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Enantiomeric Excess Analysis of (2*R*, 3*S*)-3-Deuterio-2-methylcyclohexanone and (1*S*, 2*R*, 3*S*)-3-Deuterio-2-methylcyclohexanol, through Deuterium NMR in a Polypeptide Lyotropic Liquid Crystal

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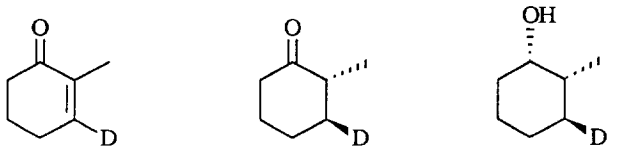
Abstract : Poly-γ-benzyl-L-glutamate (PBLG) and dichloromethane form a lyotropic liquid crystal which can be used as solvent for enantiomeric excess analysis of molecules containing several stereogenic centers, through deuterium NMR spectroscopy. All isomers of 3-deuterio-2-methylcyclohexanone and of 3-deuterio-2-methylcyclohexanol dissolved in PBLG/CH_2Cl_2 solvents, exhibit different quadrupolar splittings on their deuterium NMR spectra, which allows an accurate determination of their diastereoisomeric and enantiomeric excesses.

We have recently reported that dichloromethane solutions of poly-γ-benzyl-L-glutamate (PBLG), which forms a lyotropic liquid crystal, can be used as a chiral deuterium NMR solvent to distinguish enantiomers[1]. The discrimination originates from the fact that, in such an anisotropic chiral medium, two enantiomers exhibit different averaged molecular ordering parameters. This phenomenon is expressed in a deuterium NMR spectrum, in different values of quadrupolar splitting for each enantiomer.

We have recorded proton decoupled deuterium NMR spectra of cyclohexanone **2** and cyclohexanol **3** - in racemic and optically active forms - dissolved in PBLG/CH_2Cl_2 solvent[2], in order to see if the differences in the quadrupolar splittings between all isomers could be important enough to measure accurately their diastereoisomeric and enantiomeric purities.



1 (2*R*, 3*S*)-**2** (1*S*, 2*R*, 3*S*)-**3**

The synthesis of (2*R*, 3*S*)-3-deuterio-2-methylcyclohexanone **2**[3] and (1*S*, 2*R*, 3*S*)-3-deuterio-2-methylcyclohexanol **3**[4], accomplished from microbiological reduction of 3-deuterio-2-methylcyclohex-2-enone **1** by *Beauveria sulfurescens*, has been previously reported[3-5]. The racemic cyclohexanone (±)-**2** is obtained from catalytic hydrogenation (H_2, Pd/C) of **1**. Reduction of (±)-**2** by lithium aluminium hydride in ether, leads quantitatively to (±)-3-deuterio-2-methylcyclohexanol **3**.

In figure 1, entries a and b show the proton decoupled deuterium NMR spectra of (±)-**2** dissolved in PBLG/CH_2Cl_2 solvent, recorded at 302 K and 255 K respectively. These spectra consist of eights signals : two quadrupolar splittings corresponding to the *syn* isomer (major product) and two quadrupolar splittings corresponding to the *anti* one (minor product). The diastereoisomeric excess, estimated from relative integration, is 62%. It is interesting to note that, at 302 K, only the *syn* signals are separated enough to measure precisely an enantiomeric excess. Decreasing the temperature (255 K) increases sufficiently the resolution of the *anti* signals in order to analyse its enantiomeric purity. Entry c shows the deuterium NMR spectrum of (2*R*, 3*S*)-**2**, recorded at 255 K. This spectrum exhibits a minor component corresponding to the *syn* isomer and a major one corresponding to the *anti* isomer. Relative integration

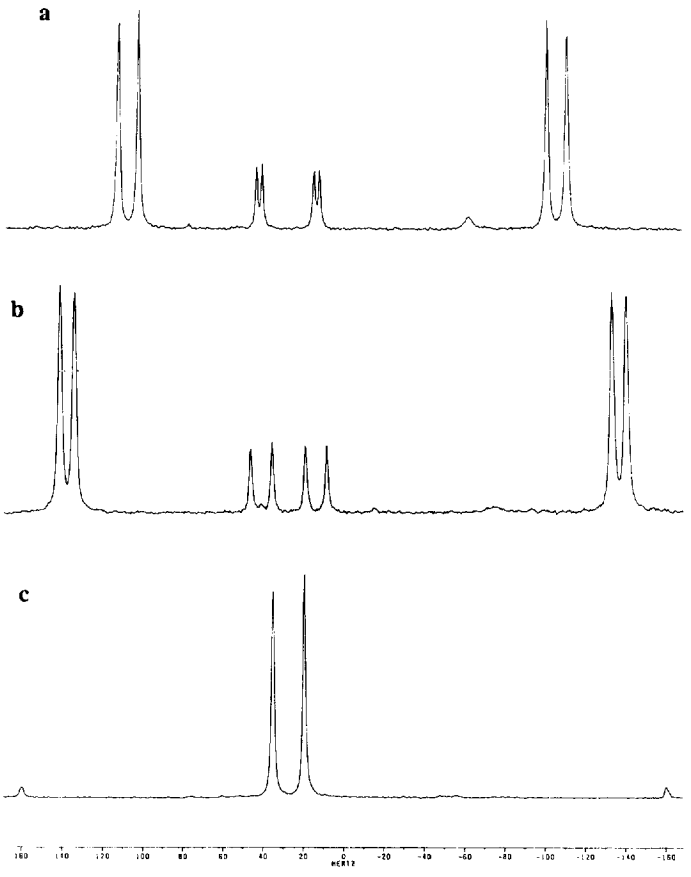


Figure 1 : Spectra of (±)-**2** recorded at 302 K (a) and 255 K (b). Spectrum of (2*R*, 3*S*)-**2** recorded at 255 K (c).

of signals gives a diastereoisomeric excess equal to 88%. For the *anti* diastereoisomer, only one quadrupolar splitting is obtained. From previous studies, we know that this method can detect without ambiguity traces of enantiomers (1%)[1c]. We can then conclude that the enantiomeric excess of (2*R*, 3*S*)-**2** is over than 98%, whereas a comparison with literature data[3] had concluded a 90% ee.

Presented in figure 2, are the deuterium NMR spectra of (±)-**3** and (1*S*, 2*R*, 3*S*)-**3**, recorded at 302 K. The racemic cyclohexanol exhibits 4 isomers : *syn-syn*, *anti-syn*, *syn-anti*, *anti-anti*. (This nomenclature indicates, for the first term, the relative position of the hydroxy and methyl groups, and for the second one, the relative position of the methyl and deutero groups). If each one allows visualisation of enantiomers, we must expect 8 doublets, in pairs of the same size, on the spectrum. As we can see in entry a, 16 distinct signals are obtained. The knowledge of the diastereoisomeric excess of the previous racemic cyclohexanone **2**, leads to a first attribution of the signals corresponding to :

- the *syn-syn* (A) or *anti-syn* (A') isomers (4 major doublets),
- the *syn-anti* (B) or *anti-anti* (B') isomers (4 minor doublets).

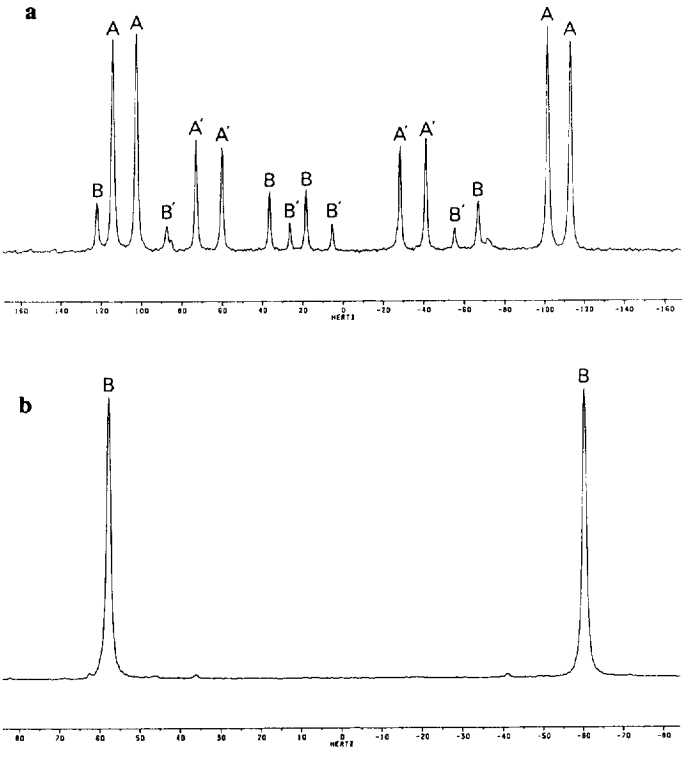


Figure 2 : Spectra of (±)-**3** (a) and (1*S*, 2*R*, 3*S*)-**3** (b). Both spectra were recorded at 302 K.

Orientation of the reduction then allows a complete attribution of the signals to each of the 4 isomers and their corresponding enantiomers, and the determination of the diastereoisomeric excess of the reduction, estimated as 37% by simple relative integration of the signals.

Determination of the diastereoisomeric and enantiomeric excess of the optically active cyclohexanol is made by a comparison between the spectrum of (1*S*, 2*R*, 3*S*)-**3** (figure 2, entry b) and the spectrum of (±)-**3**. Detection of traces of diastereoisomer on the spectrum of (1*S*, 2*R*, 3*S*)-**3** and integration of these minor signals leads to a diastereoisomeric excess equal to 97%. On the other hand, the lack of a signal associated to the enantiomer of (1*S*, 2*R*, 3*S*)-**3** on this spectrum shows the excellent enantiomeric excess of this cyclohexanol, which can be estimated as over than 98%. The two excellent enantiomeric excesses, obtained as well as for the cyclohexanone (2*R*, 3*S*)-**2** than for the cyclohexanol (1*S*, 2*R*, 3*S*)-**3**, illustrate the stereospecificity of the microbiological reduction by *Beauveria sulfurescens*.

In conclusion, we report herein the application of our new method of enantiomeric excess analysis to monodeuterated molecules containing several stereogenic centers. By recording only 4 deuterium NMR spectra - 2 of racemic compounds, 2 of the corresponding optically active compounds - it is possible to attribute completely and accurately the NMR signals to 8 isomers of a 3 stereogenic center molecule. The differences in the quadrupolar splittings of each isomer are large enough to measure precisely both diastereoisomeric and enantiomeric excesses.

Furthermore, with this application, we can prove that the enantiomeric excess of (2*R*, 3*S*)-3-deuterio-2-methylcyclohexanone **2** is higher than the enantiomeric excess previously reported[3]. For (1*S*, 2*R*, 3*S*)-3-deuterio-2-methylcyclohexanol **3**, this method allows a measurement of its diastereoisomeric excess - while this measurement is fairly difficult using isotropic proton NMR - but also, and to our knowledge for the first time, the measurement of its enantiomeric excess. Finally, the comparison between the NMR spectra of (±)-**3** and (1*S*, 2*R*, 3*S*)-**3** confirms the previously reported stereochemistry of this optically active cyclohexanol.

References and notes

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(b) Meddour, A.; Canet, I.; Loewenstein, A.; Péchiné, J.M.; Courtieu, J. *J. Am. Chem. Soc.* **1994**, *116*, 9652.
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(d) Canet, J-L.; Fadel, A.; Salaün, J.; Canet-Fresse, I.; Courtieu, J. *Tetrahedron : Asymmetry* **1993**, *4*, 31.

2) (a) PBLG is commercially available from Sigma (degree of polymerization : 1000-1200). PBLG is dissolved in a 12% w/w ratio in dichloromethane. Samples of 600 mg of PBLG-CH_2Cl_2 solvent and 10-20 mg of solute were used for NMR measurements.
(b) NMR spectra were recorded on a Bruker AM 250 spectrometer, equipped with a selective 5 mm deuterium probe (38.37 MHz) and a temperature controller (± 0.5°C regulation). Broad-band proton decoupling was achieved, using the WALTZ composite pulse scheme (1W of RF power).

3) For attribution of absolute configuration of (2*R*, 3*S*)-**2**, see : Dauphin, G.; Gourcy, J.G.; Veschambre, H. *Tetrahedron: Asymmetry* **1992**, *3*, 595.

4) For attribution of absolute configuration of (1*S*, 2*R*, 3*S*)-**3**, see : Kergomard, A. ; Renard, M.F. ; Veschambre, H. *J. Org. Chem.* **1982**, *47*, 792.

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