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Chiral Liquid Crystal NMR: A Tool for Enantiomeric Analysis

Jacques Courtieu, Philippe Lesot, Abdelkrim Meddour, Denis Merlet, and Christie Aroulanda

Université Paris-Sud, Orsay, France

1 INTRODUCTION

The NMR spectra of enantiomers are fundamentally identical. This is because the projection of magnetic properties along the magnetic field axis is independent of the "handedness" of the molecules. An other way to tell this is to recall that enantiotopic nuclei are isochronous and consequently two objects that are mirror images cannot be differentiated. On the contrary, diastereomers may be distinguished because diastereotopic nuclei are non equivalent. The determination of enantiomeric purity using NMR therefore requires the use of a chiral auxiliary that, in one way or another, converts the mixture of enantiomers into a mixture of diastereomers. Whenever the induced chemical shift inequivalence is large enough to produce well resolved lines, then integration gives a direct measure of the diastereomeric composition which can be easily related to the enantiomeric composition of the original mixture.

Since the late sixties, three types of chiral auxiliaries have been commonly in use in classical NMR in the liquid state. Chiral Lanthanide Shift Reagents[1] and Chiral Solvating Agents[2] form diastereomeric complexes with substrate enantiomers and may be use directly. Chiral Derivatizing Agents[3] require the synthesis of discrete diastereomers prior to NMR analysis. These techniques and their limitations have been nicely reviewed recently by David Parker.[4]

In this contribution we describe a more recent technique which proceeds through the use of chiral liquid crystals as the NMR solvent. Here the chiral discrimination originates in a difference of the enantiomer ordering when dissolved in such a medium. Consequently, all order sensitive NMR interactions are different, namely chemical shift anisotropies, dipolar coupling and quadrupolar splitting. The major advantage of this later method is that it works with all types of chiral molecules, independently of any functional group, as in alkanes for instance. Furthermore, this method has been shown to work amazingly well for molecules whose chirality arises by virtue of isotopic substitution. Finally, this technique has been shown to give interesting results in the study of diastereomers with remote asymmetric centres.

2 HISTORY

The idea of using chiral liquid crystal solvents to distinguish enantiomers emerged in the sixties, shortly after the discovery by Saupe and Englert of the usefulness of nematic liquid crystals as anisotropic NMR solvents.[5] The response of a cholesteric phase to an external homogeneous magnetic field has been studied by McColl et al.[6] It depends on the sign of the anisotropic magnetic susceptibility, $\Delta\chi$. When the molecular $\Delta\chi$ is positive the helix axis tends to align perpendicular to the magnetic field, B_0. In this situation the director is distributed in a plane that contains B_0. Very broad NMR spectra are then expected as there is not a homogeneous orientation of the director toward the magnetic field. However, if the field is larger than some critical field,[7] particular to each liquid crystal system, the field unwinds the supramolecular cholesteric helix, thus giving rise to a chiral nematic phase where high resolution NMR may be achieved. The situation is more interesting when the molecular $\Delta\chi$ is negative. Then the supramolecular helix axis orientates parallel to B_0 and consequently the director is distributed in a plane perpendicular to the magnetic field. The director orientation is then expected to be homogeneous and at 90° to B_0. Unfortunately, it has been shown[8,9] that in this situation the director generally does not orientate homogeneously enough to provide high-resolution spectra. This has been attributed to existing textural defects due to visco-elastic forces that the magnetic field cannot overcome. This is an unfavorable effect that prevented development of NMR in such chiral-oriented solvents, even if they were expected to act differently on enantiomers.

In 1968, Snyder et al. performed a clever experiment.[10] Realizing that the supramolecular helicity of the cholesteric phase was the origin of the low quality of the orientation, they made up a chiral nematic solvent from a compensated mixture of two different cholesteric compounds of opposite helicity. By using racemic 3,3,3-trichloropropylene oxide as a guest molecule, they announced that they obtained separate spectra for each enantiomer (Figure 1). Unfortunately, the linewidth were still rather large and the solvent used, a mixture of cholesterol derivatives, prevented any development of this technique.

In 1975, Tracey and Dieh[11] reported a small ^{1}H NMR separation observed for *D-L* alanin when dissolved in a lyotropic liquid crystal made of sodium n-decylsulfate doped with chiral sodium decyl-2-sulfate (Figure 2). This experiment, which may be seen as the first chiral discrimination using a cholesteric liquid crystal as solvent, has been reproduced several times by Tracey and Radley using lyotropic liquid crystals made of chiral polar head amphiphiles.[12–15] In these

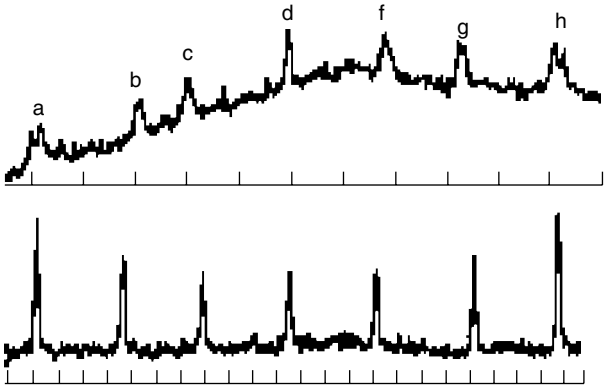

Figure 1 60 MHz proton spectrum of racemic 3,3,3-trichloropropylene oxide in a liquid crystal solvent. The lower trace solvent was a classical nematic. The upper trace solvent was made of a mixture of 0.53 g of cholesteryl chloride and 0.28 g of cholesteryl myristate. Note the apparent doubling of the external lines when using this compensated nematic mixture of cholesterics. (Reproduced by permission of the American Chemical Society from Sackmann et al.[10])

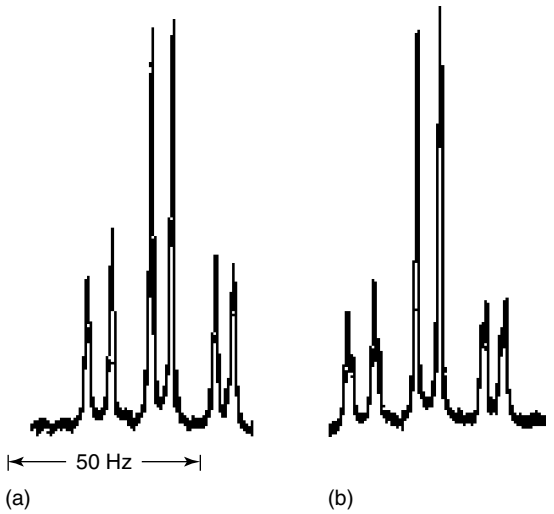

Figure 2 (a) The methyl proton resonance at 100 MHz from *D*-alanine in the chiral lyotropic phase described in the text. (b) The methyl resonance of a non-racemic mixture of *D*- and *L*-alanine. Clearly there are two superimposed spectra corresponding to the enantiomers. (Reproduced by permission of North-Holland Publishing Company, Amsterdam, from Tracey et al.[11])

experiments, the spectroscopic separation between the alanin enantiomers were correlated to the cholesteric pitch to inquire about the origin of the micelle to micelle twist. No practical applications to measuring enantiomeric excess developed, mainly because these liquid crystals are difficult to orient homogeneously in the magnetic field and also because proton NMR was used, and consequently only the study of very small molecules was possible.

Independently, in the 1960s, considerable attention was devoted to the cholesteric liquid crystal properties of organic solutions of some synthetic homo-polypeptides such as poly-γ-benzyl L-glutamate (PBLG).[16–19] In 1967 three sets of workers, Samulski and Tobolski,[20] Sobajima[21] and Panar and Philips,[22] independently found that the ^{1}H NMR spectrum of CH_2Cl_2 is split into a doublet in the liquid crystalline phase PBLG/CH_2Cl_2. This result indicates clearly that, in a strong magnetic field, the supramolecular pitch is unwounded due to the bulk anisotropy of the diamagnetic susceptibility, thus producing a cholesteric to chiral-nematic transition. This medium thus furnishes a very interesting oriented solvent for high resolution NMR.[22]

Most of the work done between 1965 and 1990 was essentially dedicated to the study of the rather unusual liquid crystal properties of these polymeric solutions.[23] Nevertheless, in 1981, Czarniecka and Samulski[24] noticed that the enantiotopic deuterons in benzyl alcohol-d_7 give each a quadrupolar doublet when dissolved in PBLG liquid crystal solution. This means that in such a chiral anisotropic medium enantiotopic nuclei are not equivalent, as they are in non-chiral liquid crystalline solvents. We will see later that this finding has important consequences regarding isotopic chirality.

In 1989, our group presented a new chiral liquid crystal solvent made of a mixture of cholesteryl propionate (60%) and ZLI-2806 (40%), the latter being a commercially available nematic eutectic mixture of different cyano-bicyclohexyl derivatives.[25] This cholesteric $\Delta\chi < 0$ mixture has the unique property to orient homogeneously with the helicity axis parallel to the NMR magnetic field. In this situation, the director being entirely perpendicular to Bo, good high-resolution dipolar spectra were obtained for dissolved molecules. The next step was to study the high-resolution spectrum of a simple chiral molecule using the above solvent. The first ^{1}H spectrum obtained using racemic 3,3,3-trichloropropylene oxide is shown in Figure 3. Due to the size of the dipolar couplings an ABC pattern was expected for the three spin system and two superimposed ABC patterns are easily visible, one spectrum for each enantiomer.

An analysis of the sub-spectra attributed to each enantiomers has been realized, and lead to the following results:

(a) In each sub-spectra the chemical shifts and the scalar couplings are the same within experimental error.
(b) The only difference between the spectra originates from a difference in the inter proton dipolar couplings.

The importance of this last point is seen when looking at the parameters involved in the dipolar coupling:

$$D_{ij} = -\left(\frac{\mu_o}{4\pi}\right)\frac{h\gamma_i\gamma_j}{4\pi^2 r_{ij}^3}\cdot\frac{1}{2}\langle 3\cos^2\theta_{ij}^z - 1\rangle$$

It is clear that the observed difference in the dipolar couplings cannot come from the magnetogyric ratios γ_i and γ_j because the same nuclei are involved in the enantiomers. The difference also cannot come from the internuclear distance r_{ij} since symmetry through a plane keeps distances constant. So it must be concluded that the dipolar coupling difference between the enantiomers originate from a difference in the so-called order parameters, $S_{ij} = \langle 3\cos^2\theta - 1\rangle/2$, of the internuclear vector, θ being the angle between the ij direction and the magnetic field and the brackets meaning an ensemble average over the anisotropic molecular motion.

The fundamental conclusion is that two enantiomers are not ordered in the same way when dissolved in a cholesteric liquid crystal, $S_s \neq S_r$, and consequently all the order sensitive NMR parameters are in principle different: the dipolar coupling as

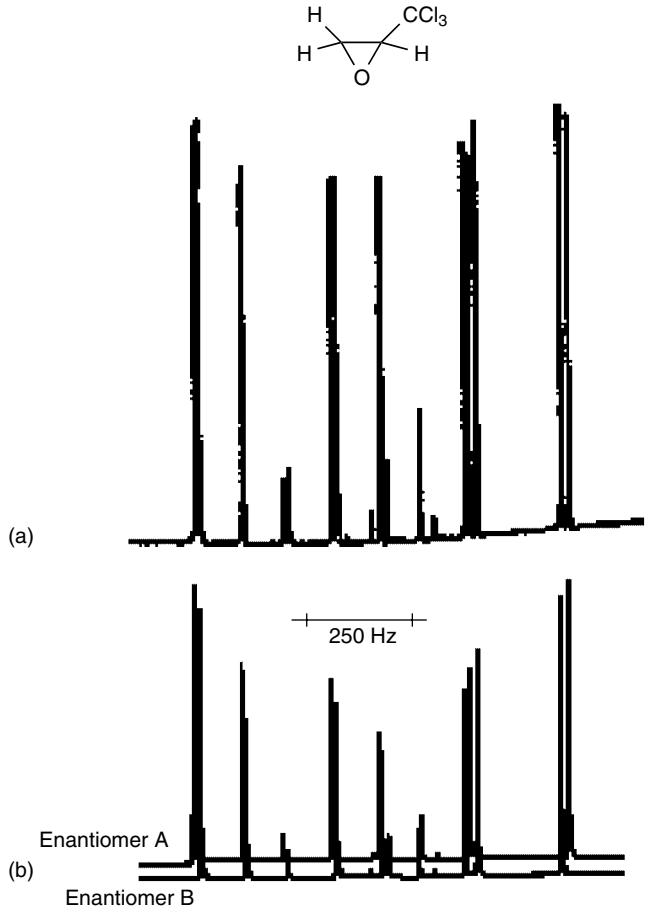

Figure 3 250 MHz proton spectrum of racemic 3,3,3-trichloropropylene oxide obtained in the cholesteric liquid crystal described in the text, together with the simulated ABC sub-spectra associated with each enantiomer

we have shown, but also the chemical shift anisotropy and the quadrupolar coupling for a spin larger than one half.

Unfortunately, no efficient applications can be made using spectra dominated by dipolar couplings except for very simple molecules. This is because of the tremendous complexity of second order dipolar spectra, which is due to the large values of the dipolar couplings compared to chemical shift differences. Actually, it is possible to overcome this problem using proton-decoupled deuterium NMR.[26] Now the spectra are dominated by the deuterium quadrupolar couplings. It is well known that quadrupolar interaction is purely anisotropic and a nucleus with $I = 1$ depends on the ordering through the following relationship:

$$\Delta\nu_Q = {}^{3e^2qQ}$$

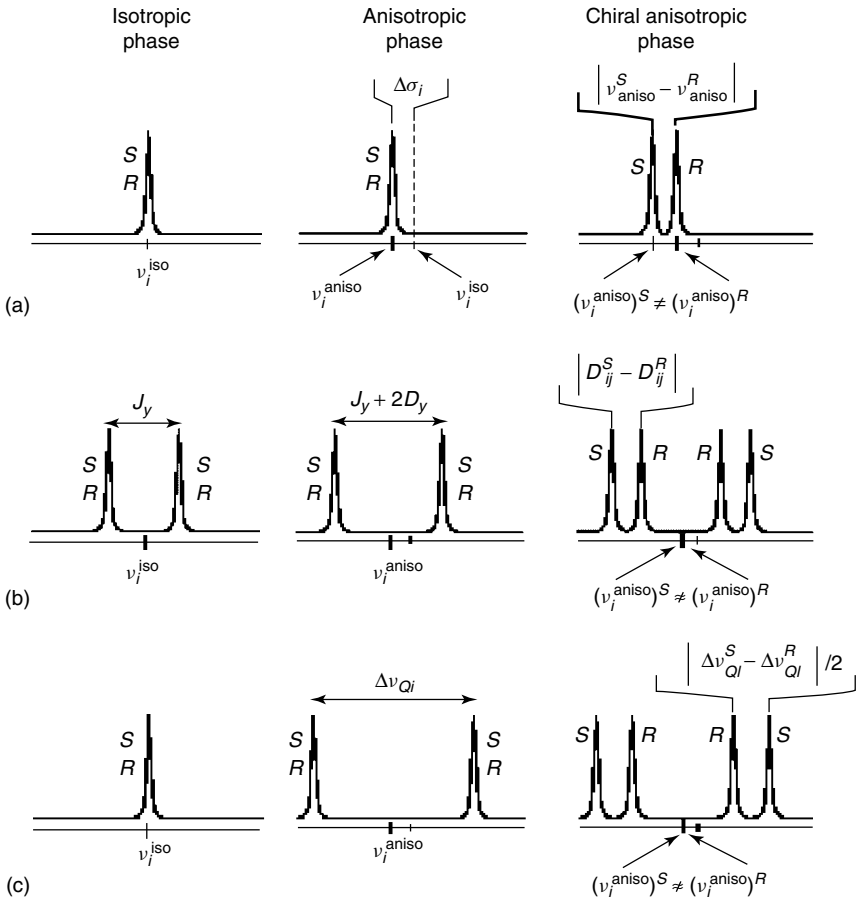

Figure 4 Schematic representation of the effect of a difference in the ordering of enantiomers on the NMR spectra when observing the following interactions (a) chemical shift anisotropy (b) dipolar coupling (c) quadrupolar splitting. (Reproduced by permission of the Royal Society of Chemistry from Sarfati et al.[41])

such a solvent all the effects coming from the chirality of the solvent disappear.

4 CHIRAL DIFFERENTIATION USING QUADRUPOLAR SPLITTING

The principles have been described above. If two deuterated enantiomers are not ordered the same in the polypeptide lyotropic liquid crystal then a quadrupolar doublet will be observed, one for each enantiomer.[29] In Figure 6 is an example on an allenic compound.

Clearly, the quadrupolar splitting is without contest the most sensitive to order differences as, in a diamagnetic molecules, it is the strongest NMR interaction. The main disadvantage is of course that it is necessary to deuterate selectively the molecules because natural abundance deuterium content, 0.015%, is too small to be of routine use at the moment (see Section 9 for the perspectives).

Beside deuterium other quadrupolar nuclei may be used, in the extent where the quadrupolar relaxation is long enough to provide high-resolution spectra. Some interesting applications have been discussed by Hosseini et al. involving ^{133}Cs, ^{11}B or ^{14}N NMR on different ions inserted in chiral cages.[32]

5 CHIRAL DIFFERENTIATION USING CHEMICAL SHIFT ANISOTROPY

It is possible to obtain a chiral discrimination via a difference in the anisotropy of the chemical shift, $\Delta\sigma$, which is also sensitive to order parameters through:

$$\Delta\sigma = \frac{2}{3}\sum \sigma_{\alpha\beta} S_{\alpha\beta}$$

where $S_{\alpha\beta}$ are the elements of the order matrix and $\sigma_{\alpha\beta}$ are the elements of the electronic screening tensor expressed in the same frame. To illustrate the expected effect consider a ^{13}C nucleus in a chiral molecule. Following Figure 4(a), the proton-decoupled spectrum obtainable in classical isotropic NMR is a single line centred on the isotropic shift, ν^{iso}. Using a non chiral nematic solvent the resonance frequency will be different as the chemical shift anisotropy is not averaged to zero anymore, $\nu^{aniso} = \nu^{iso} + \Delta\nu$, where $\Delta\nu = \gamma B_o \Delta\sigma/2\pi$. Here again, $\Delta\nu$ depends on the order parameters and consequently if two enantiomers are not ordered the same we can have $\Delta\nu_R$ different to $\Delta\nu_S$. This will split the signal in two lines, one for each enantiomer. This is exactly what is observed in Figure 7 for most of the aromatic carbons of an enriched mixture of 1,1′-bi-2-naphthols.

Nevertheless, to be efficient this method needs nuclei with a large chemical shift anisotropy. It has been rather successful

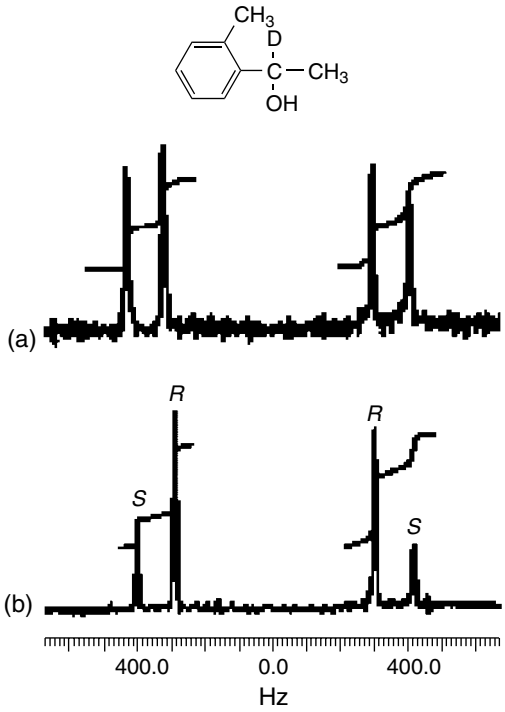

Figure 5 250 MHz proton decoupled deuterium spectrum of a chiral alcohol dissolved in the cholesteric liquid crystal described in the text. Note that we see two quadrupolar doublets, one for each enantiomer. (Reproduced by permission of Taylor and Francis Ltd from Courtieu et al.[26])

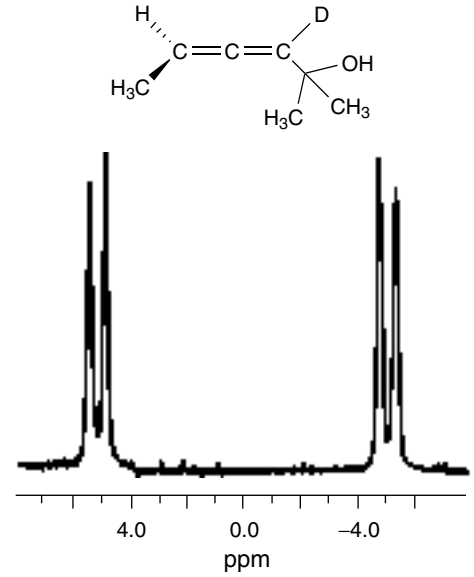

Figure 6 61.4 MHz proton-decoupled deuterium spectrum of a racemic mixture of an allenic alcohol dissolved in the PBLG-CH_2Cl_2 chiral liquid crystal system. Note again a quadrupolar splitting for each enantiomer

using sp and sp^2 ^{13}C, ^{19}F in –N–CO–CF_3 group,[35] ^{77}Se NMR. But the chemical shift anisotropy is generally too small to give measurable effects using NMR on the following nuclei ^{1}H, ^{2}H, sp^3 hybridized ^{13}C, ^{19}F in fluorocarbons, ^{31}P in phospine

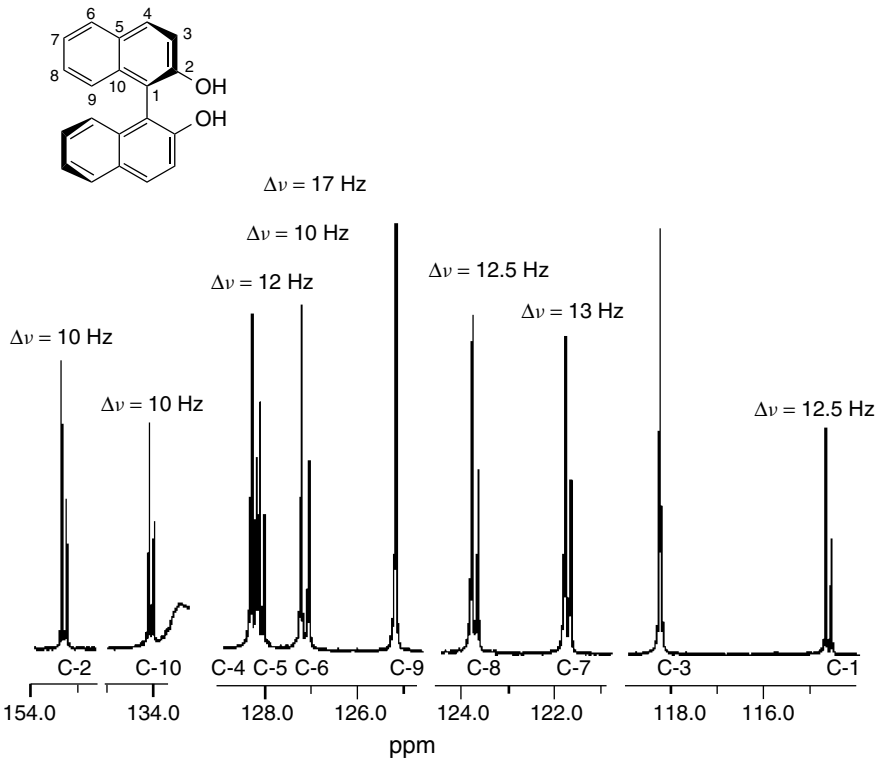

Figure 7 100.1 MHz proton-decoupled carbon-13 spectrum of a non-racemic mixture of the enantiomers of binaphthol dissolved in the PBLG-DMF-d_7 chiral liquid crystal. Note the chiral separation due to the chemical shift anisotropy on many of the ^{13}C transitions. (Reproduced by permission of the American Chemical Society from Meddour et al.[34])

oxides. So using chemical shift anisotropy is far from general and less efficient than the deuterium quadrupolar splitting. However, whenever it works no chemistry is involved to discriminate enantiomers and the use of higher fields will make it more efficient.

6 CHIRAL DIFFERENTIATION USING DIPOLAR COUPLING

Dipolar spin-spin couplings are also sensitive to ordering and may be used to differentiate enantiomers.[34] As already described, inter proton dipolar coupling will generally not be measurable using ^{1}H NMR. Indeed, the large number of couplings, even if they are small with this liquid crystal solvent, usually makes proton NMR lines not resolved. But the rather large dipolar $^{13}C-^1H$ coupling may often be used. To see the effect consider an isolated $^{13}C-^1H$ in a chiral molecule. Using isotropic proton coupled ^{13}C NMR we will observe a doublet due to the isotropic part of the scalar coupling, J_{CH}, as shown in Figure 4(b). In a non-chiral nematic solvent the same experiment will also furnish a doublet but with a different line spacing. This is due to the $^{13}C-^1H$ dipolar coupling that adds to the scalar: $\Delta\nu = J_{CH} + 2D_{CH}$. As D_{CH} is sensitive to order, using a chiral liquid crystal will yield two doublets, one for each enantiomer, when the dipolar couplings are different enough for the *R* and *S* enantiomers. Such an experiment is shown in Figure 8 for different enantiomeric mixtures of (±)-β-(trichloromethyl)-β-propiolactone.

The method is rather general, though less efficient than deuterium NMR. The main limitation here arises when numerous long distance dipolar and scalar couplings make the ^{13}C linewidth large and unresolved. But it works very nicely as soon as there is an isolated group like –COO–CH_3 for instance. Again the advantage here is that no chemistry is involved. It may be noted also that the method works rather well using $^{19}F-^{19}F$ dipolar coupling in poly-fluorinated compounds.[35]

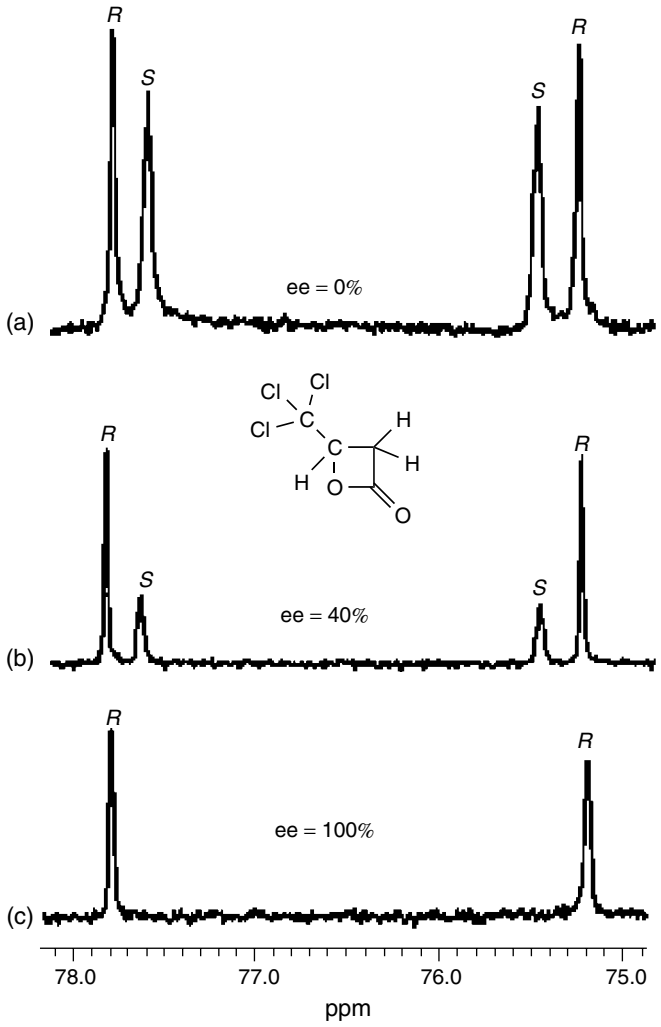

Figure 8 101.1 MHz proton-coupled carbon-13 spectra of the methine group of (±)-β-(trichloromethyl)-β-propiolactone in PBLG-CD_2Cl_2 chiral liquid crystal solvent. (a) Racemic mixture. (b) *R*(+) enriched mixture, 40% *ee*. (c) pure *R*(+) enantiomer. (Reproduced by permission of the Royal Chemical Society from Lesot et al.[33])

7 VISUALIZING ISOTOPIC CHIRALITY

One of the most remarkable properties of these polypeptide liquid crystals is their ability to distinguish perfectly well enantiomers of chiral molecules by virtue of isotopic substitution.[42] An example is shown in Figure 9 of the monodeutero-propionic acid.

In this case the differentiation does not come from a difference in the ordering of the enantiomers. Intuitively, the small difference in geometry between a proton and a deuterium could not produce a differential ordering effect as large as that in Figure 9. Here the discrimination comes from the symmetry properties of the orientational distribution function, which may be lower than the molecular point group symmetry.[44] For instance, for a molecule having a plane of symmetry, C_S, the orientational distribution function in a chiral liquid crystal has no symmetry, C_1, due to the orientational

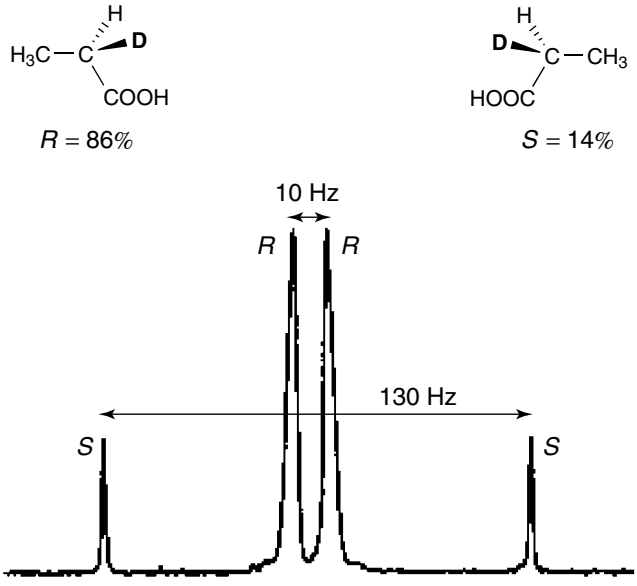

Figure 9 38.4 MHz proton-decoupled deuterium spectrum of *R*-enriched mixture of CH_3–CHD–COOH enantiomers (*ee* 72%) dissolved in PBLG-CD_2Cl_2 chiral liquid crystal. (Reproduced by permission of the American Chemical Society from Meddour et al.[42])

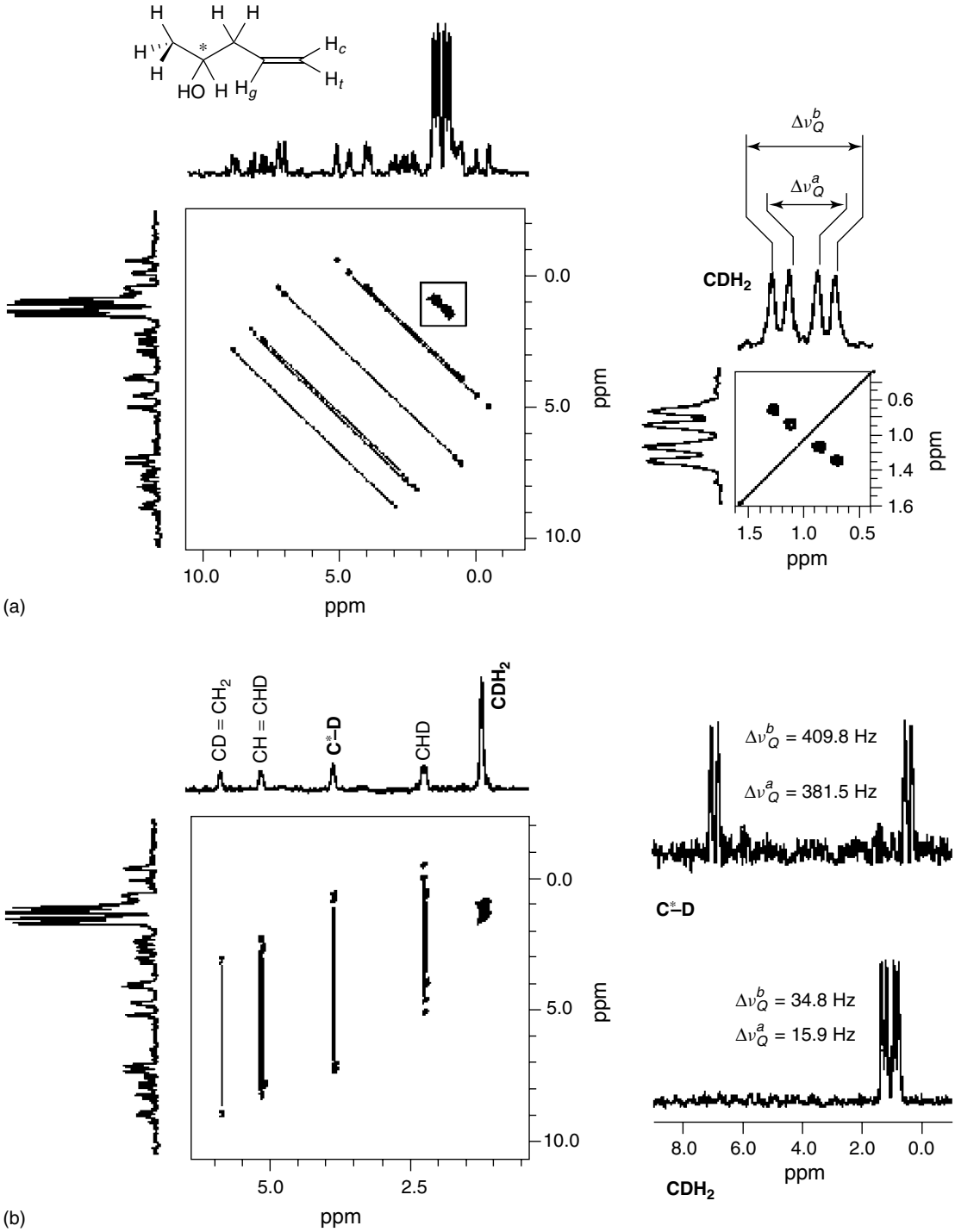

Figure 10 (a) 61.4 MHz natural abundance Q-COSY 2D deuterium spectrum with proton decoupling of a racemic mixture of 4-penten-2-ol. Note that chemical shifts appear along the main diagonal and that quadrupolar doublets lie perpendicular to the diagonal. (b) Same spectrum after a 45° tilt of the 2D matrix. Note that a quadrupolar decoupled spectrum appears in dimension one and that a column extracted at a given chemical shift furnishes a very simple spectrum: a quadrupolar doublet for each enantiomer. Two such columns are shown on the right of the figure. (Reproduced by permission of The Owner Societies from Merlet et al.[43])

chiral field. This means that enantiotopic deuterons in such a C_S molecule are not equivalent as is the case in non-chiral solvents. Consequently one observes a quadrupolar doublet for the pro-*S* and an other one for the pro-*R* deuterons. The chiral discrimination of isotopic enantiomers appears then as a simple consequence of the inequivalence of enantiotopic nuclei.

8 USING ACHIRAL DERIVATIZING AGENTS

When deuteration is not possible and when neither the CSA nor the dipolar coupling give good results there may be the opportunity to use derivatizing agents. Contrary to the classical method in isotropic solvents one does not

need chiral agents when using a chiral solvent, but we do need deuterium nuclei in the agent.[36–40] These achiral, but deuterated, derivatizing agents have the advantage when compared to their chiral equivalent because they react at the same rate with enantiomers and consequently no care has to be taken about the completeness of the reaction.

9 USING NATURAL ABUNDANCE DEUTERIUM

Clearly the deuterium quadrupolar splitting is the most useful way of detecting differences in orientational order. But it generally needs the synthesis of labelled compounds, which may be difficult. Is it possible to work at natural abundance level? Two problems have to be resolved to do so. First, the spectra are going to be quite crowded because we are expecting two quadrupolar doublets for all the possible isotopomers. Second, we will have a severe sensitivity problem as deuterium is only 0.015% abundant. This very low natural abundance results in one of the less sensitive nuclei in the periodic table, 1.45 10^{-6}, relative to proton.

The spectrum-crowding problem has been solved using a specific 2D experiment.[43] The sequence $90° - t_1 - 180° - t_2$ produces a total single quantum coherence transfer between the quadrupolar doublets, resulting in a very simple 2D pattern where the chemical shifts appear along the diagonal and the quadrupolar splitting perpendicular to the diagonal. This technique, called Q-COSY, allows a very straightforward assignment of auto-correlated quadrupolar doublets. An example is shown in Figure 10(a)where two quadrupolar doublets may be observed for each isotopomer of (±)-4-penten-2-ol. In Figure 10(b) the same spectrum is shown following a simple 45° tilt of the original spectrum resulting in a quadrupolar decoupled deuterium spectrum in dimension one. Extracting out a column of the 2D matrix gives a simple 1D spectrum with a doublet for each enantiomer that allows an eventual enantiomeric excess (*ee*) to be measured.

The 2D proton-decoupled deuterium spectra in Figure 10 were obtained at natural abundance levels using a solution containing 100 mg of the molecule and 17 hours acquisition time on a Bruker 400 MHz instrument equipped with a 5 mm o.d. BBI probe. Clearly the sensitivity has to be increased to get a precise *ee* measurement. But we think that higher magnetic fields joined with the use of a specific deuterium cryoprobe could solve the sensitivity problem. Then this technique would become some kind of a panacea for enantiomeric measurements.

10 SUMMARY

When dissolved in polypeptidic lyotropic liquid crystals enantiomers are not ordered the same and consequently all the anisotropic NMR observables are different. This technique, which allows measurements of enantiomeric excesses, is still in its infancy. Many other stereochemical problems need to be addressed. Among them are the differentiation of enantiotopic nuclei[42] and the visualization of diastereoisomers with remote stereogenic centres.[45]

One challenging question remains open: are we going to be able to predict the absolute configurations non-ambiguously? This is an old dream of the NMR spectroscopist, but there is still a lot to do to succeed on this point.

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Biographical Sketches

Jacques Courtieu, *b* 1944. Ph.D. 1974, Chemistry, University of Paris-Sud-Orsay, France. Research associate, University of Utah with D. M. Grant, 1976–78. Lecturer University of Paris-Sud, 1968–83; Professor at University of Paris-sud since 1983. Director, Institute for Molecular Chemistry, Orsay since 1998. Approx. 150 publications. Current research interest: NMR in chiral liquid crystals and its applications in stereochemistry.

Philippe Lesot, *b* 1967. Ph.D. 1995, Chemistry, University of Paris-Sud-Orsay, France. Research associate, University of Southampton with J. W. Emsley, 1995–96. Lecturer, University of Paris-Sud-Orsay 1997–98. Scientific Researcher at the CNRS, Institute for Molecular Chemistry, Orsay since 1998. Approx. 30 publications. Current research interest: NMR methodology in liquid crystal solvents.

Abdelkrim Meddour, *b* 1968. Ph.D. 1996, Chemistry, University of Paris-Sud-Orsay, France. Research associate, Wrije Universteit with R. Willem, 1966–97. Lecturer, University of Paris-Sud-Orsay since 1997. Approx. 20 publications. Current research interest: NMR in oriented systems and stereochemistry.

Denis Merlet, *b* 1970. Ph.D. 1998, Physical-Chemistry, University Paris VII, France. Research associate, University of Southampton with J. W. Emsley, 1998–99. Lecturer, University of Paris-Sud since 1999. Approx. 15 publications. Current research interest: NMR in oriented media.

Christie Aroulanda, *b* 1974. Ph.D. student, Physical Chemistry, University of Paris-Sud-Orsay, France. 4 Publications. Current research interest: NMR in oriented media.