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Discrimination and analysis of the NMR spectra of enantiomers dissolved in chiral liquid crystal solvents through 2D correlation experiments

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The discrimination and analysis of the NMR spectra of optically active molecules dissolved in chiral liquid crystal solvents through 2D correlation experiments is studied. The technique allows the identification of the line positions of each enantiomer, thus providing a notable simplification of the spectral analysis. The 2D HOHAHA and multiple-quantum experiments are investigated and discussed. The potential of the method is illustrated using a sample of (±) 3,3,3-trichloroepoxypropane dissolved in a thermotropic cholesteric solvent. The case of chiral molecules bearing a fluorine or deuterium nucleus has also been studied. In addition, it is shown that 2D heteronuclear correlation experiments are powerful methods for correlating carbon and proton spectral data of two enantiomers. A specific example is given through (±) 2-bromopropanoic acid dissolved in a lyotropic polypeptide liquid crystal. Spectral parameters of each enantiomer are calculated for the different examples.

1. Introduction

From the pioneering works of Snyder *et al.* it has been shown that *R* and *S* enantiomers give different NMR spectra in chiral liquid crystal media [1, 2]. More recent studies have extended the usefulness of NMR spectroscopy of liquid crystalline samples to the study and analysis of the spectra of the enantiomers of chiral compounds dissolved in cholesteric thermotropic or lyotropic polypeptide solvents [3–7]. Indeed, in the chiral anisotropic solvents, the observation of enantiomers is obtained through a doubling of the spectra, from which spectral parameters can be extracted, providing subsequently a wealth of detailed information about the geometry or the orientation of *R* and *S* isomers, which is not available from isotropic liquids [8]. The differential orientational ordering effect (DOE) of the *R* and *S* enantiomers is an essential element for the understanding of the intermolecular interactions involved in the chiral recognition mechanism [9]. Hence, there is a necessity to increase the number of experimental studies with the final aim of correlating the Saupe order parameters with the geometries of the molecules. In addition, such studies might also provide information about possible deformations of enantiomers in an anisotropic chiral medium.

The analysis of the proton spectra of enantiomers in a racemic mixture is often difficult for two reasons. First, in liquid crystal solvents, the partially averaged dipolar couplings are usually much larger than the chemical shift differences. Consequently, the ^{1}H NMR spectra of solutes are often second order and inherently very complex to decipher. Second, in the case of chiral solutes oriented in a chiral anisotropic phase, the degree of orientation of optically active molecules differs for the *R* and *S* geometries, and two distinct spectra for each enantiomer are observed due mainly to a difference of dipolar couplings [3, 9]. The result is then two complex superimposed spectra in which the number of transitions increases dramatically with the number of spins.

A calculation indicates that 30 transitions are predicted by theory for the proton spectrum of two enantiomers for a chiral ABC spin system. In a general case, the maximum number of transitions of *p* quantum ($I = 1/2$) detected for the proton spectrum of two enantiomers of *n* spins ($I = 1/2$) is given by:

$$Z_p^{(R+S)} = 2\left[\frac{(2n)!}{(n-p)!(n+p)!}\right] \qquad (1)$$

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Experimentally, this number is reduced because some transitions have very low intensities. Nevertheless, numerous overlapping resonances are observed and the recognition of different transitions for each enantiomer can be difficult. Consequently, the first task with the analysis of a 1D spectrum of a mixture of enantiomers is to identify which lines are associated with each enantiomer and it is important to find an effective method of discriminating between the spectra of each optical isomer, in order to exploit the analytical potential of the chiral anisotropic media. The simplest approach to simplify the analysis of a crowded proton spectrum is the use of 2D NMR spectroscopy. In the present case, the use of 2D correlation experiments is investigated. Among the numerous 2D NMR sequences, we have investigated 2D HOHAHA, multiple-quantum and heteronuclear correlation experiments.

To illustrate this idea, it will be shown in the first part of this paper how a 2D HOHAHA or multiple-quantum experiment allows us to discriminate and analyse the enantiomer spectra of the ABC spin system of a chiral molecule, (±) 3,3,3-trichloroepoxypropane (ETP), dissolved in a cholesteric solvent. We will also investigate theoretically the case of chiral molecules bearing a fluorine or deuterium nucleus through n quantum experiments.

In the second part, we describe the role of 2D heteronuclear correlation experiments to correlate coherently proton and carbon spectral data of two enantiomers. This last approach will be illustrated using the example of racemic (±) 2-bromopropanoic acid (BPA) dissolved in the liquid crystalline phase of poly-γ-benzyl-L-glutamate, (PBLG), in methylene chloride.

2. Experimental section

The sample of (±) ETP was dissolved in a binary mixture made from a 1·35/1 by weight ratio of cholesteryl propanoate (Chol-Pr) from Sigma and ZLI 2806 (a nematic mixture of $\Delta\chi_m < 0$ from E Merck) and gives a proton spectrum which is that of two ABC spin systems. It has been shown that such a cholesteric mixture orients homogeneously on a macroscopic scale, with the helical axis parallel to the magnetic field direction, and consequently allows high resolution spectra to be obtained [3]. The solute molecules were dissolved in the mixture at about 10% by weight. NMR experiments were carried out using a Bruker AM 250 high resolution spectrometer operating at 250·16 MHz.

The sample of (±) BPA was made from 100 mg of PBLG (DP1183, from Sigma), weighed directly into a 5 mm NMR tube, and a solution of about 70 mg of (±) BPA dissolved in 560 mg of CD_2Cl_2. These latter compounds were obtained from the Aldrich Chemical Co. The tube was degassed and sealed under vacuum in order to avoid the effects of paramagnetic oxygen and evaporation of the solvent. The tube was then centrifuged in both directions until an optically homogeneous sample was obtained [6]. NMR experiments were performed using a Bruker AM 400 high resolution NMR spectrometer, equipped with a $^1H/^{13}C$ dual probe, and operating at frequencies of 400·13 MHz for proton and 100·16 MHz for carbon-13. One component of the deuteriated methylene chloride doublet provided the lock signal.

In all experiments, the 5 mm samples were spun at 20 Hz along B_o and the temperature was regulated under air flow by the Bruker BVT 1000 system.

3. Results and discussion

3.1. *The 2D HOHAHA experiment*

Basically, the 2D HOmonuclear HArtmann–HAhn experiments produce a transfer of coherence between all the nuclei of a spin system which are scalar coupled to each other in isotropic liquids, by the application of a phase alternated spin-lock field [10, 11]. It has been pointed out earlier that this type of experiment gives in many cases enhanced resolution and sensitivity compared with the 2D COSY experiment [12]. In a liquid crystalline sample, the spins are coupled through dipolar as well as scalar interactions and consequently such a 2D experiment should be a reliable method for connecting the resonances belonging to each enantiomer of a racemic mixture.

The 2D HOHAHA experiment was recorded using the 2D pulse sequence developed by Bax and Davis [11] (figure 1). The net magnetization transfer between homonuclear coupled spins was achieved by the MLEV-17 pulse sequence, flanked by two 2·5 ms trim pulses to defocus magnetization not parallel to the x-axis. It has been established for isotropic samples that, for short mixing times, coherence transfers are mainly restricted to protons which are scalar coupled, whereas the remote connectivities are observed when the length of the mixing time is increased [11]. In the case of a dipolar coupled system, this condition is less critical because all the spins are generally coupled together.

The experimental 2D spectrum of (±) ETP was acquired at $T = 330$ K, with a $256(t_1) \times 1024(t_2)$ data matrix. An unshifted sine-bell filtering in F_1 and F_2 dimensions has been used to enhance the resolution (see

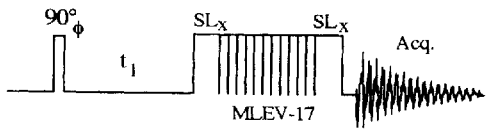


Figure 1. Pulse scheme of the 2D HOHAHA sequence using MLEV-17. The phase of pulses is cycled as described in [10].

the 2D spectrum in figure 2). As we expected, the correlation peaks between the F_1 and F_2 projections, allow a direct access to the line position for each enantiomer. Indeed, each line for an enantiomer in the first dimension is correlated to the corresponding lines in the second dimension. This effect is due to the numerous coherence transfers created by the pulse sequence on the spin system via the couplings. Moreover, as the two enantiomers do not have any common dipolar or scalar couplings, no correlations between them are observed in the 2D spectrum.

An expansion of two particular rows of the 2D spectrum, which are correlated to the two last high-field lines in the F_2 dimension, allows a detailed analysis of all the line positions belonging to both optical isomers. We can then observe the relative position of each line in the F_2 projection, (as illustrated by the direction of the arrows in figure 2), in view of the positions of the two respective lines in the F_1 projection. In other words, as each transition is correlated with one or other of both spectra of the mixture, we can observe with a good discrimination the spectrum of each enantiomer along either a column or a row on the 2D surface.

After examination and identification of the line positions of each spectrum on the 2D surface, we can then analyse the spectrum of each enantiomer. The analysis of the proton spectra was carried out using PANIC (Parameter Adjustment in NMR by Iterative Calculation) provided by Bruker, on an ASPECT 1000 computer. The ABC spectrum cannot be iterated by using all the nine spectral parameters. Consequently, the scalar couplings were assumed equal to their isotropic values, i.e. $J_{12}=4{\cdot}6$ Hz, $J_{13}=3{\cdot}6$ Hz and $J_{23}=2{\cdot}1$ Hz. These values have been obtained by fitting the spectrum of (±) ETP dissolved in the cholesteric solvent at a temperature above the clearing point. The signs of scalar couplings are assumed positive [1].

The chemical shifts and dipolar couplings obtained through spectrum simulation and iteration in the 15 experimental line positions of each enantiomer detected on the high resolution 1D proton spectrum (16 K) at $T=330$ K are given in table 1.

In this case the HOHAHA experiment is a very useful method for separating and establishing without ambiguity, all the transitions of each enantiomer.

3.2. *The multiple-quantum experiment*

The number of resonances in the spectrum of a molecule can be significantly decreased through a

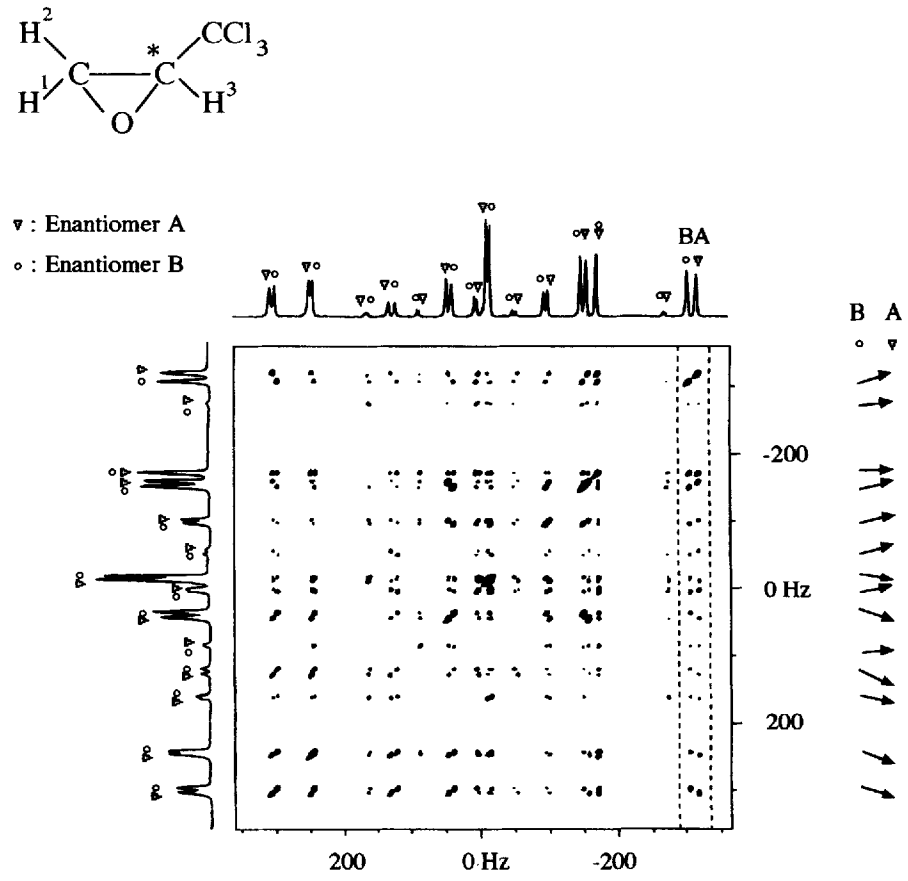


Figure 2. 2D HOHAHA magnitude-mode spectrum of (±) ETP at $T=330$ K resulting from a 512 × 1024 data matrix after zero filling in the F_1 dimension. The mixing time consisted of only one MLEV-17 (total time 0·9 ms), plus two trim pulses of 2·5 ms each; the recycle delay is 2 s. Sixteen scans were recorded for every value of t_1. Note the direction of the arrows for two specific resonances belonging to the F_2 dimension.

Table 1. Parameters[a] of the spin Hamiltonian in Hz of the spectrum of (±) ETP dissolved in the cholesteric solvent at 330 K.

Enantiomer	Lines[b]	$\nu_1-\nu_2$	$\nu_2-\nu_3$	D_{12}	D_{13}	D_{23}
A[c]	15	15·4 ± 0·2	157·0 ± 0·2	−83·1 ± 0·1	140·1 ± 0·1	−12·1 ± 0·1
B[c]	15	14·1 ± 0·2	157·3 ± 0·2	−75·5 ± 0·1	137·5 ± 0·1	−13·6 ± 0·1

[a] Parameters fitted on the 1D spectrum of the racemic mixture.
[b] Number of lines fitted in the spectrum.
[c] Arbitrary assignment for both enantiomers.

multiple-quantum experiment. This could reduce the problem posed by overlapping lines in the spectra of racemic mixtures. The application of a multiple-quantum experiment affords us interesting perspectives. The general exploitation and the potential of such experiments for facilitating the analysis of proton spectra of oriented non-chiral molecules have been demonstrated by Pines *et al.* [13–15].

For our purpose, we must obtain a multiple-quantum spectrum in which all the spectral information for both enantiomers is still present, i.e. chemical shifts, scalar and dipolar couplings. In theory, this can be achieved for an n spin system by obtaining the $(n-2)$ or $(n-1)$ quantum spectra [16]. In the case of an $(n-1)$ quantum spectrum, the number of transitions for two enantiomers of n spins is given by:

$$Z_{p=n-1}^{(R+S)} = 2\left[\frac{(2n)!}{(2n-1)!}\right] \qquad (2)$$

In a multiple-quantum experiment, two steps must be considered. First, the identification of each resonance of the spectrum of an enantiomer using correlations between the single and multiple-quantum spectra. Second, there is the analysis of the $(n-1)$ quantum spectrum to give the spectral parameters. These may then provide convenient starting data for the iteration on the single-quantum spectrum. Considering the three spin system in (±) ETP, we carried out a 2D double-quantum experiment. A number of different pulse sequences have been suggested for exciting double-quantum coherences, but for our purpose, we have applied the 2D pulse sequence developed by Freeman *et al.* and depicted in figure 3 [17, 18].

The experimental two dimensional double-quantum spectrum of (±) ETP, displayed in figure 4, has been recorded with $512(t_1) \times 1024(t_2)$ points of digitisation at $T = 335$ K. An unshifted sine-bell filtering is used in F_1 and F_2 dimensions. As previously, the correlation peaks between the F_1 and F_2 projections allow a direct identification of the transitions of each optical isomer in the single- and double-quantum spectra. The double-quantum spectra were then analysed using a program

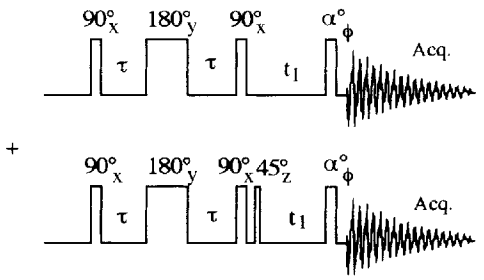


Figure 3. Pulse scheme of the 2D double-quantum sequence. The phase of pulses is cycled as described in [17, 18]. The angle α is 135°.

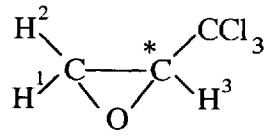
for analysing multiple-quantum spectra which is a development of the LAOCOONOR program [19].

The NMR spectral parameters computed through the analysis of the $(n-1)$ quantum spectra are then used as starting values for iterations on the high resolution 1D spectrum (16 K). During iterations on the 1Q and 2Q spectrum, the scalar couplings are kept constant and equal to their isotropic values. The NMR spectral parameters calculated from the 2D double-quantum and high resolution 1D spectrum at $T = 335$ K are listed in table 2.

We can see the good agreement between the spectral parameters computed from the double- and single-quantum spectrum, thus showing the value of obtaining an $(n-1)$ quantum 2D spectrum.

The small differences observed between the two spectral data sets result essentially from the lower digital resolution of the $(n-1)$ quantum spectrum compared to the high resolution 1D spectrum. Consequently, the NMR spectral parameters calculated through the analysis of the $(n-1)$ quantum spectra should be considered as valuable starting values for an accurate solution of the high-resolution 1D spectrum.

Note that an n quantum experiment cannot in this case be used to assign lines in the single-quantum spectrum. Indeed, the frequency of the single n quantum transition for an n spin 1/2 system is equal to the sum of the chemical shifts of the n nuclei. A calculation from the chemical shifts given in Table 2 indicates that the



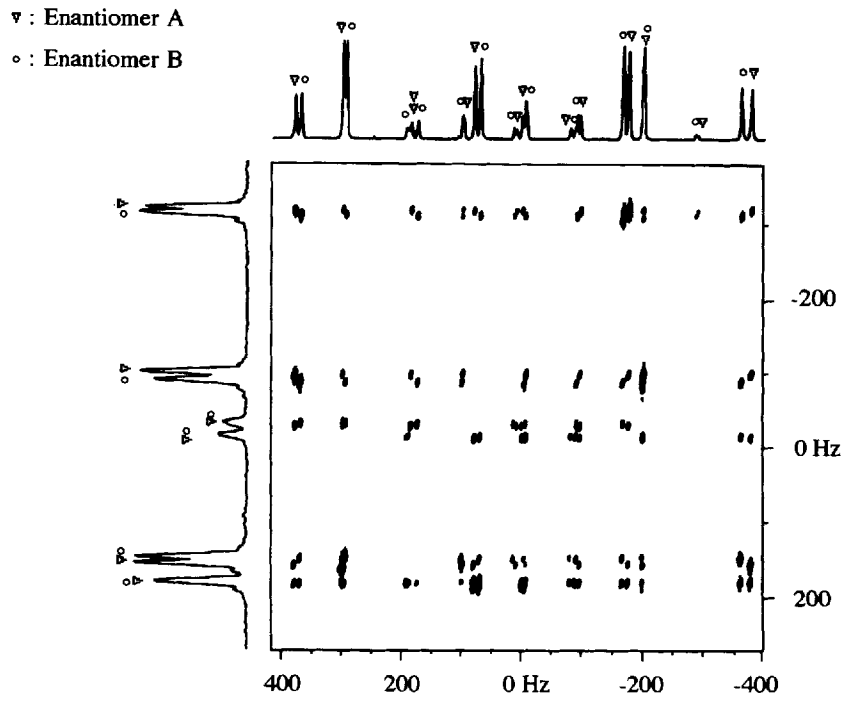


Figure 4. 2D double-quantum spectrum of (±) ETP (in magnitude mode) at $T=335$ K resulting from a 512×1024 data matrix. The recycle delay is 2 s and the mixing time is 1·7 ms. Sixteen scans were recorded for every value of t_1.

Table 2. Parameters of the spin Hamiltonian in Hz of the spectrum of (±) ETP dissolved in the cholesteric solvent at 335 K.

n Q	Enantiomer	N^a	$\nu_1-\nu_2$	$\nu_2-\nu_3$	D_{12}	D_{13}	D_{23}
$2Q^b$	**A**[d]	6	10±2	156±1	−93±1	172±1	−16±1
	B[d]	6	6±2	153±1	−101±1	177±1	−15±1
$1Q^c$	**A**[d]	15	6·4±0·2	154·5±0·1	−91·9±0·1	172·8±0·1	−16·6±0·1
	B[d]	15	7·7±0·2	154·9±0·1	−101·2±0·1	175·8±0·1	−15·8±0·1

[a] Number of lines fitted in the spectrum.
[b] Parameters fitted in the F_1 projection of the 2D spectrum.
[c] Parameters fitted in the high resolution 1D spectrum.
[d] Arbitrary assignment for both enantiomers.

difference between for the *R* and *S* enantiomers would be about 1·4 Hz. Such a value is lower than the linewidths generally observed in an *n* quantum experiment. Consequently, this identification of line positions on the single-quantum projection would be impossible in this case.

It is interesting to note that the *n* quantum proton spectrum in the case of chiral molecules bearing an NMR active heteroatomic label such as a fluorine nucleus can be much more useful. Indeed, in this particular example, the *n* quantum proton spectrum of a monofluorinated molecule appears as a single dipolar doublet with a splitting which is equal to the sum of the fluorine-proton couplings, $\sum(J_{ij}+2D_{ij})$. Consequently, for a chiral molecule, there is the possibility of an enhanced separation in the F_1 dimension.

To illustrate this clearly, we have simulated the double-quantum 2D spectrum of a fictitious AMX spin system at 250·16 MHz where X is a fluorine nucleus, using the NMRSIM computer program provided by Bruker. In order to simulate a realistic spin system, we have assumed that the proton and fluorine chemical shifts in

the two enantiomers are equal and the differences of dipolar couplings between each enantiomer are small (see details in table 3). The scalar couplings were set to zero. For the simulation, a basic three-pulse sequence, $90_{\phi 1}$–τ_m–$90_{\phi 2}$–t_1–$90_{\phi 3}$–$Acq._{\phi r}$ was used, and the number of points used was 512 in t_1 and 2048 in t_2, typical of a real experiment. The simulated 2D spectrum is presented in figure 5.

As expected, two doublets at the frequency of the double-quantum transition, i.e. the sum of the proton chemical shifts, are observed in the F_1 dimension. The dipolar splittings measured on the vertical projection are equal to the sum of the residual fluorine–proton dipolar couplings, $\sum(2D_{ij})$, i.e. respectively 55 and 74 Hz for each enantiomer arbitrarily noted as *R* and *S* (see table 3).

The correlations on the 2D surface allow the NMR lines for each enantiomer in the single quantum spectrum to be discriminated and identified. Note that the correlations for each enantiomer are distributed on rows belonging to both components of each doublet. Consequently, only the sum of both rows for each

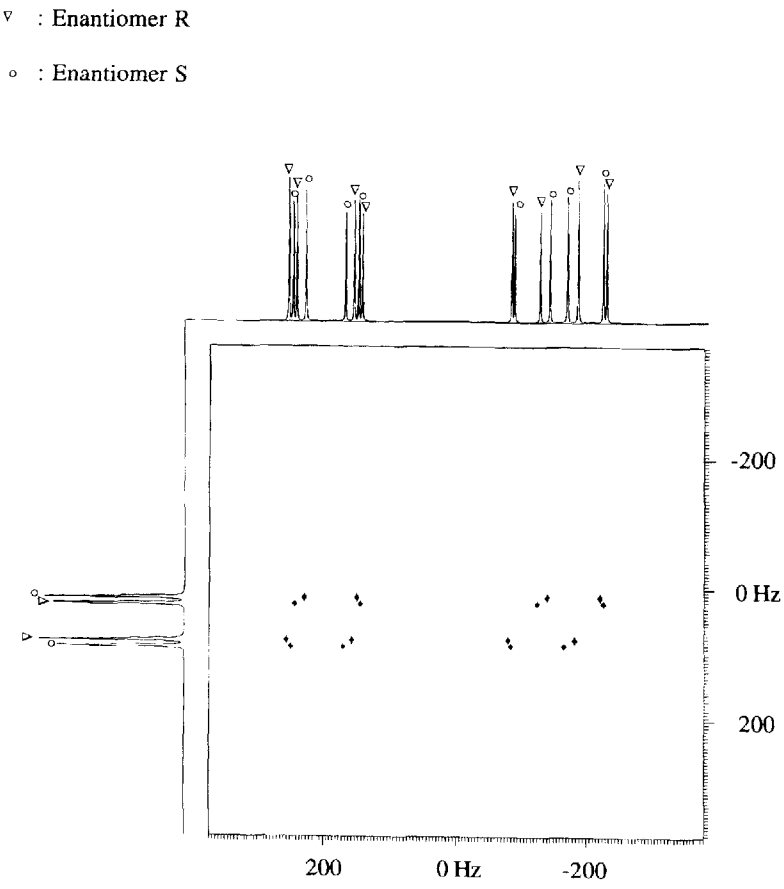


Figure 5. Simulated 2D double-quantum proton spectrum (in magnitude mode) of two enantiomers for a fictitious 'AMX' spin system. The 'X' part is a fluorine nucleus (for details, see table 4). The 2D data matrix is 512 × 2048 points; the delay τ_m is 2·8 ms. Thirty two scans were recorded for every value of t_1. A sine-bell apodisation function is applied in the F_1 and F_2 dimension.

Table 3. Parameters of the spin Hamiltonian in Hz of the fictious 'AMX' spin system associated with the simulated *n* quantum spectrum of figure 5.

Enantiomer	ν_A[a,c]	ν_M[a,c]	ν_X[b,c]	D_{AM}[e]	D_{AX}[e]	D_{MX}[e]
R[d]	200	−150	0	−50	6	21·5
S[d]	200	−150	0	−40	10	27

[a] Proton frequency at 250·16 MHz.
[b] Fluorine frequency at 235·35 MHz.
[c] For the spectrum simulation, the T_2 and T_1 relaxation times of nuclei are assumed identical and equal to 0·7 s.
[d] Arbitrary assignment for the *R* and *S* enantiomers.
[e] The dipolar couplings uses the PANIC definitions: D_{ij}(NHRSIM) = $-2D_{ij}$(PANIC).

Table 4. ^1H–^1H and ^1H–^{13}C dipolar couplings in Hz associated with the methyl group of (±) BPA dissolved in PBLG/CD_2Cl_2 at 305 K.

		Enantiomer A[b]			Enantiomer B[b]		
NMR	Nuclei ij[a]	T_{ij}[c]	J_{ij}[d]	D_{ij}[e]	T_{ij}[c]	J_{ij}[d]	D_{ij}[e]
^1H	$-CH_3$	87·9±0·1	—	29·3±0·1	9·6±0·1	—	3·2±0·1
^1H	$CH-CH_3$	18·7±0·1	6·9±0·1	5·9±0·1	8·4±0·1	6·9±0·1	0·8±0·1
^{13}C	$-CH_3$	136·3±0·2	130·9±0·2	2·7±0·2	126·9±0·2	130·9±0·2	−2·0±0·2
^{13}C	$CH-CH_3$	4·1±0·2	2·5±0·2	0·8±0·2	2·5±0·2	2·5±0·2	0±0·2

[a] The coupled nuclei are in bold.
[b] Arbitrary assignment to A and B enantiomers.
[c] Dipolar splittings measured on the 1D spectrum.
[d] Isotropic scalar coupling constants, measured in CD_2Cl_2 solvent at 305 K.
[e] Dipolar coupling constants.

doublet furnishes the total spectrum of both enantiomers. These results on a fictitious AMX spin system demonstrate that a 2D n quantum experiment can be used to discriminate between the spectra of chiral fluorinated molecules.

In a real molecule, the success of the method will depend on the sums of the ^{19}F–^1H dipolar couplings being different for the enantiomers. In practice, we can speculate that this situation will be that usually encountered, but the observed differences could be quite small. It is also reasonable to expect that the observed differences in the F_1 dimension will be larger than the differences in the F_2 dimension. Note that identical experiments can be carried out on chiral molecules bearing a deuterium label. In such a case, two different triplets will be observed in the F_1 dimension, from which the spectra of the enantiomers can be identified.

3.3. *The XH-correlation experiment*

In previous work, it has been shown that measurements of carbon–proton dipolar couplings made in the study of two optical isomers can be used to obtain

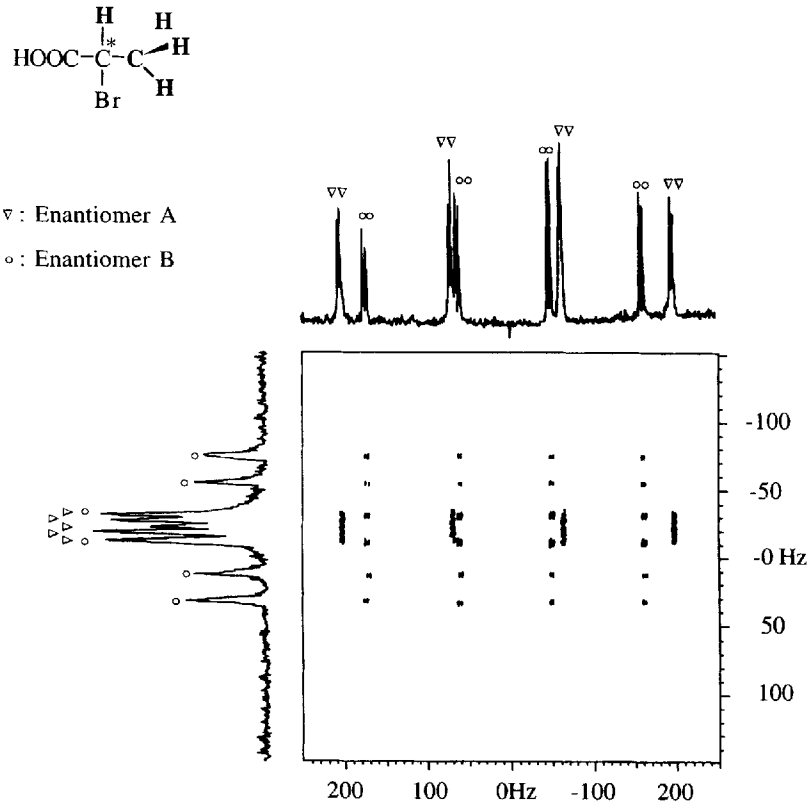


Figure 6. 2D carbon–proton correlation magnitude-mode spectrum of (±) BPA dissolved in the PBLG/CD_2Cl_2 mixture at T=305 K. The 2D spectrum is recorded with a 256 × 1024 data matrix. Zero filling in the F_1 dimension has been used to yield a 512 × 1024 matrix. No apodisation or other beautifying routine was applied in either dimension of the spectrum to enhance spectral appearance. The recycle delay is 3 s and the polarisation transfer is 2·1 ms. Sixteen transients were added for every value of t_1.

the five elements of the Saupe order matrix, when the number of proton–proton dipolar constants is insufficient [9]. Nevertheless, this approach, already developed for a non-chiral molecule by Khetrapal *et al.* [20], cannot be applied in the case of chiral molecules in a racemic mixture. Indeed, as no difference of line intensity is observed, it is then not possible to correlate directly the 1D proton spectrum of one enantiomer with the corresponding 1D carbon-13 spectrum, and then obtain a coherent set of spectral data for each optical isomer.

To overcome this problem, we propose the application of 2D ^{13}C–^{1}H correlation experiments. In order to illustrate our purpose, we present in figure 6, the 2D carbon–proton correlation spectrum of (±) BPA dissolved in the PBLG/CD_2Cl_2 mixture at $T = 305$ K. The 2D spectrum has been recorded with the pulse sequence (see figure 7) described by Freeman and Morris [21]. The receiver and the proton and carbon transmitter phases are derived from the phase cycling reported further by Morris [22]. Contrary to the basic experiment, the carbon signal is obviously not decoupled during the t_2 acquisition period. We obtain then a carbon and proton spectrum in which the ^{1}H–^{1}H and ^{13}C–^{1}H dipolar splittings are present and correlated together.

The offset of the 2D spectrum is adjusted on the chemical shift of the proton and carbon signal belonging to the methyl group of the molecule in order to increase the digital resolution. A detailed analysis of proton and carbon spectra shows that we have to correlate two doubled triplets (proton) with two doubled quadruplets (carbon). The 2D map allows us to connect the proton and carbon multiplets for each enantiomer. In this example, we thus get four connected dipolar coupling constants for each enantiomer, instead of two independent sets of measurements of dipolar couplings.

In this specific example, the spectral information extracted from the 2D spectrum demonstrates that XH correlation experiments are powerful tools for the analysis of the spectra of enantiomers. Consequently, their use appears as an essential part of obtaining coherent sets of spectral data when the number of homonuclear dipolar couplings is insufficient to calculate the order parameters.

In a general case, we should also expect to determine the whole set of dipolar couplings belonging to each enantiomer by combining the analysis of proton resonances from a 2D HOHAHA spectrum.

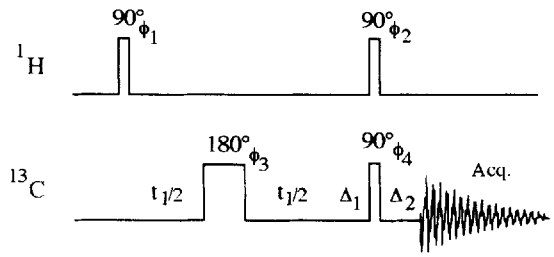


Figure 7. Pulse scheme for obtaining the 2D correlation carbon–proton spectrum. The phase of the pulses is cycled as described in [22].

4. Conclusion

We report here the possibility through 2D NMR experiments currently in routine use of discriminating and identifying correctly the experimental resonances of each enantiomer of a racemic mixture oriented in chiral liquid crystal hosts, thus facilitating the spectral analysis. The method furnishes an elegant and useful way to overcome the complexity of proton 1D spectra resulting from the doubling of lines, especially in the case of chiral molecules bearing a fluorine or deuterium label. Moreover, the necessity for non-standard spectrometer hardware does not arise.

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