Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 737–744

TETRAHEDRON: *ASYMMETRY*

Enantiomeric recognition of chiral invertomers through NMR in chiral oriented phases: a study of *cis*-decalin

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Received 26 January 2001; accepted 1 March 2001

Abstract—We describe a deuterium 1D and 2D NMR study of *cis*-decalin in various chiral and achiral polypeptide oriented solvent systems and the effect of the acquisition temperature. Organic solutions of poly-γ-benzyl-L-glutamate (PBLG) or poly-ε-carbobenzyloxy-L-lysine (PCBLL) in dichloromethane or chloroform allow the chiral invertomers of *cis*-decalin to be differentiated at low temperature. At high temperature, it is possible to distinguish between deuterium nuclei of the molecule which become enantiotopic under rapid kinetic averaging. The results obtained illustrate the capability of such polypeptide liquid-crystalline solvents to enantioselectively interact with unfunctionalised chiral cycloalkanes and highlight the analytical potential of NMR analysis in chiral liquid crystal based solvents in the investigation of interconverting chiral conformers. © 2001 Published by Elsevier Science Ltd.

1. Introduction

NMR differentiation of chiral molecules known to exist as a mixture of enantiomers interconverting by ring inversion is of practical importance in numerous applications and is additionally an interesting challenge in stereochemical analysis. Especially intriguing is the case of *cis*-decahydronaphthalene (*cis*-decalin) for which the interconversion between two predominant, chair–chair conformers, **1a** and **1b**, each having equal energy and overall C_2 symmetry, is possible at room temperature. Freezing of the ring inversion at low temperature leads to a racemic mixture of chiral invertomers.[1–3] For clarity, the two interconverting D,L-conformational forms of **1** are given in Fig. 1. Note that the two chair–chair conformers of *trans*-decalin, **2**, are identical, thus precluding all possibility of finding two chiral conformational isomers.[2] Among the various isotropic NMR approaches developed in the field of the enantiomeric analysis, few are suited to analysing unfunctionalised chiral compounds such as *cis*-decalin. It was, however, recently found that methodology involving β-cyclodextrin (CD) as a chiral shift reagent enabled the discrimination of chiral conformers **1a** and **1b** through proton-decoupled carbon-13 ($^{13}C\{^1H\}$) NMR.[4] However, this elegant method showed rather small chemical shift differentiation and the largest peak separation measured using an 11.7 T field was less than 7 Hz.

To provide an alternative when isotropic NMR techniques fail or give poor results, we have developed a resourceful NMR method based on the use of chiral liquid-crystalline solutions (CLCs) made of the polypeptide poly-γ-benzyl-L-glutamate (PBLG), dissolved in various organic solvents.[5] In systems such as this, because of the chirality of the phase, two enantiomeric forms exhibit different molecular ordering, and hence different NMR spectra are generally observed. We have also shown that the symmetry of the ordering in a prochiral molecule is lost in the PBLG phases (compared with achiral nematic phases), and consequently it is possible to distinguish between two enantiotopic nuclei (or groups of nuclei) in C_s, C_{2v}, D_{2d} and S_4 rigid molecules.[6] The major advantage of this analytical approach compared with isotropic methods lies in observing various anisotropic interactions (averaged to zero in an isotropic medium) which are order-sensitive. Such interactions include dipolar couplings, chemical shifts, anisotropies and, if the nuclei have a spin $I>1/2$, quadrupolar interactions can be observed.

Such a profusion of analytical NMR tools increases the possibilities for enantiomeric or enantiotopic differentiation. This is a significant advantage compared to NMR methods in chiral isotropic solvents that are usually based on rather small differences in ^1H chemical

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PII: S0957-4166(01)00103-3

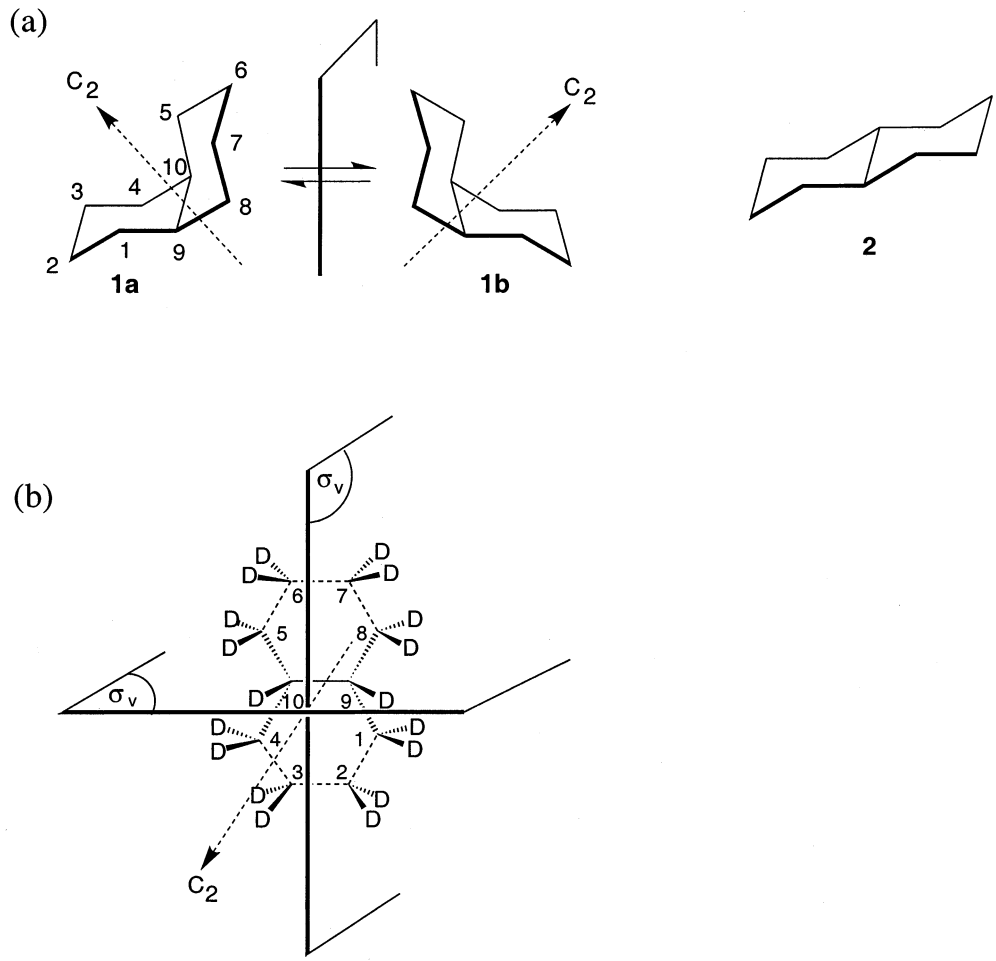

Figure 1. (a) Predominant chair–chair structures of the two invertomers, **1a** and **1b**, of *cis*-decalin and *trans*-decalin, **2**. Due to the C_2 axis in **1a** and **1b**, the pairs of deuterons on carbons 1 and 5, 2 and 6, 3 and 7, 4 and 8, and the single deuteron in carbons 9 and 10 are stereochemically equivalent (homotopic). (b) Effective geometry in average on the NMR time scale when ring interconversion is rapid. Note that both six-membered rings are planar and that deuterons on carbons 1 and 4, 2 and 3, 5 and 8 and 6 and 7 become enantiotopic.

shifts. Among the most significant results in the field of the enantiomeric and enantiotopic analysis, we have shown that the PBLG helices were able to enantioselectively interact with chiral and prochiral hydrocarbons.[6–8] In this context, it was of interest to establish if NMR analyses in polypeptide liquid-crystalline systems were also able to provide successful results in the case of hydrocarbon chiral invertomers.

Herein, we describe a deuterium NMR study of *cis*-decalin in various chiral and achiral oriented solvents made of PBLG and a racemic mixture of PBLG and its enantiomer PBDG (in $CHCl_3$ or CH_2Cl_2 solution) with varying temperature. Organic solutions of PBLG allowed the enantiomers of **1** to be unambiguously differentiated at low temperature while enantiotopic nuclei were distinguished at high temperature. Other polypeptides exhibiting liquid-crystalline properties in organic co-solvents, such as poly-ε-carbobenzyloxy-L-lysine (PCBLL), were also used to successfully discriminate between the invertomers of *cis*-decalin.

2. Experimental

cis-Decalin and its perdeuterated derivative were purchased from standard commercial sources (Aldrich and Acros). The isotopically labelled *cis*-decalin was slightly contaminated with ca. 3% of the *trans*-decalin impurity. The liquid-crystalline NMR samples were prepared using around 80 mg of polypeptide, approximately 20 mg of *cis*-decalin and 500 mg of organic co-solvent directly weighed into a 5 mm o.d. NMR tube. The exact compositions of each oriented NMR sample investigated in this work are shown in Table 1. All NMR tubes were sealed to avoid solvent evaporation and centrifuged back and forth until an optically homogeneous birefringent phase was obtained. Details on the method can be found in the literature.[5] The 1D and 2D experiments were performed at 9.4 T on a Bruker DRX 400 high-resolution spectrometer equipped with an inverse multinuclear probe (BBI) operating at 61.4 MHz for deuterium and with a standard variable temperature unit (BVT 3000). When

Table 1. Compositions of liquid-crystalline NMR samples

Sample	Solute	Polymer	DP[a] L-isomer/D-isomer	Co-solvent	Solute (mg)[b]	Co-solvent (mg)[b]	Polymer (mg)[b]	% of polymer by weight
1	**1**-H_{18}	PBLG	1352	CH_2Cl_2	11	603	60	9.0
2	**1**-D_{18}	PBLG	1352	CH_2Cl_2	11	603	60	8.9
3	**1**-D_{18}	PBG	1352/914	CH_2Cl_2	11	603	30/30	8.9
4	**1**-D_{18}	PBLG	562	$CHCl_3$	33	420	100	18.1
5	**1**-D_{18}	PBG	562/914	$CHCl_3$	33	420	50/50	18.1
6	**1**-D_{18}	PCBLL	992	CH_2Cl_2	11	600	140	18.6
7	**1**-D_{18}	PCBL	992/1296	CH_2Cl_2	11	600	140	18.6

[a] DP: degree of polymerisation.
[b] The accuracy of weighing is ±0.5 mg.

necessary, the protons were broadband decoupled using the WALTZ-16 composite pulse sequence, and deuterium 2D Q-COSY and Q-COSY Ph (phase sensitive Q-COSY) experiments were used to simplify the analysis of overcrowded 1D deuterium spectra. Specific descriptions of these 2D NMR sequences and related experiments may be found in Refs. 9 and 10. Other experimental NMR parameters or details are given in the figure captions.

3. Results, interpretation and discussion

Because of the simplicity of the proton decoupled ^{13}C NMR in chiral liquid-crystalline solvents[5] and a desire to compare our results to those reported using CDs, we recorded the $^{13}C\{^1H\}$ spectra of **1** in the PBLG/CH_2Cl_2 phase (sample 1) at 230 K. The major advantage of CH_2Cl_2 over other organic co-solvents is its very low freezing point, which ensures good fluidity of the sample even at low temperatures and should help provide higher resolution NMR spectra. Although the C-13 resonances are very sharp, with line widths of around 2 Hz, no measurable chiral discrimination of PBLG was observed at this temperature. Indeed only five sharp C-13 resonances, instead of ten if the differentiation occurred on all non-equivalent carbon-13 atoms of the molecule, are detected in the spectrum as in the case of any achiral isotropic solvent. Actually, this unsuccessful result is not surprising for two reasons. Firstly, the differential ordering effect (DOE) in polypeptide oriented solvent for unfunctionalised apolar molecules is in almost all cases rather small.[8] Secondly, the sensitivity of the carbon-13 chemical shift anisotropy to small DOEs is generally too weak for experimentally detecting a chiral discrimination on sp^3 carbon atoms in 100 MHz $^{13}C\{^1H\}$ spectra,[5] hence making this analytical approach poorly suited to this analysis.

To benefit from the most sensitive anisotropic NMR interaction to a difference of orientational order, we turned our attention to deuterium NMR spectroscopy. The efficiency of this approach in enantiodiscrimination in PBLG originates from the magnitude of the deuterium quadrupolar coupling constant, QCC (QCC = 170±10 kHz for sp^3 carbon nuclei).[5,11] Thus, even when the DOE between two enantiomers is small, the magnitude of QCC for a C–D bond can make the difference in their residual quadrupolar splittings, $|\Delta\nu_{Q_i}{}^S - \Delta\nu_{Q_i}{}^R|$, measurable in the ^2H spectra.[7,11] In addition, the T_2 relaxation time of deuterium nuclei is sufficiently long in small molecules to obtain high-resolution quadrupolar NMR spectra for solutes.

It could be argued that this method requires the isotopic labelling of the compound, and such a synthetic step can be time-consuming. Although true, this remark is partially unjustified. Indeed, we have recently shown that enantiomeric analysis of chiral molecules in PBLG using natural abundance deuterium (NAD) NMR spectroscopy was possible with reasonable acquisition times, despite the very low deuterium sensitivity (1.45×10^{-6} with respect to proton), and this approach provided an interesting alternative to ^2H NMR of isotopically labelled compounds.[5,8,11] However, to avoid the relatively long experimental time (overnight at 61.4 MHz) associated with NAD 1D or 2D NMR experiments,[9,10] we used perdeuterated *cis*-decalin (**1**-D_{18}) in this study. Unless otherwise specified, all spectra of *cis*-decalin in oriented phases presented below were run using the perdeuterated derivative of *cis*-decalin (samples 2–5). A study of the ^2H spectrum of perdeuterated *trans*-decalin in a PBLG phase at various temperatures has been described recently by Szalontai,[12] while the study of interconversion kinetics of **1**-D_{18} using an achiral thermotropic nematic liquid crystal has been reported by Luz et al.[13]

In contrast to the $^{13}C\{^1H\}$ 1D NMR, analysis of the deuterium 1D NMR spectrum of **1**-D_{18} recorded at 230 K in PBLG/CH_2Cl_2 is not trivial to analyse. Although the ^2H spectrum presents an excellent dispersion of all quadrupolar splittings with no excessive peak overlap, the identification of the various quadrupolar doublets is not straightforward. To facilitate its analysis, we recorded the 2D Q-COSY Ph spectrum of **1**-D_{18}. Such 2D NMR experiments allow the two components for each deuterium quadrupolar doublet in overcrowded ^2H spectra to be easily correlated.[9] Fig. 2(a) reports the ^2H Q-COSY Ph spectrum of **1**-D_{18} at 230 K. The analysis of the auto-correlation peaks visible in the 2D contour plot unambiguously shows 17 distinct quadrupolar doublets (the doublets b′ and d are overlapped).

To understand this result, we must consider that, for symmetry reasons (a C_2 axis), only nine inequivalent

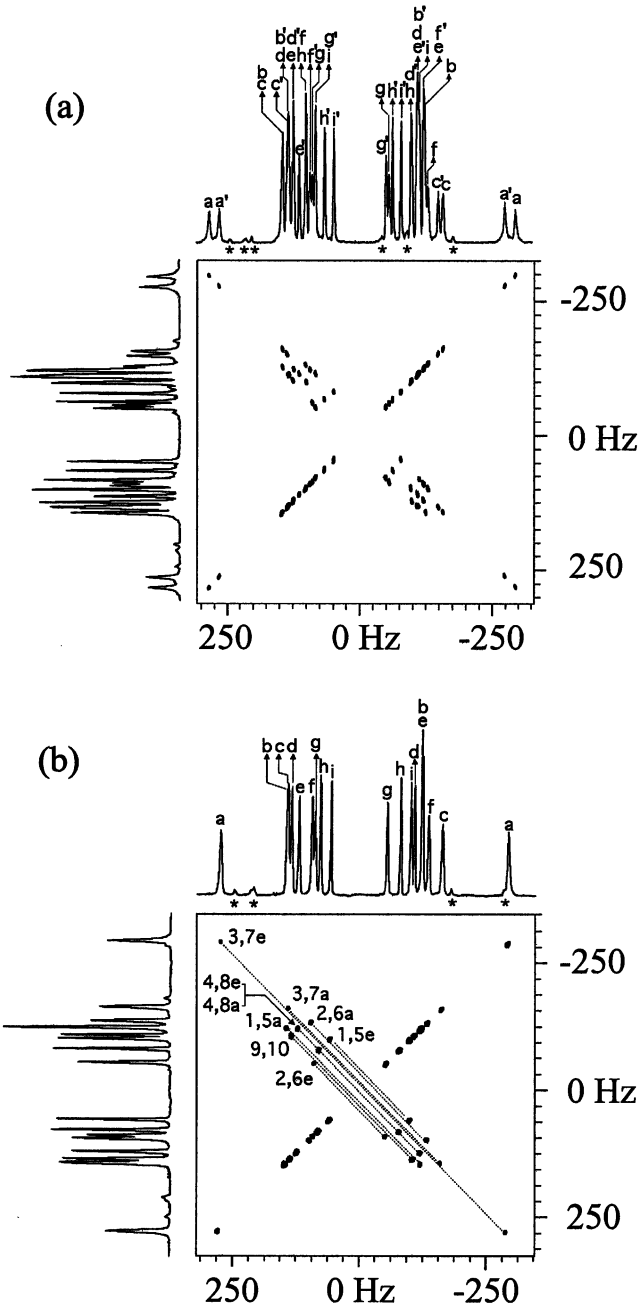

Figure 2. 61.4 MHz deuterium 2D Q-COSY Ph spectra for **1**-D_{18} at 230 K in: (a) the PBLG/CH_2Cl_2 phase and (b) in the PBG/CH_2Cl_2 phase. These phased spectra were recorded using 512 (t_1)×1024 (t_2) data points and the number of free induction decays added for each t_1 increment is 64. The spectra were filtered using a sine window prior to the complex Fourier transformation according to the echo–antiecho mode. Peaks marked with a star arise from the deuterium nuclei of the perdeuterated *trans*-decalin impurity.

pairs of C–D directions in **1a** (or **1b**) exist when the ring inversion is frozen, whatever the orientation in an oriented phase is. Thus, in an achiral liquid crystal, nine quadrupolar doublets are expected if no overlap occurs (see Table 2). Assuming now that the molecular ordering for the enantiomers **1a** and **1b** is different in the chiral phase,[14,15] we may expect to observe up to 18 quadrupolar splittings if all peaks are resolved (see Table 2). Here, we detect eight further doublets compared to the theoretical number observed in an achiral liquid crystal. Consequently, we interpret this as evidence of the chiral recognition of D,L-conformers of *cis*-decalin in the PBLG/CH_2Cl_2 phase.

To confirm our interpretation, we recorded the *cis*-decalin ^{2}H spectrum in a non-chiral nematic solvent made of a racemic mixture of PBLG and its enantiomer PBDG, in CH_2Cl_2 (hereafter this is denoted PBG, sample 3). In such a racemic mixture, the (*S*)- and (*R*)-enantiomers of any chiral molecule are in the fast exchange limit by diffusing very rapidly on the NMR time scale from the vicinity of PBLG and PBDG. Consequently, we observe only an average of these situations, thus eliminating all chiral discriminations possible.[16] The 2D deuterium Q-COSY Ph spectrum of **1**-D_{18} recorded in the achiral solvent at 230 K is shown in Fig. 2(b). As expected, the various quadrupolar doublets associated with equivalent deuterons in **1a** and **1b**, which were differentiated in PBLG, now collapse into nine doublets in the achiral phase.

This result is therefore consistent with our previous analysis and it can be definitely concluded in the light of this that PBLG helices differentiate between the two chiral invertomers of *cis*-decalin at low temperature. Note that the assignment of each quadrupolar doublet given in the 2D spectra is based on that reported recently by Abraham et al.[17]

As the molecular ordering of two enantiomers in the PBLG phase depends on various external factors such as the temperature, the sample composition, the degree of polymerisation and the organic co-solvent, we have prepared two new oriented samples (samples 4 and 5) by replacing CH_2Cl_2 with $CHCl_3$ and using another composition (the concentration of polymer is 18.1% by weight). The major advantage of $CHCl_3$ compared to CH_2Cl_2 is its higher boiling point, which should ensure good thermal behaviour of the sample at higher temperature, and hence, the possibility to record the ^{2}H spectrum of **1**-D_{18} over 330 K. Unfortunately, the viscosity of the liquid-crystalline sample would probably increase at low temperature, which would affect resolution due to line broadening.

Fig. 3 reports the temperature dependence of the ^{2}H NMR spectra for **1**-D_{18} embedded in PBLG/$CHCl_3$ between 230 and 360 K (sample 4). For this sample composition, the liquid-crystalline system is disrupted above 360 K, while the sample solidifies below 230 K. As expected for any dynamic system, the line shape in the various ^{2}H 1D NMR spectra is temperature dependent, and hence undergoes changes characteristic of dynamic effects due to the coalescence between all non-equivalent deuterated sites in exchange. Thus, the ^{2}H quadrupolar doublets at first narrow at low temperature, then coalesce, and finally yield an averaged spectrum of sharp doublets at high temperature.

Table 2. Comparison between the maximal theoretical and experimental number of ^2H quadrupolar doublets observed at high and low temperature (H.T. and L.T.) in the PBLG systems

Sample	Co-solvent	Type of oriented phase	Number of ^2H quad doublets at H.T.	Number of ^2H quad doublets at L.T.
2	CH_2Cl_2	Chiral	–[a] (9)[b]	17 (18)
3	CH_2Cl_2	Achiral	– (5)	9 (9)
4	$CHCl_3$	Chiral	7 (9)	15 (18)
5	$CHCl_3$	Achiral	5 (5)	9 (9)

[a] No experimental data.
[b] The number given in parentheses is the maximum expected number of ^2H quadrupolar doublets when all signals are resolved.

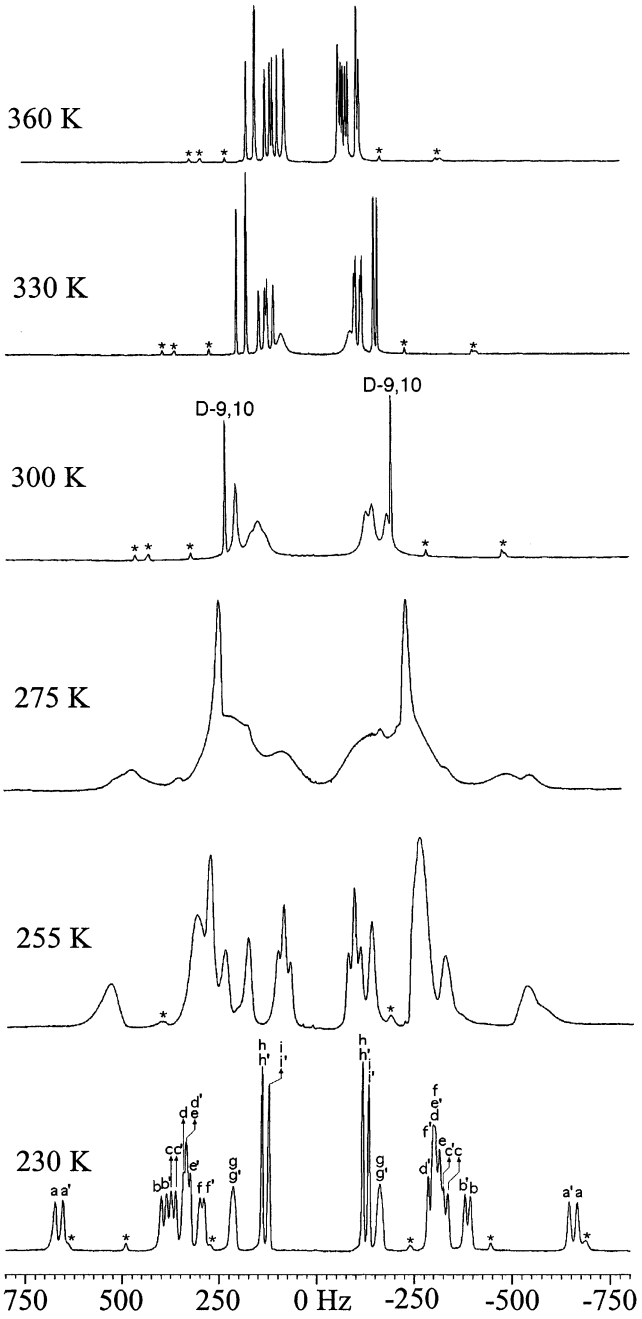

Figure 3. 61.4 MHz deuterium NMR spectra for **1**-D_{18} in PBLG/$CHCl_3$ phase as a function of temperature. 208 scans of 3 k data points were added for each spectrum and a recycle delay of 1.5 s was used. Gaussian filtering and zero filling to 16 k data points were employed to improve the spectral appearance and the digital resolution.

At 230 K, the ^2H deuterium spectrum of **1**-D_{18} (reported at the bottom of Fig. 3) shows numerous resolved quadrupolar doublets. Compared with the previous ^2H spectra, this spectrum shows, as expected, slightly lower resolution. In addition, the dispersion of all quadrupolar splittings is much less favourable than in the PBLG/CH_2Cl_2 system and leads to a high degree of peak overlap even though the amplitude of splittings is increased by up to 100%. In fact, these larger quadrupolar splittings reflect the bigger molecular order parameters for **1a** and **1b**. We interpret this as an effect of the increase of the fraction of polymer (18.1% instead of 8.9%) in the mixture. As before, the identification of the two components for each quadrupolar doublet in the 1D spectrum is not straightforward and was performed by analysing the 2D Q-COSY Ph experiments of **1**-D_{18} in the PBLG/$CHCl_3$ and PBG/$CHCl_3$ phases. These 2D spectra are not reported here. The correlation between the two components of each doublet is given in the 1D spectrum in Fig. 3, but not their assignment. The simultaneous analysis of the autocorrelation peaks on the 2D spectra shows that 15 quadrupolar doublets are clearly visible in the chiral phase. Although the 1D spectral resolution does not permit total resolution of all deuterium resonances on the 2D spectrum in this case, the number of differentiated doublets already demonstrates unequivocally the chiral differentiation of **1a** and **1b** isomers in this second chiral oriented solvent at 230 K.

At 300 K, excepting a very sharp quadrupolar doublet, all ^2H signals exhibit coalescence and the spectrum is uninformative from an analytical point of view. However, the single high-resolution doublet can be confidently assigned to the deuterons **9** and **10** on the bridgehead because, whatever the temperature, they exhibit no kinetic averaging between the conformational forms **1a** and **1b**.[13]

At 360 K, all coalescence effects have disappeared owing to the very high rate of chair-to-chair interconversion, and hence a high-resolution deuterium spectrum is now observed (see top of Fig. 3). Note, however, that the line width of the internal quadrupolar doublet is slightly larger compared with other ^2H resonances. Disregarding any effect due to ^2H–^2H scalar and dipolar couplings or unresolved resonances, this could suggest a very small residual kinetic effect. Again, to facilitate the analysis of this 1D deuterium spectrum, we have recorded the 2D Q-COSY spectrum of **1**-D_{18} at 360 K in PBLG/$CHCl_3$.[9,10] In Fig. 4(a) is displayed the 2D Q-COSY spectrum of **1**-D_{18} after tilting the 2D data

matrix, which allows the quadrupolar splittings to be cancelled out in the F_2 dimension. Disregarding a small increase of line widths due to the tilt procedure, the F_2 projection is essentially identical to the isotropic ^2H spectrum. In this 2D spectrum, we can distinguish seven quadrupolar doublets centred on five different chemical shifts. To understand the ^2H spectrum observed at 360 K, we must consider that under the assumption of fast exchange limit between **1a** and **1b**, and for symmetry reasons, just five distinct ^2H doublets in a non-chiral nematic phase should be expected, disregarding the ^2H–^2H couplings (see Table 2). Actually, even though chair–chair conformational forms **1a** and **1b** are of C_2 symmetry, we may consider that the effective average conformation of *cis*-decalin on the NMR time scale belongs to C_{2v} symmetry point group (see Fig. 1b). In this situation, it appears that pairs of deuterons on carbons 7, 8, 1 and 2 can be exchanged by a mirror plane (but not by a C_2 axis) with those of carbons 6, 5, 4 and 3, respectively, and hence can be seen as enantiotopic

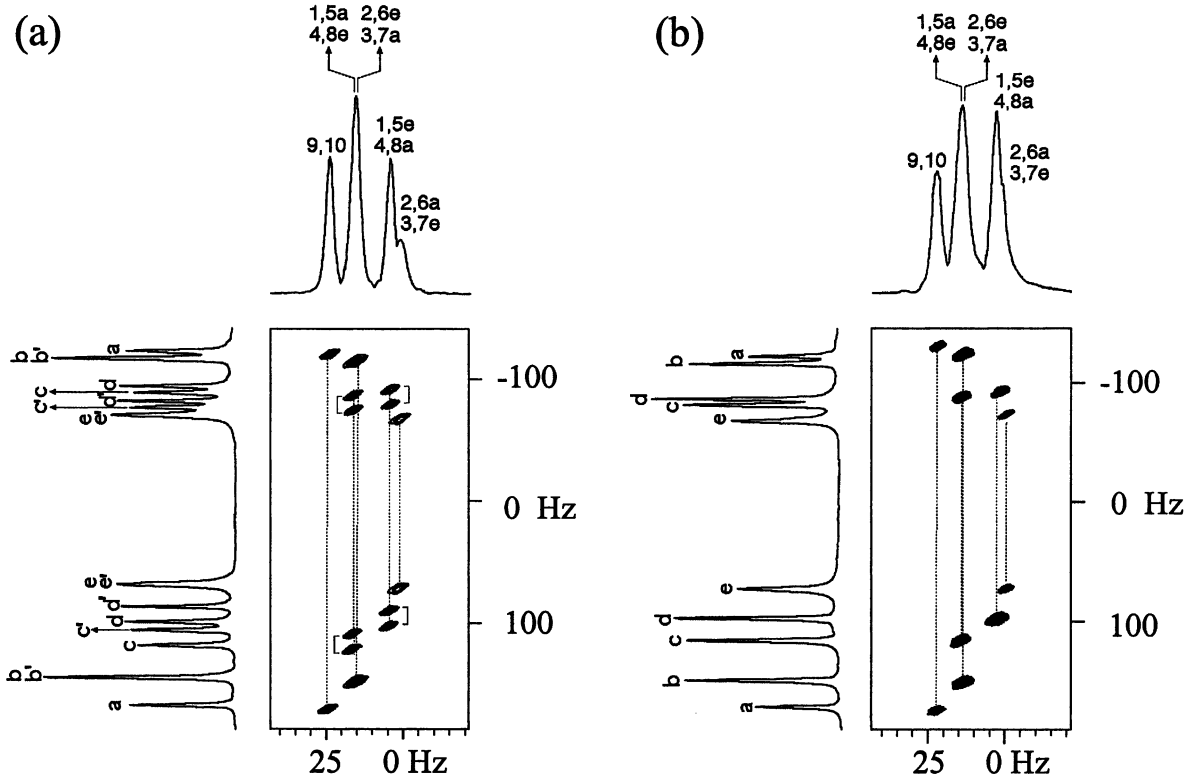

Figure 4. 61.4 MHz deuterium 2D Q-COSY tilted spectra for **1**-D_{18} at 360 K in: (a) the PBLG/$CHCl_3$ phase and (b) in the PBG/$CHCl_3$ phase. Both 2D spectra were symmetrised prior to the tilting procedure and are displayed in magnitude mode. The F_1 projections presented correspond to the ^2H 1D spectrum recorded at the same temperature. 2D spectra were recorded using 166 (t_1)×1488 (t_2) data points and the number of free induction decays added for each t_1 increment is 8. A sine filtering was used.

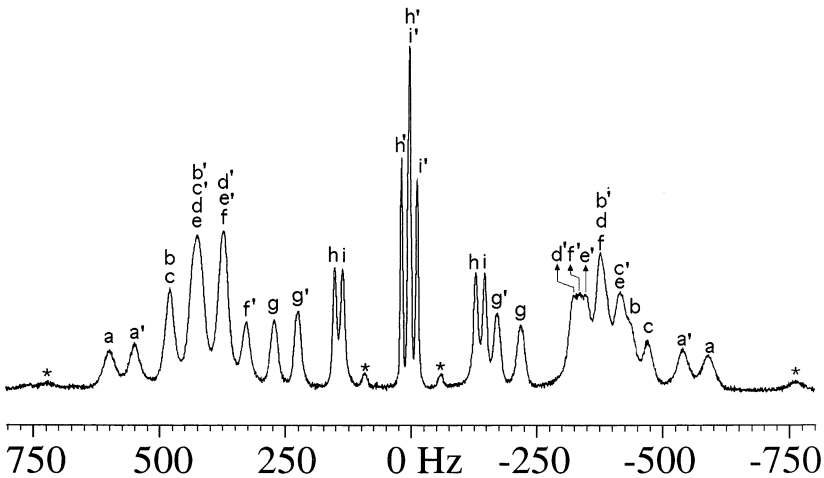

Figure 5. 61.4 MHz deuterium 1D spectrum for **1**-D_{18} at 240 K in the PCBLL/CH_2Cl_2 phase. 208 free induction decays were added. No filtering was used.

nuclei. If such nuclei are indistinguishable in achiral isotropic as well as anisotropic solvents, this situation is no longer true in a chiral oriented phase.[6] Theoretically, nine quadrupolar doublets should be observed if all deuterium signals are perfectly resolved. Experimentally, only seven splittings are distinguished, but this number of doublets is already sufficient to evidence the discrimination of enantiotopic deuterium nuclei in the molecule. The assignment of various doublets, which is also based on that published,[17] shows that only the pairs of deuterons bonded to the α-carbon (1, 4, 5, 8) are differentiated. To unequivocally confirm this result, we have recorded the ^{2}H spectrum of **1**-D_{18} in the PBG/$CHCl_3$ phase. Due to the loss of chirality of the PBG phase, all enantiotopic discriminations, which were visible in the PBLG/$CHCl_3$ phase, are now eliminated.[6] The deuterium Q-COSY spectrum of **1**-D_{18} recorded in the achiral solvent (sample 5) at 360 K is shown in Fig. 4(b). As expected, just five quadrupolar doublets are observed. Not surprisingly, the four quadrupolar doublets, c, c′ and d, d′, associated with the enantiotopic deuterons which were differentiated in PBLG by 24.5 and 25.1 Hz, respectively, now collapse into two doublets (c and d). This result is identical to that reported by Luz et al. for a thermotropic achiral liquid crystal,[13] and demonstrates, therefore, that PBLG helices also differentiate between the enantiotopic nuclei of *cis*-decalin at high temperature.

To complete the study, we explored the ability of other chiral homopolypeptides to interact enantioselectively with the two invertomers of *cis*-decalin. It was recently found that organic solutions of poly-ε-carbobenzyloxy-L-lysine (PCBLL) provided suitable chiral liquid-crystalline NMR solvents able to differentiate between enantiomers or enantiotopic elements.[18] We therefore prepared a new liquid-crystalline NMR sample (sample 6) using 18.6% of PCBLL in CH_2Cl_2 (see Table 1 for details). Fig. 5 shows the 1D deuterium spectrum of this new sample recorded at 240 K. Note that the correlation between two components of each doublet is given, but not their assignment. Examination of this ^{2}H spectrum and the 2D Q-COSY spectrum (not presented) shows that 15 of the 18 possible resolved quadrupolar doublets are visible, which can be confidently interpreted as being a result of chiral discrimination of **1a** and **1b** conformers in the phase (see Table 2).

As previously, this result was confirmed by recording the deuterium NMR spectrum of **1**-D_{18} at 240 K using a racemic mixture, denoted hereafter PCBL, made of PCBLL and its enantiomer PCBDL (also purchased from Sigma) in CH_2Cl_2 (sample 7). For these two oriented samples, we noted a significant increase in line widths (in particular for the larger splittings) compared to those measured in the PBLG/$CHCl_3$ or PBLG/CH_2Cl_2 phases. This decrease in resolution probably reflects a degraded macroscopic homogeneity of the PCBLL liquid-crystalline phase at 240 K and shows the variability in the behaviour of one polypeptide liquid-crystalline solvent to another at low temperature. Indeed, at this temperature, the exchange rate is sufficiently slow to cancel out all coalescence effects and so cannot explain the peak broadening observed.

An examination of the magnitude of various chiral differentiations, $|\Delta\nu_{Q_i}{}^S - \Delta\nu_{Q_i}{}^R|$, at low temperature for the various deuterons of **1**-D_{18} is of interest. Indeed, it can be seen that $|\Delta\nu_{Q_i}{}^S - \Delta\nu_{Q_i}{}^R|$ measured experimentally varied between 10 Hz (doublets noted g, g′) and 70 Hz (doublets noted i, i′) in PBLG/CH_2Cl_2, and between 0 Hz (doublets noted g, g′) and 41 Hz (doublets noted a, a′) in PBLG/$CHCl_3$. Amazingly, we found a difference of quadrupolar splitting for isomers **1a** and **1b** of 273 Hz (doublets noted h and h′) in the PCBLL system. These values are surprisingly large compared with those measured recently for a series of chiral flexible alkanes (3-methylhexane, -heptane and -octane) oriented in a PBLG system at ordinary temperature (1–10 Hz).[8] Disregarding a temperature effect, this result indicates that the PBLG or PCBLL helices interact very differently with the two enantiomers of *cis*-decalin. To understand these differences of enantiodiscrimination, we speculate a better topological recognition of a 'banana shaped' molecule, such as *cis*-decalin, when the ring interconversion is frozen (see Fig. 1) compared to molecules which can be crudely termed 'rod-like'. If this unprecedented result can be extended to other examples, the role of the molecular shape anisotropy in the mechanisms of chiral discrimination in polypeptides could be unambiguously established.

4. Conclusions

cis-Decalin and its substituted derivatives are of biochemical interest because they are commonly encountered as fragments in natural products. However, the study of these compounds is not simple from an enantiomeric analysis point of view. In this work, we have established the analytical potential of NMR in chiral liquid-crystalline solvents for investigating such molecules. Thus, using ^{2}H NMR in the PBLG/CH_2Cl_2, PBLG/$CHCl_3$ and PCBLL/CH_2Cl_2 phases, we have shown that the nine non-equivalent deuterons in **1a** and **1b** conformers give rise to a sufficient number of distinct quadrupolar doublets when ring inversion is frozen, thus evidencing unequivocally chiral discrimination of the enantiomers of *cis*-decalin in these three chiral, oriented solvents.

Consequently, as in the case of $^{13}C\{^1H\}$ NMR with β-cyclodextrins used as chiral solvating agents, ^{2}H NMR in organic solutions of polypeptides exhibiting liquid-crystalline properties allowed direct and convenient differentiation of chiral invertomers at low temperature. Clearly we have also shown that at high temperature it is possible to distinguish between deuterium nuclei of the molecule which become enantiotopic under rapid kinetic averaging. The possibility of obtaining such stereochemical information using straightforward NMR techniques opens up substantial prospects in studying chiral or prochiral dynamic systems.

The results reported in this work perfectly illustrate the excellent enantioselective power of the polypeptide helices to discriminate between chiral invertomers or enantiotopic nuclei in cycloalkanes. From a practical point of view, this study also shows that this method is applicable over a wide range of working temperatures (over 100 K).

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