Polymer Bulletin 36, 585–592 (1996)

Polymer Bulletin

Stereoisomers composition of 4-[(1′-methylpropyl)-oxycarbonyl]-2-oxetanone and related compounds, as precursors of functional polyesters, determined by chiral gas chromatography

Estelle Renard, Karine Boutault, Valerié Langlois*, Philippe Guerin

Laboratoire de Physico-Chimie des Biopolymères, UMR 27, Université Paris XII, CNRS, 2-8, rue Henry Dunant, F-94320 Thiais, France

Received: 15 January 1996/Revised version: 14 February 1996/Accepted: 15 February 1996

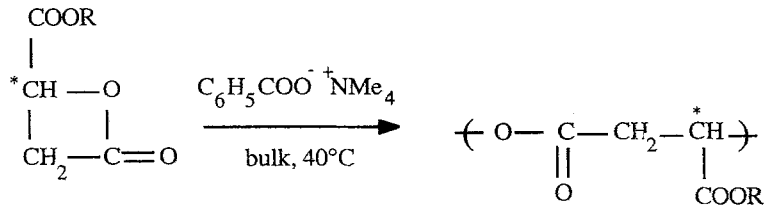
Summary

The configurational analysis of racemic and optically active stereoisomers of 4-[(1'-methyl propyl)oxycarbonyl]-2-oxetanone has been carried out by using chiral gas chromatography. This technique has been successful in the stereoisomers composition determination of these β-substituted β-lactones prepared by two different routes and used as monomers in the preparation of malic acid stereocopolymers. Results are in good agreement with those obtained from high resolution ^1H NMR, in the presence of an Europium salt, as chiral shift reagent. This method has been extended to 3-methyl-4-[(1',2',2'-trimethyl propyl)oxycarbonyl]-2-oxetanone. The exact knowledge of precursors configurational structure is very important in regard to the obtention of the corresponding polystereoisomers with a strictly controlled enantiomeric or diastereoisomeric composition and consequently with predictable properties.

Introduction

The development of new synthetic routes to optically active monomers and polymers is connected to fast-emerging technologies as electrooptic, asymmetric catalysis and biocatalysis, molecular recognition and enantiomeric separation[1]. In these applications, chirality is required for chiroptic and chain conformational properties rather than configuration. On the contrary, the presence of stereogenic centers in the macromolecular chain can be a major structural factor as in the case of naturally occuring chiral polymers[2]. The most important limitation to the preparation of optically active polymers with a controlled configurational structure concerns the preparation of the corresponding optically active monomers. It is therefore necessary to determine the enantiomeric excess for each stereogenic center of the precursors and to access to the stereochemical progress of the polymerization reaction.

In the case of the poly(β-malic acid) derivatives[3], optically active stereocopolymers are accessible from optically active β-substituted β-lactones with an enantiomeric excess



(S) (R)

Synthesis of poly(β-malic acid ester)

* Corresponding author

depending on the lactonization reaction conditions and on the lateral ester group chemical structure[4]. In many cases, the cyclisation reaction proceeds, according to an intra-bimolecular mechanism, with inversion of the chiral center configuration. Furthermore, the anionic ring opening polymerization proceeds without any racemization and the enantiomeric or diastereisomeric composition of the resulting polyester is directly correlated to the enantiomeric or diastereoisomeric composition of the monomer feed[5].

For varying the structure/properties relationship of this polyesters family, different malolactonic acid esters with miscellaneous chiral ester pendant groups and/or 2-oxetanones with two chiral centers have been synthetized, characterized and polymerized. At first, polystereoisomers[6] of malic acid 2-methylbutyl ester have been prepared from racemic and optically active 4-[(2-methylbutyl)oxycarbonyl]-2-oxetanones[7] and the configurational analysis / properties relationship has been established for monomers and polymers using 400 MHz ^{1}H NMR. In this case, crystallinity and thermal properties of the polystereoisomers are dependent on the configurational structure of the main chain and are very poorly sensitive to the enantiomeric composition of the ester pendant group . In the goal to bring closer the asymmetric center of the lateral ester group to the poly(β-malic acid ester) main chain, chiral precursors as 2-butanol and 3,3-dimethyl-2-butanol have been used for the preparation of corresponding β-substituted β-lactones.

Due to the complexity of the ^{1}H NMR spectra of these new compounds and to the variable sensitivity of the protons to the configurational structure of the different chiral centers, it was necessary to introduce a second configurational analysis technique. In this paper we want to report the use of chiral gas chromatography for determining, with high precision, the proportion of the different stereoisomers in the monomer feed and to compare the results obtained by high resolution ^{1}H NMR.

Experimental part

Chemicals

4-[(1'-methylpropyl)oxycarbonyl]-2-oxetanone,1:
The different compounds **1a** to **1f** have been prepared from commercial (R)- or (S)- or (RS)-aspartic acid and (S)- or (RS)-2-butanol (Janssen chemica) according to the aspartic synthesis route[8] previously described. **1'c** has been prepared from commercial (S)- malic acid and (S)-2-butanol (Janssen chemica), using the malic synthesis route[9].

3-methyl-4-[(1',2',2'-trimethylpropyl)oxycarbonyl]-2-oxetanone, 2:
2a and **2b** products (figure 3) have been prepared starting from (2S,3S)-3-methylaspartic acid[10] and (RS)- or (S)-3,3- dimethyl-2-butanol[11].

^{1}H NMR spectra

0.4 eq. of Tris [3-heptafluoropropylhydroxymethylene)-d-camphorato] Europium (III) (Eu[hfc]$_3$) (Janssen Chemica) was added to **1a** to **1f**, **2a** and **2b** in $CDCl_3$ (δ ppm). Spectra were recorded on a Bruker AC 400 at 22°C.
The different stereoisomers (4R,1'R), (4R,1'S), (4S,1'S), (4S,1'R) are noted respectively St_a, St_b, St_c, St_d.

1d 1.3 (2t, ^{3}'CH_3); 1.80 (d, ^{4}'CH_3, 0.38 St_b); 1.87 (d, ^{4}'CH_3, 0.62 St_c); 1.7-2.02 (m, ^{2}'CH_2); 4.28-4.75 (m, $^3CH_2$); 6.27 (m, ^{4}CH, St_b); 6.33 (m, ^{4}CH, St_a); 6.46 (m, ^{4}CH, St_d); 6.53 (m, ^{4}CH, St_c); 6.61 (m, ^{1}'CH, St_b); 6.70 (m, ^{1}'CH, St_c).

1c 1.25 (2t, ^{3}'CH_3); 1.77 (d, ^{4}'CH_3, 0.6 St_b);1.82 (d, ^{4}'CH_3, 0.4 St_c); 2.0-2.4 (m, ^{2}'CH_2); 4.24-4.66 (m, $^3CH_2$); 6.16 (m, ^{4}CH, St_b); 6.21 (m, ^{4}CH, St_a); 6.35 (m, ^{4}CH, St_d); 6.39 (dd, ^{4}CH, St_c); 6.48 (m, ^{1}'CH, St_b); 6.64 (m, ^{1}'CH, St_c).

1e 1.25 (m, ^{3}'CH_3); 1.72(d, ^{4}'CH_3, 0.32 St_b); 1.77 (d, ^{4}'CH_3, 0.68 St_c); 1.9-2.26 (m, ^{2}'CH_2); 2.42 (m, ^{2}'CH_2); 4.55 (m, $^3CH_2$); 6.05 (m, ^{4}CH, St_b); 6.10 (m, ^{4}CH, St_a); 6.120 (m, ^{4}CH, St_d); 6.25 (m, ^{4}CH, St_c); 6.35 (m, ^{1}'CH, 0.45 St_b , St_d); 6.5(m, ^{1}'CH, 0.55 St_c, St_a).

1a 1.2 (m, $^{3'}CH_3$); 1.72 (d, $^{4'}CH_3$, 0.25 St_b); 1.77 (3d, $^{4'}CH_3$, 0.75 St_a, St_c, St_d); 1.90-2.20 (m, $^{2'}CH_2$); 4.20-4.6 (2m, $^{3}CH_2$); 6.1 (m, ^{4}CH, 0.25 St_b); 6.18 (m, ^{4}CH, 0.21 St_a); 6.30 (m, ^{4}CH, 0.26 St_d); 6.35 (m, ^{4}CH, 0.28 St_c); 6.45 (m, $^{1'}CH$, 0.49 St_b St_d);(6.48 (m, $^{1'}CH$, 0.51 St_c, St_a).

1f 1.25 (m, $^{3'}CH_3$); 1.78 (d, $^{4'}CH_3$, 0. 28 St_b); 1.83 (3d, $^{4'}CH_3$, 0.72 St_d, St_c,St_a); 2.00-2.40 (m, $^{2'}CH_2$); 4.25-4.69 (m,$^{3}CH_2$); 6.20 (m, ^{4}CH, 0.34 St_b); 6.25 (m, ^{4}CH, 0.26 St_a); 6.38 (m, ^{4}CH, 0.2 St_d); 6.44 (m, ^{4}CH, 0.2 St_c); 6.54 (m, $^{1'}CH$, 0.54 St_b, St_d); 6.67 (m, $^{1'}CH$, 0.46 St_a, St_c).

1b 1.4 (m, $^{3'}CH_3$); 1.9 (d, $^{4'}CH_3$, 0. 5 St_b); 2.05- (3d, $^{4'}CH_3$, 0.5 St_d, St_c,St_a); 2.2-2.5 (2m, $^{2'}CH_2$); 4.51-5.27 (m, $^{3}CH_2$); 6.65 (m, ^{4}CH, St_b); 6.7 (m, ^{4}CH, St_a); 6.85 (m, ^{4}CH, St_d); 6.95 (m, ^{4}CH, St_c); 7.05 (m, $^{1'}CH$, St_b St_d); 7.2 (m, $^{1'}CH$, St_c, St_a).

2a 0.92 (s, $^{3'}CH_3$); 1.20 (d, $^{2'}CH_3$); 1.52 (d, $^{5}CH_3$); 3.76 (2q, ^{3}CH); 4.54 (d, ^{4}CH); 4.84 (q,$^{1'}CH$)

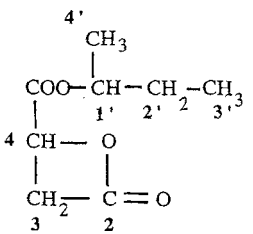
2b 0.93 and 0.94 (2s, $^{3'}CH_3$); 1.20 and 1.21 (2d, $^{2'}CH_3$); 1.52 (2d, $^{5}CH_3$); 3.76 (2m, ^{3}CH); 4.54 (d, ^{4}CH); 4.84 (q, $^{2'}CH$)

Gas Chromatography

The lactones were analyzed with a Varian 3300 chromatograph equipped with a fused-silica capillary column (column Cydex-B, Scientific Glass Engineering, 25 m x 0,33 mm id, 0,25 µm film thickness). Nitrogen was used as carrier gas, the column flow rate was: 1,4 $mL.mn^{-1}$. The on-column injector temperature was programmed from 50 °C to 180 °C at a rate of 100 °C/mn. The column temperature was programmed from 50 °C to 90 °C at a rate of 1 °C/mn, then from 90 °C to 140 °C at a rate of 0,2 °C/mn. The FID detector temperature was set at 300 °C. Each compound was dissolved in chloroform stabilized with amylene, and 0,5 µm of these solutions was injected in the capillary gas chromatograph. The experimental conditions were the same for all samples. The chromatograph was used in conjunction with a Spectra-Physics Integrator. The stereoisomers percentages were determined from the integral ratios of signals obtained by GC.

Results and discussion

Six different compounds of (2-butyl)oxycarbonyl-2-oxetanone **1a** to **1f** have been prepared according to the now well established synthesis route starting from (R,S)-, (R)-, (S)- aspartic acid[8].



	Aspartic acid	2-butanol
1a	(RS)	(RS)
1b	(RS)	(S)
1c	(S)	(S)
1d	(R)	(S)
1e	(R)	(RS)
1f	(S)	(RS)

The second chiral center was introduced by the addition of 2-butanol to intermediate bromosuccinic acid anhydride for obtaining 3-[(2-butyl)oxycarbonyl]-2-bromopropionate, which is then ring-closed. For example, **1d** is the lactone prepared from (R)- aspartic acid and (S)-2-butanol as chiral precursors. In order to determine the enantiomeric and diastereoisomeric composition before the anionic ring-opening polymerization, 400 MHz ^1H NMR has been used, at first, in the presence of $Eu(hfc)_3$ as chiral shift reagent, previously described as the most efficient compound for the resolution of enantio- or diastereotopic resonances in such products[5,7]. The assignment of the different peaks corresponding to stereosensitive protons has been made by comparison of the spectra expanded regions including $^{4'}CH_3$, $^{3'}CH_3$, $^{1'}CH$ of **1a** to **1f**. Figure 1 displays expansions of the $^{4'}CH_3$, $^{1'}CH$, ^{4}CH regions. Racemic **1a** presents four doublets in the $^{4'}CH_3$ region and four quadruplets in the ^{4}CH region indicating these protons are stereosensitive to both chiral centers configurations ($^{1'}C$ and ^{4}C) contrarely to $^{1'}CH$ proton which is stereosensitive only to $^{1'}C$. In the case of **1d** and **1c**, two doublets are observed for $^{4'}CH_3$

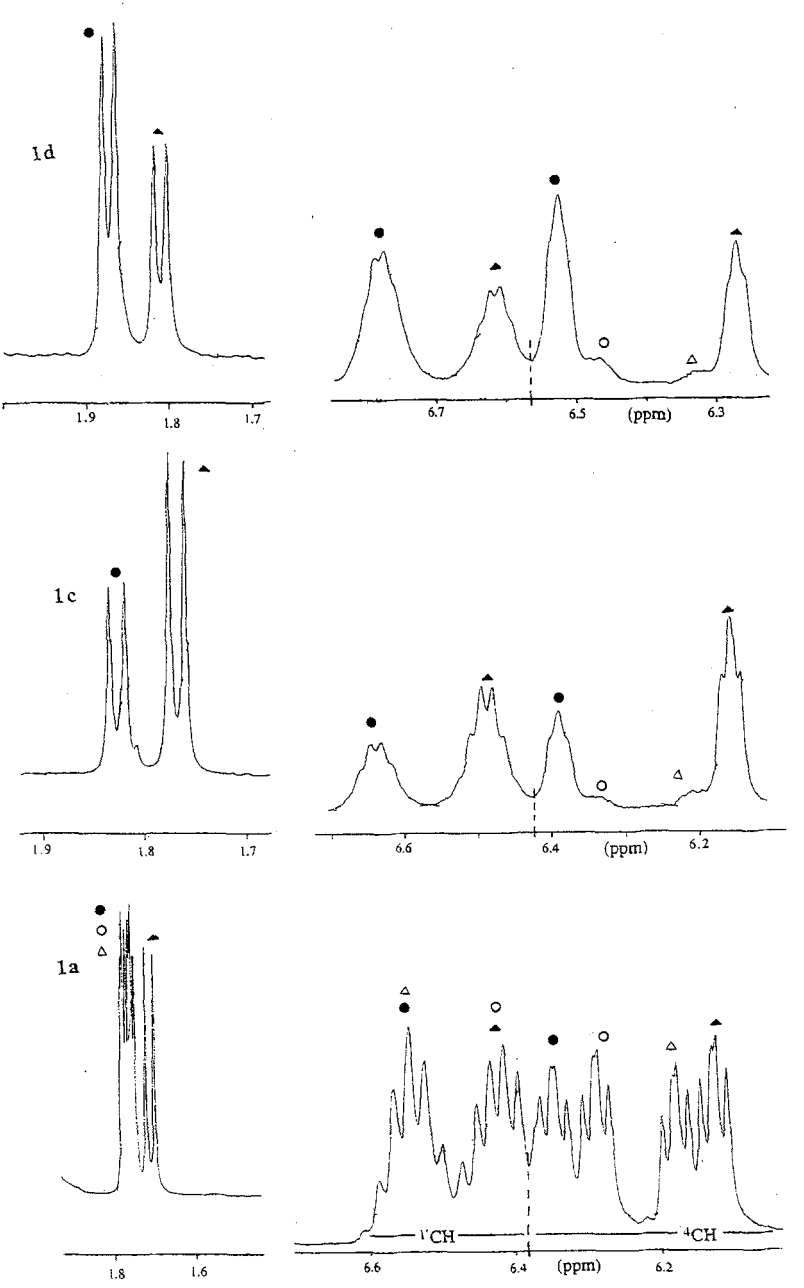


Figure 1: ^{1}H NMR spectra of β-lactones **1a**, **1c** and **1d**
(● :(S,S); ○ :(S,R); ▲ :(R,S); △ :(R,R))

with peaks intensities in the ratio 60/40 and 40/60. They have been assigned to stereoisomers (4S,1'S) and (4R,1'S) and can be explained by an important racemization of ^{4}C during the lactonization step, due to the presence of the lateral optically active bulky ester group. For **1b**, this spectrum region presents definitively two doublets of equal intensity. The proportion of the four stereoisomers can be better estimated by considering the ^{4}CH proton region; for example, **1c** displays two important signals and two very small signals due to (4R,1'R) and (4S,1'R) (presence of (R)-2-butanol in the precursor). Nevertheless, due to very close or partially overlapped signals, a complete and exact quantification is not easy by ^{1}H NMR as previously reported for substituted β-lactones[14], and in order to specify previous results, the stereoisomers composition of the different products has been determined by an alternative method: chiral gas chromatography. A chiral stationnary phase containing β-cyclodextrin molecules (CD) has been selected. The CD assisted enantioselective resolution is based on the difference of complexation constant between two optical isomers. The assignment of the different peaks was made by comparison with the different chromatogram profiles. The stereoisomers composition was determined from the chromatographic peaks integrations. Figure 2 displays such chromatogram corresponding to racemic **1a** and optically active, **1c**, **1c'**, **1d**, **1e** and **1f** products.

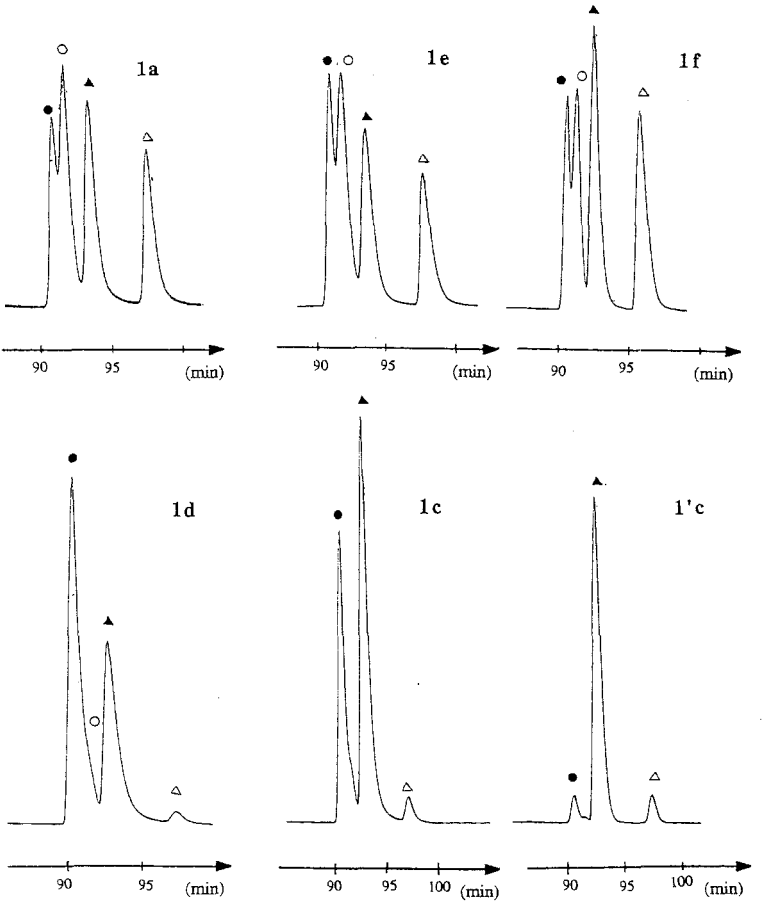


Figure 2: Gas chromatography separation of diastereoisomers of **1a**, **1c**, **1c'**, **1d**, **1e** and **1f** (●:(S,S); ○ :(S,R); ▲ :(R,S); △ :(R,R))

The separation ability of the column can be quantified by calculating power R which is defined by $R = 2(t_b - t_a) / (w_a + w_b)$, where t_i and w_i are respectively the retention time and the base width of the species peak. The R values determined for the following stereoisomers (4S,1'S) , (4R,1'S) , (4R,1'R) was between 1.8 and 4.6. These values indicate a complete separation, with R values equal or larger than 1.5. However, between stereoisomers (4S,1'S) and (4S,1'R) the resolution is lower than 1.5.

Table 1: Stereoisomers composition determined from ^{1}H N.M.R. and gas chromatography (GC).

Compound	Assignments	^{1}H NMR (%)*	GC (%)
	(4S, 1'S)	62	60
1d	(4S, 1'R)		nd
	(4R, 1'R)		nd
	(4R, 1'S)	38	40
	(4S, 1'S)	40	~ 40
1c	(4S, 1'R)		nd
	(4R, 1'R)		nd
	(4R, 1'S)	60	~ 60
	(4S, 1'S)		5
1'c **	(4S, 1'R)		nd
	(4R, 1'R)		5
	(4R, 1'S)		90
	(4S, 1'S)	50	~ 45
1b	(4S, 1'R)		nd
	(4R, 1'R)		nd
	(4R, 1'S)	50	~ 55
	(4S, 1'S)		25
1e	(4S, 1'R)	75	26
	(4R, 1'R)		26
	(4R, 1'S)	25	23
	(4S, 1'S)		20
1f	(4S, 1'R)	72	20
	(4R, 1'R)		35
	(4R, 1'S)	28	25
	(4S, 1'S)	28	23
1a	(4S, 1'R)	26	28
	(4R, 1'R)	21	26
	(4R, 1'S)	25	23

*: values determined from proton region ^{4}C and $^{4'}$C
**: compound prepared according to the malic acid synthesis route
nd: not determinable < 2%

Table 1 gives a comparison of the stereoisomers composition measured from both analytical methods. The results are in good agreement. The chromatographic investigation allow to specify the assignments described for the ^{1}H NMR spectra and to conclude definitively that the racemization of the stereogenic center ^{4}C was occured. However, it is important to note that the GC method is very simple to set up and precise. This technique has been used for analysing, in the same series, a (4R,1'S) compound, **1'c**, prepared by the malic acid synthesis route[9], from (S)-malic acid and (S)-2-butanol. In this case, the percentage of the (4R,1'S) stereoisomer was about 90% compared with 60% when the aspartic acid was used, demonstrating a better adaptation for preparing optically active malolactonic acid esters with bulky pendent groups.

At last, it has been shown, this analytical method could be extended to more complex monomers, in the same derivatives family. In the goal to obtain polyesters with very high melting temperature and high crystallinity index, two polystereoisomers of 3-methylmalate of 1',3',3' trimethylpropyl have been prepared starting from (2S,3S)-3-methylaspartic acid[11,12] and (2RS) or (2S)-3,3-dimethyl-2-butanol. Both monomers **2a** and **2b** (Fig. 3) contain three asymmetric centers ^{3}C, ^{4}C and $^{2'}C$. By ^{1}H NMR, it has been shown[12,13] in the case of **2a** that only one stereoisomer is present and that ^{3}C, ^{4}C and $^{2'}C$ have only one configuration and in the case of **2b,** two stereoisomers exist

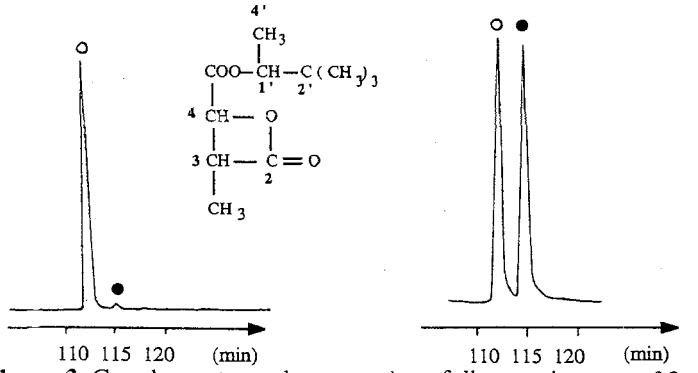


Figure 3: Gas chromatography separation of diastereoisomers of **2a, 2b**
(O : (S,S,S); ● : (S,S,R))

in the same proportion (3S,4R,2'R) and (3S,4R,2'S). No racemization was occuring at the C_4 during the lactonization reaction, which takes place usually through an intra-bimolecular reaction. This result has been confirmed by the new resolution technique and can be explained by the assistance of the methyl $^{3}CH_3$ group to avoid any conformation favourable to the racemization as shown on close compounds[12,14]. Chromatograms displayed one peak for **2a** and two peaks for **2b**.

In conclusion, the chiral gas chromatography can be a usefull method for the elucidation of stereoisomers composition in the series of malolactonic acid derivatives. In addition to the gas chromatography properties (speed, sensitivity, simplicity), this technique applied to enantiomeric and diastereoisomeric resolution is high resolution, precision and reproductibility. This method can be also used as an analytical tool to make easier the stereoisomers identification compared with overlapped or multiple resonances often observed in ^{1}H N.M.R. This method will be extended to new chiral β-substituted β-lactones conducting to polyesters for temporary or specific applications, with possible limitations, due to geometric constraints imposed to the guest molecule by the restricted cyclodextrin cavity.

References

1 BELFIELD K.D.; BELFIELD S., *Trends Polym. Sci.*, **1995**, 3, 180
2 MULLER H.M.; SEEBACH D., *Angew. Chem. Ed. Engl.*, **1993**, 32, 477
3 VERT M., *Angew. Makromol. Chem.*, **1989**, 155, 166
4 GUERIN Ph.; FRANCILLETTE J.; BRAUD C.; VERT M., *Makromol. Chem. Makromol. Symp.*, **1986**, 6, 305
5 GUERIN Ph.; VERT M., *Polymer Communication*, **1987**, 28,11
6 BOUTAULT K.; CAMMAS S.; HUET F.; GUERIN Ph., *Macromolecules*, **1995**, 28,3516

7 CAMMAS S.; BOUTAULT K.; HUET F.; GUERIN Ph., *Tetrahedron Asymmetry,* **1994**, 5, 1589
8 GUERIN Ph.; VERT M.; BRAUD C.; LENZ R.W., *Polymer Bulletin*, **1985**, 14, 187
9 CAMMAS S.; RENARD I.; BOUTAULT K.; GUERIN Ph., *Tetrahedron Asymmetry*, **1993**, 4, 1925
10 BROCHU S.; PLESU R.; PRUD'HOMME R.E.; SPASSKY N.; LE BORGNE A., *Polymer Bulletin*, **1993**, 30, 223
11 MONNE C.; ROBIC D.; CAMPION G.; BOURBOUZE R.; RIMBAULT A.; MASURE M.; LANGLOIS V.; HEMERY P.; GUERIN Ph, *Chirality*, accepted, **1995**
12 MABILLE C.; MASURE M.; HEMERY P.; GUERIN Ph, *Makromol. Rapid Comm.*, accepted, **1995**
13 BOUTAULT K., Thèse Université de Nantes, **1995**
14 MITONNEAU S., DEA Chimie des Polymères, Université Paris VI,**1995**