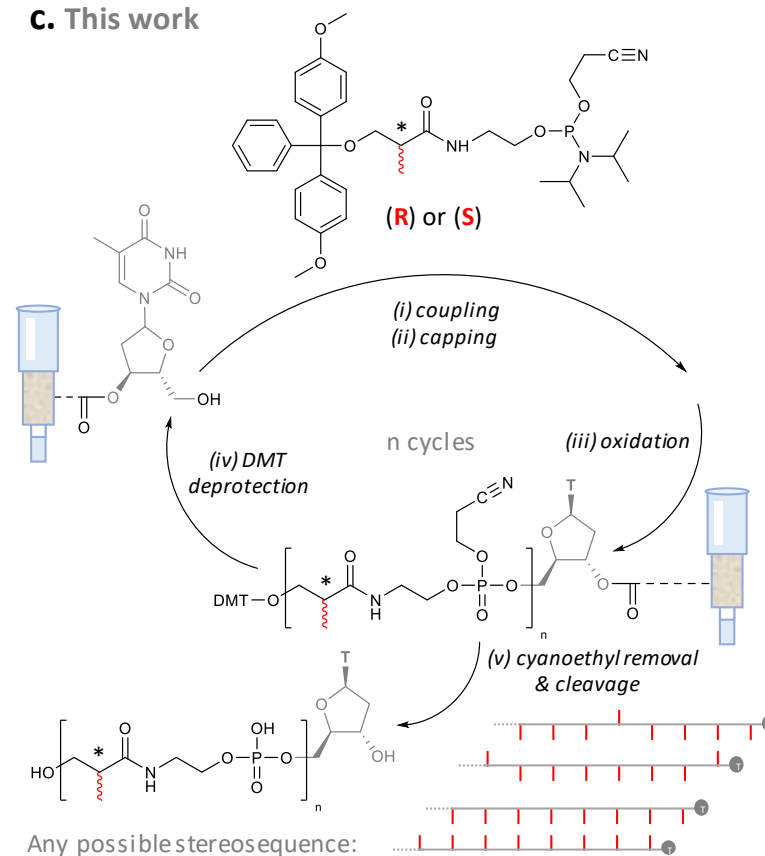


Figure 1. Stereochemical control in natural and synthetic macromolecules. (a) Examples of homochiral biopolymers found in nature such as DNA, proteins and starch. Some cyclic peptides, such as antimicrobial gramicidin S, have alternating stereocenters. (b) Overview of the current state-of-the-art in classical synthetic polymers. While a limited range of stereochemically controlled architectures, such as isotactic, syndiotactic, heterotactic, and stereoblocks, have been achieved, the majority of synthetic polymers still fall within the broadly defined atactic category. According to IUPAC recommendations,²¹ the letters *m* and *r* denote dyads in which consecutive stereogenic units have identical or opposite configurations, respectively. (c) General concept studied herein for synthesizing uniform polymers ($\bar{D} \sim 1$) with precisely-controlled stereosequences.

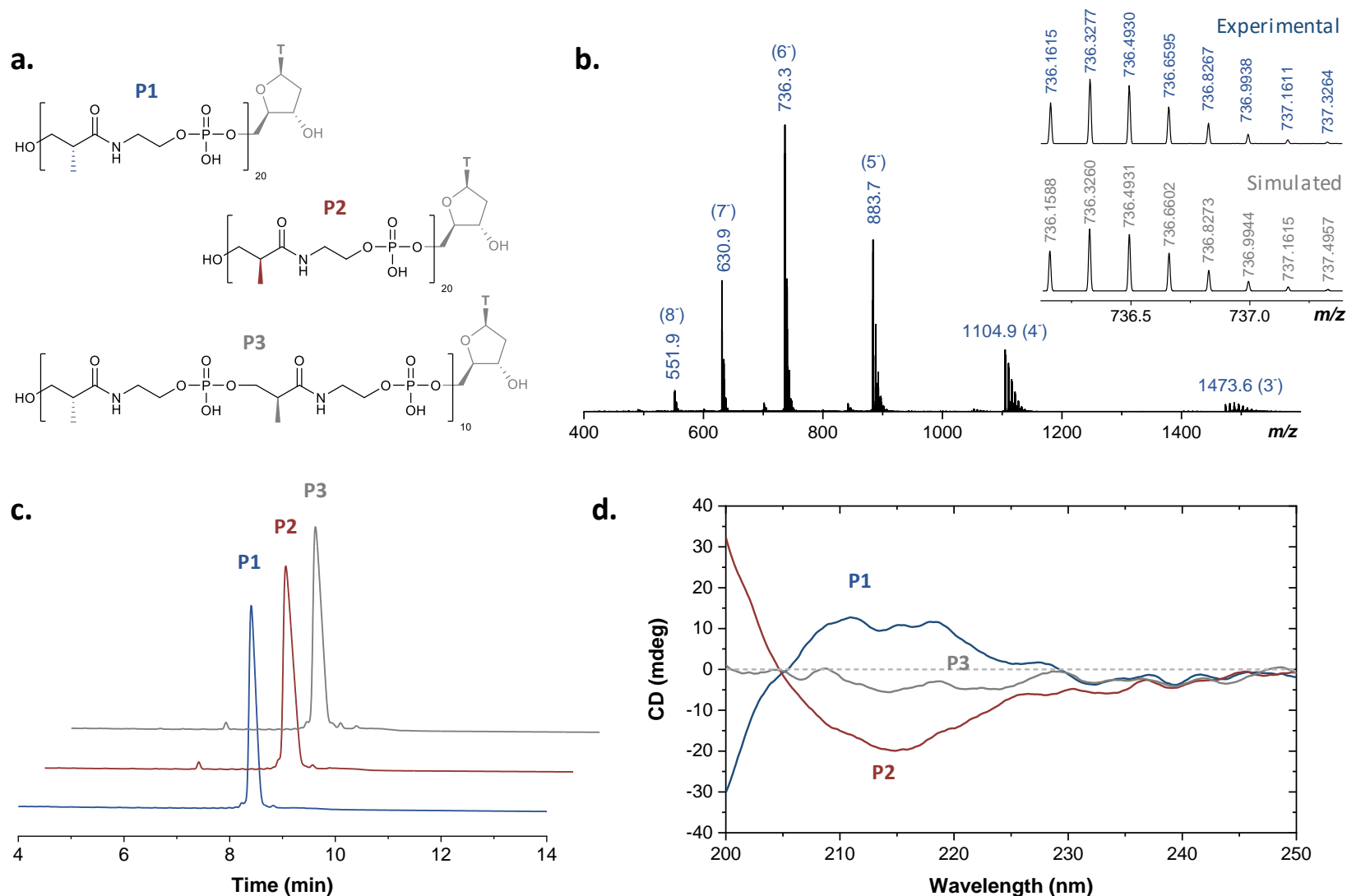


Figure 2. Characterization of uniform isotactic and syndiotactic polymers. (a) Molecular structure of isotactic polymers **P1-P2** and syndiotactic polymer **P3**. The letter T represents a thymine nucleobase. (b) Negative mode ESI-MS spectrum of **P1**. The inset compares the experimental and simulated isotopic distribution of the $[\text{P1-6H}]^{6-}$ ion. (c) Ion-exchange HPLC traces recorded for polymers **P1-P3**. (d) Circular dichroism spectra recorded for polymers **P1-P3** in water at a concentration of $0.07 \text{ mg}\cdot\text{mL}^{-1}$.

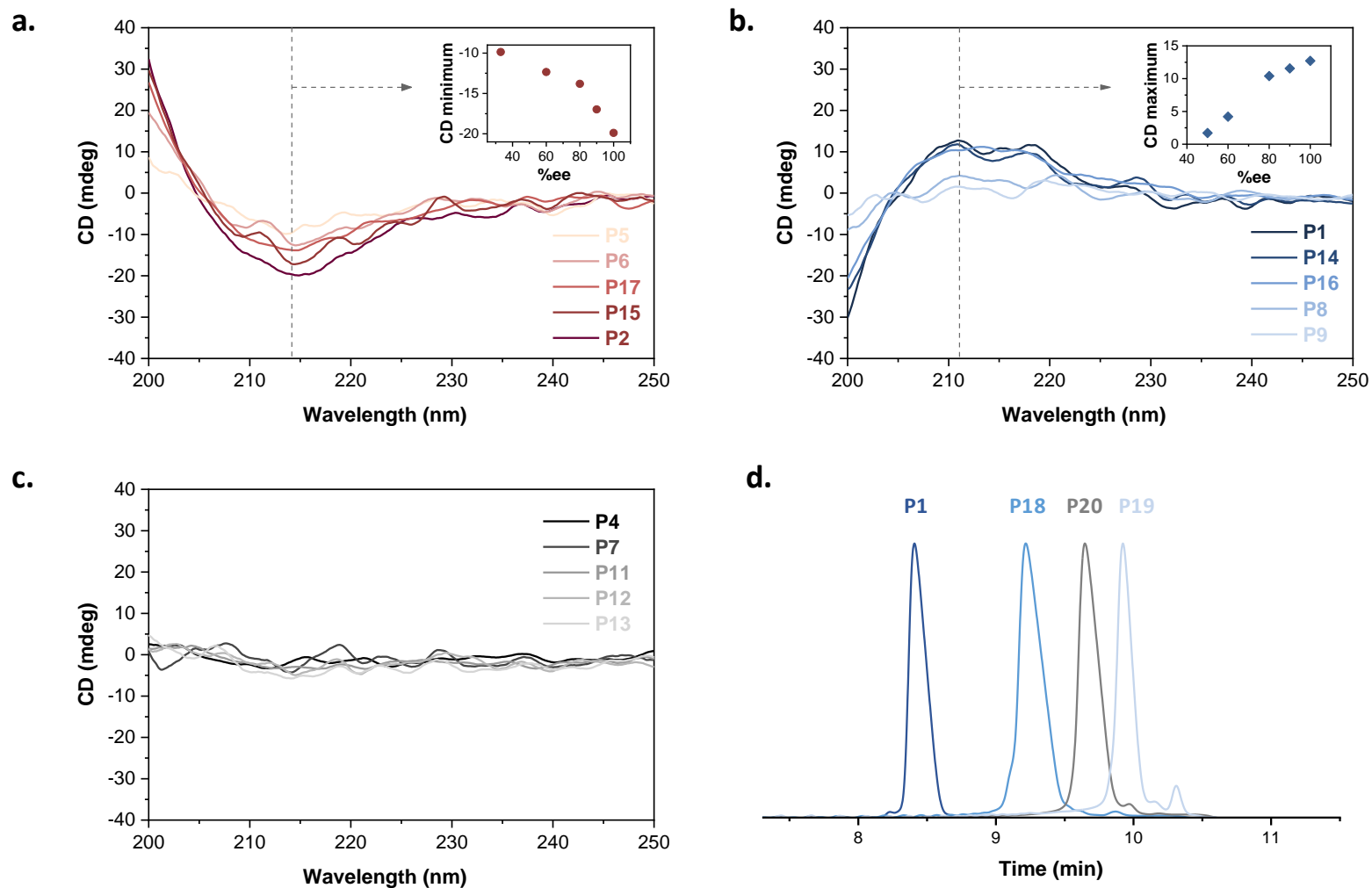


Figure 3. Comparison of various stereosequences. (a) Circular dichroism spectra recorded for polymers **P2**, **P5-P6**, **P15** and **P17** containing a majority of left-handed *m* dyads. The inset shows a plot of the CD minimum at 214 nm as a function of *ee*. (b) Circular dichroism spectra recorded for polymers **P1**, **P8-P9**, **P14** and **P16** containing a majority of right-handed *m* dyads. The inset shows a plot of the CD maximum at 211 nm as a function of *ee*. (c) Circular dichroism spectra recorded for polymers **P4**, **P7** and **P11-P13** containing complex stereosequences. All CD spectra were recorded in water at a concentration of 0.07 mg·mL⁻¹. (d) Ion-exchange HPLC traces recorded for polymers **P1** and **P18-P20** having different chain-lengths.

Table1. Stereodefined polymers synthesized in this work.

	Stereosequence ^a	Dyad sequence ^b	F_m^c [%]	ee^d [%]	Mass [Da]	m/z^e	m/z_{th}
P1	[R] ₂₀ -T	$[m]_{19}$	100	100 (R)	4422.9965	736.1615 ^f	736.1588
P2	[S] ₂₀ -T	$[m]_{19}$	100	100 (S)	4422.9965	736.1608 ^f	736.1588
P3	[RS] ₁₀ -T	$[r]_{19}$	0	0	4422.9965	630.8502 ^g	630.8494
P4	[RRSS] ₅ -T	$[mr]_9m$	53	0	4422.9965	630.8521 ^g	630.8494
P5	[RSS] ₇ -T	$[rmr]_6rm$	35	33 (S)	4632.0418	660.7141 ^g	660.7130
P6	[RSSSS] ₄ -T	$[rmmmr]_3rmmm$	63	60 (S)	4422.9965	736.1618 ^f	736.1588
P7	[R] ₁₀ - <i>b</i> -[S] ₁₀ -T	$[m]_9r[m]_9$	95	0	4422.9965	736.1613 ^f	736.1588
P8	[R] ₁₆ - <i>b</i> -[S] ₄ -T	$[m]_{15}[r]_1[m]_3$	94	60 (R)	4422.9965	736.1607 ^f	736.1588
P9	[R] ₁₀ - <i>b</i> -[SR] ₅ -T	$[m]_9[r]_{10}$	47	50 (R)	4422.9965	736.1605 ^f	736.1588
P10	[R] ₁₂ - <i>b</i> -[SSRR] ₃ -T	$[m]_{11}[rm]_6$	73	50 (R)	5259.1777	656.3928 ^h	656.3899
P11	[R] ₅ - <i>b</i> -[S] ₅ - <i>b</i> -[R] ₅ - <i>b</i> -[S] ₅ -T	$[mmmmr]_3mmmm$	84	0	4422.9965	736.1610 ^f	736.1588
P12	[R] ₄ -S-[R] ₃ -[S] ₂ -[R] ₂ -[S] ₃ -R-[S] ₄ -T	$[m]_3[r]_2[m]_2[rm]_2r[m]_2[r]_2[m]_3$	63	0	4422.9965	736.1618 ^f	736.1588
P13	SRRRSSRSRSRSRSRSRS-T	$r[m]_2rm[r]_6[rm]_3[r]_3$	32	10 (S)	4422.9965	736.1605 ^f	736.1588
P14	[R] ₉ -S-[R] ₁₀ -T	$[m]_8[r]_2[m]_9$	89	90 (R)	4422.9965	736.1621 ^f	736.1588
P15	[S] ₉ -R-[S] ₁₀ -T	$[m]_8[r]_2[m]_9$	89	90 (S)	4422.9965	736.1624 ^f	736.1588
P16	S[R] ₁₈ S-T	$r[m]_{17}r$	89	80 (R)	4422.9965	630.8532 ^g	630.8494
P17	R[S] ₁₈ R-T	$r[m]_{17}r$	89	80 (S)	4422.9965	736.1624 ^f	736.1588
P18	[R] ₃₀ -T	$[m]_{29}$	100	100 (R)	6513.4496	650.3409 ⁱ	650.3377
P19	[R] ₅₀ -T	$[m]_{49}$	100	100 (R)	10694.3558	711.9513 ^j	711.9498
P20	[RS] ₂₀ -T	$[r]_{39}$	0	0	8603.9027	660.8335 ^k	660.8314

^a The letter T denotes the thymidine nucleoside end group that comes from the solid-support after cleavage. ^b The end-group T is not taken into account in the dyad sequence. ^c Molar fraction of *m* dyads in the formed polymer. ^d Enantiomeric excess of chiral monomer units in the formed polymer. The letter R or S in brackets indicates which repeat unit is in excess. ^e Measured by negative mode ESI-HR-MS. ^f Detected as [M-6H]⁶⁻. ^g Detected as [M-7H]⁷⁻. ^h Detected as [M-8H]⁸⁻. ⁱ Detected as [M-10H]¹⁰⁻. ^j Detected as [M-15H]¹⁵⁻. ^k Detected as [M-13H]¹³⁻. All mass data correspond to monoisotopic values.

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