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J. Courtieu[a]; C. Aroulanda[a]; P. Lesot[a]; A. Meddour[a]; D. Merlet[a]
[a] University Paris Sud 11, ICMMO, (CNRS UMR 8182), Laboratoire de RMN en Milieu Orienté, Orsay, France

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INVITED ARTICLE

Evolution of the Saupe order parameters of enantiomers from a racemic to a non-racemic liquid crystal solvent: an original light on the absolute configuration determination problem

J. Courtieu*, C. Aroulanda, P. Lesot, A. Meddour and D. Merlet

University Paris Sud 11, ICMMO, (CNRS UMR 8182), Laboratoire de RMN en Milieu Orienté, 91405 Orsay, France

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Chiral liquid crystals used as solvents have been shown to be very powerful in giving separate nuclear magnetic resonance (NMR) signals for enantiomers. However, a fundamental problem remains: how to attribute absolute configurations to the various NMR responses? In this paper it is demonstrated that the absolute configuration problem could be solved in predicting the sign of the rotation of the principal axis system of the Saupe matrix in the molecular frame when going from an achiral (racemic) to a chiral anisotropic solvent.

Keywords: chirality; absolute configuration; Saupe order parameters; NMR; molecular orientation

1. Introduction

It was in the early years of nuclear magnetic resonance (NMR), in 1963, that Alfred Saupe proposed a totally original experiment together with Gerhardt Englert [1]. They were the first to use a liquid crystal as an NMR solvent. This seminal paper, where the proton spectrum of benzene dissolved in a thermotropic nematic is obtained, describes the very first NMR experiment in a partially ordered medium, a method now so popular among physicists, chemists and biostructuralists.

More astonishing may be the fact that, one year after this major achievement, Alfred Saupe published alone the whole theory of the dissolved molecule orientation phenomenon and its effect on NMR spectra [2]. In this paper the notion of molecular order parameters was introduced, these so important parameters that the scientific community knows today under the name of Saupe order parameters and that are collected into the so-called Saupe matrix or Saupe ordering tensor.

Strangely, these two papers have only been cited 305 and 408 times respectively during the last 45 years even if nowadays several hundreds of papers reporting the use of an ordered medium as the NMR solvent are published each year. This is probably due to the fact that this first experiment arrived too much in advance of its time, taking account of the technical difficulties of NMR in the 1960s. Therefore, these papers did not have an immediate strong impact. It was only with the arrival of Fourier transform NMR and with the advent of superconducting magnets that the Saupe technique was allowed to develop under the impulse of a few pioneers such as Snyder [3], Meiboom [4], Buckingham [5], Luckhurst [6], McLauchlan [7], Diehl [8] and Samulski [9] *et al.* to name but a few among the earliest researchers.

As is common among the brightest scientific people, Alfred Saupe did not try to continue to work on the technique he invented and left to others the care of developing various applications. As a creator he thought he went around the problem and addressed other themes about the various amazing properties of liquid crystals. Nevertheless, he remains and will also remain the creator of the thematic 'NMR in ordered media' that is still quite fashionable today.

In this article, in honour of Alfred Saupe, we will talk about Saupe order parameters in the specific context of chiral liquid crystals that are used in our group to analyse chiral or pro-chiral molecules. This technique has developed rapidly since the use of liquid crystals obtained from the dissolution into various organic solvents of some synthetic homopolypetides, whose chiral discrimination power is amazing. Nevertheless, a fundamental problem remains unsolved concerning the absolute configuration assignments. Here, we will demonstrate that this problem could be solved by predicting the evolution of the principal axis system of the Saupe matrix when going from non-chiral racemic to chiral orientating solvents.

The origin of the chiral discrimination of enantiomers through NMR in chiral liquid crystals is clear and unambiguous. Two enantiomers dissolved in a chiral orienting medium do not orient the same and consequently all the order sensitive magnetic interactions are different, namely, chemical shift anisotropies, dipole–dipole coupling and quadrupolar splitting for nuclei with spin larger than 1/2 such as

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*Corresponding author. Email: courtieu@icmo.u-psud.fr

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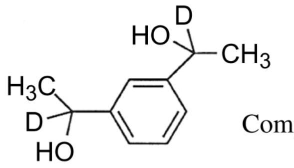
deuterium [10–16]. These interactions are sensitive to the molecular order parameters. Consequently, the problem of absolute configurations will be solved when we are able to calculate *ab initio* the Saupe ordering matrix elements for each enantiomer embedded in the chiral ordering medium. Obviously this is a very complex multi-molecular dynamic task, and the question can be raised as to whether the problem could be simplified. The following studies of various experimental results will tend to demonstrate that this is indeed possible.

2. Evolution of the order of enantiomers from non-chiral to chiral ordering media

In this first experiment we follow the evolution of the deuterium quadrupolar splitting of the three stereoisomers of diol (**1**) when the solvent chirality evolves (see Figure 1). The liquid crystal is made of THF/$CDCl_3$ solutions of various mixtures of poly-γ-benzyl *L*-glutamate (PBLG) and poly-γ-benzyl *D*-glutamate (PBDG, the enantiomer of PBLG), from pure PBLG to pure PBDG through the racemic mixture 50% PBLG/50% PBDG where all chiral effects disappear. A typical proton-decoupled deuterium spectrum (^{2}H-{^{1}H}) of a mixture of diols **1** is presented in Figure 1 and the evolution of quadrupolar splitting with increasing PBDG/(PBLG+PBDG) weight fraction is plotted in Figure 2.



Compound **1**

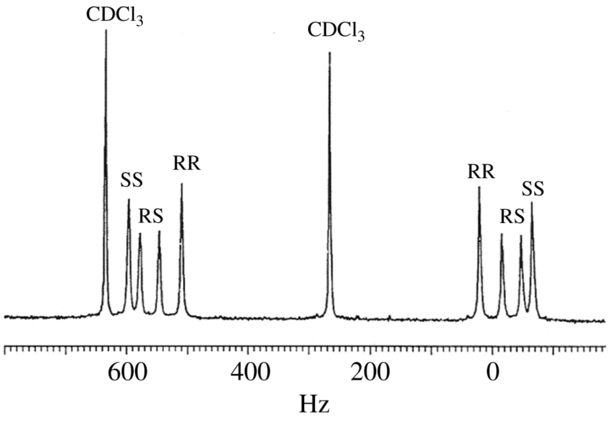


Figure 1. ^{2}H-{^{1}H} 61.4 MHz spectrum of a mixture of diols **1** dissolved in the chiral liquid crystal made of a 13 wt% solution of PBLG in THF/$CDCl_3$. Note the single quadrupolar doublet associated with each enantiomer *RR* or *SS* of the *threo* diastereomer and the two doublets associated with the *RS meso* diastereomer.

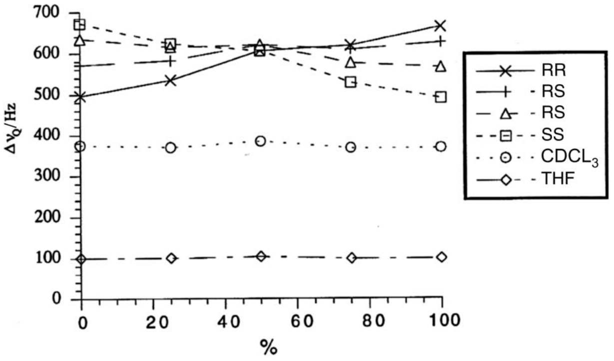


Figure 2. Evolution of the quadrupolar splitting for diols **1** and solvents versus the mass proportion PBDG/(PBLG+PBDG) weight fraction in the chiral liquid crystal solvent, from 0% (pure PBLG) to 100% (pure PBDG) through the racemic mixture 50% PBDG/ 50% PBLG.

The deuterium spectrum in Figure 1 is made of five quadrupolar doublets. The high field doublet is due to $CDCl_3$. The other four doublets are due to the various stereomers of **1**. The assignment of the various signals is made easily because the concentrations of the *threo* and *meso* forms are different: [*threo*]>[*meso*]. So the most intense doublets have to be attributed to the enantiomers *RR* and *SS* of the *threo* form. Each of these enantiomers possesses two equivalent deuterons because they are homotopic, i.e. related by a C_2 axis of symmetry. The *RR* and *SS* signals are separated because of the differential ordering effect of enantiomers in this chiral liquid crystal solvent [17]. Note that the stereodescriptors *RR* and *SS* reported on this spectrum are arbitrary, but this is of no concern in the following because inversion of the absolute assignation would lead to the same conclusions.

In contrast, the *RS meso* diastereomer is non-chiral because it possesses a plane of symmetry. Nevertheless, this achiral compound exhibits two quadrupolar doublets. This is because the two deuterons in the *meso* form are enantiotopic, i.e. related by a plane of symmetry and we have shown that enantiotopic nuclei are not equivalent in a chiral orienting solvent [18, 19].

In Figure 2 the evolutions of the various quadrupolar doublets with the chirality of the liquid crystal solvent from pure PBLG to pure PBDG are plotted. The first point to note is that these evolutions are not linear. This is first due to the difficulties in preparing samples with exactly the same amounts of all the components; secondly it is due to the probable difference in the liquid crystal properties of pure PBLG (or pure PBDG) and the racemic PBLG–PBDG mixture. Clearly, the interactions between PBLG polypeptidic fibres should be slightly different from those between PBLG and PBDG fibres. This is actually observable for the quadrupolar splitting of the $CDCl_3$ co-solvent that evolves with the PBDG/(PBLG+PBDG) percentage.

In order to try to have reliable data we make the following assumption: if the liquid crystalline polypeptidic solutions were 'ideal' in the thermodynamic sense, the deuterium quadrupolar splitting of the $CDCl_3$ co-solvent should remain constant whatever the PBDG/(PBLG+PBDG) weight fractions. This is why we decided to normalise the various quadrupolar splittings of solute **1** to the quadrupolar splitting of $CDCl_3$ to remove the non-ideal behaviour of PBLG–PBDG mixtures [20]. These normalised data are reported in Figure 3. It is clear that this normalisation of the data is efficient as the evolutions of the quadrupolar splittings with the chirality of the solvent are now nicely linear from pure PBLG to pure PBDG.

Examination of Figure 3 leads to the following remarks.

(1) Evolutions of normalised quadrupolar splitting with chirality are linear.
(2) The chiral separation between *RR* and *SS* disappears in the racemic mixture.
(3) Enantiotopic discrimination in the *RS meso* stereoisomer also disappears in the racemic mixture.
(4) In both of these cases the quadrupolar splitting measured in the racemic mixture is half the sum of the *RR* and *SS* splitting in PBLG (or PBDG).
(5) In the racemic mixture there remains only an order difference between the diastereomers *threo* and *meso* due to their difference in geometry.

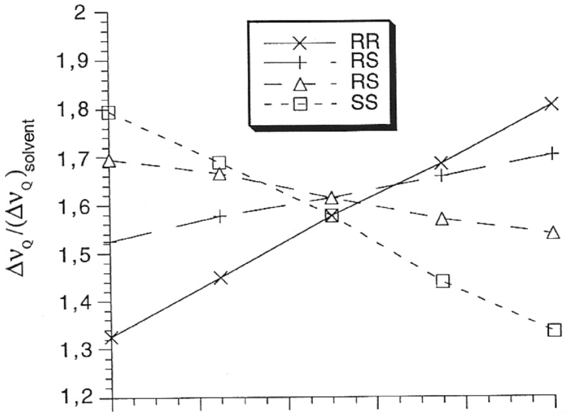


Figure 3. Evolution of the quadrupolar splittings of diols **1** normalised to that of the $CDCl_3$ versus PBDG/(PBLG+PBDG) weight fraction, from 0% (pure PBLG) to 100% (pure PBDG) through the racemic mixture 50% PBDG/50% PBLG.

(6) *RR* in PBLG is equivalent to *SS* in PBDG and, reciprocally, *RR* in PBDG is equivalent to *SS* in PBLG. Actually, this has to be so because *RR* in PBLG is the mirror image of *SS* in PBDG and NMR alone is not able to distinguish mirror image situations.

These remarks lead to the following conclusions:

(1) When the problem of the absolute configuration is raised, the *ab initio* calculation of the order parameters may not be necessary. Indeed we can start from the identical and measurable orientational order of the enantiomers in the racemic mixture. In this situation the absolute configuration will be solved if we can predict how the order parameters evolve when chirality appears in the anisotropic solvent, i.e. when the PBDG/(PBLG+PBDG) percentage moves away from 50%. Intuitively, this should be easier to realise than the full *ab initio* calculation of the order parameters.
(2) When comparing the orientational order of the enantiomers this is equivalent to comparing the order of both the enantiomers in PBLG or to comparing the order of a single enantiomer in PBLG and PBDG. Actually, the later situation is easier to handle than the former [21].
(3) The evolution of the enantiotopic discrimination follows the same law as the evolution of the enantiomeric separation. So to understand what is happening to the molecular order when chirality arises in the solvent it may be easier to begin with the study of the evolution of the ordering in molecules bearing enantiotopic nuclei. This is the subject of the next section.

It must be clear that the important result here is that to determine the absolute configuration we need only to account for the chiral effects on the order starting from the identical ordering of the enantiomers in the racemic anisotropic solvent. First, this ordering in the racemic medium may be obtained by using half the sum of the interactions measured for each enantiomer to calculate the Saupe order parameters (dipolar coupling for instance). Secondly, when an interaction potential is introduced to try to account for the effect of chirality on the ordering (electrostatic, Lennard-Jones, etc), an expansion of this potential into chiral and non-chiral terms will simplify the calculations because only chiral terms can contribute to the chiral separation. Non-chiral terms contribute identically to the ordering of the enantiomers and define the ordering in the racemic medium, which is supposed to be known because we can calculate it.

3. Evolution with chirality of the Saupe principal axis system for ordering in prochiral molecules with C_{2v} symmetry

In this example we study the evolution of the principal axis system of the Saupe ordering tensor of norbornadiene **3** in a liquid crystal solvent varying from racemic to non-racemic [22]. Norbornadiene is a C_{2v} molecule (see Figure 4). Consequently, in a racemic liquid crystal solvent the principal axis system for order is easily defined from symmetry arguments. The C_2 axis is a principal axis, and the other two must belong to the two perpendicular σ planes. In such a situation the four nuclei D_2, D_3, D_5 and D_6 are equivalent [14, 17].

In Figure 4 the natural abundance deuterium 2D Q-COSY spectrum of norbornadiene in the chiral liquid crystal solvent PBLG/$CHCl_3$ is presented [22]. In such a 2D Q-cosy spectrum, deuterium chemical shifts appear along the diagonal, as do quadrupolar splittings perpendicular to the diagonal, so it becomes easy to correlate the various quadrupolar doublets [12, 13].

Five quadrupolar doublets are apparent that are easy to assign through chemical shift arguments. The low field doublet is due to the natural abundance deuterium spectrum of the $CHCl_3$ co-solvent. The high field doublet is due to homotopic nuclei H_7 and $H_{7'}$ on the bridge. They are equivalent. The doublet centred at 3 ppm is due to the homotopic equivalent protons H_1 and H_4. Finally, two quadrupolar splittings are observed for the four ethylenic protons at 6.6 ppm. Clearly, protons H_2 and H_5 are homotopic so they must be equivalent. The same is true for H_3 and H_6. However, these two proton pairs are no longer equivalent even if they are enantiotopic, i.e. related by a plane of symmetry. Consequently, the apparent symmetry seen on the NMR spectrum is no longer C_{2v}, but only C_2. Where did the planes of symmetry disappear to?

This phenomenon has been rationalised in terms of group theory arguments about the symmetry of the singlet ordering distribution function [18]. Indeed, an effective symmetry for the ordering, G'_M, of a molecule of symmetry G_M embedded in an ordering phase with symmetry G_P, can be defined as $G'_M = G_M \otimes G_P$.

In this equation it is only recognised that the symmetry of the singlet ordering distribution function depends on both the symmetry of the molecule and the symmetry of the ordering phase. When working with non-chiral or racemic nematic phases as the solvent the phase symmetry is $D_{\infty h}$. In this case the effective symmetry G'_M will always be identical to G_M because $D_{\infty h}$ belongs to the O_3 group that includes all rotations and reflections. However, when working with chiral nematic solvents, the phase symmetry is only D_∞. D_∞ belongs to the group of pure rotations, SO_3, and consequently G'_M will be the subgroup of G_M belonging to SO_3. A C_{2v} or C_{3v} molecule will orient on average as a C_2 or C_3 molecule respectively, a D_{2d} molecule will orient on average as if it were D_2, a C_s molecule will orient on average as C_1 and so on.

These changes in the effective symmetry of the orientational order will not always be apparent from the NMR spectrum. For instance, we will not see a spectral multiplicity change from C_{3v} to C_3 because in both cases the C_3 axis is a principal axis of the Saupe

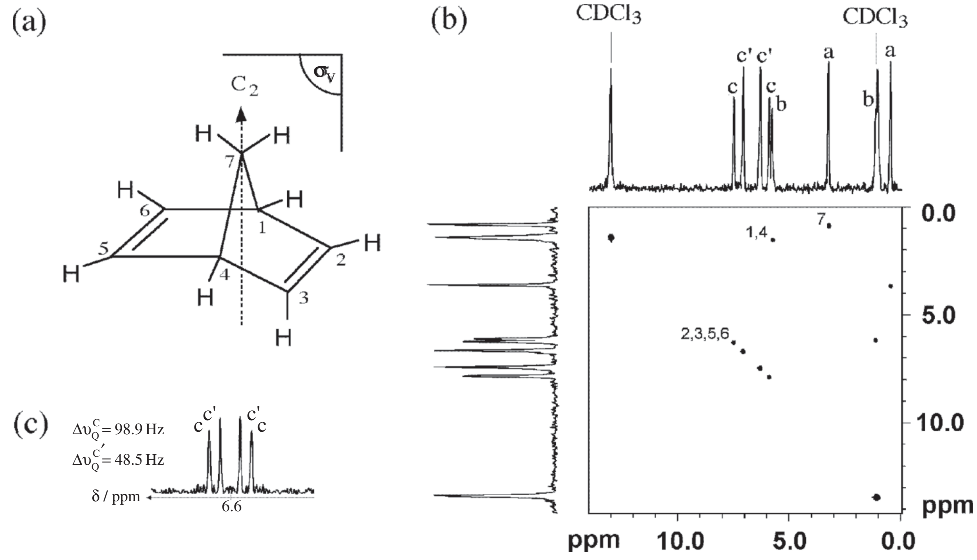


Figure 4. 61.4 MHz deuterium 2D Q-COSY spectrum of compound **2** in the chiral liquid crystal solvent PBLG/$CHCl_3$ Note the doubling of the quadrupolar splitting of the ethylenic nuclei at 6.6 ppm due to the non-equivalence of the enantiotopic nuclei in the chiral liquid crystal solvent.

ordering tensor and the two others can be taken anywhere in the perpendicular plane because order is isotropic in that plane (for non-rigid molecules the problem may be more complicated [23, 24]). So enantiotopic nuclei, if they exist, in a C_{3v} rigid molecule will not be discriminated. In contrast, in a C_{2v} molecule, the C_2 axis is a principal axis for the Saupe matrix. In a nematic medium the other two principal axes belong to the two perpendicular σ planes. However, in a chiral nematic the effective symmetry becomes C_2, so the C_2 axis remains a principal axis, but the other two are no longer in the plane of symmetry because as far as the ordering is concerned there are no longer any symmetry planes [18, 25]. In this situation, two enantiotopic nuclei will be non-equivalent. This is exactly what we observed from the experimental spectrum in Figure 4.

These dramatic changes in the NMR spectrum will appear systematically, with molecules with C_s symmetry appearing as C_1 and the normal to the symmetry plane no longer being a principal axis for the order, C_{2v} and S_4 molecules appearing as C_2 with the only principal axis known being the C_2 axis, and D_{2d} molecules appearing as D_2 with the three C_2 axes remaining as principal axes for order, but the order parameters of these axes will all have different values corresponding to the appearance of an asymmetry in the ordering compared to D_{2d}.

Going back to the norbornadiene example, we can calculate the position of the principal axis system of the Saupe ordering matrix using the experimental quadrupolar splittings measured on Figure 4 and a calculated geometry using the semi-empirical force field PM_3.

In the first step, the Saupe order parameters are calculated in a molecular fixed frame $\{x,y,z\}$ were x is the C_2 axis and y and z belong to the molecular planes of symmetry. Note that the S_{xy} order parameter is not zero in accordance with the C_2 effective symmetry of the ordering of this C_{2v} molecule dissolved in a chiral liquid crystal.

In the second step, the real, symmetric and traceless Saupe ordering tensor is diagonalised to obtain the principal values of the ordering tensor reported in Table 1. The transformation matrix is then used to calculate the position of the Saupe matrix principal axis system $\{x',y',z'\}$ in the initial molecular frame. This is pictured in Figure 5 where it appears that the principal axis system for the Saupe matrix in the chiral medium can be deduced from the principal axis system in the non-chiral solvent by a simple anticlockwise rotation around the C_2 axis by an angle $\alpha = 9.5°$.

However, when carrying out these calculations a bet has to be made: which one of the pro-*R* and pro-*S* nuclei (H_2 or H_3) exhibits the largest and the smallest quadrupolar splitting? Assuming that $\Delta\nu_Q(H_2)>\Delta\nu_Q(H_3)$ yields the results reported in Table 1 where S_{yz} is negative and $\alpha = 9.5°$. If we now make the opposite bet and suppose that $\Delta\nu_Q(H_2)<\Delta\nu_Q(H_3)$ we find exactly the same numerical results, but with a positive sign for S_{yz} that leads to an opposite clockwise rotation of the principal axis system with $\alpha = -9.5°$.

Table 1. Values of the Saupe ordering matrix elements for **2** in the $\{x,y,z\}$ molecular frame and in the principal axis system for the order matrix $\{x',y',z'\}$ (see Figure 5). These two frames are related to each other through a simple rotation through an angle $|\alpha| = 9.5°$ around the C_2 axis whose sign depends on the sign of S_{yz}.

S_{xx}	S_{yy}	S_{zz}	S_{yz}
7.8×10^{-4}	4.4×10^{-4}	-12.2×10^{-4}	$\pm 2.8 \times 10^{-5}$
$S_{x'x'}$	$S_{y'y'}$	$S_{z'z'}$	$\lvert\alpha\rvert$
7.8×10^{-4}	4.9×10^{-4}	-12.7×10^{-4}	$9.5° \pm 1°$

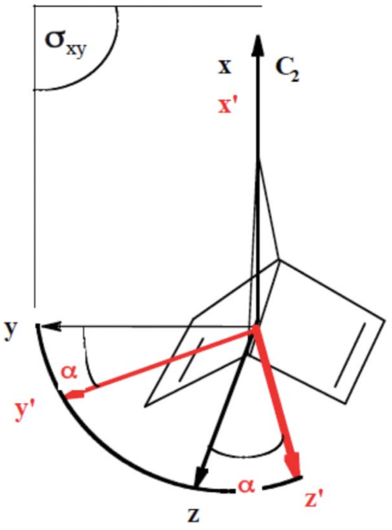


Figure 5. Evolution of the principal axis system for the Saupe ordering matrix from the non-chiral to the chiral liquid crystal solvent. The principal axis system is rotated around the C_2 axis by an angle of ±9.5°. If the sign could be determined *ab initio* the absolute attribution of prochiral H_2 and H_3 NMR signals could be possible.

So this experiment and the calculations demonstrate that the absolute attribution of the enantiotopic pairs (H_2, H_5) and (H_3, H_6) will be possible if we can *ab initio* determine the sign of rotation of the principal axis system when chirality is introduced in the ordering solvent. In other words, the absolute pro-*R* or pro-*S* character of the quadrupolar doublets at 6.6 ppm on the 2D spectrum in Figure 4 is actually hidden behind the sign of the rotation of the principal axis system when chirality is introduced into the liquid crystal solvent. We believe that the determination of the sign of this angle should be much easier to carry out than the full *ab initio* calculation of the order parameters proposed in the Introduction.

In the next two experiments we will demonstrate that this result is general: the attribution of the absolute configurations is hidden behind the determination of the sign of the rotation of the principal axis system of the Saupe ordering tensor when going from a non-chiral racemic to a chiral ordering solvent.

4. Evolution with chirality of the Saupe principal axis system for ordering in prochiral molecules of C_s symmetry

This paragraph follows the same framework as the preceding one but for norbornene, (**3**), a molecule with C_s symmetry. In Figure 6 the natural abundance deuterium 2D Q-COSY (tilted) spectrum of norbornene is reported [26, 27]. This spectrum shows clearly that all enantiotopic deuteron pairs (D_{11}–D_{12}), (D_{10}–D_{13}), (D_{14}–D_{16}) and (D_{15}–D_{17}) exhibit two quadrupolar doublets. Consequently, all enantiotopic nuclei are non-equivalent, indicating the C_1 symmetry of the ordering in the chiral liquid crystal for this otherwise C_s molecule.

The analyses of the spectrum and the calculations to determine the order parameters in the chiral solvent and in the racemic mixture 50% PBLG/50% PBDG have been reported in [27, 28]. Table 2 presents the order parameters obtained using a geometry calculated with the molecular mechanics force field MM^+.

The transformation matrix that diagonalises the Saupe matrix is used to calculate the relative position of the principal axis system in each case. This evolution is pictured in Figure 7. As in the preceding example, when chirality appears in the anisotropic solvent the principal axis system for order moves, but the rotation here is more complicated and may be characterised by three Euler angles $\Omega=(5°, 8°, -17°)$. The normal to the molecular symmetry plane, (a), is no longer a principal axis and it rotates by an angle of $-14° \pm 2°$. The other two axes, b and c, move out of the symmetry plane with angles $-12° \pm 2°$ and $+8° \pm 2°$, respectively.

Here again, the results in Table 2, line PBLG-1 and those in Figure 7, needed to make a bet that recalls the old Fisher bet: we suppose that the pro-*R* nucleus D_{12} (see Figure 6) gives a smaller quadrupolar splitting than the pro-*S* D_{11}. If the opposite bet is made, column PBLG-2 in Table 2, the numerical results are the same but the signs of S_{ab} and S_{ac} change resulting in identical principal values of the Saupe matrix but with a reverse rotation $\Omega=(-5°, -7°, 17°)$ of the principal axis system compared to case PBLG-1. Consequently, the absolute

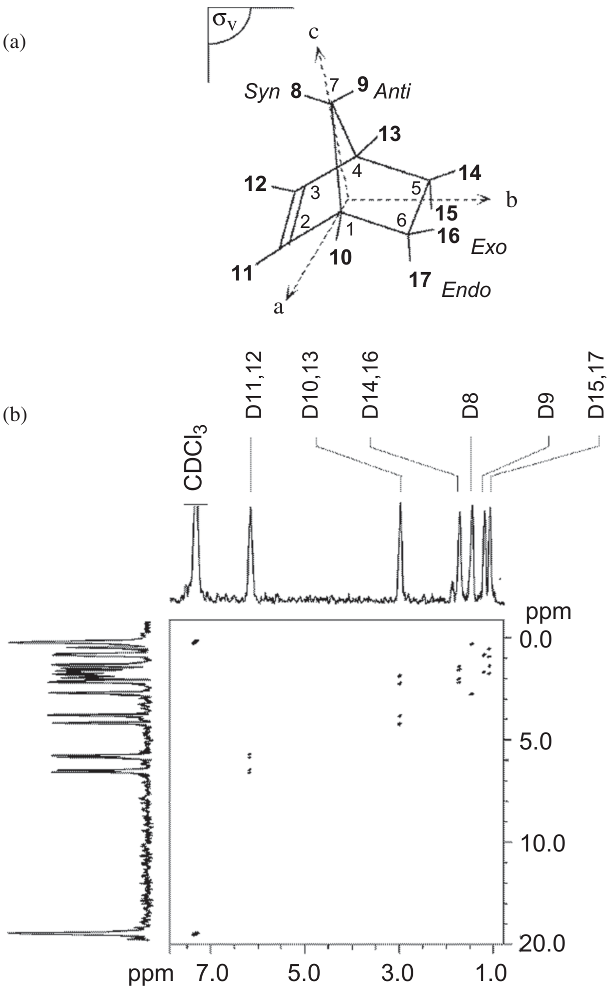


Figure 6. (a) The structure of norbornene (**3**). (b) The 61.4 MHz natural abundance $^2H\{^1H\}$ Q-COSY tilted spectrum of **3** in pure PBLG/$CHCl_3$ solvent.

Table 2. Saupe order parameters of **3** in the molecular frame (see Figure 6) for the chiral (PBLG) and the non-chiral (PBG) solvents and the corresponding principal values of the Saupe matrix. PBLG1 and PBLG2 correspond to the two possible bets: $\Delta\nu_Q(D_{11})>\Delta\nu_Q(D_{12})$ or $\Delta\nu_Q(D_{11})<\Delta\nu_Q(D_{12})$.

	Saupe order parameters in the molecular frame, x10^4						Principal values of the Saupe matrix, x10^4		
Solvent	S_{aa}	S_{bb}	S_{cc}	S_{ab}	S_{ac}	S_{ad}	$S_{a'a'}$	$S_{b'b'}$	$S_{c'c'}$
PBLG-1	−5.3	2.5	2.8	0.6	−1.8	−4.6	−5.7	−1.8	7.5
PBG	−5.3	2.5	2.8	0	0	−4.6	−5.3	−2.0	7.3
PBLG-2	−5.3	2.5	2.8	−0.6	1.8	−4.6	−5.7	−1.8	7.5

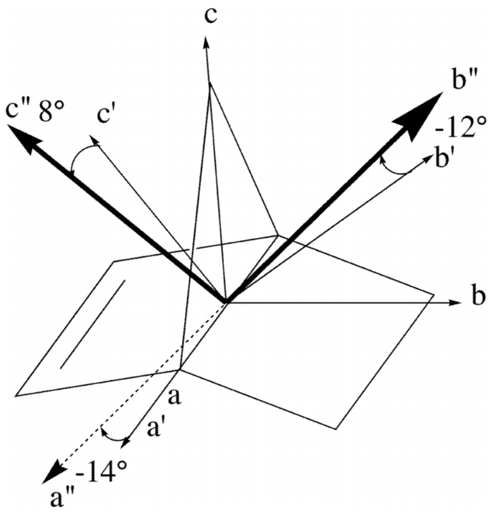


Figure 7. Evolution of the principal axis system for the Saupe matrix of norbornene when going from the non-chiral racemic PBG $\{a',b',c'\}$ to chiral PBLG $\{a'',b'',c''\}$ solvent. $\{a,b,c\}$ is the arbitrarily chosen molecular fixed frame. Note that when chirality appears, the normal to the molecular symmetry plane is no longer a principal axis.

attribution of the pro-*R* or pro-*S* characters of the NMR signals in Figure 6, i.e. the absolute configuration, will be known if we can predict *ab initio* the sign of these rotations. This result is the same as in Section 3 but with a rotation involving three Euler angles instead of only one.

The next example will generalise these results to the case of enantiomers.

5. Evolution of the Saupe principal axis system for an enantiomer from PBLG to PBDG through the racemic PBG (50% PBLG/50% PBDG)

In this example we use some of the results described in [21], for the enantiomers of (trichloromethyl)-β-propiolactone: (**4**) (see Figure 8).

Measurements of proton–proton and carbon–proton dipolar couplings have been made in the PBLG/$CHCl_3$ solvent [21]. These experimental data are reported in Table 3. In this table, the set of data denoted $D_{ij}(RS)$ PBG was calculated from the experimental data for the *R* and *S* enantiomers using the conclusion of Section 2: anisotropic interactions for *R* or *S* in the racemic mixture PBG are equal to half the sum of the *R* and the *S* interactions measured in pure PBLG. Furthermore, in order to simplify the coming discussion it is recalled that the ordering of the *S* enantiomer in PBLG is identical to that of the *R* in PBDG.

These data in combination with a model geometry using the molecular mechanics force field MM^+ allow for calculation of the Saupe order parameters for the *R* enantiomer in pure PBLG, PBG and PBDG as reported in Table 4.

It is now convenient to change the molecular frame of reference and to use the principal axis system for *R*/PBG because it is easier to understand what is happening when chirality is introduced into the solvent from this frame. The order parameters expressed in this frame are reported in Table 5.

In Table 5 it can be seen that in the molecular frame transformation the properties noted in Table 4 are retained, i.e. the values of the parameters in the PBG non-chiral solvent are half the sum of those in the PBLG and PBDG solutions. The consequence of being in the principal axis system for the Saupe matrix of the experiment *R*/PBG is that the off-diagonal elements are now zero. So the off-diagonal elements for experiments *R*/PBLD and *R*/PBDG now have the same numerical values but reverse sign in order to fulfil this property.

The representation in this frame makes quite apparent what happens when, starting from the PBG experiment, some chirality is introduced in the

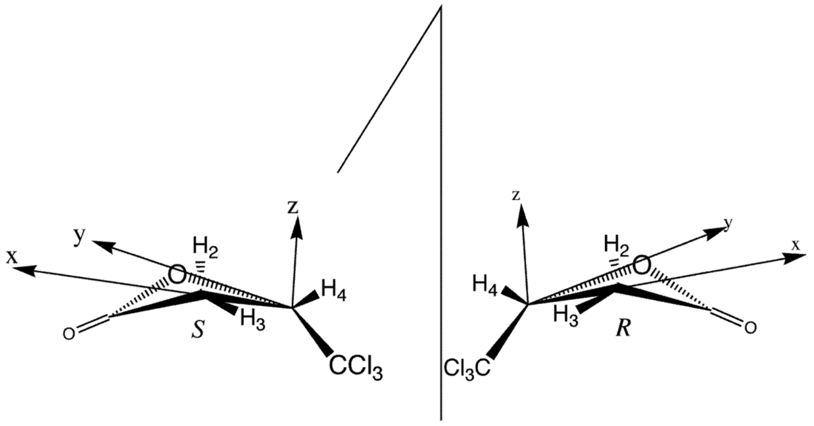


Figure 8. Schematic representation of trichloromethyl *β*-propiolacton (**4**) enantiomers and the nuclei numbering.

Table 3. Experimental dipolar couplings used to calculate the order parameters of the *R* enantiomer of **4** in PBLG, PBG and PBDG. Note that D_{ij} (*RS*)PBG = (D_{ij} (*R*)PBLG + D_{ij} (*R*)PBDG)/2.

Bond	Atoms	J_{ij}/H_z	D_{ij}/H_z (*R*)PBLG	D_{ij}/H_z (*S*)PBLG = D_{ij}/H_z(*R*) PBDG	D_{ij}/H_z (*RS*)PBG
H–H	2–3	–17.06	35.32	41.78	38.55
	2–4	5.75	–2.72	–3.25	–2.98
	3–4	3.72	4.81	0.97	2.89
One bond C–H	1–2	144.40	45.75	58.70	51.72
	1–3	144.40	19.80	15.32	17.56
	4–5	170.70	47.88	26.43	37.15
Other C–H	1–4	–0.50	0.98	–1.61	–0.31
	5–2	–2.50	1.93	2.34	2.13
	5–3	4.20	–2.17	–0.99	–1.58

Table 4. Order parameters of the *R* enantiomer of **4** in the original, arbitrarily chosen, molecular reference frame in Figure 8. Note that the order parameters of *R* in PBG are half the sum of the order parameters in PBLG and PBDG.

$S_{\alpha\beta} \times 10^4$	*R*/PBLG	*R*/PBG	*R*/PBDG
S_{xx}	+3.9	+4.2	+4.5
S_{yy}	+12.4	+13.75	+15.1
S_{zz}	– 16.3	– 17.95	– 19.6
S_{xy}	+16.5	+16.95	+17.4
S_{xz}	+7.6	+2.3	– 3.0
S_{yz}	+18.1	+14.95	+11.9

Table 5. Order parameters of the *R* enantiomer of **4** calculated in the PBG principal axis frame. Note that the PBG values remain the average of those for PBLG and PBDG. Consequently, in this frame the off-diagonal elements have the same numerical values but are reversed in sign in PBLG and PBDG.

$S_{\alpha\beta} \times 10^4$	*R*/PBLG	*R*/PBG	*R*/PBDG
S_{xx}	+32.1	+30.35	+28.6
S_{yy}	– 24.2	– 24.65	– 25.1
S_{zz}	– 7.9	– 5.7	– 3.5
S_{xy}	+5.5	0	– 5.5
S_{xz}	– 1.2	0	+1.2
S_{yz}	+2.2	0	– 2.2

anisotropic solvent. In the principal axis system of PBG, off-diagonal elements appear. Those are equal and opposite in sign in *R*/PBLG and *R*/PBDG and they are again a consequence of the rotation of the order principal axis system when chirality is introduced in the solvent. Therefore, if we are able to predict *ab initio* the sign of those off-diagonal elements we should be able to assign the absolute configurations.

Diagonalisation of the Saupe ordering matrix in the experiments *R*/PBLG and *R*/PBDG allows the calculation of the principal values of the order parameters and the position of the associated principal axes, $\{^{L}x,^{L}y,^{L}z\}$ and $\{^{D}x,^{D}y,^{D}z\}$ respectively, towards the PBG principal axis system frame chosen as the reference frame, $\{^{a}x,^{a}y,^{a}z\}$ (see Figure 9). Once again, from *R*/PBG to *R*/PBLG the principal axis system rotates through Euler angles Ω_{Λ} = (–15°,6°,7°) and from PBG to PBDG it rotates through Ω_{Δ} = (–23,–6°,28°). In contrast to preceding examples, the two rotations are not exactly opposite to each other and it is difficult to see whether the rotations are in opposite directions using only the Euler angles. However, it is relatively easy to calculate the oriented angles between these sets of principal axis systems. From *R*/PBG to *R*/PBLG the principal axes rotate by angles $\theta a_x L_x = -9°$, $\theta a_y L_y = -8°$ and $\theta a_z L_z = +6°$, and for *R*/PBG to *R*/PBDG $\theta a_x D_x = +8°$, $\theta a_y D_y = +6°$ and $\theta a_z D_z = -6°$ (see Figure 9). So, even if the rotations of the principal axis system are not exactly symmetrical, they have clearly opposite directions. This means again that the signs of the rotation angles of the principal axis system under a chiral stimulus depend on the absolute configuration.

In these experiments described in [22], the mixture of the enantiomers of **3** was not racemic and the absolute configurations were known because the enantiopure compounds are commercially available. However, if the absolute configurations were not known, we could determine two sets of data, inverting the numbers in the columns noted *R*/PBLG and *R*/PBDG in Tables 4 and 5. It must be clear that when doing this the results are just inverted, with the principal axis systems for *R* in PBLG, $\{^{L}x,^{L}y,^{L}z\}$, and PBDG,$\{^{D}x,^{D}y,^{D}z\}$, being inverted in Figure 10. So here again we demonstrate that starting from the PBG orientation the introduction of chirality in the solvent results in a rotation of the principal axis system for the Saupe matrix and the absolute configuration of the enantiomers is hidden, being the signs of the rotation angles of the former principal axis system to the

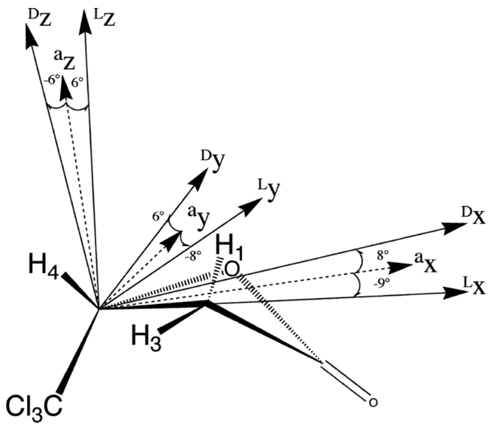


Figure 9. Evolution of the principal axis frame for the Saupe matrix for the *R* enantiomer of **4** from the achiral PBG, $\{{}^{a}x, {}^{a}y, {}^{a}z\}$, to chiral PBLG, $\{{}^{L}x, {}^{L}y, {}^{L}z\}$, and PBDG, $\{{}^{D}x, {}^{D}y, {}^{D}z\}$, anisotropic solvents.

later. If by one method or another these rotation angle signs could be predicted, it will lead to the absolute configuration assignment of the NMR signals.

6. Conclusion

The previous experiments, analyses and remarks may be summarised in the following way.

In principle, the absolute configuration assignment problem will be solved when an *ab initio* calculation of the order parameters in a chiral liquid crystal will be possible. Such an approach corresponds to a severe molecular dynamics problem involving several molecules, i.e. the polypeptidic fibres and their various conformations, the organic co-solvent and the enantiomers under study. This is quite an interesting task and some of our colleagues are working on it, but it is certainly a difficult endeavour and we have raised the question of possible simplifications.

The first simplification would be to use what we already know about the ordering. In the first step, the experiment in Section 2 suggests that one can start from the identical ordering of enantiomers in a racemic liquid crystal. This can be easily done as we have shown that the linearity of the evolution of normalised anisotropic interactions when going from pure PBLG, to racemic 50% PBLG+ 50% PBDG and to pure PBDG allows the evaluation of anisotropic interactions in the racemic mixture as half the sum of the interactions measured for each enantiomer in either pure PBLG or pure PBDG. In such a situation, only chiral effects need to be taken into account.

In the second step, we have shown that when some chirality appears in the orienting solvent, the principal axis system of the Saupe matrix rotates and that the signs of the rotation angles are opposite for the two enantiomers. Consequently, we will be able to assign absolute configurations when we will be able to predict *ab initio* the signs of these rotation angles. In trying to predict these signs we will have to take into account some kind of an interaction potential between the chiral molecules and the polypeptidic fibres. Doing so, it will be sufficient to restrict this potential to pure chiral terms because non-chiral terms will contribute with the same amount to the ordering of the enantiomers, i.e. to the ordering in the non-chiral medium that we assume to be known from the spectrum in the racemic solvent.

These various remarks should strongly simplify the problem of absolute configuration assignment. Moreover, they emphasise the importance and the relevance today of the order parameters and their principal axis system that Alfred Saupe introduced 45 years ago.

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