deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-119248 (**4**) and CCDC-119249 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[10] a) W. Strohmeier, K. Gerlach, *Chem. Ber.* **1961**, *94*, 398–406; b) B. Schwederski, W. Kaim, B. Olbrich-Deussner, T. Roth, *J. Organometal. Chem.* **1992**, *440*, 145–152.

[11] M. Pasquali, C. Floriani, A. Gaetani-Manfredotti, *Inorg. Chem.* **1981**, *20*, 3382–3388.

[12] T. Desmond, F. J. Lalor, G. Ferguson, M. Parvez, *J. Chem. Soc. Chem. Commun.* **1983**, 457–459.

Diastereomeric Shape Recognition Using NMR Spectroscopy in a Chiral Liquid Crystalline Solvent

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The use of NMR spectroscopy in liquid crystalline solvents proved to be a method of choice for enantiomeric analysis.[1] The best results have been obtained with the lyotropic liquid crystals made of organic solutions of a synthetic polypeptide, poly-γ-benzyl-L-glutamate (PBLG).[2] These lyotropic phases have been known for a long time, and many organic cosolvents such as dichloromethane, chloroform, THF, or DMF can be used.[3]

We have shown that, when dissolved in PBLG liquid crystals, enantiomers are not oriented in the same way.[4] Thus all order-dependant interactions observed by NMR spectroscopy—namely, the chemical shift anisotropies, the dipolar couplings, and the quadrupolar splittings for nuclei with $I > 1/2$, such as deuterium—are affected. With numerous examples, including isotopic chirality, we concluded that this method was more powerful and more general for enantiomeric analysis than any other NMR method.[5]

Induced orientation in liquid crystals is strongly dependent on the shape of the dissolved molecule.[6] Consequently we raised the point whether the molecular order parameters, to which NMR interactions are related, could be used to differentiate molecules that have different shapes. In other words, can NMR spectroscopy be used for shape recognition in liquid crystals?

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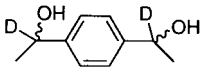
Thinking in terms of shape recognition led us to the problem of distinguishing diastereomers. One could then notice that classical NMR spectroscopy in isotropic solvents does resolve spectra of diastereomers very well, and that no fancy NMR technique in liquid crystals is needed. This remark is true when chiral centers are close to each other. However, when they are separated from each other by four bonds or more this no longer applies, and the problem of distinguishing and attributing *threo-erythro/meso* diastereomers with remote asymmetric groups is exceedingly difficult. Consequently we decided to explore the potential of NMR spectroscopy in PBLG liquid crystals to distinguish diastereomers with remote chiral centers.

We decided to study α,α'-dideuterated diol **1**, which exists as the *R*,*R* and *S*,*S* enantiomers and the *R*,*S* *meso* form. The reason is that Takemura et al. reported that the *meso* and *threo* diastereomers of the non-deuterated analogue, where the asymmetric carbon atoms are five bonds apart, cannot be distinguished by ^{1}H NMR at 500 MHz or ^{13}C NMR spectroscopy at 125 MHz.[7] Wallace et al. distinguished such stereoisomers by NMR spectroscopy[8] with their bis(α-methoxy-α-trifluoromethylphenylacetyl) (MTPA) ester derivatives.[9] Still the differences observed were extremely small.[8] Does NMR spectroscopy in PBLG liquid crystals provide an efficient tool to distinguish directly all the stereoisomers for such diols?



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Reduction of 1,4-diacetylbenzene with $NaBD_4$ yielded easily a statistical mixture (25/25/50) of the *R*,*R*/*S*,*S*/*R*,*S* isomers of **1**. Figure 1a shows the ^{1}H-decoupled ^{2}H NMR spectrum of this mixture in the PBLG/THF liquid crystalline solvent.[10] The spectrum contains four quadrupolar doublets with the same intensities. As each kind of deuterium atom produces a doublet in the ^{2}H NMR spectrum measured in PBLG liquid crystals, the interpretation is the following: For the (*R*,*R*)-diol, the two deuterium atoms are homotopic (C_2 axis of symmetry), and thus they are magnetically equivalent. Consequently we expect a single doublet, of intensity 2, for this molecule. For the same reason, the *S*,*S* isomer will also furnish a single doublet, of equal intensity but with a different splitting from the signal for the *R*,*R* isomer because of the chiral discrimination. In the achiral *R*,*S* *meso* isomer, things are different. The deuterium nuclei are enantiotopic because they are only related through a symmetry plane. We have recently shown that enantiotopic nuclei are not equivalent in this medium, in contrast to the case of isotropic solvents in classical NMR spectroscopy.[5a, 11] Besides, the probability of obtaining the *R*,*S* form upon reduction of 1,4-diacetylbenzene is twice that of the *R*,*R* or *S*,*S* isomers. Consequently, we expect two doublets, of intensity 2, for this *meso* diol, one doublet for the pro-*R* and one doublet for the pro-*S* deuterium atoms.

To check this interpretation, a mixture of enantiomerically pure (*S*,*S*)-diol[12] with some *R*,*S* diastereomer (*S*,*S*/*R*,*S* = 85/15; Figure 1b) was isolated by chromatography on silica gel of the mixture obtained by transesterification of isopropenyl acetate with the statistical mixture of diol **1** in the presence of the lipase from *pseudomonas cepacia*.[13] To the latter was

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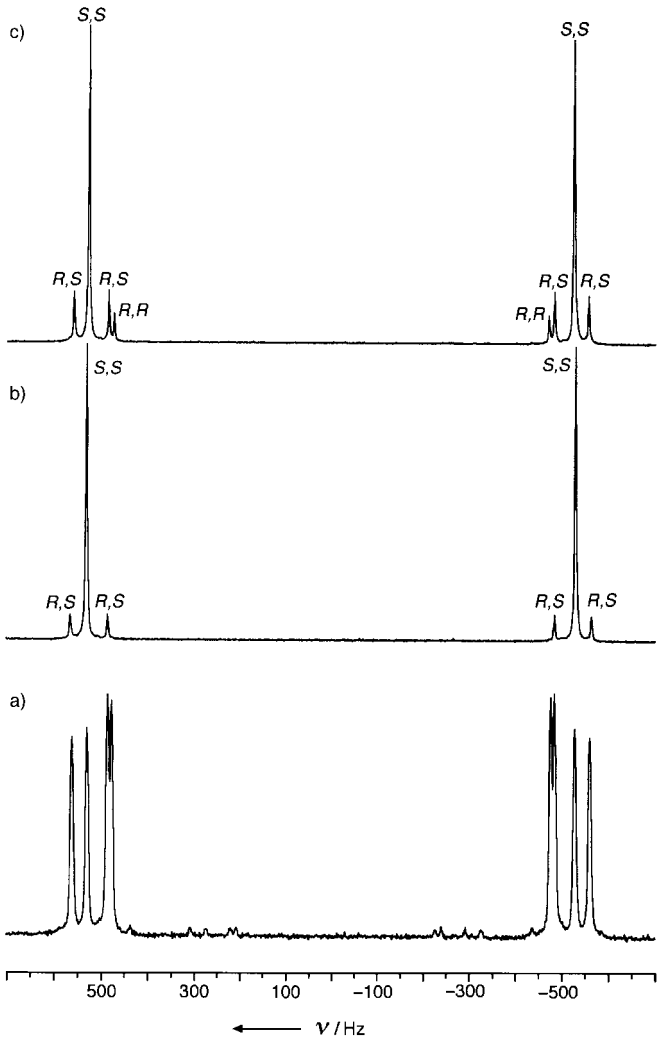


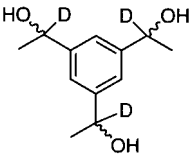
Figure 1. ^{1}H-decoupled ^{2}H NMR spectrum in PBLG/THF (28.0 wt% PBLG) at $T = 320$ K of a) a statistical mixture of stereoisomers of diol **1**, b) an enantiomerically pure and diastereomerically enriched mixture of diol **1** (*S*,*S*/*R*,*S* = 85/15), and c) an enantiomerically and diastereomerically enriched mixture of diol **1** (*threo*/*meso* = 73/27; *ee* = 85%). See text for details.

added a small amount of the statistical mixture of diol **1**. The ^{2}H NMR spectrum of this sample in PBLG/THF is presented in Figure 1c. It is clear that there is one doublet (the small "inner" peaks) for the *R*,*R* isomer, one doublet for the *S*,*S* isomer (the most intense peaks), and two equally intense doublets for the (*R*,*S*) *meso* diol.

This result is really important, and we may summarize it as follows:

a) ^{2}H NMR spectroscopy in chiral liquid crystals allows the discrimination of all the possible stereoisomers of diol **1**, which classical NMR spectroscopy cannot distinguish. Noticeably the diastereomers *R*,*R*/*S*,*S* and *R*,*S* are discriminated because molecules which do not have the same "shape" are not ordered in the same way in the liquid crystalline solvent.

b) Not only can the diastereomers be distinguished in the spectrum, but it is trivial to determine unambiguously which signals belong to the *meso* and *threo* compounds for a nonracemic mixture. Thus, only the *R*,*S* isomer can give two doublets of equal intensities. The *R*,*R* and *S*,*S* derivatives cannot give more than a single doublet each.



2

The above conclusions are totally general, as can be seen on the next example. The preparation of triol **2** by reduction of 1,3,5-triacetylbenzene should give a mixture of the four stereoisomers *R*,*R*,*R*/*R*,*R*,*S*/*S*,*S*,*R*/*S*,*S*,*S* in the statistical ratio 1/3/3/1. The ^{2}H NMR spectrum of such a mixture in PBLG/DMF liquid crystals is reported in Figure 2. As above, we

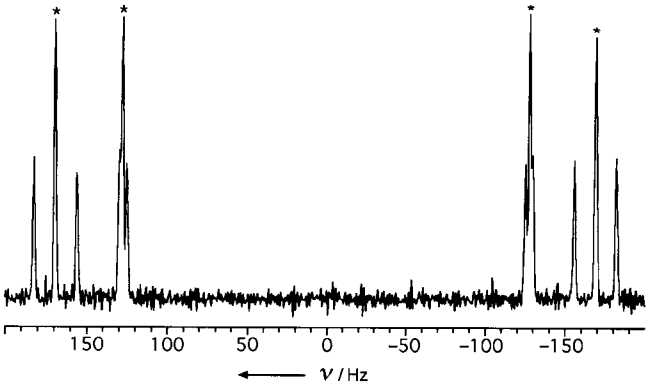
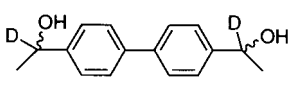


Figure 2. ^{1}H-decoupled ^{2}H NMR spectrum of triol **2** in PBLG/DMF (31.3 wt% PBLG) at $T = 340$ K. Six doublets are observed, among which the tallest (marked with *) belong to the *R*,*R*,*S*/*R*,*S*,*S* diastereomer.

expect a single doublet for the *R*,*R*,*R* isomer of intensity 3 because there are three nondiscernible nuclei and a relative probability of formation of 1. For the *R*,*R*,*S* isomer two quadrupolar doublets are expected, of relative intensity 2:1 and the relative probability of 3, thus giving one doublet of intensity 6 for the *R* deuterium atoms and another doublet of intensity 3 for the *S* deuterium atom. The multiplicity and intensity expected for the signals of the *S*,*S*,*R* (or the *S*,*S*,*S*) enantiomer will be the same as those for the *R*,*R*,*S* (or the *R*,*R*,*R*) enantiomer, but with different splittings because of the chiral discrimination of the solvent. Therefore, a spectrum with six doublets is expected for a statistical mixture of the four stereoisomers, four of them having the same intensity and two of doubled intensity. One can see in Figure 2 that we indeed obtain such a spectrum.

In this spectrum the tallest peaks have to be attributed to the *R*,*R*,*S* and *S*,*S*,*R* stereoisomers; there is no assumption to be made, and this attribution is obtained with pure logic. Besides, with an enantiomerically and diastereomerically enriched sample of stereoisomers of **2**, ^{2}H NMR spectroscopy in PBLG liquid crystals will furnish the diastereomeric excess and the enantiomeric excess for each diastereomer.

To put the discrimination power of this nonconventional NMR technique to the test, we decided to study diol **3**. It must be remembered that there are no direct spectroscopic methods to distinguish these diastereomers where the asymmetric carbon atoms are nine bonds apart. Even



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the NMR spectra of the bis-MTPA derivatives showed no difference between the stereoisomers.[8] The ^{2}H NMR spectrum of a statistical mixture of the three stereoisomers *R*,*R*/*S*,*S* and *R*,*S* is shown in Figure 3. Even though the line splittings

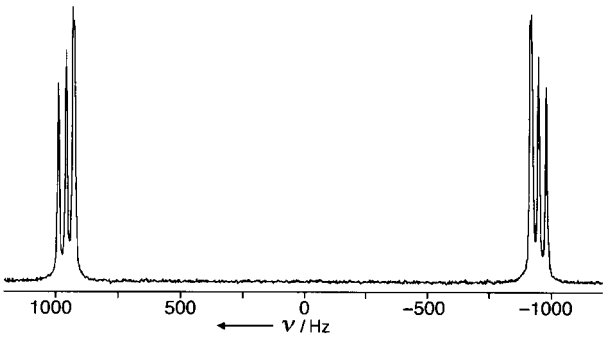

Figure 3. ^{1}H-decoupled ^{2}H NMR spectrum of diol **3** in PBLG/THF (27.5 wt% PBLG) at $T = 302$ K.

are not tremendous, the technique discriminates all the stereoisomers and would allow again a measurement of any diastereomeric and enantiomeric excess using deconvolution tools.

It has been demonstrated that ^{1}H-decoupled ^{2}H NMR spectroscopy with a chiral liquid crystalline solvent allows the NMR spectroscopic discrimination of diastereomers with remote asymmetric centers up to nine bonds apart. This discrimination originates in the difference in the molecular order parameters of the stereoisomers. To the extent where order parameters reflect the shape of a molecule, this opens up the idea of shape-recognition NMR spectroscopy. Furthermore, we have shown with a few examples that the spectral multiplicity of the ^{2}H NMR spectra leads to the unambiguous assignment of the resonances of each diastereomer.

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[1] E. Lafontaine, J. P. Bayle, J. Courtieu, *J. Am. Chem. Soc.* **1989**, *111*, 8294 – 8296.
[2] J. P. Bayle, J. Courtieu, E. Gabetty, A. Loewenstein, J. M. Péchiné, *New J. Chem.* **1992**, *16*, 837 – 838.
[3] a) A. Elliot, E. J. Ambrose, *Discuss. Faraday Soc.* **1950**, *9*, 246; b) C. Robinson, *Trans. Faraday. Soc.* **1956**, *52*, 571 – 592; c) C. Robinson, *Mol. Cryst.* **1966**, *1*, 467 – 494.
[4] P. Lesot, Y. Gounelle, D. Merlet, A. Loewenstein, J. Courtieu, *J. Phys. Chem.* **1995**, *99*, 14871 – 14875.
[5] a) A. Meddour, I. Canet, A. Loewenstein, J. M. Péchiné, J. Courtieu, *J. Am. Chem. Soc.* **1994**, *116*, 9652 – 9656; b) I. Canet, J. Courtieu, A. Loewenstein, A. Meddour, J. M. Péchiné, *J. Am. Chem. Soc.* **1995**, *117*, 6520 – 6526; c) A. Meddour, P. Berdague, A. Hedli, J. Courtieu, P. Lesot, *J. Am. Chem. Soc.* **1997**, *119*, 4502 – 4508; d) M. Jakubcova, A. Meddour, J. M. Péchiné, A. Baklouti, J. Courtieu, *J. Fluorine Chem.* **1997**, *86*, 149 – 153.
[6] E. E. Burnell, C. A. de Lange, *Chem. Rev.* **1998**, *98*, 2359 – 2387.
[7] T. Takemura, K. Saito, S. Nakazawa, N. Mori, *Tetrahedron Lett.* **1992**, *33*, 6335 – 6338.
[8] J. S. Wallace, B. W. Baldwin, C. J. Morrow, *J. Org. Chem.* **1992**, *57*, 5231 – 5239.
[9] a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543 – 2549; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512 – 519.
[10] Experimental details for sample preparation and NMR measurements have been reported.[5a]
[11] D. Merlet, A. Loewenstein, W. Smadja, J. Courtieu, P. Lesot, *J. Am. Chem. Soc.* **1998**, *120*, 963 – 969.
[12] The absolute configuration of the isolated enantiomer was deduced from the sign of its optical rotation: $[\alpha]_D^{amb} = -80.2$ ($c = 1.7$ in acetone). This value is consistent with that reported by Wallace et al.[8]
[13] R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656 – 2665.

Photoregulation of the Formation and Dissociation of a DNA Duplex by Using the *cis*–*trans* Isomerization of Azobenzene**

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Recently, much interest has been focused on chemical modifications of oligonucleotides,[1] and various types of functionalization have been successfully accomplished. However, there has been no report on the preparation of a modified oligonucleotide that can reversibly alter the duplex-forming activity in response to an external stimulus. If one can convert double-stranded DNA into two single strands (and vice versa) at a predetermined place and time, a number of promising applications, either in vivo or in vitro, would appear.[2] Here we report the first photoregulation of the duplex-forming activity of an oligonucleotide. The melting temperature of the duplex (T_m) is notably changed when the azobenzene moiety in the side chain undergoes *cis*–*trans* isomerization. The formation of the DNA duplex and its dissociation are successfully modulated simply by irradiating with either visible or UV light.

The modified oligonucleotide 5′-AAAXAAAA-3′ (**1**, X = the residue carrying an azobenzene moiety in the side chain; see Scheme 1) was synthesized as described previously.[3, 4] The two diastereomers **1a** and **1b**, based on the chirality of the

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