



Measurement of the optical purity of fluorinated compounds using proton decoupled ^{19}F NMR spectroscopy in a chiral liquid crystal solvent

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Abstract

The use of trifluoroacetic anhydride as an achiral derivatizing agent for enantiomeric excess measurement through chiral liquid crystal NMR is described. Examples involving amines, amino acids and alcohols are provided. It is shown that the proton decoupled fluorine NMR spectra of the $-\text{CO}-\text{CF}_3$ group allow good enantiomeric discrimination based on both the chemical shifts and the dipolar splitting. The spectral separation is due to the differential ordering effect of enantiomers in the oriented chiral solvent. The results are then compared to the discriminating power of the $-\text{CO}-\text{CD}_3$ group that has been previously described using deuterium NMR in the same anisotropic medium. © 1997 Elsevier Science S.A.

Keywords: ^{19}F NMR spectroscopy; Chiral liquid crystal; Trifluoroacetic anhydride

1. Introduction

A novel technique for enantiomeric analysis using NMR spectroscopy has recently been developed by Lafontaine et al. [1,2]. This method is based on dissolution of materials in a cholesteric–nematic liquid crystalline solvent made of poly γ -benzyl L-glutamate (PBLG) in organic solvents such as chloroform.

When dissolved in this chiral liquid crystal solvent, the two enantiomers are oriented differently. This difference in orientation affects all the order-sensitive NMR interactions, namely the chemical shift anisotropy, the dipolar coupling constants and the quadrupolar splittings for spin larger than $F_{1/2}$. Various nuclei have been used to study this differential ordering effect of enantiomers (DOE): ^1H [1], ^{13}C [3] and ^2H [4–6].

In this work, we were hoping to analyse the sensitivity of ^{19}F NMR to the DOE and to compare the results to those

obtained using deuterium NMR [7]. For this purpose we decided to use trifluoroacetic anhydride as an achiral derivatizing agent for alcohols, amines or amino acids, in order to reversibly introduce fluorine atoms into the chiral molecule under study. The trifluoroacetyl substituent ($\text{CF}_3\text{CO}-$) has been chosen as a ‘fluorine probe’ as it presents some advantages, as enumerated below.

(1) In anisotropic solutions, the ^{19}F NMR spectrum of a CF_3 group, a 1:2:1 triplet, permits measurement of two anisotropic interactions: the anisotropy of the electronic shielding, $\Delta\sigma$, and the dipolar coupling constant between the fluorine nuclei, D_{FF} . A slight difference in orientation between the R and S enantiomers would then lead to a difference in both the chemical shifts δ and the CF_3 splitting, $T = 3D_{\text{FF}}$, for each enantiomer.

(2) The trifluoroacetyl substituent can easily be attached to any alcohol or amine. Furthermore the reaction is reversible, so trifluoroacetyl esters and amides can easily give the starting material [8].

(3) The trifluoroacetyl substituent is not chiral so there is no concern about the enantiomeric purity of the derivatizing agent or the preferential formation of one diastereoisomeric derivative [9].

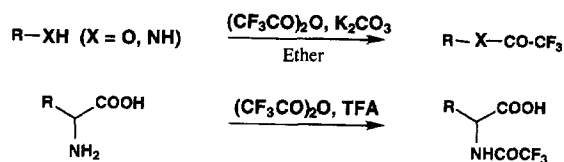
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2. Experimental

2.1. Synthesis

The derivatives of chiral amines **1–8**, amino acids **9–13** and alcohols **14–19** have been synthesised by classical methods.

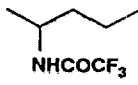
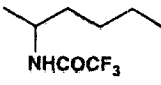
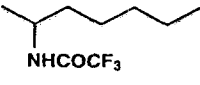
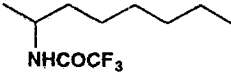
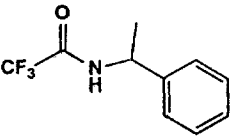
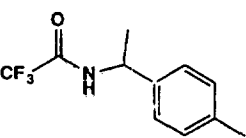
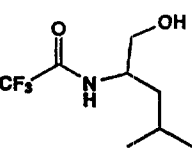


2.2. Sample preparation

PBLG (degree of polymerisation, 390, mol. wt. 30 000–70 000 from Sigma) amounting to 80 to 100 mg are weighed into a 5 mm o/d NMR tube; 20 to 50 mg of enantiomer mixture is dissolved in about 0.4 ml of chloroform and added to the polymer. Mixing and equilibration are achieved by centrifugation of the NMR tube in both directions. The sam-

Table 1

Chemical shift differences $\delta_S - \delta_R$ (ppm) for the R and S trifluoroacetyl primary amines, splitting T_S and T_R (Hz), and absolute values of the differences $|T_S - T_R|$

Amides	No.	$\delta_S - \delta_R$ (ppm)	T_S (Hz)	T_R (Hz)	$ T_S - T_R $ (Hz)
	1	0.04	21.0	≈ 0	21.0
	2	0.07	15.1	9.9	5.2
	3	0.09	10.3	22.1	11.8
	4	0.15	10.3	40.1	29.8
	5	0.24	70.3	20.1	50.2
	6	0.28	15.4	84.6	69.2
	7	-0.27	58.6	161.5	102.9

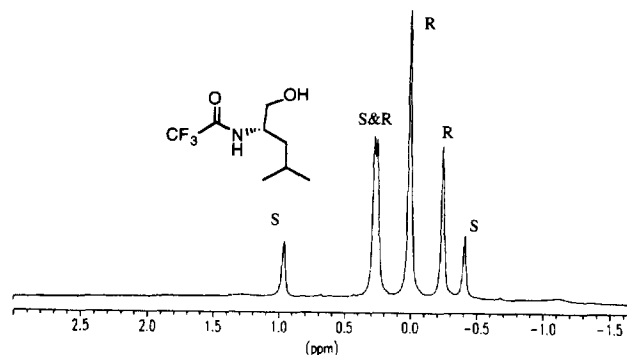


Fig. 1. Proton decoupled ^{19}F NMR spectrum of *N*(1-trifluoroacetyl)-2-amino-4-methyl-pentanol (66% R and 33% S); solvent PBLG/ CDCl_3 .

ple must look birefringent and homogeneous before introduction into the NMR field.

2.3. NMR measurements

Fluorine NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 235–31 MHz for fluorine resonance. Proton decoupling (WALTZ sequence) was applied.

Spectra are recorded at room temperature. A typical peak width is about 8–9 Hz.

3. Results and discussion

Proton decoupled fluorine NMR spectra of trifluoroacetyl amine or alcohol derivatives exhibit a triplet from the CF₃ group. The triplet splitting T is equal to $3|D_{FF}|$ where D_{FF} is the dipolar coupling constant between the fluorine atoms [10].

The NMR spectrum of a mixture of enantiomers gives rise to two triplets, one for each enantiomer, which present different chemical shifts δ_R , δ_S and different splittings T_S and T_R . A typical spectrum is shown in Fig. 1.

As each sample was made of a known enantiomeric composition, peak assignment for R and S was simple through peak integration. Within experimental errors (3%) and when the peaks were sufficiently separated, peak integration values were always consistent with the known enantiomeric excess. This confirms that there was neither enantiomeric discrimination nor racemization during the introduction of the trifluoroacetyl group.

3.1. Amine derivatives

The data obtained from proton decoupled ¹⁹F NMR spectra of the amine derivatives are summarised in Table 1.

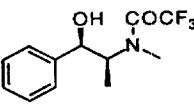
For the amides 1–6 the chemical shift of the R enantiomer is always larger than that of the S enantiomer. 7 gives the opposite result, but it is an amino–alcohol and we may suppose that the hydroxy group drives the molecule into a completely different orientation in the liquid crystal.

The CF₃–CO–NH–CH(R)–CH₃ amides, 1–6, show an interesting correlation between the volume of the R substituent (in Å³) [11,12] and the difference of the chemical shifts $\delta_S - \delta_R$. $\delta_S - \delta_R$ increases with the volume of R, i.e., with the volumic dissymmetry of the molecule around the NC*H plane (see Fig. 2).

The splitting difference does not follow the same rule as the chemical shift difference. However in the homologous 1–4 series, the splitting of the R enantiomer increases with the volume of the R substituent while the splitting of the S enantiomer decreases.

Table 2

For the two conformations (I) and (II). Differences of chemical shifts $\delta_S - \delta_R$ (ppm) from the R and S trifluoroacetyl secondary amines 8, splitting T_S and T_R (Hz), and absolute values of the differences $|T_{1S-2R} - T_{R-2S}|$

Amide	No.	% conformations	$\delta_{1S-2R} - \delta_{1R-2S}$ (ppm)	T_{1S-2R} (Hz)	T_{R-2S} (Hz)	$ T_{1S-2R} - T_{R-2S} $ (Hz)
	8	(I) 80	0.10	33.7	8.2	25.5
		(II) 20	0.07	12.0	9.7	2.3

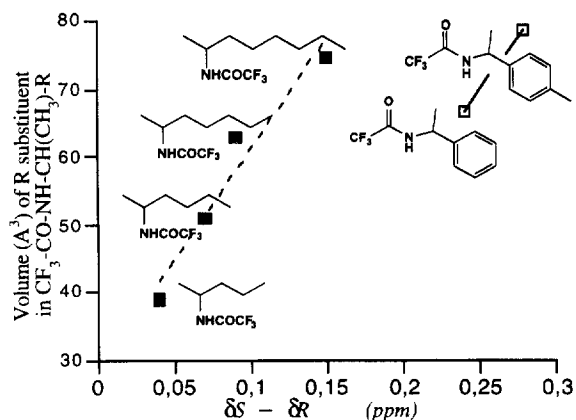


Fig. 2. Correlation between the volume of the R substituent, in Å³, and the difference of the chemical shifts $\delta_S - \delta_R$ of the CF₃ group in the anisotropic ¹⁹F NMR, for the CF₃–CO–NH–CH(R)–CH₃ amides.

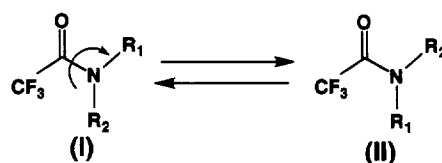


Fig. 3. The two conformations of a *N,N*-disubstituted amide.

The enantiomeric excess is simply measured by peak integration. The accuracy of this measurement depends on the peak separation, so for amides 1–3, as peaks overlap, enantiomeric excesses have been obtained with a 10% uncertainty. On the other hand for compounds 4–7, where the enantiomer peaks are well separated, the NMR spectra give values of enantiomeric excesses within $\pm 2\%$.

For secondary amine derivatives two rotamers (I) and (II) exist at room temperature as shown in Fig. 3. Table 2 shows the results obtained with the trifluoroacetyl amide derivative of *N*-methylephedrine 8. The two conformations are detected. A population ratio (I):(II) = 80:20 was found.

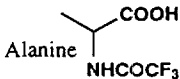
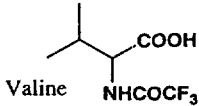
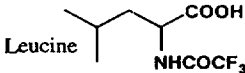
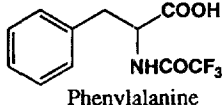
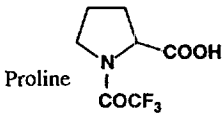
3.2. Amino acid derivatives

Amino acid derivatives show very low solubility in PBLG/CDCl₃ solutions. In order to obtain workable spectra, a larger number of acquisitions had to be performed (≈ 1000). Results are summarised in Table 3.

With the exception of 10 and 11, every spectrum shows good separation for each enantiomer peak, so that the enan-

Table 3

Differences of chemical shifts $\delta_S - \delta_R$ (ppm) for the R and S *N*-trifluoroacetyl-amide-acids, splitting T_S and T_R (Hz), and absolute values of the differences $|T_S - T_R|$

Amido acids	% conformation	No.	$\delta_S - \delta_R$ (ppm)	T_S (Hz)	T_R (Hz)	$ T_S - T_R $ (Hz)
 Alanine		9	0.25	130.1	72.5	57.6
 Valine		10	0.09	230.6	240.1	9.5
 Leucine		11	0.08	307.4	314.3	6.9
 Phenylalanine		12	-0.09	198.9	266.2	67.3
 Proline	(I) 86 ^a	13	0.08	101.3	112.5	11.2
	(II) 14		0.35	288.0	169.5	118.5

^a For 13 the rotamer ratio (I):(II) is 86:14.

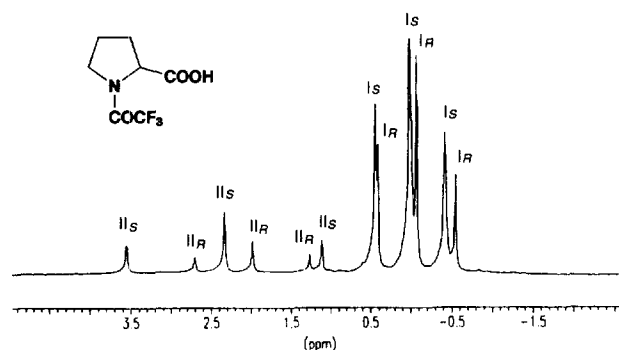


Fig. 4. The ^{19}F NMR proton decoupled spectrum of *N*-trifluoroacetyl-proline (66% S and 33% R); solvent PBLG/ CDCl_3 . For each enantiomer, two conformations were detected in a ratio 86:14.

tiomeric excess can be obtained with good accuracy. The splittings are generally 10 times larger for amino acids than for amine and alcohol derivatives. These large splittings may be due to the carboxy group that can give strong interactions with the PBLG. This phenomenon has also been observed for the amine derivative 7 which possesses a polar hydroxy group. As for the amines, in all cases, except 12, the S enantiomer chemical shift is larger than the R.

With the proline derivative two rotamers were also observed and their populations measured as shown in Fig. 4.

It must be noted that the enantiomeric discrimination is much larger for rotamer (II) than for rotamer (I).

4. Alcohol derivatives

The results of the ^{19}F NMR proton decoupled spectra for the trifluoroacetates 14–19 are summarised in Table 4.

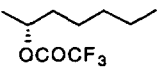
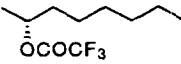
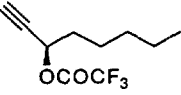
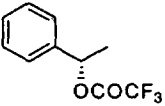
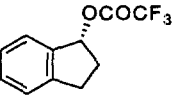
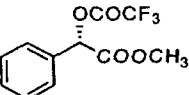
For the alcohols under study the data in Table 4 showed a discrimination between enantiomers, but chemical shift differences are within 0.01 and 0.03 ppm and dipolar splitting differences do not exceed 8 Hz. With such a low separation between peaks it was impossible to reliably measure enantiomeric excess. This would eventually become possible if we used a higher magnetic field. However, in all cases, except 17, the chemical shift is larger for R than for S enantiomers.

5. Conclusions

Trifluoroacetic anhydride reacts easily with chiral amines, amino acids and alcohols and gives fluorinated derivatives through a reversible reaction. In solution in a chiral crystal liquid PBLG/ CDCl_3 these derivatives exhibit interesting ^{19}F NMR features: (i) The CF_3 group gives signals which have specific chemical shifts for each enantiomer; (ii) For each

Table 4

Differences of chemical shifts $\delta_S - \delta_R$ (ppm) for the R and S trifluoroacetyl esters, splitting T_S and T_R (Hz), and absolute values of the differences $|T_S - T_R|$

Esters	No.	$\delta_S - \delta_R$ (ppm)	T_S (Hz)	T_R (Hz)	$ T_S - T_R $ (Hz)
	14	-0.01	12.4	14.5	2.1
	15	-0.01	11.4	13.8	2.4
	16	-0.01	30.6	23.9	6.7
	17	0.02	24.3	17.0	7.3
	18	~0	13.1	14.5	1.4
	19	-0.03	22.1	29.4	7.3

^a Nonmeasurable.

enantiomer, the CF_3 group also gives different dipolar splittings, $3D_{FF}$.

This transformation allows an easy identification of enantiomers by NMR and gives access to the enantiomeric excess whenever the peak separations are large enough. Consequently, trifluoroacetic anhydride may be used as a convenient achiral derivatizing agent.

This fluorinated nonchiral derivatizing agent may be compared to the recently proposed deuterated equivalent [7], [12]. Generally, the differential ordering effect of enantiomers leads to a larger discrimination when using the quadrupolar splitting among the CD_3 group than the dipolar splitting among the CF_3 . However, owing to the strong chemical shift anisotropy of the fluorine nuclei, the CF_3 groups in each enantiomer can be distinguished through their chemical shifts. The $(\delta_R - \delta_S)$ seems to be a rather reliable tool for absolute configuration assignment inside an homologous series of compounds. This will have to be confirmed using other systematic studies. This work is presently underway.

The above results show that a CF_3 group may be used as a probe to measure enantiomeric excess using chiral liquid crystal NMR and should be of interest to chemists involved in the synthesis of poly-fluorinated compounds.

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