Acetyl-d_3 Chloride: A Convenient Nonchiral Derivatizing Agent (NCDA) for a Facile Enantiomeric Excess Determination of Amines through Deuterium NMR

Jean-Louis Canet,*,† Isabelle Canet,*,‡
Jacques Courtieu,§ Sandrine Da Silva,†
Jacques Gelas,† and Yves Troin†

Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, BP 187, 63174 Aubiere Cedex, France, Laboratoire de Synthèse et Etude de Systèmes à Intérêt Biologique, URA CNRS 485, Université Blaise Pascal, 63177 Aubiere Cedex, France, and Laboratoire de Chimie Structurale Organique, URA CNRS 1384, ICMO, Bât. 410, Université de Paris-Sud, 91405 Orsay Cedex, France

Received June 17, 1996

Introduction

Different methods have been proposed for the determination of the enantiomeric purity of chiral amines by NMR.[1] These methods are mainly based on the use of chiral auxiliaries which react with enantiomers creating diastereomers. Among the chiral auxiliaries, chiral derivatizing agents (CDAs), combined with ^{1}H, ^{19}F, or ^{31}P NMR spectroscopy, are the most widely used.[1,2] However, to be efficient, this technique must fulfill several criteria such as the following: derivatizing agents must be in an enantiomerically pure form; reactions must proceed in high yields, without racemization or enrichment of one diastereomer and must provide pure adducts; the diastereomeric shift difference must be large enough to allow an accurate quantification of an enantiomeric excess.

On the other hand, we previously reported a new and convenient method for enantiomeric analysis through deuterium NMR in a chiral liquid crystal solvent.[3] The latter consists of a chiral nematic liquid crystal, obtained by dissolution of poly(ç-benzyl-L-glutamate), PBLG, in various organic solvents (commonly dichloromethane, 1,2,3-trichloropropane (TCP), or *N*,*N*-dimethylformamide (DMF)). In such anisotropic media, the discrimination originates from the fact that enantiomers interact with the chiral centers of the PBLG helix and, consequently, orient differently in the solvent. In a deuterium NMR spectrum, this differential ordering effect is expressed in different values of the quadrupolar splittings for each enantiomer. Study of a deuteriated chiral solute becomes, therefore, facile as its spectrum, if enantiomers are distinguished, is only composed of two doublets, one for each enantiomer (Figure 1).

Generally, deuterium was incorporated during the synthesis of the substrate, close to the chiral center. However, we have reported the enantiomeric analysis of chiral amino acids, in which solubilization of the compounds in the NMR solvent required the derivatization of the acid function to an ester function.[3c] This derivatization has been made using perdeuteriated methanol (a nonchiral derivatizing agent, NCDA), thus allowing incorporation of deuterium into the molecule in the same step. On the other hand, we previously reported that visualization of the enantiomers of the amines was not possible by our technique, owing to reactions between the amines and PBLG which cause extra lines on the spectra.[3a] Following the success encountered with the amino acids for the visualization of the enantiomers, we decided to apply the same derivatization concept to amines.

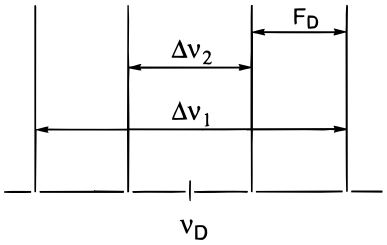
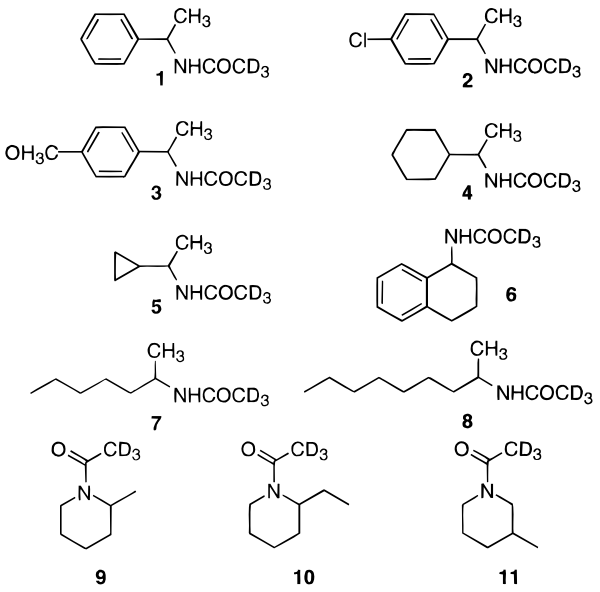


Figure 1. Schematic proton-decoupled deuterium NMR spectra of a monodeuteriated racemic molecule dissolved in a PBLG/organic solvent liquid crystal solvent whenever the (*R*) and (*S*) averaged orientations are different. $\Delta\hat{\imath}_1$ and $\Delta\hat{\imath}_2$ are the quadrupolar splittings of each enantiomer; as $\Delta\ddot{a}$ mentioned for chiral auxiliaries, F_D, discrimination factor [$F_D = (\Delta\hat{\imath}_1 - \Delta\hat{\imath}_2)/2$], gives an indication of the quality of the discrimination between enantiomers (see Table 1).

Results and Discussion

The primary amines, if not commercially available, were synthesized from the corresponding ketones by reductive amination using sodium cyanoborohydride and ammonium acetate.[4] Cyclic secondary amines were commercially available. Derivatization has been achieved using acetyl-d_3 chloride and triethylamine in ether to quantitatively provide amides **1**−**11** (see Scheme 1 and Experimental Section).

Scheme 1



NMR Analysis of Derivatives of Primary Amines. We have recorded proton-decoupled deuterium NMR

* Authors to whom correspondence should be addressed. Fax: (33)-04-73-40-77-17/(33)-04-73-40-70-95. E-mail: canet@chimtp.univ-bpclermont.fr.

† Ecole Nationale Supérieure de Chimie de Cleremont-Ferrand.

‡ Laboratoire de Synthèse.

§ Laboratoire de Chimie Structurale Organique.

(1) For reviews, see: (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. (b) Hulst, R.; Kellog, R. M.; Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115.

(2) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326 and references cited therein.

(3) (a) Canet, I.; Courtieu, J.; Lœwenstein, A.; Meddour, A.; Pechine, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 6520. (b) Meddour, A.; Canet, I.; Lœwenstein, A.; Pechine, J. M.; Courtieu, J. *J. Am. Chem. Soc.* **1994**, *116*, 9652. (c) Canet, I.; Meddour, A.; Courtieu, J.; Canet, J. L.; Salaün, J. *J. Am. Chem. Soc.* **1994**, *116*, 2155.

(4) Borch, R. F.; Bernstein, M. D.; Dupont Durst, H. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

S0022-3263(96)01141-3 CCC: $12.00

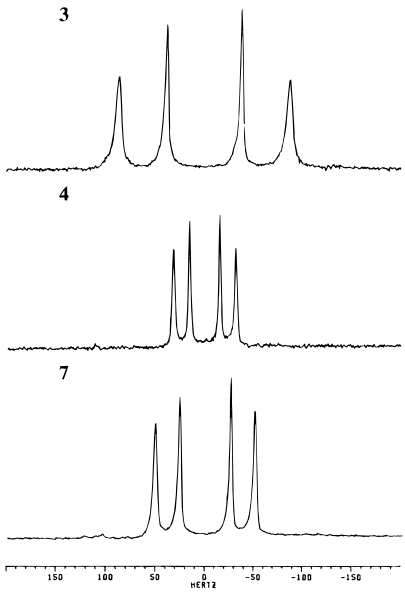


Figure 2. ^{2}H NMR spectra of amides **3**, **4**, and **7**.

Table 1. Values of Quadrupolar Splittings for Enantiomers of Amides 1−8

amide	T (K)	$\Delta\hat{\imath}_1$[a] (Hz)	$\Delta\hat{\imath}_2$[a] (Hz)	F_D (Hz)[b]
1	300	106.2	13.4	46.4
2	299	131.7	9.9	60.9
3	299	173.9	76.0	48.9
4	299	63.3	30.7	32.6
5	296	28.4	0.0[c]	14.2
6	299	234.1	26.0	104.0
7	299	101.8	52.2	24.8
8	299	143.7	94.9	24.4

[a] By convention, $\Delta\hat{\imath}_1$ corresponds to the larger quadrupolar splitting on the spectrum, $\Delta\hat{\imath}_2$ to the smallest one. [b] For definition of F_D, see Figure 1. [c] This value of the quadrupolar splitting is obtained when the averaged orientation of the C−D bond of an enantiomer corresponds to the magic angle ($\imath_m = 54.7°$).

spectra of amides **1**−**8** dissolved in PBLG−dichloromethane (see Experimental Section). The results are listed in Table 1. For all the amides, it was possible to distinguish enantiomers on the ^{2}H NMR spectra with good resolution.[5] Furthermore, in all cases, as illustrated on Figure 2, the difference of the quadrupolar splittings between the enantiomers was large enough to allow an accurate measurement of an enantiomeric excess of the same compounds if in an optically active form.

For instance, for compound **1**, NMR measurements have been made on the derivatives of the racemic and the optically pure[6] amines (Figure 3). On entry c, the amide derived from the optically pure amine exhibits only one quadrupolar splitting in its spectrum. As previously proven, 1% of an isomer can be unambiguously detected in spectra;[3c] we can thereby assume that derivatization using acetyl-d_3 chloride occurs without racemization.

NMR Analysis of Derivatives of Secondary Amines. In derivatization of secondary amines leading to tertiary amides, the presence of amide rotamers must be accounted for in the analysis of the NMR spectra. If rotamer equilibrium is fast on the NMR time scale, the amide spectrum will be composed of two doublets, one for each enantiomer. If equilibrium is slow, the spectrum must consist of four doublets, two sets of two, corresponding to the visualization of the enantiomers for each rotamer. Otherwise, a coalescence phenomenon will appear.

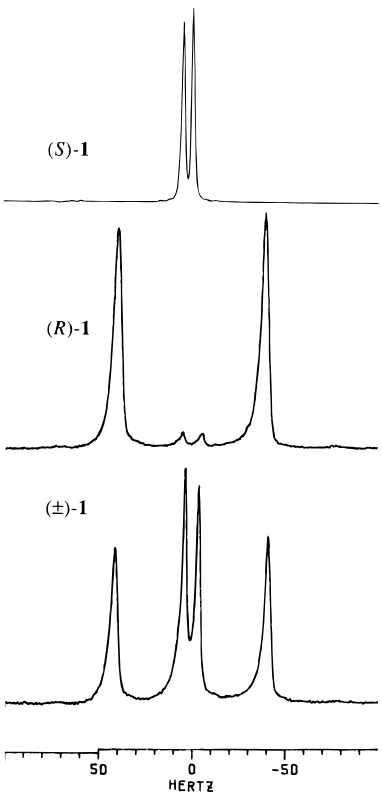


Figure 3. ^{2}H NMR spectra of (a) amide (±)-**1**, (b) amide (*R*)-**1** (96% ee), and (c) amide (*S*)-**1** (99% ee).

The first studies have been performed on amides **9**−**11** dissolved in PBLG−dichloromethane. In this solvent, at room temperature, the spectra showed a typical coalescence phenomenon (Figure 4).[7] Decreasing the temperature (lower than 243 K) allowed us to obtain spectra in which both the rotamers and the enantiomers were distinguished (see Table 2).

However, as the quality of the spectral resolution decreases a little at lower temperatures, we made an attempt to study these compounds at higher temperatures, hoping for spectra on which the enantiomers could be visualized.

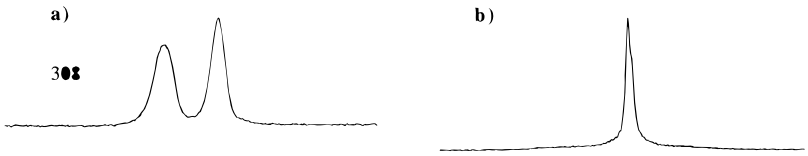
To this purpose, we prepared samples of amides **9**−**10**, first in a PBLG/TCP solvent (see Experimental Section). NMR spectra were recorded from 290 to 350 K. In all cases, similar results were obtained: heating to 350 K was not sufficient to reach the fast exchange limit.

As conformational equilibrium also depends on the solvent, we then decided to make an other attempt with a different solvent, in this case PBLG/DMF (see Experimental Section). The NMR spectra of amides **9**−**11** were recorded from 300 to 350 K. For amides **10** and **11**, at the lowest temperatures (i.e., 300 K), we obtained spectra in which both the rotamers and the enantiomers were distinguished (Figure 4). Increasing the temperature led to a coalescence phenomenon. For amide **9**, all of the spectra were typical of a coalescence phenomenon. In all cases, when using PBLG/TCP as the solvent, we did not succeed in obtaining spectra in the fast exchange regime.

(5) Using 5 mm tubes in a 10 mm probe leads to 5 Hz line widths. Better resolution (1−3 Hz) is obtained using a selective 5 mm deuterium probe (see ref 3).

(6) (*R*)-(+)-α-Methylbenzylamine (96% ee) and (*S*)-(−)-α-methylbenzylamine (99% ee) were purchased from Acros.

(7) When two doublets are obtained, the difference between the visualization of enantiomers (doublets are centered on the same frequency and have the same intensities) and a coalescence phenomenon (doublets are not centered or intensities are different) can be determined easily.



Conclusion

For chiral primary amines, acetyl-d_3 chloride represents a convenient NCDA for the visualization of enantiomers. The corresponding amides dissolved in PBLG/CH_2Cl_2 solvent furnish well-resolved deuterium NMR spectra in which discrimination between the enantiomers is efficient at 295 K. Furthermore, this new approach eliminates some criteria imposed by the use of CDAs (*vide supra*): the derivatizing agent is nonchiral and, consequently, less expensive; as derivatization leads to enantiomers, purifications can be performed with minor risk of enrichment; the enantiomeric quadrupolar splitting difference can be easily improved, just by a modification of temperature.[3] Study of the same amides, in an optically active form, is underway in order to know if, as for amino acids,[3c] we could correlate the obtainedquadrupolar splittings with the absolute configuration of the amides.

For chiral tertiary amides, enantiomers can be theoretically visualized in either a slow exchange regime or a fast exchange regime. In our case, all of the experimental conditions that were studied corresponded to a slow exchange regime. Using two solvents, PBLG/CH_2Cl_2 or PBLG/DMF, we obtained deuterium NMR spectra allowing the visualization of the enantiomers, but slightly complicated by the presence of the signals for the rotamers. Anyway, these spectra are resolved enough to make a possible quantification of an enantiomeric excess. Optimal conditions for the use of acetyl-d_3 chloride as a NCDA for enantiomeric analysis of secondary amines are still under investigation.

Experimental Section

The ^2H NMR spectra have been recorded on a spectrometer equipped with a multinuclear 10 mm probe at 46.01 MHz; the temperature was controlled to ±1 °C. Broad band proton decoupling was achieved using 1 W of rf power. Samples were prepared in 5 mm o.d. NMR tubes. PBLG was purchased from Sigma (M_W: 150000−350000). The amines were commercially available or prepared from the corresponding ketone, according to ref 4.

Procedure for Preparation of Acetamides-d_3. Acetyl-d_3 chloride (1.1 equiv) was added at 0 °C to a stirred solution of the studied amine (1 equiv) and triethylamine (1.2 equiv) in dry ether (0.1−0.2 M) under a nitrogen atmosphere. The reaction mixture was stirred for 10 min, and the triethylamine hydrochloride precipitate that formed was eliminated by filtration. Evaporation of the solvent followed, if necessary, by column chromatography on silica gel (elution with 1:1 AcOEt/cyclohexane) afforded the corresponding amide-d_3 (commonly 90−95% yield).

Preparation of ^2H NMR Samples. (a) PBLG/Dichloromethane Solvent. PBLG (72 mg, 12% w/w ratio in CH_2Cl_2) was introduced in the NMR tube. Five to twenty milligrams of amide dissolved in dichloromethane (400 íL) was added. The sample was mixed by centrifugation of the tube (1 min, 3000 rpm) alternatively in both directions (6 times), until an homogeneous and birefringent solution was obtained.

(b) PBLG/1,2,3-Trichloropropane Solvent. The same procedure was followed as with dichloromethane for the preparation of the sample, using 72 mg of PBLG, 5−20 mg of amide, and 380 íL of 1,2,3-trichloropropane. Homogenization is longer than with dichloromethane.

(c) PBLG/DMF Solvent. PBLG (60 mg, 12% w/w ratio in DMF) was placed in the NMR tube. Five to twenty milligrams of solute dissolved in DMF (465 íL) was added. As the PBLG/DMF forms gel at room temperature, alternative heating at 50−60 °C and centrifugation of the tubes in both directions were necessary to obtain a homogeneous sample.

JO961141F