Structural Ambiguities Revisited in Two Bridged Ring Systems Exhibiting Enantiotopic Elements, Using Natural Abundance Deuterium NMR in Chiral Liquid Crystals

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The natural abundance deuterium 2D Q-COSY NMR spectra of two apolar bridged ring systems, norbornene (C_s symmetry) and quadricyclane (C_{2v} symmetry), oriented in a chiral liquid crystal made of an organic solution of poly-γ-benzyl-L-glutamate (PBLG), are analyzed. In such a chiral oriented solvent, enantiotopic nuclei or directions are nonequivalent. Consequently, it is possible to measure many more anisotropic interactions compared to those obtained from NMR spectra in nonchiral nematic solvents. From the measurement of all residual quadrupolar splittings, $\Delta\nu_Q$, and one-bond carbon−proton residual dipolar couplings, $^1D_{C-H}$, all the elements of the second rank order tensor, $\mathbf{S}_{\alpha\beta}$, were calculated. Knowledge of the $\mathbf{S}_{\alpha\beta}$ values allows all deuterons and subsequently proton NMR resonances to be assigned unambiguously. The reason is that there exists a one-to-one mathematical relationship linking the orientational order parameters of a solute molecule, the molecular geometry, and the anisotropic interactions measured on oriented spectra. In the case of norbornene, it was possible to assign nuclei to each enantiotopic face in this prochiral molecule. Such an analytical approach yields original stereochemical information probing the diastereotopicity and/or enantiotopicity of molecules, and is revealed to be a very useful alternative to conventional 2D-NMR experiments in isotropic solvents.

Introduction

Since the pioneering work of Saupe and Englert, it has been recognized that NMR in liquid crystals, LCs, is an efficient approach for the structural and stereochemical analysis of rigid or flexible solutes.[1−3] This is because anisotropic NMR spectra depend on order-dependent observables such as chemical shift anisotropies, $\Delta\sigma_i$, residual dipolar couplings, D_{ij}, and, for spin I larger than $^1/_2$, residual quadrupolar splittings, $\Delta\nu_{Q_i}$, that can be used to calculate the elements of the molecular Saupe's order matrix, $\{S_{\alpha\beta}\}$, and also to investigate both the structure and the orientational order of solutes.[1−3] The unique analytical features of NMR spectra in ordered media have ensured a continuous interest for studying rigid as well as flexible solutes using ^{1}H−^{1}H, ^{1}H−X, X−X, and X−Y residual dipolar couplings[1,3−4] or deuterium quadrupolar splittings for isotopically enriched compounds[5] and at the natural abundance level.[6,7] During the last five years, the application of NMR in weakly aligned aqueous liquid crystalline solutions has been found to be a powerful tool for providing valuable structural information on macromolecules of biological interest through the measurement of ^{13}C−^{1}H and ^{15}N−^{1}H residual dipolar couplings. In the latter case, the anisotropic NMR information can be advantageously used for determining the topology of biomolecules such as proteins, refining their local structures, or determining the relative orientation of remote parts.[8]

Until now, most of the NMR structural studies of solutes in oriented solvents have been achieved using liquid crystals made of achiral molecules. The most commonly used LC phases are the nonchiral uniaxial nematics with $D_{\infty h}$ symmetry. In such mesophases solute−solvent interactions are invariant under any rotation around the director, **n**, or any 180° rotation around an axis perpendicular to **n**.[9,10] As a consequence, the enantiotopic nuclei, groups, or directions which are only related through improper symmetry operations (S_{2n}) are equivalent and, hence they cannot be distinguished using NMR spectroscopy in a nonchiral nematic phase. This situation is typically observed for prochiral molecules with C_s symmetry, and it leads to a non-negligible loss of dipolar and quadrupolar information that could be useful or essential for a correct stereochemical analysis of the molecule under investigation.

This problem can be, however, solved by recording spectra in chiral liquid crystalline solvents in which the signal of the enantiotopic nuclei can be distinguished and analyzed. In such media, the symmetry properties of the intermolecular ordering potential of dissolved molecules may change compared with the case of achiral LC systems, and hence, the symmetry group describing the orientational behavior of a solute may be different from the molecular group symmetry.[10] This effect can lead to important spectral modifications in NMR spectra with respect to those recorded in an achiral LC.[10−14] The NMR consequences of this loss of symmetry are interesting from a structural or stereochemical point of view. First, the additional spectral information allows us to reveal the prochirality in the solutes of C_s, C_{2v}, S_4, or D_{2d} symmetry.[11,12] Second, it can provide various further anisotropic data which cannot be obtained in an achiral LC. For instance, this approach could be used to obtain a total set of spectral data associated with each of two enantiotopic faces in molecules with C_s symmetry.

In this article, we will show that the determination of $\{S_{\alpha\beta}\}$ from the deuterium quadrupolar splittings measured in the natural abundance deuterium NMR spectra, recorded in a weakly ordering chiral liquid crystalline solvent, allows a reliable assignment of all deuterons (and subsequently the corresponding

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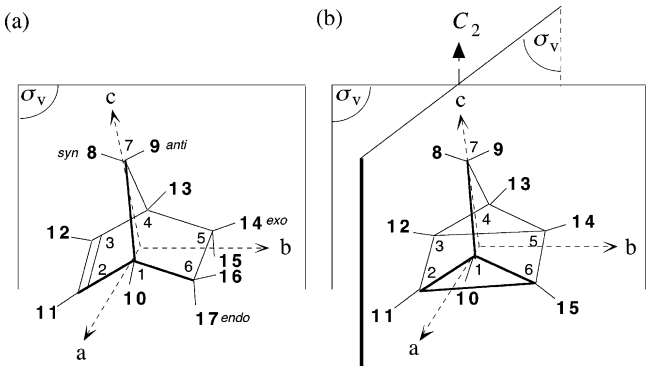

Figure 1. Definition of axes (*a*, *b*, *c*) of the reference molecular frame and numbering of atoms. The bond pairs noted (1−10/4−13), (2−11/3−12), (5−14/6−16), and (5−15/6−17) for the norbornene and the bond pairs noted (2−11/3−12) and (5−14/6−15) for the quadricylane are enantiotopic and, hence, should be inequivalent in a chiral oriented solvent.

protons) in a prochiral molecule. The reason is that an incorrect assignment of any one of the quadrupolar doublets experimentally observed produces an inconsistent calculation of $\{S_{\alpha\beta}\}$.[2,9] As illustrating examples, we investigate the case of norbornene (bicyclo[2.2.1]hept-2-ene), noted **1**, and quadricyclane (tetracyclo-[3.2.0.0.0]heptane), noted **2**, dissolved in organic solutions of poly-γ-benzyl-L-glutamate (PBLG). Figure 1 shows the structures of compounds **1** and **2**, the labeling of the various nuclei, and the position of the molecular reference frame used in the calculations. As we can see, compounds **1** and **2** are apolar rigid molecules of C_s and C_{2v} symmetry, respectively, and both possess enantiotopic elements.[11,12]

The choice of these examples was motivated by two main reasons. First, they possess a large enough set of quadrupolar splittings to calculate all the independent elements of the Saupe's matrix in a chiral liquid crystal. Second, in the earliest literature, it appeared that the structural analyses of these highly strained molecules were very controversial. Thus, for compound **1**, contradictory assignments of proton chemical shifts due to unexpected shielding/deshielding effects resulting from the anisotropic effect of the double bond appeared, while, for compound **2**, problems mainly came from geometry for the cyclopropanic rings.[15] Consequently, from a methodological point of view, it is pertinent to assess the efficiency of this analytical approach using known examples already reported in the literature, before investigating the cases of newly synthesized compounds.

Theoretical Aspects and Advantages of the Natural Abundance Deuterium NMR of Weakly Ordering, Chiral Liquid Crystal

Although numerous spectroscopic solutions have been designed to simplify complex anisotropic spectra,[2,16] the simplest way lies in the use of weakly ordering systems, such as phospholipid bicelles in water,[8] *n*-alkylpoly(ethylene glycol)/*n*-alkyl alcohol mixtures,[17] or organic solutions of synthetic homopolypeptides.[18] In the first case, the weak degree of molecular orientation of solutes yields relatively small residual dipolar couplings, and generally the anisotropic spectra can be easily analyzed. In the case of organic solutions of polypeptides, the magnitude of order parameters, $S_{\alpha\beta}$, is not usually sufficiently small to totally cancel out the long-distance residual dipolar couplings. Consequently, the loss of spectral resolution often precludes the possibility to easily distinguish between signals of two enantiotopic elements in prochiral molecules. Under these circumstances, the additional spectral information that NMR in a chiral ordered solvent can basically provide is lost. Thus, no enantiotopic discrimination has ever been directly detected so far using proton NMR; likewise, the results obtained using proton-coupled carbon-13 spectra often do not allow us to draw any conclusion.[12] Two-dimensional NMR experiments such as gradient enhanced heteronuclear single quantum cohrence (HSQC) or selective refocusing (SERF) experiments can be used in order to simplify the spectral patterns.[19] However, these techniques are inefficient when the enantiotopic discrimination is too small to be spectroscopically resolved.

In the frame of the analysis of organic prochiral molecules in an oriented solvent, the deuterium NMR is the most efficient tool because ^{2}H quadrupolar interaction is very sensitive to the differential ordering effect (DOE). Furthermore, this isotope is naturally occurring at the level of 0.015% in all molecules possessing proton nuclei.[7] Assuming axial symmetry of the electric field gradient along the C−D bond, this purely anisotropic interaction can be written as[2]

$$\Delta\nu_{Q_i} = \frac{3}{2}K_{C-D_i}S_{C-D_i} \quad \text{with} \quad K_{C-D_i} = \frac{e^2 Q_{D_i} q_{C-D_i}}{h} \qquad (1)$$

where S_{C-D_i} is the order parameter along the C−D$_i$ bond and K_{C-D_i} is the deuterium quadrupolar coupling constant of the *i*th deuteron. K_{C-D} depends on the hybridization state of the carbon atoms bonded to a given deuteron. Thus, K_{C-D} is generally assumed to be equal to 170 ± 5, 185 ± 5, and 210 ± 5 kHz, for sp^3, sp^2, and sp carbon atoms, respectively.[2] Due to the relatively large magnitude of the K_{C-D} constants, we can expect to differentiate the quadrupolar splitting between two C−D bonds showing only a small orientational difference.[7,18] Considering our initial aim, there are no doubts that proton-decoupled natural abundance deuterium NMR should be the most appropriate technique because spectra are dominated by the quadrupolar interaction without requiring isotopic labeling.

Beyond the fact that quadrupolar splittings give anisotropic data from which the order parameters can be derived, other practical reasons justify the use of the natural abundance deuterium NMR in polypeptidic, weakly ordering liquid crystalline solvents. First, the detection of rare spins such as deuterons in natural abundance is not anymore an obstacle using present-day magnets, standard NMR equipment, and a reasonable amount of solute (50−100 mg).[7,18] A satisfactory signal-to-noise (S/N) ratio can be achieved rather quickly (i.e. 12−15 h) on a 400 MHz instrument equipped with a selective deuterium probe.

Second, the analysis of proton-decoupled natural abundance deuterium NMR spectra of ordered solutes is rather simple because it consists of the superposition of independent quadrupolar doublets centered on their respective chemical shifts and corresponding to all nonequivalent deuterons in the molecule.[18,20] Furthermore, as there are no spin−spin couplings between rare atoms, peaks are quite sharp, thus permitting small enantiotopic discriminations to be observed on spectra. This can be a great advantage compared with the case of the deuterium spectra of perdeuterated molecules where the ^{2}H−^{2}H couplings usually increase the line width or provide additional splittings that can obscure the spectral analysis.

Last but not least, we have recently shown that polypeptide helices were able to interact enantioselectively with nonfunctionalized rigid or flexible enantiomers and/or prochiral molecules.[12,21]

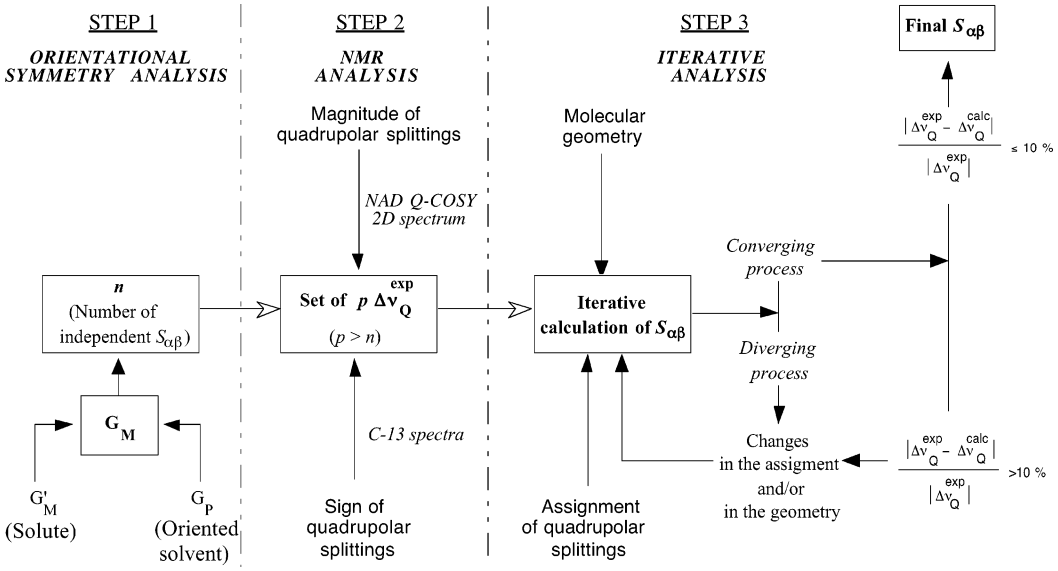

Figure 2. Flowchart showing the three-step analytical procedure adopted for the analysis of weakly ordered organic molecules through natural abundance deuterium NMR.

Results and Discussion

Analytical Strategy Used in the Assignment of Anisotropic Data. To determine how a molecule is ordered when dissolved in a LC, we need to calculate the Saupe's second rank order parameters, $S_{\alpha\beta}$, which can be derived from anisotropic spectral data measured on the oriented spectra. Beyond the orientational information, these parameters also contain structural information about the solute because there exists a mathematical relationship between the order parameter of any direction *ij*, the molecular geometry, and the elements of $\{S_{\alpha\beta}\}$:[2]

$$S_{ij} = \sum_{\alpha,\beta=a,b,c} \cos\theta_{ij}^{\alpha} \cos\theta_{ij}^{\beta} S_{\alpha\beta} \qquad (2)$$

where $\alpha,\beta = a, b, c$ are the axes of the molecular fixed reference frame and θ_{ij}^{α} are the angles between the *ij* internuclear direction and the molecular axes *a*, *b*, and *c*. Actually, the combination of eqs 1 and 2 shows that there exists an univocal relationship relating the orientational order parameters of a solute molecule, its geometry, and the anisotropic interactions determined from the spectral analysis. The determination of $S_{\alpha\beta}$'s is therefore the key step to this analytical approach, considering that the geometry is known.

Figure 2 presents the flowchart describing the three-step procedure adopted for the analysis of weakly ordered organic molecules dissolved in a chiral nematic liquid crystalline solvent. The first step of this strategy consists of the determination of the pertinent number of independent order parameters, which is directly related to the effective orientational symmetry of the solute in the achiral or chiral phase.[10−12] For example, five independent order parameters are required for correctly describing the orientational behavior of C_s symmetry molecules in a chiral liquid crystal, while only three parameters are required when the solute is embedded in an achiral LC, as long as two axes of the chosen reference frame lie in the molecular symmetry plane of the molecule.[2] In the case of C_{2v} symmetry molecules, the number of order parameters is reduced to three in a chiral liquid crystal and to two otherwise.[10−12]

In practice, this number, *n*, of independent second rank order parameters is very important because it defines the minimum number of independent quadrupolar splittings which should be imperatively extracted from the natural abundance deuterium spectra in order to be able to calculate the order matrix elements. When the amount of anisotropic spectral data available on the oriented spectra is insufficient, the correct evaluation of the order parameters becomes impossible. The reason is that the results obtained during the iterative calculation process (third step of the analysis) are only consistent when the available number of independent anisotropic data (*p*) exceeds the number of unknown parameters ($p > n + 1$).

As can be seen from the flowchart, the second step is dedicated to the experimental determination of a set of quadrupolar splittings associated with the molecule under investigation. The magnitude of $\Delta\nu_Q$ can be directly extracted from the analysis of the 2D Q-COSY map. Such an analysis will be detailed in the next section.

A priori, the main disadvantage of the natural abundance deuterium NMR in liquid crystals is the lack of information about the absolute sign of the quadrupolar splittings that cannot be directly deduced from the analysis of the deuterium spectra. However, it is possible to measure the one-bond proton−carbon-13 dipolar couplings, $^1D_{C-H}$, whose signs are opposed to those of the corresponding quadrupolar splittings.[2,18,22] This procedure is possible because the local order parameters for a given C−D and C−H bond are assumed identical ($S_{C-D} = S_{C-H}$). The $^1D_{C-H}$ values derive from the total splitting, $^1T_{C-H} = (2 \cdot {}^1D_{C-H} + {}^1J_{C-H})$, measured on the proton-coupled carbon-13 spectra and the $^1J_{C-H}$ scalar couplings measured in isotropic solvents, which are known to be always positive:[23]

$$^1D_{C-H} = \frac{^1T_{C-H} - {}^1J_{C-H}}{2} \qquad (3)$$

Note that the anisotropy of the $^{13}C-{}^1H$ scalar coupling is generally negligible.[2] Due to the low ordering power of the oriented PBLG phases, the absolute values of $^1D_{C-H}$ are usually much smaller than $^1J_{C-H}$, and consequently, from the magnitude of $^1T_{C-H}$, the absolute signs of $^1D_{C-H}$ can be easily determined.

The third and last step consists of the iterative calculation of the elements of the Saupe matrix from the set of experimental quadrupolar splittings, assuming a model geometry. The calculation of $S_{\alpha\beta}$ parameters is achieved by a least-mean-square fitting procedure derived from the SHAPE program initially developed by P. Diehl et al. and suitably modified to handle quadrupolar splittings as input data.[24]

As a first parameter involved in the iterative process comes the choice of the model geometry for the solute (bond lengths and angles). This point may be drastically important, as we will see in the case of quadricyclane. The molecular geometry can derive from X-ray diffraction, neutron scattering, or molecular modelization (empirical, semiempirical, or ab initio calculations). Generally, vibrational corrections do not significantly improve the quality of the results.[25] As a second parameter comes the set of quadrupolar splittings and their assignment relative to the molecular geometry as well as the choice and number of $\Delta\nu_Q$'s that may be computed, considering that at least $n + 1$ independent anisotropic data are needed when n order parameters have to be calculated. The last parameter is the magnitude of the deuterium quadrupolar coupling constant, K_{C-D}, which is not a priori known with accuracy for each deuteron of the molecule. However, a series of calculations have shown that the standard values of K_{C-D} for the different types of hybridization state of the carbon atom bonded to a given deuteron (see eq 1) were sufficient to give valuable starting data. Actually, no significant differences have been observed by fitting on these values.

At the end of the convergent process, the computer program gives a final set of $S_{\alpha\beta}$ parameters and back-calculated quadrupolar splittings. Note here that the choice of the initial values for $S_{\alpha\beta}$ does not interfere with the final result. The final back-calculated data are carefully compared to experimental ones. If the assignment and the geometry are adequate, both the difference between calculated and experimental data as well as the rms errors are small. In contrast, when the calculation diverges or gives some unacceptably large differences between experimental and back-calculated data, it means that the assignment−geometry relationship is inconsistent, and hence, a new assignment or a new geometry must be tested. This double control during the iterative analysis ensures that the program leads to the best fit between experimental and back-calculated values. Obviously, the more experimental data (with $p > n + 1$), the better the quality of the fitting procedure, but in principle, this does not change the final result. However, to limit the initial calculations during the interactive iterative procedure, it is faster to compute a limited number of anisotropic data to test the assignment and then refine the calculation using all available spectral data.

Analysis of Norbornene. To illustrate our approach, norbornene, **1**, is an interesting bridged ring system because, during several years with earlier NMR, the assignment of the *syn* and *anti* protons with regard to the double bond was unclear.[26−28] Thus, it was claimed that the *syn* proton is more shielded than the *anti*[15] before the opposite conclusion was drawn by other authors using the lastest NMR techniques.[29,30] Although the modern, isotropic NMR techniques are powerful, there remain some situations where no definitive assignments are possible. Consequently, it is pertinent to propose new methodologies to go beyond such analytical limitations. Among these, the recent development of NMR in chiral, weakly ordering liquid crystals proves to be quite efficient.[31]

From a stereochemical point of view, norbornene is a C_s prochiral molecule, and hence, G_M associated with its orientational behavior in the PBLG phase is C_1. So, there are no symmetry arguments to decide a priori where the order principal axis is, and the order matrix required five independent $S_{\alpha\beta}$'s, as for a chiral molecule.[11,12] Consequently, at least six experimental anisotropic data points must be extracted from anisotropic spectra to be used in the iterative process. In fact, this molecule possesses intrinsically 10 independent quadrupolar splittings if the four pairs of enantiotopic deuterons quoted from 10 to 17 (see Figure 1) are discriminated on the natural abundance deuterium spectrum recorded in the PBLG phase.

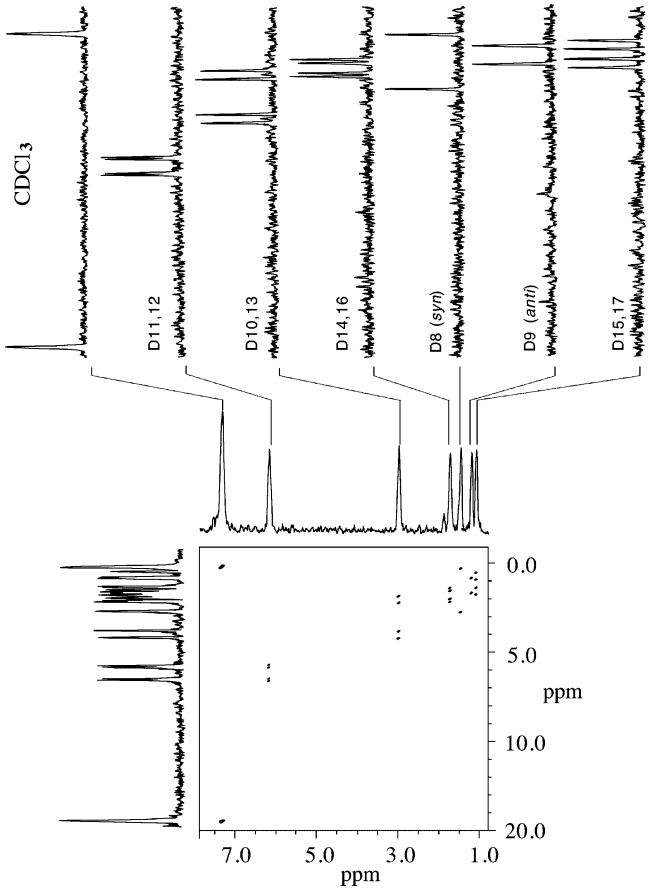

Figure 3. Tilted Q-COSY 2D spectrum (61.4 MHz) of the norbornene in the PBLG/$CHCl_3$ phase. The number of free induction decays added for each t_1 increment was 384. The recycling delay was 0.5 s, and the spectral width in both dimensions is 2500 Hz. The data matrix was zero-field to 512 (t_1) × 2048 (t_2) prior to applying the 2D Fourier transform. The 2D spectrum was symmetrized, tilted, and displayed in magnitude mode. The contour plot is presented without any filtering. On the top, the deuterium signals of all monodeuterated isotopomers are shown.

Figure 3 shows the tilted Q-COSY 2D spectrum of **1** recorded in the PBLG/$CHCl_3$ phase.[22] Each pair of enantiotopic deuterons of the molecule is featured by two deuterium quadrupolar doublets centered on the same chemical shift, thus indicating their spectral enantiodifferentiation in the chiral oriented solvent.[7,18]

In contrast, the *syn* and the *anti* deuterons exhibit a single doublet located at δ_{syn} and δ_{anti}, respectively, thus facilitating their distinction with the enantiotopic nuclei on the 2D map. The largest quadrupolar splitting is less than 150 Hz, while the differences of $\Delta\nu_Q$ between two enantiotopic deuterons are rather small and vary between 10 and 50 Hz. The experimental data are listed in Table 1.

The analysis of the proton-coupled carbon-13 spectrum (not shown) indicates that none of the carbon-13 signals show any visible spectral enantiodiscrimination due to dipolar couplings or chemical shift anisotropy. As mentioned above, this result emphasizes the interest in recording natural abundance deuterium spectra, as the quadrupolar interaction is the most sensitive order-dependent interaction to a difference of local orientational order, S_{C-D}. On the other hand, the simplicity of this spectrum allows the proton−carbon-13 total coupling to be evaluated very

TABLE 1. Spectral Data of the Norbornene Dissolved in Organic Solutions of PBLG and PBG at 305 K

δ ^{2}H (PBLG)/ppm	6.1		2.9		1.7		1.4	1.1	1.0	
no. of H-2	11	12	10	13	16	14	8	9	17	15
no. of C-13	2	3	1	4	6	5	7		6	5
δ ^{13}C(PBLG)/ppm	135.0		41.5		24.4		48.3		24.4	
$^1J_{CH}(CHCl_3)^a$/Hz	167.6		147.3		130.7		136.8		128.8	136.6
sign of $^1D_{C-H}$	>0		>0		<0		<0	<0	>0	
$\Delta\nu_Q^{exp}$(PBLG)^a/Hz	−50.2	−40.0	−146.1	−98.6	47.1	28.1	151.7	51.3	−74.2	−28.4
$\Delta\nu_Q^{calc}$(PBLG)^b/Hz	−46.3	−36.5	−144.8	−97.8	49.3	29.7	156.2	47.4	−73.2	−27.1
error/%	7.7	8.6	0.8	0.8	4.7	5.6	3.0	7.5	1.4	4.5
$\Delta\nu_Q^{exp}$(PBG)/Hz	−41.2		−112.6		35.9		139.5	48.8	−49.0	
$\Delta\nu_Q^{corr}$(PBG)^c/Hz	−46.5		−127.2		40.6		157.6	55.1	−55.4	
$\Delta\nu_Q^{exp\ av}$(PBLG)^d/Hz	−45.1		−122.1		37.6		/	/	−51.3	

^{a} The accuracy of the J_{ij} and $\Delta\nu_{Qi}$ values is around ±1 and ±2 Hz, respectively. ^{b} Calculated values using $K_{C-D}(sp^3) = 170$ kHz and $K_{C-D}(sp^2) = 185$ kHz. ^{c} To take into account solvent order variations in the comparison of data recorded in the PBLG and PBG phases, the $\Delta\nu_Q$'s measured in this latter phase were corrected by the ratio ($\Delta\nu_Q$ of $CDCl_3$ in PBLG)/($\Delta\nu_Q$ of $CDCl_3$ in PBG). The values of $\Delta\nu_Q(CDCl_3)$ in PBLG and PBG are equal to −875.3 and −775.1 Hz, respectively. ^{d} Algebraic average of the $\Delta\nu_Q$ values calculated from the data given in line 6.

TABLE 2. Orientational Order Parameters, $S_{\alpha\beta}$,^{a} of Norbornene and Quadricyclane Dissolved in Organic Solutions of PBLG at 305 K

	S_{aa}	S_{bb}	S_{cc}	S_{ab}	S_{bc}	S_{ac}
norbornene	−0.000 53	0.000 25	0.000 28	0.000 06	−0.000 46	−0.000 18
quadricyclane	−0.000 80	−0.000 49	0.001 29	−0.000 09		

^{a} The errors on $S_{\alpha\beta}$ were estimated to be smaller than 2×10^{-5}. The chosen molecular axis systems associated with compounds **1** and **2** are displayed in Figure 1.

easily. The comparison between $^1T_{C-H}$ and $^1J_{C-H}$ measured in the $CHCl_3$ solvent allows for determining the absolute sign of $^1D_{C-H}$ and, hence, that of the corresponding $\Delta\nu_Q$.

Knowing the magnitude and the absolute sign of the quadrupolar splittings, and assuming a geometry calculated using the simplest and least time-consuming force field (MM2) calculations, the iterative step can begin. Note that, in this example, the final result is the same whatever the complexity of the force field chosen. At the beginning, we iterated only on six (5 + 1) quadrupolar splittings, for which the assignments relative to the molecular geometry are nonambiguous, and assumed standard values for the K_{C-D}, namely 170 and 185 kHz for sp^3 and sp^2 carbon atoms, respectively. Obviously, to avoid any irrelevant results, the quadrupolar splittings associated with *syn* and *anti* deuterons have been disregarded for the initial calculations. This starting set of data yielded a good fit with a small rms and with no significant differences between the six experimental and back-calculated quadrupolar splittings. In particular, no change in the sign of $\Delta\nu_Q$'s was observed. The sign and magnitude of the quadrupolar splittings for all deuterons in the molecule can now be obtained by back-calculation from the iterated values of $S_{\alpha\beta}$ parameters evaluated through SHAPE, and then compared with experimental values.

When the full set of experimental $\Delta\nu_Q$'s is used, the rms error is 2.7 Hz and the largest difference between the experimental and back-calculated values is below 9%. This result shows that calculation allows for assigning unequivocally all quadrupolar splittings of the natural abundance deuterium spectrum even if the exact values of K_{C-D} are not a priori known. The final assignment is given in Table 1, and the $S_{\alpha\beta}$ values of **1**, calculated from the complete set of experimental quadrupolar splittings, are listed in Table 2. Figure 4 shows correlations of experimental residual quadrupolar splittings, $\Delta\nu_Q$(exp), and back-calculated values, $\Delta\nu_Q$(calc), for norbornene. The fit between the experimental and calculated sets of data is excellent and indicates that the assignment−geometry fit is consistent.

As expected, an irrelevant assignment of quadrupolar splittings for the *syn* and *anti* deuterons causes the fitting to diverge or lead to an unacceptably large rms error, and hence, a unique choice for the assignment of the experimental data to the NMR

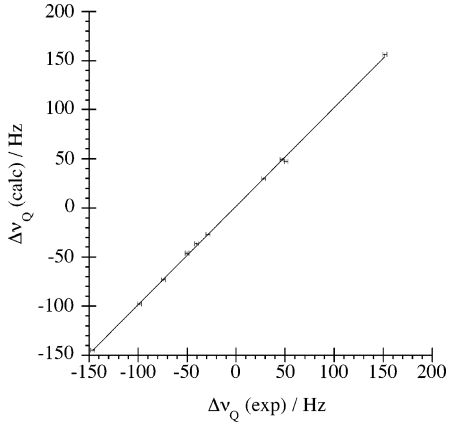

Figure 4. Correlations between the experimental residual quadrupolar splittings $\Delta\nu_Q$(exp) and the back-calculated values $\Delta\nu_Q$(calc) for the norbornene. The solid line corresponds to the ideal line $\Delta\nu_Q$(exp) = $\Delta\nu_Q$(calc).

signals is possible. This new analytical approach in the field of the structural analysis demonstrates clearly that the deuteron in the *syn* position is more deshielded than that in the *anti* position. Assuming that the deuterium and proton chemical shifts in the oriented solvent are identical and neglecting the proton chemical shift anisotropy, we are then able to assign the proton signals on the anisotropic and isotropic proton spectrum. Our own results confirm therefore the results reported in the literature.[30]

It could be argued here that the effects of the vibrational corrections cannot be always neglected in comparison to the values of the quadrupolar splittings. However, previous results have shown that only small vibrational effects are involved for weakly ordered solutes, and hence, such a correction could not invert any of the assignments that we have made without vibrational corrections.[25] In other words, the differences between experimental and back-calculated values obtained by inverting any one of the quadrupolar splittings are too large to be compensated through vibrational corrections. Besides it could also be argued that the K_{C-D} values are not the same for all deuterons of the molecule, and hence, a better knowledge of these constants could improve the quality of the fit. In particular,

we can anticipate that the K_{C-D} values for the deuterons in the *syn* and the *anti* positions are not the same because the electric field gradient (EFG) of the syn deuteron could be perturbed by the presence of the double bond.[29] Actually, a series of calculations indicates that the K_{C-D} value for the syn deuteron is smaller and that for the *anti* deuteron is larger than the average value usually used for an sp^3 hybridized carbon atom. Keeping constant the K_{C-D} values for the other deuterons, the rms error reaches a minimum of 0.6 Hz when using $K_{C-D}(syn) = 160$ kHz and $K_{C-D}(anti) = 190$ kHz. This result suggests a significant electronic effect of the double bond on the EFG at the *syn* and *anti* deuterons.[29]

Similarly to the assignment of the quadrupolar splittings for the deuterons in the syn and the anti positions, it is also possible to define the various nuclei belonging to the same prostereogenic face of the molecule. Indeed, if one of the deuterons is not correctly assigned to the corresponding face, then the calculation breaks down. In the case of norbornene, we were able to determine a coherent set of quadrupolar splittings for each prostereogenic face of this prochiral compound and hence distinguish between them using NMR spectroscopy. The $\Delta\nu_Q$'s underlined in Table 1 correspond to the deuterons belonging to the same face. This ability to distinguish each side of a prochiral molecule is due to the chirality of the orientating liquid crystal and has to be compared to the action of chiral complexing agents in asymmetric synthesis. In this sense, this approach is an original tool for solving such stereochemical assignments rather easily and probing enantiotopicity in prochiral molecules. However, we are not able to assign an absolute configuration descriptor *Re* or *Si* to each face thus far. This problem is similar to that of absolute configuration determination for enantiomers. The reason is that the inversion of all the quadrupolar splittings among each pair of enantiotopic deuterons of the molecule would lead to the same fit and the same results. Consequently, the absolute configuration of the two prostereogenic faces is undetermined. For solving such stereochemical ambiguity, a priori evaluation of Saupe's matrix elements is needed. This should be possible through molecular dynamics simulations using some adequate intermolecular potential, for instance. It will require the development of a realistic model in order to take into account all contributions involved in the enantiotopic discrimination and their subtle balance.[32] The problem is being studied in this laboratory.

For larger molecules, it could be anticipated that the analysis of proton-coupled carbon-13 1D or even 2D spectra in a chiral oriented solvent is not simple due to numerous peak overlaps, and so the access to the sign of quadrupolar splittings is not straighforward. To partly overcome this situation, we can record the Q-COSY 2D spectra of the molecule under investigation using an achiral oriented solvent made of a racemic mixture of PBLG and PBDG (the enantiomer of PBLG) dissolved in chloroform.[32] In such a racemic ordered solvent, noted hereafter PBG, the values of the quadrupolar splittings of enantiotopic deuterons measured in the PBG phase correspond to the algebraic average of those obtained in the PBLG phase.[33] Such information gives a simple way to access the relative signs of the quadrupolar splittings of the enantiotopic deuterons, but it requires the preparation of a second sample. Then the knowledge of only one absolute sign is needed to define the full set of absolute signs of the various $\Delta\nu_Q$ values. In the case of norbornene, the results obtained in the PBG phase (Table 1) are found to be in excellent agreement with the calculated averages from the experimental quadrupolar splittings measured in the PBLG system. In fact, this kind of experiment allows for corroborating the anisotropic spectral data extracted from the spectrum recorded in a chiral oriented phase, and it can also yield further valuable information for the analysis, as we will demonstrate in the second example investigated here. Note that, for norbornene, it might be possible to assign the *syn* and the *anti* deuterons using only an achiral oriented solvent, because in this case we have five experimental quadrupolar splittings for only three unknown order parameters. However, describing the two enantiotopic faces of this molecule would not then be possible, thus limiting the application field of this structural tool.

Analysis of Quadricyclane. Encouraged by the previous results, we have explored the case of quadricylane, **2** (Figure 1). This rigid polycyclic molecule is also noteworthy because the literature reports that this highly strained compound can be synthesized from the norbornadiene structure (which is naturally rather abundant) using a photochemically induced [2 + 2] cycloaddition and could be a means to store photochemical energy.[34]

From a stereochemical point of view, quadricyclane is a C_{2v} symmetry molecule containing enantiotopic directions, and hence, G_M associated to its orientational behavior in the PBLG phase is C_2. According to the molecular frame shown in Figure 1, three independent order parametes $S_{\alpha\beta}$ describe its orientation.[11,12] Consequently, at least four experimental anisotropic data must be extracted from liquid crystal spectra for iteration. In this compound, only four quadrupolar splittings are expected to be measured from the analysis of the natural abundance deuterium spectrum in a chiral liquid crystal, assuming that the spectral discrimination of enantiotopic deuterons is observed. Such a situation is a priori less advantageous than that for compound 1, because a cross-check of the final results will not be possible.

In the case of norbornene, we have shown that the quality of the molecular geometry model used does not interfere with the final results, mainly because the various types of classical molecular modeling yielded very similar geometries. In contrast, the geometry of quadricyclane depends drastically on the method used for the modelization. Problems arise from the nature of the carbon−carbon bonds forming the strained cyclopropane rings, because these bonds are shorter than usual aliphatic C−C distances and, hence, present some π character. Actually, the calculated $C_2-C_6 = C_3-C_5$, as well as the $C_2-C_3 = C_5-C_6$, bond lengths (see Figure 1) vary between the σ-bond and the π-bond. Thus, MM2 models give distances of 147.7 and 149.1 pm for the $C_2-C_6 = C_3-C_5$ and $C_2-C_3 = C_5-C_6$ bonds, respectively, while the semiempirical PM3 model (or ab initio models) clearly foresees a lower π-bond character and, hence, longer internuclear bonds (152.8 and 154.8 pm, respectively) are calculated. These calculations agree with earlier results reported in the literature.[35] To select between these various molecular modeling methods, it was therefore pertinent to explore whether the NMR in the chiral oriented phase was able to provide valuable arguments to choose among them.

Figure 5 presents the Q-COSY 2D spectrum of **2** recorded in the PBLG/$CHCl_3$ mesophase. Here again, the enantiotopic discrimination power of PBLG is large enough to give well separated signals for pairs of enantiotopic deuterons in this molecule. As above, the absolute signs of $\Delta\nu_Q$'s were deduced from the analysis of proton-coupled carbon-13 spectra in isotropic and chiral anisotropic phases (not shown).

The fitting procedure using the geometry given by MM2 was not satisfactory at all. Indeed, the relative differences between experimental and back-calculated data were larger than 30% and the quality of the iteration was too poor to be acceptable

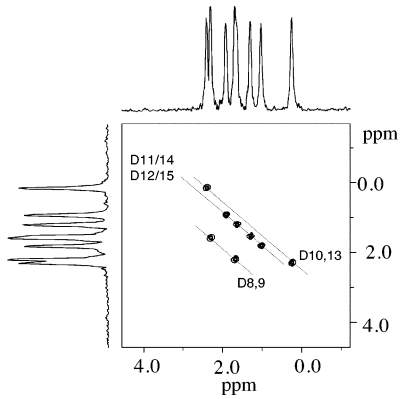

Figure 5. Q-COSY 2D spectrum (61.4 MHz) of quadricyclane in the PBLG/$CHCl_3$ phase. The NMR parameters are identical to those used for recording the Q-COSY 2D spectrum of norbornene in Figure 3. The contour plot is presented after Gaussian filtering in the t_1 and t_2 dimensions ($GB_1 = 50\%$, $LB_1 = -2.0$ Hz and $GB_2 = 45\%$, $LB_2 = -1.5$ Hz), respectively.

TABLE 3. Spectral Data of the Quadricyclane Dissolved in Organic Solutions of PBLG and PBG at 305 K

δ ^{2}H (PBLG)/ppm	2.03	1.49		1.35
no. of H-2	8, 9	11, 14	12, 15	10, 13
no. of C-13	7	2, 5	3, 6	1, 4
δ ^{13}C (PBLG)/ppm	31.6	14.4		22.6
$^1J_{CH}$ ($CHCl_3$)[a]/Hz	131.2	184.6		166.3
sign of $^1D_{C-H}$ (PBLG)	<0	>0		>0
$\Delta\nu_Q^{exp}$(PBLG)[a]/Hz	39.0	−21.5	−56.6	−132.8
$\Delta\nu_Q^{calc}$(PBLG)[b]/Hz	34.8	−19.0	−54.1	−135.3
error/%	10.7	8.6	4.4	1.9
$\Delta\nu_Q^{exp}$(PBG)/Hz	32.4	−34.5		−117.5
$\Delta\nu_Q^{corr}$(PBG)[c]/Hz	36.1	−38.4		−130.9
$\Delta\nu_Q^{exp\ av}$(PBLG)[d]/Hz		−39.1		

[a] The accuracy of the J_{ij} and $\Delta\nu_{Qi}$ values is around ±1 and ±2 Hz, respectively. [b] Calculated values using $K_{C-D}(sp^3) = 170$ kHz. [c] See footnote given in Table 2. The values of $\Delta\nu_Q(CDCl_3)$ in PBLG and PBG are equal to −961.0 and −862.6 Hz, respectively. [d] Algebraic average of the $\Delta\nu_Q$ values calculated from the data given in line 6.

(rms > 20 Hz). Possible reasons to explain the bad quality of the fit could be an incorrect sign assignment for the $\Delta\nu_Q$'s for the enantiotopic nuclei. This is possible because the magnitudes of $^{13}C-^1H$ dipolar couplings are very small, and the accuracy on the $^1D_{C-H}$ measurements is rather weak, mainly due to large ^{13}C line widths. In this example, the magnitude of $^1D_{C-H}$ associated with the pairs of enantiotopic nuclei is $+2 \pm 2$ Hz, and hence, an inversion of the sign of the $\Delta\nu_Q$'s could be considered. However, whatever the sign of $\Delta\nu_Q$ for the two enantiotopic nuclei, the results remained unsatisfactory. In contrast, results obtained with geometries calculated using either semiempiric or ab inito models (and keeping the sign given in Table 3) are much better because in this case the rms is less than 3 Hz and the differences between $\Delta\nu_Q$(exp) and $\Delta\nu_Q$(calc) do not exceed now 10%. Using an ab initio geometry calculation led to $\Delta\nu_Q$ values of −19.0 and −54.1 Hz for the two enantiotopic deuterons (see Table 3). Using now the same geometry but different signs for the quadrupolar splittings leads

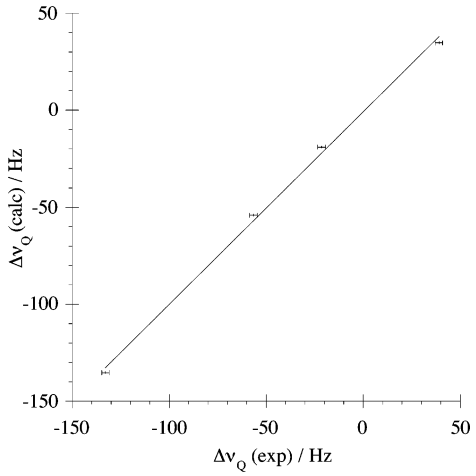

Figure 6. Correlations between the experimental residual quadrupolar splittings $\Delta\nu_Q$(exp) and the back-calculated values, for the quadricyclan. The solid line corresponds to the ideal line $\Delta\nu_Q$(exp) = $\Delta\nu_Q$(calc).

to a bad quality iteration (rms > 20 Hz and unacceptably large errors). These calculations demonstrate that only the solution with negative signs for the two quadrupolar splittings associated with enantiotopic deuterons is acceptable. Note that, in this example, the assignment−geometry fit reported in Table 3 is totally independent of the K_{C-D} values used. The $S_{\alpha\beta}$ values of **2** calculated with $K_{C-D} = 170$ kHz for all C−D bonds are given in Table 2.

To confirm our conclusions, we have compared the previous results with those obtained through NMR in the PBG solvent. As mentioned above, the values obtained in this achiral solvent are the average of the two splittings recorded in the chiral solvent. Consequently, if the signs are different, the absolute value of the splitting should be 17.6 Hz, compared to 39.1 Hz if the signs are the same. The experimental absolute value obtained after correction of data to take into account any solvent order variation[11,33] is 38.4 Hz, thus clearly confirming the previous results.

Again, Figure 6 shows correlations of experimental residual quadrupolar splittings $\Delta\nu_Q$(exp) and back-calculated values $\Delta\nu_Q$(calc) for quadricyclane. Also, in this second example, order parameters have proven to be useful in selecting among several molecular modeling techniques to derive a geometry compatible with anisotropic NMR measurements. Note that the scope of such studies is not to acquire a very high precision on the molecular geometry but to provide a tool able to decide between two quite different models which one better fits the structure of the molecule when no structural information is available.

Conclusion

Despite the development of a wide range of new 2D/3D NMR experiments based on heteronuclear long-range couplings or NOE effects, classical methods in isotropic solvents do not always solve all structural ambiguities, particularly on the assignment of enantiotopic nuclei. In this context, NMR in

TABLE 4. Compositions of Liquid Crystalline NMR Samples

sample	solute	polymer	DP[a] PBLG/PBDG	organic solvent	amount of solute[b]/mg	amount of polymer[b]/mg	amount of org solvent[b]/mg	% of polymer by wt
1	**1**	PBLG	562	$CHCl_3$	105	102	356	18.2
2	**1**	PBLG + PBDG	562/858	$CHCl_3$	104	50 + 50	356	17.9
3	**2**	PBLG	562	$CHCl_3$	101	101	359	18.0
4	**2**	PBLG + PBDG	562/914	$CHCl_3$	101	50 + 50	356	17.9

[a] DP: Degree of polymerization of the polypeptide. [b] The accuracy of the weights is ±0.5 mg.

weakly ordering chiral liquid crystalline solvents furnishes important new stereochemical information mainly because such spectra contain order sensitive NMR observables that can be used to investigate the structure and orientational order of solutes.

In this paper, we have re-examined the assignment and the structure of two bridged ring molecules possessing enantiotopic deuterons using natural abundance deuterium 2D NMR spectroscopy in chiral liquid crystals. The advantage of this method is to yield more spectral information compared to that from the achiral oriented systems and isotopic media as well. This is due to the ability of PBLG systems to discriminate between enantiotopic elements and directions. The method allows for a nonambiguous complete assignment of all nuclei in a molecule including diastereotopic as well as enantiotopic nuclei. Furthermore, the knowledge of order parameters associated with different directions in the molecule allows for studying their relative orientations, from which a shape compatible with the molecule structure may be derived. We believe this technique should develop in the future to become a routine for nonambiguous structural analysis of diamagnetic compounds. The next step of this work will be the investigation of natural products of which the structure is not known. Such a study is currently underway.

Finally it could be claimed that natural abundance deuterium NMR is a time-consuming spectroscopic approach. There is no doubt, however, that taking advantage of higher magnetic field NMR spectrometers and/or using a deuterium cryogenic probe should enhance the present potentialities and applications of this technique soon.

Materials and Methods

The PBLG (DP = 562, MW $\approx$ 120 000 g·mol^{-1}) and PBDG polymers (DP = 858, MW $\approx$ 190 000 g·mol^{-1}) were purchased from Sigma. The NMR samples of norbornene and quadricyclane were made from about 100 mg of polymer, 100 mg of solute, and 350 mg of dry $CHCl_3$, which were weighed directly into a 5 mm o.d. tube (see Table 4). All NMR samples were then centrifuged in both directions until an optically homogeneous birefringent phase was obtained. Numerous details on the sample preparation can be found in ref 18. NMR experiments were performed on a Bruker DRX 400 MHz high-resolution spectrometer equipped with a 5 mm broadband inverse probe. Note that the use of a broadband probe allows the ^{1}H, ^{13}C, and ^{2}H spectra to be recorded successively. The temperature was maintained at 305 K by the BVT 3000 system. Other experimental details are given in the legends of the figures. Detailed descriptions of natural abundance deuterium 2D NMR experiments can be found in previous papers.[18,20]

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