

Enantiomeric Analysis of Homologous Series of Secondary Alcohols by Deuterium NMR Spectroscopy in a Chiral Nematic Liquid Crystal: Influence of Molecular Geometry on Chiral Discrimination

A. Meddour, D. Atkinson, A. Loewenstein, and J. Courtieu*

Abstract: NMR measurements of the differential ordering effect (DOE) are presented for homologous series of 22 chiral secondary aliphatic alcohols dissolved in a poly-(γ -benzyl-L-glutamate) (PBLG)/dichloromethane liquid-crystalline solvent. The quadrupolar splittings of the solutes, which were deuterated at their chiral centres, were measured as a function of the PBLG

concentration and temperature. The proton dipolar splittings of the dichloromethane in each sample were also measured and used as a reference. The results are analysed qualitatively in

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terms of the structures of the molecules and their asymmetric (or chiral) characteristics. Emphasis is put on comparative analysis of the chiral discrimination in members of each particular homologous series and on evaluating the limits of the technique for molecules that have two very similar groups attached to their stereogenic centres.

Introduction

We have shown that enantiomeric analysis of chiral compounds could be achieved by measuring their NMR spectra in a chiral nematic liquid-crystalline solvent.^[1] The system employed was a solution of poly-(γ -benzyl-L-glutamate) (PBLG) in various organic solvents.^[2] The NMR spectra of different nuclei such as ^1H , ^2H , ^{13}C or ^{19}F of the chiral compounds can be used for the analysis.^[3]

The underlying principle of the method is that *R* and *S* enantiomers of chiral materials orientate differently when dissolved in a chiral liquid-crystalline solvent. Molecular orientation in liquid crystals originates from solute-solvent interactions, the nature and strength of which determine the degree of solvent-induced orientation. Different orientations (or order parameters) of the enantiomers imply that different dipolar couplings or chemical shift anisotropies and, for spins $> 1/2$, different quadrupolar interactions should be observed in their NMR spectra.^[4] As the quadrupolar interactions are often the largest, we found that in practice the most convenient procedure is to measure quadrupolar nuclei such as deuterium (spin = 1), which is used exclusively in this study.

The ^2H NMR spectrum of a racemic mixture of a mono-deuterated compound dissolved in an achiral liquid crystal exhibits a doublet resulting from the interaction of the deuterium quadrupole moment with the electric field gradient at the nuclear site.^[5] The spectrum of this racemic mixture dissolved in the PBLG/ CH_2Cl_2 system is composed of two doublets that reflect the different orientation for the *R* and *S* enantiomers. This situation is presented schematically in Figure 1. The measured difference between the quadrupolar

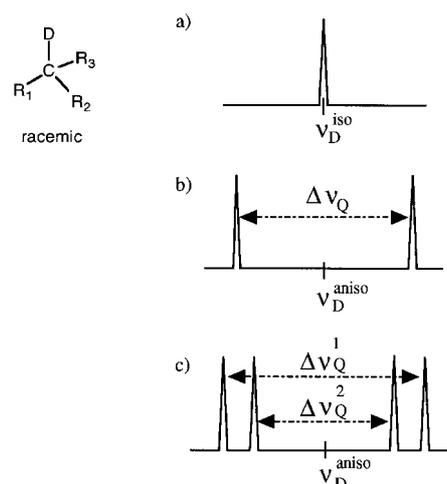


Figure 1. Schematic proton-decoupled ^2H NMR spectra of a mono-deuterated racemic molecule dissolved in various solvents: a) Isotropic solvent. b) Nonchiral nematic solvent; $\Delta\nu_Q$ is the quadrupolar splitting. c) Chiral nematic or cholesteric solvent in which the *R* and *S* order parameters are different; $\Delta\nu_{Q1}$ and $\Delta\nu_{Q2}$ are the quadrupolar splittings for each enantiomer.

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splittings of the enantiomers is called a differential ordering effect (DOE).

The magnitude of the DOE depends on several factors such as the composition of the samples (volume fractions of PBLG and chiral solute), the temperature and, to some extent, the molecular weight of the PBLG. It also depends on the chemical nature and molecular shape of the chiral solute. In order to achieve a better understanding of some of these

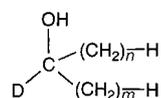


Figure 2. General structure of the secondary alcohols studied. The following compounds were prepared: a) $n=1$; $m=2, 3, 4, 5, 6, 7, 12, 14$; b) $n=2$; $m=3, 4, 5, 6, 7, 11, 12$; c) $n=4, 5$; $m=13-n$; d) $n=3, 4, 5, 6, 8$; $m=n+1$.

factors (mainly the molecular geometry of the chiral compound, volume fraction of PBLG and temperature) we have undertaken a systematic study of various organic compounds that possess the same functional group. Another purpose was to evaluate the discrimination limits of the method for molecules that have two very similar groups attached to their stereogenic centres. We have chosen for this purpose an homologous series of secondary alcohols with the general structural formula given in Figure 2.

This series was chosen because of the relatively facile synthesis of the deuterium-labelled derivatives and the relatively large DOEs that are generally observed

for alcohols. Measurements, at a given solute concentration, were taken as function of the PBLG concentration and temperature. The results of these measurements and their qualitative interpretation are presented in this paper.

Results and Discussion

Background: The quadrupolar splitting, $\Delta\nu_Q$, for the *R* or *S* enantiomers is given in Equation (1).^[4]

$$\Delta\nu_Q = 3/2 Q_D V_{CD} / h (1/2 (3\cos^2\theta_{CD} - 1)) \quad (1)$$

It is assumed that the asymmetry parameter of the electric field gradient (η) is zero. Here, Q_D is the deuterium quadru-

pole moment, V_{CD} is the electric field gradient along the C–D bond and $S_{CD} = (1/2 (3\cos^2\theta_{CD} - 1))$ is defined as the order parameter along the C–D bond. θ_{CD} is the angle between the electric field gradient (directed along the C–D bond) and the external magnetic field and the $\langle \rangle$ brackets denote the total average value over the anisotropic molecular reorientations. The difference between the $\Delta\nu_Q$ values for the *R* and *S* enantiomers (the DOE) is essentially due to the difference in the S_{CD} term, though very small changes in the values of V_{CD} might also exist. While the quadrupolar interaction can be positive or negative, only its absolute value can be measured in a spectrum. This implies that when changes in $\Delta\nu_Q$ are observed, it is not possible to decide in which direction they occur. Since this problem is yet unsolved, we have assumed that all the splittings have the same sign. The uniform behaviour that we observed for measurements in some of the homologous series supports our assumption.

This work is designed to compare the orientation of enantiomers of different compounds. It is known that the phase diagrams of lyotropic liquid-crystalline systems (like those obtained with PBLG), and consequently their order parameters, are closely related to the volume fraction of the compounds in the mixture.^[6] A solution of a chiral compound in PBLG/CH₂Cl₂ forms a ternary system. The molecular weights of the alcohols studied are different (they vary from 75.15 g mol⁻¹ for 2-deutero-2-butanol to 271.50 g mol⁻¹ for 9-deutero-9-octadecanol) whereas the densities of the undeuterated alcohols are in the range 0.8–0.9. Consequently, we used equal weights for the chiral solutes and kept the same ratio between them and the PBLG, since these are the two important components of our system. Also since the densities of the monodeuterated alcohols have not been measured, it was convenient to express the PBLG content of the sample in weight percent (wt %).

When we wish to compare measurements taken at different PBLG concentrations, it is necessary to apply a normalisation factor to the measured DOEs that will take into account the variation in the ordering of the liquid crystal. This normalisation factor is also expected to minimise the effect of the solute on the liquid-crystal order parameter; this makes the DOEs comparable for different compounds. The normalisation factor can be derived either from the average deuterium quadrupolar splittings of the enantiomers or from the proton dipolar coupling (D_{HH}) of the dichloromethane.^[7] Both quantities are related to the total order prevailing in the system. We chose to use the latter and measured the dipolar splittings of the proton doublet of dichloromethane ($\Delta\nu_H = 3D_{HH}$) in each sample as a normalising factor.

Effect of PBLG concentration and temperature on chiral discrimination:

All the compounds studied can be represented by the general structure: R¹–CD(OH)–R² in which R¹ and R² represent linear aliphatic chains of various lengths. In order to analyse the dependence of the DOEs upon molecular dissymmetry, it is convenient to subdivide them into three groups: C₁(or C₂)–C_n, C_n–C_{n+1} and C_n–C_{13–n}, in which C_n are alkyl chains with *n* carbons and the dash represents the CD(OH) group. A typical NMR spectrum for one of the alcohols (C₁–C₆) is shown in Figure 3. The two doublets that

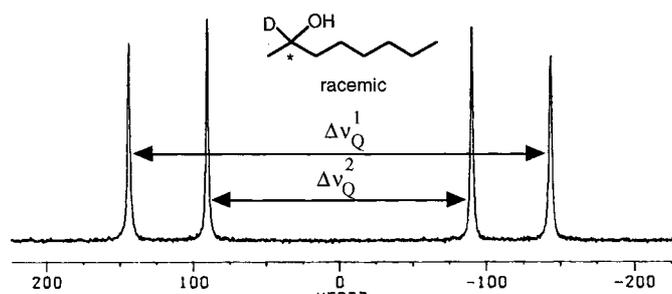


Figure 3. ^2H NMR spectrum of $\text{CH}_3\text{-CD(OH)-(CH}_2)_5\text{CH}_3$ in a solution of PBLG/ CH_2Cl_2 (18.0 wt% PBLG) at $T=302$ K.

result from the quadrupolar splittings of the *R* and *S* enantiomers are clearly evident. The quadrupolar splittings of each solute have been measured as a function of PBLG concentration between 13 and 26 wt%. Below 13 wt% of PBLG the system tends to become biphasic, whereas above 26 wt% the viscosity becomes high and the spectral resolution is too low. An increase in the PBLG concentration invariably results in the increase of the measured quadrupolar splittings. This is due to the enhanced ordering of the system.

Table 1 presents the quadrupolar splittings for both enantiomers of the 22 secondary alcohols and their DOEs

Table 1. Quadrupolar splittings, $\Delta\nu_{\text{O}_1}$ and $\Delta\nu_{\text{O}_2}$, and their difference (DOE in Hz) measured for enantiomers of secondary alcohols at 18.0 wt% PBLG and at $T=302$ K. $\Delta\nu_{\text{H}}$ is the proton dipolar splitting (in Hz) of the dichloromethane in the sample. DOEnorm is the ratio $\text{DOE}/\Delta\nu_{\text{H}}$ and $(\Delta\nu_{\text{O}_1} + \Delta\nu_{\text{O}_2})/2\Delta\nu_{\text{H}}$ is the normalised average quadrupolar splitting.

	$\Delta\nu_{\text{O}_1}$	$\Delta\nu_{\text{O}_2}$	$\Delta\nu_{\text{H}}$	DOE	DOEnorm	$(\Delta\nu_{\text{O}_1} + \Delta\nu_{\text{O}_2})/2\Delta\nu_{\text{H}}$
$\text{C}_1\text{-C}_2$	244	239	76	5	0.07	3.18
$\text{C}_1\text{-C}_3$	306	276	79	30	0.38	3.68
$\text{C}_1\text{-C}_4$	316	247	81	69	0.85	3.48
$\text{C}_1\text{-C}_5$	268	182	78	86	1.10	2.88
$\text{C}_1\text{-C}_6$	285	178	80	107	1.34	2.89
$\text{C}_1\text{-C}_7$	322	212	81	110	1.36	3.30
$\text{C}_1\text{-C}_{12}$	404	272	85	132	1.55	3.98
$\text{C}_1\text{-C}_{14}$	389	253	87	136	1.56	3.69
$\text{C}_2\text{-C}_3$	394	372	81	22	0.27	4.73
$\text{C}_2\text{-C}_4$	419	358	82	61	0.74	4.74
$\text{C}_2\text{-C}_5$	445	363	83	82	0.99	4.87
$\text{C}_2\text{-C}_6$	463	370	80	93	1.16	5.21
$\text{C}_2\text{-C}_7$	512	410	82	102	1.24	5.62
$\text{C}_2\text{-C}_{11}$	621	511	84	110	1.31	6.74
$\text{C}_2\text{-C}_{12}$	610	500	84	110	1.31	6.61
$\text{C}_4\text{-C}_9$	958	908	87	50	0.58	10.72
$\text{C}_5\text{-C}_8$	1004	979	88	25	0.28	11.27
$\text{C}_6\text{-C}_7$	989	989	86	0	0.00	11.50
$\text{C}_3\text{-C}_4$	570	530	83	40	0.48	6.63
$\text{C}_4\text{-C}_5$	733	711	87	22	0.25	8.30
$\text{C}_5\text{-C}_6$	854	838	86	16	0.19	9.84
$\text{C}_8\text{-C}_9$	1281	1281	87	0	0.00	14.72

measured at 302 K and at 18.0 wt% PBLG. This table also includes the ratios of $\text{DOE}/\Delta\nu_{\text{H}}$, which we denote as DOEnorm, and the normalised average quadrupolar splittings $(\Delta\nu_{\text{O}_1} + \Delta\nu_{\text{O}_2})/2\Delta\nu_{\text{H}}$, which reflect the molecular ordering. Additional data for other concentrations and temperatures can be found in ref. [8].

Figure 4 (a and b) shows the dependence of the measured DOE and DOEnorm values on the PBLG concentration for the $\text{C}_2\text{-C}_n$ series. Similar behaviour is observed for all the alcohols studied. It is evident from the figures that while the concentration dependence of the DOE is roughly linear with

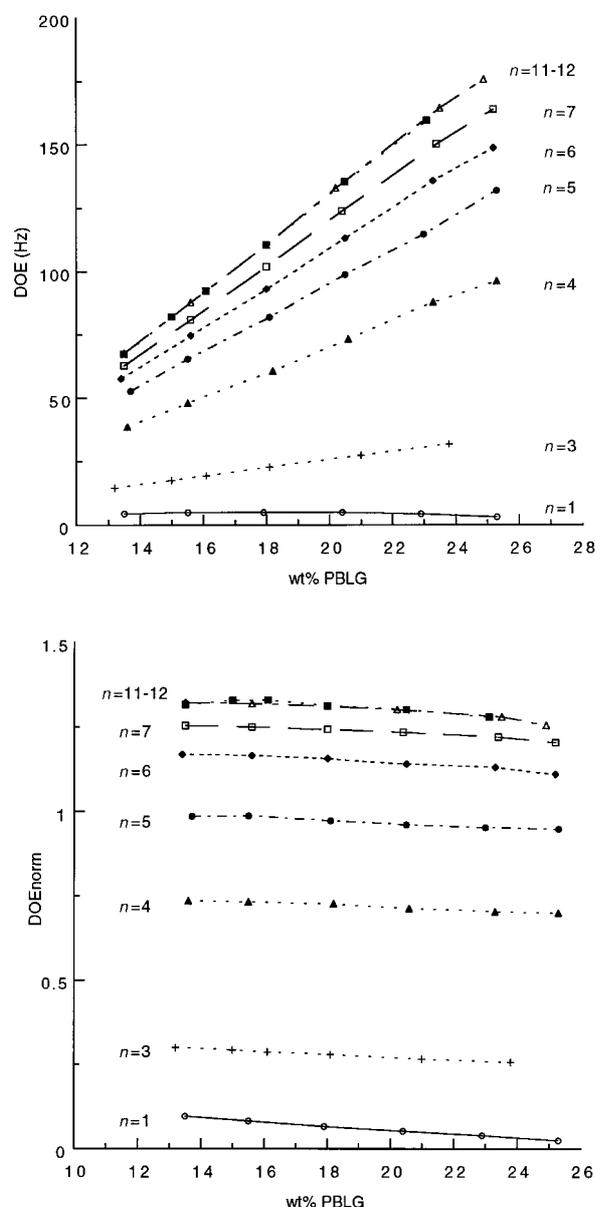


Figure 4. a) Plot of the DOE values vs. the concentration of PBLG for the $\text{C}_2\text{-C}_n$ series at $T=302$ K. b) Plot of the DOEnorm ($=\text{DOE}/\Delta\nu_{\text{H}}$) vs. the concentration of PBLG for the same compounds.

PBLG concentration and with different positive slopes for each compound, these slopes almost disappear when the normalisation with $\Delta\nu_{\text{H}}$ is applied. However, the remaining slopes in Figure 4b suggest that these normalisation factors are not perfect.

The temperature dependence of the DOE was measured for several samples between 300 and 315 K. Generally, the quadrupolar splittings decrease with increasing temperature, following the decrease in the order parameters.^[6] The relative changes in the splittings with the temperature for the *R* and *S*

enantiomers are not necessarily identical; this is due to the functional form of the order parameter given above. However, the general patterns of the results are not affected by varying the temperature.

Effect of molecular dissymmetry on chiral discrimination:

The initial aim of this work was to determine the limit of chiral discrimination by means of the ^2H NMR technique in PBLG/ CH_2Cl_2 . For this purpose, we measured a series of secondary alcohols bearing the general formula $\text{C}_n\text{--C}_{n+1}$ with n varying from 1 to 8. It was found that enantiomers were discriminated till $n = 5$. To our knowledge, this is the first direct observation of the enantiomers of 6-dodecanol.

The results of the chiral discrimination for this series are presented in Figure 5 for solutions in 18 wt % PBLG at 302 K. While the increase in n results in a decrease in molecular

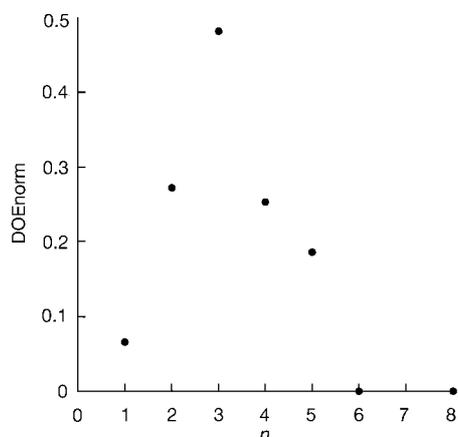


Figure 5. Plot of the DOEnorm values in the $\text{C}_n\text{--C}_{n+1}$ series vs. n in solutions of PBLG/ CH_2Cl_2 (18.0 wt % PBLG) at $T = 302$ K.

dissymmetry, the chiral discrimination, as reflected by DOEnorm, increases till a maximum is reached for $n = 3$ ($\text{C}_3\text{H}_7\text{--CD(OH)--C}_4\text{H}_9$) and thereafter diminishes and disappears at $n = 6$. In other words, chiral discrimination does not appear to have a simple uniform dependence on molecular dissymmetry.

In order to understand this rather unexpected behaviour, we undertook the study of other series of secondary alcohols. We began by examining the results for the C_1 (or C_2)– C_n series: we expected that the DOEs would increase with n , which would correspond to an enhancement of both the molecular ordering and the dissimilarity (or volume difference) between the two alkyl chains. The results, for solutions of 18.0 wt % of PBLG at 302 K, are shown in Figure 6, which depicts the DOEnorm as a function of n for the $\text{C}_1\text{--C}_n$ series. The DOE does indeed increase with n , but reaches an asymptotic value for $n \approx 11$. This means that the chiral discrimination ceases to be sensitive to a small increase in the dissimilarity between the two attached chains beyond a certain value of n . In other words, a small change in the molecular structure remote from the chiral centre ceases to have an effect on the measured DOEs. Similar behaviour is observed for the $\text{C}_2\text{--C}_n$ series. In order to estimate the dissymmetry evolution in these series, we have calculated the

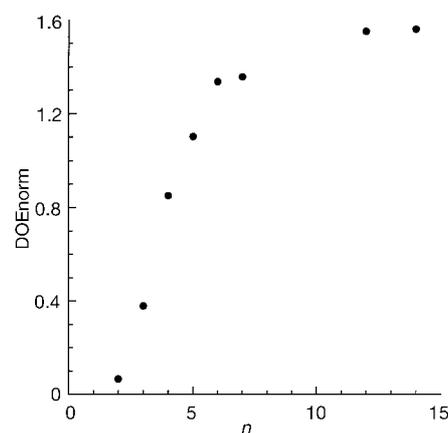


Figure 6. Plot of the DOEnorm values in the $\text{C}_1\text{--C}_n$ series vs. n in solutions of PBLG/ CH_2Cl_2 (18.0 wt % PBLG) at $T = 302$ K.

volume (V) of each alcohol and that of both alkyl chains, R^1 and R^2 , using the volumes given by Gavezzotti.^[9] It was found that $\Delta V/V$ (where ΔV is the volume difference between the two alkyl chains) versus n produces curves similar in shape to those obtained with DOEnorm versus n in the $\text{C}_1\text{--C}_n$ and $\text{C}_2\text{--C}_n$ series. Consequently, it appears that in the $\text{C}_1\text{--C}_n$ and the $\text{C}_2\text{--C}_n$ series, chiral discrimination is closely related to the difference in length of the two alkyl chains. Furthermore, it should be pointed out that the normalised average quadrupolar splittings $[(\Delta\nu_{\text{O}1} + \Delta\nu_{\text{O}2})/2\Delta\nu_{\text{H}}]$ do not change dramatically (between 2.88 and 3.98 for $\text{C}_1\text{--C}_n$ and between 3.18 and 6.61 for $\text{C}_2\text{--C}_n$).

Next we focused our attention on the $\text{C}_n\text{--C}_{13-n}$ series: all molecules belonging to this series are expected to have almost the same length and approximately the same shape. Cerius2 simulations together with MOPAC semiempirical minimisation calculations of quantum mechanical energy are in agreement with this. Hence, the ordering of these molecules should be similar. In practice it was found that this is valid only for $n = 4, 5$ and 6 , where $(\Delta\nu_{\text{O}1} + \Delta\nu_{\text{O}2})/2\Delta\nu_{\text{H}}$ lies between 10.72 and 11.50. The differences in their measured DOEs should reflect the dissimilarity (or volume difference) of the attached C_n and C_{13-n} groups. As the chiral centre moves from the end of the C_{14} chain to its centre this dissimilarity decreases and therefore the DOEs are expected to decrease accordingly. This is indeed the case as seen from the results given in Figure 7 in which the measured DOEnorm values are shown as a function of n for solutions of 18.0 wt % of PBLG at 302 K.

At this point, the results obtained for the $\text{C}_n\text{--C}_{n+1}$ series (Figure 5) can be interpreted rationally. The behaviour of the molecular ordering in this series, which is reflected by $(\Delta\nu_{\text{O}1} + \Delta\nu_{\text{O}2})/2\Delta\nu_{\text{H}}$, is shown in Figure 8. It varies from 3.18 to 14.72 for $n = 1$ to $n = 8$, respectively. Figure 5 shows the combination of two effects. The first is an increase in molecular ordering due to an increase in molecular length. The second is a decrease of the DOEnorm that is induced by a decrease in molecular dissymmetry, as observed for the $\text{C}_1\text{--C}_n$ or $\text{C}_2\text{--C}_n$ series when n decreases and for the $\text{C}_n\text{--C}_{13-n}$ series when n increases. Here, the dissimilarity of C_n and C_{n+1} groups decreases with increasing n . However, the increase in

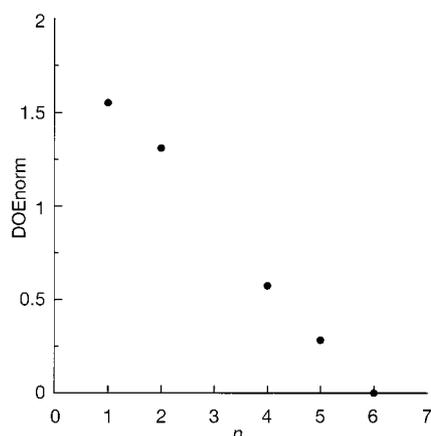


Figure 7. Plot of the DOE_{norm} values in the C_n-C_{13-n} series vs. *n* in solutions of PBLG/CH₂Cl₂ (18.0 wt % PBLG) at *T* = 302 K.

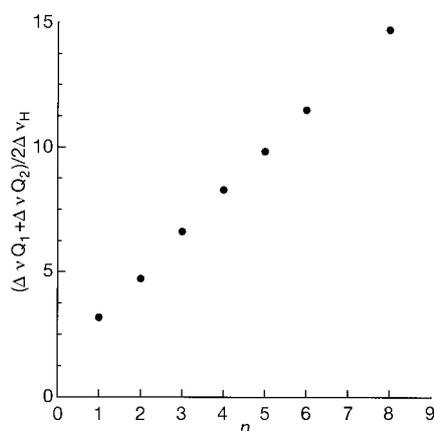


Figure 8. Plot of the $(\Delta\nu_{Q1} + \Delta\nu_{Q2})/2\Delta\nu_H$ values in the C_n-C_{n+1} series vs. *n* in solutions of PBLG/CH₂Cl₂ (18.0 wt % PBLG) at *T* = 302 K.

molecular ordering in the C_n-C_{n+1} series appears to be the dominant factor up to *n* = 3, which results in an increase in the chiral discrimination. Beyond *n* = 3, the difference in molecular ordering between the two enantiomers approaches zero and is not compensated by a further increase in the molecular ordering. Consequently, the chiral discrimination decreases. Therefore the results shown in Figure 5 present a combination of the effects deduced from Figures 7 and 8.

Conclusion

Summing up, we offer a qualitative interpretation for the relative magnitudes of the DOEs in homologous series of secondary alcohols. It appears that chiral discrimination increases with molecular dissymmetry only in series where the molecular ordering is comparable. The DOE is a composite measure that depends on molecular order parameters and on the enantioselective interactions with PBLG. As far as molecular orderings are comparable, it seems that the DOE provides a measure of the dissimilarity of the two alkyl chains attached to the stereogenic centres. Therefore when the results for different compounds are to be compared, both

the overall molecular shapes and the special dissymmetry features have to be taken into account.

For a more quantitative approach, it is interesting to look for a possible correlation between our results and the chirality measurements recently proposed.^[10-13] Such attempts at correlation have indeed failed. We believe that the main reason for this stems from the fact that the DOE is a measure of the difference in the orientation of a C-D bond of two enantiomers, which is related to the nature of their chiral centres, whereas chirality measurements evaluate the asymmetry of the entire molecule. As NMR measures local magnetic properties in molecules, one should think in terms of the recently proposed atomic chirality^[14] that might be better related to the measured DOE values.

From the practical point of view, we have observed that the enantiomers of 6-deutero-6-dodecanol appear to be at the limit of chiral discrimination in the PBLG/CH₂Cl₂ system.

Experimental Section

Synthesis: The deuterated alcohols were prepared by the reduction of the corresponding ketones with lithium aluminium deuteride (LiAlD₄) following standard procedures. Those ketones, which were not commercially available, were synthesised in two steps: the addition of the alkylmagnesium bromide to the appropriate aliphatic aldehydes followed by oxidation to the desired ketone.

NMR sample preparation: PBLG (100 mg; Sigma, degree of polymerisation about 400) and a deuterated alcohol (40 mg) were put in a 5 mm (o.d.) NMR tube. Dichloromethane (distilled over calcium chloride) was added to obtain around 25 wt % PBLG concentration. The sample was centrifuged in both directions to promote the dissolution of PBLG. The solution thus obtained is homogeneous. After measuring the NMR spectrum at this particular concentration, the sample was diluted again with CH₂Cl₂ in order to obtain the next desired concentration. This procedure was repeated for all alcohols till the lowest PBLG concentration (about 13 wt %), which still produces a neat liquid-crystalline phase, was reached.

NMR measurements: Deuterium NMR measurements were performed on a Bruker AM250 NMR spectrometer equipped with a selective 5 mm deuterium probe and operating at 38.39 MHz. The temperature was controlled with a Bruker BVT-1000 temperature-regulation system and samples were spun at about 20 Hz. Broad-band proton decoupling was achieved by applying the WALTZ composite pulse sequence. 100–300 scans were acquired in order to obtain a good signal to noise ratio. Proton NMR spectra were recorded with the same probe operating at 250.16 MHz.

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