Weakly Oriented Liquid-Crystal NMR Solvents as a General Tool to Determine Relative Configurations

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Abstract: A new NMR method to determine the relative configuration of asymmetric centres is presented. It proceeds through the use of a weakly ordered solvent and the measurement of orientational order parameters. The method is illustrated by using dihydropyridone derivatives for which the orientations and the relative configurations of the asymmetric carbon atoms are determined unambiguously.

Keywords: configuration determination · diastereomers · dipolar couplings · liquid crystals · NMR spectroscopy

Introduction

The determination of relative configurations of asymmetric centres is an important challenge in chemistry. It is sometimes possible to make such an assignment either from the distance information obtainable through NOE measurements, chemical shifts or scalar couplings. However, often these NMR interactions do not allow unambiguous conclusions to be drawn, either because the NOE between the concerned nuclei is zero or because the couplings are identical.

It was shown recently that it is possible to determine diastereomeric and enantiomeric excesses through deuterium NMR spectroscopy by using a chiral liquid-crystal solvent composed of poly-γ-benzyl-L-glutamate (PBLG) dissolved in an organic solvent.[1, 2] Furthermore, such weakly oriented liquid-crystal NMR solvents have proven their efficiency in solving many stereochemical problems.[3–5] Thus, by using this method it was possible to determine the relative configurations in *threo–meso* mixtures provided that one studies a nonstatistical mixture of the isomers, that is, a sample with both enantiomeric and diasteromeric excesses.[2] The method is very simple, but remains limited to deuterated molecules and symmetrically substituted compounds. Furthermore, the synthesis of a nonstatistical mixture of all the isomers may not be trivial.

Herein we present a completely general method to assign relative configurations through the analysis of orientational order parameters. To obtain these order parameters the NMR spectra of the diastereoisomers dissolved in an achiral, weakly oriented, liquid-crystal solvent are first analysed to extract the dipolar couplings. It is well known that there is a simple mathematical relationship between the anisotropic dipolar couplings, molecular geometry and order parameters. The major point is that this is a one-to-one relationship (univocal) and we will show that the knowledge of the molecular order parameters allows the assignment of relative configurations without ambiguity.

Results and Discussion

To illustrate the method through an example, we use two samples that contain separate diastereomers (A and B) of the dihydropyridones shown in Figure 1. Diastereomers A and B were synthesised as an approximately 1:1 mixture and could be separated by column chromatography. The synthesis is described in reference [6]. In these compounds, NOE measurements do not give information on the spatial proximity of the protons H3 and H6. These equilibrium structures have been minimised by using the semiempirical force field, AM1, through the HYPERCHEM molecular modelling package. At this point it is important to note that, as far as the ordering is concerned, the compounds may be separated in three parts: the phenyl ring, the benzylic group and the dihydropyridone moiety; the last part contains the two chiral centres of interest in this study. The dihydropyridinone ring involves atoms labeled H3, H4, H5, H6, N1, C2, C3, C4, C5, C6, which can be assumed to be rigid and will be referred to as the (1–6) ring in the following. The molecular modelling shows that for the

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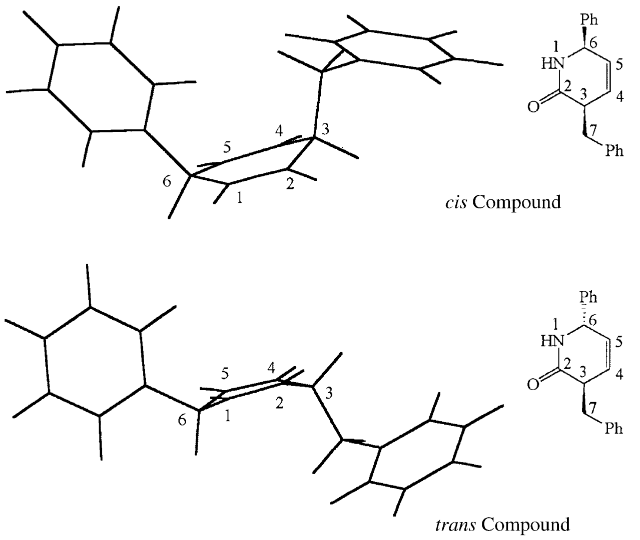

Figure 1. Structure obtained by molecular modelling and nuclei numbering of the *cis* and *trans* compounds.

trans compound, the C6–H6 and the C3–H3 bonds or directions are nearly parallel to each other and that this is not the case for the *cis* compound (Figure 1). This fact is important in oriented solvents as it is known that a simple relationship exists between the geometrical structure and the orientational order parameter (S_{ij}) of a direction (ij) for a rigid part of a molecule. This is given by Equation (1):

$$S_{ij} = \sum_{\alpha=a,b,c} \sum_{\beta=a,b,c} \cos(\theta_{ij}^{\alpha})\cos(\theta_{ij}^{\beta})\, S_{\alpha\beta} \qquad (1)$$

in which α and β are the axes of an arbitrary (a,b,c) reference frame attached to the molecule. The θ_{ij}^{α} are the angles between the ij direction and the α axis of the molecular frame ($\alpha \in a$, b or c), and the $S_{\alpha\beta}$ are the elements of the second-rank-order tensor of the rigid part of the molecule expressed in the reference frame. Consequently, due to the fact that two parallel directions will give the same θ_{ij} angles, we should find the same order parameter, S_{ij}, associated with the C6–H6 and C3–H3 directions in the *trans* isomer, but not for the *cis* compounds in an oriented solvent.

To obtain the order parameters of internuclear directions, the dipolar couplings must be measured from the spectra obtained by using an anisotropic solvent. At first order the ^{13}C–H total splitting (T_{ij}) observed on the proton coupled ^{13}C NMR spectrum is given by Equation (2):

$$T_{ij} = J_{ij} + 2D_{ij} \qquad (2)$$

in which here J_{ij} is the scalar coupling between nuclei i and j, and D_{ij} is the dipolar coupling, which is related with the order parameter S_{ij} by Equation (3):

$$D_{ij} = -\frac{\mu_0 \gamma_i \gamma_j \hbar}{8\pi^2} r_{ij}^{-3} S_{ij} \qquad (3)$$

Here r_{ij} is the distance between the i and j nuclei, γ_i and γ_j are the magnetogyric ratios of the nuclei i and j, and S_{ij} is the order parameter of the ij direction. From these definitions it must be seen that for the dihydropyridones studied here, the dipolar couplings between C6–H6 and C3–H3 nuclei should be nearly the same for the solute with the *trans* configuration, but not for the solute with the *cis* configuration.

In this study the achiral weakly oriented liquid crystal solvent used was made of a racemic mixture of poly-γ-benzyl-L-glutamate (PBLG) and its enantiomer (PBDG), dissolved in chloroform.[2] The mixture will be named hereafter PBG. It is important to note that it is not necessary to use a chiral liquid crystal to solve our problem as we are studying two diastereomers in racemic mixtures. The use of a chiral liquid crystal would result in an enantiomeric discrimination. Consequently, we would observe a doubling of the different spectra and this would complicate the analysis without bringing any new information about the relative configuration at C3 and C6.

The assignments of the chemical shifts and the scalar couplings were made from the analysis of the proton, ^{13}C, HSQC and HMBC NMR spectra in CDCl$_3$. These spectra are not presented here, but results concerning the dihydropyridone part are shown in Table 1.

Table 1. Scalar and dipolar couplings.

	C6–H6	C3–H3	C4–H4	C5–H5	H6–H5	H5–H4
sample A						
scalar coupling [Hz]	+141	+129	+161	+165	0	+10
dipolar coupling[a] [Hz]	+89	+85	+80	−22	−28	−5
sample B						
scalar coupling [Hz]	+141	+130	+162	+162	+2	+10
dipolar coupling[a] [Hz]	+97	−65	+34	−81	25	4

[a] Error on the dipolar coupling is ±4 Hz.

By using the PBG, we were able to determine the C3–H3 and C6–H6 dipolar couplings from the ^{13}C spectra of the two samples containing each diastereomer. The spectra for these two carbon atoms are shown in Figure 2 for sample A. It is clear that, for this sample, the total splitting $|T_{ij}|$ is larger than $|J_{ij}|$ the splitting in the isotropic medium. Due to the weak orientation in the PBG phase, the dipolar coupling is smaller than the scalar coupling. Consequently, the C3–H3 and C6–H6 dipolar couplings have the same sign as the scalar

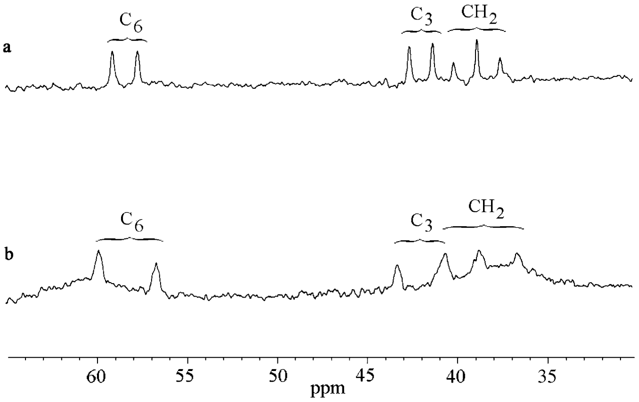

Figure 2. Selected part of the proton-coupled ^{13}C NMR spectra for sample A a) in isotropic solvent, b) in liquid-crystalline solvent.

couplings, which are positive. In contrast, from the spectra of the C3 and C6 carbon atoms shown in Figure 3 for sample B, we can conclude immediately that the C3–H3 and C6–H6 dipolar couplings have opposite signs. The results are summarised in Table 1. We can also see that the C3–H3 and C6–H6 dipolar couplings are similar in size for sample A and very different for sample B. It is now trivial to assign the compounds to the correct relative configuration: the compound of *trans* relative configuration is in sample A, while the *cis* compound is in sample B.

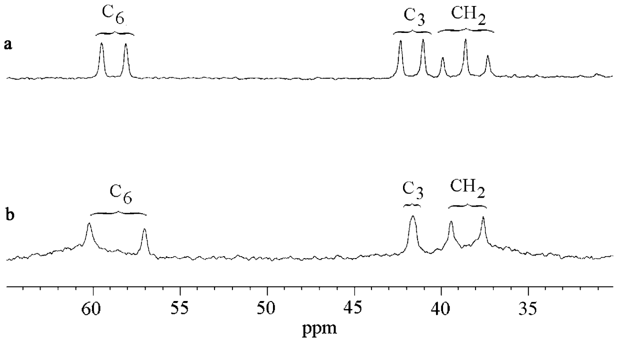

Figure 3. Selected part of the proton coupled ^{13}C NMR spectra for sample B a) in isotropic solvent, b) in liquid-crystalline solvent.

To confirm this preliminary result and generalise the methodology, we have determined the elements of the order tensors of the rigid part, the (1–6) ring, for compounds A and B. In fact, this situation, in which two C–H directions are parallel in one of the diastereoisomers is not general. Therefore, we have to calculate all the elements of the Saupe order matrix $\{S_{\alpha\beta}\}$, which describes the orientation of the rigid part of the molecule that contains the asymmetric centres. To do this and to remove the complications coming from the rotational parts, we have limited the calculation to the rigid part composed of the (1–6) ring. This heterocycle has no symmetry and at least five experimental dipolar couplings are required to characterise $S_{\alpha\beta}$. Here we can easily determine four one-bond $^{13}C-^{1}H$ dipolar couplings from the proton-coupled ^{13}C spectra and/or the spectra obtained with a standard HSQC experiment. The two other dipolar couplings used are the H6–H5 and H5–H4 couplings. These values have been obtained from two-dimensional SERF experiments.[7] We have recently demonstrated the potential of this experiment for chiral liquid-crystal samples by simplifying the proton spectra and easing the enantiomeric discrimination using proton NMR spectroscopy.[8] This sequence is a *J*-resolved experiment that uses only selective pulses. From this, on the two-dimensional map we visualise only one coupling, the coupling between the selectively excited nuclei. The power of this experiment is that 1) we simplify greatly the proton spectra and 2) the sequence is very sensitive and the experimental time is short (less than one hour). Note that the signs of the $^{1}H-^{1}H$ total splittings cannot be determined from the SERF experiments, and two possible values of each $^{1}H-^{1}H$ dipolar couplings resulted. Such ambiguities did not prove to be a problem during order matrix calculations, as in all the cases only a single combination of the possible signed values yielded a satisfying solution in the fitting procedure.

From the experimental dipolar couplings and the geometry obtained by molecular simulation, the orientation of the solutes have been determined with the SHAPE fitting program.[9] In Figure 4, the calculated dipolar couplings are compared to the experimental values for each sample with the *cis* or *trans* geometry. The results obtained show that the NMR data for sample A do not fit with the *cis* geometry, but agree very well with the *trans* geometry, whilst the reverse is true for sample B. It is clear then that the unique solution is that sample A contains the *trans* diastereomer and sample B contains the *cis* diastereomer. These results are in agreement with what was found previously in this work by comparing only the C3–H3 and C6–H6 dipolar couplings, but this latter method is much more general.

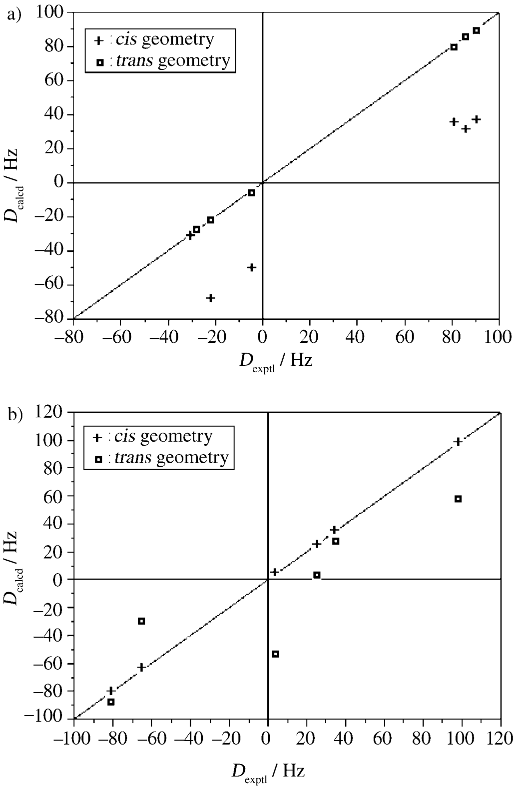

Figure 4. Comparison between the experimental dipolar couplings, D_{exp}, and the calculated dipolar couplings for the two geometrical structures considered, D_{calcd}, a) for sample A and b) for sample B. Note the ideal results are for the line $D_{\mathrm{calcd}} = D_{\mathrm{exptl}}$. Error on the experimental dipolar coupling is ±4 Hz.

Conclusion

We have demonstrated that the use of weakly oriented solvent is a powerful method to determine the relative configurations of different asymmetric centres. For two diastereomers of dihydropyridone, we have been able to attribute the relative configurations without ambiguity by using standard ^{1}H and ^{13}C NMR experiments. In this case, the different dipolar couplings were measured by using SERF and two-dimensional HSQC experiments. From the dipolar couplings we have computed easily the orientational order matrices of the solutes in the mesophase and then attributed the diastereomers due to the relationship between geometry and order matrix elements. In other words, an experimental set of dipolar couplings was shown to be compatible with a single geometry. It is also demonstrated that this method can be an interesting alternative to classical methods such as NOE experiments when they are ambiguous or when they do not work. This method is now being developed to be used routinely.

Experimental Section

Sample preparation: The two liquid-crystalline NMR samples investigated in this work were prepared by using standard procedures described elsewhere.[10] The samples were made up of PBLG ($M_W \sim 120000$, 50 mg), PBDG ($M_W \sim 120000$, 50 mg), the solute (10 mg) and dry $CDCl_3$ (605 mg). Note all NMR tubes (5 mm o.d.) were centrifuged back and forth until an optically homogeneous birefringent phase was obtained.

NMR spectroscopy: Proton and ^{13}C one- and two-dimensional NMR spectra in oriented solvents were performed on a high-resolution Bruker DRX 400 spectrometer equipped with a standard variable-temperature unit (BVT 3000) by using a Broadband inverse probe and a Z-gradient unit. The temperature was kept constant at 300 K for all samples.

[1] a) I. Canet, J. Courtieu, A. Loewenstein, A. Meddour, J. M. Péchiné, *J. Am. Chem. Soc.* **1995**, *117*, 6520–6525; b) M. Sarfati, P. Lesot, D. Merlet, J. Courtieu, *Chem. Commun.* **2000**, 2069–2081; c) C. Aroulanda, M. Sarfati, J. Courtieu, P. Lesot, *Enantiomer* **2001**, *6*, 281–287.

[2] C. Canlet, D. Merlet, P. Lesot, A. Meddour, A. Loewenstein, J. Courtieu, *Tetrahedron: Asymmetry* **2001**, *11*, 1911–1918.

[3] a) P. Lesot, D. Merlet, T. P. Rantala, J. Jokisaari, J. W. Emsley, J. Courtieu, *J. Phys. Chem. A.* **1997**, *101*, 5719–5724; b) E.E Burnell and C. A. De Lange, *Chem. Rev.* **1998**, *98*, 2359–2387.

[4] a) D. Merlet, J. W. Emsley, J. Jokisaari, J. Kaski, *Phys. Chem. Chem. Phys.* **2001**, *3*, 4918–4925; b) C. Algieri, F. Castiglione, G. Celebre, G. De Luca, M. Longeri, J. W. Emsley, *Phys. Chem. Chem. Phys.* **2000**, *2*, 3405–3413.

[5] a) M. Zweckstetter and A. Bax, *J. Am. Chem. Soc.* **2000**, *122*, 3791–3792; b) M. Cai, H. Wang, E. T. Olejniczak, R. P. Meadows, A. H. Gunasekera, N. Xu, S. W. Fesik, *J. Magn. Reson.* **1999**, *139*,451–453; b) M. Cai, H. Wang, E. T. Olejniczak, R. P. Meadows, A. H. Gunasekera, N. Xu, S. W. Fesik, *J. Magn. Reson.* **1999**, *139*, 451–453; c) N. Tjandra, A. Bax, *Science*, **1997**, *278*, 1111; d) E. de Alba, N. Tjandra, *Prog. Nucl. Magn. Reson. Spectrosc.* **2002**, *40*, 175–197.

[6] V. Boucard, H. Sauriat-Dorizon, F. Guibe, *Tetrahedron* **2002**, *58*, 7275–7290.

[7] T. Fäcke, S. Berger, *J. Magn. Reson.* **1995**, *113*, 114–116.

[8] J. Farjon, D. Merlet, P. Lesot, J. Courtieu, *J. Magn. Reson.* **2002**, *158*, 169–172.

[9] P. Diehl, P. M. Henrichs, W. Niederberger, *Mol. Phys.* **1971**, *1*, 139.

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