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TETRAHEDRON: *ASYMMETRY*

Achiral deuterated derivatizing agent for enantiomeric analysis of carboxylic acids by NMR in a chiral liquid crystalline solvent

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Abstract

The use of a deuterated 'probe' for the enantiomeric analysis of chiral carboxylic acids is proposed. The probe is the perdeuterobenzyl fragment which can be easily attached to the acid and removed from the corresponding ester. The analysis is performed through the measurement of the proton-decoupled deuterium NMR spectrum of the chiral benzyl ester dissolved in poly-γ-benzyl-L-glutamate/dimethylformamide liquid crystal. Enantiomeric discrimination was observed for all the studied compounds on the *para* and/or α deuterons. There is no need for the deuterons to be located close to the stereogenic centre. Thus enantiomers were correctly distinguished from the signal of a deuterium located 12 bonds away from the asymmetric carbon. The major interest of this general technique is that no kinetic resolution should occur during the derivatization process.

1. Introduction

NMR spectroscopy in chiral liquid crystalline solvents has proven to be a powerful tool for enantiomeric analysis.[1] The best separations were obtained using liquid crystalline solutions of poly-γ-benzyl-L-glutamate (PBLG) in various organic solvents, such as dichloromethane, tetrahydrofuran or dimethylformamide (DMF).

We have shown that, in such media, two enantiomers of a chiral solute are not oriented in the same way. This difference in orientation can be observed in the NMR spectra through the orientation-dependent interactions such as the dipolar couplings, D^{ij}, the chemical shift anisotropies, $\Delta\sigma^i$, and the quadrupolar splittings, $\Delta\nu^i_Q$, for spins >1/2.[2] Various nuclei such as ^1H, ^{13}C or ^{19}F may be used for enantiomeric analysis.[3–5] However, most results have been obtained through the use of deuterium (spin = 1) NMR.[3,6,7] Deuterium NMR is efficient for the

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observation of enantiomers because the quadrupolar interaction is manifested through the observation of large quadrupolar splittings ($\Delta\nu_Q$). A slight difference in the orientation of enantiomers gives rise to a noticeable difference in their $\Delta\nu_Q$'s.

The main disadvantage in the use of deuterium NMR in liquid crystals for enantiomeric analysis is the need for deuterium labelling which may require complex synthetic procedures. The alternative, which consists of acquiring the deuterium NMR spectrum in natural abundance, although efficient, requires the use of quite large amounts of chiral solutes.[8] In order to avoid these constraints, we proposed the use of deuterated 'probes' to attach to the solute to be studied. These probes can be described as achiral deuterated derivatizing agents (ADDA). In contrast with the classical chiral derivatizing agents (CDA's), ADDA's do not need to be chiral as the enantiomeric discrimination is made by the oriented solvent. Thus, we showed that the use of the perdeuterobenzyl fragment (C_6D_5–CO–) was a powerful method to obtain the enantiomeric excess (*ee*) of alcohols, amines and aminoacids.[9]

While a plethora of isotropic NMR methods exist for the enantiomeric analysis of alcohols and amines, relatively few are reported for carboxylic acids.[10] One of the most efficient consists of using chiral oxazolidine-2-selones as CDA's.[11] However the enantiomers clearly react at different rates with these CDA's. This may induce partial kinetic resolution if the reaction is not complete, as pointed out by the authors.[11]

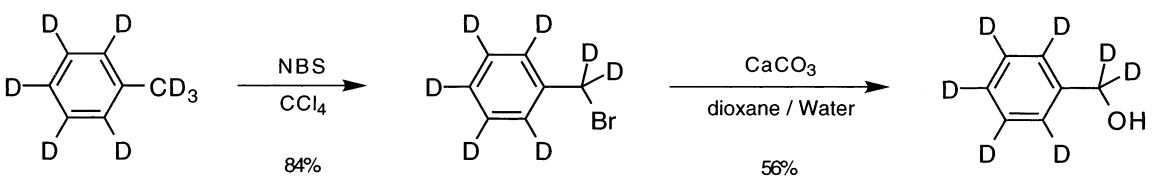
Herein, we report the use of the perdeuterobenzyl group as ADDA to determine the enantiomeric purity of carboxylic acids. This probe is preferred for the following reasons:

- The benzyl fragment can be easily attached to a carboxylic acid. Moreover, it can be readily removed by simple hydrogenolysis.[12] This may be important in the case where one needs to recover the chiral starting material.
- Heptadeuterobenzyl alcohol is achiral and therefore no kinetic resolution should occur in the course of derivatization. Therefore, the esterification reaction does not need to be complete.
- The heptadeuterobenzyl ester of a chiral acid possesses five magnetically different deuterium atoms which are in the α_A, α_B, *ortho*, *meta* or *para* positions. This provides the possibility of measuring the enantiomeric excess on different sites in a molecule.

2. Results and discussion

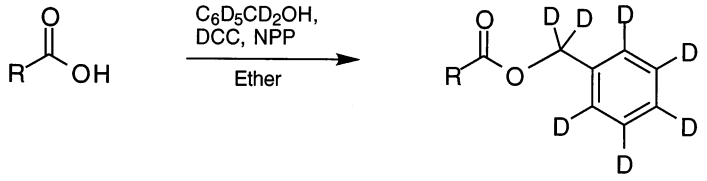
2.1. Synthesis

Benzyl alcohol-d_7, although commercially available, was readily prepared in two steps starting from toluene-d_8 (Scheme 1). A monobromination of toluene-d_8 in the α position is achieved with *N*-bromosuccinimide (NBS).[13] Substitution of the bromine with a hydroxy group is realised in a mixture of dioxane/water in the presence of calcium carbonate providing benzyl alcohol-d_7 with 47% overall yield.[14]



Scheme 1.

Eleven α,α,2,3,4,5,6-heptadeuterobenzyl esters have been prepared by reacting the corresponding carboxylic acids with benzyl alcohol-d_7 using dicyclohexylcarbodiimide (Scheme 2).[15] Esters were obtained in the range of 59–89% yield (Table 1). Esters **3**, **6**, **9** and **12** were prepared in an enantiomerically enriched mixture starting from non-racemic acids. The *ee* measured on the esters are consistent with those of the related acids, which shows that no racemisation or kinetic resolution occurs during the esterification reaction.



Scheme 2.

2.2. NMR results

A proton-decoupled deuterium (^{2}H-{^{1}H}) NMR spectrum of one enantiomer of such esters in PBLG liquid crystal contains ten signals which are to be seen as five doublets: two doublets with intensity 2 for the *ortho* and *meta* deuterons, one doublet with intensity 1 for the *para* deuterium and one doublet with intensity 1 for each of the diastereotopic α deuterons. In isotropic NMR, the diastereotopic benzylic deuterons are isochronous when they are remote from the stereogenic centre. In PBLG liquid crystalline solvent, it was found that, even when they have the same chemical shift, these two deuterons generally give different quadrupolar splittings, which implies that the order parameters of the C–D direction for the two benzylic deuterons are different. Besides, while the *ortho*, *meta* and *para* doublets are centred on approximately the same chemical shift, the benzylic deuterons give doublets with close to identical chemical shift, which is about 2.2 ppm upfield from that of the aromatic deuterons. Consequently, a racemic mixture of a heptadeuterobenzyl ester should contain up to ten quadrupolar doublets, six with intensity 1 and four with intensity 2, if there is no signal superposition and in the case where enantiomers are discriminated on all sites.

Our first ^{2}H-{^{1}H} NMR experiments were performed using PBLG/CH_2Cl_2 liquid crystalline solvent. It was found that, although enantiomeric visualisation was effective, line separations were usually too small to allow an accurate measurement of *ee*. We therefore used the liquid crystalline solvent obtained with PBLG/DMF which led to larger line separations. A typical spectrum, obtained with ester **3** prepared from (*S*)-2-methylbutyric acid (32% *ee*) is presented in Fig. 1. The two outer doublets are due to the *para* deuterium: the larger is due to the (*S*)-enantiomer and the smaller is from the (*R*)-enantiomer. The next three doublets with a relatively large linewidth correspond to the α deuterons. Among the latter, the two doublets with the largest quadrupolar splittings belong to different enantiomers. The line separation is total and an accurate integration can be made from these signals, which leads to 32% *ee*. Finally, the inner doublets with large intensities are relative to the *ortho* and *meta* deuterons and show no enantiomeric discrimination. This behaviour is general since only a small or even no discrimination was observed on the *ortho* and *meta* deuterons for all the compounds under study.

Table 2 summarises the data obtained with ^{2}H-{^{1}H} NMR in PBLG/DMF for all compounds. This Table includes the quadrupolar splittings of the *para* (*p*) and the two α deuterons.

Table 1
Heptadeuterobenzyl esters

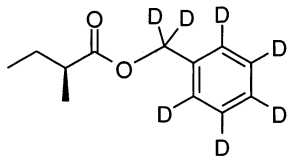
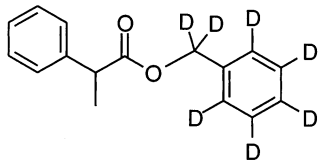
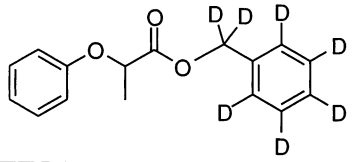
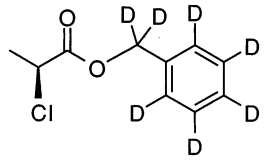
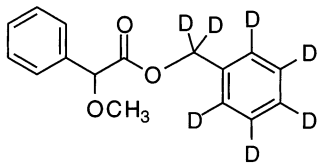
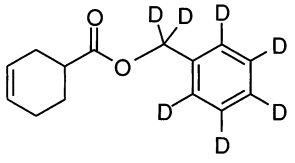
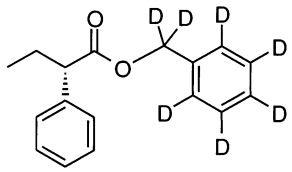
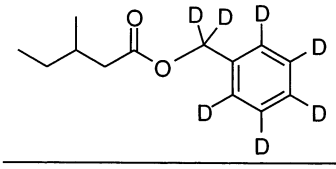
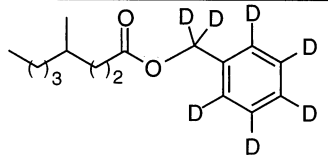
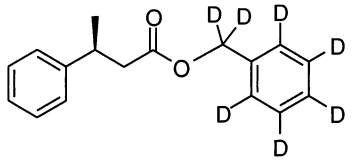
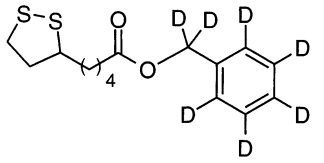
Ester		Yield (%)	ee_{acid}[a] (%)	ee_{ester}[b] (%)
	**3**	59	32 (*S*)	32
	**4**	75	/	/
	**5**	89	/	/
	**6**	67	34 (*S*)	34
	**7**	70	/	/
	**8**	72	/	/
	**9**	81	34 (*S*)	32
	**10**	70	/	/

Table 1 (Continued)

	**11**	77	/	/
	**12**	80	36 (*S*)	33
	**13**	84	/	/

[a] Enantiomeric excess of the starting carboxylic acid.

[b] Enantiomeric excess of the ester measured from the ^{2}H-{^{1}H} NMR spectrum in PBLG/DMF liquid crystal.

It also includes the value $|\Delta\nu_Q^1-\Delta\nu_Q^2|/2$, which is the spectral line separation of enantiomers for a given deuterium.

The NMR signals of the α deuterons are broad in comparison with those of the aromatic ring. They also exhibit the structure of a non-resolved multiplet. This lineshape is due to dipolar coupling between the benzylic nuclei. Besides, the assignment of the two doublets for the α deuterons of each enantiomer is not obvious. These two nuclei are diastereotopic. However, as they are remote from the stereogenic centre, they show the same chemical shift in isotropic deuterium NMR except for esters **4**, **6**, **7** and **9**, where a difference smaller than 0.07 ppm was measured. The same behaviour of the chemical shift was observed in PBLG/DMF liquid crystal. However, four doublets were obtained for these deuterons, i.e. two doublets for each enantiomer. In the case where no difference in the chemical shift of the diastereotopic deuterons is observed, there is no way to assign the two doublets for a given α deuterium in two enantiomers from the spectrum. Therefore, the $|\Delta\nu_Q^1-\Delta\nu_Q^2|/2$ values could not be calculated for esters **5**, **8**, **10**, **11** and **13**. Consequently, we have reported the values of the four quadrupolar splittings measured, which are not to be viewed as assigned.

Enantiomeric discrimination was observed for all the compounds under study. Noticeable separations have been observed on the *para* deuterium signal for esters **5**–**7**, **12** and **13**, while the α deuterium atoms are good discriminating sites for esters **3**–**12**. Therefore, no correlation can be drawn between the spectral discrimination and the position of the deuterium with regard to the stereogenic centre.

The quadrupolar splitting for the *para* deuterium of the (*S*)-enantiomer is larger than that of the (*R*)-enantiomer for esters **3**, **6** and **12**. In contrast, the quadrupolar splittings of the (*R*)- and (*S*)-enantiomers for this deuterium are equal in esters **9** and **10**. This results implies that no correlation can be made between the absolute configuration and the relative values of quadrupolar splittings for these compounds.

The discrimination power of this method is illustrated with ester **13** (Fig. 2). A slight spectral separation is observed on the α deuterons, although this part is not obvious to analyse. However, for the *para* deuterium which is 12 bonds away from the asymmetric centre, a spectral separation of 19.5 Hz is observed. This line splitting is sufficient for the measurement of an eventual *ee*.

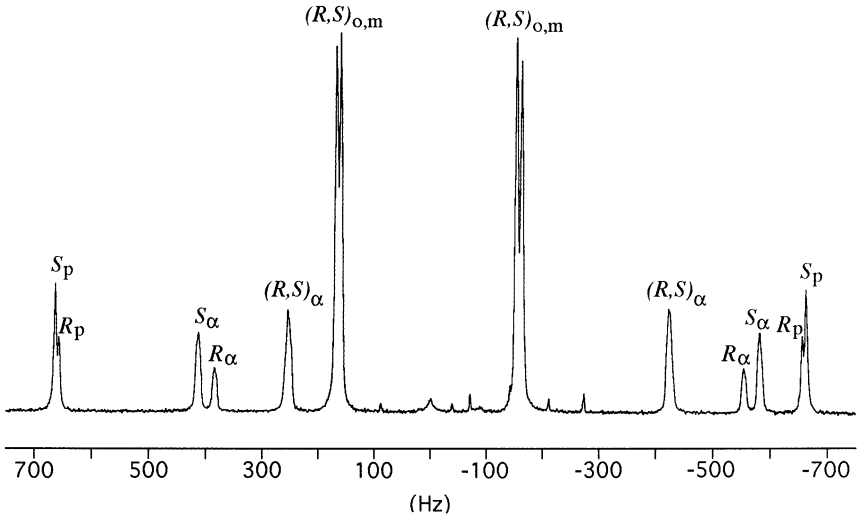


Figure 1. ^{2}H-{^{1}H} NMR spectrum obtained with 3.6 mg of an enantiomerically enriched mixture of **3** in PBLG/DMF (34.8 wt% PBLG) at $T=310$ K. Enantiomeric discrimination is mainly observed on the *para* and α deuterons

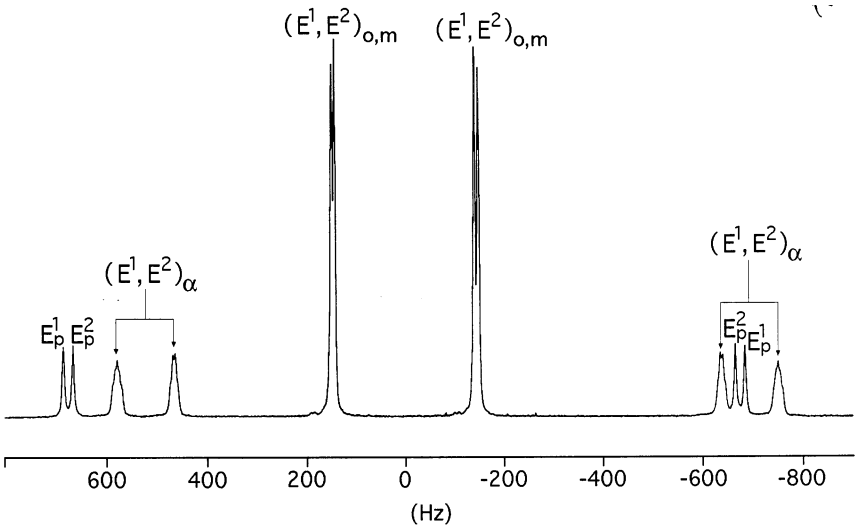


Figure 2. ^{2}H-{^{1}H} NMR spectrum obtained with 53 mg of a racemic mixture of ester **13** in PBLG/DMF (31.1 wt% PBLG) at $T=310$ K. In this spectrum, E^1 represents one enantiomer and E^2 the other one. Enantiomeric discrimination is mainly observed on the *para* deuterium

Table 2
Quadrupolar splittings (Hz) of heptadeuterobenzyl esters in PBLG/DMF liquid crystal at $T=310$ K[a]

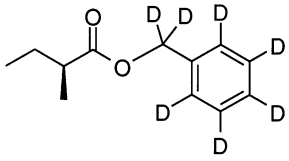
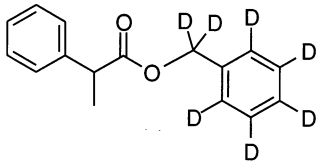
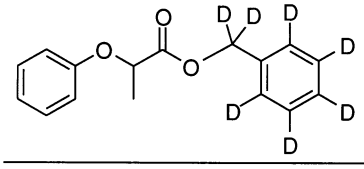
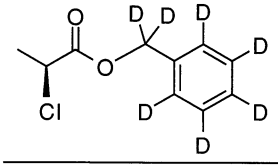
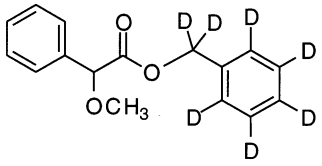
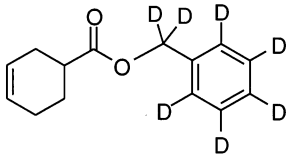
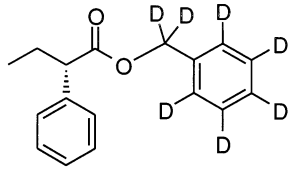
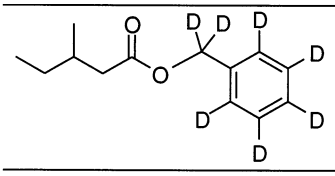
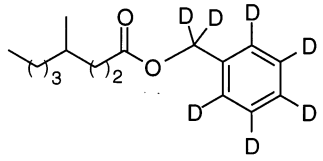
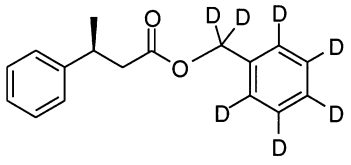
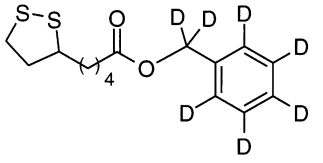
Esters			$\Delta\nu_Q^1$ (Hz)	$\Delta\nu_Q^2$ (Hz)	$\lvert\Delta\nu_Q^1-\Delta\nu_Q^2\rvert/2$ (Hz)
	**3**[b]	p	1328 (*S*)	1315 (*R*)	6.5
		α_A	996 (*S*)	678 (*R*)	159
		α_B	678 (*S*)	939 (*R*)	130.5
	or	α_A	996 (*S*)	939 (*R*)	28.5
		α_B	678 (*S*)	678 (*R*)	0
	**4**	p	1302	1293	4.5
		α_A	985	644	170.5
		α_B	872	691	90.5
	**5**[c]	p	1355	1226	64.5
		α	920	609	
		α	832	814	
	**6**	p	1128 (*S*)	1027 (*R*)	50.5
		α_A	452 (*S*)	758 (*R*)	153
		α_B	741 (*S*)	549 (*R*)	96
	**7**	p	1314	1208	53
		α_A	898	635	131.5
		α_B	870	736	67
	**8**[c]	p	1022	990	16
		α	1031	805	
		α	1014	779	
	**9**	p	1067 (*S*)	1067 (*R*)	0
		α_A	831 (*S*)	582 (*R*)	124.5
		α_B	640 (*S*)	791 (*R*)	75.5

Table 2 (Continued)

	**10**[c]	*p*	1020	1020	0
		α	930	704	
		α	877	739	
	**11**[c]	*p*	1260	1250	5
		α	1221	985	
		α	1176	1011	
	**12**[b]	*p*	1110 (*S*)	1042 (*R*)	34
		α_A	1112 (*S*)	908 (*R*)	102
		α_B	884 (*S*)	1040 (*R*)	78
	or	α_A	1112 (*S*)	1040 (*R*)	36
		α_B	884 (*S*)	908 (*R*)	12
	**13**[c]	*p*	1369	1330	19.5
		α	1337	1099	
		α	1319	1109	

[a] Only the data relative to the *para* (*p*) and the α deuterons are reported.

[b] For esters **3** and **12**, the two possible assignments for the benzylic deuterons signals are given in the table.

[c] For esters **5**, **8**, **10**, **11** and **13**, several assignments are possible for the benzylic deuterons signals, consequently the quadrupolar splittings given are not to be viewed as assigned.

3. Conclusion

We have shown that benzyl alcohol-d_7 can be used as an achiral deuterated derivatizing agent to achieve enantiomeric analysis of carboxylic acids through their ester derivatives by deuterium NMR in PBLG/DMF liquid crystal. Large enantiomeric discriminations were obtained mainly on the *para* and α deuterons. No racemisation or kinetic resolution was observed during the synthetic procedure, which enables the measurement of reliable values of *ee*. Furthermore, the deuterium probe does not need to be close to the stereogenic centre. Consequently, this technique appears to be of a very general use for enantiomeric analysis of chiral carboxylic acids.

4. Experimental

4.1. General

^{2}H NMR spectra were recorded on a Bruker AM 250 NMR spectrometer equipped with a broad-band reverse 5 mm probe at 38.39 MHz. For isotropic spectra, the $CHDCl_2$ residual signal, used as internal reference, was assigned to 5.32 ppm. Enantiomeric excesses of the esters were measured by ^{2}H-{^{1}H} NMR in PBLG/DMF liquid crystal.

4.2. Synthesis

4.2.1. Benzyl bromide-d_7 **1**

Benzoyl peroxide (50 mg, 0.21 mmol) was added to a solution of *N*-bromosuccinimide (17.80 g, 100.0 mmol) and toluene-d_8 (10.00 g, 100.0 mmol) in carbon tetrachloride (250 ml). The reaction was refluxed for 40 minutes under magnetic stirring. The precipitate was filtered off at room temperature and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, using pentane as eluant, to give 14.97 g (84%) of **1**; ^{2}H NMR (38.4 MHz, CH_2Cl_2): δ (ppm) 7.44 (s, 2D); 7.38 (s, 2D); 7.34 (s, 1D); 4.50 (s, 2D).

4.2.2. Benzyl Alcohol-d_7 **2**

Water (230 ml) and $CaCO_3$ (41.2 g, 412 mmol) were added to a solution of **1** (14.24 g, 80 mmol) in dioxane (230 ml) and the mixture was refluxed for 8 hours. The solution was cooled and the dioxane was removed under reduced pressure. Methylene chloride (200 ml) was added, followed by treatment with dilute HCl, at 0°C, until all solids had dissolved. Phases were separated and the aqueous phase extracted twice with methylene chloride. The combined organic phases were washed with an $NaHCO_3$ solution, dried with $MgSO_4$ and filtered. Removal of the solvent left an oil which was distilled under reduce pressure to give 5.14 g (56%) of **2**; ^{2}H NMR (38.4 MHz, CH_2Cl_2): δ (ppm) 7.40 (s, 4D); 7.33 (s, 1D); 4.63 (s, 2D).

4.2.3. General procedure for the synthesis of esters

An ether solution (10 ml) of carboxylic acid (1.82 mmol), benzyl alcohol-d_7 **2** (2.00 mmol), *N*,*N*-dicyclohexylcarbodiimide (2.73 mmol) and 4-pyrrolidino-pyridine (0.27 mmol) was stirred at room temperature for 24–48 hours. The precipitate was filtered off and the solvent was evaporated under reduced pressure. Heptadeuterobenzyl ester was isolated by chromatography on silica gel.

4.3. NMR sample preparation

PBLG (130 mg) (degree of polymerisation 562, mol. wt. 70 000–150 000 purchased from Sigma) was weighted into a 5 mm o.d. NMR tube, dry DMF (250 μl) was added and the mixture was heated to 70°C until complete dissolution of the polymer. Then heptadeuterobenzyl ester (3.6–53 mg) was introduced into the NMR tube. In order to homogenize the viscous mixture, the NMR tube was centrifuged back and forth about 20 times.

4.4. NMR measurements in PBLG/DMF

Deuterium NMR measurements in PBLG/DMF were performed at 310 K using the Bruker BVT-1000 temperature regulation system and samples were spun at about 20 Hz. Broad-band proton decoupling was achieved by applying the WALTZ-16 composite pulse sequence. Transients (500–10 000) with 4 k of data points were acquired to obtain a good signal to noise ratio.

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