Electronic Supplementary Material (ESI) for Polymer Chemistry.

Exploiting Controlled Transesterification as a "Top Down" Approach to Tailor Poly(ε-caprolactone)-Poly(lactic acid) Copolymer Structures with bis-Zn Catalysts

- Supporting Information

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General Experimental Details

Materials

Rac-Lactide (99%) and BnOH (99%) were purchased from Fluorochem (UK). *ε*-Caprolactone (98%), and $CDCl_3$ (> 99 %) were purchased form Sigma Aldrich (UK). *ε*-Caprolactone and BnOH were dried over CaH_2, and used after distillation at reduced pressure. *Rac*-Lactide was purified by double recrystallisation from toluene and subsequent sublimation. $CDCl_3$ was degassed by freeze-pump-thaw cycles and stored over activated 4 Å molecular sieves under an argon atmosphere. Dry toluene and THF solvents were collected from an Innovative Technologies purification system and stored under an argon atmosphere over activated 4 Å molecular sieves. SEC grade THF was purchased from Fisher Scientific and used as received (UK). The LZn_2Et complex used in this study was prepared as described in the literature.[1] All manipulations involving air or water sensitive compounds were performed either in a glove box or using standard Schlenk techniques under an argon atmosphere.

General procedure for the synthesis of PCL homopolymers

Below is an example synthesis for PCL_{200} at 22% w/w in toluene.

In a glove box, in an air-tight vial with a magnetic stirrer bar, complex LZn_2Et (10.5 mg, 13.1 μmol) was dissolved in dry toluene (1.27 mL). To this, 25 μL of a BnOH stock solution in dry toluene (54 μL/mL) was added. This solution was stirred at 70 °C for 1 h using DrySyn heating blocks. Subsequently, 291 μL of *ε*-CL (200 eq., 2.63 mmol) was added to the heated solution. The polymerisation was stirred at 70 °C for the required time, when an aliquot was taken and quenched in excess chloroform.

General procedure for the synthesis of PLA homopolymers

Below is an example synthesis for PLA_{200} at 25% w/w in toluene.

In a glove box, in an air-tight vial with a magnetic stirrer bar, complex LZn_2Et (8.3 mg, 10.4 μmol) was dissolved in dry toluene (0.5 mL). To this, 20 μL of a BnOH stock solution in dry toluene (54 μL/mL) was added. The solution was pre-stirred at 70 °C for 1 h using DrySyn heating blocks. In a separate air-tight vial 300 mg of *rac*-LA (200 eq., 2.08 mmol) was dissolved in dry toluene (0.57 mL) and stirred at 70 °C for 1 h (some *rac*-LA remained undissolved after this time). After 1 h the LZn_2Et/BnOH solution was added to the solution of *rac*-LA. The polymerisation was stirred at 70 °C for the required time. Upon completion, an aliquot was taken and quenched in excess chloroform.

General procedure for the synthesis of PCL-PLA diblock copolymers

Below is an example synthesis for PCL_{200}-*block*-PLA_{200} at 22% w/w in toluene (Table 1, Control).

In a glove box, in an air-tight vial with a magnetic stirrer bar, complex LZn_2Et (10.5 mg, 13.1 μmol) was dissolved in dry toluene (1.27 mL). To this, 25 μL of a BnOH stock solution in dry toluene (54 μL/mL) was added. The solution was pre-stirred at 70 °C for 1 h using DrySyn heating blocks. In a separate air-tight vial, 357 mg of *rac*-LA (200 eq., 2.48 mmol) was dissolved in dry toluene (1.46 mL) and stirred at 70 °C for 1 h (some *rac*-LA remained undissolved after this time). 291 μL of *ε*-CL (200 eq., 2.63 mmol) was added to the heated LZn_2Et solution. The polymerisation was stirred at 70 °C for the required time (10 minutes for the PCL block of PCL_{200}-*block*-PLA_{200}). A 100 μL aliquot was subsequently taken and quenched in excess chloroform. The hot polymerisation solution was then transferred to the solution of *rac*-LA in one batch. The combined solution was stirred at 70 °C for 1 h. Upon completion, an aliquot was taken and quenched in excess chloroform. The final copolymer solution was diluted by a factor of two with chloroform and precipitated in cold acidified methanol (50 mL). The white precipitate was collected using filtration.

General procedure for transesterification reactions

Below is an example protocol for the transesterification of PCL_{200}-*block*-PLA_{200} with 20 eq. of *ε*-CL (Table 1, sample **2**).

The diblock copolymer PCL_{200}-PLA_{200} was prepared in a glove box as described above. Prior to quenching, 27 μL of *ε*-CL (20 eq., 240 μmol) was added to the PCL_{200}-PLA_{200}* solution (0.63 g, 12 μmol, at 22% w/w in dry toluene), and the reaction mixture was stirred at 70 °C for 24 h. Upon completion, the reaction was quenched in excess chloroform. Note that the PCL_{200}-PLA_{200}* solution is at 12 μmol not 13.1 μmol due to the aliquots that were taken during the course of the reaction.

Procedure for transesterification reactions *via* sequential addition of *ε*-CL to PCL_{200}-PLA_{200} (Table 1, sample 5)

In a glove box, 18 μL of *ε*-CL (10 eq., 164 μmol) was added to a solution of unquenched PCL_{200}-PLA_{200}* (0.86 g, 16.4 μmol, at 22% w/w in dry toluene, see above for details of a similar reaction on a different scale). The reaction mixture was stirred at 70 °C for 24 h, and a 100 μL aliquot was subsequently taken and analysed by ^{1}H NMR spectroscopy. Another 18 μL of *ε*-CL (10 eq., 164 μmol) was then added to the unquenched copolymer solution, which was stirred at 70 °C for another 24 h. Upon completion, an aliquot was taken and quenched in excess chloroform. The final copolymer solution was diluted by a factor of two with chloroform and precipitated in cold acidified methanol (50 mL). The white precipitate was collected using filtration. This sequential addition gave an *R* value of 0.12 after addition of the first 10 eq. of *ε*-CL, which increased to 0.20 after the second addition, whereas adding 20 eq. of *ε*-CL in one portion gave an *R* value of 0.18.

Procedure for transesterification reactions *via* sequential addition of *δ*-VL to PLA_{20} (Table 3, sample 10)

In a glove box, 35 μL of *δ*-VL (20 eq., 356 μmol) was added to a solution of unquenched PLA_{20}* after 10 minutes (66 mg, 18.4 μmol, at 30% w/w in dry toluene, see above for further details). The reaction mixture was stirred at 70 °C for 24 h, and an aliquot was subsequently taken and analysed by ^{1}H NMR spectroscopy. The reaction was then quenched in excess chloroform.

Procedure for transesterification reactions *via* sequential addition of *δ*-VL to PCL_{20} (Table 3, sample 11)

In a glove box, 21 μL of *δ*-VL (20 eq., 231 μmol) was added to a solution of unquenched PCL_{20}* after 10 minutes (35 mg, 11.5 μmol, at 30% w/w in dry toluene, see above for details of a similar reaction on a different scale). The reaction mixture was stirred at 70 °C for 24 h, and an aliquot was subsequently taken and analysed by ^{1}H NMR spectroscopy. The reaction was then quenched in excess chloroform.

Procedure for transesterification reaction of isolated PCL_{200}-PLA_{200} diblock copolymer

In a glove box, in an air-tight vial with a magnetic stirrer bar, complex LZn_2Et (7.7 mg, 9.7 μmol) and PCL_{200}-PLA_{200} diblock copolymer (500 mg, 9.7 μmol) were dissolved in dry toluene (2.4 mL). The solution was pre-stirred at 70 °C for 2 h using DrySyn heating blocks. After 2 h, 43 μL of *ε*-CL (40 eq., 387 μmol) was added to the PCL_{200}-PLA_{200} solution. The polymerisation was stirred at 70 °C for 24 h. Upon completion, the reaction was quenched in excess chloroform.

Procedure for the synthesis of PCL-PLA statistical copolymer

In a glove box, in an air-tight vial with a magnetic stirrer bar, complex LZn_2Et (8.3 mg, 10.4 μmol) was dissolved in dry toluene (0.5 mL). To this, 20 μL of a BnOH stock solution in dry toluene (54 μL/mL) was added. The solution was pre-stirred at 70 °C for 1 h using DrySyn heating blocks. In a separate air-tight vial 300 mg of *rac*-LA (200 eq., 2.08 mmol) was dissolved in dry toluene (0.77 mL) and stirred at 70 °C for 1 h (some *rac*-LA remained undissolved after this time). After 1 h the LZn_2Et/BnOH solution was added to the solution of *rac*-LA followed by the addition of 240 μL of *ε*-CL (200 eq., 2.09 mmol). The polymerisation was stirred at 70 °C for the required time. Upon completion, an aliquot was taken and quenched in excess chloroform.

NMR spectroscopy

^{1}H and quantitative ^{13}C NMR spectra were recorded at 300 K on either a 500 MHz or Bruker Ascend 2 channel spectrometer with a DCH ^{13}C/^{1}H CryoProbe™ or a 400 MHz Bruker Ultrashield 3 channel

spectrometer with a 5 mm BBFO+/TBO-X,FH ^{15}N-^{31}P/^{1}H/^{19}F broadband probe. Chemical shifts were noted on the δ scale in parts per million (ppm). ^{1}H NMR spectra were performed in chloroform-*d* ($CDCl_3$) using the residual signal 7.26 ppm as a reference. ^{13}C NMR spectra were measured in chloroform-*d* ($CDCl_3$) using the residual signal 77.2 ppm as a reference. For the quantitative carbon experiment the receiver gain was set to 128. Further parameters used for any ^{1}H and quantitative ^{13}C NMR spectra recorded are shown below:

	^{1}H	^{13}C
Pulse sequence	Standard Bruker *zg30* sequence	Standard Bruker *zgig* sequence
Number of scans	8	128
Number of dummy scans	2	4
Recycle delay	1 s	5 s
90° pulse length	10 µs	8 µs
Number of points	65536	65536
Spectral width	20.66 ppm/10330 Hz	259.8 ppm/32680 Hz
Centre of spectrum	6.175 ppm	110 ppm
Acquisition time	3.17 s	1.00 s
Total experiment time	42 s	13 min

DSC analysis

DSC experiments were performed using a DSC (DSC 2500, TA Instruments) with a refrigerated cooling accessory (RCS90). In all experiments, the DSC cell was purged with nitrogen at 50 mL/min. Indium was used to calibrate the cell constant. Materials were sealed in Tzero aluminium pans with a pierced hole on the lid. Runs were performed at a ramp rate of 5 °C /min from -80°C to 200°C.

The relative degree of crystallisation (x_c) can be measured by the following equation.

$$x_c = \frac{\Delta H_m}{\Delta H_f} \times 100 \qquad \text{(S1)}$$

where ΔH_m is the enthalpy change associated with melting the sample and ΔH_f the is the theoretical enthalpy of melting for a 100% crystalline sample.

SEC analysis

Polymer samples (2 – 10 mg) were dissolved in SEC grade THF (1 mL) and filtered using a 0.2 µm PTFE syringe filter. SEC analyses of the filtered polymer samples were carried out in SEC grade THF

at a flow rate of 1 mL min^{-1} at 35 °C on a 1260 Infinity II SEC single detector system with mixed bed C PLgel columns (300 x 7.5 mm). The RI detector was calibrated using narrow molar mass polystyrene standards.

Fractionation *via* SEC

Polymer sample **3** was separated *via* SEC. Fractions were collected at regular intervals (30 s) as the sample passed through the SEC column, where copolymers of higher molar mass have the shortest retention times. This procedure was performed ten times in order to collect enough sample to analyse. The solvent was subsequently removed from these aliquots, which were then analysed by SEC and ^{1}H NMR spectroscopy.

Calculation of Randomness *R* and Number Average Sequence Length *l*

^{1}H NMR spectroscopy can be used to quantify the PCL-PLA copolymer structure produced after transesterification has taken place. The relative intergrals (i) of the of the diad resonances (see Figure S1) were used to calculate randomness (R) and the number average sequence lengths for LA and CL (l_{LA} and l_{CL}) using the following equations:[2]

$$i_{LA} = i_{L-L} + i_{L-C} \tag{S2}$$

$$i_{CL} = i_{C-C} + i_{C-L} \tag{S3}$$

$$f_{LA} = \frac{i_{LA}}{i_{LA} + i_{CL}} \tag{S4}$$

$$f_{CL} = \frac{i_{CL}}{i_{LA} + i_{CL}} \tag{S5}$$

Where f_{LA} and f_{CL} are relative mole fractions of PLA and PCL in the copolymer, respectively. Following this the average dyad relative molar fractions $f_{C\text{-}C}$, $f_{C\text{-}L}$, and $f_{L\text{-}L}$, were calculated:[2]

$$f_{C-C} = f_{CL} \times f_{C-C/CL} \tag{S6}$$

$$f_{C-L} = f_{CL} \times f_{C-L/CL} \tag{S7}$$

$$f_{L-L} = 1 - (f_{C-C} + f_{C-L}) \tag{S8}$$

Where,

$$f_{C-C/CL} = \frac{i_{C-C}}{i_{CL}} \tag{S9}$$

$$f_{C-L/CL} = \left(\frac{i_{C-L}}{i_{CL}}\right) \times 2 \tag{S10}$$

Finally, the l_{LA} and l_{CL} and R can be calculated using the following equations:

$$l_{LA} = \frac{2f_{LA}}{f_{C-L}} \tag{S11}$$

$$l_{CL} = \frac{2f_{CL}}{f_{C-L}} \quad \text{(S12)}$$

$$R = \frac{f_{C-L}}{2 \times f_{LA} \times f_{CL}} \quad \text{(S13)}$$

Additional Figures

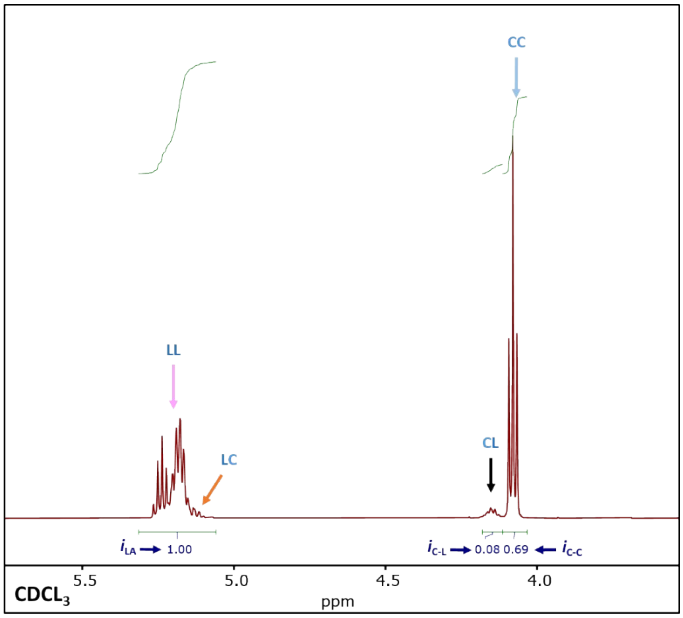
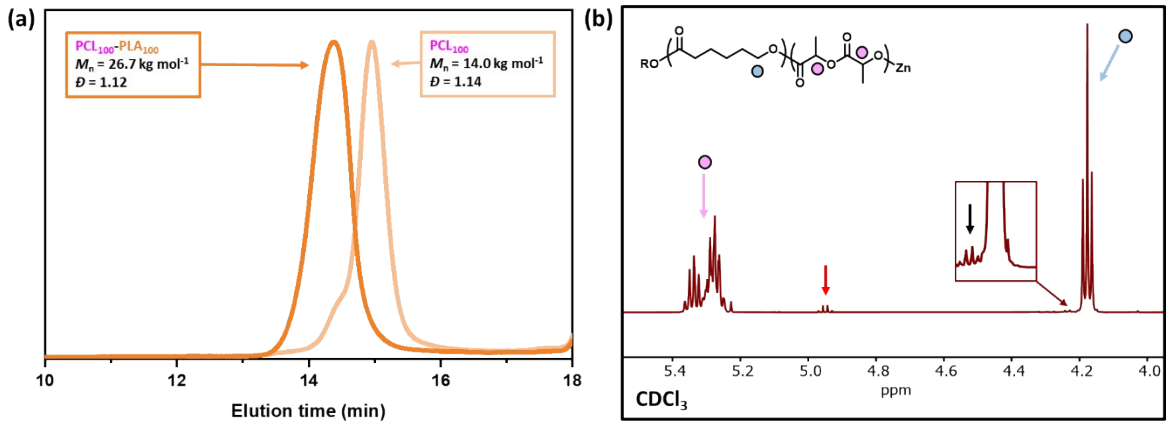


Figure S1. An example ^{1}H NMR spectra of PCL_{200}-*block*-PLA_{200} with 20 eq. of ε-CL added (sample **2**) to demonstrate the information extracted from the experimental NMR spectra to calculate average sequence length *l* and randomness *R*.

Figure S2. (a) THF SEC traces recorded at the different stages of copolymerisation for the synthesis of PCL_{100}–*block*-PLA_{100} and (b) the ^{1}H NMR spectrum of PCL_{100}-*block*-PLA_{100} where the black arrow indicates PCL protons adjacent to a P*rac*LA unit and the red arrow indicates residual unreacted *rac*-LA monomer. Values of M_n are not corrected to enable comparisons to be made between the homopolymers and the copolymers produced.



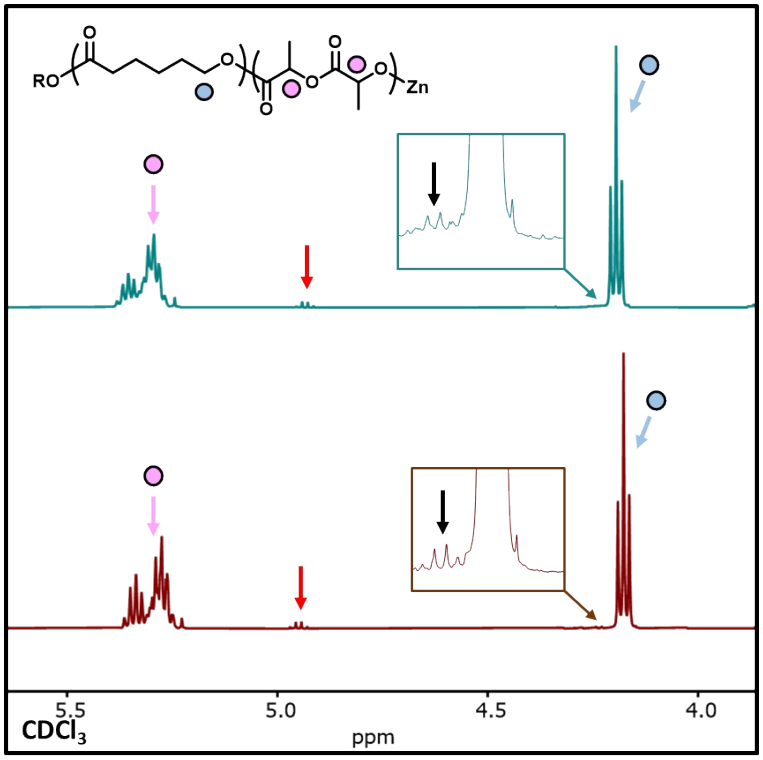


Figure S3. ^{1}H NMR spectra of PCL_{100}-*block*-PLA_{100} after 1 h at 70 °C (red trace) and after 24 h at 70 °C (turquoise trace), where the black arrow indicates PCL protons adjacent to a PLA unit and the red arrow indicates residual unreacted *rac*-LA monomer. The similarity between the spectra indicate that the PCL_{100}-*block*-PLA_{100}* diblock structure is stable during and after polymerisation in the absence of ε-CL.

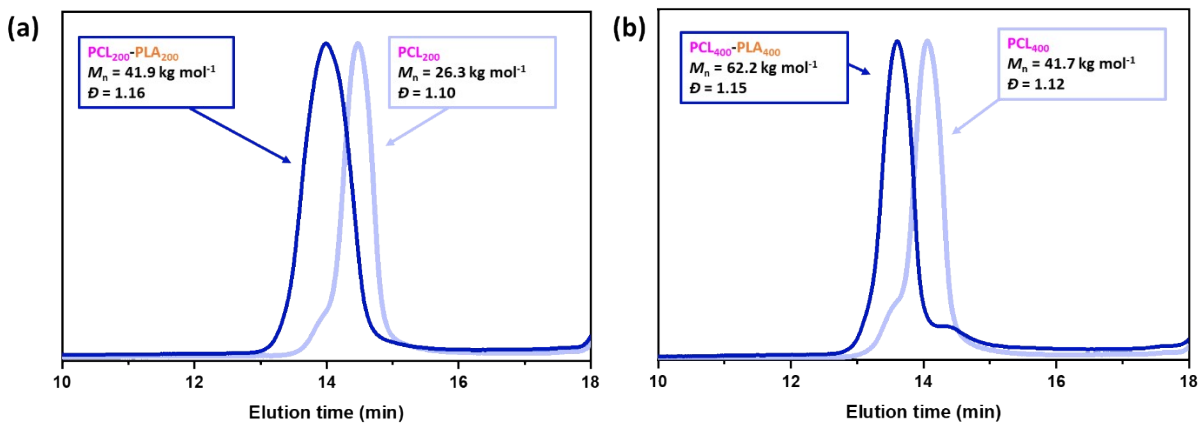


Figure S4. THF SEC traces recorded at the different stages of copolymerisation for the synthesis of (a) PCL_{200}-PLA_{200} and (b) PCL_{400}-*block*-PLA_{400}. Values of M_n are not corrected to enable comparisons to be made between the homopolymers and the copolymers produced.

Table S1. Targeted copolymer composition, and uncorrected molar masses from THF SEC calibrated against near-monodisperse polystyrene standards.

	PCL Homopolymer			Diblock Copolymer			Post-Transesterification	
Sample	Conv.%[e]	M_n (kg mol^{-1})[f]	$Đ$	Conv.%[g]	M_n (kg mol^{-1})[f]	$Đ$	M_n (kg mol^{-1})[f]	$Đ$
1[a]	> 99	21.6	1.12	90	38.4	1.13	48.9	1.30
2[a]	> 99	24.7	1.35	97	53.3	1.14	48.8	1.49
3[a]	95	26.3	1.10	97	41.9	1.16	35.2	1.53
4[a]	96	25.1	1.11	98	51.5	1.13	38.6	1.56
5[a,b]	> 99	28.8	1.30	95	44.9	1.20	44.5	1.44
6[c]	> 99	14.6	1.19	97	30.4	1.21	28.9	1.40
7[d]	93	41.7	1.12	80	62.2	1.15	61.2	1.31

[a] PCL_{200}-*block*-PLA_{200} diblock copolymer precursor, [b] 10 equivalents of ε-CL added initially and then another 10 equivalents were added, [c] PCL_{100}-*block*-PLA_{100} diblock copolymer precursor, [d] PCL_{400}-*block*-PLA_{400} diblock copolymer precursor, [e] Conversion after 10 minutes, [f] Values of M_n are not corrected to enable comparisons to be made between the homopolymers and the copolymers produced, [g] Conversion after 1 h and before the addition of ε-CL.

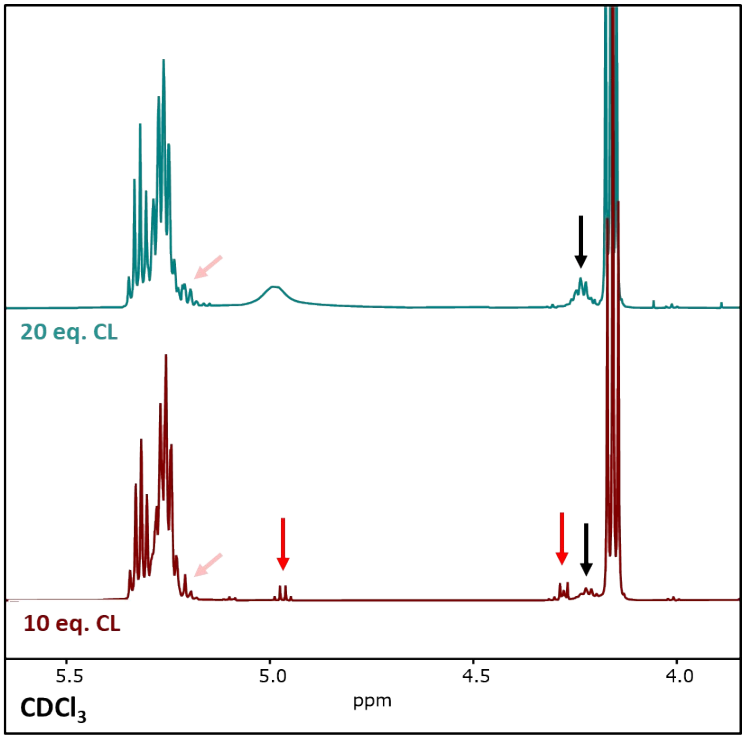


Figure S5. ^{1}H NMR spectra of PCL_{200}-*block*-PLA_{200} with 10 eq. (red trace) of ε-CL added, with a further 10 eq. of ε-CL subsequently added to give 20 eq. in total (teal trace). The black arrow indicates PCL protons adjacent to a PLA unit, the pink arrow indicates PLA protons adjacent to a PCL unit and the red arrow indicates residual unreacted monomer present.

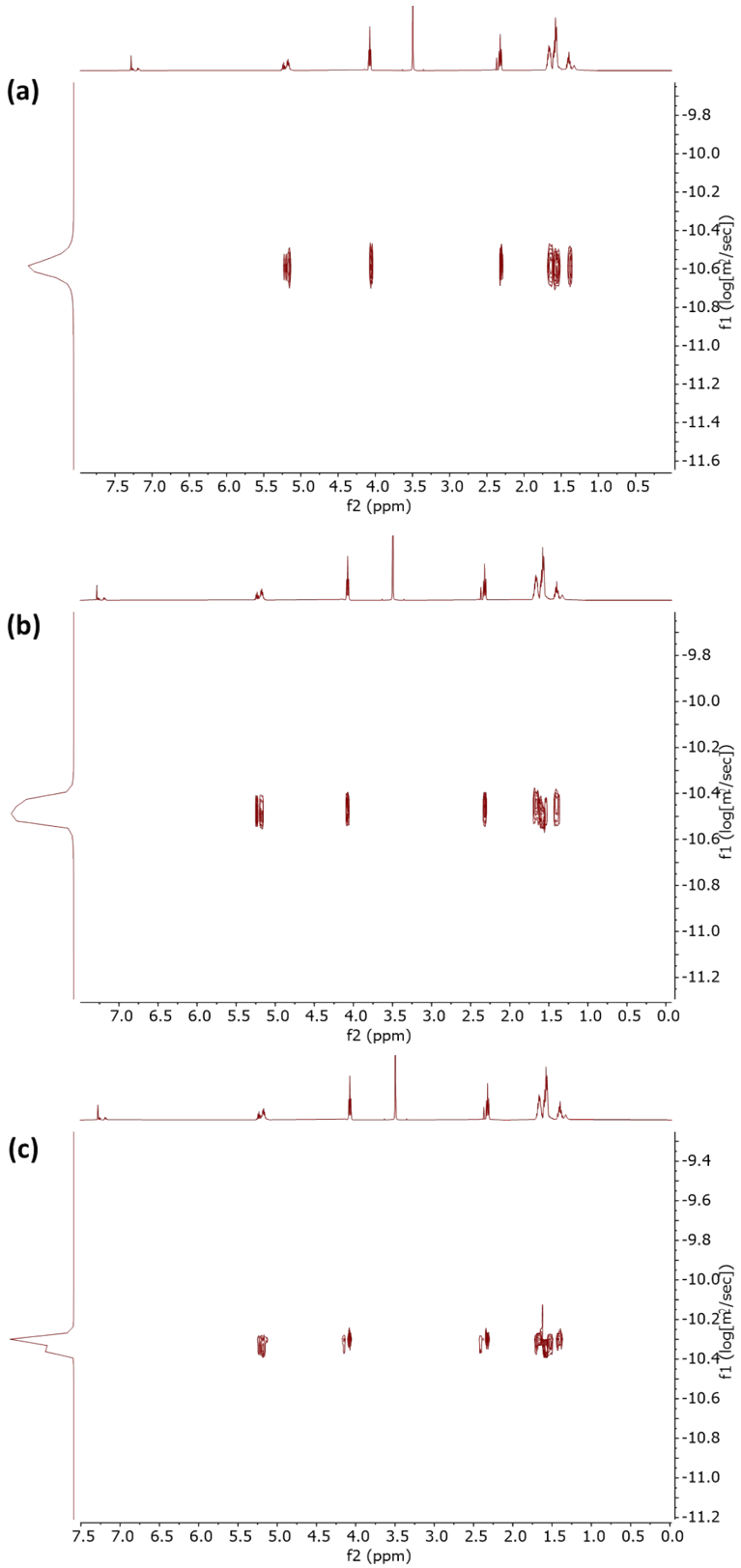


Figure S6. DOSY ^{1}H NMR spectra for PCL_{200}-*block*-PLA_{200} reacted with (a) 20, (b) 40, and (c) 80 eq of ε-CL (i.e. Samples **2**, **3** and **4**, respectively).

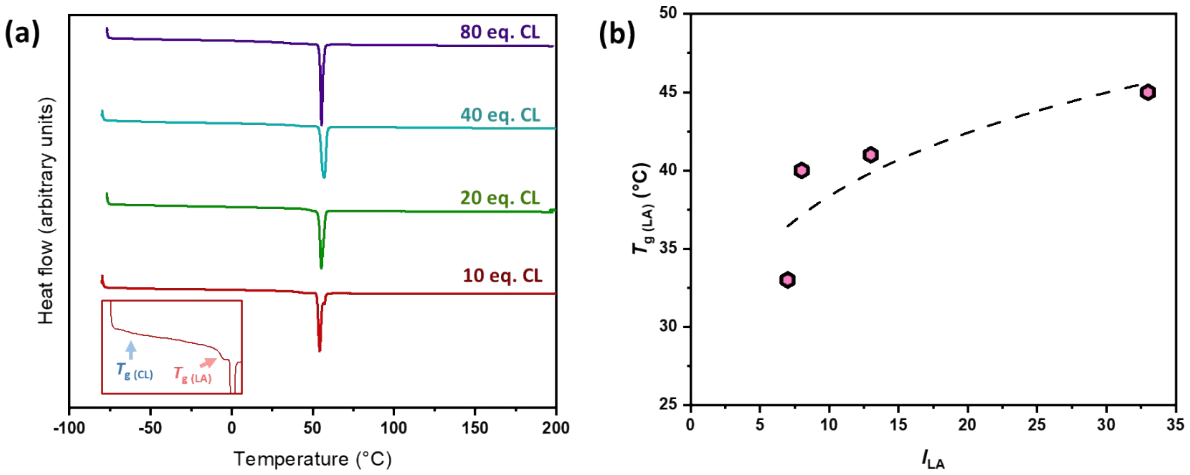


Figure S7. (a) The DSC thermograms for the PCL_{200}-*block*-PLA_{200} copolymers with various equivalents of ε-CL added (indicated on the thermograms) and (b) a plot of PLA T_g against the number average sequence length for PLA (l_{LA}).

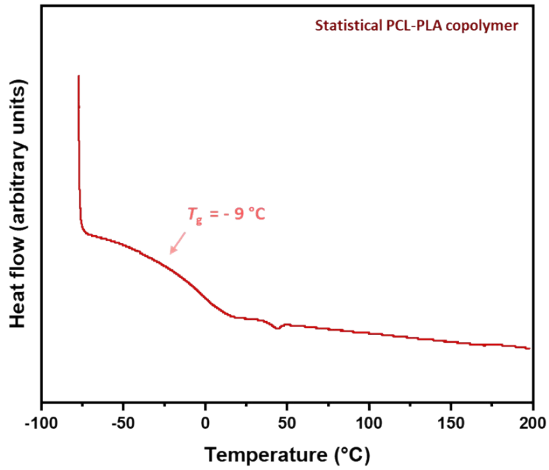


Figure S8. DSC thermogram of a PCL_{200}-PLA_{200} statistical copolymer used as a reference.

Table S2. Thermal properties of transesterified PCL-PLA copolymers analysed by DSC.

Sample	PCL T_g (°C)	PLA T_g (°C)	PCL T_m (°C)	Degree of Crystallinity (%)
1	-59	45	54.2	15.0
2	-61	41	55.3	15.8
3	-56	40	56.7	16.5
4	-65	33	55.4	16.3
Statistical copolymer		- 9	44.0	0.2

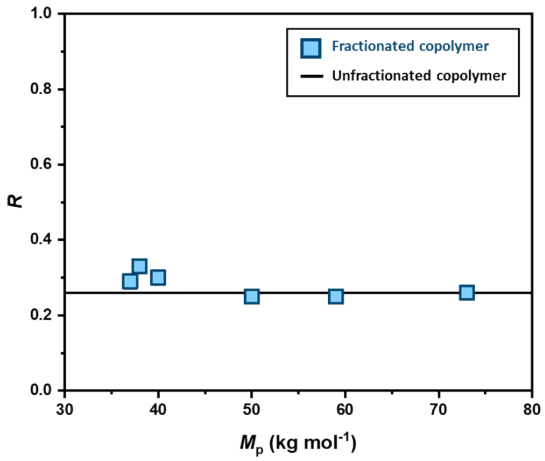


Figure S9. Plot of the randomness value *R* calculated using ^{1}H NMR spectroscopy against the peak molecular weight (M_p) of the copolymer from SEC for the fractionated and unfractionated copolymer.

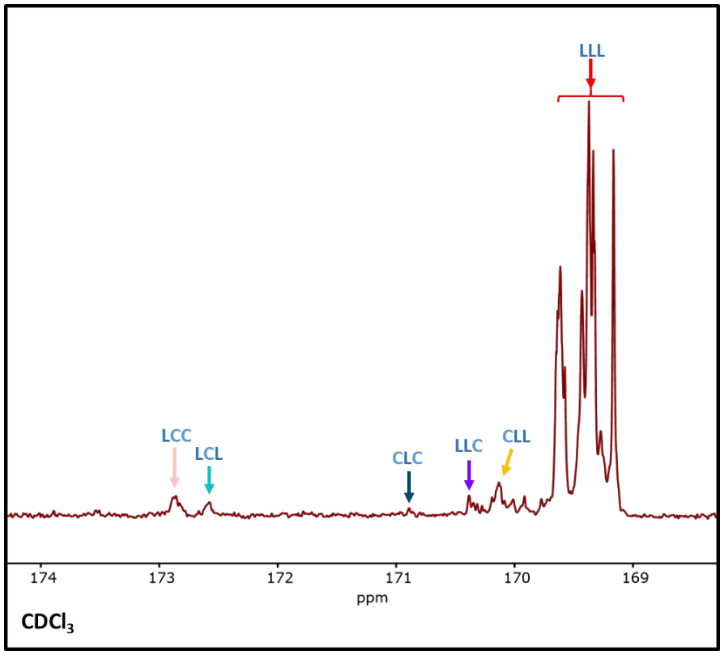


Figure S10. (a) Expanded ^{13}C NMR spectra of PLA_{200} with 20 eq. of CL added and the respective peak assignments indicated on the spectra.

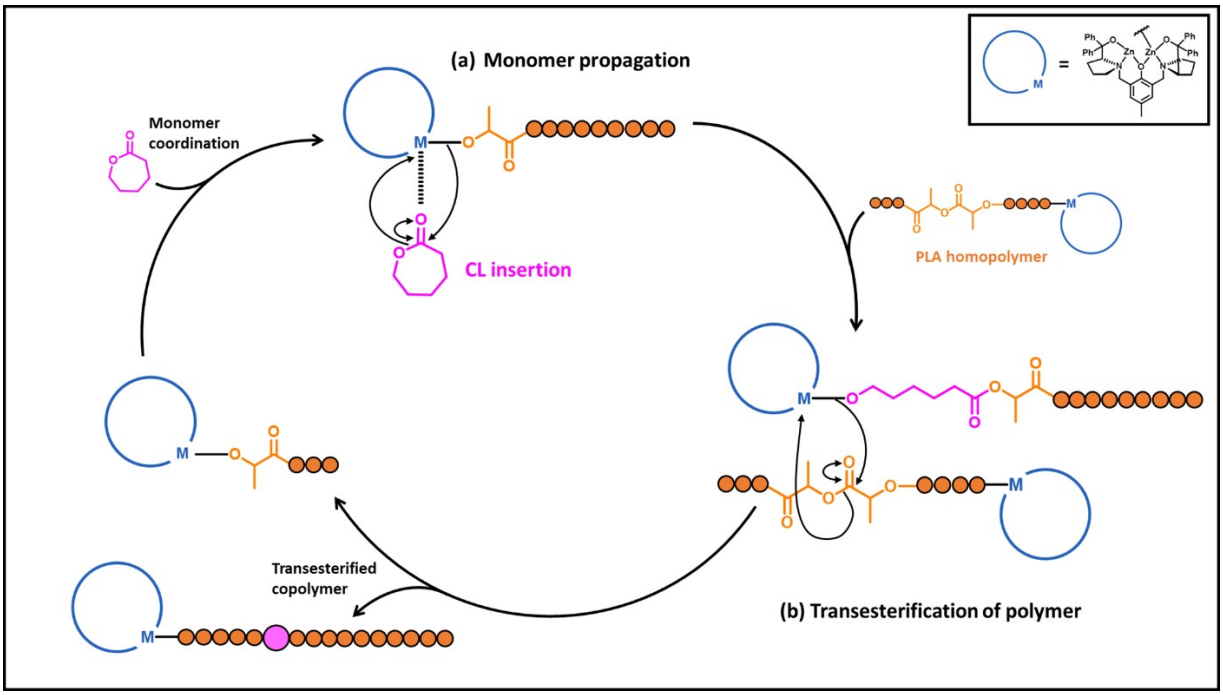


Figure S11. Proposed mechanism for ε-CL initiated transesterification in the presence of a bis-zinc catalyst, where the bis-zinc catalyst is denoted by M, and units of PLA and PCL are represented by orange and pink circles, respectively.

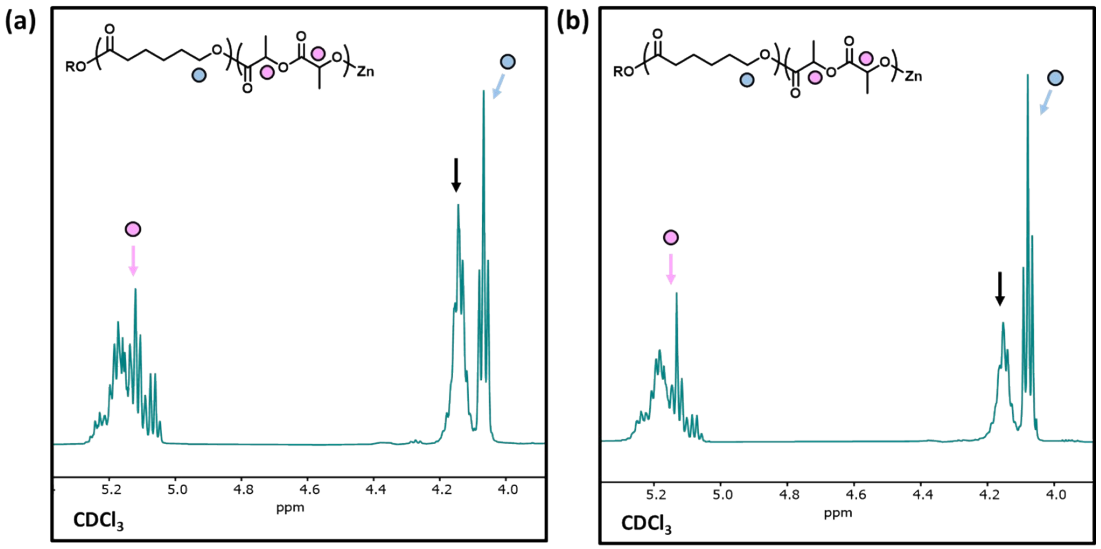


Figure S12. ^{1}H NMR spectra of (a) PLA_{20}-PCL_{20} (sample **8**) and (c) PCL_{10}-PLA_{20}-PCL_{10} (sample **9**) where the black arrow indicates PCL protons adjacent to a PLA unit, and the pink arrow indicates PLA protons adjacent to a PCL unit.

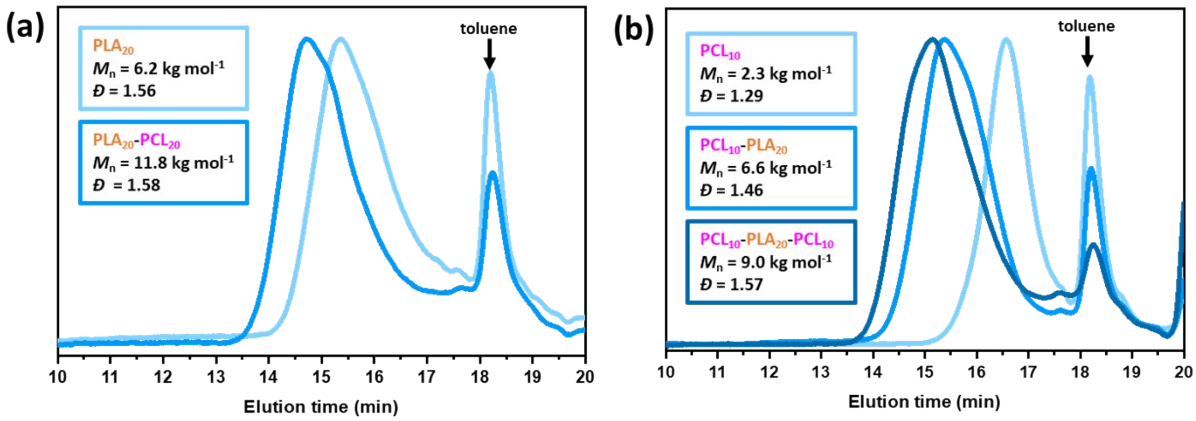


Figure S13. THF SEC traces recorded at the different stages of copolymerisation for the synthesis of (a) PLA_{20}-PCL_{20} oligomers (sample **8**) and (b) PCL_{10}-PLA_{20}-PCL_{10} oligomers (sample **9**). Values of M_n are not corrected to enable comparisons to be made between the homopolymers and the copolymers produced.

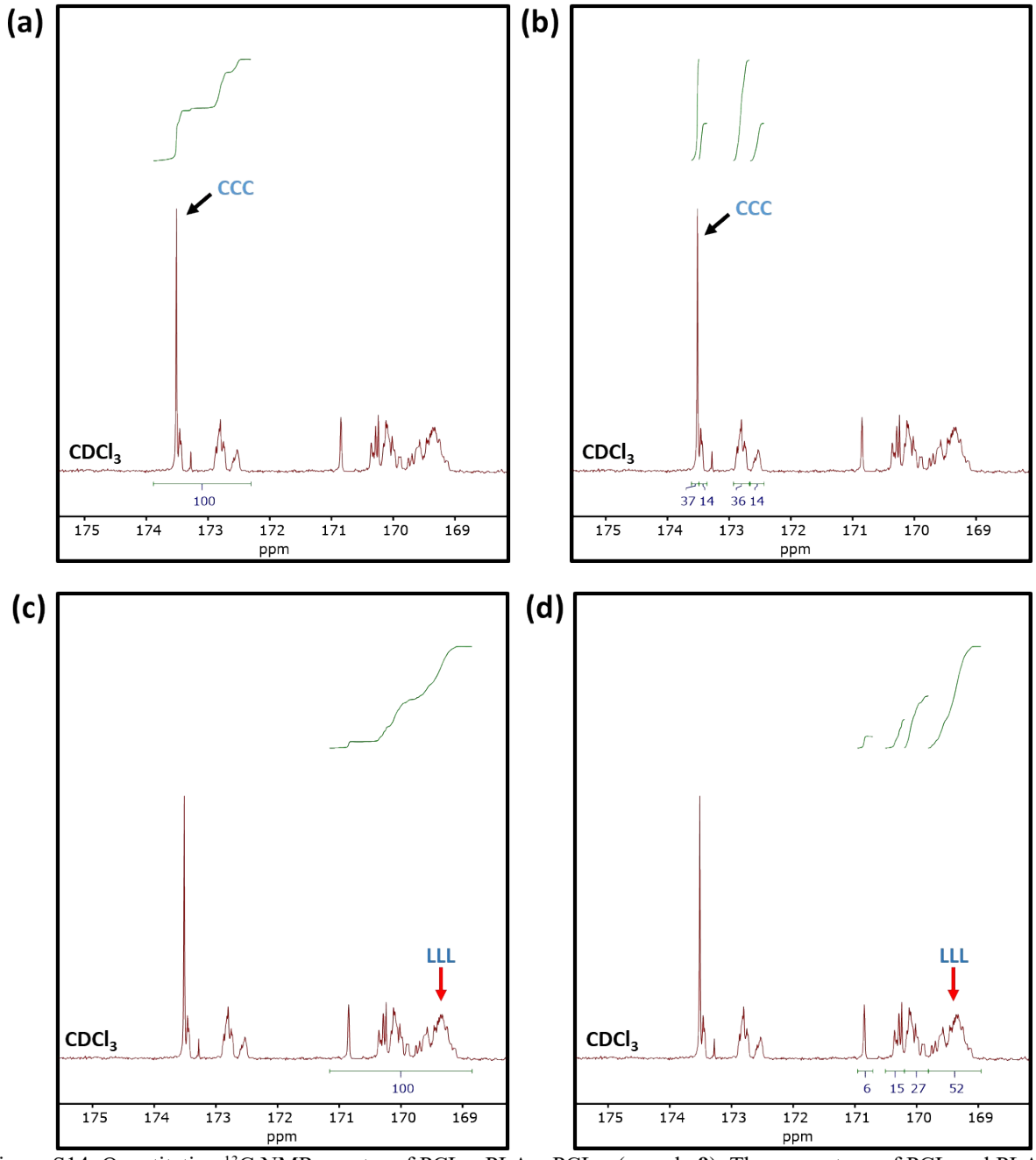


Figure S14. Quantitative ^{13}C NMR spectra of PCL_{10}-PLA_{20}-PCL_{10} (sample **9**). The percentage of PCL and PLA units in CCC (black arrow) and LLL (red arrow) sequences, respectively, were calculated using the relative integrals of the triad signals. A value of 100 was set as integral for the combined PCL or PLA resonance (a and c) so that the integrals for the individual triads would be then be a percentage of the total resonance (b and d). It was found that 37% of PCL units were in a CCC sequence and 52% of PLA units were in a LLL sequence. If ε-CL was exclusively inserted into the PLA block of the PCL_{10}-PLA_{20} precursor then the minimum percentage of ε-CL in CCC sequences would be 45%. This minimum percentage is made up of the 9 PCL units in CCC sequences from the original PCL_{10}-PLA_{20} precursor out of a total 20 PCL units present after transesterification. Additionally, this calculated minimum percentage of 45% does not take into account the sequential propagation or adjacent insertion of ε-CL observed for sample **8**.

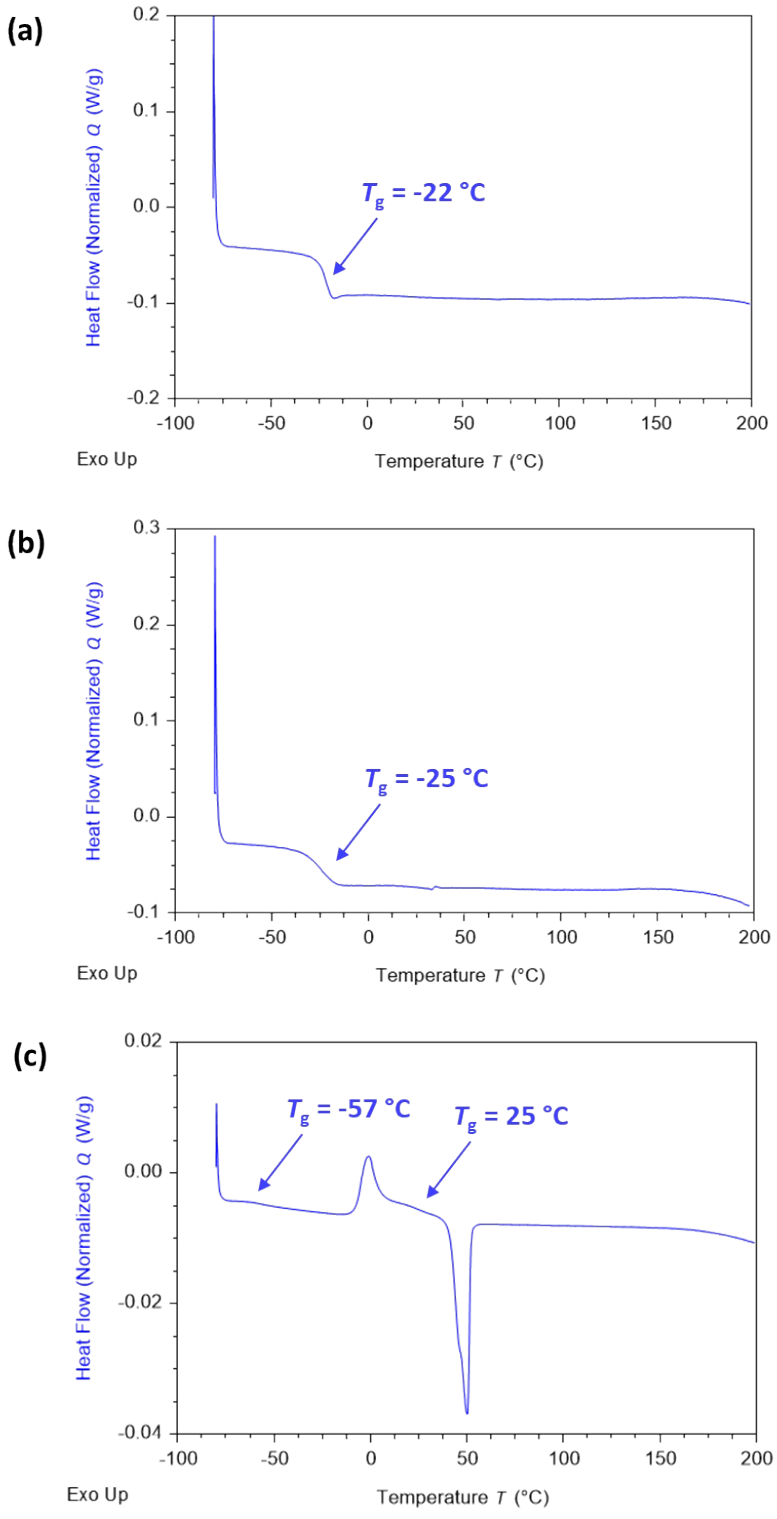


Figure S15. DSC thermograms of (a) sample **8**, (b) sample **9** and (c) a PCL_{20}-PLA_{20} diblock copolymer used as a reference.

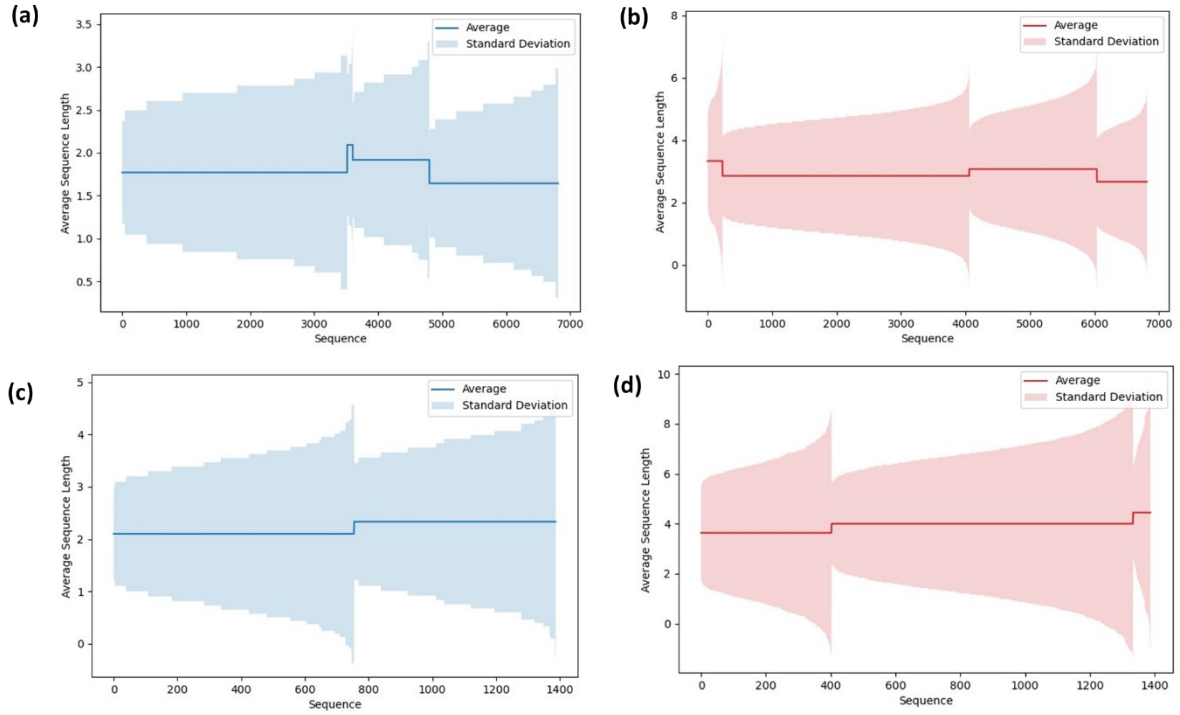


Figure S16. Plots of average sequence length against sequence iteration number for (a) monomer *x* and (b) monomer *y* for PLA_{20}-PCL_{20} (sample **8**) and for (c) monomer *x* and (d) monomer *y* for PCL_{10}-PLA_{20}-PCL_{10} (sample **9**), where monomer *x* and monomer *y* are ε-CL and lactic acid (i.e. half of a *rac*-lactide unit), respectively.

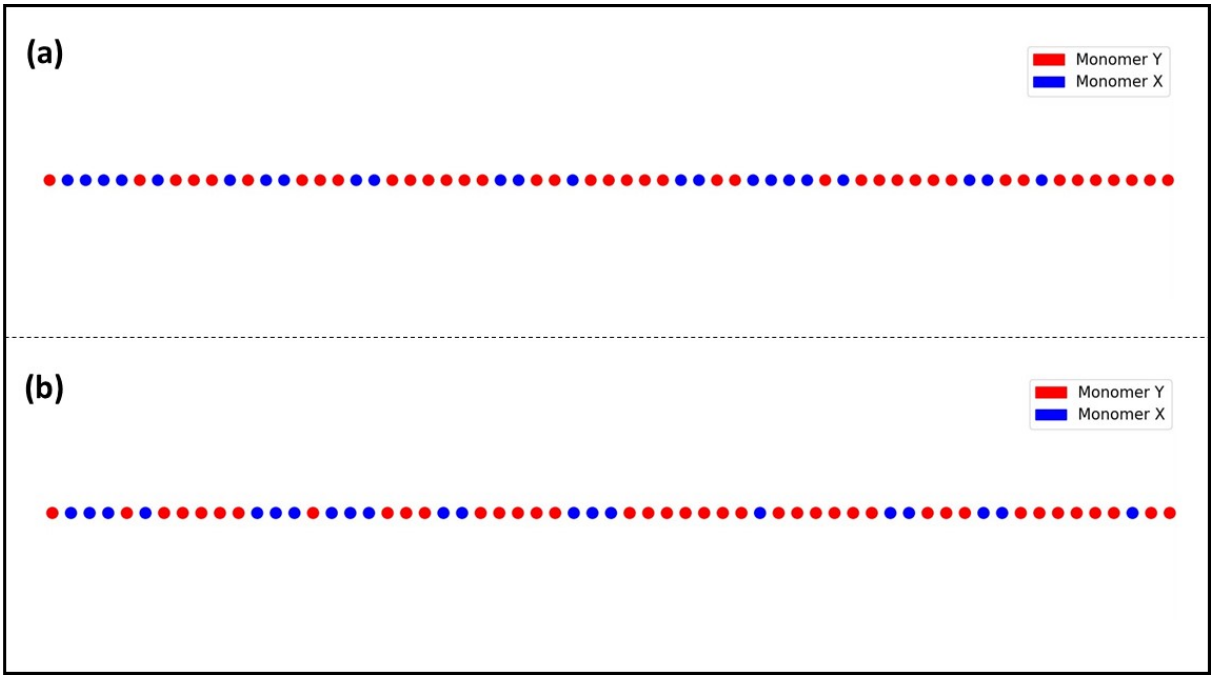
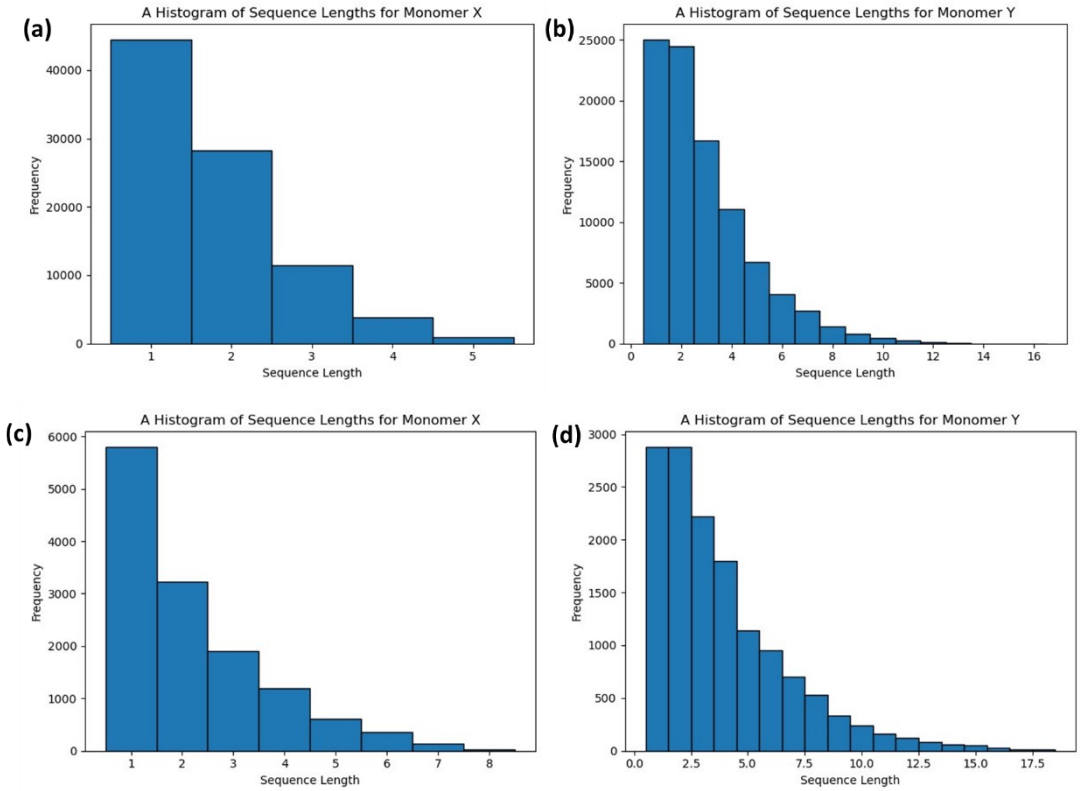


Figure S17. Example graphical depictions of the monomer distribution for (a) PLA_{20}-PCL_{20} (sample **8**) and (b) PCL_{10}-PLA_{20}-PCL_{10} (sample **9**) produced following a Monte Carlo random sequence simulator, where monomer *x* and monomer *y* are ε-CL and lactic acid (i.e. half of a *rac*-lactide unit), respectively.

Figure S18 Histograms of sequence length for PLA_{20}-PCL_{20} (sample **8**), where (a) is CL and (b) is lactic acid (i.e.



half of a *rac*-lactide unit), and for PCL_{10}-PLA_{20}-PCL_{10} (sample **9**), where (c) is ε-CL and (d) is lactic acid (i.e. half of a *rac*-lactide unit).

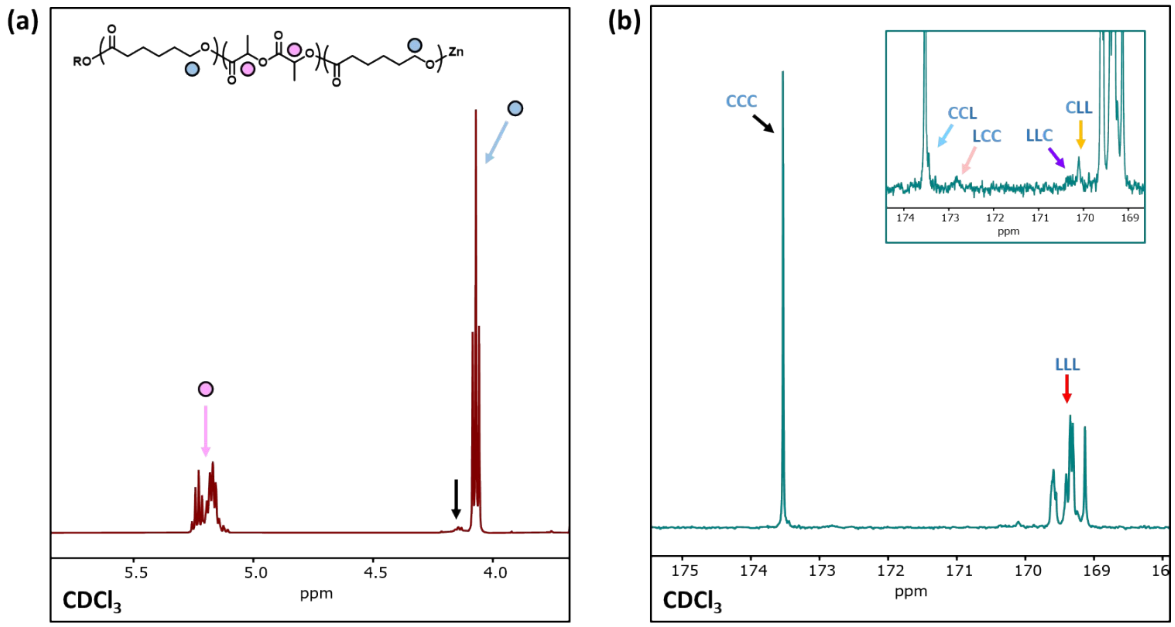


Figure S19. NMR spectra of the purified PCL_{200}-PLA_{200} diblock copolymer with 40 eq. of ε-CL reacted (sample **8**), where (a) is the ^{1}H NMR spectra, where the black arrow indicates PCL protons adjacent to a PLA unit, and (b) is the expanded ^{13}C NMR spectra with the respective peak assignments indicated on the spectra.

Outline of the Model for Simulating Polymer Chain Patterns from NMR Results[3]

Monte Carlo methods cover a broad range of computational techniques that employ randomness to solve mathematical problems.[4] The basic concept of most Monte Carlo methods involves transitioning a system from its present state to a new state based on a probability function known as the 'cost funtion'.[5] For example, when simulating polymer systems that converge to the lowest potential energy, U, the probability, P, of transitioning from an old state, o, to a new state, n, can be given by,

$$P(o \rightarrow n) = min\left[1, exp\left(-\frac{\Delta U}{k_B T}\right)\right], \tag{S14}$$

where k_B is the Boltzmann constant, T is temperature and ΔU is the change in energy from state o to state n.[5] Unlike the example in S14 the polymer simulation model described here is not dependent on energy or stability and is instead intended to provide examples of valid monomer configurations within a polymer chain based on NMR information given by the user.

At the start of a simulation the user provides the following values from NMR measurements (Figure S20), noting that the model is confined to sequencing chains of two different monomers, referred to in the program as C and L:

The number of each triad pattern (*n*), labelled *A* to *H* and given in the table below.

The total number of each monomer, referred to as *nC* and *nL*.

The average sequence length for each monomer, referred to as l_{CL} and l_L *(*where l_L refers to the average sequence length of the lactic acid unit and therefore $l_L=2l_{LA}$).

Table S3. The triad patterns A to H with the corresponding variable (*n*) that the user sets to be the number of each pattern measured. C and L represents the monomers within the program.

Pattern Label	Pattern	Variable denoting Number (*n*)
A	C, C, C	a
B	C, C, L	b
C	L, C, C	c
D	L, C, L	d
E	C, L, C	e
F	L, L, C	f
G	C, L, L	g
H	L, L, L	h

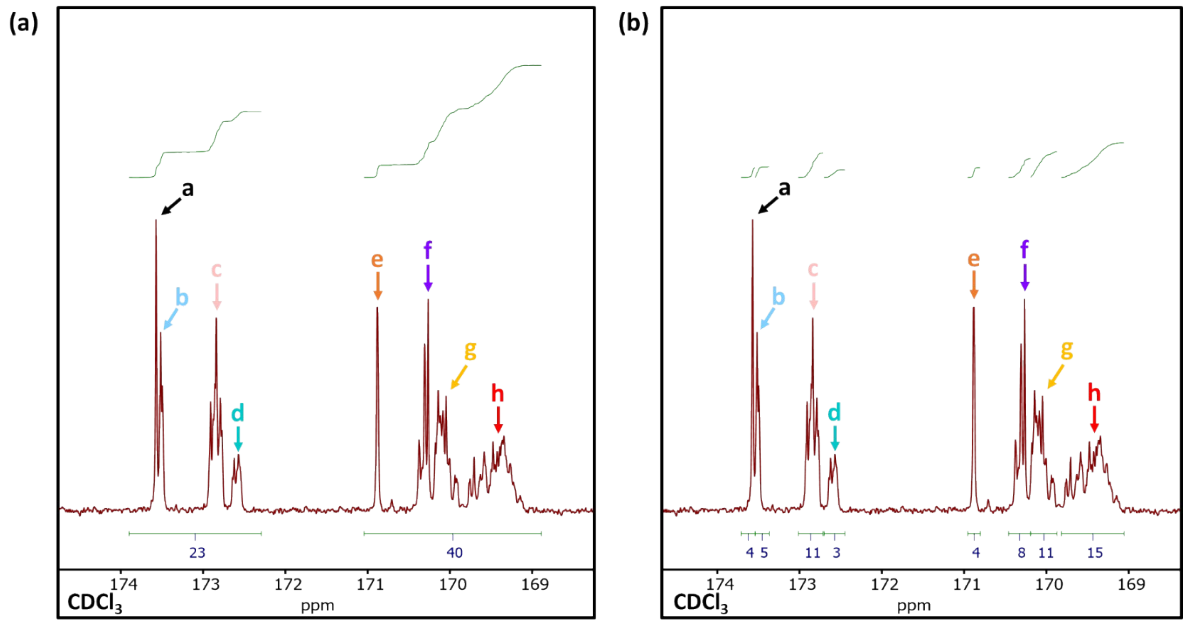


Figure S20. An example ^{13}C NMR spectra PLA_{20}-PCL_{20} (sample **8**) to demonstrate what information is extracted from the experimental NMR spectra and input into the Monte Carlo simulation.

The number of each triad is extracted from the ^{13}C NMR spectra of the chosen copolymer by taking the integral of each triad resonance. Typically, averaged, non-integer values will be obtained for NMR integrals however these parameters must be integer for the program to function and hence the values should be rounded appropriately. A consideration when rounding is that an exact solution is only possible under certain conditions, for example:

$$Total\ number\ of\ monomers = Total\ number\ of\ triads - 2 \quad \text{(S15)}$$

$$nC = a + b + c + d - 2 \quad \text{(S16)}$$

$$nL = e + f + g + h \quad \text{(S17)}$$

Additionally, the average sequence length for each monomer (l_{CL} and l_L) was calculated using the relative integrations of the diad signals in the ^1H NMR spectra (Figure S21) following a previously reported procedure.[2]

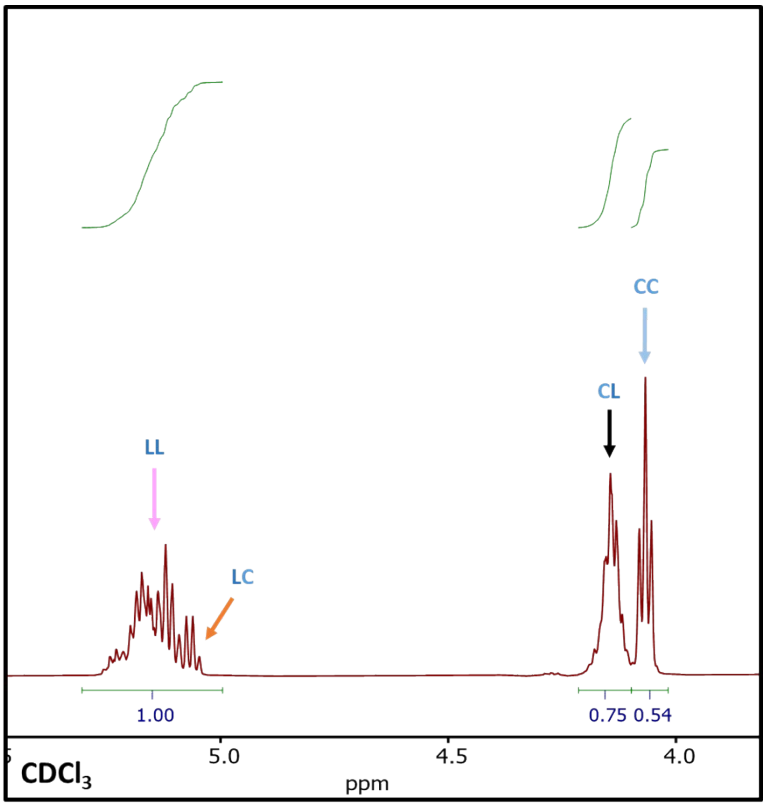


Figure S21. An example ^{1}H NMR spectra of PLA_{20}-PCL_{20} (sample **8**) to demonstrate what information is extracted from the experimental NMR spectra to calculate average sequence length

With this information a preliminary sequence is established by alternating the predicted average sequence length of each monomer until nC and nL have been satisfied. For example if $nC = 10$, $nL = 12$, $l_{CL} = 2$ and $l_{L} = 2$ then the initial sequence would be given by

[0, 0, 1, 1, 0, 0, 1, 1, 0, 0, 1, 1, 0, 0, 1, 1, 0, 0, 1, 1, 1, 1].

A calculation can then be applied to this sequence, known as a pattern score, to assess the similarity between this sequence and the actual NMR results. The number of each triad in the sequence is determined and denoted with the subscript seq. The equation for patten score is then given by,

$$Pattern\ Score = \sum |n - n_{seq}| \qquad \text{(S18)}$$

Hence a lower pattern score indicates a greater conformity to the given NMR results.

From this initial sequence a random iterative method is implemented to evaluate the pattern scores for a large number of possible polymer chains. During each iteration the following steps are executed:

1. Calculate the pattern score for the present sequence.

2. Swap the position of a user specified number of monomers. Swapping the position of two identical monomers is not possible so the new sequence must be unique compared to the present.

3. Calculate the pattern score for the new sequence.

4. Evaluate the ratio,
$$\varphi = {}^{Old\ Pattern\ Score}/_{New\ Pattern\ Score}. \quad \text{(S19)}$$

If the ratio is greater than 1 then the new sequence is an improvement on the previous and hence the sequence will transition to this chain for the next iteration.

If the ratio is less than 1 then the new sequence is deemed less similar to the NMR results however a transition from old to new sequence is still possible. A random number, x, between 0 and 1 is generated and if $x \geq 1 - \varphi^4$ then the sequence will transition. (S20)

If below the present sequence continues to the next iteration. It is necessary to have this possibility of transition to prevent the simulation from permanently residing in a local pattern score minima without the ability to explore other sequences.

The 'cost function', equation S20, is an arbitrary power law and can be altered to vary the harshness and leniency of the simulation, however, a power of 4 was used for all simulations presented here. Steps S14 to S20 are then repeated for a given number of iterations chosen by the user. The program hence allows for a vast number of sequences to be analysed and the user to gain an understanding of the range of patterns possible from a given set of NMR results.

The graphs below (Figure S22) demonstrate how the 'cost function' allows low scoring patterns to be found preferentially. When a power of 20 is used (high harshness) the simulation converges quickly to a minimum, however, once converged is unable to explore anymore potential space (Figure S22a). Alternatively, when a power of 4 is used the simulation is able to locate low scoring sequences but is able to escape any local minimums in order to explore more patterns (Figure S22b). When random sequences are generated without a 'cost function' the equivalent low scoring sequences are not found in a similar number of iterations (Figure S22b).

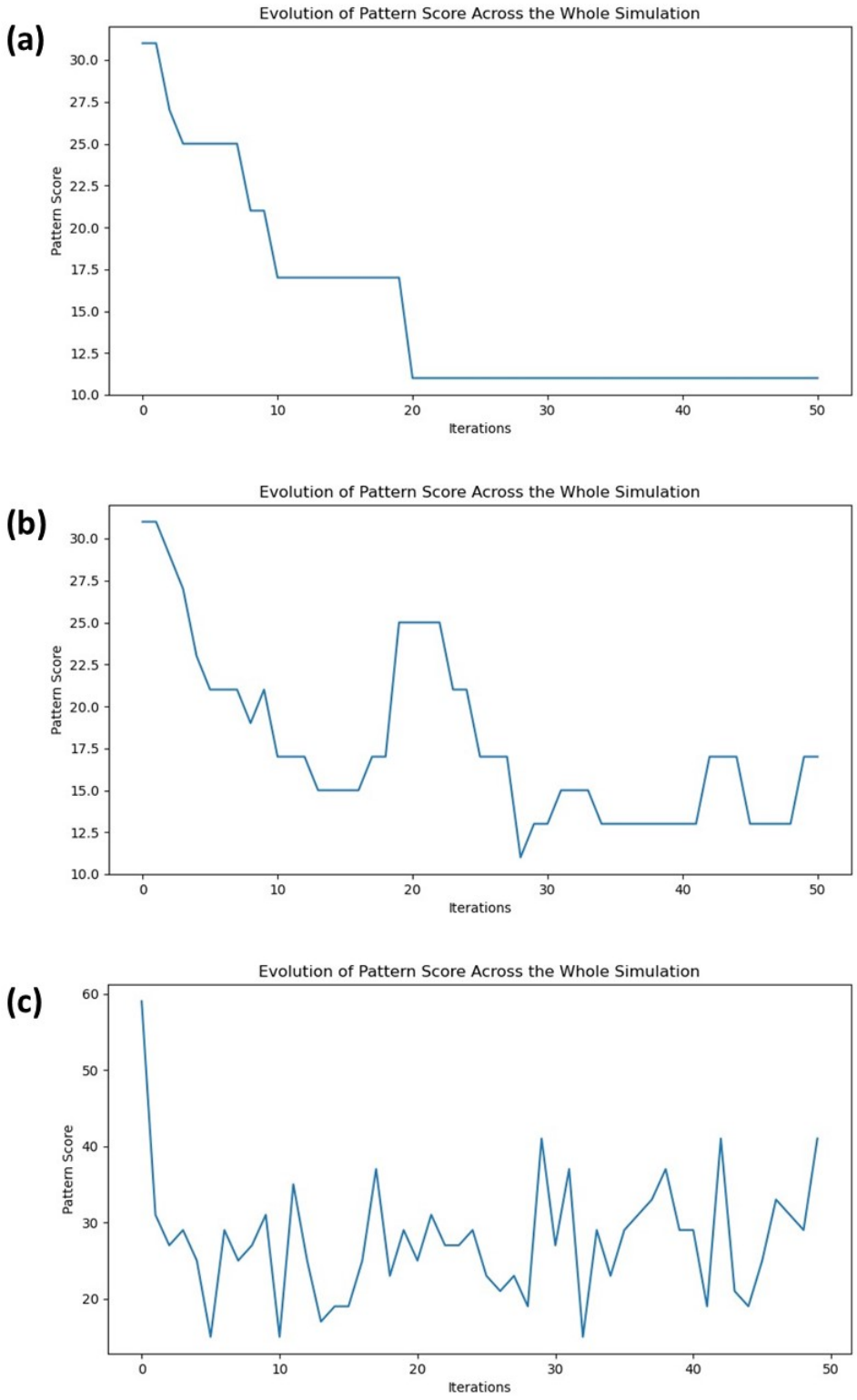


Figure S22. Graphs of pattern of pattern score against iteration for (a) a power law of 20, (b) a power law of 4 and (c) no cost function.

The program was written in Python (version 3.9.13) and executed in a Jupyter Notebook. The remaining sections of the notebook after the main simulation is complete are dedicated to analysis and result visualisation. This includes selecting only the sequences that have scored the lowest pattern scores, removing any duplicate sequences (i.e., any identical sequences that have appeared more than once will only be counted as one low scoring pattern) and evaluating their average sequence lengths for each monomer alongside standard deviations for each value.

References

1 W. Gruszka, L. C. Walker, M. P. Shaver and J. A. Garden, *Macromolecules*, 2020, **53**, 4294–4302.

2 J. Fernández, A. Etxeberria and J. R. Sarasua, *J. Mech. Behav. Biomed. Mater.*, 2012, **9**, 100–112.

3 E. Neal and T. Neal, 2023, Zenodo, DOI: 10.5281/zenodo.10410624.

4 A. Johnson, in *International Encyclopedia of Education*, Elsevier Science, Amsterdam, Third Edition, 2010, pp. 245–252.

5 V. G. Mavrantzas, *Front. Phys.*, 2021, **9**, 1–19.