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Extreme enantiomeric discrimination of fluoroalkanes using deuterium NMR in chiral liquid crystalline media

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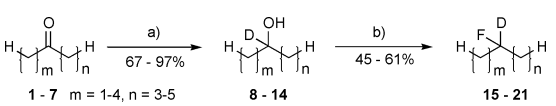
Received (in Cambridge, UK) 30th January 2002, Accepted 7th March 2002
First published as an Advance Article on the web 19th March 2002

The enantiomeric assay of fluoroalkanes using ^{2}H-NMR in a chiral liquid crystalline medium is demonstrated, and at its limit the enantiomers of [5-^{2}H]-5-fluorodecane were successfully resolved.

NMR spectroscopy in chiral liquid crystalline solvents provides a powerful method for the measurement of enantiomeric purity of a large variety of molecules. Optimum results have been obtained using concentrated solutions of homopolypeptides such as poly-γ-benzyl-L-glutamate (PBLG) or poly-γ-carbobenzoxy-L-lysine (PCBLL) in various organic solvents (*e.g.* chloroform, dimethylformamide (DMF)).[1] In these media, enantiomers become oriented differently. This difference in orientation can be observed in the NMR spectra through dipolar couplings, D_{ij}, chemical shift anisotropies, $\Delta\sigma^i$, or quadrupolar splittings, $\Delta\nu_Q{}^i$, for spins > 1/2.[2] It should be noted that dipolar couplings cannot be obtained directly from NMR spectra. Taking into account that the anisotropic part of scalar coupling is often negligible, for two non-equivalent nuclei such as deuterium and fluorine, one observes the total spin–spin coupling $T_{ij} = 2D_{ij} + J_{ij}$ where J_{ij}, the scalar coupling, is equal to the isotropic value.[2] Most results of enantiomeric analysis have been obtained through deuterium (spin = 1) NMR.[3] The latter emerges as a most efficient method to observe enantiomers because the large quadrupolar interaction (150–200 kHz) induces large quadrupolar splittings. A small difference in the orientation of enantiomers gives rise to measurable differences in their $\Delta\nu_Q$'s.

The Van der Waals radius of fluorine (1.47 Å) is larger than that of hydrogen (1.20 Å) and close to that of oxygen (1.52 Å).[4] Nevertheless the replacement of hydrogen by fluorine induces very little distortion in two-dimensional molecular packing,[5] which suggests a close isosteric relationship between hydrogen and fluorine. Therefore, assaying enantiomers of fluoroalkanes emerges as a significant challenge. Enantiomeric discrimination by NMR spectroscopy in chiral liquid crystals stems mainly from shape recognition.[6] Therefore, fluoroalkanes provide an extreme case study for enantiomeric resolution. For this purpose, chiral deuterium-labelled fluoroalkanes with various chain lengths were prepared, where both fluorine and deuterium were gradually moved towards the center of the molecules. The racemic deuterofluoroalkanes **15–21** were prepared by reduction of ketones **1–7** followed by dehydroxyfluorination of alcohols **8–14** using diethylaminosulfur trifluoride (DAST)[7] as shown in Scheme 1.



Scheme 1 The synthesis of deuterofluoroalkanes **15–21**. a) $LiAlD_4$ (0.5 equiv.), THF, 0 °C to rt, reflux, 3 h. b) DAST (1.1 equiv.), CH_2Cl_2, −78 °C to rt, reflux, 3 h.

In a chiral liquid crystalline solvent, the proton-decoupled deuterium (^{2}H-{^{1}H}) NMR spectrum of each enantiomer of a deuterofluoroalkane was a doublet of doublets.[8] The larger splitting is due to the quadrupolar interaction and the smaller one originates from the deuterium–fluorine total spin–spin coupling (T_{DF}). This was confirmed after recording the ^{19}F-{^{1}H} NMR spectrum in each case. A typical spectrum, *e.g.* that obtained with 3-deutero-3-fluorohexane **18** in PBLG–$CHCl_3$ at 302 K, is shown in Fig 1. The enantiomers are clearly discriminated both by their quadrupolar splitting and their deuterium–fluorine coupling.

Table 1 summarizes the results obtained from the ^{2}H-{^{1}H} NMR in liquid crystalline solvents. Experiments 1–7 were run at 302 K in PBLG–$CHCl_3$ (13 wt% PBLG). In the case of the 5-deutero-5-fluorodecane **21**, ^{2}H-{^{1}H} NMR spectra were also acquired in PCBLL–DMF (27 wt% PCBLL) at T = 302 and 320 K (Entry 8 and 9). In the PBLG–$CHCl_3$ liquid crystal, enantiomeric discrimination was achieved for all compounds (Entries 1–7) until 5-deutero-5-fluorodecane **21**. Both quadrupolar splittings and total spin–spin fluorine–deuterium couplings are different for each of the enantiomers. The difference in the spin–spin fluorine–deuterium coupling is measured only in ^{2}H-{^{1}H} NMR spectra. In the ^{19}F-{^{1}H} NMR spectra, a single triplet was obtained (intensity 1 : 1 : 1) without enantiomeric resolution.

It is interesting to compare the variation of the enantiomeric discrimination ($(\Delta\nu_Q{}^1 - \Delta\nu_Q{}^2)_{norm}$) with the difference in geometry between two alkyl chains in this series. However, to make this comparison between the samples with different solutes, it is necessary to apply a correction factor to take into account small variations in sample composition.[8] The correction factor applied was derived from the co-solvent ($CDCl_3$) quadrupolar splitting, $\Delta\nu_Q{}^{Sol}$ observed at natural abundance in the ^{2}H-{^{1}H} NMR spectrum. In an ideal situation this splitting is the same in all samples. However as there is always some experimental variation, $\Delta\nu_Q{}^{Sol}{}_{ref}$ was used as a reference. The experimental values of ($\Delta\nu_Q{}^1 - \Delta\nu_Q{}^2$) were then corrected

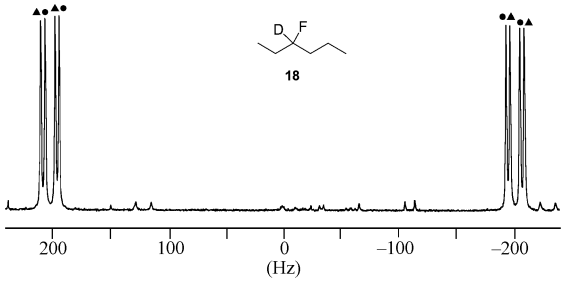


Fig. 1 ^{2}H-{^{1}H} NMR spectrum of 3-deutero-3-fluorohexane **18** in a solution of PBLG–$CHCl_3$ (13 wt% PBLG) at T = 302 K. Peaks marked with ● belong to one enantiomer and those marked with ▲ are due to the other enantiomer.

DOI: 10.1039/b200992g

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Table 1 Quadrupolar splittings $\Delta\nu_Q^1$ and $\Delta\nu_Q^2$, and spin–spin couplings, T_{DF}^1 and T_{DF}^2, measured for the enantiomers of fluoroalkanes by ^{2}H-{^{1}H} NMR spectroscopy

Entry	Compound[a]	$\Delta\nu_Q^1$/Hz	T_{DF}^1/Hz	$\Delta\nu_Q^2$/Hz	T_{DF}^2/Hz	$(\Delta\nu_Q^1 - \Delta\nu_Q^2)_{norm}$/Hz[e]
1	**15:** C_1-CDF-C_3[b]	356.0 ± 0.4	11.3 ± 0.4	351.2 ± 0.4	10.7 ± 0.4	4.7 ± 0.8
2	**16:** C_1-CDF-C_4[b]	422.5 ± 0.5	12.0 ± 0.5	417.8 ± 0.5	11.2 ± 0.5	4.6 ± 1.0
3	**17:** C_1-CDF-C_5[b]	458.1 ± 0.6	12.6 ± 0.6	453.5 ± 0.6	11.7 ± 0.6	4.6 ± 1.2
4	**18:** C_2-CDF-C_3[b]	406.7 ± 0.6	12.4 ± 0.6	399.7 ± 0.6	11.9 ± 0.6	7.0 ± 1.2
5	**19:** C_2-CDF-C_4[b]	525.7 ± 0.8	13.8 ± 0.8	516.4 ± 0.8	13.1 ± 0.8	8.7 ± 1.6
6	**20:** C_2-CDF-C_5[b]	585.4 ± 0.8	14.9 ± 0.8	576.1 ± 0.8	14.0 ± 0.8	8.8 ± 1.6
7	**21:** C_4-CDF-C_5[b]	833.7 ± 1.0	18.2 ± 1.0	833.7 ± 1.0	18.2 ± 1.0	0.0 ± 2.0
8	**21:** C_4-CDF-C_5[c]	56.0 ± 1.0	9.0 ± 1.0	51.9 ± 1.0	8.7 ± 1.0	4.1 ± 2.0[f]
9	**21:** C_4-CDF-C_5[d]	129.3 ± 0.8	9.4 ± 0.8	125.9 ± 0.8	9.2 ± 0.8	3.4 ± 1.6[f]

[a] The C_m-CDF-C_n notation is used for fluoroalkanes with formula: $C_mH_{2m+1}CDFC_nH_{2n+1}$. Compounds **15**–**21** were characterized spectroscopically. [b] Recorded in PBLG–$CHCl_3$ (13 wt% PBLG) at T = 302 K. [c] Recorded in PCBLL–DMF (27 wt% PCBLL) at T = 302 K. [d] Recorded in PCBLL–DMF (27 wt% PCBLL) at T = 320 K. [e] Normalized by reference to $CDCl_3$, $\Delta\nu_Q^{Sol}{}_{ref}$. [f] Value recorded in DMF without normalization.

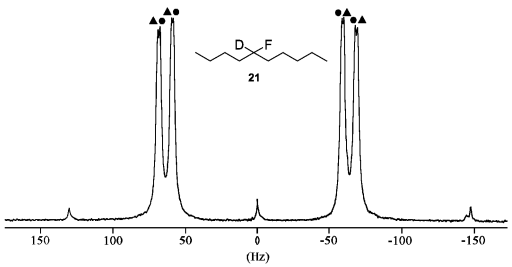

Fig. 2 ^{2}H-{^{1}H} NMR spectrum of 5-deutero-5-fluorodecane **21** in a solution of PCBLL–DMF (27 wt% PCBLL) at T = 320 K. Peaks marked with ● belong to one enantiomer and those marked with ▲ are due to the other enantiomer.

through $(\Delta\nu_Q^1 - \Delta\nu_Q^2)$. $\Delta\nu_Q^{Sol}{}_{ref}/\Delta\nu_Q^{Sol}{}_{sample}$, thus providing normalised values for $(\Delta\nu_Q^1 - \Delta\nu_Q^2)_{norm}$.

We observe that the normalised average quadrupolar splittings increase when the alkyl chain increases ($n + m$ increases). This behaviour is expected since the longer a molecule is, the better it is oriented and consequently the larger the quadrupolar splittings should be. The variation in enantiomeric discrimination *vs*. n for a given m is more problematical. We have recently shown for alkyl secondary alcohols[9] that the enantiomeric discrimination increases with an increase in the difference in the alkyl chains lengths ($n - m$). Fluoroalkanes do not follow this behaviour. Thus for C_1-CDF-C_n (Entries 1–3) the $(\Delta\nu_Q^1 - \Delta\nu_Q^2)_{norm}$ value is almost constant, and for C_2-CDF-C_n (Entries 4–6) the $(\Delta\nu_Q^1 - \Delta\nu_Q^2)_{norm}$ increases only between C_2-CDF-C_3 and C_2-CDF-C_4, and then remains constant despite a further increase in n. Consequently, it appears that enantiomeric discrimination of fluoroalkanes in the PBLG–$CHCl_3$ liquid crystal is not very sensitive to molecular dissymmetry.

As no enantiomeric discrimination was observed for 5-deutero-5-fluorodecane **21** in PBLG–$CHCl_3$, PCBLL–DMF was used as an alternative liquid crystalline solvent. ^{2}H-{^{1}H} NMR spectra were measured at 302 and 320 K (Entries 8 and 9). The enantiomers of this most challenging fluoroalkane now became discriminated as shown in Fig. 2. The small peak separation obtained suggests that this is close to the limit of discrimination of chiral secondary fluoroalkanes by this method. To our knowledge, these are the first enantiomeric resolutions of unsubstituted fluoroalkanes, by NMR.[10]

In conclusion, it has been demonstrated that ^{2}H-{^{1}H} NMR spectroscopy in chiral liquid crystalline solvents allows the discrimination of enantiomers of linear secondary fluoroalkanes. The spectral separation is not very sensitive to molecular dissymmetry. We have observed resolutions of compounds **15**–**21**. The enantiomers of 5-deutero-5-fluorodecane **21** are at the limit of the chiral discriminating power of this technique. Compounds containing fluorine at a remote stereogenic centre are becoming increasingly important as ferroelectric liquid crystalline materials.[11] This technique offers a method to assay the chirality of such materials.

We thank the Isle of Man Education Authority for a Studentship (RJMG) and EPSRC and CNRS for the award of a collaborative CERC-3 research grant.

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