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^2H and ^{13}C NMR-based Enantiodetection using Polyacetylene *versus* Polypeptide Aligning Media: Versatile and Complementary Tools for Chemists

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ABSTRACT:

In this work, we examine the practical/analytical potential of an L-valine-derived polyacetylene (PLA) lyotropic liquid crystal (LLC) to spectrally discriminate enantiomers (racemic mixture) or enantiotopic directions of a large collection (twenty three) of (pro)chiral model compounds (from rigid to flexible and polar to apolar ones), thus covering various important aspects of enantiomorphism. Experimental ^2H - $\{^1\text{H}\}$ (deuterated analytes and at natural abundance level) and ^{13}C - $\{^1\text{H}\}$ NMR results are discussed in terms of difference of ^2H -RQCs or ^{13}C -RCSAs and compared to those obtained in polypeptide-type LLCs (PBLG). The analysis of the NMR results provides an overview of the enantiodifferentiation capability of PLA and gives useful/practical hints for the chemist to select the most appropriate chiral oriented system. From a theoretical viewpoint, the data collected highlight the key molecular factors involved in orientation/discrimination processes, as a basis for optimizing computational prediction (molecular dynamics simulation), as well as designing novel helically chiral polymers as new enantiodiscriminating aligning media. In addition, a new, robust and efficient protocol to synthesize PLA and its enantiomer (PDA) at large scale and with small polydispersities is proposed.

Keywords: NMR • deuterium and carbon-13, anisotropic media • helically chiral polymer • enantiodiscrimination

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Introduction

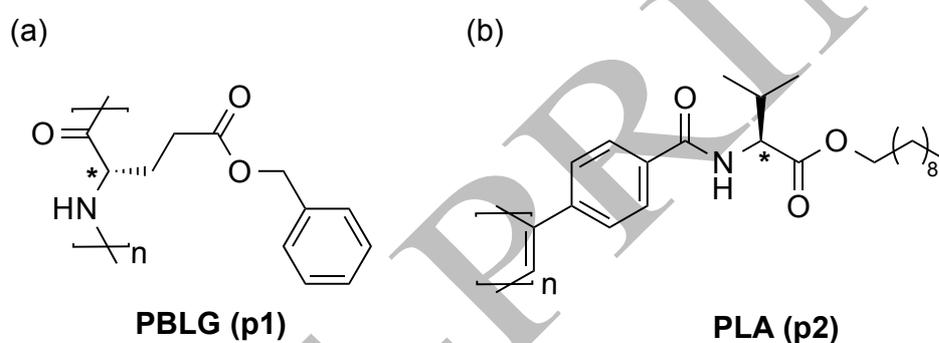
NMR using weakly orienting helically-chiral polymers such as enantiodiscriminating lyotropic liquid crystals (LLCs) is a powerful alternative when isotropic NMR tools fail or lead to very poor spectral enantiodifferentiations.^[1] The advantage of this approach originates from the incomplete averaging of all relevant order-sensitive NMR interactions, such as residual chemical shift anisotropy (RCSA), residual dipolar coupling (RDC) or residual quadrupolar coupling (RQC; spin $I > 1/2$), that can be exploited to distinguish signals of enantiomers but also enantiotopic directions in prochiral analytes.^[2] *De facto*, whatever their natural abundance, any magnetically-active nucleus (^1H , ^2H , ^{13}C , ^{19}F , ...) is a potential probe to reveal discriminations, widening the panel of available tools whereas the extent of enantiodifferentiation depends both on the nucleus and the anisotropic NMR interaction considered.^[2b,3]

Concomitantly with practical aspects, the power of the method is related to the efficiency of the (global and local) discrimination processes of helically chiral LLCs, which lead to orient differently any mirror-image molecular objects or elements on average.^[2b,2c,4] Over the past two decades, special attention was paid to polypeptide-based homopolymers with different achiral lateral chains such as poly-*g*-benzyl-*L/D*-glutamate (PBLG / PBDG), poly-*g*-ethyl-*L/D*-glutamate (PELG / PEDG), poly- ϵ -carboxybenzoyl-*L/D*-lysine (PCBLL/ PCBDL) or mixtures thereof, and more recently of poly- β -phenethyl-*L/D*-aspartate (PPLA / PPDA) for three main reasons:^[5] i) commercial availability with a large range of degree of polymerization (DP) for some of them; ii) vast choice of compatible organic co-solvents; iii) a simple preparation of samples. In this context, the capability of PBLG to differentiate enantiomers or enantiotopic elements was established for almost all classes of (pro)chiral organic molecules, leading to unexpected analytical developments, such as enantiomeric excess (*ee*) determination, conformational dynamic studies, structural elucidation purposes, or even the investigation of site-specific (D/H) isotopic analysis of natural compounds.^[6]

Recently, new enantiodifferentiating helically chiral polymeric LLCs made of polyguanidines,^[7] polyisocyanopeptides,^[8] polyaryisocyanides,^[9] or polyarylacetylenes with chiral side chains,^[10] were reported. As generally conducted in the structure elucidation work-frame, enantiodiscriminations are only experimentally revealed through differences of (^{13}C - ^1H)-RDCs (via HSQC-type 2D experiments) measured on a limited number of typical model solutes (IPC, menthol, *b*-pinene, ...). In practice, the orientational differentiation capability is evaluated using the generalized "9D" inter-tensorial angle (β) or its cosine (generalized cosine β ; GCB) derived from the alignment tensors of the individual enantiomers,^[10a,11]. Although this analysis of the orientational properties is possible for samples containing only one enantiomer, this does not necessarily mean that their scalemic mixtures can be easily analyzed quantitatively. In addition, the few examples of chiral molecules examined for exploring

enantioproperties of new chiral media are only limited to most common causes for chirality (stereogenic center), thus omitting the particular case of isotopic chirality by virtue of the isotopic (H/D) substitution, but also other important aspects of enantiomorphism, such as chiral molecules without stereogenic center, or the enantiotopicity in prochiral molecules.^[4,12] The lack of general knowledge about the enantiodiscrimination potential of these new systems does not favour neither their use nor their dissemination among chemists as alternative or complementary media to already known alignment systems.

Using ^2H - $\{^1\text{H}\}$ NMR (^2H -RQCs) and ^{13}C - $\{^1\text{H}\}$ NMR (^{13}C -RSCAs), we have compared the analytical potential of chloroform-based organic solutions of an L-valine-derived polyacetylene (PPA-L-Val-dec) LLC relative to L-glutamate derived polypeptide LLC (PBLG). The structures of the two chiral polymers are depicted in **Scheme 1**.



Scheme 1. Structures of (a) poly- γ -benzyl-L-glutamate (PBLG / **p1**) and (b) L-valine derived polyacetylene (PLA / **p2**) homochiral polymers. Note the difference of positioning of the stereogenic center (backbone *versus* side chain).

For a short notation, we will use PLA in this work instead of “PPA-L-Val-dec” and “PDA” for the enantiomer of PLA (PPA-D-Val-dec). Both sets of samples were prepared with the same composition (ca 19% w/w in polymer), and a very close degree of polymerization (750 for PLA and 743 for PBLG).

Compared to PBLG where helicity-inducing stereogenic centers are located in the backbone, the valine derived polyacetylene **PLA (p2)** has a helical structure induced by the stereogenic centers within the sidechain. This entails a much more dynamic helix being responsive to external stimuli (temperature, solvent) as well as structural modifications in the lateral aminoacid derivatives. Nonetheless, Yashimas^[13] and Tangs work,^[14] as well as our own experience with these polymers^[10] shows that the H-bonding network of the sidechains stabilizes the helix to such an extent that the helical excess becomes comparable to the one of static polymers like PBLG or sterically congested polymethacrylates.^[15]

Twenty three (deuterated or not) model analytes with various functional groups have been selected (**Figure 1**) in order to cover the three aspects of enantiomorphism (chirality, chirality by isotopic

substitution and prochirality) and identify the main molecular aspects (conformational flexibility, (attractive or repulsive) electrostatic interactions, shape anisotropy, ...) playing an active role in the enantiodiscrimination mechanism (EDM).^[16]

Given the diversity of structures in chemistry, the selection of molecules leading to a representative panel is a difficult task, and like any screening study, this choice can be counter-argued because: of its incompleteness; and because the results discussed prevail only for the experimental conditions chosen (sample composition, co-solvent, working temperature (295 K). Nevertheless, even with a limited number but key examples, such an overview provides important practical benchmarks on the enantiodiscrimination capabilities of PLA relative to PBLG, useful for selecting *a priori* the most appropriate chiral homopolymer for future analyses.

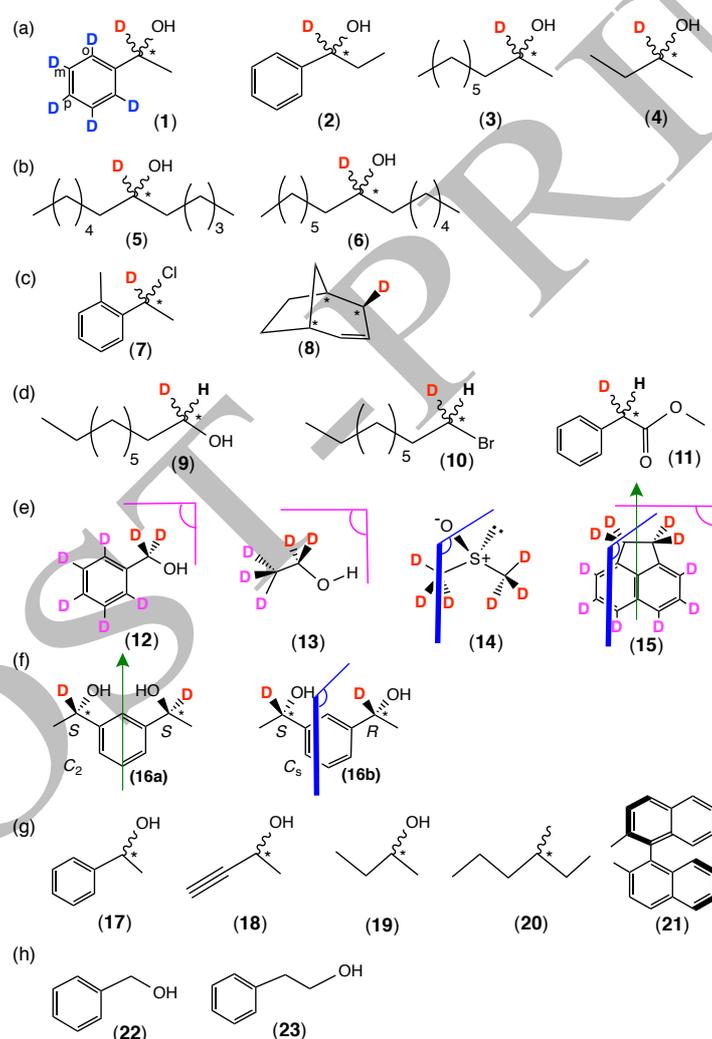


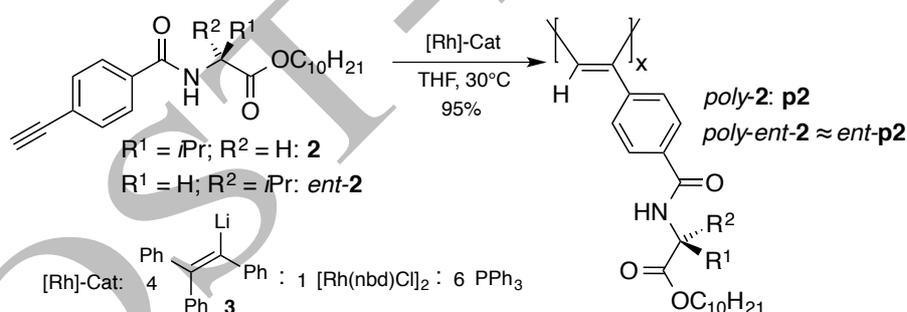
Figure 1. Structures of chiral and prochiral model molecules studied: isotopically enriched (1 to 16) and isotopically natural (17 to 23) analytes. All types of molecules are categorized from a to h.

Experimental section

Optimization of PLA synthesis

Promoting valuable LLCs, not commercially available (in contrast with PBLG) requires first the development of a rapid and optimized synthesis (overall yield, degree of polymerization (DP), polydispersity index (PDI),) to obtain polymers in a highly reproducible fashion. To fulfil this prerequisite, a new strategy for synthesizing PLA or PDA has been designed (**Scheme 2** and **SI**). The valine-based polymers (**p2** and *ent*-**p2**) used earlier as chiral alignment media have been synthesized, so far by slightly modified procedures published by Yashima for the synthesis of the alanine derivative.^[13d,17] However, especially the polymerization using $[\text{Rh}(\text{nbd})\text{Cl}]_2$ as a catalyst turned out to be inferior with respect to molecular weight distribution and reproducibility of the LLC-phase properties (critical concentration, equilibration time in the magnetic field, orientational properties). Therefore, we adapted the triphenylvinyl rhodium based initiator system of Misumi and Masuda to polymerize the monomers **2** and *ent*-**2** (**Scheme 2** and **SI**).^[18,19]

As detailed in the **SI**, we succeeded in polymerizing up to 10 g of the monomer with very low PDI (≈ 1.05), and beneficial and reproducible properties. For instance, the time needed to get a constant quadrupolar splitting from the deuterated solvent signal was reduced from 60 min at 11.4 T with a 18% phase of a polymer obtained *via* the $[\text{Rh}(\text{nbd})\text{Cl}]_2/\text{NEt}_3$ -route to around 10 min with this new protocol.



Scheme 2. New synthesis and polymerization leading to *L*- and *D*-valine-derived PA, noted PLA (**p2**) and PDA (*ent*-**p2**), respectively.

As stated in reference [19], the excess of **3** is used to compensate for moisture traces in the system, which is of particular importance if large monomer/initiator (M/I) ratios are used, as is the case here (M/I = 750 : 1). Moreover, the large amount of PPh_3 (here: $[\text{Rh}] : [\text{PPh}_3] = 1 : 3$) has proven to be beneficial to achieve small PDIs.^[19]

NMR spectroscopy

Details for the sample compositions and their preparation (fire-sealed tubes) are reported in the Supp. Info (SI).^[20] Deuterated and natural abundance level (NAD) samples were made of 8-9 mg and 40-41 mg of analyte, respectively; both with about 500 mg of freshly distilled non-deuterated chloroform (see SI). All ^2H - $\{^1\text{H}\}$ and NAD- $\{^1\text{H}\}$ 1D/2D NMR spectra were recorded on a 14.1 T Bruker (Avance II) NMR spectrometer equipped by a 5-mm ^2H selective cryogenic probe operating at 92.1 MHz. Such equipment allows the observation of the NAD quadrupolar doublet (QD) of chloroform (organic co-solvent) concomitantly with the ^2H signals of deuterated analytes as well as the anisotropic NAD NMR spectra of non-deuterated compounds even with small amounts of analyte. Obviously, all deuterated solutes can be recorded with any routine NMR spectrometer using standard probes equipped with a ^2H input (including the lock channel). ^{13}C - $\{^1\text{H}\}$ spectra were recorded on a 9.4 T Bruker (Avance III) NMR spectrometer equipped with a 5-mm QXO or TBI probe and operating at 100.1 MHz. WALTZ-16/64 CPD sequence has been used for proton decoupling (0.5 W). Specific experimental details are given in the figure captions or the SI. If not otherwise specified, the sample temperature was set to 295 K.

Results and discussion

Deuterium NMR of labelled chiral molecules

Compared to any order-dependent observable, ^2H -RQC is the most sensitive one to a local order difference of the C-D vector orientation ($S_{\text{CD}}^{R, \text{pro-}R} \neq S_{\text{CD}}^{S, \text{pro-}S}$) with respect to the B_0 axis. All relevant equations related to ^2H -RQCs are given in the SI.^[3] ^2H - $\{^1\text{H}\}$ NMR of molecules isotopically labelled on their stereogenic or prostereogenic center is a valuable, robust analytical tool for probing the magnitude of enantiotopic and enantiomeric discriminations at these positions. Thus, we have compared the results obtained with a series of labelled analytes using PLA and PBLG aligning media. For a visual support, the most illustrative ^2H NMR results are presented in **Figure 2** (compounds **2**, **4**, **8**), **Figure 4** (compounds **5**, **9**, **10**) and **Figure 5** (compounds **12** - **15**), but all the spectra recorded in PLA and PBLG together with their associated data are given in SI.

Due to the sensitivity of our ^2H cryogenic probe, we can simultaneously observe the ^2H quadrupolar doublets (^2H -QD) of deuterated analytes and of chloroform at natural abundance deuterium (NAD) level (relative abundance to ^1H : $1.5 \cdot 10^{-2}\%$) in both chiral phases. The signals marked by asterisks correspond to the NAD QD of chloroform. Values measured are $Dn_{\text{Q}}(\text{PLA}) \approx +85$ Hz and $Dn_{\text{Q}}(\text{PBLG}) \approx -870$ Hz (**Tables 10, 11, 12** and **Section II.5.2** in SI).^[21] This one-order magnitude variation of ^2H -RQCs indicates that CHCl_3 dynamics in oriented samples of PLA is much faster than in PBLG ones. In terms of molecular organization, it might suggest a smaller degree of packing of PLA helices as compared to PBLG possibly due to: i) the complex conformational dynamic of the chiral side chain in the former; ii) the larger 3D volume (corresponding to maximal conformational space) explored in PLA whose side

chain is chiral and much longer than the one of PBLG (**Scheme 1**). As a spectral consequence, broader linewidths (compared to PBLG), particularly on components of larger quadrupolar splittings (the “outer” ^2H -QD) of deuterated or NAD analytes are obtained. This effect, originating from “the disorder of order”, is observed frequently in aligned samples^[22] as it can be seen in PLA for analyte **2** (**Fig. 2a**) or **9** (**Fig. 4a**), but it does not alter the peak areas for each enantiomer, and hence does not distort the enantiomeric excess measurement.

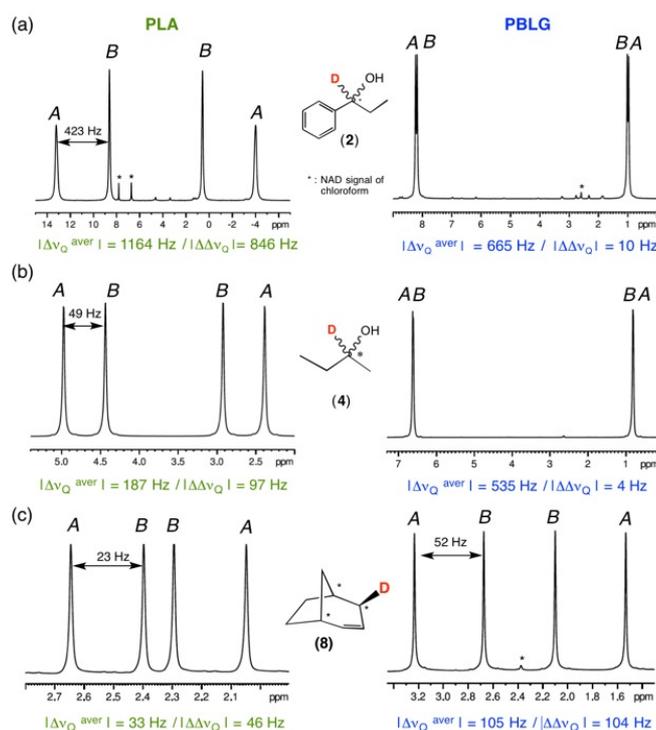


Figure 2. ^2H - $\{^1\text{H}\}$ 1D NMR spectra of (a) (\pm) -**(2)**, (b) (\pm) -**(4)** and (c) (\pm) -**(8)** oriented in PLA (left column) and PBLG (right column). Note the difference of peak intensity between the outer and inner QD of (\pm) -**(2)** due to larger linewidth for the former (“disorder of order”). See also **the SI.**

DOE parameter

A simple approach to evaluate and quantify the local enantiomeric or enantiotopic discrimination efficiency from the splitting of QDs measured in ^2H NMR spectra consists in calculating the local « Differential Ordering Effect » (DOE) parameter as the ratio of the difference of ^2H -RQCs over their average:^[23]

$$DOE = 2 * \left(\frac{||\Delta v_Q^{R, pro-R}| - |\Delta v_Q^{S, pro-S}||}{|\Delta v_Q^{R, pro-R}| + |\Delta v_Q^{S, pro-S}|} \right) \quad (1)$$

Thus the DOE varies between 0 (no discrimination) and 2 (maximum discrimination when one of both RQCs is zero), while $DOE = 1$ when $|\text{Dn}_Q^{\text{aver}}| = |\text{DDn}_Q|$. Quantitatively DOE variations can be used to evaluate and compare, for instance, the molecular dissymmetry (shape anisotropy) related to “asymmetric characteristics” of chiral molecules, for a given analogue family.

In a first step, we have examined six racemic deuterated secondary chiral alcohols of general structure, $R^1-C^*D(OH)-R^2$, (**1** to **6**). Such molecules are valuable models for evaluating the role of two kinds of factors that may be involved in the EDMs: i) the OH group able to establish hydrogen bonding (HB) with the ester group in PBLG and ester or amide groups in PLA. ii) the shape anisotropy of the analyte according to the explored volume and the nature (polarity) of R^1 and R^2 substituents attached to the stereogenic center.

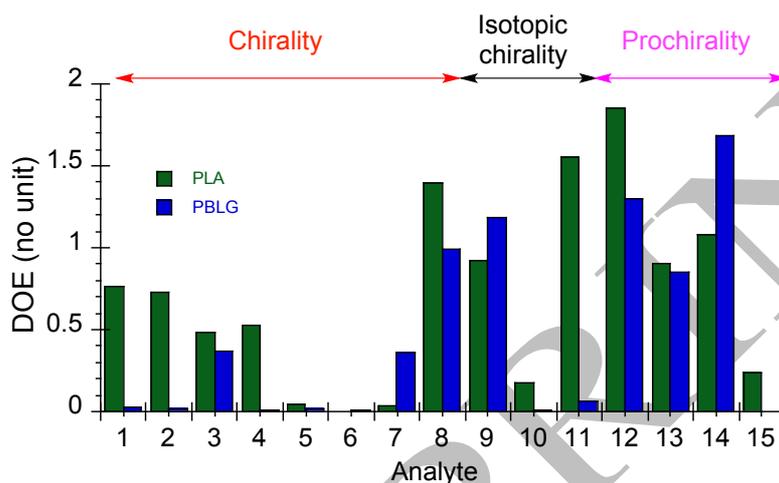


Figure 3. Variation of DOE values for deuterium-labeled analytes **1** to **15** in PLA (green bars) and PBLG (blue bars) phase.

Analysis of NMR spectra and DOE values (**Fig. 3**) indicates that the PLA system provides better 2H spectral discrimination for analytes **1** to **4**, as compared to PBLG, including 2-butanol- d_1 **4** (the simplest aliphatic chiral alcohol), facilitating the determinations of the enantiomeric excess (*ee*) by peak integration or deconvolution. Convincingly, not only for **4** (DOE \approx 0.52), a real benefit of using PLA instead of PBLG is also clearly visible with analyte **2** (DOE \approx 0.73), because for both examples, PBLG produces only poor or unexploitable discriminations. To explore the dependence of the DOE from weak molecular dissymmetry of R^1/R^2 , we investigated two chiral secondary alcohols where R^1 and R^2 are two flexible alkyl chains (C_{n+1} / C_n) with $n = 5$ (**5**) and 6 (**6**).^[23] As seen in **Figure 4**, a small enantioseparation has been obtained for **5** (DOE \approx 0.043) with PLA (see **SI**). No separation has been observed for **6**, even with strong gaussian apodization to establish the limits of shape recognition in PLA for ligands of the same nature (linear alkyl) and close volumes ($V(R^1)/V(R^2) \approx 1$). Similar results have been obtained in PBLG, although **6** shows a tiny difference (DOE \approx 0.008). In terms of shape recognition, we show here (for both polymers) that differences of the 3D volume explored by the alkyl chain is not large enough to produce a significant discrimination of the corresponding enantiomers when $n > 6$ (compared to **2** or even to **4**).

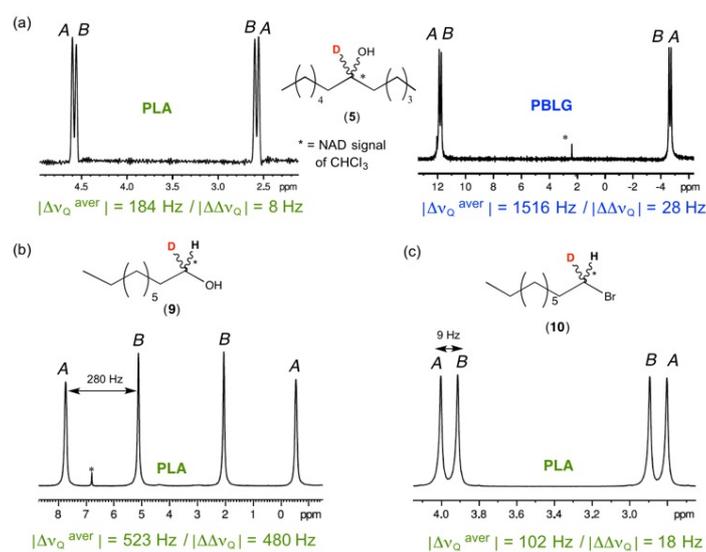


Figure 4. $^2\text{H}\{-^1\text{H}\}$ 1D NMR spectra (\pm)-**5** dissolved in PLA and PBLG (a) and (\pm)-**9** and (\pm)-**10** in PLA LLC (b).

Shape recognition mechanisms play an important role in the enantiodiscrimination phenomena.^[16,24] From a topological point of view, it appears that **5** and **6** are recognized as pseudo C_s -symmetric structures with the C-D vector residing in the plane of symmetry and not as C_1 -symmetric objects. In other words, the shape recognition mechanisms are not able to really differentiate the persistent volumes associated with the two ($\text{C}_6\text{H}_{13}/\text{C}_5\text{H}_{11}$ and $\text{C}_7\text{H}_{15}/\text{C}_6\text{H}_{13}$) alkyl substituents around the stereogenic center. Under this condition, the C-D internuclear direction appears to be in the pseudo plane of symmetry, thus leading to very small or even no spectral enantiodiscriminations. **Figure 5** depicts a schematic representation of the phenomenon.

Evaluating the potential of PLA to orient chiral compounds, other than secondary alcohols, we tested a semi-flexible aromatic halide, **7** (**Fig. SI-16**) within which the global geometry and the shape anisotropy of R^1/R^2 substituents (orthomethyl phenyl vs methyl) are quite close to those of analyte **1** (phenyl vs. methyl), and a weakly polar, bicyclic rigid compound, **8** (**Fig. 2c**). Although the enantiodiscrimination in PLA is still observed for **7**, the RQC difference (6 Hz) and DOE (0.034) are unexpectedly small compared to **1** (612 Hz, DOE = 0.76), and also compared to values in PBLG (146 Hz, DOE = 0.36). The replacement of the OH group by a Cl atom (weakly donor group for HB) in **7** induced an important change with a significant reduction of the enantiodiscrimination magnitude. This may indicate a certain significance of H-bonding capabilities of the analyte in the chiral recognition process. This suspicion is supported by the comparison of alcohol **9** and bromo alkane **10**, which are isotopically-chiral molecules (**Figs. 4b,c**, **SI-16** and **SI-17**). A plausible global explanation for this behaviour is as follows. When labile hydrogens are highly topologically accessible, HB is likely to bring

solutes close to the helical polymer, thus leading generally to an amplification of the degree of orientation of solute but also a better efficiency of shape-recognition processes (short-range intermolecular interaction).

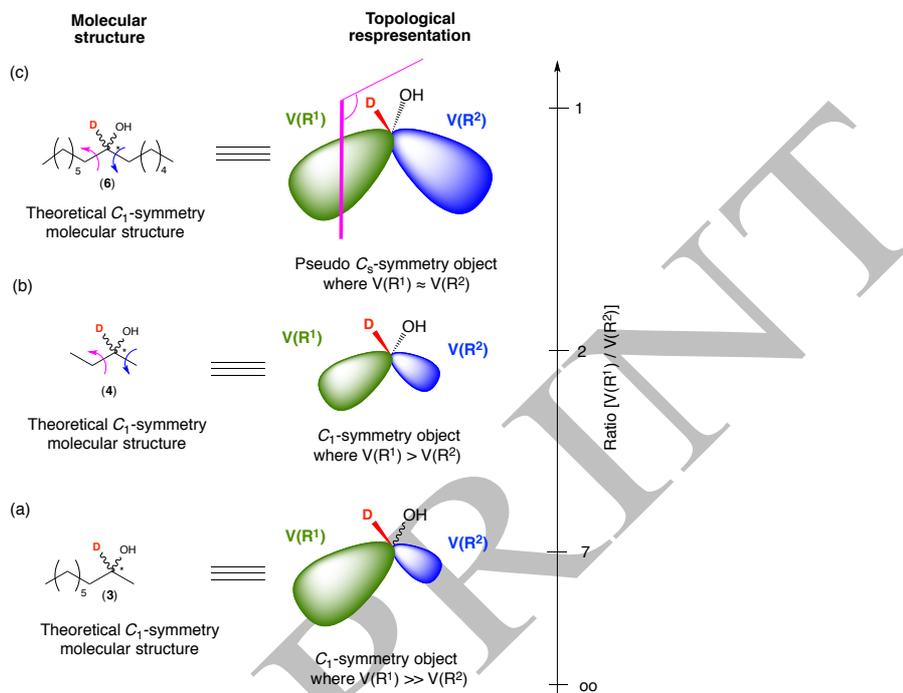


Figure 5. Examples of schematic representation of the variation of the 3D volume (corresponding to maximal conformational space) explored by the alkyl chains (R^1 and R^2) for (a) (\pm)-**(3)**, (b) (\pm)-**(4)** and (c) (\pm)-**(6)**.

A priori, such a situation promotes in turn better enantiodiscriminations.^[16] This effect can be increased when aryl, ethynyl or acyl groups in the analyte may promote further specific solute-helix attractive non-covalent interactions (as p-p stacking interaction) as in case of **1**, **2** or **12**.^[16] In the absence of strong and specific attractive interactions (HB), the degree of order is expected to be lower, but the molecular shape-based recognition phenomena can remain sufficiently active to generate visible enantiodifferentiations (as in case of **7**, **10** and **11**). The important ^2H discrimination in PLA detected for **8** (46 Hz, DOE = 1.39) results from both the rigidity and the strong shape anisotropy of the bicyclic structure. The comparison of the data from **10** and **11** in PLA with those obtained in PBLG also shows smaller quadrupolar splittings for both, but a much more pronounced enantiodiscrimination for PLA (**Fig. 3**).

Prochirality

Enantiotopicity in prochiral compounds is an important form of enantiomorphism where mirror-image internuclear directions (bonds or vectors) ($\text{H}\cdots\text{H}$, $\text{C}\cdots\text{H}$, $\text{C}\cdots\text{D}$, ...) in C_s , C_{2v} , D_{2d} and S_4 symmetry

molecules are not oriented the same in a chiral LC, and thereby can be spectrally discriminated by ^1H , ^2H or ^{13}C NMR.^[4] Analytes **12** and **13** are typical examples of prochiral structures of C_s symmetry where the C-D directions on the prostereogenic carbon are enantiotopic groups. Spectra are presented in **Fig. 6a/b** (see also **SI-19** to **SI-22**). From a phenomenological point of view, the discrimination of enantiotopic C-D directions in prochiral molecules and that of enantiomeric directions in their isotopically-chiral analogues are governed by the same mechanism.^[4,23]

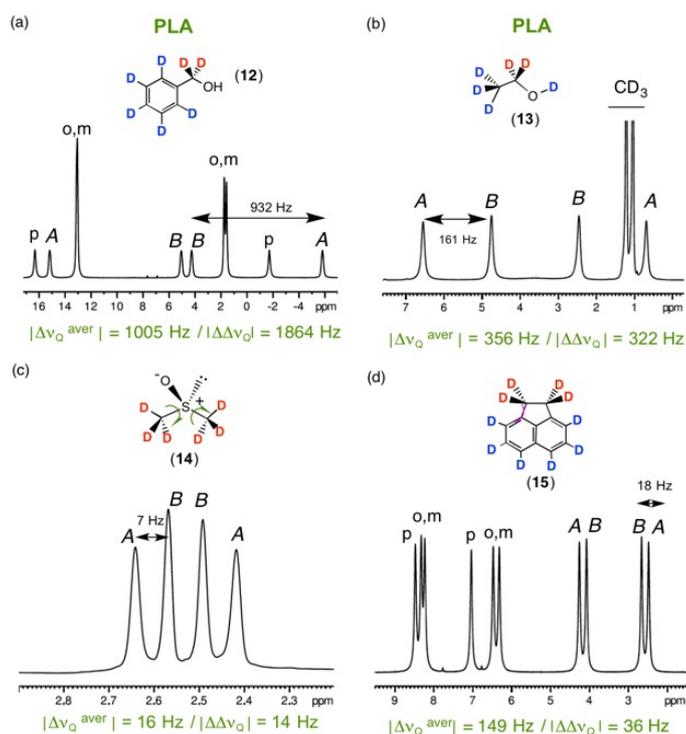


Figure 6. ^2H - $\{^1\text{H}\}$ 1D NMR spectra of (a) **12**, (b) **13**, (c) **14**, and (d) **15** all recorded in PLA system. As theoretically expected, the C-D directions (blue) contained in the plane of symmetry are not discriminated.

Given the fact that the enantiomers of the alcohols **2** and **4** are differentiated strongly, it was expected that benzyl alcohol- d_7 (**12**) and ethanol- d_5 (**13**) will show a strong degree of orientation and large differentiation magnitudes in PLA which was indeed the case. (1864 Hz / DOE = 1.85 and 322 Hz, DOE = 0.9; much higher than in PBLG). These results are consistent with arguments/explanations proposed above for analytes **1** to **4**. Sulfoxide- d_6 (**14**) and acenaphten- d_{10} (**15**) are two particular cases of prochiral molecules. The first one is of C_s symmetry where the S-O bond and the lone pair are contained in the symmetry plane, while the methyl groups are enantiotopic. The latter is a weakly apolar, C_{2v} symmetry rigid structure. As for **12** and **13**, the absence of HB does not prevent the enantiotopic discrimination that is observed in **14** (14 Hz / DOE = 1.14) and **15** (36 Hz / DOE = 0.24) in PLA (**Fig. 6c/d**). The small magnitude of methyl RQC in DMSO may result from the fast dynamic of DMSO in the LLC and the

averaging effect due to the free methyl rotation. In terms of EDM efficiency, comparison with PBLG shows contradictory results since the DOE of **14** is better in PBLG, while that of **15** is better in PLA. In all cases, magnetically-active homotopic elements that are contained in the plane of symmetry and locally exchangeable by a proper axis (aryl in **12** and methyl in **13**, or naphthyl moiety in **15**), are not spectrally discriminated as theoretically expected.

Mixture of unlike/like diastereomers

In another domain, the determination of enantiomeric and diastereomeric excesses (*ee* and *de*) in mixtures of dideuterated *unlike/like* (*u,l*) stereoisomers with two remote stereogenic centers of different configuration for each asymmetric carbon is known as an interesting analytical problem from the NMR viewpoint. As an example, we have therefore tested a mixture of statistical C_s / C_2 (*meso* / *threo*) deuterated diastereoisomers of *meta*-disubstituted aromatic diols (**16a/b**). The analysis of $^2\text{H}\{-^1\text{H}\}$ NMR results in PLA (see **Fig. SI-25**) shows four ^2H -QDs, thus indicating that both the spectral discrimination of enantiotopic directions in the *R,S-meso* form and the *R,R/S,S* enantiomers of the *threo* form occur, instead of only three QDs in PBLG with the same sample composition.^[25]

^2H 2D-NMR at natural abundance level

Anisotropic natural abundance deuterium (NAD) 2D-NMR is a powerful extension of ^2H 1D-NMR of deuterated molecules in (chiral) orienting media. This tool combines the advantages/sensitivity of discrimination on the ^2H -RQC difference basis, without the need for a partial or full isotopic enrichment with the simplicity of 2D analysis to assign all unequivalent monodeuterated isotopomers.^[3a,3c] In particular, when molecules possess CH_2 groups, it becomes possible to spectrally discriminate the NAD signals of enantio-isotopomers (associated with CH_2 enantiotopic directions of a prochiral molecule) as well as diastereo-isotopomers associated with CH_2 diastereotopic directions in chiral analytes.

Five chiral compounds with or without stereogenic center, from polar to apolar (**17** to **21**) and two aromatic prochiral ones (**22** and **23**) have been investigated using 40 mg of analyte each (20 mg of each enantiomer). NAD 2D-NMR spectra were recorded within a night with sample temperatures varying from 291-295 K. All NAD 2D-NMR spectra are given in the SI (**Figs. SI-27** to **SI-34**).

Two typical examples of phased 2D maps, the *Q*-COSY Fz experiment^[26] for (**19**) and *Q*-resolved Fz experiment^[26] for (**20**) recorded in PLA, are shown in **Figures 7** and **8**, respectively. Both NMR sequences belong to the class of NMR experiments named “Quadrupole Ordered Spectroscopy” (QUOSY) specifically designed to i) distribute the ^2H spectral information on 2D spectral dimensions (F_1 and F_2) and ii) (auto)correlate both components of each QD, corresponding to each inequivalent monodeuterated isotopomer. The difference between both types of experiments originates from the

refocusing of $d^{\text{aniso}}(^2\text{H})$ during the t_I indirect period leading to the elimination of ^2H chemical shifts in F_1 dimension (see **Fig. 8b**).^[3c,26] NAD 2D-NMR spectra were recorded within a night with sample temperatures varying from 291-295 K. All NAD NMR spectra are given in SI (**Figs. SI-27 to SI-34**).

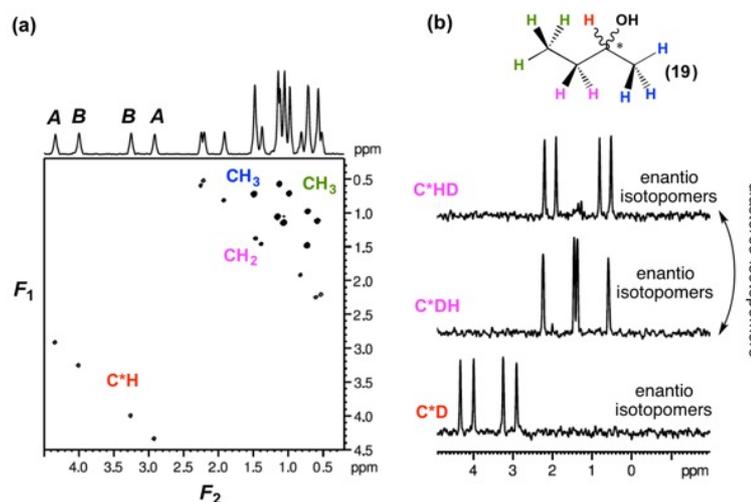


Figure 7. (a) NAD- $\{^1\text{H}\}$ Q -COSY Fz 2D NMR spectrum of (\pm) -**(19)** in PLA system 295 K. (b) Three NAD 1D-NMR subspectra associated with the methine and methylene groups. Note the spectral enantio-/diastereodiscrimination observed for each methylene group (4 QD).

As seen in **Figure 7**, all inequivalent monodeuterated enantioisotopomers (CH and CH_3 groups) and diastereoisotopomers (CH_2 group) of natural isotopomeric mixture for **19** are discriminated leading to twenty distinct QDs with spectral separations between components ($|\frac{1}{2}\text{DDn}_Q|$) varying between 12.5 to 75 Hz. Thus, the four QDs expected associated with the diastereotopic positions of the CH_2 group are clearly observed. Successfully, a spectral discrimination of all monodeuterated isotopomers has also been obtained for the semi-flexible and flexible chiral alcohols **18** and **19** (see **Fig. SI-28** and **SI-29**).

The analysis of NAD 2D spectra of **17** shows that the QD associated to the stereogenic center and *para*-aromatic position (see **Fig. SI-27**) does not clearly emerge from noise, due to a line broadening associated with larger splittings (see **Fig. SI-10a**),^[22] possibly combined to a low (H/D) isotopic ratio for those sites.^[6e] In contrast, the spectral discrimination is clearly observed for the methyl site where three equivalent isotopomers do contribute to the NAD signal intensity. A similar situation exists for **21**, a C_2 -symmetry binaphthyl atropisomer, where only the NAD QDs of the equivalent methyl groups (with three equivalent ^2H sites) are observed with sufficient S/N ratios (**Fig. SI-32**).

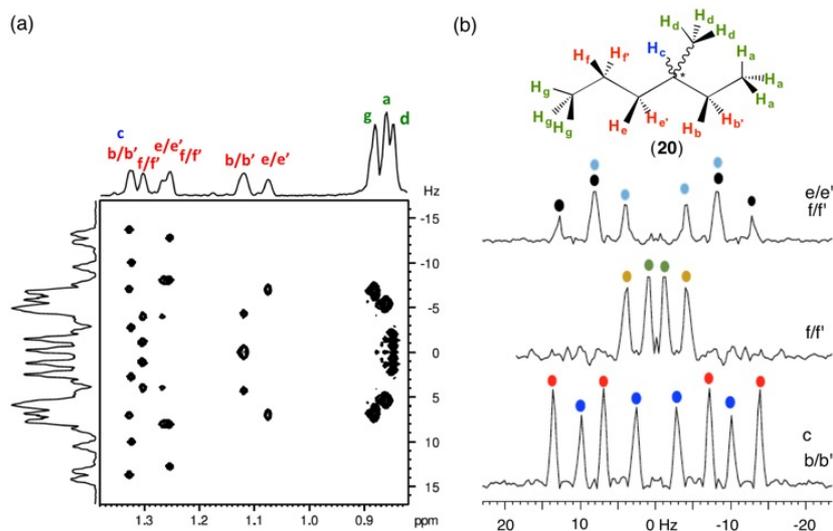


Figure 8. (a) Tilted and symmetrized NAD- $\{^1\text{H}\}$ Q -resolved Fz 2D spectrum of (\pm) -**(20)** in PLA (291 K). (b) Three examples of NAD 1D subspectra (sum of columns) extracted from the 2D map. Isotropic NAD- $\{^1\text{H}\}$ 1D spectrum (\pm) -**(20)** is shown in SI.

As theoretically expected, only the monodeuterated enantio-isotopomers associated with enantiotopic positions of CH_2 groups in prochiral aromatic compounds **22** and **23** show an enantiodiscrimination (2 and 4 QDs), since all aromatic monodeuterated isotopomers are achiral (**Figs. SI-33** and **SI-34**). Note that the magnitude of ^2H -RQCs measured for **22** are very similar to those measured on the perdeuterated prochiral compound **12**, confirming that orientations of a prochiral molecule and the isotopically-chiral analogues are mainly identical.^[4]

One of the most remarkable NAD performance in PLA was obtained with the 3-methylhexane (**20**), an apolar flexible alkane, whose enantiomeric discrimination poses a difficult analytical challenge, as for almost all apolar chiral hydrocarbons (**Fig. 7**).^[27] Moreover, in **20** the substituents attached to the CH-group differ by only one carbon each. A first noticeable result has been reported in PBLG/ CHCl_3 in 2000,^[27a] but the number of discriminated sites were few (only two, at e and f) and the enantioseparations were very small (a few Hz). In PLA, seventeen QDs (out of the 20 expected if all sites were discriminated) are observed, and unexpected large differences of RQCs (up to 13 Hz, DOE = 1.0) have been measured (**Fig. 7** and **SI-31**). These first NAD NMR results in PLA aligning media open promising prospects in terms of analytical applications, especially for saturated hydrocarbons which are difficult to crystallize and derivatize,^[27b] but also generally in the domain of the structural elucidation of small organic chiral molecules based on ^2H -RQC measurements,^[6d,28] instead of $(^{13}\text{C}-^1\text{H})$ -RDC^[29] or ^{13}C -RCSA.^[30]

Enantiodifferentiation using $^{13}\text{C}-\{^1\text{H}\}$ NMR

An alternative to ^2H NMR in chiral LLCs for determining the enantiomeric excess (ee) consists in

discriminating enantiomeric signals through a difference of ^{13}C -RCSA $^{R/S}$ (see **SI**). In practice, when the discrimination occurs for a given ^{13}C site, a doubling of ^{13}C resonances (one for each enantiomer) separated by DDs is expected to be observed (**Fig. SI-4**). Two illustrative examples of such a discrimination observed in PLA at 100.4 MHz (9.4 T) on the sp^2 carbon atoms of **17** and sp carbons of **18** are presented in **Figure 9** (see also **Figs. SI-35 to SI-37**).

For such carbons, spectral separations between the resonances of the respective enantiomers vary from 9 (0.09 ppm) to 33 Hz (0.33 ppm), while differences for sp^3 hybridized carbons are smaller (from 2 to 8 Hz), due to their lower electronic shielding anisotropy.^[3a,3b] In both cases, the values of $\text{Dd}^{R/S}(^{13}\text{C})$ measured in PLA are higher than the values obtained in PBLG (**Fig. SI-35c**).^[3b] Unlike ^2H -RQC, ^{13}C -RCSA is B_0 dependent (see **Eq. SI-2** and **SI-4**), and therefore larger differences between ^{13}C resonances facilitating peak integration, are expected when recording spectra at higher B_0 fields. Another solution may consist in working with a higher weight ratio of PLA.

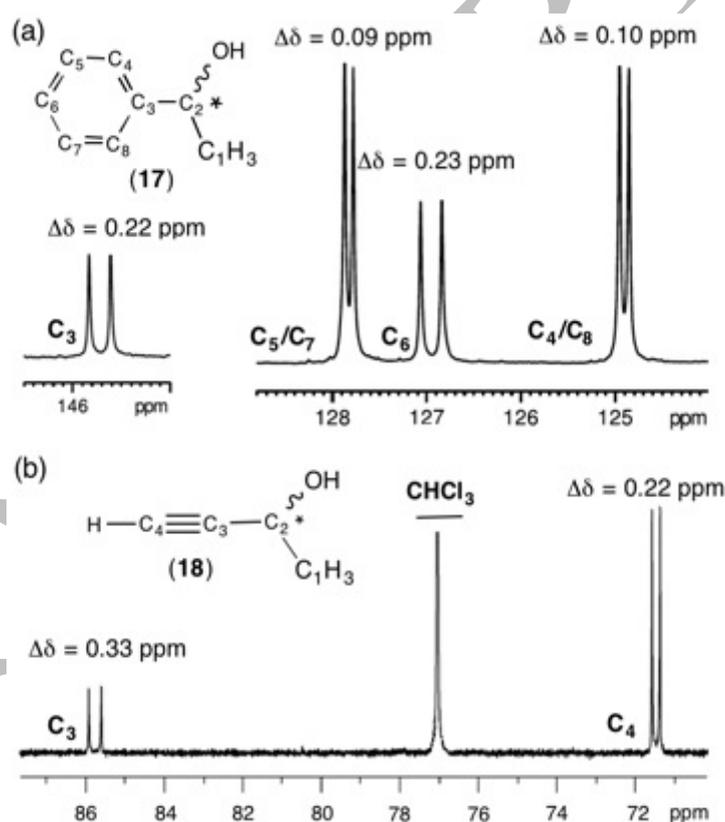


Figure 9. Two examples of ^{13}C - $\{^1\text{H}\}$ 1D-NMR enantiodiscrimination observed at 9.4 T for (a) (\pm)-**17** and (b) (\pm)-**19** and recorded in PLA at 300 K. Note the large difference of ^{13}C -RCSA.

Thus for **17**, a $\approx 30\%$ increase of $\text{Dd}^{R/S}(^{13}\text{C})$ for all ^{13}C sites has been obtained just by increasing the concentration of PLA from 19 to 22% w/w (**Fig. SI-35b**). Finally, note that some (more or less sharp) residual ^{13}C signals of the polymer (in the 10-30 ppm region) are visible in the ^{13}C - $\{^1\text{H}\}$ spectra in PLA,

originating from the terminal alkyl part of side chain where carbons are conformationally very mobile (**Fig. SI-37a**). In PBLG, residual ^{13}C signals associated with carbons of the benzyl group are located in the aromatic region (130-135 ppm) but appear spectrally less cumbersome (two broad lines) due to lower mobility (**Fig. SI-37b**). Depending on their respective spectral ^{13}C specificities, the choice of the best polymer to use in order to minimize interference with the analyte must be made in accordance with the nature/type of the latter. From a methodological viewpoint, the use of a T_2 filter incorporated as a building block to get rid of the polymer signals could be applied.^[31]

Mixtures of polymers

Two kinds of aligned mixtures of helically chiral polymers can be considered for some practical analytical purposes. A racemic mixture of enantiomeric polymers PA (PLA/PDA) similarly to PBG (PBLG/PBDG) or PCBL (PCBLL/PCBDL) (**I**)^[25] and a mixture of two chemically different polymers but built from homochiral repeating units each (**II**).^[5f,32] The first type of mixtures should lead to an achiral compensated mixture where EDMs are inactive on average, and therefore no spectral enantiodiscriminations should be observable. Such media can be useful for an unambiguous assignment of QDs originating from enantio- and diastereoisotopomers. The second type of mixture should allow a modulation of the orientation and enantiodiscrimination phenomena (enantiomers or enantiotopic elements) dependent on the molar fraction of the two polymers as in the case of “PBLG/PCBLL” mixtures explored in 2008.^[5f] In order to prove these hypotheses, we prepared two polymer mixtures. Mixture **I** consisted of a 50:50 (racemic) mixture of PLA and PDA (DPI = 1000 each) and mixture **II** was a 50:50 mixture of PLA (DP = 750) and PBLG (DPI = 743). Both mixtures were prepared in CDCl_3 as co-solvent ($w/w_{\text{Poly}} = 18.8\%$) with DPs as close as possible, namely DP = 1000 for PLA and PDA for mixture **I**, and DP = 750 and 743 for mixture **II**.

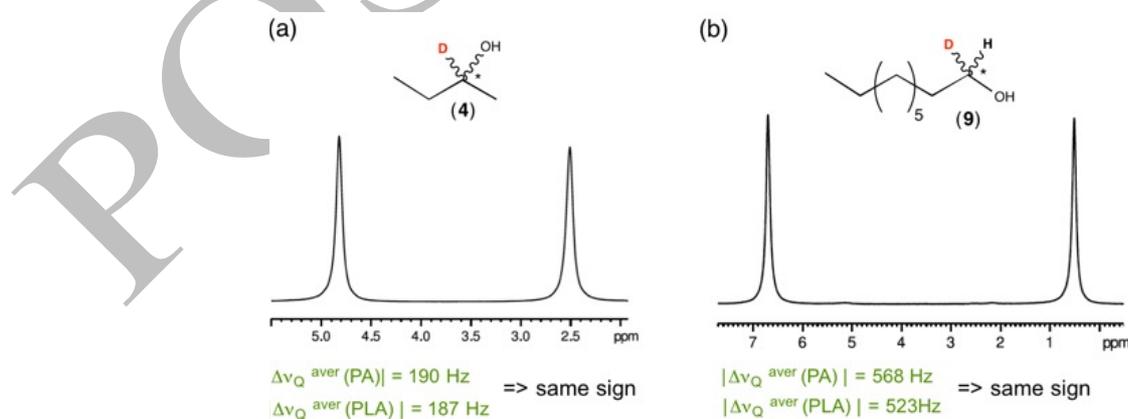


Figure 10. $^2\text{H}\{-^1\text{H}\}$ 1D-NMR spectrum of (a) (\pm)-(4) and (b) (\pm)-(9) in the racemic mixture of PLA/PDA polymer in CHCl_3 (DP (PLA/PDA) = 1000 / 1000). Note the absence of enantiodiscrimination (see **SI**).

As expected, the compensated PA mixture **I** leads to a homogenous, uniformly aligned achiral (monophasic) medium where high-resolution spectra are obtained and no enantiodifferentiation occurs (as in PBG) as seen for analytes **4**, **9** and **13** (see **Figs. 9** and **SI-38**). Such spectra demonstrate that the analyte experiences fast exchange towards PLA and PDA helices, similar to that obtained in the “PBG” or “PCBL” oriented achiral systems. As already reported, the magnitude of ^2H -RQC measured in PA corresponds to the algebraic average of the ones measured for two enantiomers (Dn_Q^R and Dn_Q^S) and enantiotopic directions ($\text{Dn}_Q^{\text{pro-R}}$ and $\text{Dn}_Q^{\text{pro-S}}$) measured in PLA.^[25a] Thus RQCs have the same sign for **4** and **9**, and opposite sign for **13**.

The orientational behaviour of the polypeptide/polyacetylene mixture **II** is very interesting and differs significantly from the PA achiral system. Indeed, the ^2H spectrum of **4** recorded in the 50% (w/w) PLA/PBLG mixture (**II**) corresponds to the sum of ^2H spectra measured separately in PLA and PBLG (see **Fig. 11**) Moreover, in the ^1H -spectrum two separate signals for the solvent as well as the corresponding ^{13}C -satellites can be observed (see **Fig. SI-40**). These observations indicate: i) the coexistence of two homogeneous chiral aligned systems, while no macroscopically phase demixing is observed visually or under polarizer after homogenization of the sample by centrifugation; ii) no fast-exchange conditions exist in this specific bipolymeric system. By increasing the sample temperature (295 to 315 K) a reduction of the quadrupolar splittings of **4** in both phases is observed until the PLA domains become isotropic above 305 K (see **Fig. SI-41**). At this temperature, three phases (two anisotropic and one isotropic one) coexist simultaneously in the sample. Above 310 K, the PLA anisotropic phase has totally disappeared. A fully isotropic sample will be accessible at higher T. However to avoid endangering of the cryogenic probe, we did not increase the temperature over 320 K and therefore no completely isotropic state was reached. It is worth mentioning, that these temperature-induced changes of the system are fully reversible.

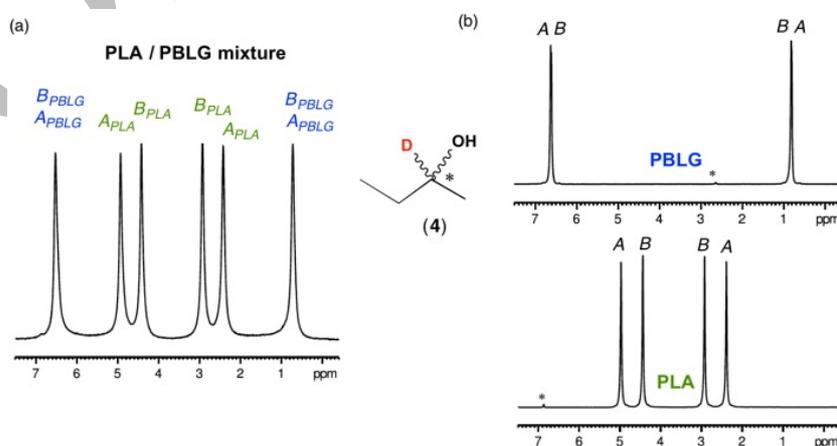


Figure 11. ^2H - $\{^1\text{H}\}$ 1D-NMR spectrum of (\pm)-**(4)** in the 50/50 mixture PLA / PBLG in CHCl_3 (DP = 750 / DP = 743) at 295 K. (b) Comparison with the ^2H - $\{^1\text{H}\}$ 1D spectrum of (\pm)-**(4)** obtained in the monopolymeric phase

PLA (bottom) and PBLG (top).

Currently these preliminary results suggest that the very large chemical difference in the helix backbone and the side chain between the two polymers leads to microphase separation, not compatible to produce a monodomain phase. Under this condition, we observe a coexistence of separated phases of the polymers combined with a diffusion of the analytes slow enough on the timescale of the NMR-relevant interactions between the respective polymer domains.

No doubt, that further NMR experiments are required to investigate and understand the properties of this mixture.

An interesting opportunity of this unexpected orientational property of PLA/PBLG mixtures may be the possibility to determine simultaneously two alignment tensors for a given solute in a single sample. Given the fact, that complex stereochemical and structural problems often require the analysis of multi-alignment data sets, this beneficial behavior of the polymer mixture could be of great practical value.^[9, 10, 29]

Conclusions

The evaluation of the practical and analytical potential of a new chiral alignment medium, such as PLA, to establish its usefulness in anisotropic NMR spectroscopy (alternative or complementary) compared to existing systems is an essential step for its promotion towards chemists. Notably, the present results reveal that PLA like PBLG can be used as an enantiodiscriminating medium for successfully probing all types of enantiomorphism, through differences of ^2H -RQC and ^{13}C -RCSA.

For most compounds studied, the enantiomer differentiating capability of PLA is more pronounced than the one of PBLG. This is especially true for secondary alcohols and some weakly polar solutes such as 3-methylhexane, a very challenging molecule. Nevertheless, although the EDMs in PLA and PBLG share some common characteristics, the arrays of interactions between a given analyte, and the chemically very different PLA and PBLG side chains (steric factor, electronic profile, positioning of functional groups relative to the α -helix), can induce very highly versatile orientational and discrimination “responses” to electrostatic contributions, to shape anisotropy and conformational behaviour. De facto, the subtle molecular balances between all molecular factors involved makes it difficult to simply establish an “overall” superiority of one system over the other. This comparative study seems to indicate that the two LLCs must be primarily considered as complementary and versatile systems for the discrimination of all aspects of enantiomorphism.

This current contribution represents the first one of a series of analytical studies using PLA and associated derivatives as promising chiral aligning media in various chemistry-related application areas.

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