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Monitoring the differential ordering of enantiomers included into cyclodextrins through deuterium NMR in lyotropic liquid crystals†

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Deuterium NMR in an aqueous non-chiral liquid crystal allows the discrimination of enantiomers through their ordering inside β-cyclodextrins.

In order to see enantiomers using NMR spectroscopy one needs to use chiral auxiliaries that give diastereomeric interactions with the enantiomers to be studied.[1] In a first step, either chiral lanthanide shift reagents, or chiral solvating agents have been used successfully. In these experiments, which are done in isotropic solvents, the diastereomeric interactions must be strong enough to modify the isotropic part of the electronic shielding in order to produce large chemical shift differences allowing separate integrations to be performed.

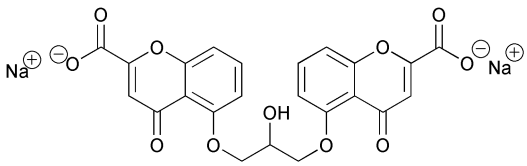
More recently we have developed another method using chiral liquid crystals as solvents.[2] The basic phenomenon is that two enantiomers are not oriented the same in these chiral oriented media. Consequently, all the order dependent NMR interactions are different for enantiomers, namely the chemical shift anisotropy, the dipolar spin–spin couplings and the quadrupolar splittings for nuclei such as deuterium. This technique appears more general than the conventional methods cited above. One of the reasons lies in the tremendous sensitivity of anisotropic magnetic interactions to molecular orientation, noticeably in the case of quadrupolar splittings.[3]

Compiling the various solvating agents commonly employed, some of them came to our attention: the chiral cages such as cyclodextrins or cryptophans.[4,5] Intuitively, when included into such chiral cages one can assume that enantiomers should not be oriented the same toward the cage. Such orientation differences have been predicted by theoretical calculations using molecular dynamics or Monte Carlo simulations.[6] Furthermore, intermolecular NOE/ROE measurements have been performed and the results gave some support to this hypothesis of a differential orientation of enantiomers in chiral cages.[7] Consequently, we raised the question as to whether this phenomenon could be large enough to be seen through the order sensitive liquid crystal NMR.

Let us assume an enantiomerically pure chiral cage is dissolved in a nematic phase. The chiral cages will be partially oriented. If two enantiomers, known to make inclusion complexes with the cage, are added to such a mixture, and if these enantiomers do not have the same orientation inside the cages, then all the NMR order sensitive magnetic interactions should be different. This would provide a new NMR method to discriminate enantiomers where not only the isotropic part of the chemical shift could be used, but also the chemical shift anisotropy, the dipolar couplings and the quadrupolar splittings. Beside, it would be an original way to directly monitor the orientation of enantiomers in a chiral cage. Finally, using theoretical calculations as those described in reference 6 and comparing the results with experiments could lead to the knowledge of the absolute configurations.[8]

The purpose of this work is to show that the difference in the orientation of enantiomers in chiral cages can be actually observed using deuterium NMR spectroscopy in a liquid crystalline solvent.

Our choice has been to test the commercially available β-cyclodextrin (β-CyD, **1a**) and hydroxypropyl-β-cyclodextrin (HP-β-CyD, **1b**) as chiral cages. In order to realize such an experiment we need a nematic liquid crystal solvent in which cyclodextrins can be dissolved. It must be clear that we do not need here a chiral liquid crystal because the chiral auxiliary will be the cyclodextrin. The nematic liquid crystal is there only to provide an ordering field to orient the cyclodextrin in order to allow the measurement of the order parameters of enantiomers inside the chiral cavity. In principle, any lyotropic liquid crystal based on water should work. Our choice has been the dilute water solution of cromolyn **2**. Cromolyn–water systems have been studied by Goldfarb *et al.*[9,10] It presents a nematic phase (denoted N-phase[9]) at temperatures between 0 and 20 °C with a weight fraction of cromolyn between 6% and 20%.



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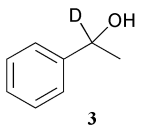
The chiral compound used in this study was the 1-deutero-1-phenylethanol both in racemic (**3a**) and (*S*)-enriched (33% *ee*, **3b**) mixtures.



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The ^{2}H-{^{1}H} NMR spectrum of **3a** dissolved in the cromolyn–water mesophase containing β-CyD is shown in Fig. 1a. Three deuterium quadrupolar splittings are observed. Running the same experiment with the (*S*)-enriched product (**3b**) allowed for peak assignation (Fig. 1b). The outer doublet must be assigned to the enantiomers outside the chiral cavity of the cyclodextrin. In this situation the enantiomers are not resolved and a single quadrupolar doublet, $\Delta\nu_Q$(free), is visible. Contrarily, the two inner doublets have to be assigned to the encaged enantiomers that exhibit different quadrupolar splittings, with $|\Delta\nu_Q(R)| < |\Delta\nu_Q(S)|$.

A difference in orientation of the encaged enantiomers of **3** was also obtained using HP-β-CyD. However, it was found in this case that $|\Delta\nu_Q(R)| > |\Delta\nu_Q(S)|$. The effect of temperature on quadrupolar splittings was studied for this sample (Fig. 2). The separation between the two enantiomers, $|\Delta\nu_Q(R)| - |\Delta\nu_Q(S)|$, increases with the orientation, *i.e.* as the temperature decreases. However the linewidth increases and below 278 K the peaks broadening prevents any spectral resolution.

The above results lead to the following conclusions: the enantiomers of 1-deutero-1-phenylethanol included in the β-cyclodextrins, (**1a**) and (**1b**), are not oriented the same inside

† Electronic supplementary information (ESI) available: products, preparation of solutions, and recording of NMR spectra. See http://www.rsc.org/suppdata/cc/b2/b205256c/

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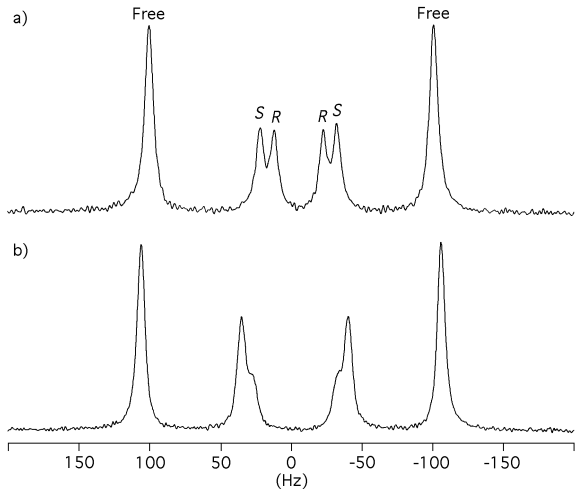

Fig. 1 ^{2}H-{^{1}H} NMR spectrum in cromolyn–water mesophase containing β-CyD of: (a) a racemic mixture of 1-deutero-1-phenylethanol; (b) a (*S*)-enriched 1-deutero-1-phenylethanol (33% *ee*). Temperature was 288 K.

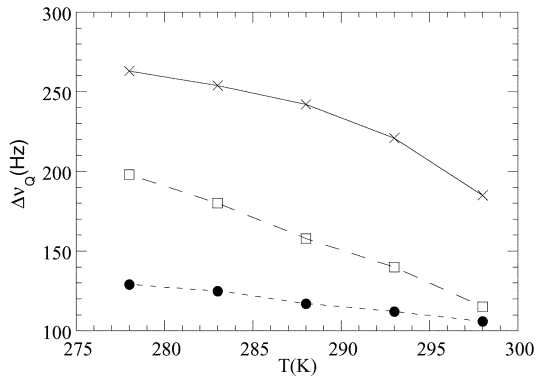

Fig. 2 Temperature dependence of quadrupolar splittings of 1-deutero-1-phenylethanol enantiomers in cromolyn–water liquid crystal solution with HP-β-CyD. × is the quadrupolar splitting of the (*R*) and (*S*) free compounds. □ is the quadrupolar splitting of the (*R*)-**3**–HP-β-CyD complex. ● is the quadrupolar splitting of the (*S*)-**3**–HP-β-CyD complex.

these hydrophobic chiral cages. Consequently, the order sensitive quadrupolar splittings are different for the two included molecules, thus furnishing an original method to discriminate enantiomers. In the conditions used, the centers of both inner quadrupolar doublets are the same. This means that the included enantiomers have the same chemical shifts. Consequently, chemical shifts do not allow differentiation of the enantiomers in these conditions. This illustrates the large sensitivity of quadrupolar splittings to this orientation phenomenon compared to the sensitivity of isotropic chemical shift to inclusion in a chiral environment.

This method cannot be used for a direct measurement of enantiomeric excess. As it can be seen on Fig. 1a, the intensities of the inner doublets attributed to each enantiomer are not exactly equal for this racemic mixture. This originates from the well-known difference in the complexation equilibrium constants, which are obviously not the same for the enantiomers. However, provided an experiment is first done with a racemic mixture, subsequent experiments would allow determination of enantiomeric excess.

Also noticeable are the differences between quadrupolar splittings $|\Delta\nu_Q(R)|$ and $|\Delta\nu_Q(S)|$ which are inverted between the β-CyD (**1a**), where $|\Delta\nu_Q(S)| > |\Delta\nu_Q(R)|$, and HP-β-CyD (**1b**), where $|\Delta\nu_Q(R)| > |\Delta\nu_Q(S)|$. Such a result should not appear surprising. Actually β-CyD (**1a**) and HP-β-CyD (**1b**) should not have the same orientation in the liquid crystal. Furthermore, the orientation of enantiomers inside a cage does depend on the host structure. Consequently, a slight difference in the orientation of either the host or the guest molecules may account for such inversion.

In conclusion, we have shown that NMR in non-chiral oriented media allows the discrimination of enantiomers through their ordering inside a chiral cage. The mesophase used was a mixture of water and cromolyn and the chiral inclusion compound were enantiomers of 1-deutero-1-phenylethanol and β-cyclodextrins.

The next step of this work will consist of the determination of the order parameters of both the chiral cage and of the enantiomers inside the cage in order to account for their relative orientation. Subsequently, the use of molecular dynamics calculations in order to reach the absolute configurations of the guest molecules appears as an important challenge.

Notes and references

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