



An achiral deuterated derivatizing agent for enantiomeric analysis through NMR in a liquid crystalline solvent

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Abstract: The application of a 'deuterium probe' for the enantiomeric analysis of chiral amines, aminoacids and alcohols is proposed. The probe is the perdeuterated benzoyl fragment which can easily and reversibly be attached to the corresponding materials. The analysis is performed through measurements of the differential ordering effect (DOE) in the deuterium NMR of the chiral material dissolved in a cholesteric–nematic liquid crystalline system. Since all the chiral compounds which we studied were not racemic, the assignments of the observed DOE's to the enantiomers enabled us to draw tentative conclusions relating the results to the absolute configurations. This may open the way for the empirical derivation of absolute configurations of enantiomers from DOE measurements. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

A novel technique for enantiomeric analysis through nuclear magnetic resonance (NMR) spectroscopy has recently been developed by Courtieu *et al.*^{1,2} In this method chiral materials are dissolved in a cholesteric–nematic liquid crystal composed of poly- γ -benzyl-L-glutamate (PBLG) in an organic solvent such as dichloromethane. In this solvent, the two enantiomers are oriented differently. This difference in the orientations is observed in the NMR spectra through the orientation dependent interactions such as the dipolar couplings, the chemical shift anisotropies for spins=1/2, or quadrupolar splittings for spins >1/2. Various nuclei have been used in these studies such as ¹H, ¹³C^{2,3}, but most results have been obtained through the use of deuterium (spin=1) NMR^{1,2}. This is so because the quadrupolar interactions are large and are manifested through the observation of large quadrupolar splittings ($\Delta\nu_Q$). These splittings are given by the product of the deuterium quadrupole coupling constant (*ca.* 170 kHz for the C–D bonds) and the order parameters of the electric field gradient at the ²H site. A slight difference in the orientations of the **R** and **S** enantiomers gives rise to a noticeable difference in the quadrupolar splitting for each enantiomer $\{\Delta\nu_Q(\mathbf{S}) - \Delta\nu_Q(\mathbf{R})\}$. We denote this difference in the measured quadrupolar splittings as the differential ordering effect (DOE).

This method is very efficient for chiral discrimination and resolves even small enantiodifferentiating groups such as those arising from isotopic substitution⁴. Furthermore, this method has the great advantage that the measured deuterium does not necessarily have to be attached to the stereogenic centre but can be positioned anywhere in the molecule.

A noticeable disadvantage in the use of deuterium NMR for enantiomeric analysis is the need to perform the deuterium labelling which sometimes requires a complex synthetic procedure. In order to facilitate this tedious process, we propose here a method which permits the reversible attachment of a deuterium probe to certain classes of molecules, but unlike the classical Chiral Derivatizing Agents (CDA), the Achiral Deuterated Derivatizing Agents (ADDA) do not need to be chiral as it is the cholesteric solvent which is responsible for the discrimination of enantiomers. We have chosen the

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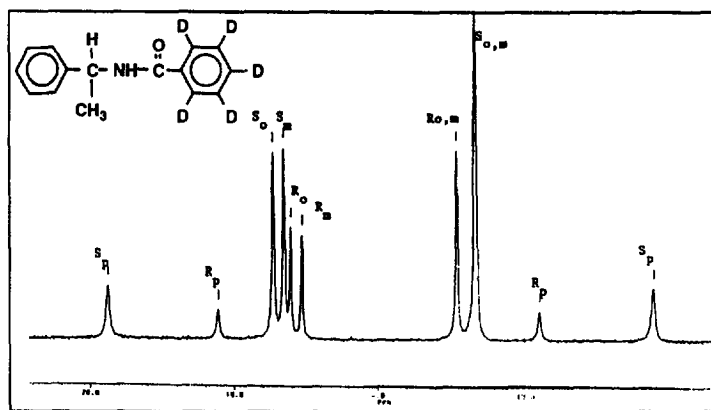


Figure 1. The proton decoupled ^2H NMR spectrum of *N*(1-phenylethyl)-5d₅-benzamide (66% *S* and 34% *R*); 302 K; solvent PBLG/CH₂Cl₂.

pentadeuterated benzoyl fragment (C₆D₅-CO-) for this purpose because it has the following useful characteristics:

- The benzoyl fragment can be easily attached to any alcohol or amine and the reaction is reversible since benzoic esters and amides can readily be reconverted to the starting materials. This may be important in cases when the need to retrieve the chiral material arises.
- The benzoyl fragment is achiral and therefore, unlike in the use of chiral derivatizing agents, no kinetic discrimination can happen⁵.
- The pentadeuterated benzoyl fragment possesses three different types of deuterium atoms which are positioned in the ortho, meta or para position with respect to the carbonyl group. Consequently, three different quadrupolar doublets show in the deuterium NMR spectra. This provides the possibility to measure the DOE on three different sites in a molecule.
- Finally, the benzoyl group, which is a fairly bulky substituent, enhances and often predominates the magnitude of the molecular order of the solute in the liquid crystal. Thus we expect that all benzoyl derivatives would have similar orientations in the liquid crystal and consequently similar differences in the orientations in pairs of enantiomers. If this hypothesis is valid, the results in chemically similar series could be used for the purpose of finding an empirical correlation between the NMR data and the absolute configurations of the products. Such an attempt is presented in this article.

Results and discussion

A typical spectrum is shown in Figure 1.

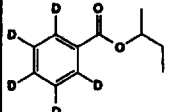
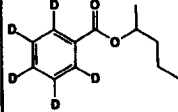
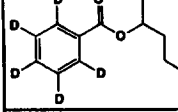
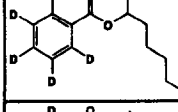
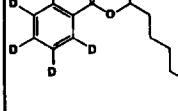
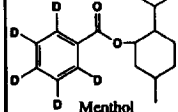
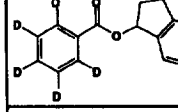
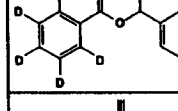
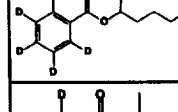
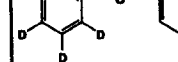
The resonances of the spectrum presented in Figure 1 are assigned as follows: para deuterons are easy to assign from integration and their splittings are always the largest. The resonances of the ortho deuterons (δ_o) are shifted to a higher magnetic field than the meta deuterons (δ_m). A difference ($\delta_o - \delta_m$) of about 15 Hz was found for the amines and aminoacids and of about 23 Hz for the alcohols. As each sample was made of a known composition of both enantiomers, peak assignment for *R* and *S* was simple through peak integration. Within experimental errors ($\pm 3\%$), the integration values were always consistent with the known enantiomeric excess. This confirms that no racemization occurred when the benzoyl group was attached to the chiral molecules.

Alcohols

The results of the ^2H NMR spectra for the alcohol derivatives are summarised in Table 1.

For the majority of benzoic esters, the *R* enantiomers (Ph(d₅)-CO-O-CHRR') exhibit larger

Table 1. Quadrupolar splittings $\Delta\nu_Q(\text{S})$, $\Delta\nu_Q(\text{R})$, and the difference $\{\Delta\nu_Q(\text{S})-\Delta\nu_Q(\text{R})\}$ for the ortho, meta and para deuterons for the R and S benzoic esters at 302 K. The absolute configurations of the enantiomer which exhibits the largest para ^2H splitting are also included

| Esters | n^{r} | D | $\Delta\nu_Q(\text{S})$ (Hz) | $\Delta\nu_Q(\text{R})$ (Hz) | $\Delta\nu_Q(\text{S}) - \Delta\nu_Q(\text{R})$ (Hz) | Config. where $\Delta\nu_Q(\text{D}_{\text{para}})$ is the largest |
|------------------------------------------------------------------------------------------------|----------------|-------------|---------------------------------|---------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------|
|  | 1 | p o m | 941 18 10 | 969 28 23 | -28 -10 -13 | R |
|  | 2 | p o m | 967 39 28 | 1021 74 68 | -54 -35 -40 | R |
|  | 3 | p o m | 800 36 30 | 854 79 79 | -54 -43 -49 | R |
|  | 4 | p o m | 681 44 39 | 761 97 92 | -80 -53 -53 | R |
|  | 5 | p o m | 637 40 34 | 738 99 94 | -101 -59 -60 | R |
|  Menthol | 6 | p o m | 907 279 272 | 949 279 272 | -42 0 0 | R |
|  | 7 | p o m | 774 128 131 | 811 98 102 | -37 30 29 | R |
|  | 8 | p o m | 989 86 90 | 971 111 115 | 18 -25 -25 | S (R_v) |
|  | 9 | p o m | 928 110 107 | 741 141 145 | 187 -31 -38 | S (R_v) |
|  | 10 | p o m | 897 0 6 | 809 15 9 | 88 -15 -3 | S (S_v) |

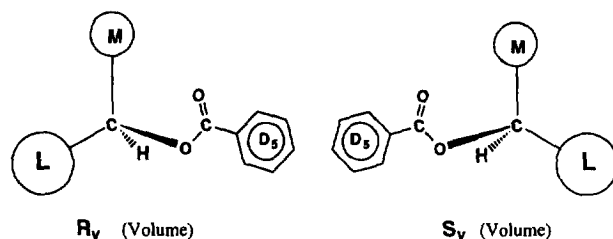


Figure 2. S_V and R_V enantiomer configurations of benzoic esters taking into account the volume of substituents (H is the smallest group, the benzoyl the largest, the remaining two substituents are denoted as M=medium and L=large)

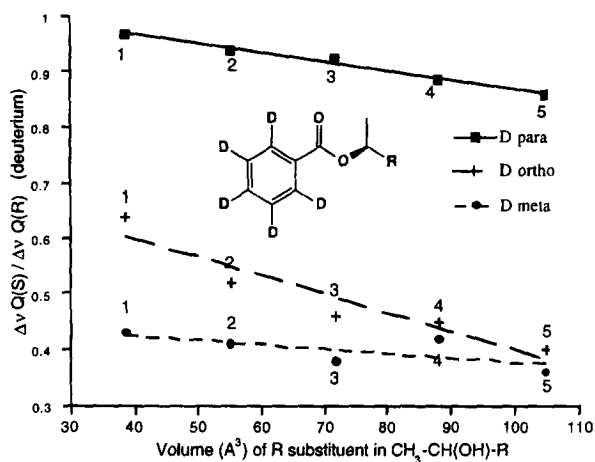


Figure 3. The correlation between the volumes of R substituents (in \AA^3) and the quadrupolar splitting ratio $\Delta\nu_Q(S)/\Delta\nu_Q(R)$ for the secondary methyl alcohols, where $R=C_nH_{2n+1}$. The numbers refer to compounds from Table 1

splittings than the S . Exceptions are when the aliphatic R substituent changes to aromatic (#8 #10) or acetylenic (#9).

When the volumes and steric crowding factors of the substituents^{6,7} are considered, instead of the accepted chiral notation suggested by Cahn, Ingold and Prelog⁸, it is possible to define 'volume absolute configuration' R_V and S_V (Figure 2).

Using this hierarchy to define absolute configurations our data appear more consistent. For compounds #8 and #9 the para deuterium of R_V enantiomers have the largest quadrupolar splitting. Only the compound #10 does not fit into this empirical definition, but it should be remarked that in this compound the volume comparison between substituents is difficult, because we have to compare the volumes of a perdeuterated benzoyl and a phenyl group.

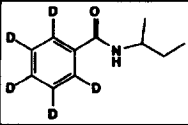
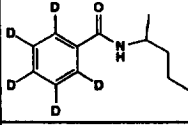
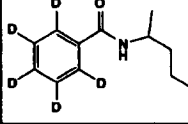
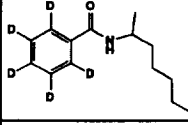
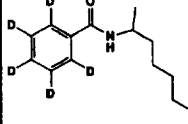
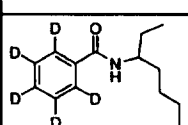
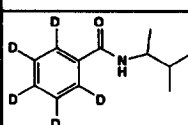
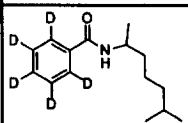
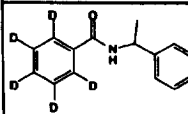
For the secondary methyl alcohols, $RCH(CH_3)OH$, where $R=C_nH_{2n+1}$ with $n=2,3,4,5,6$, we observe a good correlation between the volumes⁷ of R substituents (in \AA^3) and the ratio of the quadrupolar splittings (*c.f.* Figure 3).

Amines

The 2H NMR results for the amine derivatives are summarised in Table 2.

Differences in the quadrupolar splittings are larger for the amines than for the alcohols. Furthermore, the splittings of the S products are always larger than those of the R . This result is independent of the position of the deuterium (ortho, meta or para) in the molecules. Note that for compound #17, the

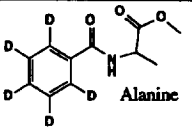
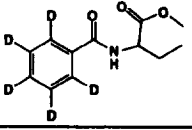
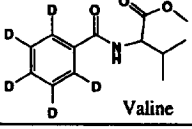
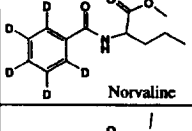
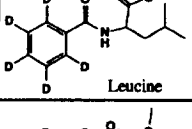
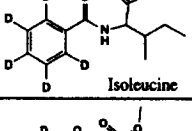
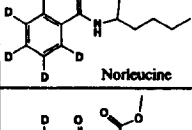
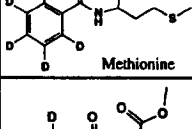
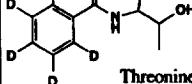
Table 2. Quadrupolar splittings $\Delta\nu_Q(S)$, $\Delta\nu_Q(R)$ and the difference $\{\Delta\nu_Q(S)-\Delta\nu_Q(R)\}$ of the ortho, meta and para deuterium for the R and S benzoic amides at 302 K. Also given are the absolute configurations of the enantiomer which presents the largest para ^2H splittings

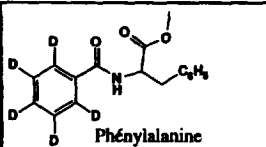
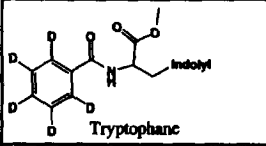
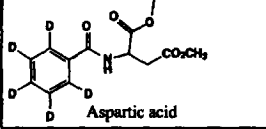
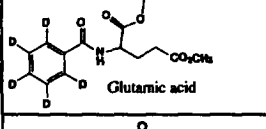
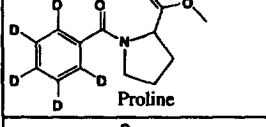
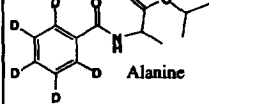
| Amides | ir ^a | D | $\Delta\nu_Q(S)$ (Hz) | $\Delta\nu_Q(R)$ (Hz) | $\Delta\nu_Q(S) - \Delta\nu_Q(R)$ (Hz) | Config. where $\Delta\nu_Q(D_{p,m,o})$ are the largest |
|-------------------------------------------------------------------------------------|-----------------|-------------|--------------------------|--------------------------|-------------------------------------------|--------------------------------------------------------------|
|  | 11 | p o m | 891 317 300 | 849 249 233 | 42 68 67 | S |
|  | 12 | p o m | 830 308 286 | 700 242 222 | 130 66 64 | S |
|  | 13 | p o m | 668 216 118 | 450 167 99 | 218 49 19 | S |
|  | 14 | p o m | 784 268 245 | 495 221 194 | 289 47 51 | S |
|  | 15 | p o m | 718 263 235 | 436 218 190 | 282 45 45 | S |
|  | 16 | p o m | 632 297 274 | 410 284 261 | 222 13 13 | S |
|  | 17 | p o m | 1020 363 339 | 1020 253 230 | 0 110 109 | S |
|  | 18 | p o m | 589 191 168 | 328 155 127 | 261 36 41 | S |
|  | 19 | p o m | 1440 538 509 | 854 443 413 | 586 95 96 | S |

para deuterium signal shows no separation, while the ortho and meta deuterium present well resolved peaks. This shows the usefulness of having several deuterons in the ADDA.

For the secondary methyl amines, $\text{RCH}(\text{CH}_3)\text{NH}_2$, where $\text{R}=\text{C}_n\text{H}_{2n+1}$ with $n=2,3,4,5,6$, we observe a good correlation between the volumes⁷ (in \AA^3), of R substituents and the para ^2H quadrupolar splittings. This is presented in Figure 4.

Table 3. Quadrupolar splittings $\Delta\nu_Q(S)$, $\Delta\nu_Q(R)$, and the difference $(\Delta\nu_Q(S)-\Delta\nu_Q(R))$ of the ortho, meta and para deuterium from the R and S benzoic amidoesters at 302 K. The absolute configurations of the enantiomer which presents the largest para ^2H splitting are included (nr=not resolved)

| Aminoacid derivatives | nr ^a | D | $\Delta\nu_Q(S)$ (Hz) | $\Delta\nu_Q(R)$ (Hz) | $\Delta\nu_Q(S) - \Delta\nu_Q(R)$ (Hz) | Config. where $\Delta\nu_Q(D_{\text{para}})$ is the largest |
|---------------------------------------------------------------------------------------------------|-----------------|----------|--------------------------|--------------------------|-------------------------------------------|-------------------------------------------------------------------|
|  Alanine | 20 | <i>p</i> | 708 | 438 | 270 | S |
| <i>o</i> | | 154 | 120 | 34 | | |
| <i>m</i> | | 149 | 107 | 42 | | |
|  Valine | 21 | <i>p</i> | 686 | 457 | 229 | S |
| <i>o</i> | | 142 | 135 | 7 | | |
| <i>m</i> | | 133 | 121 | 12 | | |
|  Norvaline | 22 | <i>p</i> | 617 | 402 | 215 | S |
| <i>o</i> | | 115 | 124 | -9 | | |
| <i>m</i> | | 108 | 111 | -3 | | |
|  Leucine | 23 | <i>p</i> | 565 | 364 | 201 | S |
| <i>o</i> | | 146 | 132 | 14 | | |
| <i>m</i> | | 135 | 117 | 18 | | |
|  Isoleucine | 24 | <i>p</i> | 564 | 348 | 216 | S |
| <i>o</i> | | 169 | 167 | 2 | | |
| <i>m</i> | | 155 | 146 | 9 | | |
|  Norleucine | 25 | <i>p</i> | 589 | 400 | 189 | S |
| <i>o</i> | | 93 | 102 | -9 | | |
| <i>m</i> | | 83 | 89 | -6 | | |
|  Methionine | 26 | <i>p</i> | 428 | 299 | 129 | S |
| <i>o</i> | | 131 | 113 | 18 | | |
| <i>m</i> | | 118 | 99 | 19 | | |
|  Threonine | 27 | <i>p</i> | 520 | 381 | 139 | S |
| <i>o</i> | | 147 | 120 | 27 | | |
| <i>m</i> | | 135 | 103 | 32 | | |
|  Threonine | 28 | <i>p</i> | 1100 | 753 | 347 | S |
| <i>o</i> | | 375 | 324 | 51 | | |
| <i>m</i> | | 379 | 321 | 58 | | |

| | | | | | | |
|----------------------------------------------------------------------------------------------------|----|----------------------------------|-------------------|-------------------|-------------------|---|
|  Phenylalanine | 29 | <i>p</i> <i>o</i> <i>m</i> | 463 82 72 | 253 98 84 | 210 -16 -12 | S |
|  Tryptophan | 30 | <i>p</i> <i>o</i> <i>m</i> | 714 168 161 | 443 168 161 | 271 0 0 | S |
|  Aspartic acid | 31 | <i>p</i> <i>o</i> <i>m</i> | 361 34 24 | 224 15 4 | 137 19 20 | S |
|  Glutamic acid | 32 | <i>p</i> <i>o</i> <i>m</i> | 368 77 67 | 288 55 43 | 80 22 24 | S |
|  Proline | 33 | <i>p</i> <i>o</i> <i>m</i> | 612 nr nr | 516 nr nr | 96 - - | S |
|  Alanine | 34 | <i>p</i> <i>o</i> <i>m</i> | 850 123 110 | 643 97 82 | 207 26 28 | S |

Aminoacids

The ^2H NMR results for the aminoacid derivatives are presented in Table 3.

For the 15 aminoacids under study, the most significant differences in splittings are observed for the para deuterons, where the para ^2H of the S enantiomer (then the L aminoacid) is always the largest. However, in contrast to the amines, this empirical rule does not apply to the ortho and para deuterons. It must be noticed that alanine derivatives #20 and #34 present similar NMR data which appear to be independent of the ester group (methyl ester #20 and isopropyl ester #34).

For the amidoesters, Figure 5 shows that for the para deuterium, the ratio $\Delta\nu_Q(\text{S})/\Delta\nu_Q(\text{R})$ is almost constant for any substituent. In fact for all the $\text{RCH}(\text{NH}_2)\text{COOCH}_3$ aminoesters the R substituent may be considered as 'small' and consequently has no preponderant effect on the orientation of the benzoic amidoesters in the chiral liquid crystal.

A full analysis of the data is not possible because it requires more independent measurements. The knowledge of the precise coordinates of the atoms in the molecules is also needed to calculate the molecular order matrix. Nevertheless, careful inspection of the data presented in the tables, allows us to draw some definite conclusions:

- (1) The values of the $\Delta\nu_Q$ s for the para deuterons are always much larger than for the ortho and meta. From this we can conclude that the direction of the principal axis for the orientation for all molecules is nearly *parallel* to the para axis of the benzoyl group. The ortho and para deuterons exhibit much smaller splittings because their directions, relative to the principal axes, are close to the magic angle⁹.
- (2) The differences $\{\Delta\nu_Q(\text{S}) - \Delta\nu_Q(\text{R})\}_{\text{ortho}} - \{\Delta\nu_Q(\text{S}) - \Delta\nu_Q(\text{R})\}_{\text{meta}}$ are very close to zero, and the

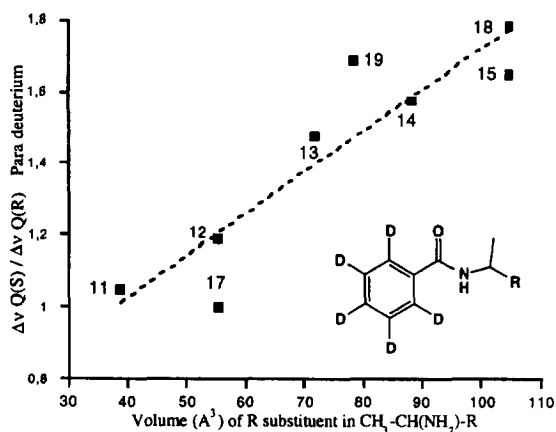


Figure 4. The correlation between the volumes (in \AA^3)⁷ of the R substituent and the para ^2H quadrupolar splitting ratio $\Delta\nu_{\text{Q}}(\text{S})/\Delta\nu_{\text{Q}}(\text{R})$ for the secondary methyl amines $\text{RCH}(\text{CH}_3)\text{NH}_2$, where $\text{R}=\text{C}_n\text{H}_{2n+1}$. The numbers refer to compounds from Table 2.

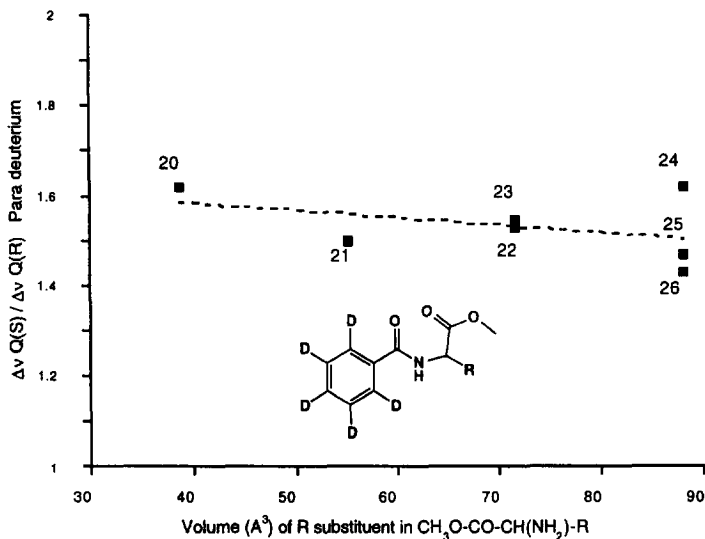


Figure 5. The correlation between the para deuterium splittings ratio, $\Delta\nu_{\text{Q}}(\text{S})/\Delta\nu_{\text{Q}}(\text{R})$, and the volumes of the R substituents (in \AA^3)⁷ for the aminoesters $\text{RCH}(\text{NH}_2)\text{COOCH}_3$. The numbers refer to compounds from Table 3

differences $\{\Delta\nu_{\text{Q}}(\text{S})-\Delta\nu_{\text{Q}}(\text{R})\}_{\text{para}}-\{\Delta\nu_{\text{Q}}(\text{S})-\Delta\nu_{\text{Q}}(\text{R})\}_{\text{ortho}}$ or *meta* have roughly a constant value for any particular series of homologous compounds. From these observations we can conclude that the difference in the molecular ordering between the **R** to the **S** configurations is *small* and approximately *equal* for all molecules. This is the consequence of using a large ADDA such as the benzoyl group which evidently predominates the molecular ordering. The absolute configuration of the enantiomers appears as a small perturbation and to first order, is constant and in the same direction for all members in each series.

These conclusions explain the internal consistencies found in the results and can also account for the rather good empirical correlation which we found between $\Delta\nu_{\text{Qpara}}$ and the absolute configurations, using a volume hierarchy of the substituents.

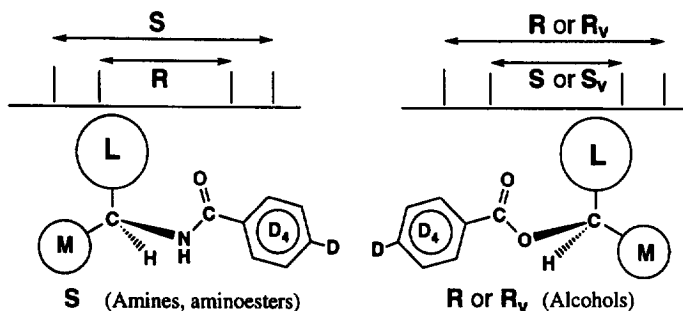


Figure 6. Empirical rule relating the values of para deuterium splittings with the S and R absolute configurations for benzoic amides, amidoesters and esters (or S_v or R_v deduced from the substituent volumes for esters). H is the smallest group, the benzoyl the largest, the remaining two substituents are quoted as L=large and M=medium.

Conclusions

The perdeuterated benzoyl group has been used as an achiral derivatizing agent. It was chosen because the reaction of perdeuterated benzoyl chloride with chiral alcohols, amines or amidoesters offers a simple and reversible synthesis of deuterated derivatives.

The deuterium NMR spectra of these derivatives, using a chiral liquid crystal (PBLG/ CH_2Cl_2) as solvent, show the following results:

- several well resolved peaks for each enantiomer allowing the determination of enantiomeric excesses
- no effect of racemisation during the synthetic procedure which enables the reliable measurements of the enantiomeric excesses. Also, no kinetic chiral discrimination is possible during the synthesis as the benzoyl chloride is achiral
- certain consistencies in the data, particularly concerning the quadrupolar splittings of the para deuterons of the benzoyl ring. For 33 of the 34 products studied here, an empirical rule can be applied which relates the relative values of the para deuterium splittings with the volumes of the different substituents and consequently with a measure for the absolute configurations of the enantiomers. This rule is illustrated through Figure 6.

The quadrupolar splittings of the para deuterons of the benzoyl group are always larger:

- for the S enantiomer in amides and amidoesters
- for the R enantiomer (or R_v) in esters.

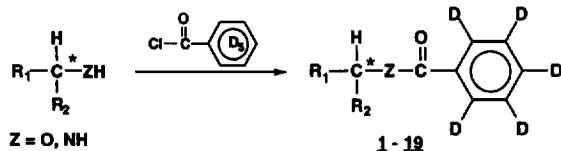
This result however, like every empirical rule, is not necessarily valid for *all* alcohols and amines. Further experimental studies on more compounds as well as theoretical work aimed at a deeper understanding of the differential ordering effect of enantiomers dissolved in a chiral liquid crystal are necessary.

Experimental

Synthesis

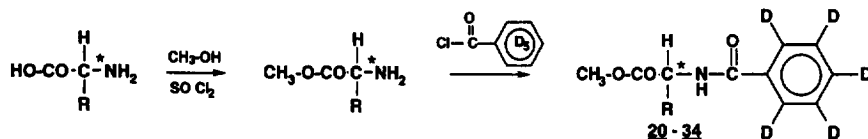
Three series of derivatives have been synthesised by classical methods.

Alcohols and amines



Aminoacids

Aminoacids were first transformed to the corresponding methyl aminoesters, in order to block the carboxylic group. The stereogenic centre of the molecule is not affected by this reaction¹⁰. Then, the reaction with pentadeuterated benzoyl chloride leads to the deuterated amidoester.



Sample preparation

80 mg of PBLG (degree of polymerisation 1183, mol. wt. 150 000–350 000 purchased from Sigma) was weighed into a 5 mm o.d. NMR tube. 20 to 50 mg of enantiomers mixture dissolved in 0.4 ml of dichloromethane were added to the polymer. Mixing and equilibration were achieved through centrifugation of the NMR tube in both directions. The samples must look birefringent and homogeneous. It has already been noted⁴ that the degree of polymerisation of the PBLG can vary from 300 to 1200 without changing the essential properties of the liquid crystalline phase.

NMR measurements

Deuterium NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 38.39 MHz for deuterium resonances. Proton decoupling (WALTZ sequence) was applied. Spectra were recorded at two temperatures: 302K and 310K ($\pm 0.5\text{K}$). The signal to noise ratio was better than 50 with about 100 scans and the line widths less than 3 Hz. The precision of the measurements is estimated at $\pm 3\text{Hz}$ for the para substituted deuterons and $\pm 2\text{Hz}$ for the ortho and meta deuterons.

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