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Polyisocyanides As a New Alignment Medium To Measure Residual Dipolar Couplings for Small Organic Molecules

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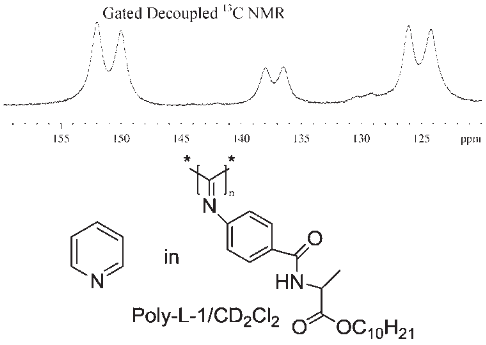
ABSTRACT



Polyisocycanides were found to give anisotropic molecular alignment in the magnetic field and are useful to measure residual dipolar couplings (RDCs) from analytes, e.g. strychnine. They show less quadrupolar splitting of the deuterated solvent signal compared with other liquid crystal systems such as Poly-γ-benzyl-L-glutamate (PBLG) and hence less undesired line broadening.

Residual dipolar couplings (RDCs) are an important parameter in organic structure determination.[1a] These RDCs are useful in configuration, conformation and constitutional analysis of molecules and support or even replace NOE information due to their r^{-3} dependence.[1b] RDCs can be observed by NMR when molecules are anisotropically oriented in a solution. For high resolution structure calculation the degree of anisotropy should be small.[2]

Liquid crystals,[3] bicelles,[4] micelles,[5−7] bacteria phages,[8,9] and paramagnetic lanthanide tags[10,11] have been developed as anisotropic media to enhance the magnetic orientation of biomolecules, but these methods are not well suited for small organic molecules due to the requirement of water as a solvent.

For water insoluble organic molecules, stretched polymer gels[12] and liquid crystals such as Poly-γ-benzyl-L/D-glutamate (PBLG/PBDG),[13−15] or Poly-γ-ethyl-L/

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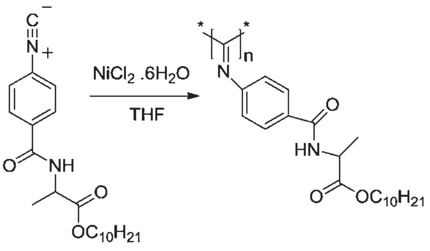
D-glutamate (PELG/PEDG),[16] have been used as alignment media. Extraction of RDCs in these liquid crystal alignment media happens to be complicated, due to the relatively large degree of orientation in these media and since the systems become unaligned below a certain LC concentration. Helically chiral nonracemic polymers are capable of foming lyotropic LC phases. These one-handed polymers such as polyisocyanates,[17] polyacetylenes,[18] polyisocyanides,[19] and polyguanidines[20] have potential applications in enantiomer separations, chirality sensing, and asymmetric catalysis. Polyguanidines have been used as chiral orienting media for organic molecules by the group of Reggelin et al.[21] They show well separated enantiomers, but the degree of orientation is too large.

After considerable unsuccessful work with low molecular weight organogelators (LMOG) we expected that polyisocyanides[19] will give a suitable degree of orientation and can separate enantiomers. Because of its chirality, and because of the side chain being similar to LMOG's, we chose helical poly(phenylisocyanide) Poly-L-1 as an orienting medium for organic molecules and report here on our initial findings.

The polyisocyanide investigated here, Poly-L-1, is known to form liquid crystalline phases in concentrated chloroform solutions due to their main chain stiffness. Synthesis of Poly-L-1 was achieved according to the literature.[19] The polymer Poly-L-1 was obtained by polymerization of the monomer with $NiCl_2 \cdot 6H_2O$ as a catalyst. (Scheme 1).

Scheme 1. Final Step in the Synthesis of Poly-L-1



Poly-L-1

We determined the number average molecular weight M_n to be 185k Da, the weight average molecular weight M_w to be 265k Da, and a polydispersity index of 1.43 through GPC. We found that Poly-L-1 exhibits a liquid crystalline phase at a critical concentration of 17.9% w/w in $CDCl_3$ (monitored by observation of concentration dependent ^2H spectra) with a quadrupolar splitting of the deuterium solvent $CDCl_3$ signal of 272 Hz (Figure 1).

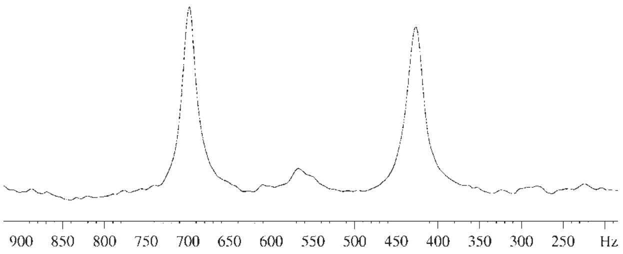


Figure 1. Quadrupolar deuterium splitting of $CDCl_3$ in the presence of 17.9% Poly-L-1.

We also found that Poly-L-1 exhibits liquid crystalline phases in tetrahydrofuran (THF) and CD_2Cl_2 solutions at a concentration of 17.9% w/w with a quadrupolar splitting of the solvent signal of 99 Hz for THF and 106 Hz for CD_2Cl_2. We first measured RDCs in these two liquid crystalline phases for the pyridine molecule. The observed RDCs (Table 1) and ^{13}C-gated decoupled NMR spectra for pyridine (Figure 2) for the liquid crystalline system in CD_2Cl_2 are presented below.

We then selected strychnine as an analyte to study the alignment properties of Poly-L-1 in $CDCl_3$ and to compare the results with our previous work with PBLG.[13]

For these experiments 170 mg of Poly-L-1, 50 mg of strychnine, and 950 mg of $CDCl_3$ were weighed into an NMR tube.

Table 1. ^{13}C Chemicals Shifts, $^1J_{CH}$ Spin Coupling Constants, Total Spin Coupling Constants T_{CH}, and RDC Values D_{CH} in Pyridine

carbon no.	δ_c	J_{CH} (Hz)	T_{CH} (Hz)	D_{CH} (Hz)
2/6	149.9	177.2	199.3	11.1
4	135.8	162.1	152.6	−4.8
3/5	123.7	162.8	185.5	11.3

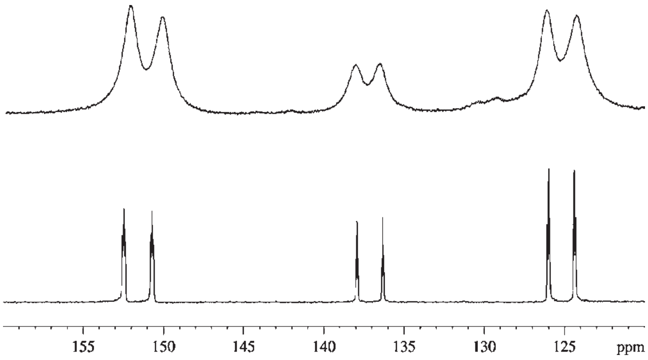


Figure 2. Gated decoupled ^{13}C NMR spectra of pyridine in CD_2Cl_2 (bottom) and CD_2Cl_2/Poly-L-1 (top).

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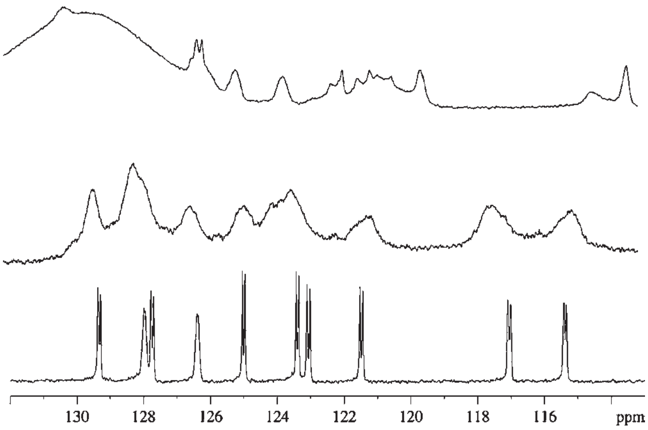

Figure 3. Gated decoupled ^{13}C NMR spectra in the aromatic/olefinic region of strychnine in $CDCl_3$ (bottom), in $CDCl_3$/Poly-L-1 (middle) and in $CDCl_3$/PBLG (top).

Table 2. ^{13}C Chemicals Shifts, $^1J_{CH}$ Spin Coupling Constants, Total Spin Coupling Constants T_{CH}, and RDC Values D_{CH} in Strychnine in $CDCl_3$/Poly-L-1

carbon no.	δ_c	J_{CH} (Hz)	T_{CH} (Hz)	D_{CH} (Hz)
1	122.3	159	229.0	35.0
2	124.2	160.9	159.6	−0.5
3	128.6	159.6	122.8	−18.4
4	116.2	168	247	39.5
8	60.1	145.4	134	−5.7
11α	42.5	126.3	137.3	5.5
11*β*		135.9	157.3	10.7
16	60.3	146.2	133.4	−6.4
17α	42.9	133.4	132.4	−0.5
18α	50.4	136.8	85.25	−25.8
23α	64.6	144.3	105.5	−19.4
23*β*		137.2	109.9	−13.7

This sample mixture was allowed to equilibrate overnight with no further preparation efforts such as intensive shaking or centrifugation compared to PBLG mixtures. RDCs were calculated from the difference of isotropic and anisotropic ^{13}C gated decoupled NMR spectra for strychnine (Figure 3).

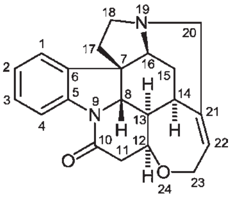

Figure 4. Molecular formula of strychnine.

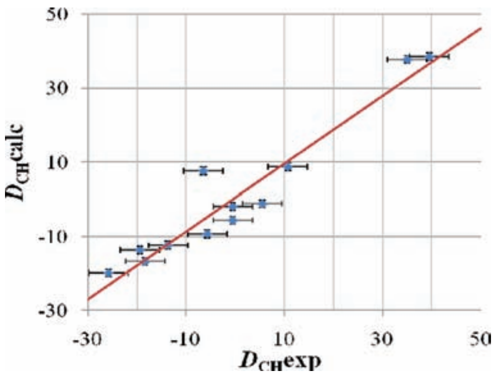

Figure 5. Plot of calculated vs experimental RDC values for strychnine in $CDCl_3$/Poly-L-1.

We observed 12 RDCs (Table 2) for the strychnine molecule in the Poly-L-1/$CDCl_3$ liquid crystal system. These RDCs were back calculated by using the program package PALES,[22] which uses the mathematical concept of singular value decomposition (SVD) to determine the alignment tensor from a given structure. A crystal structure of strychnine (Figure 4) was used as an input structure. The back calculated RDCs D_{Calc} and experimental D_{CH} are shown in Figure 5. There is a good agreement between calculated and observed RDCs, with a small deviation at C-16, which may be due to its position in the aliphatic region in the presence of the hydrogen-containing side chain of Poly-L-1.

In summary, we have presented a member of a new class of alignment medium for organic molecules based on helically chiral polyisocyanides. It is useful for not only molecules which are soluble in chloroform but also molecules which are soluble in THF or CD_2Cl_2. The deuterium quadrupolar splitting for this Poly-L-1 liquid crystal system is nearly 272 Hz for chloroform and 99 and 106 Hz for THF and CD_2Cl_2 respectively at a 61.4 MHz ^2H NMR frequency. For PBLG (poly-γ-benzyl-L-glutamate) the deuterium quadrupolar splitting was 423 Hz on the same spectrometer in $CDCl_3$.[13]

Polyisocyanides therefore show a smaller degree of alignment, when compared to PBLG. They may be of potentially better use if we succeed in deuterating the aliphatic side chain of Poly-L-1 to get good resolution in the aliphatic region of the NMR spectra. We also will focus on the use of this alignment medium to discriminate enantiomers.

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Supporting Information Available. Experimental procedure and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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