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Analysis of the Diastereoselectivity of a Diels-Alder Cycloaddition through ^{2}H NMR in chiral liquid crystals

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Abstract : Deuterium NMR in chiral liquid crystal solvents is used to measure the diastereoselectivity in asymmetric Diels-Alder cycloadditions on 2-alkoxy-2-vinyl-1,3-dioxolanes issued from chiral 1,2 diols. Copyright © 1996 Published by Elsevier Science Ltd

The development of cationic Diels-Alder reactions mediated by chiral heterocycles seemed to be of interest in regard of the great reactivity of such species.[1] In this respect, 2-alkenyl-1,3-dioxolane-2-ylium cations appeared as promising candidates for such reactions.[2] Recently, Y. Langlois et al. have studied such an asymmetric Diels-Alder reaction activated by a Lewis acid and have obtained compounds of general type **A**:


d.e. = 25-68%
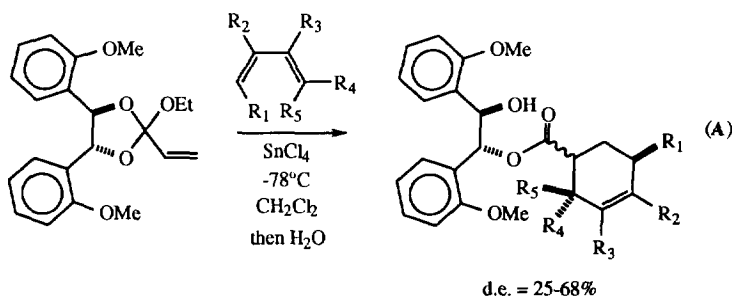
NMR spectra (^{1}H and [13]C-{H}) of obtained diastereoisomers do not always show differences large enough to measure a diastereoisomeric excess and there is still a problem to identify the absolute configuration of the newly created stereogenic centre. Diastereoisomeric excess can however be determined indirectly by measure of enantiomeric excess of derivatives of Diels-Alder adducts.

On the other hand, an original method to obtain enantiomeric excess has recently been proposed by Courtieu *et al* [3-5]. This method consists in the use of chiral liquid crystals as NMR solvents. These are obtained by dissolution, in different organic solvents, of the synthetic polypeptide, the poly γ-benzyl L-glutamate (PBLG). When dissolved in such anisotropic media, it has been demonstrated that two enantiomers

are differently oriented.[3] As a direct consequence of this differential ordering effect of the enantiomers (DOE), the anisotropic NMR interactions (namely the quadrupolar and dipolar couplings and the chemical shifts anisotropies) are different for optical isomers. This technique appeared to be particularly efficient and sensitive when observing the ^{2}H NMR quadrupolar splittings in the case of deuterated molecules.

The work we would like to present herein concerns the use of this technique to solve the problem of cycloaddition enantioselectivity (*vide supra*). Deuterium NMR being the most sensitive to this orientation phenomenon, compounds of type **A** were reduced with lithium aluminium deuteride (LiAlD$_4$). The so-obtained alcohols possess two diastereotopic deuterons:
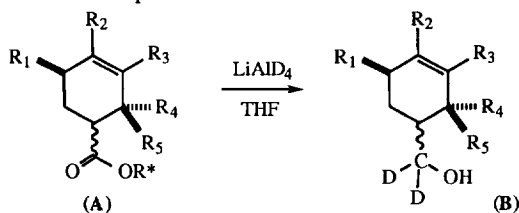
Results obtained by ^{2}H NMR in nematic chiral liquid crystals with primary alcohols are presented in table 1. One characteristic spectrum is given in figure 1.

NMR spectra show a discrimination in the quadrupolar couplings of enantiomers for all the studied compounds. The splitting difference can exceed 100 Hz. Furthermore, the presence of two non-equivalent deuteria increases the probability of resolving the enantiomers. For instance, in the 260 K spectrum of mixture **B2** no discrimination was observed on one of the deuteria while the second one showed a difference in the quadrupolar couplings of 93 Hz equivalent to a discrimination factor $2(\Delta v^M_{;Q1}-\Delta v^m_{;Q2})/\Sigma\Delta v_{;Q}$ equal to 3.33. For the compounds with a reported specific optical rotation, calculated optical purities are also reported bracketed in the last column.

In the table of values, the DOE was defined as the difference between the quadrupolar couplings of the major enantiomer (M) and the minor enantiomer (m) in the mixtures : $(\Delta v^M_{;Q1}-\Delta v^m_{;Q2})$.
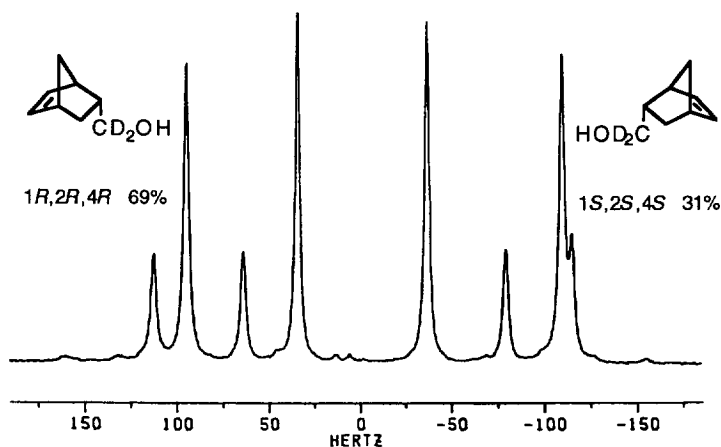

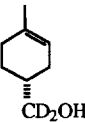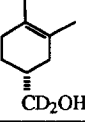Figure 1: ^{2}H NMR spectrum of mixture B7 in nematic chiral liquid crystal PBLG-CH$_2$Cl$_2$.
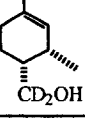
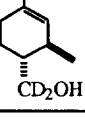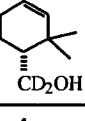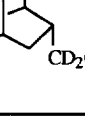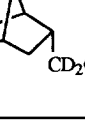|			T(K)	$\Delta v^M{}_{;Q1}$ (Hz)	$\Delta v^m{}_{;Q2}$ (Hz)	$(\Delta v^M{}_{;Q1}-\Delta v^m{}_{;Q2})$ (Hz) DOE	<ee %>
CD$_2$OH	B1	D$_A$	260	259	140	119	25 (29*)
		D$_B$		140	241	-101	
		D$_A$	280	209	68	141	
		D$_B$		66	200	-134	
CD$_2$OH	B2	D$_A$	260	133	40	93	68
		D$_B$		55	55	0	
		D$_A$	280	95	95	0	
		D$_B$		108	27	81	
CD$_2$OH	B3	D$_A$	280	62	110	-48	50
		D$_B$		11	34	-23	
		D$_A$	300	90	68	22	
		D$_B$		3	3	0	
CD$_2$OH	B4	D$_A$	280	126	264	-128	50
		D$_B$		11	140	-129	
CD$_2$OH	B5	D$_A$	300	281	456	-175	36** (impure)
		D$_B$		60	92	-32	
CD$_2$OH	B6	D$_A$	300	184	169	15	40 (42)
		D$_B$		114	17	97	
CD$_2$OH	B7	D$_A$	300	68	164	-96	38 (28***)
		D$_B$		160	67	93	

Table 1: Quadrupolar splittings of enantiomers of derivatives Bn in liquid crystal PBLG-CH$_2$Cl$_2$. Mass ratio of PBLG (DP~1279) was equal to ~ 13.8%. $\Delta v^M{}_{;Q1}$ (respectively $\Delta v^m{}_{;Q2}$) is the quadrupolar coupling of the major enantiomer (respectively minor). <ee %> is the average value obtained from measures of enantiomeric excess, by use of several well separated signals. Enantiomeric excesses estimated by specific rotations are given in brackets if the $[\alpha]_D$ of the corresponding compound is known. * Correlation was made by comparison with (+) α-terpineol. ** In this case the reaction gave a mixture from which signals corresponding to compound B5 could be identified with their chemical shifts and compared with the racemic compound synthesised using standard methods. *** The difference between the ee measured by ^{2}H NMR and specific rotation is due to the presence of a chiral unidentified impurity.

Conclusion

Deuterium NMR in nematic chiral liquid crystals made of PBLG-CH_2Cl_2 mixtures has been applied successfully to resolve the enantiomers issued from an asymmetric Diels-Alder reaction. Such discrimination of the deuterated enantiomers, originating from the differential ordering effect, allows a reliable measure of the enantiomeric excess in all cases and consequently provides a good measure of the stereochemistry of the Diels-Alder reaction. The use of this technique "routinely" for studies of asymmetric reactions proved to be easy and highly competitive with any of the other conventional NMR methods.

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