First successful enantiomeric discrimination of chiral alkanes using NMR spectroscopy

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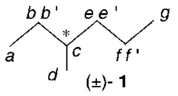
Natural abundance deuterium NMR spectroscopy in a chiral polypeptide liquid crystal solvent (PBLG) is used to successfully discriminate between chiral alkanes.

The enantiomeric differentiation of saturated chiral hydrocarbons is an interesting but difficult task using NMR spectroscopy. Among this class of compounds, 3-methylhexane **1**, -heptane **2** and -octane **3** are excellent illustrative examples.

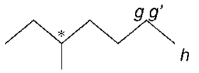
Although the separation of 3-methylhexane by gas chromatography using undiluted cyclodextrin derivatives as a chiral stationary phase is noteworthy,[1] to the best of our knowledge, all isotropic NMR techniques have failed to discriminate between such chiral alkanes, as no successful results have been reported to date. This situation occurs mainly because these compounds do not possess any functional groups, making the derivatisation of the chiral molecule or the preparation *in situ* of specific complexation agents impossible.[2] Consequently, only NMR analytical approaches in which shape recognition plays an important role in the chiral discrimination mechanisms, compared with the electrostatic interaction contributions, are likely to produce successful results.

In this preliminary work, we demonstrate for the first time that enantiomeric discrimination of chiral alkanes is possible using natural abundance deuterium (NAD) NMR spectroscopy in a chiral polypeptide liquid-crystalline solvent composed of poly-γ-benzyl-L-glutamate (PBLG) dissolved in chloroform.[3,4]

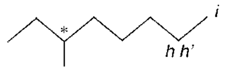
Four different reasons justify the use of this unusual NMR tool. First, we have recently shown that the shape of solutes plays a important role in the differential orientation effect (DOE) of two enantiomers in the PBLG phase.[5,6] Second, since it may be expected that the difference in the interaction between the *R* and *S* isomers and the polypeptide helices will generate a rather small DOE, it is necessary to observe a very sensitive order-dependent NMR interaction, such as the quadrupolar interaction for deuterium ($I = 1$) nuclei.[3] Indeed, when the orientational difference between the *R* and *S* isomers is small, the relatively large magnitude of the deuterium quadrupolar coupling constant for a C–D bond (QCC $\approx$ 170 kHz)[7] can give a sufficiently large difference in their residual quadrupolar splittings ($\Delta\nu_Q^R - \Delta\nu_Q^S$), enabling their observation. Third, since the detection of rare spins such as deuterons in natural abundance is not an insurmountable obstacle in terms of sensitivity (*i.e.* detection using standard NMR equipment and reasonable experimental time), the site-specific labelling of the chiral molecules is not required, avoiding time-consuming synthetic work.[3] Finally, all possible deuterated sites of the molecule can be simultaneously probed, thus increasing the probability of observing a chiral differentiation.[3]



(±)- **1**



(±)- **2**



(±)- **3**

Proton-decoupled NAD NMR spectra in organic solutions of PBLG consist of the superposition of independent quadrupolar doublets, $\Delta\nu_{Q_i}$, corresponding to all non-equivalent deuterons in each of the two enantiomers.[3,4] Thus, in the case of (±)-**1**, (±)-**2**, and (±)-**3**, 20, 24 and 28 different chiral isotopomers exist in the mixture respectively, and a maximum of 20, 24 and 28 doublets, respectively, are expected to be detected if all deuterated sites show a chiral discrimination. Consequently, even if dipolar couplings between two rare atoms cannot be detected, the correlation between the two components for each quadrupolar doublet is not always simple, mainly due to overlapping of peaks, and requires the use of proton-decoupled deuterium 2D-NMR experiments.[4]

Fig. 1 reports the NAD 2D Q-COSY spectrum† of (±)-**1**‡ in the PBLG–CHCl$_3$ phase recorded at 298 K over 16 h at 61.4 MHz.[4] In this 2D spectrum, we can observe 12 different quadrupolar doublets. This result clearly indicates that two deuterons in the molecule are differentiated between, as only 10 doublets would be observed if no chiral separation occured. To confirm this result, we have recorded the NAD 2D Q-COSY spectrum of (±)-**1** in a racemic mixture of PBLG and PBDG (the enantiomer of PBLG) in CHCl$_3$.[6,8] In this mixture, the fast exchange between chiral solutes and the vicinity of PBLG and PBDG eliminates the chiral discrimination, hence only 10 quadrupolar doublets can be (and were) observed. The assignment of each doublet is non-trivial because all deuterons in methylene groups are diasteorotopic (non-equivalent),[3,4] and deuterium chemical shift dispersion in apolar alkanes is rather small. However, we can indirectly identify them from analysis of HMQC (^{1}H–^{13}C) and INADEQUATE (^{13}C–^{13}C) 2D spectra of (±)-**1** in an isotropic state, which enable a clear assignment of ^{13}C and ^{1}H signals. Assuming that deuteron chemical shifts in

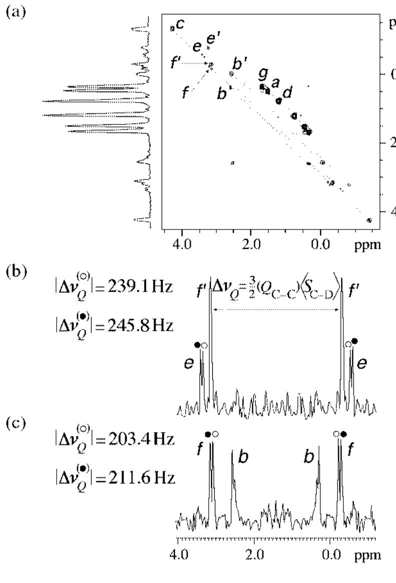


Fig. 1 2D contour plot of a NAD Q-COSY experiment obtained for (±)-**1** (a). The two columns extracted after tilting of the 2D spectrum show a chiral discrimination of the deuterons denoted *e*(b) and *f*(c). The doublet due to each enantiomer is arbitrarily labelled with (●) and (○). The chloroform doublet is not shown in the spectrum.

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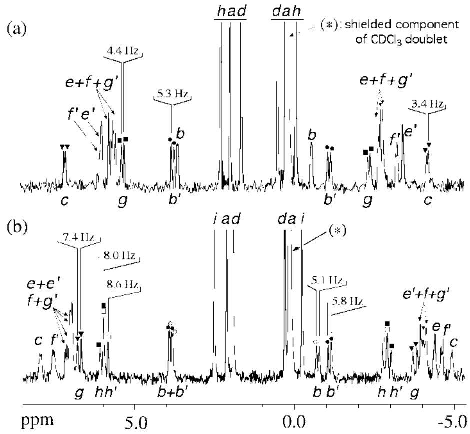

Fig. 2 NAD 1D spectra of (±)-**2** (a) and (±)-**3** (b). All clearly discriminated deuterons are labelled with different symbols.

PBLG are similar to those of protons measured in neat CHCl$_3$, it becomes possible to unambiguously assign almost all deuterium quadrupolar doublets. In addition, this assignment can be confirmed by measuring the proton–carbon dipolar couplings, $D_{\text{C-H}}$, in the carbon-13 spectrum of (±)-**1** in PBLG.[9] Since the ratio $|\Delta\nu_{Q_{\text{C-D}}}/D_{\text{C-H}}|$ can be quantified as 11.8 ± 0.2 (because $S_{\text{C-D}} = S_{\text{C-H}}$), we may *a priori* calculate the magnitude of $\Delta\nu_{Q_{\text{C-D}}}$ of the deuterons for a given assigned carbon and then compare with experimental values. Using this procedure, we were able to confirm that the deuterons *e* and *f* are discriminated between [Fig. 1(*b*) and (*c*)], while deuterons *b, b*' and *c* show broad peaks, indicating an unresolved chiral discrimination. In contrast, no chiral discrimination was detected between the methyl signals (*a*, *d*, *g*).

Fig. 2 reports the NAD 1D-NMR spectra† of (±)-**2**‡ and (±)-**3**‡ recorded at 298 K in the PBLG–CHCl$_3$ phase. Notably, we can unambiguously observe the doubling of numerous peaks, indicating that enantiomers of (±)-**2** and (±)-**3** are discriminated between in the PBLG–CHCl$_3$ phase. Here again, the assignment procedure previously described shows that the largest chiral separations are measured for the diastereotopic deuterons denoted *b*' and *g*, and *b*,*b*',*h*,*h*' and *g* for (±)-**2** and (±)-**3**, respectively. As for (±)-**1**, none of the methyl groups is discriminated between, but a small chiral separation has been observed on the deuteron attached to the asymmetric carbon on these compounds.

The successful enantiomeric differentiation of chiral flexible alkanes using deuterium NMR spectroscopy in PBLG is possible because the polypeptide helices are able to interact enantioselectively with non-functionalized enantiomers and because the sensitivity of the quadrupolar interaction to the DOE is sufficiently large to reveal small orientational differences. This result establishes the significant role of shape recognition in chiral discrimination mechanisms involved in the PBLG phase. An evaluation of the potential of this approach on a wide range of saturated and unsaturated chiral hydrocarbons is currently underway and will be extensively discussed in a subsequent publication.

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Notes and references

† NMR experiments: NMR experiments were performed on a Bruker DRX-400 using a 5 mm selective deuterium probe. The sample was not spun in the field and the temperature was controlled by the BVT 2000 system. Due to the good long term stability of the magnet, no field-frequency lock was used. The WALTZ-16 sequence was applied as broad-band proton decoupling. The 2D Q-COSY spectrum of (±)-**1** was recorded using 300 (t_1) × 1700 (t_2) data points. 400 transients for each t_1 increment were added, leading to a total of 120 000 scans. Gaussian filtering was applied in both dimensions. The 1D interferograms of (±)-**2** and (±)-**3** were acquired using a pulse angle of *ca.* 70°, a recycle delay of *ca.* 0.5 s and 1.7 k of data points, summing over 230 000 and 140 000 scans, respectively. No digital filtering was used.

‡ Sample composition: The liquid-crystalline NMR samples of (±)-**1**, (±)-**2**, (±)-**3** were prepared from 80, 50 and 60 mg of racemic material, 81 mg [degree of polymerisaton (DP) = 562(50%)+1078(50%)], 100 mg (DP = 562) and 100 mg (DP = 562) of PBLG (purchased from Sigma corp.) and 445, 400 and 400 mg of CHCl$_3$, respectively. For sample preparation, see refs. 4 and 5.

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