Enantiomeric Analysis in a Polypeptide Lyotropic Liquid Crystal by Deuterium NMR

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Abstract: A new method for enantiomeric analysis through the measurements of nuclear magnetic resonance in a lyotropic chiral liquid crystal is presented. Under favourable circumstances proton NMR can be used; however, deuterium NMR is in general more convenient for this purpose. Partly deuterated chiral molecules dissolved in liquid-crystalline solutions of poly-γ-benzyl-L-glutamate (PBLG) in methylene chloride, or other organic solvents, exhibit different deuterium NMR spectra for each enantiomer. This phenomenon is caused by the fact that the enantiomers interact with the chiral centers of the PBLG helix and consequently each of them orients differently in this medium (a differential ordering effect). We show that our technique is convenient in use and very general in application. A detailed analysis is given for one particular molecule, and other results are presented and discussed according to the functional groups present in the molecules.

Introduction

The recent evolution of asymmetric synthesis has led to an increasing demand for accurate, reliable, and convenient methods of measuring enantiomeric excesses. It is therefore important to develop new and improved analytical techniques for this purpose and to understand the mechanism through which they operate. Amongst the techniques used for this purpose, nuclear magnetic resonance (NMR) occupies an important position. Several methods for enantiomeric analysis using the NMR technique have been reviewed recently by Parker.[1] In general these methods are based on the association of chiral compounds with chiral reagents, producing new species which exhibit different NMR spectra for each enantiomer. These species may be diastereoisomers formed through chemical binding with an enantiopure compound or molecular complexes formed with lanthanide chiral shift reagents or chiral solvating agents. Severe limitations of these methods have been described in the literature[1] such as partial racemization during the reaction with a derivatizing agent or the need for specific complexing agents for each class of compound. Furthermore, these techniques often fail in observing cases of small chirality such as isotopic enantiomers.

A different approach to enantiomeric analysis by NMR has been recently suggested by Courtieu *et al.*[2-4] This method is based on the measurements of NMR spectra of chiral molecules dissolved in a binary mixture of nematic and cholesteric thermotropic liquid crystals. The *R* and *S* species have different ordering properties in these solvents which implies that their spectra are different. The main disadvantages of this procedure are as follows: (a) The need for very carefully prepared mixtures in order to obtain well resolved spectra. (b) The liquid-crystalline mixtures which are used are rather poor solvents. (c) The very narrow temperature range at which these spectra are well resolved. Also, it is not known how general the method is, meaning whether it functions well for most classes of compounds. A similar approach has been suggested by Tracey and Radley[5] who obtained a differential ordering effect for some amino acids in amphiphilic cholesteric liquid crystals which contain a chiral polar head group.

In this paper we describe in detail a new method of enantiomeric analysis through NMR which is both simple and convenient and performs very well for many compounds possessing diverse functional groups. It consists of using chiral lyotropic liquid crystals obtained by the dissolution of poly-γ-benzyl-L-glutamate (PBLG) in various organic solvents. Preliminary description of the technique and some of its applications have been reported previously.[6-8] The application of this technique to the NMR observation of isotopic enantiomers has been recently published.[9] In the present communication, only classical chiral molecules are addressed. In the first part of this paper the study of a model molecule is described in detail to show the main NMR spectral characteristics of the differential ordering effect of enantiomers. In the second part we will demonstrate the power, the simplicity, and the generality of our technique through the presentation of a large collection of examples, many of them known to be difficult to solve with other NMR techniques. We believe that our procedure will prove to become quite useful for the enantiomeric analysis of most chiral materials.

Background

Solutions of poly-γ-benzyl-L-glutamate (PBLG), in various organic solvents, are known to produce lyotropic cholesteric liquid crystals.[10] In this report methylene chloride is used almost

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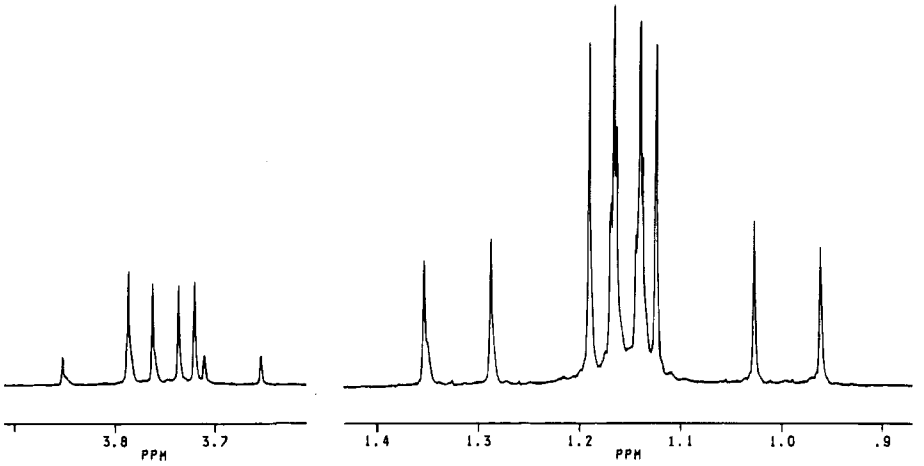

Figure 1. 400 MHz ^{1}H NMR spectrum of racemic $CH_3CHBrCOOH$ in the PBLG/CD_2Cl_2 liquid–crystalline solvent at 298 K. Note that it appears as two different superimposed AX_3 spectra (A parts on the left and X_3 parts is on the right).

exclusively as solvent, but several other solvents were found to perform as well. When submitted to a strong NMR magnetic field, B_o, the cholesteric pitch unwinds, and the solutions behave like a chiral nematic phase with the director aligned parallel to B_o.

The polypeptide chains exist in a helical conformation similarly to natural biopolymers such as DNA or polysaccharides. The side chains, which branch from the main helix, form a secondary molecular helical structure. The pitch of the rigid backbone is that of the α helical conformation, while the pitch of the secondary helix varies in a complex manner as a function of the solvent and the temperature.[11–14]

In isotropic solutions the anisotropy of the electronic shielding (chemical shift anisotropy), the dipolar and the quadrupolar interactions, of the different nuclei in the molecule, average to zero due to rapid isotropic molecular tumbling. Consequently the shifts or the splittings which arise in the NMR spectra due to these interactions cannot be observed. On the other hand, solute molecules embedded in any liquid–crystalline system are partly ordered, and consequently their NMR spectra exhibit all anisotropic interactions, i.e., the anisotropy of the chemical shifts, the dipolar couplings, and quadrupolar splittings for spins larger than 1/2. The measure of these interactions is related to the degree of order of the solute molecule in the liquid–crystalline medium.[15] Our method of chiral analysis is based on the fact that the *R* and *S* enantiomers orient differently when dissolved in the PBLG/organic solvent liquid crystals, which implies that the chemical shift anisotropies, the dipolar interactions, or the quadrupolar interactions are different for each of them. The change in orientation between the *R* and *S* enantiomers reflect the variance in their interactions with the chiral polymer. We therefore observe different NMR spectra for the *R* and *S* enantiomers when dissolved in this solvent.

To illustrate the differential ordering effect we present an example using *proton* NMR, for a racemic mixture of 2-bromopropanoic acid. The 400 MHz spectrum of this compound in PBLG/CD_2Cl_2 is shown in Figure 1. It consists of two different AX_3 first order spectra, one for each enantiomer. The A part is a 1:3:3:1 quartet with a $(2D_{AX} + J_{AX})$ splitting, and the X_3 part is a 1:2:1 dipolar triplet $(3D_{XX})$, doubled by the couplings to A. The chemical shifts of each AX_3 are slightly different. The *R* and *S* molecules have differences in their order which modifies the proton chemical shift through

$$\nu^{R \text{ or } S} = \hbar\gamma B_o\left[1 - \frac{1}{3}(\sigma_{aa} + \sigma_{bb} + \sigma_{cc}) - \frac{2}{3}\sum_{\alpha\beta}^{c}\sigma_{\alpha\beta}S^{R \text{ or } S}_{\alpha\beta}\right] \quad (1)$$

where the $\sigma_{\alpha\beta}$ are the elements of the shielding tensor, and $S^R_{\alpha\beta}$ and $S^S_{\alpha\beta}$ are the order parameters of the *R* and *S* enantiomers, respectively.

The dipolar couplings D_{HH} for each spectrum are appreciably different since the proton dipolar couplings are much larger than the ^{1}H chemical shift anisotropies. The relationship between the dipolar interactions and the ordering is given by

$$D^{R \text{ or } S}_{ij} = \frac{-h\gamma_i\gamma_j}{4\pi^2 r_{ij}^3}S^{R \text{ or } S}_{ij} \quad (2)$$

where r_{ij} are the interproton distances and S^R_{ij} and S^S_{ij} are the order parameters in the ij direction for each enantiomer. The NMR parameters derived from the spectrum shown in Figure 1 are as follows:

	one enantiomer	other enantiomer
δ_{Me} (ppm)	1.157	1.153
δ_H (ppm)	3.754	3.750
$(2D + J)_{Me-H}$ (Hz)	26.4	10.4
$3D_{Me}$ (Hz)	65.4	1.0

It should be noted that since the chemical shifts (but *not* the dipolar interactions) depend upon the magnetic field B_o, the use of high field proton NMR is advantageous. Also, at low fields, proton spectra may become second order which will considerably complicate their interpretation.

Proton spectra of ordered molecules become extremely complex when the number of nuclei becomes larger, and interference may also be caused from the background resonances due to the solvent. The use of proton decoupled ^{2}H NMR of deuterium labeled chiral compounds provides a much more powerful tool for our purpose since the spectra are much simpler. This is schematically presented in Figure 2. The need for deuterium labeling might be considered as an inconvenience and a disadvantage to the method. Still, deuteration procedures are well-known, numerous, and relatively easy to apply, especially, as will be demonstrated later, when the particular site chosen for deuteration is not important for a successful analysis.

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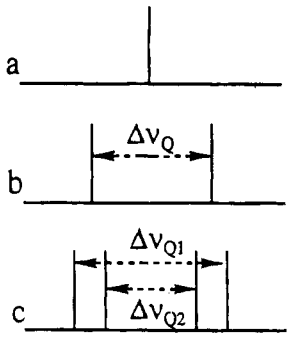

Figure 2. Schematic proton decoupled ^2H NMR spectra of a monodeuterated racemic molecule dissolved in various solvents: (a) isotropic solvent, (b) nonchiral nematic solvent. $\Delta\nu_Q$ is the quadrupolar splitting. (c) Chiral nematic or cholesteric solvent whenever the *R* and *S* order parameters are different. $\Delta\nu_{Q_1}$ and $\Delta\nu_{Q_2}$ are the quadrupolar splittings for each enantiomer.

As shown in Figure 2, the $I = 1$ deuterium NMR spectrum of each nonequivalent deuteron dissolved in a liquid–crystalline solvent consists of a doublet due to the coupling of the electric quadrupole moment of the deuterium nuclei with the electric field gradient (EFG) at the site of the nucleus. This interaction is independent of the magnetic field, the latter serving only for the purpose of aligning the liquid–crystalline medium (B_0 larger than about 0.5T). The quadrupolar splittings, measured as the frequency difference between the components of each doublet, $\Delta\nu_Q$, are given by the following expression

$$\Delta\nu_Q^{R \text{ or } S} = \frac{1}{2}Q_D\{3S_{kk}^{R \text{ or } S} + \eta(S_{ll}^{R \text{ or } S} - S_{mm}^{R \text{ or } S})\} \qquad (3)$$

where Q_D is the deuterium quadrupolar coupling constant, η is the asymmetry parameter of the EFG, and S_{kk}, S_{ll}, and S_{mm} are the elements of the ordering tensor in the principal axis system of the electric field gradient tensor. The S_{ii}'s are related to the molecular order parameters through the relationship

$$S_{ii}^{R \text{ or } S} = \sum_{\alpha\beta}^{c}{}_a \cos\theta_\alpha^i \cos\theta_\beta^i S_{\alpha\beta}^{R \text{ or } S} \qquad (4)$$

where the θ_α^i are the angles between the principal axis of the EFG tensor and the molecular axis.

For CD bonds, Q_D is about 170 kHz, and η is very small and can be neglected. The deuterium quadrupolar couplings are much larger than the chemical shift anisotropies or the proton–proton dipolar couplings and therefore are a more sensitive tool to detect any differential ordering effect between enantiomers.

Dipolar and scalar couplings between deuterons and neighboring protons are often observed, and this may somewhat complicate the interpretation of the spectra. To eliminate any such interferences, we always applied proton broad band decoupling when measuring the spectra. Due to the small magnetogyric ratio of deuterium and the very small ordering parameters in our solvent, the interdeuteron dipolar couplings are too small to be measured, but they may sometime show as a small increase in the line width of the deuterium transitions. Nevertheless, with ^1H decoupling the deuterium line widths are quite narrow and permit rather good resolution, usually between 1 and 3 Hz. This turns out to be a very important factor in cases where the difference in the quadrupolar splitting between the *R* and *S* enantiomers is small and also for the analysis of complex spectra of polydeuterated molecules.

It should be added that in solutions containing equal parts of PBLG and PBDG (its enantiomer), the differential ordering effect vanishes. This means that, in such a mixture, identical spectra are observed for the *R* and *S* enantiomers and indicates that the association of the enantiomers with the polymer is in fast dynamic equilibrium on the NMR time scale. This point has been confirmed, for several solutes, down to about 210 K.

The basic question to be addressed concerns the mechanism through which the enantiomers associate with the PBLG and thus bring about the differential ordering effect. At present we may just speculate that it is a function of the molecular shapes (entropic effects) and of specific bindings. The latter are possibly dominated by electrostatic interactions between functional groups in PBLG and the solutes. Molecular dynamic studies[16,17] of such systems may provide an answer to these questions.

Sample Preparation and NMR Experimental Details

The quality of the spectra is strongly dependent on the homogeneity of the samples, and much care should be taken in their preparation. PBLG (80–100 mg) (degree of polymerization, (DP), 1183, mol wt 150 000–350 000 from Sigma) are weighted into a 5 mm o.d. NMR tube. The enantiomer mixture (20–50 mg) under study is dissolved in about 400 μL of dichloromethane and added to the polymer. After plugging or sealing the tube, thorough mixing and equilibration are achieved by centrifugation of the NMR tube in both directions. The sample must look birefringent and homogeneous. We may note here that the DP of the PBLG does not seem to be so crucial as long as it is large enough to produce a liquid–crystalline solution when dissolved in an organic solvent. At DP = 71 no liquid–crystalline phase was observed at the concentrations indicated above. At DP = 265 resolution is possible only in a limited temperature range. DP from 515 to 1100 perform well.

After a few minutes in the magnetic field, the deuterium spectrum, with broad band proton decoupling, is measured. Whenever the observed deuterium line widths are greater than 1–3 Hz, it indicates that the solution may not be sufficiently homogeneous (assuming that the magnetic field homogeneity is good).

Unless otherwise specified an AM 250 Bruker instrument, equipped with a 5 mm selective deuterium probe operating at 38.37 MHz without field-frequency lock, was used. The samples were spun at 15 Hz. Proton broad-band decoupling was achieved through the WALTZ composite pulse scheme using 1 W of RF power. Spectra in an oriented medium are sensitive to the temperature because thermal motion changes the ordering parameters and consequently the anisotropic interactions. We used the Bruker BVT 1000 temperature regulation system (±0.2 K). In order to minimize the effect of a temperature gradient along the sample in the probe, it is recommended to use a small receiving coil (5 mm in height, in our instrument).

Typically, 4 Kwords interferograms for a 2000 Hz spectrum width are acquired following a 90° pulse of 12 μs and a small relaxation delay. Zero filling was used to achieve good digital resolution, but no apodization was applied. Under such conditions only 32–100 scans were needed to obtain a good signal to noise ratio. Whenever we wished to measure the enantiomeric excess with a 1% precision, through deuterium signal integration, it was necessary to acquire more transients.

Synthetic procedures for various deuterated compounds can be obtained as suplementary material.

Study of a Polydeuterated Molecule: $C_6D_5CDOHCH_3$

We begin by a detailed analysis of the results for one particular molecule, $C_6D_5CDOHCH_3$ (1-deutero-1-pentadeu-

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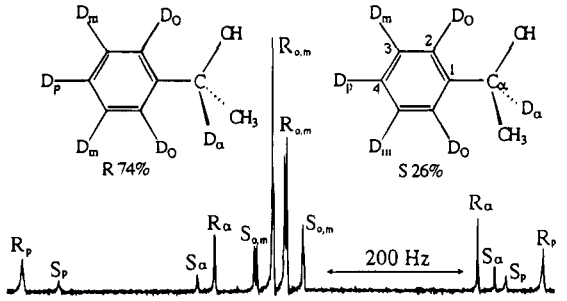

Figure 3. Proton decoupled ^2H NMR spectrum of $C_6D_5CDOHCH_3$ **44**, 48% ee (*R*), in the PBLG/CH_2Cl_2 liquid crystal solvent at 300 K.

terophenyl ethanol) which serves to illustrates various features of the technique.

This molecule contains four nonequivalent deuterons: ortho, meta, para, and α (the D bonded to the asymmetric carbon). Consequently, if the enantiomers do not orient identically in PBLG, the spectrum of a mixture is expected to show 16 transitions, i.e., one doublet for the four deuterons in each optical isomer. The deuterium NMR spectrum of this compound, enriched with the *R* component (48% *ee*), at 300 K, is shown in Figure 3. It indeed contains eight doublets, and they have been assigned to the various nuclei of each enantiomers using chemical shifts and relative intensities argments. The quadrupolar splittings for each deuteron, as a function of the temperature, are shown in Figures 4. Several important characteristics of the results should be pointed out as they often appear in spectra of other materials as well.

(**a**) All the deuterium signals are split into two doublets, one for the *R* and one for the *S* enantiomers, but we note that the largest differential ordering effect is observed for the deuterons in the *para* position which is the farthest removed from the asymmetric center. This has an important significance for the general application of our technique. We realize that a good discrimination between the deuterium spectra of enantiomers does not necessitate the deuterons to be on the chiral center, it can sometimes be achieved even when deuteration is far removed from the chiral center of the molecule. Expressing it otherwise, deuteration on or near the chiral center is not essential to obtain well resolved spectra for each enantiomer. This result can be qualitatively understood by inspecting the term which describes the angular dependence of the order parameters in eq 3. The latter has the functional form of $S_{CD} = \frac{1}{2} <3 \cos^2 \theta - 1>$, where θ is the angle between the CD bond direction (assumed to be axially symmetric and parallel to the direction of the EFG) and the external magnetic field, and <> denotes the ensemble average. It is obvious that the quadrupolar splitting depends on θ and that for a particular deuterium in the molecule the differential ordering effect may be small or even null, while for another it may be large because the CD bond forms a different angle θ with B_0.

(**b**) The temperature dependence of the quadrupolar splittings reflects the changes in the molecular ordering with thermal motion, assuming that Q_D does not vary much with the temperature. In Figure 4 we note that the temperature dependence of the splittings is not the same for all the deuterons in the molecule. The para deuterons show the commonly observed decrease of the absolute value of the splitting with increasing temperature. This, however, is not the case for the splittings of the α and meta deuterons of the *R* enantiomer that are increasing with temperature. Due to the functional form of the order parameters, the quadrupolar interactions and hence the splitting may vanish or even change sign at the magic angle. This may happen due to molecular reorientation processes.

(**c**) Some of the splittings for the *R* and *S* enantiomers become

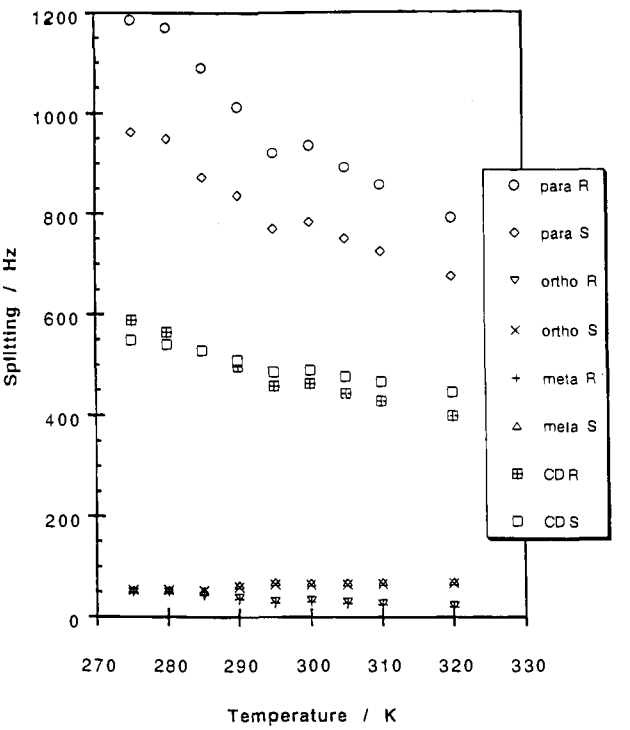

Figure 4. Temperature dependence of the quadrupolar splittings of $C_6D_5/CDOHCH_3$ **44**. (Measurements taken at deuterium frequency of 61.4 MHz, AM 400 WB).

equal at certain temperatures which means that at these particular temperatures no differentiation can be observed for this nuclear site. In other words, the $\Delta\nu_Q^R$ and $\Delta\nu_Q^S$ *vs* temperature curves cross at these temperatures. Similar behavior for another compound has been reported by us previously[6] and also for the prochiral methylene deuterons in deuterated benzyl alcohol by Czarniecka and Samulski.[12] These authors suggested that the crossing temperature corresponds to the temperature at which the pitch of the secondary (*i.e.*, of the side chains) helical structure reverses sign. Our results indicate that this cannot be the sole reason for the effect since different resonances in this molecule do not cross at the same temperature.

It is important to emphasize, for the practical aspects of the application of our method, that such situations as described above may occur. It means that when the differential ordering for a compound is not observed at any particular temperature, a change of the temperature in either direction may produce the desired effect.

Systematic Study of Organic Compounds

The different molecules, possessing various functional groups, that were studied in this part can be classified into four groups.[1]

(**1**) **Alcohols and Amines.** These are compounds for which visualization of enantiomers can be performed by other NMR methods such as the use of chiral lanthanide shift reagents, chiral derivatizing agents, or chiral solvating agents. The study of these compounds will serve as a test for the effectiveness of our procedure and for comparison with other methods.

(**2**) **Carboxylic Acids and Esters.** While several methods exist for the NMR analysis of chiral amines and alcohols, there are few reports of good, reliable analyses for carboxylic acids and acid derivatives.[18]

(**3**) **Ethers, Epoxides, and Tosylates.** For this group only chiral lanthanide shift reagents can be used for the differentiation of enantiomers by NMR. However, in some cases, this

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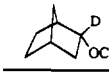
Table 1. Quadrupolar Splittings and Differential Ordering Data for Alcohols

Alcohol			T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
o-MePh—CD(OH)—CH_3	1		296	88	28	60	3.16
			305	83	22	61	3.78
			315	75	16	59	4.58
C_6H_{11}—CD(OH)—CH_3	2		306	261	201	60	1.30
			317	236	182	54	1.30
n-C_7H_{15}—CD(OH)—CH_3	3		306	238	168	70	1.41
			317	225	163	62	1.38
t-Bu—CD(OH)—CH_3	4		306	121	21	100	5.89
			317	107	20	87	5.32
	5	endo	306	241	43	198	5.54
			318	202	39	163	5.22
		exo	306	75	58	17	1.30
			318	65	48	17	1.36

Table 2. Quadrupolar Splittings and Differential Ordering Data for Acids and Esters

Acid, ester			T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
Ph—CD(CO_2H)—CH_3	12		305	130	56	74	2.30
			320	78	21	57	3.76
C_6H_{11}—CD(CO_2H)—CH_3	13		301	364	195	169	1.87
			315	278	124	154	2.23
n-C_7H_{15}—CD(CO_2H)—CH_3	14		300	368	309	59	1.19
			310	324	266	58	1.21
Ph—CD(CO_2CD_3)—CH_3	15	CD	302	333	333	0	1.00
			317	309	309	0	1.00
		CD_3	302	68	48	20	1.41
			317	64	46	18	1.38
C_6H_{11}—CD(CO_2CD_3)—CH_3	16	CD	233	458	448	10	1.02
			273	355	355	0	1.00
			302	315	315	0	1.00
			317	292	292	0	1.00
		CD_3	233	76	69	7	1.11
			273	66	62	4	1.07
			302	59	57	2	1.03
			317	56	56	0	1.00
n-C_7H_{15}—CD(CO_2CD_3)—CH_3	17	CD	302	382	371	11	1.03
			317	354	345	9	1.03
		CD_3	302	50	50	0	1.00
			317	49	49	0	1.00

Table 3. Quadrupolar Splittings and Differential Ordering Data for Ethers

Ether		T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
o-MePh—CD(OCH_3)—CH_3	18	303	191	135	56	1.41
		317	178	130	48	1.37
C_6H_{11}—CD(OCH_3)—CH_3	19	303	284	263	21	1.08
		317	267	248	19	1.08
n-C_7H_{15}—CD(OCH_3)—CH_3	20	303	364	359	5	1.01
		317	342	334	8	1.02
	21	303	229	81	148	2.82
		317	186	68	118	2.73

procedure cannot be applied, because of problems of complexation or of degradation of the solute by the weak acidity of the lanthanide shift reagents.

(4) Halides and Hydrocarbons. These are compounds for which it is important to develop suitable methods of enantiomeric analysis, since no applicable NMR method to solve this problem seems to have been reported.

The results obtained for the visualization of enantiomers in the PBLG-dichloromethane solvent are presented in Tables 1−7 for alcohols, acids and esters, ethers, epoxides, tosylates, halides, and unsaturated hydrocarbons, respectively. Compounds were

Table 4. Quadrupolar Splittings and Differential Ordering Data for Epoxides

Epoxide			T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
	22		303	337	299	38	1.13
			311	249	221	28	1.13
	23	Z	306	105	95	10	1.10
			320	149	135	14	1.10
		E	306	283	283	0	1.00
			320	349	349	4	1.01
	24	Z	291	275	241	34	1,14
			306	258	235	23	1.10
			317	241	228	13	1,06
		E	291	541	517	24	1.05
			306	496	496	0	1.00
			317	464	464	0	1.00
	25		306	314	286	28	1.10
	26		306	393	378	15	1.04
		endo	304	96	40	56	2.41
	27		316	90	39	51	2.30
		exo	304	43	12	31	3.55
			316	43	7	36	6.35

Table 5. Quadrupolar Splittings and Differential Ordering Data for Tosylates[a]

Tosylate			T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
o-MePh—CD(OTs)—CH_3	28		296	146	86	60	1.69
			318	132	86	46	1.54
C_6H_{11}—CD(OTs)—CH_3	29		296	490	473	17	1.04
			318	448	437	11	1.02
n-C_7H_{15}—CD(OTs)—CH_3	30		296	669	642	27	1.04
			318	619	596	23	1.04
t-Bu—CD(OTs)—CH_3	31	DCM	275	430	430	0	1.00
			298	403	403	0	1.00
		TCP	318	340	335	5	1.01
			305	329	329	0	1.00
			355	249	240	9	1.04
	32		296	155	139	16	1.12
			318	140	130	10	1.08

[a] DCM = dichloromethane; TCP = trichloropropane.

studied in a racemic form. For all cases where it was possible to distinguish the spectra of the enantiomers in a racemic mixture, it would also be possible to measure the enantiomeric purity of the compound in an optically active form. The tables give the temperatures at which the measurements were performed, the observed quadrupolar splittings for each enantiomer (we usually attribute the largest quadrupolar splitting as $\Delta\nu_{Q_1}$ and the smallest one as $\Delta\nu_{Q_2}$), their difference ($\Delta\nu_{Q_1} - \Delta\nu_{Q_2}$), and their ratio ($F_D = \Delta\nu_{Q_1}/\Delta\nu_{Q_2}$). From inspection of these tables, some general comments about the results may be made.

(**a**) For most of the studied compounds, F_D is different from 1, showing that we were able to resolve the NMR spectra of enantiomers for a variety of classes of organic compounds in the same chiral solvent. To our knowledge, this technique is the only one which enables direct visualization of enantiomers of halides by NMR. Figure 5 shows the deuterium NMR spectra of halide **33** and hydrocarbon **43** (where the deuterium has been introduced stereospecifically in the endo position), which illustrates the capability of the method.

Still, with some classes of compounds we encountered difficulties which may limit the applicability of the method:

Amines. For primary amines, we could distinguish the NMR spectra of the enantiomers only for a single amine, **6** (C_6H_5-$CD(NH_2)CH_3$), in whatever solvent or temperature we used. In

Table 6. Quadrupolar Splittings and Differential Ordering Data for Halides

Halide		T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
o-MePh—CD(Cl)—CH_3	**33**	306	229	141	88	1.58
		311	217	141	76	1.54
C_6H_{11}—CD(Cl)—CH_3	**34**	306	408	400	8	1.02
		311	400	392	8	1.02
n-C_7H_{15}—CD(Cl)—CH_3	**35**	306	549	549	0	1.00
		311	549	541	8	1.02
	**36**	306	178	162	16	1.09
		318	165	151	14	1.09
	**37**	304	138	10	128	14.31
		316	126	12	114	10.48
o-MePh—CD(Br)—CH_3	**38**	306	218	139	79	1.57
		311	214	139	75	1.53
C_6H_{11}—CD(Br)—CH_3	**39**	306	438	431	7	1.02
		311	428	420	8	1.02
n-C_7H_{15}—CD(Br)—CH_3	**40**	306	604	589	15	1.03
		311	586	572	14	1.02
	**41**	306	236	216	20	1.09
		318	221	203	18	1.09

Table 7. Quadrupolar Splittings and Differential Ordering Data for Hydrocarbons

Hydrocarbon		T (K)	$\Delta\nu_{Q1}$ (Hz)	$\Delta\nu_{Q2}$ (Hz)	$\Delta\nu_{Q1} - \Delta\nu_{Q2}$ (Hz)	FD
	**42**	303	342	318	24	1.07
		317	348	319	29	1.09
	**43**	302	78	35	43	2.21
		316	69	28	41	2.45

two other cases, compounds **7** and **8**, spectral resolution was bad, and extra lines, with different intensities, appeared in the spectra. Methylation of these primary amines, in the cases of amines **10** and **11**, failed to solve the problem. We assume that amines and PBLG are reacting chemically as indicated by the fact that diamines can be used to establish bridges between PBLG fibres.[19] To overcome this problem, we propose to transform the amines into amides since derivatives of acids are well distinguished by our method. The incorporation of deuterium can be done directly using a deuterated acid as a nonchiral derivatizing agent. Another possibility would be to protect the amino group as was previously demonstrated for aminoacids.[7]

Hydrocarbons. Only two unsaturated hydrocarbons were measured, and it should be emphasized that we are quite uncertain whether our technique will be useful for others. We are especially concerned about saturated hydrocarbons, and this problem is presently under study.

(**b**) Most of the observed quadrupolar splittings are small (<900 Hz), showing that the order parameters are unusually low in this solvent. All spectra exhibit good resolution (line widths $\approx$ 2 Hz). Usually, a difference in the quadrupolar splittings larger than about 10 Hz is sufficient to permit an accurate measurement of the enantiomeric purity.

(**c**) For a mixture of diastereoisomers, the big differences in the quadrupolar splittings, for the enantiomers as well as for the diastereoisomers, permits a direct measurement of all isomeric ratios. This point is particularly important whenever complex isotropic spectra are obtained for such a mixture. In this case, other NMR methods, which are based on the differences in chemical shifts, often do not distinguish clearly between all isomers. In Figure 6, the spectra of a mixture of *endo*/*exo*-norborneol (**5**) and of a mixture of *Z*/*E*-epoxide (**24**) are presented, where all isomers are clearly distinguished in the PBLG-dichloromethane solvent.

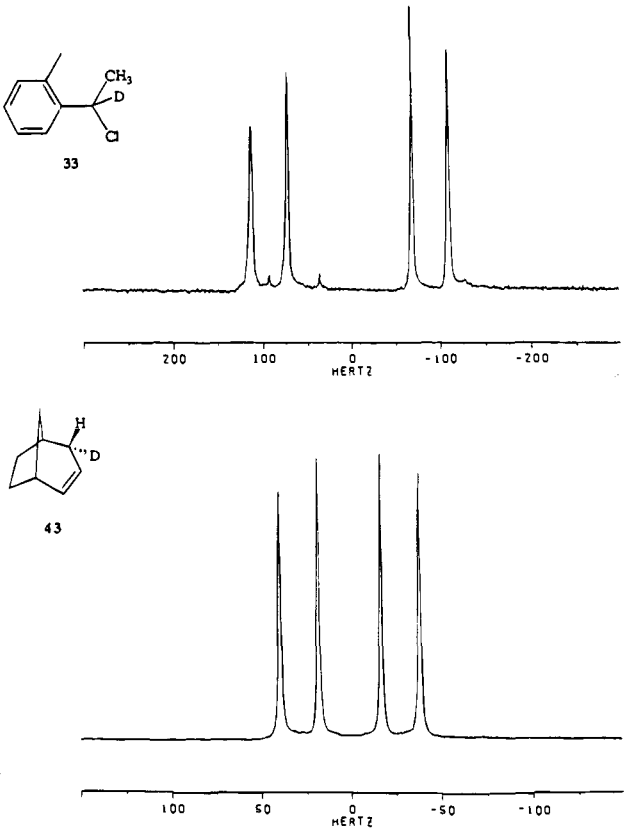


Figure 5. Proton decoupled ^2H NMR spectra of (a) 1-chloro-1-deutero-1-(2-methylphenyl)ethane **33** (306 K) and (b) *endo*-4-deuterobicyclo-[3.2.1]oct-2-ene **43** (302 K). Note that in this molecule there is three chiral carbons. All three must be inverted to visualize the enantiomer.

(**d**) In some cases, the difference in the quadrupolar splittings between enantiomers, at room temperature, is not sufficient to obtain their distinct spectra. The quadrupolar splittings are however sensitive to the temperature, and the effect is different for each enantiomer. Therefore, through variation of the temperature, changes occur in the NMR spectra that are usually sufficient to obtain well resolved *R* and *S* spectra (see for example compound **24**, Table 4).

(**e**) If temperature variations do not produce the desired difference between the spectra of the enantiomers, it is possible to modify them by changing the organic solvent (cf. compound **31**, Table 5). For example, substitution of dichloromethane by 1,2,3-trichloropropane also produces a liquid crystal with PBLG that can be used over a different temperature range. The change in the temperature range, associated with the changes of behavior of the PBLG in a different solvent, can result in better resolved spectra for the enantiomers. Liquid crystals made from PBLG and other solvents, such as dioxane−dichloromethane (1:1), chloroform, dimethylformamide, and pentachloroethane, have been successfully used.

(**f**) Another interesting characteristic which should be pointed out are the results for the esters (Table 2) which possess two sites of deuteration. Depending on the ester and on the temperature, visualization of enantiomers is realized in their spectra by deuteration of one site (deuteriums located on the ester function, compound **15**) or the other one (deuterium located on the asymmetric center, compound **17**) or of both sites

(19) Kishi, R.; Sisido, M.; Tazuke, S. *Macromolecules* **1990**, *23*, 3779.

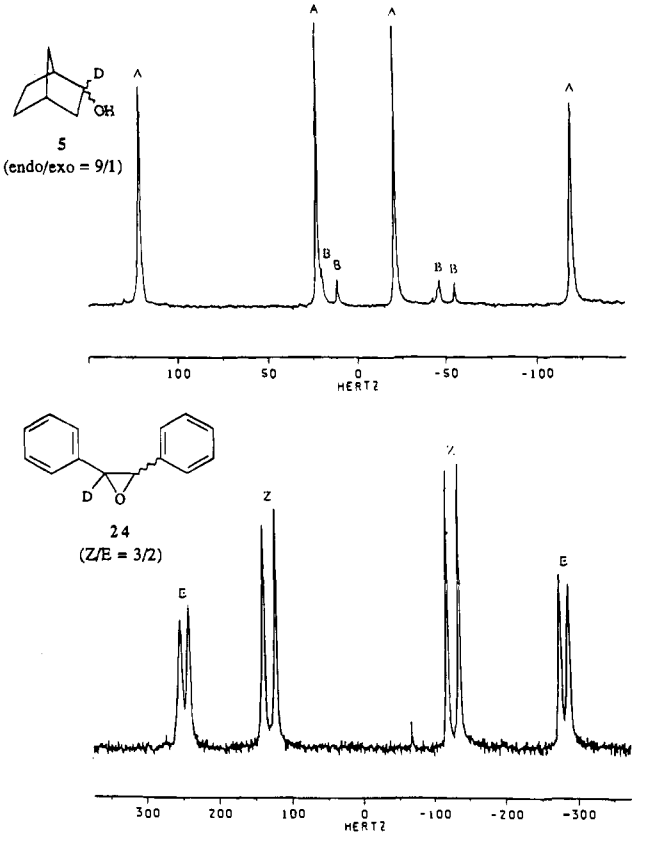


Figure 6. Proton decoupled ^2H NMR spectra of (a) 2-deuterobicyclo-[2.2.1]heptane-2-ol **5** (306 K) and (b) 1-deutero-1,2-diphenyloxyrane **24** (291 K).

(compound **16**). Visualization of enantiomers is, in principle, possible for wherever the location of the deuterium is in the molecule.

(**g**) In the case of the acids and of their corresponding esters, deuterium has been incorporated to the extend of only 50–70%. These lower degrees of deuteration do not affect the measurements as long as both enantiomers are enriched to the same extent. It might even be conceivable to work with deuterium in natural abundance; however, the low sensitivity of ^2H detection is a severe limitation.

(**h**) There seems to exist no simple structure-ordering relationship. Inspection of some results for materials which differ by substitution of the functional group (say, Cl by Br or OH,...) seems to indicate some correlation between the magnitude of the differential ordering effect and the van der Waals radii of the substituent. We are, however, not certain that in general this is the case. It should be noted that the results are both concentration and temperature dependent in a specific manner to each compound and that this specificity depends also on the nature of the functional group. Admittedly, these conclusions are disheartening because they do not enable us to predict the magnitude of the expected differential ordering effect for any particular compound.

Conclusions

We have shown that chiral liquid crystals consisting of organic solutions of PBLG provide an appropriate medium for the observation of proton decoupled deuterium NMR spectra of enantiomers. The analysis of a large number of compounds, bearing various functional groups, has been presented. The main features of this method, as compared to other NMR techniques, are as follows.

Our method, based on the difference in the averaged orientation of enantiomers, is convenient and general in its applicability. Deuterium quadrupolar splittings seem to be a far more sensitive tool than the isotropic chemical shifts to probe enantiomers.

A single chiral solvent is sufficient for many classes of compounds, while other NMR techniques requires the choice of different chiral auxiliaries which depend on the nature of the substrate. Yet, in some cases, it is necessary to search for the appropriate conditions (temperature, solvent, site of deuteration, and concentration) in order to obtain good resolution.

Contrary to chiral derivatization methods, there is no chemical reaction on the molecules under study, the former may often lead to partial racemization.

Deuterium NMR spectra are very simple and well resolved, with no NMR interference from the chiral solvent, permitting rapid and precise evaluation of isomeric composition.

Some drawbacks should be pointed out: the need for deuterium labeling. Still, deuteration procedures are well known and relatively easy to apply, especially if the choice of a particular site for deuteration and the degree of deuteration are not crucial for the success of the analysis. Where deuteration is difficult we have shown that ^{13}C NMR might provide an alternative route.[20]

We are presently unable to predict the experimental conditions under which the biggest differentiation between the spectra of enantiomers will be observed. A better apprehension of this problem would require a detailed understanding of solute–solvent interactions prevailing in these systems. These interactions eventually determine the order parameters of the enantiomers and consequently the magnitude of the differential ordering effect for any specific molecule.

To solve these problems and further develop this technique we are now investigating the possible use of other helical polymers and the chemical modification of PBLG through the introduction of chiral or mesogenic side chains.

Finally we wish to suggest that the system and technique presented here might serve as a simple model for the study and understanding of chiral recognition in complex biological systems.

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Supplementary Material Available: Syntheses of compounds (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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