

# Analyses of the complex proton NMR spectra: Determination of anisotropic proton chemical shifts of oriented molecules by a two dimensional experiment

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## Abstract

NMR spectra of molecules oriented in the liquid crystalline media provide information on the molecular structure and order parameter. However, the numerical iterative analysis of the proton spectra of strongly coupled spins is difficult and time consuming. Such analysis is simplified if nearly accurate starting parameters are available. One such parameter is the chemical shift which in the oriented media is very different from the isotropic values due to anisotropic contributions. In this study, we have explored the possibility of obtaining chemical shifts in the oriented phase to aid the analysis of the spectra. A two dimensional experiment in which FSLG decoupling employed during the  $t_1$  period eliminates the homonuclear dipolar couplings and retains only the chemical shifts has been implemented. Experiments on the molecule *cis,cis*-mucononitrile demonstrate that the chemical shifts obtained by this procedure are nearly the same as the chemical shifts derived by iterative analysis of the one dimensional spectrum of the molecule following the standard procedure. The method has also been used to analyse the spectrum of 1-iodopropane using the chemical shifts obtained from the proposed experiment as the starting parameters.

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## 1. Introduction

Intramolecular partially averaged dipolar couplings,  $D_{IJ}$ , (also referred to as residual dipolar couplings), are the dominant parameters in the NMR spectra of the molecules aligned in liquid crystalline solvents. From the set of partially averaged dipolar couplings between the interacting spins, obtained by the analyses of such spectra, the molecular geometry and order parameter are determined [1–4]. For molecules oriented in thermotropic liquid crystals, the dipolar coupling varies from few Hz to few kHz and renders the spin systems strongly coupled. The spectra are quite complex with a spread of several kHz and the first order analyses of such spectra are therefore not possible.

One has to numerically diagonalize the Hamiltonian, adapting the least square fit techniques. The numerical analysis requires chemical shifts ( $\nu_I$ ), the indirect spin–spin couplings ( $J_{IJ}$ ) and the direct dipolar couplings ( $D_{IJ}$ ) as starting parameters. All these parameters are unknown for an oriented system. Initially, the chemical shifts and the indirect spin–spin couplings are usually taken as the values in the isotropic media. The dipolar couplings are calculated assuming the molecular geometry and certain guessed values for the orientational tensor components.

The generally practiced method is to simulate the spectrum. The trial spectrum simulated should closely resemble the experimental spectrum such that sufficient number of transitions can be assigned for subsequent iteration and refinement of parameters. Then certain specific experimental lines are assigned to theoretical ones and all the parameters are varied iteratively. The iteration procedure is

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continued until all the experimental lines are assigned to the simulated ones and the root-mean-square (rms) error between the calculated and experimental line positions reaches a global minimum. When the spectra are very complex and the starting parameters are far from real values, the iterative analysis can get captured in the local minimum, making further analysis very tedious. Basic ingenuity lies in the judicious choice of the initial starting parameters. However, there are several difficulties in choosing the initial parameters as described below.

There are anisotropic contributions to the chemical shifts which depend on the chemical shift tensor components scaled by the order parameters along the respective axes. In addition to the scant knowledge available about proton chemical shift tensors, the magnitude and sign of the order parameter are unknown and consequently it is very difficult to predict the chemical shifts in the oriented phase. These values can vary very much from the isotropic values. Therefore, choosing of the correct starting parameters of the chemical shifts is one of the bottlenecks in the analysis.

There is also anisotropic contribution to the indirect spin–spin couplings and due to similar functional dependence, they are reflected in the dipolar couplings. For the precise determination of dipolar couplings these contributions must be subtracted from the experimental values of dipolar couplings. As far as the proton–proton couplings are concerned, such contributions are shown to be negligible [5] and the isotropic values are used as the starting parameters and kept constant during the initial iterations.

The  $D_{IJ}$  on the other hand, are dependent on the geometry and the elements of the ordering matrix in the coordinate frame required to define the orientation of the molecule. A prior knowledge about the geometry and symmetry of the molecule is necessary in order to obtain the guessed dipolar couplings so that the iterative calculation is speeded up. Thus the analyses of the spectra becomes nontrivial when there are many unknown parameters. To circumvent the tedium of analyses, several experimental strategies [6–18] have been developed to derive additional information on any of the unknown parameters, viz. chemical shifts or the dipolar couplings. There are studies for the automated analyses [19–27] which do not require any line assignments. Due to several limitations, automatic analysis is not routinely employed and most of the published works in the literature utilize computer program requiring manual interaction proving it to be more robust.

In this paper, we propose the determination and use of the chemical shifts in the oriented phase to aid the analyses of the proton spectra. To obtain the anisotropic chemical shift, it is necessary to eliminate the homonuclear dipolar couplings among protons. For this purpose the use of multiple pulse techniques proposed earlier [28] is the obvious choice. Multi pulse techniques have been earlier exploited to achieve partial dipolar decoupling and to simplify the spectra by scaling the dipolar couplings [13,14]. The two dimensional versions of the experiment on oriented sam-

ples have been utilized to demonstrate the scaling achieved. The multi pulse experiments are, in general, technically demanding. On the other hand the use of off resonance Lee Goldberg (LG) decoupling [29] is a simple and convenient means of removing homonuclear dipolar couplings which is widely employed in recent times in solid state studies and is easy to implement. There are many LG sequences reported in the literature such as, flip flop Lee Goldberg (FFLG) [30], frequency switched Lee Goldberg (FSLG) [31,32], phase modulated Lee Goldberg (PMLG) [33], Lee Goldberg Cross polarization (LGCP) [34]. These LG sequences are designed to remove homonuclear dipolar couplings and find extensive applications in the separated local field (SLF) experiments involving liquid crystals and weak aligning media like bicelles [35–38]. In a review both PMLG and FSLG sequences is referred to as FFLG [39].

Using PMLG the homonuclear decoupling has been achieved using low power and the proton detected local field spectra (PDLF) [40–43] of fluorine-substituted benzene derivatives dissolved in thermotropic nematic liquid crystalline solvents have [44] obtained. In the two dimensional version of this experiment the application of PMLG removes  $^1\text{H}$ – $^1\text{H}$  dipolar couplings along  $t_1$  dimension and the  $^1\text{H}$  magnetization is allowed to evolve under chemical shifts,  $^{19}\text{F}$ – $^1\text{H}$  dipolar couplings and  $J$  couplings in the  $t_1$  dimension. The heteronuclear dipolar couplings directly read in the  $t_1$  dimension are used as the starting parameters for the analysis of the normal dipolar coupled spectra obtained in the  $t_2$  dimension.

In the present work, we have obtained proton chemical shifts of molecules in the oriented phase by adopting a two dimensional approach, wherein we employ, during the  $t_1$  period, frequency switched Lee Goldberg (FSLG) sequence to suppress the homonuclear dipolar couplings and retain only the anisotropic proton chemical shifts. To our knowledge, this is the first attempt at obtaining chemical shifts of inequivalent protons in the oriented phase and their use for the analyses of spectra. We show that in the case of the molecule *cis,cis*-mucononitrile, the chemical shifts thus obtained are very nearly the same as the chemical shifts obtained by the standard analysis of the 1D proton spectrum in which the isotropic chemical shifts are used as the starting parameters in the iterative procedure. We have also applied the method to obtain the chemical shifts and to analyse the spectrum of 1-iodopropane.

## 2. Experimental

Approximately five weight per cent solutions of commercially available *cis,cis*-mucononitrile and 1-iodopropane were prepared in the liquid crystals ZLI-1114 (*trans*-pentyl-(4-cyanophenyl)-cyclohexane) and ZLI-1132 (a mixture of three phenyl cyclohexanes and one biphenyl cyclohexane), respectively. The one dimensional proton spectra of these two solutions as well as the isotropic spectra of the compounds in  $\text{CDCl}_3$  solvent were recorded. The chemical structure, numbering of interacting spins and the

corresponding one dimensional spectrum in the liquid crystalline phase of these molecules are shown in Fig. 1. All the experiments were carried out on Bruker DRX-500 NMR spectrometer at ambient temperature using dedicated proton probe. The pulse sequence used for the two dimensional experiment shown in Fig. 2 achieves homonuclear decoupling during the  $t_1$  period by the use of the FSLG decoupling and retains only scaled chemical shifts. During the  $t_2$  period the normal proton spectrum that corresponds to the ones shown in Fig. 1 is recorded. The flip angle of the pulse at the beginning of the evolution period and the angle of the mixing pulse has been chosen so as to optimize the decoupling efficiency. In order to determine the scaling factor of the LG sequence, experiments were also carried out on an isotropic sample of benzene and the scaling factor was found to be 0.58; same as theoretical scaling factor. Other experimental and processing parameters are given in the respective figure captions. In these experiments the

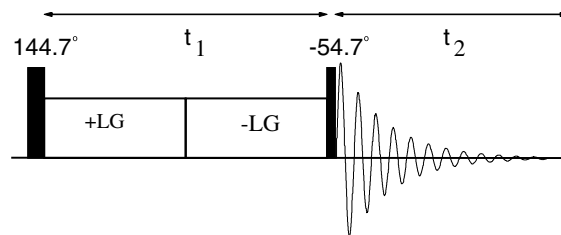


Fig. 2. The pulse sequence used for the 2D experiment.

peaks are tilted in the F1 dimension which was dependent on the LG offset. This we believe might be due to pulse imperfections or probe characteristics. However, the chemical shift differences measured along any F2 cross-section was the same. Because of the tilt, the F1 projections might appear broad or split. This can be circumvented by proper choice of processing parameters.

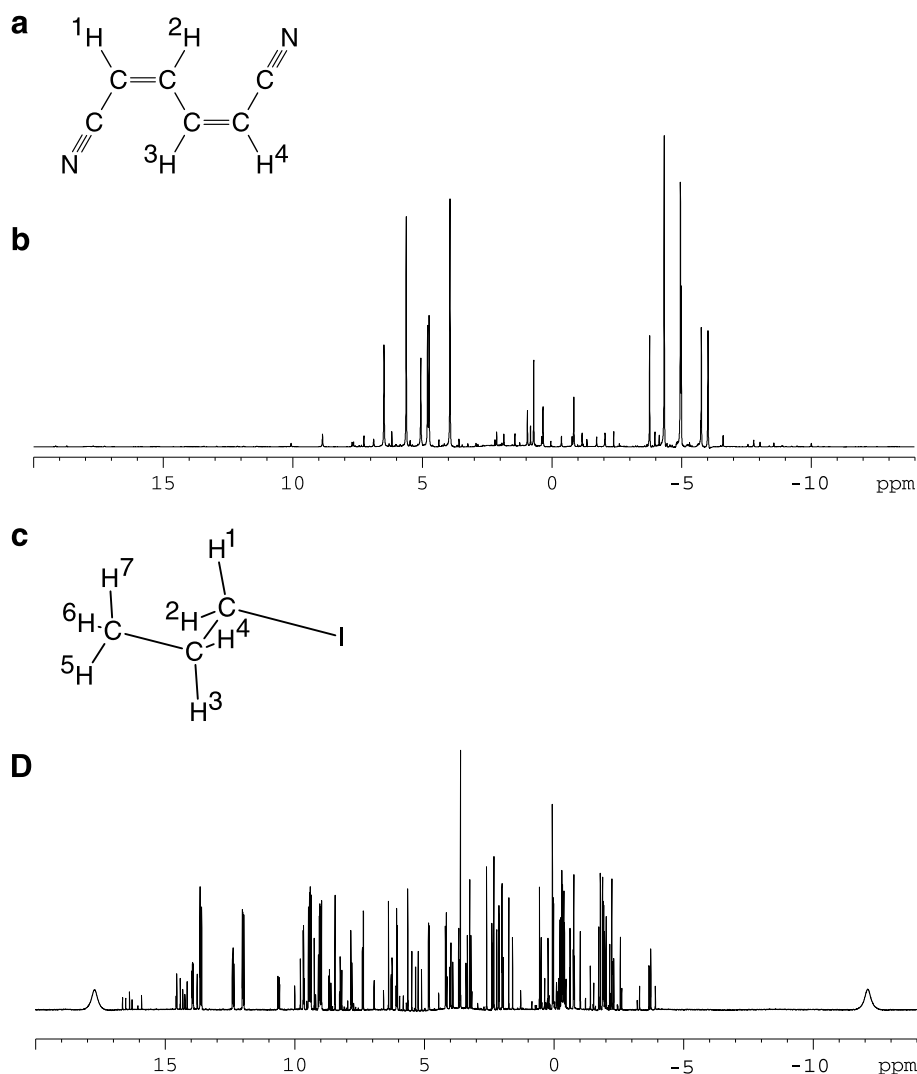


Fig. 1. (a) The chemical structure and numbering of the protons of *cis,cis*-muconitrile; (b) The one dimensional proton spectrum of the molecule oriented in the liquid crystal solvent ZLI-1114. The  $\pi/2$  pulse of 8.6  $\mu$ s corresponding to rf field strength of 29.06 kHz; (c) The structure and numbering of the protons in 1-iodopropane; (d) The one dimensional proton spectrum of the molecule oriented in the liquid crystal solvent ZLI-1132. The  $\pi/2$  pulse of 8  $\mu$ s corresponding to rf field strength of 31.25 kHz.

### 3. Results and discussion

The molecule *cis,cis*-mucononitrile, whose geometry and orientation in the liquid crystalline phase reported earlier [26,45], was chosen as a test sample to implement the 2D experiment. In the liquid crystalline phase, the protons of this molecule form a strongly coupled AA'BB' spin system. The molecule has  $C_{2h}$  symmetry and requires three elements of the ordering matrix to define its orientation. The 2D spectrum of this molecule is shown in Fig. 3a along with the F1 and F2 projections. The projection on the F1 axis provided two peaks corresponding to chemical shift positions of AA' (numbered 1 and 4 in Fig. 1a) and BB' (numbered 2 and 3 in Fig. 1a) protons. For comparison the isotropic spectrum and the projection on the F1 axis of Fig. 3a are plotted in Figs. 3b and c, respectively. It is observed from the figure that the chemical shift difference between two protons in the liquid crystalline phase is significantly different from that of the isotropic phase. The

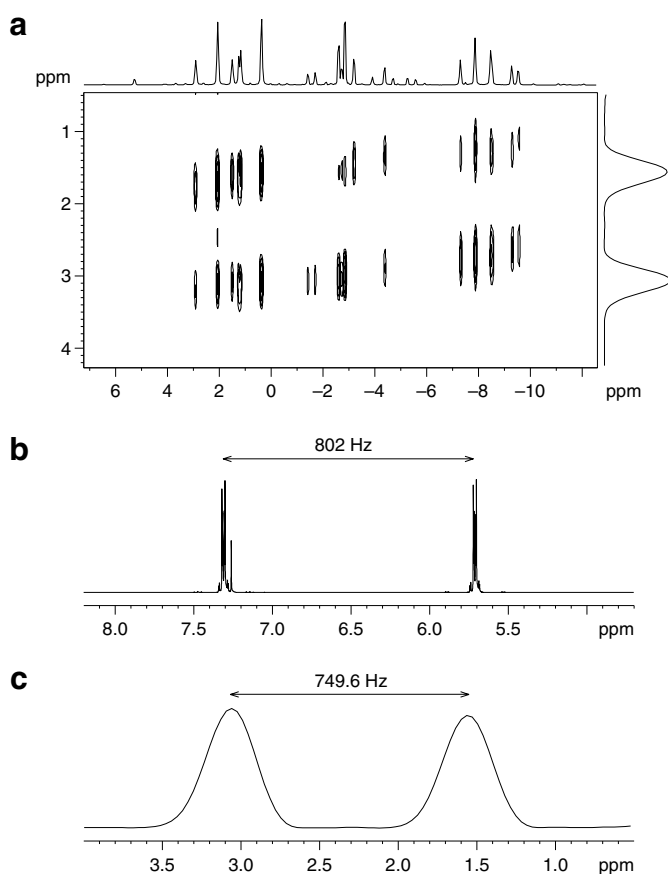


Fig. 3. (a) The 2D spectrum of *cis,cis*-mucononitrile oriented in the liquid crystal ZLI-1114 with corresponding F1 and F2 projections; Proton is detected in both direct and indirect dimensions; dataset consisted of 8K and 256 time domain points with 24 transients co-added per  $t_1$  increment. The LG offset was alternated at 25555.4 Hz and  $-17555.4$  Hz from the carrier offset of 4000 Hz for each  $t_1$  increment. The total length of the LG decoupling pulse increased twofold for each  $t_1$  increment. The digital resolution is 20.1 Hz and 17.4 Hz in the F2 and F1 dimensions, respectively. (b) The isotropic spectrum in the solvent  $CDCl_3$ ; (c) The F1 projection of the spectrum of (a) plotted separately for comparison.

chemical shift separation of the protons AA' and BB' in oriented phase corresponds to 1.50 ppm (749.6 Hz), which gives the unscaled chemical shift difference of 2.58 ppm. The digital resolution in the F1 dimension is 17.4 Hz. The error in the measurement of this was taken to be at least two digital points, which corresponds to 0.07 ppm. Thus the chemical shift difference obtained from the 2D experiment was taken as  $2.51 \pm 0.07$  ppm. For the analysis of the spectrum, as far as chemical shifts are concerned, this represents the totality of the information that is required. As discussed below, we have used this information for spectral analysis and notice that the final iterated values are in close agreement with the above experimental result within the difference of 0.01 ppm.

The projection on F2 axis corresponds to the usual dipolar coupled proton spectrum shown in Fig. 1b. The F2 cross-sections taken at different chemical shift positions of protons in the F1 dimension correspond to individual dipolar coupled spectra of AA' and BB' protons. However, in the AA'BB' system all the protons form a single coupled spin network in the liquid crystalline phase and the cross-sections are identical.

An analysis of the spectrum shown in Fig. 1b was carried out with the chemical shift difference obtained from the 2D experiment. Along with this, the indirect spin-spin couplings already reported [26] were used as the starting parameters. The analysis was carried out iteratively using the computer program LEQUOR [46]. However, the chemical shifts and  $J_{IJ}$  were kept fixed during initial iterations and only the dipolar couplings were varied. In the final step the chemical shifts were also iterated for better precision of the spectral parameters. All the experimentally observed lines were assigned to an rms error of 0.13 Hz, with no line deviating by more than 0.4 Hz. The final spectral parameters are shown in Table 1. As seen in the table, the final iterated chemical shift difference of 2.59 ppm is nearly the same as the value of  $2.58 \pm 0.07$  ppm obtained from the 2D experiment.

The spectral parameters were also obtained by the conventional method of analysis of the spectrum using isotropic chemical shift values as the initial starting parameters. It was observed that the spectral parameters including the

Table 1

Final spectral parameters derived for *cis,cis*-mucononitrile oriented in the nematic liquid crystal ZLI-1114

Parameter	Value in Hz
$D_{12}$	$1459.53 \pm 0.08$
$D_{13}$	$241.74 \pm 0.04$
$D_{14}$	$55.80 \pm 0.10$
$D_{23}$	$-509.50 \pm 0.07$
$\nu_1 - \nu_2^a$	$1293.5 \pm 0.24$ (2.59 ppm)
rms error	0.14

The chemical shifts obtained from the 2D experiment was used as the starting parameters for the iterative analysis.

<sup>a</sup> The chemical shift difference obtained from the experiment is  $2.58 \pm 0.07$  ppm.

chemical shift difference obtained by both this method of analysis was identical within the error bar to the values shown in Table 1. It may be mentioned that the isotropic chemical shift difference between two types of protons in *cis,cis*-mucononitrile is 1.6 ppm (800.2 Hz) compared to 2.56 ppm in the oriented phase (1293.5 Hz). This difference is very significant. The simulated spectra with isotropic chemical shifts, which are far from real values, would not resemble the experimental one and the assignment would be very difficult. The values obtained from the 2D experiment are more realistic and it is easy to assign the simulated spectra to experimental frequencies. Although it is not possible to obtain such a precise value due to experimental limitations, considering the significant difference in the chemical shifts between isotropic and nematic phases, it will suffice if this information is obtained within about 50 Hz to use as the starting parameters for iterative analysis.

We have also applied the experimental method developed here for the analysis of the proton spectrum of another sample with more number of interacting spins and with different spin symmetry. For this purpose a nonplanar molecule with seven interacting spins, 1-iodopropane whose chemical structure and proton numbering is shown in Fig. 1c, was chosen.

The isotropic chemical shifts and  $J_{IJ}$  for this molecule was obtained by the iterative analysis of the spectrum in the solvent  $\text{CDCl}_3$ . The isotropic chemical shifts with reference to TMS are;  $\nu_1$  ( $\nu_2$ ) = 3.17 ppm,  $\nu_3$  ( $\nu_4$ ) = 1.83 ppm and  $\nu_5$  ( $\nu_6, \nu_7$ ) = 0.98 ppm. The proton spectrum of this molecule in the liquid crystal solvent ZLI-1132 shown Fig. 1d corresponds to a strongly coupled spin system of the type  $A_3BB'CC'$ . In order to analyse by utilizing the knowledge of proton chemical shifts in the oriented phase, the 2D spectrum of this molecule was recorded and is shown in Fig. 4a along with projections on F1 and F2 axes. The isotropic spectrum of the molecule and the projection on F1 axis of the 2D spectrum (Fig. 4a) are compared in Figs. 4b and c, respectively. The F1 cross-section of the 2D spectrum provided three different peaks, corresponding to three independent chemical shift positions of protons in the oriented phase. However, due to anisotropic contribution there may not be one to one correspondence between the chemical shifts of individual protons of the liquid crystalline phase and the isotropic phase. As a first approximation, we assumed that the assignments of the three peaks to be in the same order as in the isotropic phase. The scaled chemical shifts difference obtained for  $\nu_3-\nu_1$  and  $\nu_3-\nu_5$  from the LG experiment are  $-0.58$  ppm (293 Hz) and  $0.85$  ppm (424 Hz), respectively. These correspond to unscaled values of  $-1.01$  ppm and  $1.46$  ppm, respectively. As in the earlier case, the error in the measurement of these shift positions were taken to be at least two digital points. These chemical shift values and  $J_{IJ}$  derived by the analysis of isotropic spectrum and the dipolar couplings estimated with assumed geometry and order parameter

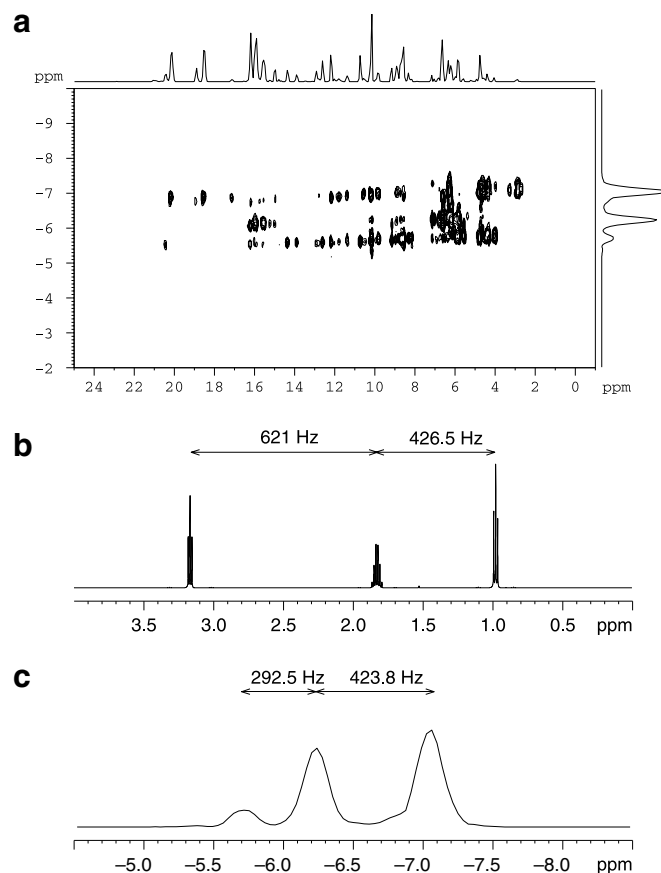


Fig. 4. (a) The 2D spectrum of 1-iodopropane oriented in the liquid crystal ZLI-1132 with projections on F1 and F2 axis, Proton is detected in both direct and indirect dimensions; dataset consisted of 16K and 256 data points in F2 and F1 dimensions, respectively, with 16 transients co-added for each  $t_1$  increment. The LG offset was alternatively shifted to 18565.84 Hz and  $-27628.3$  Hz from the carrier offset of  $-4531.25$  Hz for each  $t_1$  increment. The total length of the LG decoupling pulse increased two times for each  $t_1$  increment. The digital resolution was 29.3 Hz and 18.7 Hz in the F2 and F1 dimensions, respectively. (b) The isotropic spectrum of 1-iodopropane in the solvent  $\text{CDCl}_3$ ; (c) The F1 projection of the spectrum given in (a) plotted for comparison.

were used as the starting parameters. Iterative analysis was carried out by varying only dipolar couplings during initial iteration. In the final step, the chemical shifts were also iterated for the precise determination of the spectral parameters. The rms error reached a global minimum of 0.25 Hz with no line deviating by more than 0.4 Hz when all the experimentally observed transitions were assigned. The derived parameters are given in Table 2. It may be mentioned that since the spectrum is very complex, even with the availability of the anisotropic chemical shifts as starting parameters several spectra had to be simulated with different sets of dipolar couplings until the visual resemblance is seen with the experimental one. However, it should be pointed out that the information on the chemical shifts in the oriented phase is very crucial and aids the analysis. Thus the method proposed promises to be an important step towards simplification of analyses of the spectra of oriented molecules.



Table 2

Final spectral parameters derived for 1-iodopropane oriented in the nematic liquid crystal ZLI-1132

Parameter	Value in Hz
$D_{12}$	$-2294.68 \pm 0.02$
$D_{13} = D_{24}$	$52.56 \pm 0.06$
$D_{14} = D_{23}$	$-59.83 \pm 0.05$
$D_{15} = D_{25}$	$395.3 \pm 0.0$
$D_{34}$	$-1559.3 \pm 0.02$
$D_{35} = D_{45}$	$101.74 \pm 0.01$
$D_{55}$	$-706.32 \pm 0.0$
rms error	0.25
$\nu_3 - \nu_1^a$	$-461.68 \pm 0.03$ ( $-0.92$ ppm)
$\nu_3 - \nu_5^a$	$669.4 \pm 0.03$ (1.34 ppm)

The chemical shifts obtained from the 2D experiment was used as the starting parameters for iterative analysis.

<sup>a</sup> The parameters obtained by the experiment are:  $\nu_3 - \nu_1 = -1.01 \pm 0.08$  ppm and  $\nu_3 - \nu_5 = 1.46 \pm 0.08$  ppm.

#### 4. Conclusions

Dominated by the dipolar couplings, the spin system of the molecules aligned in liquid crystals are generally strongly coupled resulting in very complex proton spectra. The iterative analysis requires realistic starting values of all the parameters that influence the spectra. The individual proton chemical shift is one such parameter. In the oriented phase, the chemical shifts are unknown and may be different from that in the isotropic phase. It is demonstrated in the present study that using 2D experiment it is possible to determine the values of chemical shifts of protons in the oriented phase which may be kept constant during initial iterations. This not only renders the analysis easier but also results in considerable saving of the computation time as the number of parameters required to be iterated gets reduced. The methodology has been demonstrated on oriented four spin system *cis,cis*-mucononitrile and on oriented 1-iodopropane which is a seven spin system.

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