Analysis of the ^{13}C NMR Spectra of Molecules, Chiral by Isotopic Substitution, Dissolved in a Chiral Oriented Environment: Towards the Absolute Assignment of the pro-*R*/pro-*S* Character of Enantiotopic Ligands in Prochiral Molecules

Philippe Lesot,* Olivier Lafon, Jacques Courtieu, and Philippe Berdagué[a]

Abstract: We examined and discuss the proton- and deuterium-decoupled carbon-13 1D spectrum of a molecule, chiral by virtue of the isotopic substitution, dissolved in a chiral oriented medium which simultaneously exhibits chiral discrimination, enantiomeric enrichment and isotope effect. Using the 1-deutero-(2′,3′,4′,5′,6′-pentadeuterophenyl)phenylmethanol orientationally ordered in a chiral nematic liquid crystal as illustrative example, we point out three important features. First, we demonstrate that the absolute assignment of the pro-*R*/pro-*S* character may be derived from the absolute configuration of the isotopically chiral analogue. Second, we report evidence that isotopic effect on ^{13}C chemical shift anisotropy is negligible in a weakly orienting solvent. Third, we definitely establish that the molecular orientation of prochiral C_s symmetry molecules and their parent compounds that are chiral by virtue of the isotopic substitution is the same.

Keywords: chirality · enantioselectivity · isotope effect · liquid crystals · NMR spectroscopy

Introduction

NMR spectroscopy of chiral liquid crystal is a powerful methodology in the arsenal of analytical techniques.[1–3] The numerous 1D or 2D NMR tools developed to take advantage of the information contents of anisotropic interactions have shown that this approach could be considered as the most general method dedicated to the enantiomeric and enantiotopic analysis. However, the assignment of the absolute configuration of NMR signals in orientationally ordered, chiral or prochiral molecules is difficult and remains an exciting challenge.

To reach this goal, we need to improve our understanding of the enantiodiscriminating mechanisms in such oriented solvents. The investigation of molecules, which are chiral by virtue of isotopic substitution, is interesting for this purpose because the nature of the recognition mechanisms differs from ordinary enantiomers.

[a] Dr. P. Lesot, O. Lafon, Prof. J. Courtieu, Dr. P. Berdagué
Laboratoire de Chimie Structurale Organique
CNRS UMR 8074, ICMMO, Bât. 410, Université de Paris-Sud
91405 Orsay cedex (France)
Fax: (+33) 169-15-81-05
E-mail: philesot@icmo.u-psud.fr

In our previous work, we have reported that ordinary enantiomers differ both in the magnitude of the elements of the Saupe order matrix, $S_{\alpha\beta}$, and in the orientation of their principal axis systems while this is not true for the isotopic enantiomers.[4] This result implies that the average orientation of two ordinary enantiomers in a chiral liquid crystal (CLC) differs and points out that both molecular size and shape play an important role in the solute–CLC interactions involved in the chiral discrimination mechanisms. For isotopic enantiomers, the situation is rather different because the origin of their chiral discrimination is a consequence of the fact that two enantiotopic ligands are non equivalent in CLC such as organic solutions of poly-γ-benzyl-L-glutamate (PBLG).[5,6]

The phenomenon of enantiotopic discrimination in chiral liquid crystalline solvents is due to the change in the symmetry of the intermolecular potential experienced by the solute when the environment is chiral compared with achiral oriented media.[6,7] Due to the chiral environment, no plane of symmetry will be conserved in the orientational probability function in such a way that C_s molecules will behave as if it were C_1, C_{2v} molecules will behave as if they were C_2 and so on.[6,8]

The chiral discrimination mechanism described above was derived from the analysis of proton-decoupled deuterium NMR spectra,[5] but no investigations using ^{13}C NMR spectroscopy have been made so far.[1] It is the purpose of this

 DOI: 10.1002/chem.200400065

paper to study the consequences of such symmetry lowering in the ^{13}C NMR of prochiral molecules and in isotopically chiral analogues.

To illustrate our purpose we have investigated the case of a chiral di-aromatic compound, the *R* enriched 1-deutero-(2′,3′,4′,5′,6′-pentadeuterophenyl)phenylmethanol (**1**) (20% *ee)* and the related deuterated and protonated prochiral molecules (**2** and **3**). All of them were dissolved in the PBLG/$CHCl_3$ chiral liquid crystal solvent. The molecular structures of compounds **1** to **3** and the notations are sketched in Figure 1. In case of **1**, we have a molecule chiral by virtue of the deuterium isotopic substitution. Compounds **2** and **3** are analogous to **1**, but are not chiral.

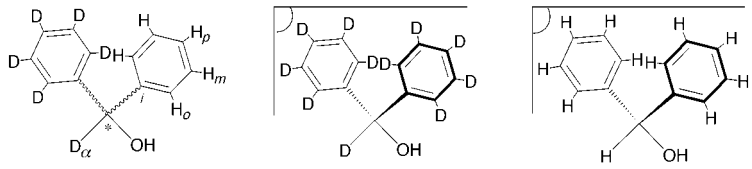

Figure 1. Drawing of the studied compounds **1** to **3**. The chemical notation (α, *i*, *o*, *m*, *p*) used here defines both the deuterium and the carbon atoms. Compound **1** is a *R*-enriched mixture of the enantiomers (20% *ee*).

Results and Discussion

Spectral analysis and assignment: Figure 2a presents the aromatic region of proton- and deuterium-decoupled carbon-13 (^{13}C-{^1H,^2H}) 1D spectrum of **1** recorded in the PBLG/$CHCl_3$ oriented phase at 300 K. Interesting and unexpected questions arise when analysing the ^{13}C NMR spectrum that exhibits sixteen resonances with various peak intensities. As we will demonstrate below, this apparent complexity originates from three distinct NMR effects: the chiral discrimination in the PBLG phase, the enrichment of the mixture and the $^1H/^2H$ isotope effect observed on ^{13}C chemical shift of deuterium labelled compounds. To understand the analysis and the following discussion, we have to remember that the NMR resonance frequency, $\tilde{\nu}_i$, of a ^{13}C nucleus *i* contains both an isotropic, σ_i^{iso}, and an anisotropic, $\Delta\sigma_i$, contribution to the electronic shielding and may be written for a pair of enantiomers as:[1,9,10]

$$\nu_i^{R\text{ or }S} = \frac{\gamma}{2\pi}\left[1-\sigma_i^{iso}-\Delta\sigma_i^{R\text{ or }S}\right]B_0 \qquad (1)$$

Equation (1) clearly reveals that chiral discrimination in chiral oriented solvent is detected in NMR spectra when $\nu_i^S - \nu_i^R \neq 0$, namely when $\Delta\sigma_i^S$ significantly differs from $\Delta\sigma_i^R$, assuming that $\Delta\sigma_i^{iso}$ is identical[7] for both enantiomers.

As a visual evidence, the analysis of the spectrum of **1** recorded in the PBLG phase suggests the existence of two sub-systems with two ranges of peak intensity. Each of them is made of four pairs of resolved resonances whose differences in peak intensity originate from the enantiomeric enrichment of the mixture. Actually the existence of two series of peaks results from the well-known $^1H/^2H$ isotope shielding effect.[11] Both types of NMR signals are noted *x*-H and *x*-D (*x* = *i*, *m*, *p*, and *o*) for the protonated and perdeuterated benzene groups, respectively, and the ^{13}C peak assignment reported in the spectra is based on additive rules for benzene substituents.[12]

As it can be seen in Figure 2b, the isotopic effects on ^{13}C chemical shifts exists also on the ^{13}C-{^1H,^2H} 1D spectrum of **1** recorded in achiral isotropic phase ($CHCl_3$). Indeed two sub-spectra with two ranges of peak intensity are clearly obtained again while no chiral discrimination occurs in this case. In both phases, the large difference in peak intensity between the "*x*-H" and "*x*-D" signals is a direct consequence of the lack of deuterium-to-carbon NOE effect even if the deuterium decoupling is turned on.[13] All relevant spectral data about the spectrum of **1** are given in Table 1.

To confirm this analysis, we have recorded the ^{13}C-{^2H} and ^{13}C-{^1H} 1D spectrum of prochiral compounds **2** and **3**, respectively, both embedded in the PBLG/$CHCl_3$ mesophase using the same conditions than for the chiral compound **1**. The superposition of the ^{13}C-{^1H,^2H} signals of **1** with those of prochiral entities allows us to definitely assess the assignment all ^{13}C signals associated with the deuterated and protonated aromatic core in the chiral compound. As expected the aromatic ^{13}C NMR resonances of the perdeuterated prochiral molecule show a significant shielding isotopic effect compared with those of the protonated one (traces c and d in Figure 2).

The assignment of *R* and *S* descriptors displayed in the spectrum 2a is based on the difference of peak intensity for each pair of signals originating from the known enantiomeric enrichment of the mixture. The relative inversion of ^{13}C chemical shifts of the *R* and *S* enantiomers associated with the protonated and perdeuterated aromatic cycle is rather intriguing because a priori it could be thought that the relative position of ^{13}C NMR signals, for the protonated and deuterated phenyl group would be the same. In fact this simplistic argument is false. Considering that the molecular ordering is not affected by the isotopic substitution, we are going to demonstrate that the relative positions (shielded/deshielded) of a given aromatic ^{13}C NMR signal in the deuterated aromatic ring for the *R*- and *S*-enantiomers are opposite to that observed for the protonated one. The different steps of this demonstration using a series of schematised ^{13}C-{^1H,^2H} NMR spectra are presented in Figure 3 (from a to e).

To illustrate our purpose, we have assumed fictitious protonated and perdeuterated prochiral molecules (noted M-H and M-D, respectively) as well as the corresponding compound chiral by virtue of the isotopic substitutions (noted M-HD). The various ligands around the prostereogenic or stereogenic tetrahedral center are X, Y, CD_3 and/or CH_3. The absolute configuration of the chiral molecule and the pro-*R*/pro-*S* character of the enantiotopic substituents around the prostereogenic centre are given according to the priority rules used in the CIP system, namely X > CD_3 > CH_3 > Y.[14]

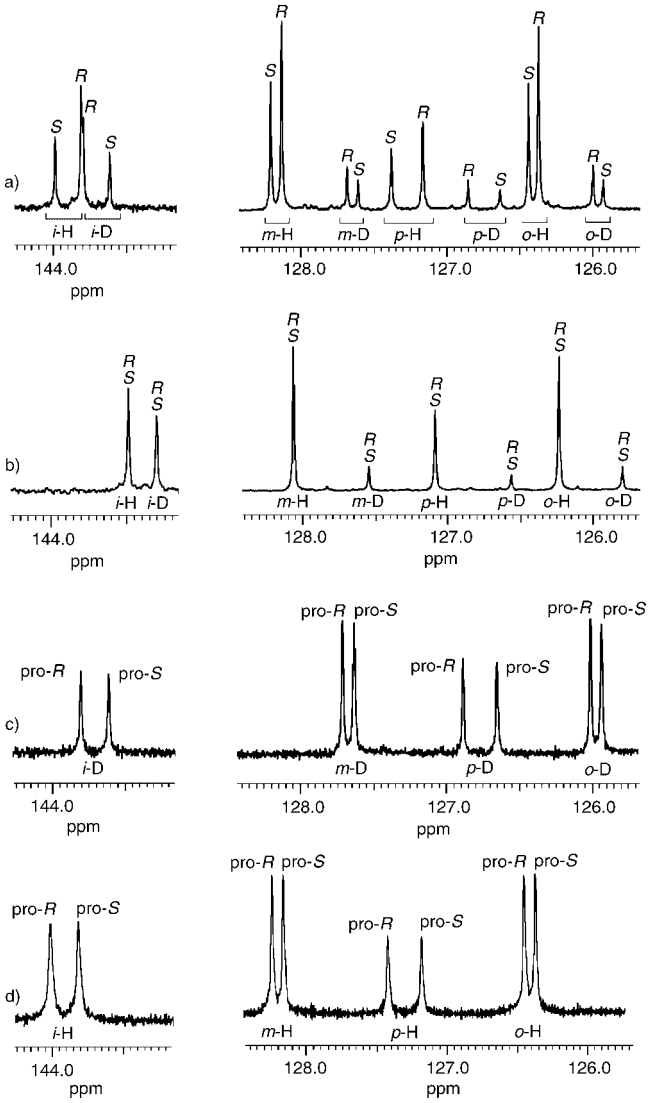

Figure 2. a) and b) Aromatic region of the ^{13}C-{^{1}H,^{2}H} 1D NMR spectra of compound **1** recorded at 300 K in the PBLG/$CHCl_3$ phase and in $CHCl_3$, respectively. c) ^{13}C-{^{2}H} NMR signals of aromatic carbon nuclei of prochiral compound **2** in the PBLG/$CHCl_3$ phase. d) ^{13}C-{^{1}H} NMR signals of aromatic carbon nuclei of prochiral compound **3** in the PBLG/$CHCl_3$ phase. The four spectra were recorded using the same experimental conditions. For spectra a, b, c and d, a Gaussian filtering was applied to enhance the spectral resolution. The comparison of trace a with traces c and d allows the determination of stereodescriptors (pro-*R* and pro-*S*) associated with the ^{13}C resonances of compounds **2** and **3**.

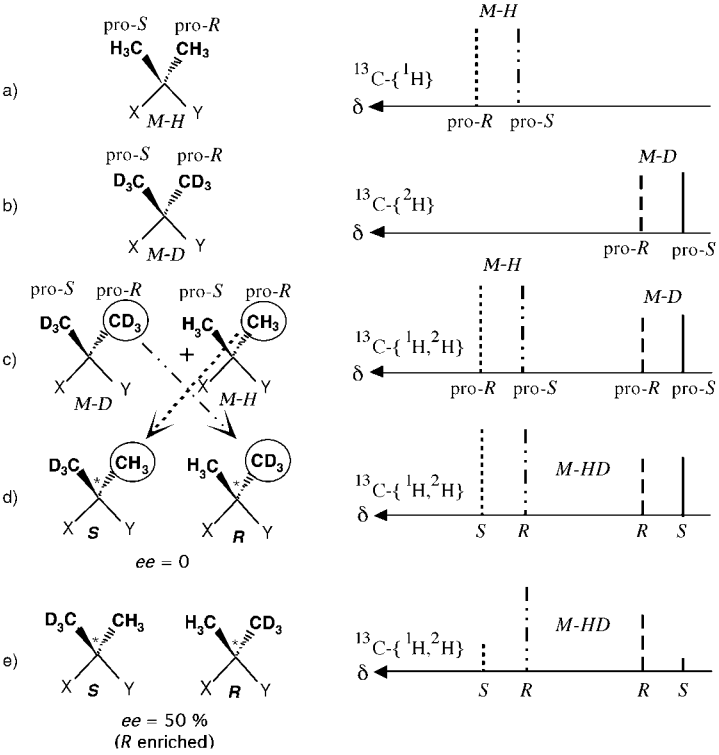

Figure 3. Series of schematic representations illustrating the origin of the inversion of peak intensity in ^{13}C-{^{1}H,^{2}H} spectra for an hypothetical molecule chiral by virtue of isotopic substitution compared to the prochiral analogues, all of them dissolved in a chiral oriented system. Only the ^{13}C signals of methyl groups are presented. The four resonances are displayed by four lines with different dash patterns. a) ^{13}C-{^{1}H} spectrum of the M-H molecules. b) ^{13}C-{^{2}H} spectrum of M-D molecules. c) ^{13}C-{^{1}H,^{2}H} spectrum of a 50/50 mixture of M-H and M-D molecules. d) ^{13}C-{^{1}H,^{2}H} spectrum of M-HD molecules in racemic mixture. The arrows show the relationship between the pro-*R* methyl groups in the protonated and deuterated prochiral molecules and the *R* and *S* enantiomers. e) Same as d) but using a *R*-enriched mixture (50 % *ee*).

The traces a and b schematically display the pro-*R* and pro-*S* ^{13}C signals of the methyl group associated to the deuterated and protonated prochiral molecules, respectively. In these spectra, we have considered that the isotopic shielding effect for carbon nuclei directly interacting with deuterons occurs and that this effect is sufficiently large to preclude overlaps between ^{13}C NMR signals of protonated and deu-

Table 1. Quantification of the isotope effects observed at 300 K for compound **1** in the isotropic and chiral oriented phase.

Atom	Isomer	$\delta^{H^{iso}}_{^{13}C}$/ppm[a,b]	$\delta^{D^{iso}}_{^{13}C}$/ppm[a,c]	$\Delta C(D)_{iso}$/ppb[a,c]	$\delta^{H^{aniso}}_{^{13}C}$/ppm[a,b]	$\delta^{D^{aniso}}_{^{13}C}$/ppm[a,c]	$\Delta C(D)^{aniso}$/ppb[a]	$\Delta C(D)^{average}_{aniso}$/ppb[a]
α	*R*	–	75.20	–	–	74.95	–	–
	S							
(*i*)	*R*	143.49	143.30	−190	143.79	143.78	−10	−190
	S				143.97	143.60	−370	
(*o*)	*R*	126.23	125.80	−430	126.36	126.00	−360	−430
	S				126.43	125.93	−500	
(*m*)	*R*	128.06	127.54	−520	128.12	127.67	−450	−520
	S				128.19	127.60	−590	
(*p*)	*R*	127.08	126.56	−520	127.15	126.85	−300	−520
	S				127.37	126.63	−740	

[a] The accuracy of the δ_i values is around ± 0.01 ppm (10 ppb). [b] Data relative to carbon atoms of the protonated aromatic group. [c] Data relative to ^{13}C atoms of the deuterated aromatic group.

terated methyl groups. Also, the difference in peak intensities between labelled and non-labelled entities simulates the lack of nuclear Overhauser effects in deuterium–carbon nuclei pairs. Finally, to be comparable with the relative position of resonances observed in the experimental ^{13}C NMR spectra (Figure 2), the ^{13}C signals of methyl group defined as pro-*S* correspond to the most shielded resonances in the M-D and M-H fictitious molecules. Spectrum c should be theoretically obtained if we add the M-D and M-H molecules in equal quantity (the difference of M_w for M-D and M-H is neglected). If we now assume that the molecular order parameters for enantiomers of a molecule chiral by virtue of the isotopic substitution and their corresponding prochiral molecule are the same, then we expect to observe the same ^{13}C-{^{1}H,^{2}H} spectrum in both cases (trace d). However, for a mixture made of M-HD isotopic enantiomers, the resonance associated to the pro-*R* carbon atom in M-D corresponds now to the peak associated to the deuterated methyl group in the *R*-isomer.

By contrast the resonance associated to the pro-*R* carbon atom in M-H entity corresponds to the peak of the protonated methyl group of the *S*-enantiomer (spectra c and d). If the M-HD mixture is enantio-enriched in *R*-enantiomer, then the intensity of ^{13}C-{^{1}H,^{2}H} resonances for the *R*- and *S*-isomers differs as seen in the trace e.

The above demonstration fully explains the apparent inversion of the ^{13}C signal assignment associated with the protonated and deuterated aromatic group of **1** as shown in Figures 2a and 3e. In addition, by inverting the "sense" of the demonstration, we can assign without ambiguity the stereochemical descriptors, pro-*R* and pro-*S*, for all the ^{13}C NMR signals in the related prochiral molecules, as shown in Figure 3a and b or in Figure 2c and d for the experimental case. As expected, the relative position of ^{13}C signals associated with the pro-*S* and pro-*R* substituents is the same for the protonated and perdeuterated prochiral entities.

Two important features of the NMR in weakly orienting chiral liquid crystal can be drawn from the previous discussion. First, we have found that the assignment of ^{13}C NMR signals of two enantiotopic ligands chemically differentiated by the isotopic substitution in a chiral molecule are inverted and this result is general whatever the molecule is. Second, we have shown that such analysis allows for explicitly assigning the stereochemical descriptors, pro-*R* and pro-*S*, to the corresponding ^{13}C resonances in the protonated and perdeuterated prochiral molecule, both of them being related to the molecule chiral by virtue of the isotopic substitution.

Study of the isotope effects: The quantitative analysis of the isotope effect measured both in the isotropic and the chiral oriented solvents is interesting and merits some attention. Indeed it provides some insights into the relationship existing between the isotope effect and the orientational behaviour of the perdeuterated and protonated aromatic ring of compounds **1** to **3** dissolved in the PBLG phase.

The isotope effect measured on a carbon atom in the case of a monodeuterated molecule is defined usually as, $^{n}\Delta C(D) = \delta_{deuterated} - \delta_{protonated}$, where n is the number of bonds between the deuterium and ^{13}C atom considered.[11c] In our case, we observe the contribution of several deuterons for a given carbon atom, consequently the notation n cannot be used further. In this example the magnitude of $\Delta C(D)_{iso}$ values measured in the isotropic phase varies between -190 and -520 ppb ($1\ ppb = 10^{-3}$ ppm). The values measured on C-1′, C-2′/6′, C-3′/5′ and C-4′ atoms on compound **1** are listed in Table 1.

In a first step, we have compared $\Delta C(D)_{iso}$ with the average values of $\Delta C(D)_{aniso}$ measured in the chiral anisotropic phase ($\Delta C(D)^{average}_{aniso} = \Delta C(D)^{R}_{aniso} + \Delta C(D)^{S}_{aniso}/2$)). This average value of $\Delta C(D)_{aniso}$ corresponds to the value that would be measured in an achiral oriented phase made of a racemic mixture of PBLG and PBDG (the PBLG's enantiomer).[15] In such a racemic ordered solvent, denoted PBG, a solute is diffusing very rapidly on the NMR time scale from PBLG to PBDG fibres, consequently we observe only an average of these two situations, thus eliminating the spectral enantiodiscrimination.[15] The comparison between and $\Delta C(D)^{average}_{aniso}$ and $\Delta C(D)_{iso}$ shows no differences within the experimental errors. Such a result suggests therefore that the contribution of the isotope effect to the anisotropic component, $\Delta\sigma_i$, of ^{13}C chemical shift is negligible at least, in a weakly ordering, chiral solvent. In other words, the isotope effect modifies only the isotropic term in Equation (1). If this was not the case, the value of $\Delta C(D)^{average}_{aniso}$ should significantly differ from $\Delta C(D)_{iso}$.

Also, the spectral analysis shows that ^{13}C NMR signals associated with the perdeuterated and protonated phenyl groups are enantiodiscriminated. The ^{13}C chemical shifts for the *R*- and *S*-isomers are given in Table 1. To analyse the results, we have plot in the same graph the quantity $\delta^{D^{aniso}}_{R} - \delta^{D^{iso}}$ (deuterated phenyl group) versus $\delta^{H^{aniso}}_{S} - \delta^{H^{iso}}$ (protonated phenyl group) as well as the reciprocal quantity $\delta^{D^{aniso}}_{S} - \delta^{D^{iso}}$ versus $\delta^{H^{aniso}}_{R} - \delta^{H^{iso}}$. As it can be seen in Figure 4, the

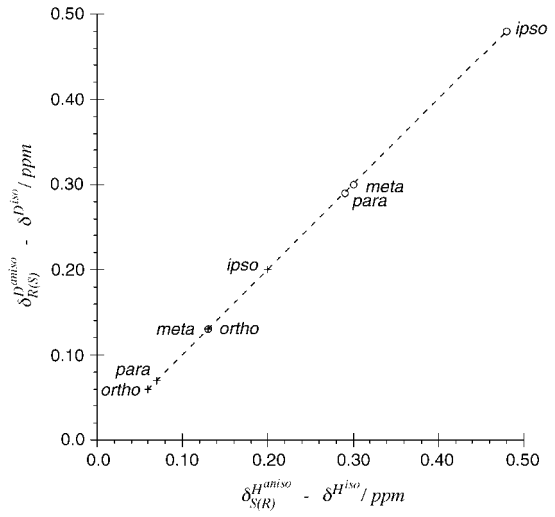

Figure 4. a) Plot of the quantities (data from the deuterated phenyl group) as a function of (data from the protonated phenyl group). See text for explanation. Data points associated with *R*- and *S*-enantiomers (deuterated aromatic ring) are labelled with an open circle and a cross, respectively. The slope of the line is one and passes zero. The correlation coefficient of the fit is 0.9999.

calculated points can be fit by a single linear function which equation is of the form $Y = X$ with a correlation coefficient equal to 0.9999. The linear evolution of data is not fortuitous and two important conclusions in terms of orientational behavior and chiral discrimination mechanisms can be drawn from this result. First, it appears that the deuterated aromatic ring in the *R*-enantiomer and the protonated aromatic ring in the *S*-enantiomer have the same Saupe order matrix, namely $(S_{\alpha\beta}^{D-ring})^R = (S_{\alpha\beta}^{H-ring})^S$. In other words, they possess the same orientational ordering characteristic and conformational dynamic. The same occurrence exists for protonated phenyl group in *R*-enantiomer and the deuterated phenyl group in the *S*-enantiomer, namely $(S_{\alpha\beta}^{H-ring})^R = (S_{\alpha\beta}^{D-ring})^S$.

The inverted role of protonated and deuterated aromatic ring in the enantiomeric couple indicates that the local interactions between the aromatic cores and the surrounding chiral matrix are unaffected by the isotopic substitution. Second, the enantiomeric discriminations observed for carbons of aromatic ring occur because for each enantiomer the local parameters for the two aromatic rings are different, namely $(S_{\alpha\beta}^{D-ring})^{R(S)} \neq (S_{\alpha\beta}^{H-ring})^{R(S)}$. This local differential ordering implies that the enantiodiscrimination of two isotopic enantiomers is a direct consequence of the differentiation of enantiotopic elements existing in the prochiral compound either protonated or deuterated when embedded in a chiral oriented environment. In no way, this discrimination involves a difference of molecular ordering as in the case of ordinary enantiomers.[4] If it was the case the graph of quantities $\delta_{R(S)}^{D^{aniso}} - \delta^{D^{iso}} = f(\delta_{S(R)}^{H^{aniso}} - \delta^{H^{iso}})$ would not be along the bisector. This last result definitely establishes that the molecular orientational order parameters of prochiral, C_s symmetry molecules, and their parent derivatives, which are chiral by virtue of the isotopic substitution, are identical in this weakly ordering chiral liquid crystal. This new evidence therefore confirms previous qualitative initial results observed using deuterium NMR spectroscopy in the PBLG phase[5] and shows explicitly that the spectral discrimination between enantiotopic elements in prochiral compounds and between the corresponding isotopic enantiomers involves the same enantiorecognition mechanisms.

Conclusion

In this article we have investigated the proton- and deuterium decoupled ^{13}C spectrum of molecule chiral by isotopic substitution, dissolved in chiral oriented environment. Several important conclusions were drawn from this analysis. First we have pointed out that the contribution of the isotope effect on ^{13}C chemical shift anisotropy is negligible in a weakly orienting solvent. Second we have definitely confirmed previous results observed using ^{2}H NMR spectroscopy in PBLG that suggested that the molecular orientation of prochiral, C_s symmetry molecules and their parent compounds that are chiral by virtue of isotopic substitution was the same. Third, we have found out that the assignment of ^{13}C signals of two substituents chemically differentiated by the isotopic substitution in a chiral molecule was inverted compared with the prochiral parent molecules and this result is general. Fourth, but not the least, we have shown an interesting way for assigning the absolute pro-*R*/pro-*S* character of enantiotopic ligands.

Experimental Section

NMR sample preparation: The synthesis of compounds **1** enriched in *R*-enantiomer (20% *ee*) and **3** were synthesised following referenced literature.[16,17] Compound **2** is commercially available. The liquid-crystalline NMR samples were prepared using a procedure already described.[1,2] The NMR sample compositions are 100 mg of M_w ~112000 PBLG (commercially available from Sigma), 100 mg of solute **1**, **2** or **3**, and 400 mg of $CHCl_3$ directly weighed into a 5 mm o.d. NMR tube.

NMR spectroscopy: The NMR experiments were performed at 9.4 T on a Bruker DRX 400 high-resolution spectrometer equipped with a direct multinuclear broadband probe (BBO) operating at 100.6 MHz for carbon-13. The variable temperature unit BVT 3200 controlled the temperature of the sample. The NMR tubes were not spun. All 1D NMR experiments have been recorded at 300 K. Proton and deuterium broadband decoupling was achieved using the standard WALTZ-16 composite pulse sequence on both nuclei.[1] The lock channel of the BBO probe was used as deuterium channel. Other experimental NMR parameters or details are given in Figure captions. For all ^{13}C spectra, the chloroform signal was used as internal reference and assigned at 77.0 ppm.

Acknowledgement

The authors thank Dr. J. M. Péchiné for the gift of compounds **1** and **3** and Profs. J. W. Emsley and Z. Luz for their helpful discussions and fruitful comments.

[1] M. Sarfati, P. Lesot, D. Merlet, J. Courtieu, *Chem. Commun.* **2000**, 2069–2081, and references therein.
[2] P. Lesot, M. Sarfati, J. Courtieu, *Chem. Eur. J.* **2003**, *9*, 1724–1745.
[3] C. Aroulanda, M. Sarfati, J. Courtieu, P. Lesot, *Enantiomer* **2001**, *6*, 281–287.
[4] a) P. Lesot, D. Merlet, T. P. Rantala, J. Jokisaari, J. W. Emsley, J. Courtieu, *J. Phys. Chem. A* **1997**, *101*, 5719–5724; b) J. W. Emsley, P. Lesot, D. Merlet, *Phys. Chem. Chem. Phys.* **2004**, *6*, 522–530.
[5] A. Meddour, I. Canet, A. Loewenstein, J. M. Péchiné, J. Courtieu, *J. Am. Chem. Soc.* **1995**, *116*, 9652–9656.
[6] a) D. Merlet, A. Loewenstein, W. Smadja, J. Courtieu, P. Lesot, *J. Am. Chem. Soc.* **1998**, *120*, 963–969; b) D. Merlet, J. W. Emsley, P. Lesot, J. Courtieu, *J. Chem. Phys.* **1999**, *111*, 6890–6896.
[7] P. Lesot, D. Merlet, M. Sarfati, J. Courtieu, H. Zimmermann, Z. Luz, *J. Am. Chem. Soc.* **2002**, *124*, 10071–10082.
[8] C. Aroulanda, D. Merlet, J. Courtieu, P. Lesot, *J. Am. Chem. Soc.* **2001**, *123*, 12059–12066.
[9] P. Lesot, D. Merlet, A. Meddour, A. Loewenstein, J. Courtieu, *J. Chem. Soc. Faraday Trans.* **1995**, *91*, 1371–1375.
[10] A. Meddour, P. Berdagué, A. Hedli, J. Courtieu, P. Lesot, *J. Am. Chem. Soc.* **1997**, *119*, 4502–4508.
[11] a) P. E. Hansen, *Ann. Rep. NMR Spectrosc.* **1983**, *15*, 105–231; b) P. E. Hansen, *Prog. Nucl. Magn. Reson. Spectrosc.* **1988**, *20*, 207–257; c) J. R. Wesener, D. Moskau, H. Günther, *Tetrahedron. Lett.* **1985**, *26*, 1491–1492; d) S. Berger, *Isotope Effects in NMR Spectroscopy, NMR Basic Principles and Progress, Vol. 2*, Springer, **1990**, p. 1; e) C. J. Jameson, in *Encyclopedia of NMR* (Eds.: G. M. Grant, R. K. Harris), Wiley, Chichester, **1995**, pp. 2638–2655.
[12] H. A. Kalinowski, S. Berger, S. Braun, in *Carbon-13 NMR Spectroscopy*, Wiley, New York, **1988**.
[13] P. L. Rinaldi, N. J. Baldwin, *J. Am. Chem. Soc.* **1982**, *104*, 5791–5793.
[14] a) R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem.* **1966**, *78*, 413–433; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385–415; b) A. L. Eliel,

A. H. Wilen, in *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.
[15] C. Canlet, D. Merlet, P. Lesot, A. Meddour, A. Loewenstein, J. Courtieu, *Tetrahedron: Asymmetry* **2000**, *11*, 1911–1918.
[16] R. H. Newman-Evans, R. J. Simon, B. K. Carpenter, *J. Org. Chem.* **1990**, *55*, 695–711.
[17] G. R. Sood, D. M. Ashworth, A. A. Ajaz, J. A. Robinson, *J. Chem. Soc. Perkin Trans.* **1988**, *1*, 3183–3193.

Received: January 20, 2004
Published online: June 15, 2004

