Polystereoisomers with Two Stereogenic Centers of Malic Acid 2-Methylbutyl Ester Configurational Structure/Properties Relationship

Karine Boutault,[†] Sandrine Cammas,[†,‡] François Huet,[§] and Philippe Guérin*,[†]

Laboratoire de Physico-Chimie des Biopolymères, UMR 27, Université de Paris XII, CNRS, 2−8, rue Henri Dunant, F-94320 Thiais, France, and Laboratoire de Synthèse Organique, URA CNRS 482, Université du Maine, Avenue Olivier Messiaen, BP 535, F-72017 Le Mans Cedex, France

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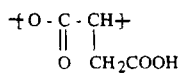
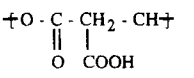
ABSTRACT: Poly(β-malic acid alkyl esters) with two stereogenic centers have been synthesized by anionic ring-opening polymerization of racemic and optically active 4-[(2-methylbutyl)oxycarbonyl]-2-oxetanones and characterized. The two asymmetric centers have been introduced in the monomer by using malic acid or aspartic acid enantiomers as chiral synthons and 2-methyl-1-butyl alcohol enantiomers as lateral ester groups. By combining the different enantiomers during the β-substituted β-lactone synthesis route, it has been possible to prepare five stereoisomers which have conducted to five different stereocopolymers. The configurational structure of racemic and optically active poly(2-methylbutyl β-malates) has been determined by ^{13}C NMR analysis, and differentiation between polydiastereoisomers has been possible by using this spectroscopy method. Several main-chain and side-chain carbon atoms were stereosensitive to the presence of the two asymmetric centers per repeat unit, and the optical purities of main-chain and side-chain stereogenic centers have been deduced from ^{13}C NMR spectra. Thermal properties of the different polystereoisomers have been correlated with the configuration of the two chiral sites in the macromolecular chain. It has been shown that crystallinity was dependent on the configurational structure of the main chain and very poorly sensitive to the enantiomeric composition of the ester pendant group.

Introduction

The necessary adjustment of the material properties for specific applications conducts the tailor-making of synthetic polymers with different but complementary chemical structures and reproducible characteristics. The building of such polyvalent polymers may be achieved by copolymerization, cross-linking, and chemical modification, starting from a parent compound. Poly(malic acid),[1] a polyester with pendant carboxy groups and a stereogenic center in the monomer unit, is a very good candidate for tailor-making such multimeric derivatives. The parent polymer exists with alternative ester linkages of α or β type, which can be prepared by polycondensation (α-type repeating unit) or by ring-opening polymerization[2] from a β-substituted β-lactone, leading to high molecular weight compounds (β-type repeating unit).



α-type repeating unit



β-type repeating unit (PMLA H_{100})

In the field of temporary therapeutic applications, the presence of an aliphatic polyester backbone makes poly(malic acid) degradable in aqueous media and even in mammalian organisms as shown on PMLA H_{100}.[3−6] Moreover, a large family of functional polymers, copolymers, and stereocopolymers of poly(β-malic acid), which can be made by direct copolymerization and/or chemical modification, have been prepared.[7,8] These compounds contain different types of pendant ester groups (neutral, reactive)[9−11] and pendant hydrophilic sites arranged in variable proportions and distributions in the macromolecular chain for modulating solubility and rate degradation. Polymeric drug carriers have been exemplified by attaching bioactive molecules through the pendant carboxyl group of the malic acid unit as 5-fluorouracil[12] and chloramphenicol.[13] Furthermore, attention was paid to poly(malate esters) with chiral liquid-crystalline phases,[14] by synthesis and ring-opening polymerization of optically pure mesogenic malolactonates. The polymer showed high optical rotation, a high degree of isotactic stereoregularity, and enantiotopic liquid-crystalline properties.

At last, the presence of stereogenic centers in the macromolecular chain is a major structural factor: not only for the possibility of investigation on chirality, conformational relationship, and chiroptical properties but, first and foremost, for taking advantage of modifying physical and mechanical properties of polymeric material, as in the case of lactic acid stereocopolymers[15] applied for different medical devices.[16] Synthetic poly(β-malic acid) stereocopolymers prepared from L-(*S*)- and (D)-(*R*)-aspartic acid[17] or L-(*S*)- and D-(*R*)-malic acid[18,19] yielded optically active poly(β-malic acid) with stereoregularity strictly connected with monomer feed enantiomeric excess.[8] Optically active poly(β-malic acid) with enantiomer excess ≥98% prepared from natural L-precursors has produced L-malic acid by *in vitro* degradation.[3,8] Moreover, natural poly(L-malic acid) can be produced by different microorganisms as *Penicillium cyclopium*,[20] *Physarum polycephalum*,[21] and *Aureobasidium SP-A*.[22]

For increasing the versatility of the poly(β-malic acid) derivatives family, we have used the particular structure of poly(β-malic acid) by introducing a second stereogenic center, with several objectives: polystereoisomers NMR configurational analysis, catalytic enan-

[†] Université de Paris XII.
[‡] Present address: Department of Material Sciences and Research Institute for Biosciences, Science University of Tokyo, Noda, Chiba 278, Japan.
[§] Université du Maine.
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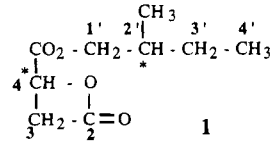
tioselective reactions, drug encapsulation, or temporary devices building. Two ways have been used: first, a chiral precursor with two asymmetric carbons conducting to main chains combining enantiomers and diastereoisomers, threo racemic β-methylaspartic acid, has conducted to a new polyester, poly(β-3-methyl malic acid) under threo racemic form.[23] This amino acid is accessible by chemical synthesis, and one stereoisomer (2*S*,3*S*) is present in living species. The second possibility consists of the introduction of a chiral center in the pendant ester group of the β-substituted β-lactone.

In this paper, we report the synthesis of the different polystereoisomers corresponding to a series of 4-[(2-methylbutyl)oxycarbonyl]-2-oxetanone stereoisomers[24] as monomer **1**, the configurational structure analysis



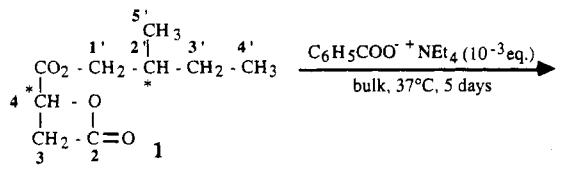
1

a (4RS, 2'RS), c (4R, 2'RS)
b (4RS, 2'S) d (4R, 2'S)
e (4S, 2'S)

by ^{13}C NMR, and the thermal properties of these materials, in relation with the enantiomeric and diastereoisomeric composition of the macromolecular chain and in relation with the place of the stereogenic center in the monomer unit.

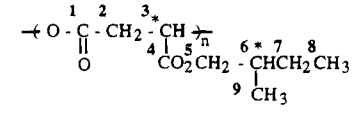
Results and Discussion

The five stereoisomers of compound **1** have been synthesized according to the two synthesis routes starting from malic acid or aspartic acid enantiomers. The enantiomeric excess of the pendant asymmetric carbon is identical to the optical purity of the initial 2-methyl-butanol, and the enantiomeric excess of the chiral carbon atom in the lactone ring varies between 76 and 98%, as determined by ^1H NMR in the presence of a chiral shift reagent, according to the experimental conditions of the monomer preparation.[19] Polystereoisomers have been prepared at 37 °C, in bulk, by anionic ring-opening polymerization, using tetraethylammonium benzoate as initiator.[8,17]



1

a (4RS, 2'RS) c (4R, 2'RS)
b (4RS, 2'S) d (4R, 2'S)
e (4S, 2'S)



a P (3RS, 6RS) c P (3S, 6RS)
b P (3RS, 6S) d P (3S, 6S)
e P (3R, 6S)

Results of polymerization are collected in Table 1. At first, it is important to note that high molecular weight, narrow polydispersity polymers have been obtained from racemic or optically active malolactonate of 2-methyl-1-butyl.

DSC results have shown that enantiomeric composition of the malate monomer unit is essential in regard to crystallinity. The second chiral center configuration influences only the melting temperature of the polymeric material. Indeed, when malate monomer units present a large excess of (*R*)- or (*S*)-enantiomer (asymmetric carbon C_3), polymers P(3*S*,6*RS*), P(3*S*,6*S*), and P(3*R*,6*S*) are semicrystalline (Table 1). Melting points are different between the two polydiastereoisomers P(3*S*,6*S*), 120 °C, and P(3*R*,6*S*), 84 °C. When the lateral ester group (C_6) is racemic, polymer P(3*S*,6*RS*) is still semicrystalline and the melting point is reduced (80 °C). The presence of a bulky pendant group modifies melting and glass transition temperatures; optically active poly(benzyl β-malate) (PMLABe) melts at 190 °C and has a T_g = 37 °C, whereas racemic poly(butyl β-malate) softens at 20 °C and (3*RS*,6*RS*) at around −2 °C. Solubility of the different polydiastereoisomers is not dependent on the enantiomeric and diastereomeric composition. The five compounds are soluble in the usual organic solvents (acetone, chloroform, dioxane, tetrahydrofuran, and diethyl ether) contrary to PMLABe. Racemic PMLABe was soluble in the same solvents, except diethyl ether, whereas optically active PMLABe was insoluble in acetone and tetrahydrofuran.

Table 1. Characterization of Polystereoisomers

	P(3*RS*,6*RS*)	P(3*RS*,6*S*)	P(3*S*,6*RS*)	P(3*S*,6*S*)	P(3*R*,6*S*)
T_g[a] (°C)	−2	−2	−8	−5	+2
mp[a] (°C)			+80	+120	+83.6
$[\alpha]^{25}_D$[b] (deg)		+3	−15	−20	+19
$\bar{M}_n$[c]	48 000	48 000	68 000	44 000	94 000
$\bar{M}_w$[c]	73 000	74 000	92 000	66 000	121 000
I_p	1.5	1.5	1.3	1.5	1.3

[a] Measured by DSC. [b] c = 1, CH_2Cl_2. [c] SEC in THF, PS standards.

According to the structure of the polystereocopolymers, effects of tacticity as well as diastereoisomerism could be expected. The configurational structure analysis was realized by ^{13}C NMR spectroscopy in order to determine the enantiomeric and diastereomeric compositions of the different compounds. Figure 1 displays the ^{13}C NMR spectrum of racemic polymer P(3*RS*,6*RS*).

Due to the stereosensitivity of different carbon atoms and the presence of two carbonyl atoms in the monomer unit, this spectrum was complicated. Assignment of the carbon atom signals has been completed by using the DEPT 135 sequence, and the peaks corresponding to the main-chain C_1 and pendant C_4 carbonyl atom were assigned by using the unidimensional SINEPT sequence[25] for P(3*RS*,6*RS*) (Figure 2). After that sets of selective radio-frequency pulses were applied to $^5CH_2$ preselected protons, and by setting in the pulse sequences Δ_1 and Δ_2 delays related to long-range C−H heteronuclear coupling constants of ca. 5 Hz, the pulse sequence can transfer proton magnetization to ^{13}C nuclei which have a significant long-range scalar interaction with the selected protons. The detectable selective INEPT signals corresponded to a C_4 (168.0 ppm) carbonyl carbon nucleus, determining three bond connectivity by bridging one oxygen nucleus.

The two carbonyl carbon atoms C_1 and C_4 displayed three peaks, in a 1/2/1 relative line intensity ratio, in the case of P(3*RS*,6*S*) and P(3*RS*,6*RS*) and only one peak in the case of P(3*S*,6*S*) and P(3*S*,6*RS*) (Table 2). Correlation to Bernouillian statistics was feasible in terms of triads: the two carbonyl carbon atoms are sensitive to the configurational structure of C_3 (main-chain triad effect) but are not stereosensitive to the second stereogenic center C_6 in the pendant group.

Main-chain (C_2) and side-chain (C_5 and C_7) methylene carbons appeared, for all polystereoisomers, as singlets;

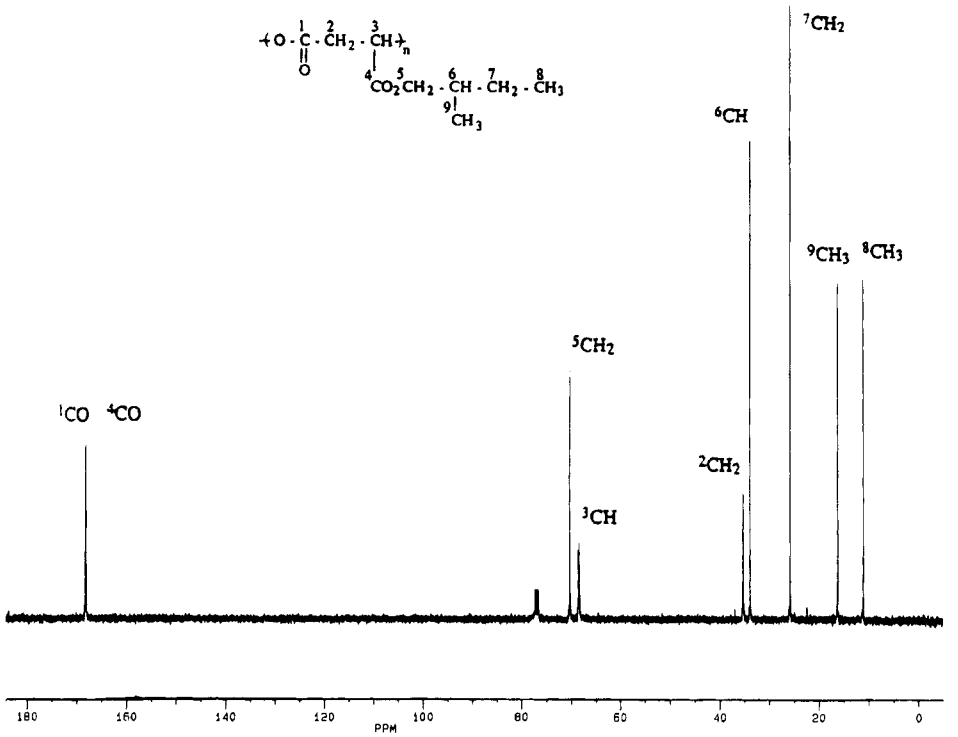


Figure 1. ^{13}C NMR spectrum of P(3*RS*,6*RS*) in $CDCl_3$.

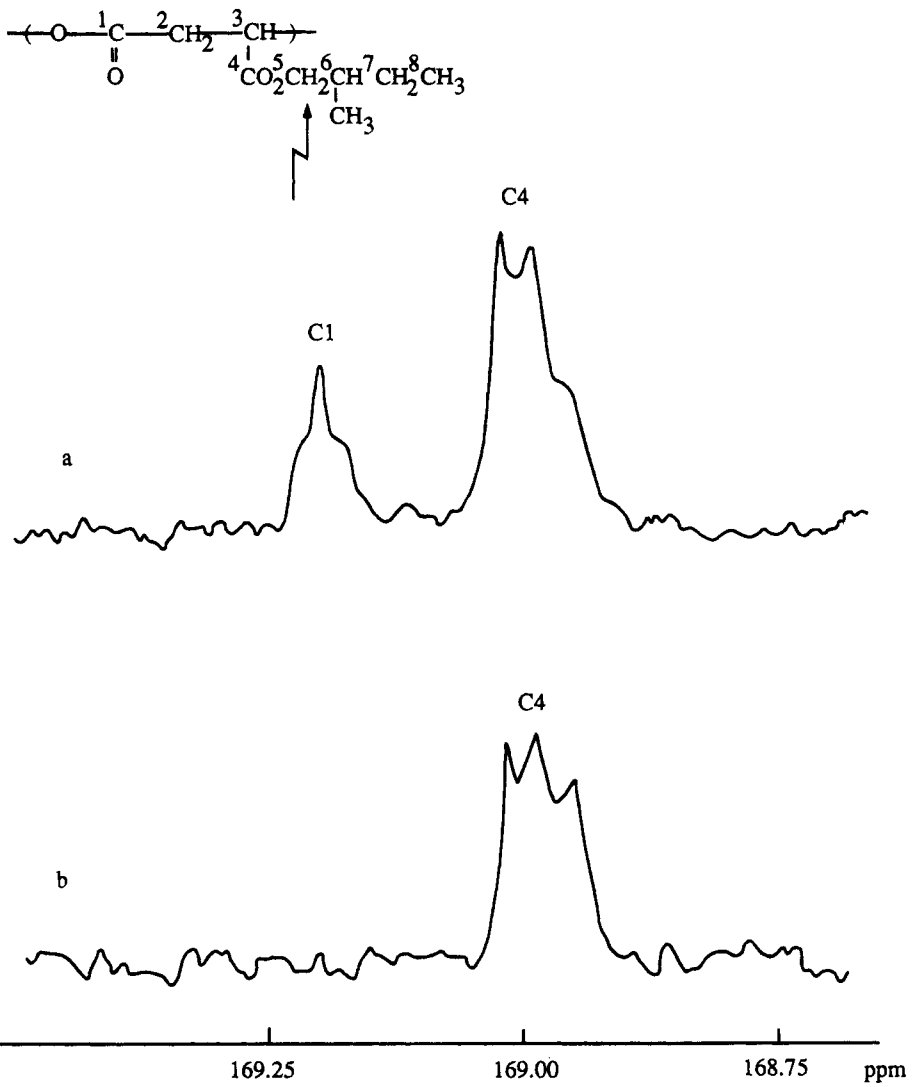


Figure 2. ^{13}C NMR spectra: carbonyl carbon atom region of P(3*RS*,6*RS*) in deuterated acetone (a) under normal conditions and (b) after selective INEPT sequence with ^1H selective pulses on $^5CH_2$.

Table 2. Stereosensitivity Comparison between Carbon Atoms of Polystereoisomers by ^{13}C NMR in $CDCl_3$ (ppm)

polymer	C_9 (CH_3)	C_8 (CH_3)	C_3 (*CH)	C_1 (CO)	C_4 (CO)
P(3*RS*,6*RS*)	16.24	11.10	68.61	168.20	
	16.23	11.09	68.54	168.16	168.01
	16.22	11.08	68.44	168.11	*d*
	a	*a*	68.37	*b*	
P(3*RS*,6*S*)	16.23	11.08	68.59	168.18	168.01
	16.21	11.06	68.54	168.14	167.99
	16.19	11.04	68.43	168.09	167.96
	a	*a*	68.37	*b*	*b*
P(3*S*,6*RS*)	16.23	11.07	68.36	168.15	167.99
	16.17				
	c				
P(3*S*,6*S*)	16.22	11.07	68.36	168.15	167.99
P(3*R*,6*S*)	16.17	11.04	63.36	168.15	168.00

[a] Peak relative intensity; 3/2/1. [b] 1/2/1. [c] 1/1. [d] Groups of peaks located at 168.01 ppm.

no stereosensitivity was observed. The situation was identical in the case of the side-chain stereogenic center C_6, which displayed a singlet regardless of its configuration (*S* or *RS*), and the configuration of the C_3 stereogenic center located in the main chain (*R* or *S* or *RS*). On the contrary, the methine C_3 was stereosensitive to triad effects of the malate repeating unit but did not allow us to observe the second stereogenic center C_6: four lines of equal intensity corresponding to the four types of triads for a Bernouillian distribution were present in the P(3*RS*,6*S*) and P(3*RS*,6*RS*), with C_3 containing both configurations *R* and *S* and with C_6 containing one or both configurations. This result was confirmed for P(3*S*,6*S*), P(3*R*,6*S*), and P(3*S*,6*RS*), with C_3 containing only one configuration and with C_6 containing one or both configurations: in all cases, only one singlet corresponding to isotriads was observed for C_3. Both methyl carbon atoms C_8 and C_9 in the side chain gave rise to interesting observations: they are sensitive to diastereomeric effects. Indeed, P(3*R*,6*S*) and P(3*S*,6*S*) each displayed one peak respectively at 11.07 and 11.05 ppm for C_8 and 16.20 (Figure 3b) and 16.17 (Figure 3a) ppm for C_9; (3*R*,6*S*) and (3*S*,6*S*) constitute diastereomeric repeating units.

These results were confirmed by the presence of well-resolved doublets at 11.07–11.04 (C_8) and 16.20–16.15 ppm (C_9) for P(3*S*,6*RS*) (Figure 3c), containing (3*S*,6*R*) and (3*S*,6*S*) diastereoisomeric repeating units. The small peaks at 16.22 and 16.24 ppm (Figure 3b) and the dissymmetry of the two peaks at 16.22 and 16.24 ppm (Figure 3c) can be explained by syndio- and heterosequences in P(3*S*,6*S*) and P(3*S*,6*RS*) due to the presence for C_3 of a low proportion of (*S*)-configuration; the corresponding atom C_2, in the lactone **1e** and **1c**, was not optically pure as determined by ^1H NMR in the presence of chiral shift reagent.[8] When the main-chain stereogenic center presented both configurations *R* and *S*, signals of C_8 and C_9 were more complex; for P(3*RS*,6*S*) and P(3*RS*,6*RS*), the C_8 and C_9 peaks displayed three lines with relative intensities in a 3/2/1 ratio due to the overlap of the different (iso, syndio, and hetero) sequence contributions of the main-chain repeat unit (Figure 3c,d). Complementary to diastereoisomerism, a large effect of tacticity for the racemic main chain with C_3 *R* and *S* randomly distributed configurations was observed.

In conclusion, the capacity for tailor-making polymeric materials with two chiral centers has been demonstrated. The possibility for adjusting the enantiomeric and diastereomeric compositions of polystereoisomers from the monomer feeds and analyzing the macromolecular chain configurational structure is important. In the area of temporary polymeric applications, it will be possible to fit properties such as degradation, solubility, compatibility, with specific devices. The presence of these two chiral carbons will also be exploited for asymmetric supported catalysis, optically active molecular separation, and chiral liquid crystal polymers. At last, this study opens the route to the binding of other chiral complex molecules and the use, for coupling, of new polymers with two stereogenic centers in the main chain.

Experimental Part

Chemicals. Stereoisomers of 4-[(2-methylbutyl)oxycarbonyl]-2-oxetanones have been synthesized and purified according to the two routes described previously,[17,19] starting from aspartic acid or malic acid enantiomers (Janssen) and by using (*RS*)- or (*S*)-2-methyl-1-butanol (Fluka). The polymerization procedure was the same for all the stereoisomers:

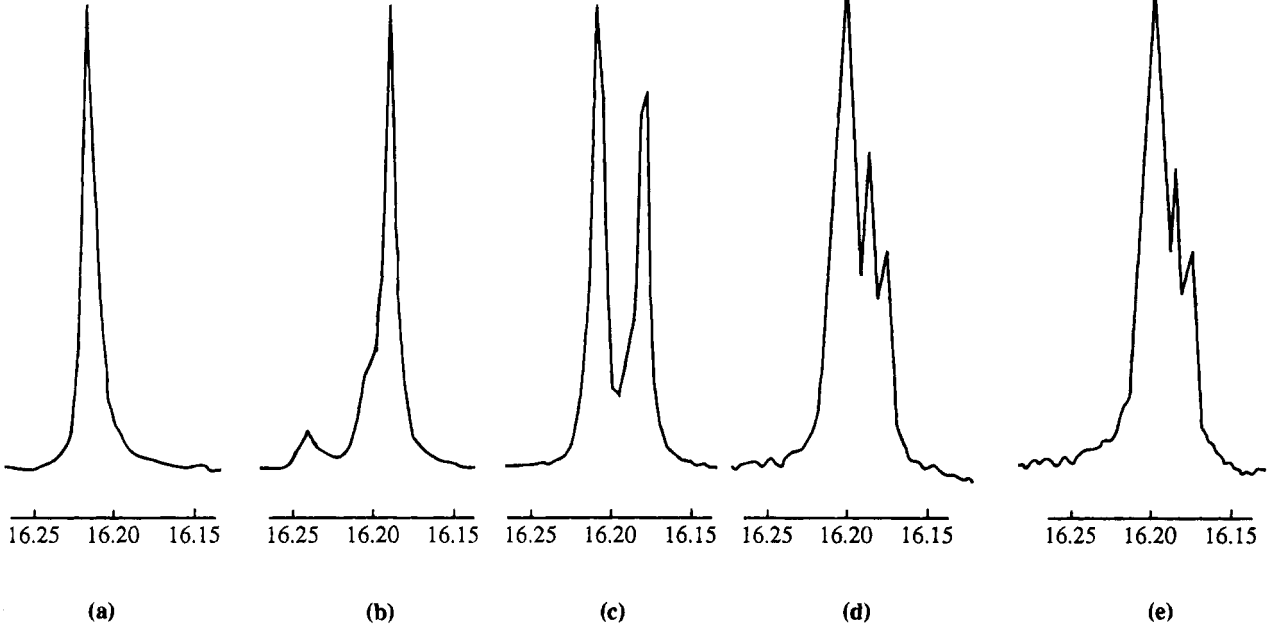


Figure 3. ^{13}C NMR spectrum of $^9CH_3$ carbon atom region of polystereoisomers: (a) P(3*S*,6*S*), (b) P(3*R*,6*S*), (c) P(3*S*,6*RS*), (d) P(3*Rs*,6*S*), (e) P(3*RS*,6*RS*).

122 μL of an initiator solution (10^{-3} equiv) was placed in a flask; solvent (anhydrous ethanol) was eliminated under vacuum (2×10^{-2} mmHg) at room temperature. Tetraethylammonium benzoate was dried at room temperature (2 h, 2×10^{-2} mmHg) and then in a N_2 atmosphere. A total of 1 g of monomer **1a** kept under a N_2 atmosphere was transferred in the polymerization flask. Polymerization was carried out at 37 °C for 3 days (disappearance of the lactone band at 1825 cm^{-1} in IR spectroscopy). Polymer was therefore dissolved in acetone and, after HCl addition (1 drop), precipitated by addition of ethanol. The sample was dried under vacuum at 40 °C for 48 h (880 mg, yield 88%).

NMR Spectra. All compounds were dissolved in CD_3COCD_3 or $CDCl_3$. ^1H and ^{13}C NMR spectra were recorded at 297 K, on a Bruker AC400 spectrometer using 5 mm sample tubes. ^1H and ^{13}C chemical shifts are reported in ppm from tetramethylsilane. The selective INEPT experiments have been carried out by using conditions described by Guerin et al.[10] DEPT 135 sequence is usual for the assignment of CH_2, CH, or CH_3 carbon atoms.

Polymer P(3*RS*,6*RS*): yield = 88%; T_g = −1.9 °C; SEC (THF, PS standards) $\bar{M}_n$ = 48 000, $\bar{M}_w$ = 73 000, I_p = 1.5; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88−0.94 (m, 6H), 1.13−1.27 (m, 1H), 1.33−1.45 (m, 1H), 1.68−1.79 (m, 1H), 2.90−3.09 (m, 2H), 3.90−4.09 (2m, 2H), 5.50 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.08 (CH_3), 16.24 (CH_3), 25.79 (CH_2), 33.93 (CH), 35.10 (CH_2), 68.37−68.61 (CH); 70.32 (CH_2), 167.98−168.02 (CO), 168.13−168.18 (CO).

Polymer P(3*RS*,6*S*): yield = 81%; T_g = −1.9 °C; $[\alpha]^{25}_D$ = +3 (*c* = 1, CH_2Cl_2); SEC (THF, PS standards) $\bar{M}_n$ = 48 000, $\bar{M}_w$ = 74 000, I_p = 1.5; ^1H NMR (400 MHz, $CDCl_3$), see above; ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.08 (CH_3), 16.23 (CH_3), 25.77 (CH_2), 33.91 (CH), 35.29 (CH_2), 68.37−68.59 (CH), 70.30 (CH_2), 167.96−168.01 (CO), 168.10−168.18 (CO).

Polymer P(3*S*,6*RS*): yield = 86%; T_g = −8 °C; mp = +80 °C; $[\alpha]^{25}_D$ = −15° (*c* = 1, CH_2Cl_2); SEC (THF, PS standards) $\bar{M}_n$ = 68 000, $\bar{M}_w$ = 92 000, I_p = 1.3; ^1H NMR (400 MHz, $CDCl_3$), see above; ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.04−11.07 (CH_3), 16.15−16.20 (CH_3), 25.76 (CH_2), 33.89 (CH_2), 35.27 (CH_2), 68.36 (CH), 80.28 (CH_2), 167.99 (CO), 168.15 (CO).

Polymer P(3*S*,6*S*): yield = 93%; T_g = −5.2 °C; mp = +120 °C; $[\alpha]^{25}_D$ = −20° (*c* = 1, CH_2Cl_2); SEC (THF, PS standards) $\bar{M}_n$ = 44 000, $\bar{M}_w$ = 66 000, I_p = 1.6; ^1H NMR (400 MHz, $CDCl_3$), see above; ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.07 (CH_3), 16.20 (CH_3), 25.76 (CH_2), 33.89 (CH), 35.27 (CH_2), 68.37 (CH), 70.30 (CH_2), 167.97 (CO), 168.12 (CO).

Polymer P(3*R*,6*S*): yield = 86%; T_g = 2.3 °C; mp = +82.5 °C; $[\alpha]^{25}_D$ = +19° (*c* = 1, CH_2Cl_2); SEC (THF, PS standards) $\bar{M}_n$ = 94 000, $\bar{M}_w$ = 121 000, I_p = 1.3; ^1H NMR (100.5 MHz, $CDCl_3$), see above; ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.05 (CH_3), 16.17 (CH_3), 25.78 (CH_2), 33.90 (CH), 35.30 (CH_2), 68.39 (CH), 70.31 (CH_2), 168.00 (CO), 168.15 (CO).

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