Polymers with Pharmacological Activity. 3. Stereochemical Configuration of Acrylic Polymers Bearing Paracetamol and Phenacetin Side Groups

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ABSTRACT: This paper reports the analysis of the stereochemical configuration of poly[4-(methacryloyloxy)acetanilide] (PMOA) and poly[4-[[2-(methacryloyloxy)ethyl]oxy]acetanilide] (PMOEA) by ^1H and ^{13}C NMR spectroscopy. PMOA is an acrylic polymer bearing "paracetamol" units as side substituents of the acrylic backbone, whereas PMOEA can be considered an acrylic polymer having side substituents with a chemical structure similar to "phenacetin". Polymers prepared by free radical polymerization are predominantly syndiotactic with a Bernoullian distribution of the tactic sequences, defined by an isotacticity parameter $p_m = 0.26$ for PMOA and $p_m = 0.22$ for PMOEA, independent of the polymerization temperature. Differences in chemical shifts of ^1H and ^{13}C NMR signals of both polymers are discussed according to the alkyl or aryl character of the corresponding ester side group.

Introduction

The synthesis and behavior of pharmacologically active polymeric systems has claimed the attention of a great number of scientific research groups.[1-7]

In recent papers[8,9] we have reported the synthesis and free radical polymerization of 4-(methacryloyloxy)acetanilide (MOA) and 4-[[2-(methacryloyloxy)ethyl]oxy]acetanilide (MOEA). MOA is an acrylic compound derived from "paracetamol" (4-hydroxyacetanilide), a nonprescription analgesic and antipyretic drug that in recent years has become an increasingly popular substitute for aspirin, whereas MOEA can be considered an acrylic derivative of "phenacetin" (4-ethoxyacetanilide) whose major metabolite in the living body is paracetamol. It is clear that both monomers differ only in the presence of an oxyethylenic spacer group in MOEA, which modifies the kinetic parameters in free radical polymerization and changes the hydrolytic behavior accordingly. Apart from the physicochemical properties of both monomers and polymers, we have analyzed the pharmacological behavior of macromolecular systems prepared by the free radical polymerization of MOA by means of a well-known test in vivo.[10] The monomer and polymers exhibit average lethal doses (DL > 400 mg/kg) as well as interesting analgesic and antiinflamatory activities. Testing of MOEA and its macromolecular homologues is in progress.

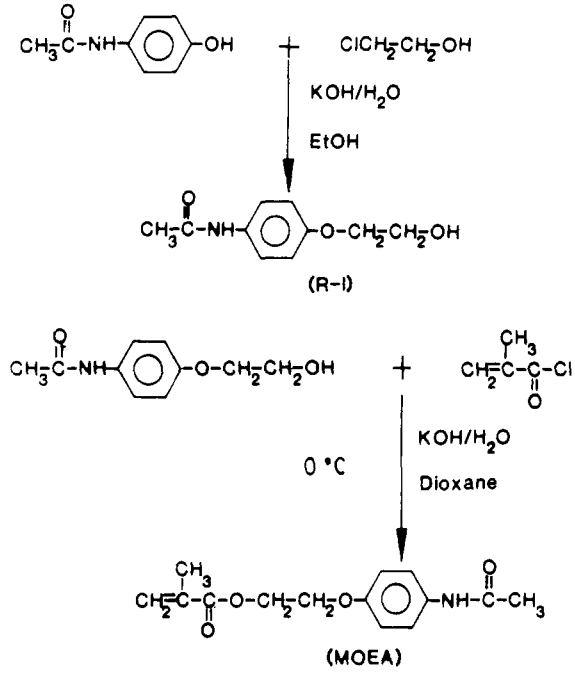
On the other hand, it is recognized[11] that the stereochemistry of biologically active compounds plays an important role in their enzymatic activity. Therefore, we think that it may be of interest to analyze the stereochemical configuration of PMOA and PMOEA in order to determine the average tacticity of their chains and the influence of the oxyethylene spacer group on the stereochemical configuration of PMOEA.

Experimental Section

Monomer Synthesis. 4-[[2-(Methacryloyloxy)ethyl]oxy]acetanilide (MOEA) was prepared by a two-step reaction according to Scheme I.

Polymerization. MOEA was polymerized at different temperatures from 50 to 160 °C, in a thermostatic bath regulated with a precision of ±0.1 °C, with 2,2′-azobis(isobutyronitrile) (AIBN) ($|I| = 1.5 \times 10^{-2}$ mol/L) and dimethylformamide (DMF) as solvent ($|M| = 1$ mol/L). All experiments were carried out in Pyrex glass ampules sealed under high vacuum. Other experimental details have been reported previously.[9]

Scheme I



Characterization of Polymers. The monomer and the polymers were characterized by IR and NMR spectroscopy. IR spectra were recorded by use of KBr pellets on a Perkin-Elmer 457 spectrometer at room temperature. NMR spectra of deuterated dimethyl sulfoxide (DMSO-d_6) solutions were recorded on a Bruker AM-200. ^1H NMR experiments were performed at 80 °C on 5% (w/v) DMSO-d_6 solutions. ^{13}C NMR spectra were recorded also at 80 °C on 25% (w/v) solutions, with the spectrometer operating at 50.3 MHz, by using an inverse gated decoupling sequence pulse with a flip angle of 90° (pulse width of 3.7 μs) and a relaxation delay of 4 s (which can be considered higher than $4T_1$ for the carbon atoms analyzed[12]). We have also recorded spectra with relaxation delay times of 8 s, which give similar intensities to those obtained with the delay time of 4 s. The relative peak intensities were measured from the integrated peaks area, calculated by means of an electronic integrator or by triangulation and planimetry.

Results and Discussion

In earlier reports[8,9] we described the free radical polymerization of MOA and MOEA in DMF solution, initi-

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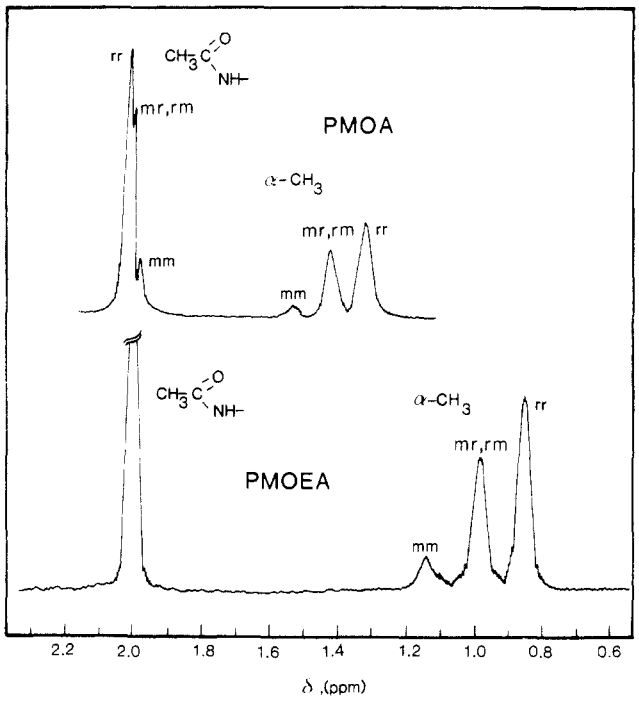

Figure 1. ^{1}H NMR (200 MHz) expanded resonances of the α-CH_3 groups for poly[4-(methacryloyloxy)acetanilide] (PMOA) and poly[4-[[2-(methacryloyloxy)ethyl]oxy]acetanilide] (PMOEA).

ated by AIBN. The results indicated that both monomers polymerize easily at relatively low or moderate temperatures (50–70 °C) but that increasing the reaction temperature gave rise to a drastic decrease of the degree of conversion. This behavior was ascribed to the influence of the ceiling temperature of these monomers (T_c) on the propagation–depropagation process of the corresponding polymerization reactions. The application of kinetic data to well-known semiempirical treatments[13] gave a T_c of 137 °C for the polymerization of MOA and a T_c of 175 °C for that of MOEA. The difference in these values was explained by taking into consideration the difference in the flexibility of the growing radical end associated with the introduction of the oxyethylene spacer between the carbonyl ester group and the rigid functional side group.[9]

The aim of the present work is to investigate the influence of the oxyethylene spacer group on the stereochemistry of PMOEA sequences compared to that of PMOA. In this regard we analyze and compare the proton and ^{13}C NMR spectra of PMOEA and PMOA. Figure 1 shows the high-field ^{1}H NMR peaks of the α-methyl and acetamido (CH_3CONH) groups of both polymers.

The resonance signal of the α-CH_3 (PMOEA) splits into three well-resolved peaks at 1.15, 1.00, and 0.85 ppm from TMS, which have been assigned to iso (*mm*), hetero (*mr* + *rm*), and syndiotactic (*rr*) triads in order of increasing field, similar to the classical assignment of the α-CH_3 resonance signals for pure poly(methyl methacrylate) (PMMA)[14] and PMOA.[8] It is noteworthy that the chemical shifts of the three α-CH_3 resonance signals of PMOEA are very close to those of a poly(methyl methacrylate) prepared under similar experimental conditions at a polymerization temperature of 60 °C, since the 2-(ethyloxy) group causes an essentially aliphatic character that, from a magnetic point of view, is very similar to that of a methoxy group.

The experimental values of the molar fraction of tactic sequences are given in Table I. They are independent of the polymerization temperature in the range 60–120 °C. Also in this table are shown the corresponding values of tactic triads for PMOA, determined previously,[8] as well as those of poly(methyl methacrylate). It is clear that the molar fractions of syndio- (*rr*), hetero- (*rm* + *mr*), and isotactic (*mm*) triads are very similar for these three polymers and correspond to predominantly syndiotactic chains. However, as is shown in Figure 1, two main differences are observed with respect to the ^{1}H NMR spectrum of PMOA.

Table I
Triad Molar Fraction Determined from the ^{1}H NMR Resonance Signals of α-CH_3 Groups

		tacticity		
polymer	polym temp, °C	*mm*	*mr* + *rm*	*rr*
PMOEA	60	0.06	0.36	0.58
	70	0.05	0.35	0.60
	90	0.05	0.36	0.59
	120	0.06	0.35	0.59
PMOA	50–120	0.06	0.40	0.54
PMMA[a]	60	0.04	0.35	0.61

[a] Taken from ref 18.

First, the chemical shifts of the α-CH_3 resonances of PMOA are shifted downfield about 0.5 ppm with respect to those of PMOEA, as a consequence of the aromatic character of the ester group, which makes clear the deshielding effect of the this group in PMOA compared to the aliphatic ester in PMOEA. Also, it can be clearly observed that the chemical shift of the three α-CH_3 resonance peaks is somewhat higher for PMOEA (~0.15 ppm) than for PMOA (~0.11 ppm).

Second, as we have reported previously,[8] the acetyl side group resonance of PMOA is sensitive to the stereochemistry of the polymer segments, although this group is relatively far from the pseudoasymmetric quaternary carbon. This fact was explained by taking into consideration that PMOA presents a rigid 1,4-disubstituted aromatic nucleus and a very polar amido group that can interact with the carbonyl ester group of the neighboring units, this interaction being dependent on the stereochemical triad configuration. However, as shown in Figure 1, the acetyl group gives only one sharp singlet for PMOEA, independent of tacticity. This result may be satisfactorily explained by taking into account that the introduction of the oxyethylene spacer between the ester group and the aromatic nuclei ($COOCH_2CH_2OC_6H_4$) provides enough flexibility to cancel the dipolar interactions between the acetamido and the carbonyl ester groups of neighboring units. A possible contribution of the β-CH_2 resonances to the splitting of the acetamido signals can be rejected because the β-CH_2 resonances of PMOA are shifted downfield about 0.5 ppm with respect to those of PMMA (in a similar way to the α-CH_3 resonances), giving rise to a relatively broad and poorly resolved band with maxima at about 2.34 and 2.80 ppm.

On the other hand, the decoupled ^{13}C NMR spectra provide excellent and accurate information on the stereochemical configuration of the chains. Figure 2 shows the decoupled ^{13}C NMR spectra of PMOA and PMOEA recorded in DMSO-d_6 at 80 °C. All the signals have been assigned to the corresponding carbon atoms according to the chemical structures shown in this figure. The α-CH_3 carbons that appear between 15 and 20 ppm from TMS seem to be sensitive to the triad tacticity of the polymer segments. However, the CH_3 of the acetamido residue gives rise to a very sharp singlet for both polymers, independent of the chemical structure of the side group, indicating the lack of sensitivity to the stereochem-

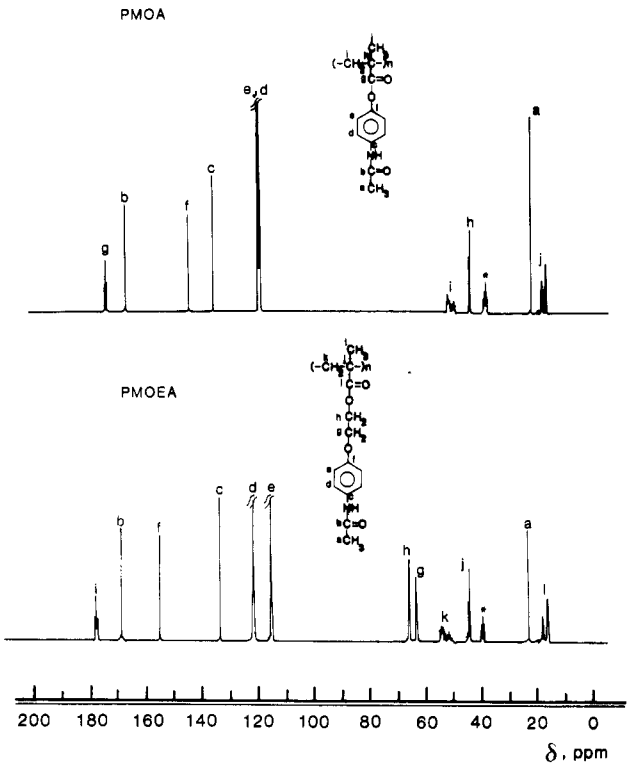

Figure 2. Decoupled ^{13}C NMR (50.3 MHz) spectra in DMSO-d_6 at 80 °C of poly[4-(methacryloyloxy)acetanilde] (PMOA) and poly[4-[[2-(methacryloyloxy)ethyl]oxy]acetanilide] (PMOEA).

ical configuration of the monomer units. Although this result seems to disagree with the splitting of the acetamido methyl protons in the ^1H NMR spectrum of PMOA, we must consider that there are several polymer and copolymer systems in which the splitting of the resonance of a given functional side group in ^1H NMR is not detected in the corresponding ^{13}C NMR spectrum.[15] This is the case with the signal of the CH_3O group in methyl methacrylate–styrene random or alternating copolymers in which the ^1H NMR spectrum shows splitting according to the tacticity of copolymer segments,[16,17] but the ^{13}C-NMR spectrum shows a sharp singlet independent of the tacticity.

The signals assigned to the resonance of the quaternary acrylic carbon and β-CH_2 group (h, i for PMOA and j, k for PMOEA in Figure 2) seem to split into several peaks according to configurational sequences, as is reported subsequently. But the main differences arise from the influence of the spacer ethyloxy group upon shielding of the aromatic carbons. As is schematically represented in Figure 2, the carbon atom signal (f) of PMOEA, directly linked to the oxyethyl spacer group, is shifted about 8 ppm toward lower field with respect to that of the same atom in PMOA. Also the other aromatic carbons, c, d, and e, present different chemical shifts for both polymers. Finally, although the carbonyl carbon of the acetamido group is not sensitive to tacticity, the carbonyl carbon of the acrylic ester group shows a clear sensitivity to the stereochemical configuration of monomer units in sequences of triads or pentads.

Figure 3 shows the expanded ^{13}C NMR decoupled spectrum of the α-CH_3 and quaternary carbon resonance signals of PMOA and PMOEA. For clarity the signals of DMSO have been drawn with reduced intensity. Both groups present three resonances, which can be assigned to iso- (*mm*), hetero- (*rm* + *mr*), and syndiotactic (*rr*) triads in order of increasing field, in a similar way to the classical assignment of the same groups for pure poly-

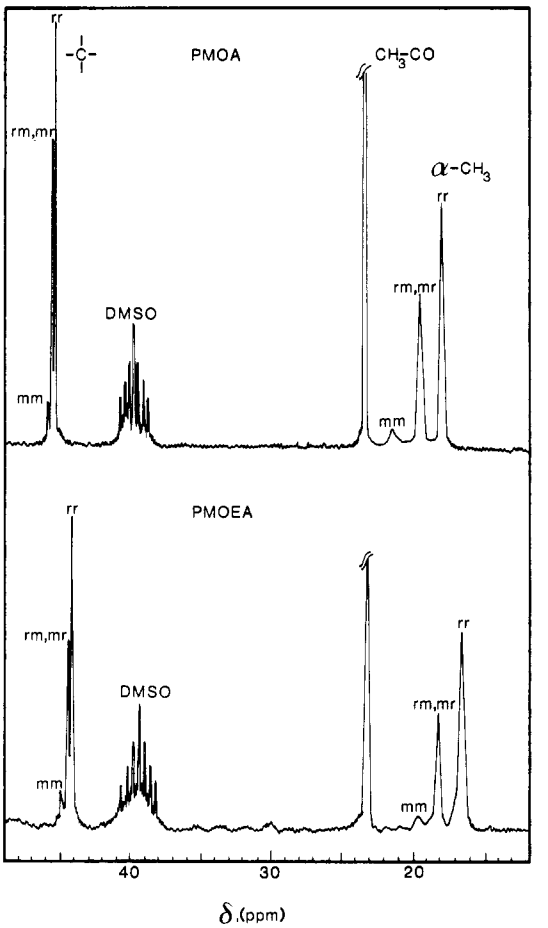

Figure 3. ^{13}C NMR expanded resonance signals of the α-CH_3, acetamido, and quaternary carbons of PMOA and PMOEA.

Table II
^{13}C Chemical Shifts and Molar Fractions of Tactic Triads Determined from the Resonance Signals of α-Methyl and Quaternary Carbons

		PMOA		PMOEA		PMMA	
signal	sequence	δ, ppm	molar fractn	δ, ppm	molar fractn	δ, ppm	molar fractn
α-CH_3	*rr*	17.87	0.56	16.48	0.60	16.43	0.59
	mr + *rm*	19.36	0.39	18.12	0.36	18.39	0.35
	mm	20.85	0.05	19.76	0.04	20.67	0.05
quat C	*rr*	45.12	0.55	44.15	0.60	43.89	0.60
	mr + *rm*	45.28	0.40	44.46	0.34	44.22	0.36
	mm	45.44	0.05	44.77	0.06	44.75	0.04

(methyl methacrylate).[18,19] It is clear from this figure that the α-CH_3 and quaternary carbon resonances of PMOA are shifted toward lower field with respect to the corresponding signals of PMOEA as a consequence of the presence of the ethyloxy spacer group. The experimental values of the chemical shifts and relative intensities of the signals assigned to both carbon atoms are quoted in Table II, together with those of similar atoms of PMMA.

As in the ^1H NMR resonances, the α-CH_3 carbon of PMOEA present signals with chemical shifts very close to those of the same carbon of PMMA. This is also observed in the splitting of the quaternary pseudoasymmetric carbon in which the separation of the resonance signals assigned to different triads is about 0.31 ppm for PMOEA and PMMA whereas the corresponding value for PMOA is only of 0.16 ppm. The statistical parameters quoted in Table III have been determined from the *mm*, *mr* + *rm*, and *rr* triad molar fractions given in Tables

Table III
Comparative Stereochemical Parameters of the Free Radical Polymerization of MOA, MOEA, and MMA

parameter	PMOA	PMOEA	PMMA
	Addition Probabilities		
p_m	0.26	0.22	0.23
p_r	0.74	0.78	0.77
	Conditional Probabilities		
$p(m/m)$	0.25	0.23	0.22
$p(r/r)$	0.73	0.77	0.77
$p(m/r)$	0.27	0.23	0.23
$p(r/m)$	0.75	0.77	0.78
$p(m/r) + p(r/m)$	1.02	1.00	1.01

I and II. The average conditional probabilities for iso- and syndiotactic additions to meso or racemic growing chain ends, $p(i/j)$, $i, j = m, r$ (i refers to the relative configuration of the chain end and j to the adding monomer), indicate a random distribution of the meso and racemic diads along the polymer chains[15] since the sum $p(m/r) + p(r/m)$ is very close to unity. Therefore, the stereosequence distribution of the monomer units in the macromolecular chains is consistent with the Bernoullian distribution of stereosequences with a single parameter describing the probability for isotactic placements as defined by Bovey,[20] $\sigma = p_m = 0.22$. In view of the results quoted in Table III, it is clear that the introduction of the ethyloxy spacer group between the acrylic ester group and the acetanilide side group does not drastically modify the stereochemical configuration of the monomeric units with respect to that of PMOA. We may also consider that the aromatic acrylic polymers have a stereochemistry very similar to that of poly(methyl methacrylate).

On the other hand, the resolution of the ^{13}C NMR spectra recorded at 50.3 MHz allows the experimental discrimination of sequences longer than triads (i.e., tetrads or pentads) by the analysis of the resonances signals of the carbonyl ester group and even the β-CH_2 carbons. In this sense, Figure 4 shows the resonance pattern of the C=O ester group of PMOEA and PMOA samples. In both cases, eight of the ten possible pentad peaks are well resolved, being the signals of PMOEA clearly shifted downfield about 1.4 ppm with respect to the signals assigned to the same sequence in PMOA. However, the splittings and the relative intensities of the resonance signals are rather similar in both cases. This is better shown in Table IV, which gives values of chemical shifts of the pentad signals as well as the corresponding molar fractions of sequences, together with those calculated by considering the Bernoullian statistics of the propagation step with the isotacticity parameters p_m given in Table III. The excellent agreement between calculated and experimental data supports the assignment suggested in the present work. This assignment is also similar to that of the C=O resonance signals for PMMA reported by Hatada et al.,[18] Peat and Reynolds,[19] and Ferguson and Ovenall.[21]

The analysis of the β-CH_2 resonances presents more difficulty, since, as reported by Ferguson and Ovenall,[21] the ^{13}C NMR signals of this group for PMMA may reveal hexad effects, but is not suitable for sequence analysis because of overlapping with the methyloxy resonance (CH_3O). In the case of PMOA and PMOEA, there are no overlapping effects, and therefore we may analyze the resonance signals of β-CH_2 in terms of tetrad effects. Figure 5 shows the expanded spectra of these resonances for both PMOA and PMOEA polymers. The assignment of the six rather well-resolved peaks is based on

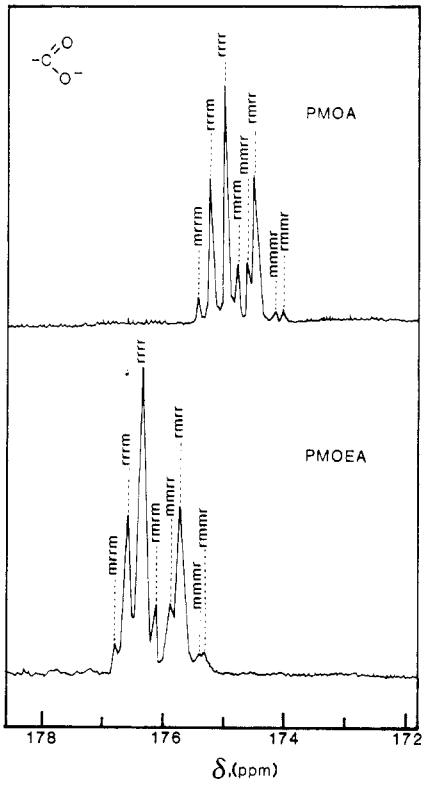

Figure 4. ^{13}C NMR expanded resonances of the carbonyl ester group (C=O) of PMOA and PMOEA.

Table IV
Tentative Assignment of Pentad Sequences to C=O Ester Group Resonance Signals of the ^{13}C NMR Spectra

			molar fractn	
polymer	δ, ppm	sequence	exptl	calcd[a]
PMOA	175.38	*mrrm*	0.05	0.04
	175.19	*mrrr*	0.18	0.20
	174.91	*rrrr*	0.29	0.30
	174.75	*rmrm*	0.08	0.07
	174.59	*mmrr*	0.07	0.07
	174.50	*rmrr*	0.19	0.21
		mmrm		0.03
	174.16	*mmmr*	0.03	0.03
	174.05	*rmmr*	0.04	0.04
		mmmm		0.01
PMOEA	176.78	*mrrm*	0.04	0.03
	176.56	*mrrr*	0.18	0.20
	176.31	*rrrr*	0.36	0.37
	176.12	*rmrm*	0.06	0.06
	175.87	*mmrr*	0.06	0.06
	175.72	*rmrr*	0.20	0.21
		mmrm		0.02
	175.36	*mmmr*	0.03	0.02
	175.29	*rmmr*	0.03	0.03
		mmmm		0.00

[a] According to the Bernoullian trial with $p_m = 0.26$ for PMOA and $p_m = 0.22$ for PMOEA.

similar results reported by Matsuzaki et al.[22] for the β-CH_2 resonance signals of poly(α-methylvinyl alkyl ether)s, by Carman[23] for those of poly(vinyl chloride), and by Chûjô et al.[24] for those of PMMA. Table V depicts the chemical shifts of β-CH_2 groups assigned to sequences of tactic tetrads, together with the corresponding molar fractions and those calculated by the Bernoullian statistics with the isotacticity parameters quoted in Table III. The complete assignment was made after a careful analysis of the observed versus calculated intensity distribution for both PMOA and PMOEA.

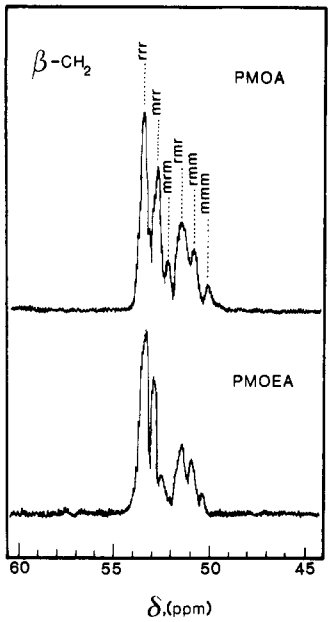

Figure 5. ^{13}C NMR expanded resonances of the β-CH_2 carbon for PMOA and PMOEA.

Table V
Tentative Assignment of Tetrad Sequences to β-CH_2 Resonance Signals of the ^{13}C NMR Spectra

			molar fractn	
polymer	δ, ppm	sequence	exptl	calcd[a]
PMOA	53.30	*rrr*	0.42	0.41
	52.60	*mrr*	0.24	0.28
	52.15	*mrm*	0.03	0.05
	51.45	*rmr*	0.18	0.14
	50.80	*rmm*	0.09	0.10
	50.00	*mmm*	0.04	0.02
PMOEA	53.30	*rrr*	0.44	0.47
	52.95	*mrr*	0.24	0.27
	52.55	*mrm*	0.06	0.04
	51.40	*rmr*	0.15	0.13
	51.00	*rmm*	0.09	0.08
	50.35	*mmm*	0.02	0.01

[a] According to the Bernoullian trial with $p_m = 0.26$ for PMOA and $p_m = 0.22$ for PMOEA.

In conclusion, from the analysis of ^1H and ^{13}C NMR spectra of PMOEA and PMOA, we can state that the free radical polymerization of MOA and MOEA initiated by AIBN follows Bernoullian statistics with an isotacticity parameter p_m of 0.26 for PMOA and 0.22 for PMOEA, independent of the polymerization temperature. The introduction of the ethyloxy spacer into the side ester functional group does not modify appreciably the kinetic mechanism of the propagation step from a stereochemical point of view, but there is a detectable influence of the alkyl character of this group on the chemical shifts of the resonance signals in the ^{13}C NMR spectra of PMOEA.

Acknowledgment. We thank the "Comisión Asesora de Investigación Científica y Técnica" for financial support through Grant 554/84.

Registry No. PMOEA, 123643-27-6; PMOA, 37838-81-6; MOA, 37796-01-3; MOEA, 51349-95-2.

References and Notes

(1) Baker, R. *Controlled Release of Biologically Active Agents*; Wiley Interscience: New York, 1987.
(2) Rosato, D. V. In *Biocompatible Polymers, Metals and Composites*; Szycher, M., Ed.; Technomic: Lancaster, PA, 1983.
(3) Duncan, R.; Kopecek, J. *Adv. Polym. Sci.* **1984**, *57*, 51.
(4) Hastings, G. W. *Polymer* **1985**, *26*, 1331.
(5) Ringsdorf, H. *J. Polym. Sci., Polym. Symp.* **1975**, *No. 51*, 135.
(6) Ghosh, M.; Maiti, S. *Polym. Sci. Technol. (Plenum)* **1985**, *32*, 103.
(7) Overberger, C. G.; Ringsdorf, H.; Auchen, B. *J. Med. Chem.* **1965**, *8*, 862.
(8) San Román, J.; Lopez, M. E. *Polymer* **1989**, *30*, 949.
(9) Levenfeld, B.; San Román, J.; Lopez, M. E. *J. Polym. Sci., Polym. Chem. Ed.*, in press.
(10) Burgos, A.; Darias, V.; Fraile, C.; Madruga, E. L.; Martin, D.; San Román, J.; Vivas, J. M. *XXII Rencontres Internationales de Chimie Therapeutique*; Clermont-Ferrand: 1986; p 132.
(11) Kim, S. W.; Petersen, R. V.; Feijen, J. Polymeric Drug Delivery Systems. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: London, 1980.
(12) Bovey, F. A.; Schilling, F. C.; Kwei, T. K.; Frisch, H. L. *Macromolecules* **1977**, *10*, 559.
(13) Yamada, B.; Sugiyama, S.; Mori, S.; Otsu, T. *J. Macromol. Sci., Chem.* **1981**, *A15*, 339.
(14) Bovey, F. A. *High Resolution NMR of Macromolecules*; Academic Press: London, 1972.
(15) Bovey, F. A. *Chain Structure and Conformation of Macromolecules*; Academic Press: New York, 1982.
(16) San Roman, J.; Madruga, E. L.; Del Puerto, M. A. *Angew. Makromol. Chem.* **1980**, *86*, 1.
(17) Koinuma, H.; Tanabe, T.; Hirai, H. *Makromol. Chem.* **1982**, *183*, 211.
(18) Chûjô, R.; Hatada, K.; Kitamaru, R.; Kitayama, T.; Sato, H.; Tanaka, I. *Polym. J. (Tokyo)* **1987**, *19*, 413.
(19) Peat, I. R.; Reynolds, W. F. *Tetrahedron Lett.* **1972**, *14*, 1359.
(20) Bovey, F. A.; Tiers, G. V. D. *J. Polym. Sci.* **1960**, *44*, 173.
(21) Ferguson, R. C.; Ovenall, D. W. *Macromolecules* **1987**, *20*, 1245.
(22) Matsuzaki, K.; Okuzono, S.; Kanai, T. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 3447.
(23) Carman, C. J. *Macromolecules* **1973**, *6*, 725.
(24) Chûjô, R.; Hatada, K.; Kitamaru, R.; Kitayama, T.; Sato, H.; Tanaka, Y.; Horii, F.; Terawaki, Y. *Polym. J. (Tokyo)* **1988**, *20*, 627.