Study of molecular rotational isomerism using deuterium NMR in chiral oriented solvents

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Deuterium NMR in polypeptide chiral liquid crystals is used for the first time to investigate the internal rotational isomerism phenomenon, illustrated by the interconversion between conformers of 1-(2′,6′-dideutero-4′-methylphenyl)naphthalene.

Analysis of a conformational dynamic process using proton-decoupled deuterium (^{2}H-{^{1}H}) NMR in nematic liquid crystals is of great interest for three reasons: a) simple high-resolution spectra dominated by residual quadrupolar interaction ($I = 1$) are obtained; b) the coalescence phenomenon can be clearly identified; c) spectral separations between exchanging ^{2}H anisotropic signals can be much larger than those observed in isotropic ^{2}H or ^{13}C NMR, thus allowing a much wider dynamic process range to be studied.[1,2] Until now such investigations were restricted to solutes in achiral nematic phases, but this method cannot be efficiently used for studying interconversion between enantiomers or enantiotopic directions, because their spectral discrimination is not possible.

In this preliminary work, we explore the potential of ^{2}H-{^{1}H} NMR in polypeptide chiral oriented solvents to study the rotational isomerism phenomenon[3] between conformers of 1-(2′,6′-dideutero-4′-methylphenyl)naphthalene (**1**). The liquid crystal used is made of poly-γ-benzyl-L-glutamate (PBLG) dissolved in CHCl$_3$ or CH$_2$Cl$_2$.[4] In these weakly ordering, chiral solvents, deuterated enantiomers or enantiotopic C–D directions in some prochiral molecules are *a priori* not oriented the same way.[4,5] As a consequence, they can be discriminated by ^{2}H NMR spectroscopy through a difference of splittings of the corresponding quadrupolar doublets ($|\Delta v_Q^A - \Delta v_Q^B|$) with $\Delta v_Q^{A \text{ or } B} = 3/2(e^2qQ/h)S_{C-D}^{A \text{ or } B}$.[4] ($e^2qQ/h$) is the ^{2}H quadrupole coupling constant, $S_{C-D}^{A \text{ or } B}$ is the order parameter along the C–D internuclear bond relative to the magnetic field axis and the superscripts A/B correspond to either stereodescriptors R/S or *pro-R*/*pro-S*.[4,5]

Compound **1** was prepared in the framework of the asymmetric synthesis of new chiral atropoisomers, but this work will be presented in a forthcoming publication. The structure of **1** is displayed in an insert in Fig. 4. In this biaryl derivative, the internal rotation of the two aromatic rings about the sp^2–sp^2 single bond numbered 1–1′ can be hindered, and hence induces particular stereochemical relationships between the two C–D directions.

Theoretically, three situations leading to different ^{2}H-{^{1}H} anisotropic spectra can be assumed: a) if the rotation around the

aryl–aryl bond is free, the C–D directions are homotopic,[3] and no discrimination is possible (one doublet expected); b) if the rotation is sufficiently hindered, the molecule should adopt an average conformation of C_s symmetry (see Fig. 4), where the C–D directions are enantiotopic,[3,5] and *a priori* distinguishable if enantiotopic discrimination mechanisms are efficient (two doublets expected); c) if rotation is impossible and if the inter-ring torsion angle ϕ (2′–1′–1–2) is not 90°, the molecule adopts a C_1 symmetry, and then exists in enantiomeric forms in which the C–D directions are now diastereotopic, and so inequivalent (four doublets expected).[3] In practice, the stereochemical relationship existing between the C–D directions and the consequences on ^{2}H NMR spectra will depend on the exchange rate constant, k, which is related to the magnitude of the barrier to rotation, $\Delta H^\ddagger$, and the sample temperature T.

Fig. 1 reports the evolution of ^{2}H-{^{1}H} anisotropic spectra of **1** dissolved in the PBLG/CHCl$_3$ phase *vs.* temperature over the range 213–355 K, while associated spectral data are plotted in Fig. 2.†‡ Although limited by the physical properties of the co-solvent, the temperature domain for this system makes it possible to explore a wide range of dynamic processes. At room temperature (302 K) and above, only a sharp quadrupolar doublet (linewidth < 5 Hz) is observed, thus indicating the free rotation of aromatic rings about the aryl–aryl bond. Due to the increase of T$_2$ relaxation time of solute related to a reduced molecular mobility in the phase, the average linewidths increase slowly and monotonically from 355 to 270 K (Fig. 2). Below 270 K, a significant line broadening occurs until the coalescence phenomenon that is reached at T_c = 245 ± 2 K. Then linewidths decrease until 219 K. Below T_c, two quadrupolar doublets with rather sharp components are observed, thus indicating that the C–D directions are
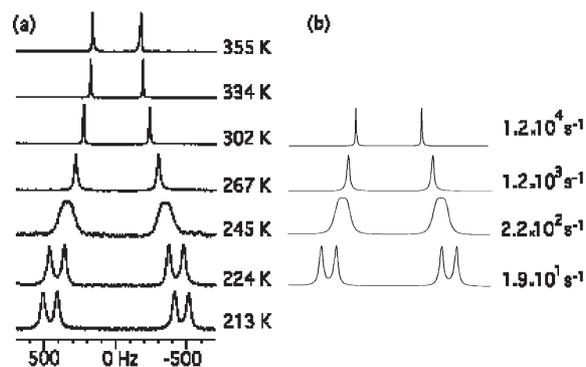

Fig. 1 (a) Temperature dependence of the 61.4 MHz ^{2}H-{^{1}H} signal of **1** dissolved in the PBLG/CHCl$_3$ phase. (b) Spectral simulations obtained with the rate constants, k, indicated on the right side.

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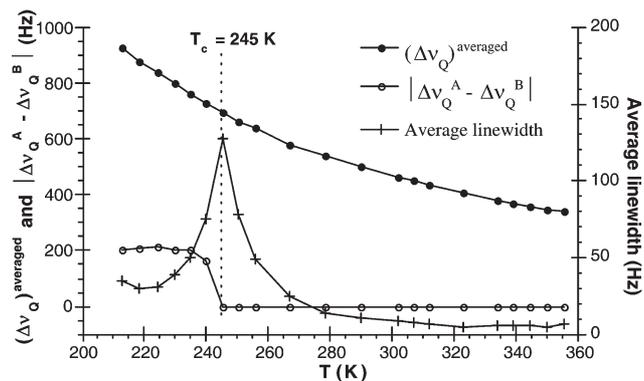
Fig. 2 Plot of the average of linewidths, the average of $\Delta\nu_Q$'s (A and B), and their difference *vs. T*. Below T_c, this difference is rather constant and equal to 205 ± 10 Hz.
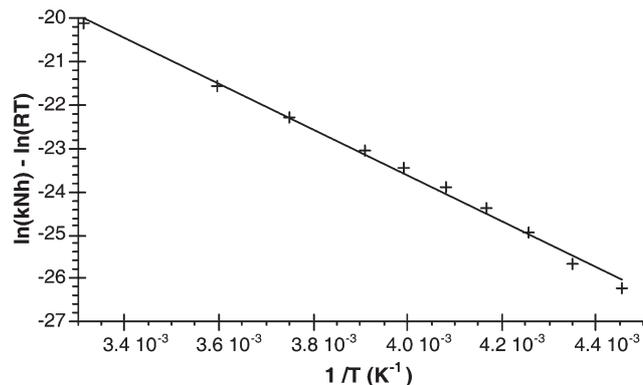

Fig. 3 Eyring plot of the exchange rate in **1**. Kinetic parameters are deduced from the plot fit ($R = 0.998$). Note that the slope and the *y*-intercept of the plot are equal to the ratio $(-\Delta H^{\ddagger}/R)$ and $(\Delta S^{\ddagger}/R)$, respectively.

now enantiotopic. This result experimentally assesses that the molecular structure resulting from averaging on all rotamers has a C_s symmetry.

To check this finding, we have recorded the ^{2}H-{^{1}H} spectra of **1** in the PBG/CHCl$_3$ phase made of an equimassic mixture of PBLG and PBDG (enantiomer of PBLG).[7][‡] In this racemic medium, any enantiodiscriminations vanish. As expected, a single doublet was experimentally observed whatever the temperature. This second argument demonstrates unambiguously that the presence of two quadrupolar doublets when T is below 245 K is the consequence of the non-equivalence of the C–D directions in the PBLG solvent, and does not originate from a particular reorientation phenomenon of solute in the phase. This conclusion is also sustained by the unusual evolution of average linewidths that does not follow a monotonic increase when T decreases,[8] while the evolution of the average of quadrupolar splittings, $(\Delta\nu_Q)^{averaged}$, *vs. T* does (see Fig. 2). Assuming an equally populated two-site exchange process, no cross-relaxation effect, identical T$_2$ for deuterons undergoing the mutual exchange and no coupling between them, the rotation rate at T_c is easily deduced from the measurement of the half-difference of $\Delta\nu_Q$'s on the ^{2}H spectrum below T_c (in absolute value):[1]

$$k = \pi \times \left| \Delta\nu_Q^A/2 - \Delta\nu_Q^B/2 \right| / \sqrt{2}, \quad (1)$$

hence the activation free energy, $\Delta G^{\ddagger}$, is equal to at T_c:

$$\Delta G^{\ddagger}(T_c) = RT_c \times \ln\left(\frac{RT_c}{Nh} \times \frac{\sqrt{2}}{\pi \times \left(\Delta\nu_Q^A/2 - \Delta\nu_Q^B/2 \right)} \right) \quad (2)$$

where R, N and h are the usual physical constants. Using $|\Delta\Delta\nu_Q/2|$ = 102 ± 5 Hz, we obtain $k = 226 \pm 11$ s^{-1} and $\Delta G^{\ddagger}(T_c) = 48.6 \pm 0.5$ kJ mol^{-1}.

The presence of a broad quadrupolar doublet at T_c implies that the signs of $\Delta\nu_Q$'s are the same. This result is consistent with the $\Delta\nu_Q$'s found in the PBG achiral phase below T_c. Indeed, these values are equal to the average of the absolute value of $\Delta\nu_Q$'s measured in the PBLG phase. Note that opposite signs would result in a broad singlet or an unresolved triplet at T_c, depending on the $|\Delta\Delta\nu_Q|$ value compared to the magnitude of $|\Delta\nu_Q$'s$|$.[1,2]

Computer-simulated lineshapes (right column in Fig. 1) for two nonequivalent deuterons were achieved using the density matrix formalism proposed by Poupko and Luz.[1] The k parameters

extracted from the simulated ^{2}H-{^{1}H} NMR spectra were analysed by plotting the natural logarithm of kNh/RT against $1/T$, an Eyring plot (see Fig. 3).[9] From the analysis of this graph, the activation parameters, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and subsequently, $\Delta G^{\ddagger}(T)$ can be calculated as $\Delta G^{\ddagger}(T) = \Delta H^{\ddagger} - (T) \times \Delta S^{\ddagger}$.[9] Thus we found $\Delta H^{\ddagger} = 44.2 \pm 0.5$ kJ mol^{-1}, $\Delta S^{\ddagger} = -19 \pm 2$ J mol^{-1} K^{-1} and $\Delta G^{\ddagger}(T_c) = 48.9 \pm 0.5$ kJ mol^{-1}. Note that the rotation rate k is around 1.2×10^4 s^{-1} at 302 K. This value is consistent with the presence of a single doublet observed at room temperature and above.

To validate the experimental value of $\Delta H^{\ddagger}$, we have analysed compound **1** by molecular modelling. Fig. 4 shows the evolution of potential energy, E_{pot}, as a function of the dihedral angle ϕ (0–180°) determined by using a semi-empirical AM1 method.[6a,b] As the substituents in the 2′ and 6′ positions are identical, the curve is symmetrical relative to $\phi = 90°$, and the regions to each side of this angle correspond to enantiomeric pairs. It is emphasised that the conformers (ϕ) and (360° − ϕ) are also mirror-images, and so the evolution of E_{pot} between 0 and 360° is also symmetrical relative to $\phi = 180°$. Here again, the regions to

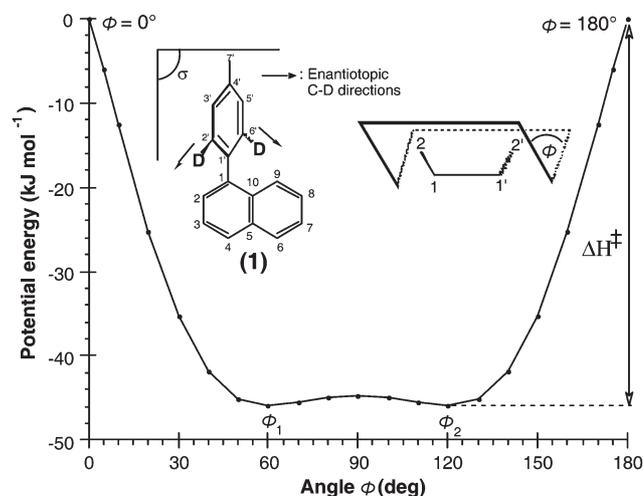**Fig. 4** Potential energy profile for **1** *vs. ϕ* over the range 0–180°. The curve maxima are set to zero. In the insert are displayed the structure of **1** when a C_s symmetry is adopted and the inter-ring torsion angle ϕ.

the two sides of the absolute maximum correspond to enantiomeric pairs. Note that the values calculated with AM1 differ by less than 1% from those obtained using the *ab initio* method.[6a,c]

Steric hindrance produces highest energy rotational conformers for $\phi = 0°$ and $180°$, while the lowest energy ones are found at $\phi = 57.4°$ or $122.6°$ (denoted by ϕ_1 and ϕ_2 on the plot) and not at $90°$. This situation results from absence of stabilization by π-orbital overlap when the aromatic rings are orthogonal.[3] The barrier height to internal rotation, $\Delta H^{\ddagger}$, is evaluated at 45.9 kJ mol^{-1}, and so the discrepancy with values derived from the NMR study is below 2 kJ mol^{-1} ($< 4\%$). This excellent agreement demonstrates the reliability of the two methods for this example.

From the graph, it can be seen also that the barrier height to interconversion between the enantiomeric conformers, ϕ_1 and ϕ_2, is smaller than 2 kJ mol^{-1}. This value explains why the spectral discrimination of enantiomeric conformers, ϕ_1 and ϕ_2, failed even on recording the ^{2}H-$\{^1$H$\}$ spectrum at 200 K (not shown). Note that below this temperature, the sample starts to form a gel phase, thus preventing the use of PBLG as an ordering solvent with a low viscosity. Actually, it can be pointed out that the evolution of the experimental deuterium spectra could also be explained by assuming a potential energy profile with just two minima set at $90°$ and $270°$, and corresponding to the prochiral conformer of C_s symmetry.

Finally, we have studied the dynamic process of **1** dissolved in the PBLG/CH$_2$Cl$_2$ phase. The evolution of ^{2}H-$\{^1$H$\}$ anisotropic spectra is identical to that observed in the PBLG/CHCl$_3$ phase.†‡ As previously, two doublets are observed at low temperature and these coalesce at 245 ± 2 K. The experimental $\Delta G^{\ddagger}$ value derived from the Eyring plot is equal to 47.6 ± 0.5 kJ mol^{-1} at T_c. The insignificant deviation between the experimental $\Delta G^{\ddagger}$ values ($< 3\%$) indicates that the nature of the co-solvent does not affect the kinetic constants of compound **1**.

In conclusion, this work shows that ^{2}H-$\{^1$H$\}$ NMR in a polypeptide chiral oriented solvent is a unique method for determining kinetic and activation parameters of enantiomers or enantiotopic directions undergoing intramolecular conformational exchange. The excellent agreement between the calculated and experimental values of $\Delta H^{\ddagger}$ explicitly indicates that the intermolecular forces between the solute and the PBLG phase do not significantly influence the conformational interconversion process of **1** (compared to an isolated molecule). This new study confirms definitely other recent results.[10] An extended investigation of the molecular rotational isomerism phenomenon using deuterium NMR in various polypeptide chiral liquid crystals is currently underway.

Notes and references

† ^{2}H-$\{^1$H$\}$ spectra were recorded by adding 1024 scans on a Bruker DRX-400 using a 5 mm QXO probe. The sample was spun in the magnetic field and the temperature was controlled by the BVT 3200 system.

‡ The PBLG samples were made from 10 mg of **1**, 102 mg of PBLG (DP = 782) purchased from Sigma corp., and 442 mg of dry CHCl$_3$ or CH$_2$Cl$_2$. The 'PBG' sample was made using 50 mg of PBLG, 50 mg of PBDG (DP = 914), 10 mg of **1** and 440 mg of CHCl$_3$. For more details on the sample preparation and NMR in oriented solvents, see ref. 4.

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