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Enantiodifferentiating Alignment

Enantiodifferentiating Properties of the Alignment Media PELG and PBLG – A Comparison

Stefanie Hansmann,[a] Tobias Larem (née Montag),[a] and Christina M. Thiele*[a]

Abstract: Homopolypeptide-based alignment media can induce different orientations of enantiomers as a result of their α-helical structures. This property enables the discrimination of enantiomers through anisotropic NMR parameters such as residual dipolar couplings (RDCs). In this paper, the enantiodiscriminating properties of two alignment media derived from polyglutamic acid derivatives – poly-γ-benzyl-L-glutamate (PBLG) and poly-γ-ethyl-L-glutamate (PELG) – are compared and discussed. The two analytes, isopinocampheol and β-pinene, are investigated, and the role of the lateral side chain of the homopolypeptide in the orientation process is examined.

Introduction

Determining the constitution of a molecule by NMR spectroscopy is often a standard procedure, whereas elucidating its conformation and configuration is more challenging. In recent years, residual dipolar couplings (RDCs) have been used to determine the spatial structure of small organic molecules.[1] RDCs provide complementary information to conventional NMR restraints such as NOE distances[2] and dihedral angles from ^3J coupling constants.[3] RDCs are thus valuable parameters for structure elucidation. However, RDCs are not observable in isotropic solution because of uniform molecular tumbling and, thus, the efficient averaging of anisotropic NMR parameters. The observation of RDCs requires the analyte under investigation to be partially oriented with respect to the magnetic field, so that resulting RDCs are comparable in size to scalar couplings. Thus, to observe RDCs, one needs a so-called alignment medium.

Although different alignment media compatible with organic solvents have been developed in the last decade,[1] we have mainly focused on lyotropic liquid crystalline (LLC) phases based on homopolyglutamates with poly-γ-benzyl-L-glutamate (PBLG) as the most prominent representative of that group.[4] PBLG has already been successfully used to determine the structures and relative configurations of a variety of analytes, including intermediates.[5] Shortly after the introduction of PBLG for organic structure determination, it has been shown that poly-γ-ethyl-L-glutamate (PELG) can also be used as a valuable alignment medium.[6]

Both polypeptides, PBLG and PELG, form an α-helical secondary structure, which has a stiff rod-like or broken rod-like character, respectively,[7] and enables the formation of LLC phases.[8] Additionally, their homochirality offers the possibility to act as chiral alignment media[9] and is the basis for their enantiodifferentiating abilities. The enantiomers of the solutes undergo diastereomorphous interactions with their surroundings, in this case with the homochiral polyglutamate. As a result, the enantiomers are oriented differently and may become distinguishable by NMR spectroscopy in anisotropic media. Valuable pioneering work on the enantiodiscriminating behavior of PBLG and PELG has been done by the groups of Lesot and Courtieu.[9,10] They showed that, while the enantiomers are oriented differently and in the ideal case two sets of signals should be detectable in any kind of NMR spectrum, this is best detected by ^{2}H NMR spectroscopy. Thus, the chiral liquid crystals enable the determination of enantiomeric excess as a result of the large quadrupolar splittings that are observed in the ^{2}H NMR spectra. Furthermore, the determination of absolute configurations by ^{2}H NMR spectroscopic analysis has been possible in rare cases (by comparing similar compounds of known absolute configuration).[11] Therefore, the determination of absolute configurations by NMR spectroscopy in anisotropic media should be possible, provided the orientation and interactions of the analyte and alignment medium are predictable.[12] This emphasizes the necessity to develop enantiodiscriminating alignment media and understand the enantiodiscrimination process.[13,14]

Although there are many factors that can contribute to enantiodiscrimination,[14] namely, steric interactions, shape anisotropy, hydrogen bonding, electronic factors/dipole moment, and π–π stacking, we can only touch on these in the current investigation of the two helically chiral homopolypeptide-based alignment media with different side chains (i.e., benzyl for PBLG; ethyl for PELG) and the two solutes with comparable shapes but different hydrogen-bond acceptor/donor abilities [i.e., isopinocampheol (IPC) and β-pinene]. To compare PBLG and PELG, first PELG has been synthesized analogous to the synthesis of PBLG established in our group, based on Deming's protocol, through a Ni-mediated polymerization of *N*-carboxyanhydrides

[a] *Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt,*
Alarich-Weiss-Str. 4, 64287 Darmstadt, Germany
E-mail: cthiele@thielelab.de
www.thielelab.de

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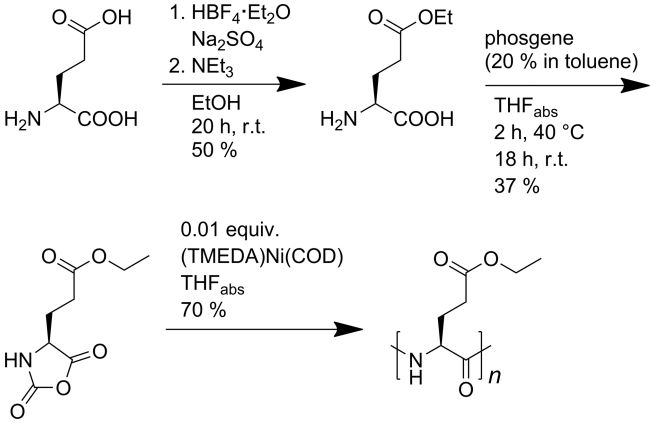
(NCAs).[15,4a] LLC phases of the synthesized PELG and PBLG in $CDCl_3$ are then used for comparison.

Enantiomeric pairs of isopinocampheol (IPC) and β-pinene have been chosen as the analytes and oriented in both alignment media. Differences in the RDCs of the enantiomers of each solute are compared, and the enantiodiscriminating behaviors of the two polyglutamic acid based alignment media are quantified by using the obtained alignment tensors, which define the mean orientation of the analytes with respect to the magnetic field. The influence of the side chain of the polyglutamic acid on the induced orientation is discussed.

Results and Discussion

The critical concentration of the LLC phase depends on the molecular weight of the polymer and the resulting aspect ratio, which is connected to the persistence length.[16] The use of high molecular weight homopolypeptides is, therefore, highly attractive. As the molecular weight increases, the critical concentration of the LLC phase decreases and thus allows the degree of orientation and consequently the magnitude of the measured RDCs to be scaled down. Commercial PELG has already been used as an alignment medium.[6] We have established the synthesis of PELG to improve its alignment properties and spectral quality. By following the same synthetic pathway as for PBLG (see Scheme 1), we have been able to obtain PELG. However, the purification of its corresponding NCA is more challenging than that of the benzyl derivative, as its tendency to crystallize is much smaller. Several recrystallization steps are necessary to obtain the highly pure NCA, which is essential to obtain the high molecular weight homopolypeptides.



Scheme 1. Synthesis of PELG by selective γ-esterification of glutamic acid,[17] activation with phosgene, conversion into the corresponding *N*-carboxyanhydride,[18] and Ni-mediated living polymerization (THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, COD = 1,5-cyclooctadiene).[19]

The PELG obtained forms an LLC phase upon addition of a suitable organic solvent. The formation of the LLC phase can be monitored by observing the quadrupolar splittings in the deuterium spectra after equilibration inside the magnet.[20] The PELG phase needs more time (several hours) than the PBLG phase to equilibrate inside the magnet. Once a stable quadrupolar splitting is observed and deuterium imaging shows homogeneity of the phase,[21] analytes are added to the LLCs. The samples are homogenized again, and the coupling constants are measured. The critical concentrations of the PELG and PBLG phases in $CDCl_3$ are all between 6.4 and 8.5 wt.-% (see Supporting Information). Because of the higher critical concentration of PBLG, its NMR experiments are performed at a slightly higher concentration (details are given in the Supporting Information).

To make the data comparable, one would ideally prepare identical samples (i.e., identical concentration of the polymer and identical amount of the solute to give identical quadrupolar splittings) for each pair of enantiomers, which is very difficult to achieve. Although the strength of the orientation is scaled via the concentration of the LLC phase, we have observed no concentration dependence of the orientation of the solute in PBLG.[4] Thus, we have used the ratios of the quadrupolar splittings of the two respective samples to scale the RDCs and make them comparable. It has been reported that these factors are crucial in polyacetylene-based alignment media[13e] and thus care must be taken whether the scaling by quadrupolar splittings is adequate.

The first analytes investigated are the enantiomers of isopinocampheol (IPC; Figure 1). IPC has been previously used in studies as a test analyte for the RDC approach,[4,13b,13c,13e,13f] as it fulfills the required criteria of high rigidity and little overlap in heteronuclear single quantum coherence (HSQC) spectra. This allows the extraction of up to 11 natural abundance proton–carbon one-bond RDCs ($^1D_{CH}$) to provide a well-defined alignment tensor.

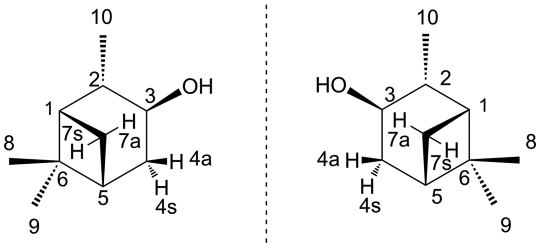


Figure 1. Structures of (+)-IPC (left) and (–)-IPC (right). Diastereotopic protons are antiperiplanar (a) and synperiplanar (s) to the dimethylmethylene bridge of IPC.

The $^1J_{CH}$ coupling constants are extracted from CLIP/CLAP-HSQC spectra.[22] The orientation of (+)-IPC and (–)-IPC in a PBLG phase has already been investigated,[4b] and different RDCs have been observed for the enantiomers, but the differences are rather small (for details, see Supporting Information). The orientation of IPC in the synthesized PELG allowed for the extraction of 11 RDCs (Figure 2). In this case, the differences between the enantiomers are larger than in PBLG. In particular, the RDCs for the diastereotopic protons (C4–H4s, C4–H4a, C7–H7s, and C7–H7a) differ significantly (up to 8 Hz).

To confirm the observations made for IPC and to get a first glimpse of the importance of hydrogen bonding in the alignment process, we have chosen the enantiomers of β-pinene as a second analyte (Figure 3). β-Pinene has a rigidity comparable to IPC because of its cyclic framework, which is beneficial for a comparison of the alignment tensors, as considerations con-

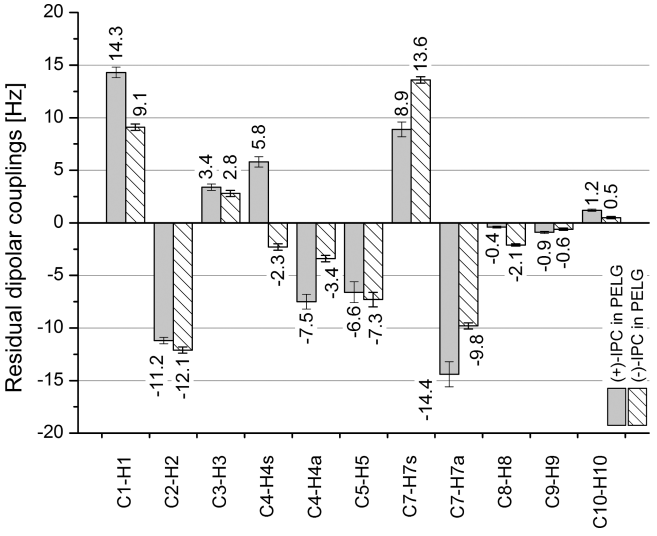


Figure 2. Comparison of the RDCs of (+)-IPC and (–)-IPC in a lyotropic liquid crystalline phase of PELG in $CDCl_3$.

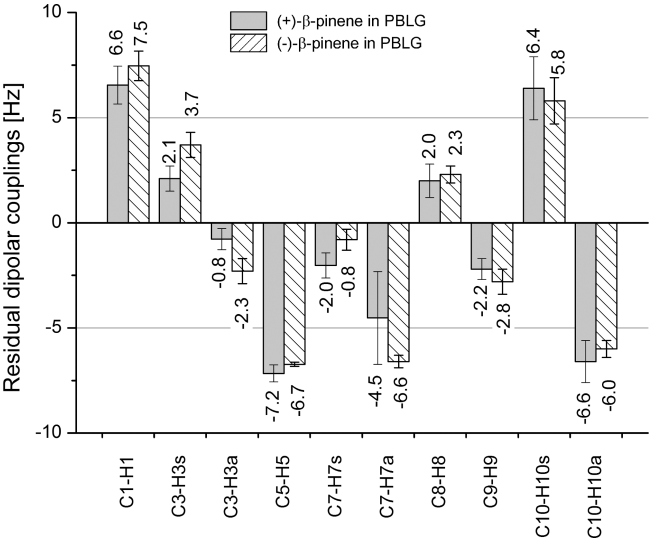


Figure 4. Comparison of the RDCs of (+)-β-pinene and (–)-β-pinene in an LLC phase of PBLG in $CDCl_3$.

cerning flexibility do not have to be taken into account. Furthermore, the spatial structure of β-pinene is relatively similar to that of IPC. Thus, one could hope that these compounds would be oriented similarly, as long as the OH group of IPC does not play a crucial role in the orientation and enantiodiscrimination process.

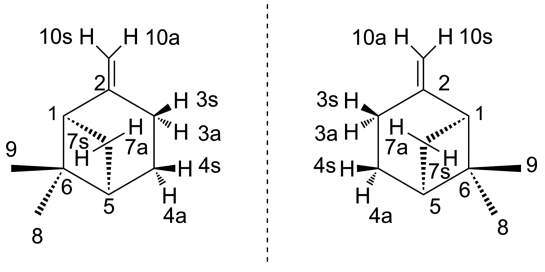


Figure 3. Structures of (+)-β-pinene (left) and (–)-β-pinene (right). Diastereotopic protons are antiperiplanar (a) and synperiplanar (s) to the dimethylmethylene bridge of β-pinene.

The CLIP/CLAP HSQC[22] experiments and *J*-scaled F1-coupled HSQC spectra[23] allow for the extraction of up to 10 one-bond RDCs ($^1D_{CH}$). However, it has become obvious that several coupling constants are not (always) extractable because of overlapping (i.e., C3–H3a, C3–H3s, C10–H10a, C10–H10s) or isochronous signals (i.e., C4–H4a and C4–H4s). As mainly coupling constants of diastereotopic protons are not extractable, additionally *J*-scaled F1-coupled HSQC experiments with multiquantum evolution are recorded,[24,23b] which allows for the individual extraction of one-bond coupling constants for the diastereotopic methylene groups in the indirect dimension. From these spectra, the desired coupling constants (i.e., C10–H10a, C10–H10s, C3–H3a and C3–H3s) can be extracted in all cases.

In Figure 4, the RDCs of (+)-β-pinene and (–)-β-pinene in an LLC phase of PBLG in $CDCl_3$ are visualized. Especially for the couplings C3–H3s and C7–H7a pronounced differences (up to 3.4 Hz) between the two enantiomers can be observed, that is, enantiodiscrimination has been achieved.

The extraction of $^1T_{CH}$ coupling constants from CLIP/CLAP-HSQC and F1-coupled experiments, as mentioned above, provides the same amount of RDC data for β-pinene in an LLC phase of PELG in $CDCl_3$ (Figure 5). Comparison of the RDCs of (+)-β-pinene and (–)-β-pinene shows that the largest differences are between the couplings of the diastereotopic protons (C3–H3a, C3–H3s, C7–H7a, C7–H7s). Again the differences (up to 3 Hz) are significantly larger than the error margin.

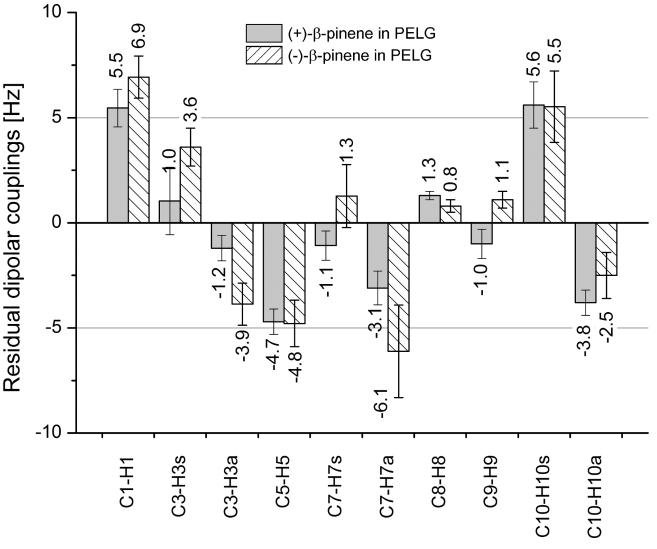


Figure 5. Comparison of the RDCs of (+)-β-pinene and (–)-β-pinene in an LLC phase of PELG in $CDCl_3$.

Discussion of the Enantiodiscriminating Properties

Determination and comparison of the RDCs for the enantiomeric pairs of two analytes in PBLG and PELG show that both alignment media allow for enantiodiscrimination. Measured (and scaled) RDCs are distinguishable, and their differences are larger than the error margin.

To quantify the enantiodiscriminating behavior of the two alignment media, the alignment tensors are determined by using the software RDC@hotfcht.[25] The mean orientations defined by the alignment tensors of the two enantiomers of each analyte and medium are then compared. The difference between the tensors can be described by the generalized angle β, which corresponds to the normalized scalar product of the two tensors.[26,13c]

The alignment tensors of (+)-IPC and (–)-IPC in PBLG (previously published data)[4b] are shown in Figure 6 (left side). Both enantiomers experience a similar alignment. The generalized angle β between the two eigenvectors of the tensors is 8.1°. The orientations of the IPC enantiomers aligned in PELG are significantly different (Figure 6, right side). In this case, the generalized angle β between the eigenvectors is 29.6°, which is in accordance with the larger differences of the RDCs (see also Figure 2).

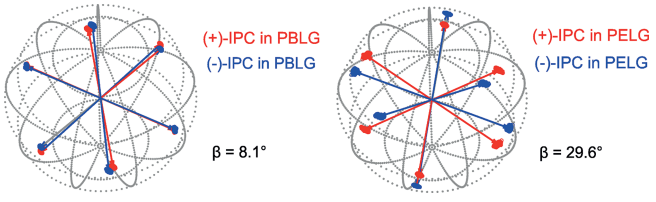


Figure 6. Orientation of (–)-IPC (blue) and (+)-IPC (red) in PBLG (left)[4b] and PELG (right).

In comparison to the orientation distributions obtained for IPC (Figure 6), the orientations of β-pinene are less defined. This is because the error margins of the RDCs are quite high (see Supporting Information). Additionally, the obtained RDCs do not allow for a precise description of the orientation of the analyte because of the linear dependency of some of the vectors belonging to the measured RDCs. Therefore, only the mean orientation of (+)-β-pinene and (–)-β-pinene are shown (see Figure 7). The generalized angle β for PBLG is 19.7°, and the one for PELG is 33.8°.

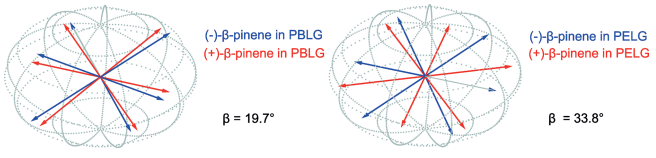


Figure 7. Mean orientation of (+)-β-pinene (red) and (–)-β-pinene (blue) in PBLG (left) and PELG (right).

The illustrations of the tensors and the generalized angles β show that the enantiodiscriminating properties of the PELG-based alignment medium for these two examples are stronger than those of PBLG.

To get access to an understanding of this phenomenon, different aspects – related to the homopolypeptide itself as well as the interaction between the homopolypeptide and solute – need to be considered. These include the orientation of the LLC helices inside the magnet (nematic vs. cholesteric LLC), the influence of the side chain (chirality, steric hindrance, possible π–π-stacking, and rotational freedom of side chain), and the interactions between the analyte and the alignment medium[14] (steric interactions/shape anisotropy, hydrogen bonding, electronic factors/dipole moment, and π–π-stacking interactions).

The LLC phase behavior of PBLG is well investigated and understood.[27,8d] PBLG forms cholesteric phases that become untwisted inside the magnet, and a nematic LLC phase behavior is observed.

To describe the chirality of a lyotropic liquid crystalline polyglutamate phase, the orientation and rotational freedom of the side chains also need to be taken into account.[27a,27b] Investigations by Yamazaki et al.[27a,28] on PBLG with regard to the orientational angle of the side chain relative to the helix prove that a strong correlation through the interdependence of neighboring bond rotations along the chain is observed, with the transverse direction to the backbone as the most prominent one. This is in accordance with the benzyl groups in the side chain stabilizing the secondary structure through electrostatic interactions of the rings (π–π stacking).

In contrast, the lateral side chain of an alkyl-substituted polyglutamic acid has more conformational freedom.[29] With the increasing length of the side chain, the rotational populations become similar to that of the corresponding paraffins, while the rotational freedom of the interior side chain is similar to that of PBLG and not affected by the length of the aliphatic side chain.

Finally, a number of different interactions between the analyte and helices have been proposed including nonspecific repulsive interactions such as anisotropic diffusion between the parallel aligned helices in the magnetic field[27b] as well as more specific interactions. Depending on the structure of the analyte and the alignment medium, electrostatic interactions such as van der Waals, hydrogen-bonding, or π–π-stacking interactions are possible. For β-pinene, an analyte that lacks functional groups, a large enantiodiscriminating effect is observed, which indicates that apolar interactions such as van der Waals forces are part of the alignment process. The enantiodiscrimination is (slightly) larger than that observed for IPC. If one could assume that from a steric/shape anisotropy perspective, both solutes would orient similarly because of their analogous spatial structures, we could conclude that hydrogen bonding does not play a key role in the enantiodiscrimination in this case. A more detailed investigation of the role of hydrogen bonding in the alignment process is currently underway by our group.

Thus, one can conclude that the concept of alignment in polypeptide-based media is complex, influenced by a wide range of factors, and not yet predictable.[9c,12,14,30] Nevertheless, we can speculate that the difference in the alignment of PBLG and PELG results from the change of the lateral side chain. The less bulky ethyl group, which has a higher mobility than the larger benzyl group, can allow the analyte to have more and stronger diastereomorphous interactions with the helical backbone.

Conclusions

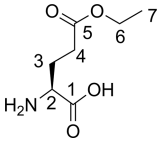
The enantiodiscriminating properties of two polyglutamate-based alignment media have been investigated by employing enantiomeric pairs of IPC and β-pinene. In both cases, a higher enantiodiscriminating effect is observed by using PELG, which

could imply that the shorter side chain allows for more and stronger diastereomorphous interactions between the analyte and the alignment medium. On the basis of this result, it is clear that the modification of the lateral side chain impacts the resulting alignment of the two enantiomers. The orientational correlation through the interdependence of the neighboring groups as well as the conformational freedom and steric demand of the lateral side chain are key variables in the alignment process, as the side chain either hinders or allows for attractive interactions between the analyte and alignment medium. This is valuable information for the development of new and highly enantiodiscriminating alignment media. The implementation of an additional chiral element in the side chain and its role in enantiodiscrimination is the next step in our group's investigation.

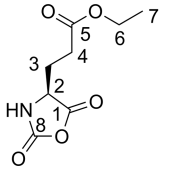
Experimental Section

General Methods: All chemicals used for the synthesis and analysis were purchased from Fisher Scientific or Sigma–Aldrich and used as delivered, unless otherwise stated. In the case of PBLG, gel permeation chromatography (GPC) analysis was carried out in *N*,*N*-dimethylformamide (DMF) with LiBr (0.5 wt.-%) at 70 °C by using polystyrene as the calibration standard. In the case of PELG, GPC analysis of PELG was performed in hexafluoroisopropanol with the addition of potassium trifluoracetate (0.05 M). The molecular weights were calibrated with polymethylmethacrylate standards.

Synthesis of Ethyl Glutamate: According to the synthesis of γ-benzylglutamate by Albert et al.,[17] L-glutamic acid (18.5 g, 121 mmol, 1.0 equiv.) and Na_2SO_4 (18.0 g, 127 mmol, 1.05 equiv.) were suspended in ethanol (180 mL). Tetrafluoroboric acid diethyl ether complex (54 wt.-% solution, 33.4 mL, 242 mmol, 2.0 equiv.) were added, and the reaction mixture was stirred overnight. The suspension was filtered through Celite. To the clear filtrate was added triethylamine (37.1 mL, 266 mmol, 2.2 equiv.), and the evaporation of the solvent led to a highly viscous suspension. A mixture of ethyl acetate/ethanol (4:1, 900 mL) was added to dissolve the ammonium salts, and the resulting mixture was stirred for 15 min. The product mixture was filtered, and the filter cake was washed with the solvent mixture and then recrystallized (water/acetone, 2:3) to give ethyl glutamate (10.6 g, 50 % yield) as a colorless solid. ^{1}H NMR (300 MHz, D_2O, 300 K): δ = 1.2 [t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 7-H], 2.1 (m, 2 H, 3-H), 2.5 (m, 2 H, 4-H), 3.7 (t, 1 H, 2-H), 4.1 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 6-H) ppm. ^{13}C NMR (75 MHz, D_2O, 300 K): δ = 13.2 (C-7), 25.4 (C-3), 30.0 (C-4), 53.9 (C-2), 61.9 (C-6), 173.9 (C-1), 174.9 (C-5) ppm.



Synthesis of Ethyl Glutamate-NCA: The synthesis and purification of the NCA derivative was performed under Ar, and the glassware was flame dried prior to use. Following the protocol of Fuller et al.[18] ethyl glutamate (6.7 g, 38.3 mmol, 1.0 equiv.) was dissolved in THF_{abs} (60 mL). At 40 °C, phosgene (20 wt.-% dissolved in toluene, 24.2 mL, 46.0 mmol, 1.2 equiv.) was added, and the resulting mixture was stirred at 40 °C for 2 h and at room temperature for an additional 18 h. The clear solution was filtered to remove the residual starting material and then added to *n*-hexane$_{abs}$ (300 mL). The mixture was cooled to –28 °C to allow for crystallization. The crude product was filtered, washed with additional *n*-hexane$_{abs}$ (120 mL), and dried in vacuo. The crude product was dissolved in THF_{abs} (8 mL g^{-1}), and a second layer of *n*-hexane was slowly added (30 mL g^{-1}) by using a syringe pump. After 2 d, the product crystallized as fine needles. The crystals were removed by filtration, washed with *n*-hexane, and dried in vacuo. The NCA derivative was recrystallized an additional time in the same manner to give the highly purified needle-like ethyl glutamate-NCA (2.83 g, 37 % yield). ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.2 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 7-H), 2.1 (m, 1 H, 3A-H), 2.2 (m, 1 H, 3B-H), 2.5 (pseudo-t, 2 H, 4-H), 4.1 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 6-H), 4.4 (pseudo-t, 1 H, 2-H), 6.6 (s, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 14.1 (C-7), 26.9 (C-3), 29.9 (C-4), 57.1 (C-2), 61.3 (C-6), 151.9 (C-8), 169.4 (C-1), 172.6 (C-5) ppm.

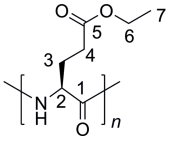


Polymerization Procedure (PELG Synthesis, Table 1): On the basis of the protocol of Deming et al.,[19a] $Ni(COD)_2$ (158 mg, 0.57 mmol, 1.0 equiv.) was dissolved in THF_{abs} (15.8 mL) in a glovebox under Ar. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (88.0 µL, 0.57 mmol, 1.0 equiv.) was added to activate the complex. [The diamine had been heated at reflux over CaH_2, distilled, degassed, and then kept over molecular sieves (4 Å) prior to use.] The $Ni(COD)_2$/TMEDA mixture was stirred for 15 min. By following Deming's[19a] procedure, the NCA was dissolved in THF_{abs} (50 mL g^{-1}), and the initiator solution (10.3 mg mL^{-1}) was added. The polymerization was allowed to run for 6 d. The polymer is precipitated by adding acidic methanol (1 mM HCl). The mixture was filtered, and the (solid) polymer was redissolved in THF and precipitated again in methanol. Poly-γ-ethyl-L-glutamate was obtained as an amorphous colorless solid. ^{1}H NMR [600 MHz, $CDCl_3$ + 0.02 V‰ trifluoroacetic acid-d_1 ([D_1]TFA), 300 K]: δ = 1.3 (br., 3 H, 7-H), 2.1 (br., 1 H, 3a-H), 2.3 (br., 1 H, 3b-H), 2.4 (br., 1 H, 4a-H), 2.6 (br., 1 H, 4b-H), 4.0 (br., 1 H, 2-H), 8.3 (br., 0.4 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$ + 0.02 V‰ [D_1]TFA, 300 K): δ = 14.1 (C-7), 25.7 (C-3), 29.9 (C-4), 56.9 (C-2), 61.7 (C-6), 174.3 (br., C-5, C-1) ppm. IR [attenuated total reflectance (ATR)-FTIR, solid state]: $\tilde{\nu}$ = 1541 (NH), 1650 (CONH), 1728 (COOR), 3290 (CONH) cm^{-1}.

Table 1. Summary of the PELG obtained under different polymerization conditions.

Entry	Monomer/ initiator	yield [%]	M_n [kDa]	M_w [kDa]	PDI[a]
PELG-1	50:1	67.0	206	506	2.45
PELG-2	100:1	81.0	259	612	2.36

[a] PDI = polydispersity index.



NMR Experiments: Experimental details for the preparations of the anisotropic samples, the parameters used in the NMR measurements, the instrumental setup, and a summary of the obtained

RDCs used for the calculations of orientational properties are given in the Supporting Information.

Acknowledgments

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