Detailed Microstructural Analysis of 4-(Methacryloyloxy)acetanilide–2-Hydroxyethyl Methacrylate Copolymers Using Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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ABSTRACT: ^{13}C NMR spectra (75.5 MHz) of 4-(methacryloyloxy)acetanilide (M)–2-hydroxyethyl methacrylate (H) copolymers prepared by free-radical copolymerization were analyzed in terms of sequence distribution and relative stereochemical configuration of monomer units along the macromolecular chains. The values of concentration of M- and H-centered triads, determined experimentally from the analysis of α-CH_3 and C=O resonance signals, were in fairly good agreement with those calculated statistically, taking into consideration the terminal copolymerization model and Bernoullian distribution of stereoregularity, with the statistical parameters P_{ij} determined from the reactivity ratios $r_M = 2.15$ and $r_H = 0.90$ and the coisotacticity parameters $\sigma_{MM} = 0.26$, $\sigma_{HH} = 0.21$, $\sigma_{MH} = \sigma_{HM} = \sigma^* = 0.30$.

Introduction

The biodegradation of polymer systems in the living organism depends predominantly on their chemical structure,[1] but the enzymatic degradation of a given susceptible bond (i.e., an ester bond) is also affected by the conformation of the polymer chain and by the stereochemical configuration of the pseudoasymmetric carbon atoms present in the repeat monomeric units along the macromolecular chains. Both factors are involved in the formation of specific enzyme–substrate complexes.[2-4] Among these factors only the configuration will be analyzed in this paper.

Our more recent studies are centered on the preparation of macromolecular systems with pharmacologically active compounds anchored to a polymeric matrix by means of covalent bonds, which can be easily degraded in the physiological environment, such as the ester group.[5-8] In this sense we have reported the synthesis and polymerization of methacrylic esters of salicylic acid (2-(methacryloyloxy)benzoic acid)[5] and of paracetaminophen or paracetamol (4-(methacryloyloxy)acetanilide),[6] being the corresponding monomers and polymeric compounds of medical interest because of their pharmacological activity, which has been tested in vitro and in vivo.[9,10]

We have also controlled the hydrophilic character of this kind of compounds by preparing copolymer systems with a suitable composition and distribution of 2-hydroxyethyl methacrylate units along the copolymer chains.[11]

Considering that the stereochemistry of biologically active compounds can play an important role in their hydrolytic and enzymatic activity,[12] we think that it may be of interest to analyze the stereochemical configuration of copolymer systems prepared from a wide range of compositions of monomer mixtures of 2-hydroxyethyl methacrylate and 4-(methacryloyloxy)acetanilide.

Experimental Section

Monomer Preparation and Purification of Reagents. 4-(Methacryloyloxy)acetanilide (M) was prepared by the reaction of paracetamol (4-hydroxyacetanilide) with methacryloyl chloride, according to a modification of the known Schotten Bauman reaction described elsewhere (6).

2-Hydroxyethyl methacrylate (H), supplied by HYDRON Europe, Ltd., containing less than 0.05 wt % of ethylene glycol dimethacrylate, was distilled under reduced pressure of nitrogen, and the fraction of bp 87–89 °C (5 mmHg) was collected.

2,2′-Azobis(isobutyronitrile) (AIBN) was purified by fractional crystallization from methanol, mp 104 °C.

N,*N*-Dimethylformamide (DMF) was dried over anhydrous magnesium sulfate for 2 days and later with phosphoric anhydride overnight. After drying, DMF was distilled under reduced pressure of nitrogen. Other reagents were of extra-pure grade and used without purification.

Copolymerization. Copolymerization reactions were carried out in DMF solution at 50 ± 0.1 °C, in Pyrex glass ampules sealed off under high vacuum. Monomer and initiator concentrations were 0.5 and 1.5×10^{-2} mol/L, respectively. The sealed ampules were shaken vigorously and immersed in a water bath held at the required temperature of polymerization. After the proper reaction time, the ampules were removed from the bath and at once the contents were poured into a large excess of diethyl ether–petroleum ether mixture. The precipitated samples were washed with the precipitant mixture and dried under vacuum until constant weight was attained.

NMR Spectra Measurements. ^{13}C NMR spectra were recorded at 80 °C on 25% (w/v) DMSO-d_6 solutions (TMS as internal reference) with a Varian XL-300 spectrometer operating at 75.5 MHz, using a flip angle of 80° (pulse width of 13 s), a relaxation delay of 4 s, an inverse gated decoupling during acquisition, a spectral width of 16 kHz, and 16K data points. These conditions ensure the complete relaxation of all the ^{13}C nuclei analyzed. The relative peak intensities were measured from peak areas calculated by means of the electronic integrator or by triangulation and planimetry.

Results and Discussion

As we have reported previously[11] the free-radical copolymerization of 4-[(methacryloyl)oxy]acetanilide with 2-hydroxyethyl methacrylate in solution of DMF, initiated by AIBN at moderated temperatures, gives rise to the formation of homogeneous random copolymers with a statistical distribution of monomer units along the copolymer chains, which corresponds to the chemical structure outlined in Scheme I.

The average composition of different copolymer samples prepared at conversions lower than 10 wt % was determined from the analysis of the corresponding ^1H NMR spectra,[11] giving the molar composition quoted in the second column of Table I. We also have determined the composition of copolymer systems from the analysis of the ^{13}C NMR spectra recorded in the experimental

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Scheme I

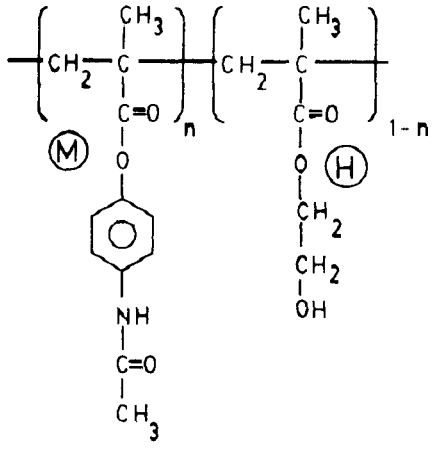

Table I
Composition Data and Conditional Probabilities P_{ij} for the Copolymerization at Low Conversion of 4-(Methacryloyloxy)acetanilide (M) with 2-Hydroxyethyl Methacrylate (H)

	f_M[a] (copolymer)			
feed F_M[a]	^{1}H NMR	^{13}C NMR	P_{MH}	P_{HM}
0.100	0.12_5	0.11_5	0.80_7	0.10_9
0.200	0.26_1	0.28_0	0.65_0	0.21_7
0.400	0.50_0	0.48_6	0.41_0	0.42_5
0.600	0.73_2	0.72_3	0.23_6	0.62_5
0.800	0.88_9	0.89_1	0.10_4	0.81_6

[a] F_M and f_M are the molar fraction of 4-(methacryloyloxy)-acetanilide in the monomer feed and in the copolymer samples, respectively.

conditions described above. To verify the accuracy of values obtained from the analysis of the ^{13}C NMR resonances, we determined the composition of copolymer samples from the analysis of the signal assigned to the methylacetamido group (δ 23.33) of M units and the methylene carbon $-CH_2OH$ (δ 58.68) of the hydroxyethyl side group of H units. These signals are very sharp single peaks in the spectra of copolymer smaples analyzed, independently of their composition; the data obtained are collected in the third column of Table I, being rather close to those obtained from the analysis of ^{1}H NMR spectra. This is better seen in the diagrams of Figure 1, which correspond to the application of the composition data collected in Table I to the linearization methods of the general copolymer composition equation proposed by Fineman and Ross[13] (Figure 1A) and by Kelen and Tüdos[14] (Figure 1B). The straight lines drawn in both diagrams correspond to the values of reactivity ratios $r_M = 2.15 \pm 0.05$ and $r_H = 0.90 \pm 0.10$, which has been determined by the application of the least-squares method to the composition data obtained from ^{1}H NMR.[11] It is clear from these figures that also the composition data determined from ^{13}C NMR give values of the parameters used as coordinates that fit adequately the straight lines drawn according to the reactivity ratios mentioned above and support the accuracy of the ^{13}C NMR spectra recorded in the experimental conditions of the present work. On this basis, we report here the microstructure and stereochemical configuration of copolymer chains prepared with different feed composition, from the exhaustive analysis of characteristic NMR resonance signals, since the decoupled ^{13}C NMR spectra provide excellent and accurate information of the chemical composition and stereochemical configuration of copolymer chain segments. In this analysis we also have considered the statistical distribu-

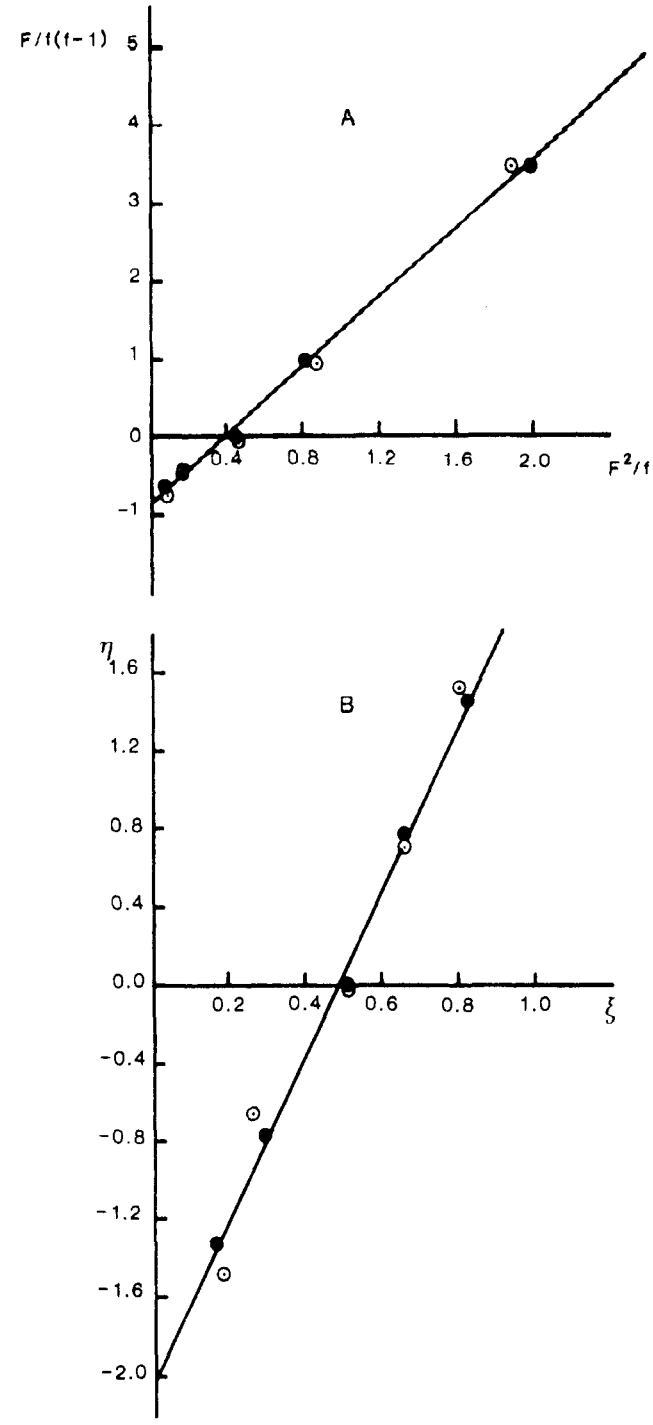

Figure 1. Fineman–Ross (A) and Kelen–Tüdos (B) linearization diagrams for the free-radical copolymerization of 4-(methacryloyloxy)acetanilide (M) with 2-hydroxyethyl methacrylate. The straight lines correspond to $r = 2.15$ and $r_H = 0.90$; (●) composition data from ^{1}H NMR, (⊙) composition data from ^{13}C NMR spectra.

tion of M- and H-centered sequences determined from the conditional probabilities P_{MH} and P_{HM} (and $P_{MM} = 1 - P_{MH}$, $P_{HH} = 1 - P_{HM}$) quoted in the fourth and fifth columns of Table I, whose values have been calculated considering that the copolymerization system follows the classical terminal model of copolymerization.[15] The parameters P_{ij} (i,j = M,H) are the conditional probabilities for the addition of monomer units j to free radical i ends.[16]

α-CH_3 Resonance Signals. Figure 2 presents the expanded ^{13}C NMR decoupled spectra of the α-CH_3 carbon resonance signals of homopolymers M and H as well as those of several M–H copolymer samples of various compositions. The α-CH_3 group is present in the chem-

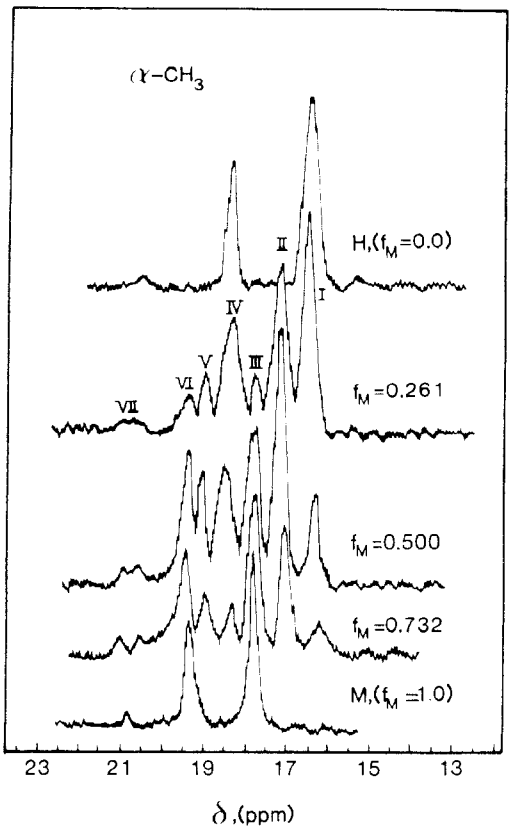

Figure 2. ^{13}C NMR spectra (75.5 MHz) of the α-CH_3 side groups of M–H copolymers.

ical structure of both mesomeric units, but, as we have reported previously[17] in the case of poly[4-[(methacryloyl)oxy]acetanilide] (M in Figure 2), this group gives three resonances at 17.87, 19.36, and 20.85 ppm from TMS, which have been assigned to iso (mm), hetero (mr + rm), and syndiotactic (rr) triads in order of increasing field, following the assignment of the same chemical residue for pure poly(methyl methacrylate).[18,19]

The α-CH_3 group of poly(2-hydroxyethyl methacrylate), (H in Figure 2) gives also three resonance signals at 16.40, 18.35, and 20.50 ppm from TMS, which have been assigned to mm, mr + rm, and rr tactic triads in order of increading field, since these values are close to those reported for the resonances of the α-CH_3 in poly(methyl methacrylate).[17-19] It is clear from Figure 2 that the α-CH_3 resonances of polyM are shifted toward lower field with respect to the corresponding signals of polyH, as a consequence of the aromatic character of the ester group in M with respect to the aliphatic one of the 2-hydroxyethyl residue in H, which in turn may be considered from a magnetic point of view, very similar to the methoxy group of poly(methyl methacrylate). The deshielding effect of the aromatic ester group on the α-CH_3 residue of M units is useful to obtain valuable information on the distribution of monomer units and also the stereochemical configuration of copolymer segments of the macromolecular chains.

Effectively, as is shown in the spectra of copolymers drawn in Figure 2, the α-CH_3 resonance of both M and H units present a complex pattern with seven distinguishable peaks, whose intensities change with the average composition of copolymer samples. A detailed analysis of these signals makes clear that the peaks named I and IV have the chemical shifts of the rr and rm + mr triads in polyH; in addition, the intensity of these signals increases with the increasing molar fraction of H in the copolymer samples analyzed. Consequently, we have assigned these

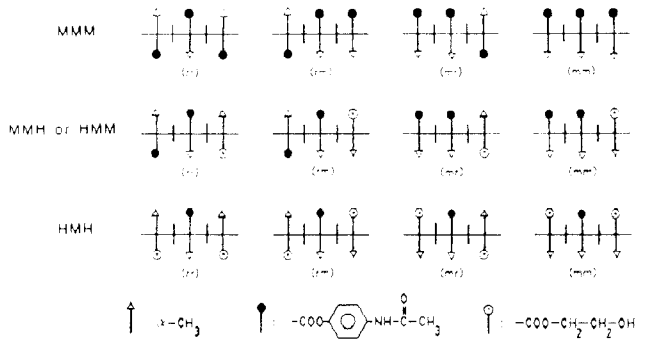

Figure 3. Schematic representation of M-centered triads in 4-(methacryloyloxy)acetanilide–2-hydroxyethyl methacrylate copolymers.

peaks to H-centered triads with stereochemical configurations rr and mr + rm, respectively. Similarly, peaks III and VI present the chemical shift of the rr and rm + mr triads in polyM, and also their intensities increase with the increasing of M molar fraction in the copolymer chains. Therefore, we assign these peaks to M-centered triads with stereochemical configurations rr and rm + mr, respectively. The poor resolved and relatively broad band about 20.5–21.0 ppm (peak VII) may be easily assigned to M- and H-centered triads with a stereochemical configuration (mm), independent of their chemical composition.

However, the assignment of two new signals designated II and V, which do not appear in the spectra of the homopolymers (see Figure 2) presents more of problem and indicates that one can expect not only an effect of stereochemical configuration but also a slight influence of the composition of M- and H-centered sequences on the chemical shift of the corresponding resonance signals.

In this sense, for a complete description of the monomers sequence distribution and relative stereochemical configuration in terms of M- and H-centered triads it is necessary to take into consideration as many as 10 different triads with a central M unit which may be magnetically distinguishable, as is shown in the scheme of Figure 3. Similarly, 10 triads with a central H unit must also be considered. It is well-known that the sensitivity of the α-CH_3 resonances to tacticity arises from the diamagnetic effects of the carbonyl ester group of the neighboring units on the α-CH_3 residue of the methacrylic central unit.[20]

It can be clearly observed in the structures drawn in Figure 3, as well as in molecular models, that the diamagnetic effects of neighboring units on the α-CH_3 central unit for MMH or HMM (rr) triads must be different from those of MMM (rr) triads or HMH (rr) triads, and according to the difference in the chemical shifts of (rr) sequences of both M and H homopolymers, it may be expected that the cosyndiotactic heterotriads MMH or HMM (rr) give a resonance signal between those of the homopolymers. Therefore, we tentatively assign the peak II to this kind of triad as is indicated in Table II. Also it can be easily understood that the α-CH_3 of the central M unit in MMH or HMM triads with the stereochemical configuration rr have the same magnetic and spatial arrangement as the MHH (rr) triads; so we have included these triads in the signal II.

On the same basis, it may be expected that the HMH (rr) sequence has the same chemical shift as the syndiotactic triad of homopolymer H and that the MHM (rr) should be similar to the syndiotactic triad of homopolymer M (see Figure 3 and Table II).

Table II
Assignment of the α-CH_3 Resonances to Sequences of M- and H-Centered Triads[a]

spectral signal no.	chemical shift, ppm	copolymer sequence: composn	copolymer sequence: confign
I	16.40	HHH	rr
		HMH	
		HHM	
II	17.15	MHH	rr
		MMH	
		HMM	
III	17.80	MHM	rr
		MMM	
		HHH	mr + rm
IV	18.40	HHM	rm
		MHH	mr
		MHM	mr + rm
		HHM	mr
V	18.90	MHH	rm
		MMH	mr
		HMM	rm
		MMM	mr + rm
VI	19.40	MMH	rm
		HMM	rm
VII	20.50–21.00	*a*	mm

[a] The signals considered in this interval correspond to all the possible isotactic triads, independent of their composition.

Table III
Molar Fraction of M- and H-Centered Triads According to Their Stereochemical Configuration[a]

triad: composn	triad: confign	f_M (copolymer): 0.125	0.261	0.500	0.732	0.889
MMM	rr	0.00_3	0.01_8	0.09_4	0.22_0	0.38_4
	mr + rm	0.00_2	0.01_3	0.06_6	0.15_6	0.26_9
	mm	0.0	0.00_2	0.01_1	0.02_7	0.04_7
MMH + HMM	rr	0.02_4	0.06_2	0.12_5	0.13_5	0.08_7
	mr + rm	0.01_9	0.04_8	0.09_8	0.10_5	0.06_8
	mm	0.00_4	0.00_9	0.01_9	0.02_0	0.01_3
HMH	rr	0.04_3	0.05_3	0.04_2	0.02_0	0.00_5
	rm + mr	0.03_7	0.04_5	0.03_6	0.01_8	0.00_4
	mm	0.00_8	0.00_9	0.00_8	0.00_4	0.0
HHH	rr	0.41_6	0.28_0	0.10_5	0.02_7	0.00_3
	mr + rm	0.22_1	0.14_8	0.05_6	0.01_4	0.00_2
	mm	0.02_9	0.01_9	0.00_7	0.00_2	0.0
HHM + MHH	rr	0.10_0	0.14_1	0.13_5	0.07_5	0.02_0
	mr + rm	0.07_0	0.09_8	0.09_4	0.05_3	0.01_4
	mm	0.01_1	0.01_6	0.01_5	0.00_9	0.00_2
MHM	rr	0.00_6	0.01_8	0.04_4	0.05_4	0.03_8
	mr + rm	0.00_5	0.01_5	0.03_7	0.04_6	0.03_3
	mm	0.00_1	0.00_3	0.00_8	0.01_0	0.00_7

[a] These data have been determined statistically from the average copolymer composition, the conditional probabilities P_{ij} collected in Table I, and the stereochemical parameters $\sigma_{MM} = 0.26$, $\sigma_{HH} = 0.21$, and $\sigma_{MH} = \sigma_{HM} = 0.30$.

With similar arguments we have assigned peak V to the contribution of sequences reported in Table II. Although this assignment must be considered as tentative, the experimental data obtained from the NMR spectra are in good agreement with the contribution of the corresponding sequences calculated statistically, as we report later.

In order to correlate the molar concentration of M- and H-centered sequences with the statistical sequence distribution and stereochemical configuration of copolymer chains, we have analyzed statistically this copolymer system according to the reactivity ratios reported, the conditional probabilities P_{ij} quoted in Table I, and the average composition of the copolymer samples. This analysis has been carried out by making the following assumptions:

(a) With respect to the chemical composition of copolymer sequences, it is assumed that the copolymerization reaction is described by the terminal unit model.[21,22]

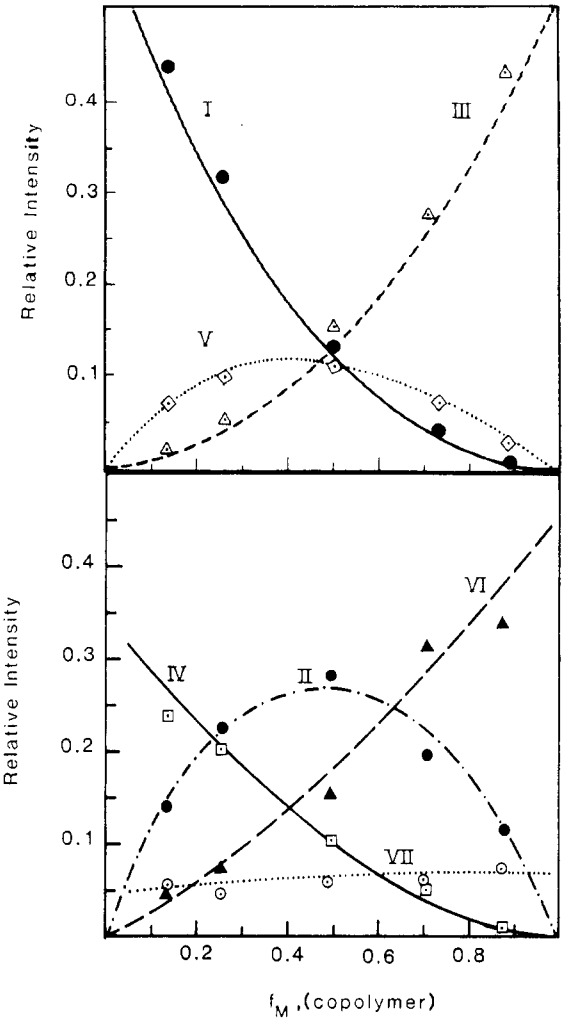

Figure 4. Variation of the relative intensity of α-CH_3 resonance signals with M molar fraction according to the assignment reported in Table II. The lines correspond to the contribution of statistical sequences reported in Table III; the points correspond to experimental data from the ^{13}C NMR spectra.

(b) From a stereochemical point of view we assume that the configurational sequence distribution may be described according to Bernoullian statistics with the isotacticity parameters σ_{MM}, σ_{MH}, σ_{HM}, and σ_{HH} as defined by Bovey[23] and Coleman,[24] where σ_{ij} is the probability of generating a meso diad between an i ending growing radical and incoming j monomer.

Values of $\sigma_{MM} = 0.26$ and $\sigma_{HH} = 0.21$ have been considered for the statistical distribution of units in pure MMM and HHH triads. These values correspond to the isotacticity parameters of M and H homopolymers and have been determined from the analysis of the α-CH_3 resonances of polyM and polyH, considering the Bernoullian distribution of tactic sequences. The coisotacticity parameters σ_{MH} and σ_{HM} are not accessible directly, but it is reasonable to assume that $\sigma_{MH} = \sigma_{HM} = \sigma^*$.[25,26] In this way we have determined this parameter by comparison of the integrated intensities of peaks I and II of the α-CH_3 resonances (assigned as indicated in Table II) for several copolymer samples. The application of well-known statistical relations[20] gives a value of $\sigma_{MH} = \sigma_{HM} = 0.30$.

From this set of stereochemical parameters and the average molar fractions of M and H units in the copolymer chains, as well as the conditional probabilities given in Table I, we obtain the molar fraction of every triad

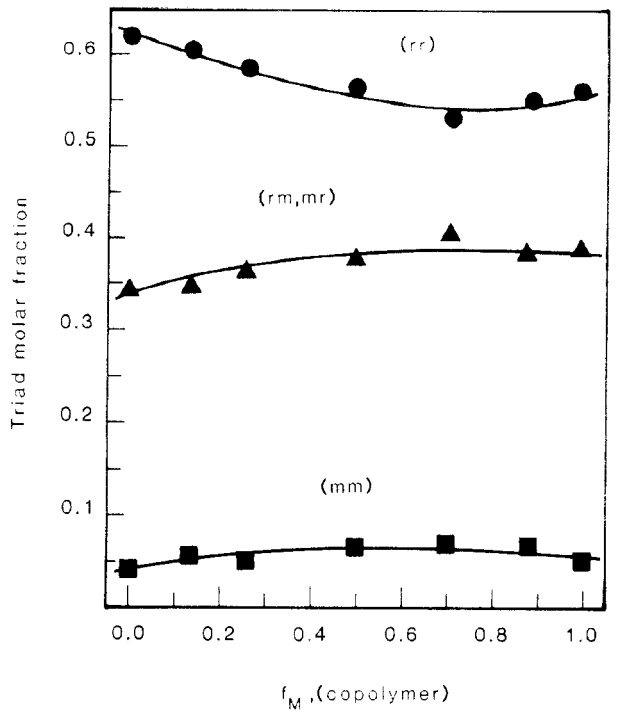

Figure 5. Variation of tactic sequences with the M molar fraction in the copolymer. The lines correspond to the contribution of statistical sequences collected in Table III; the points are experimental results from the α-CH_3 resonance signals.

quoted in Table III. In order to verify the validity of the model considered as well as the effectiveness of the assignment of α-CH_3 resonances, we have determined values of the contributions of various sequences to the resonance peaks I–VII according to Table II. Figure 4 shows the variation expected for the relative intensity of these peaks with the average molar fraction of M in the copolymer chains. The lines drawn correspond to the sum of contributions of statistical values of triads collected in Table III, whereas the points correspond to the experimental data obtained from the corresponding NMR spectra. The agreement between statistical diagrams and experimental observations provides support for the assignment of NMR signals and the validity of the stereochemical parameters considered above.

Figure 5 shows the variation of the concentration of tactic sequences (independently of their chemical composition), with the average molar fraction of M in the copolymer chains. It can be clearly observed that there is a slight increase of the coheterotactic sequences with increasing the molar fraction of M in the copolymer samples, but, in any case, from a stereochemical point of view one can conclude that there is a random distribution of tacticity following the classical Bernoulli trial.

Carbonyl Carbon Resonance Signals. We also have tested the validity of the statistical model, from the analysis of the complex pattern of the carbonyl carbon resonance signals. Figure 6 shows the spectra of the C=O resonances for three copolymer samples of different composition, together with those of the corresponding M and H homopolymers. In a previous paper[17] we have considered the C=O resonances of polyM in terms of tactic pentads. An inspection of the C=O resonances of polyH reveals that this group presents a resonance pattern very similar to that of poly(methyl methacrylate). Therefore, we can carry out the assignment in terms of tactic pentads in the same manner as for poly(methyl methacrylate).[18,19]

A careful comparison of the spectra of copolymers drawn

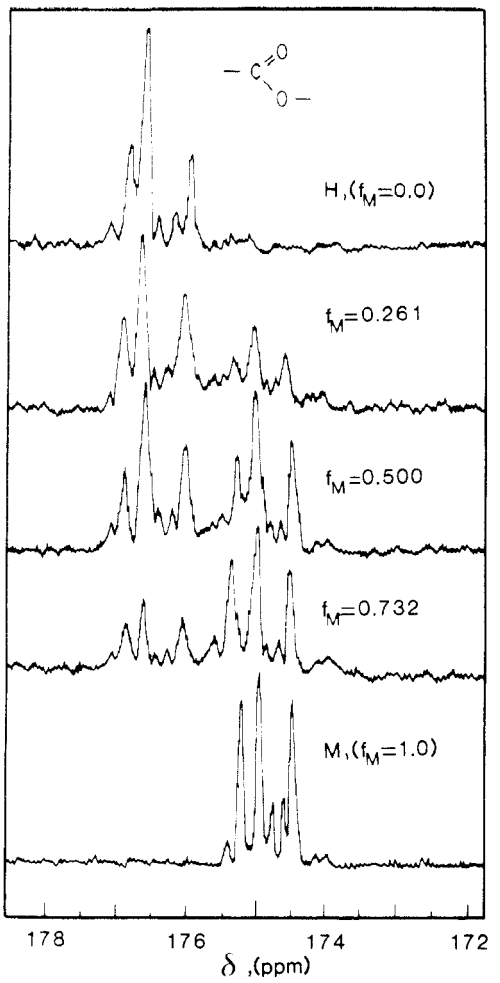

Figure 6. ^{13}C NMR (75.5 MHz) of the C=O ester group of M–H copolymers.

Table IV
Stereochemical Configuration of M-Centered Pentads, Determined from the Analysis of the C=O Resonance Signals

tactic pentad	chemical shift, ppm	f_M (copolymer) 0.125	0.261	0.500	0.732	0.889
mrrm	175.38	0.04_2	0.05_3	0.05_4	0.06_1	0.04_3
mrrr	175.20	0.15_6	0.17_7	0.17_2	0.18_4	0.19_0
rrrr	174.91	0.32_6	0.31_0	0.31_8	0.30_7	0.32_1
rmrm	174.75	0.06_4	0.07_1	0.07_2	0.08_2	0.09_5
mmrr	174.59	0.07_1	0.08_8	0.09_0	0.09_8	0.10_7
rmrr	174.50	0.26_9	0.22_1	0.22_7	0.18_4	0.19_0
mmrm						
mmmr	174.16	0.02_8	0.03_5	0.02_7	0.04_0	0.02_8
rmmr	174.00	0.04_2	0.04_4	0.03_6	0.04_0	0.02_4
mmmm						

in Figure 6, with those of the homopolymers M and H, reveals that they correspond to the superposition of both spectra, but with the intensities according to the average molar composition of copolymer chains. This means that the C=O resonances of M- and H-centered sequences are not sensitive to the chemical composition and distribution of monomeric units but are sensitive to the relative stereochemical configuration of copolymer segments in terms of sequences of tactic pentads. On this basis, the chemical shifts of signals assigned to tactic pentads centered in M units, together with the molar fraction of sequences for copolymers with different average molar fraction of M, are listed in Table IV. Similarly, Table V reports the corresponding values for H-centered sequences. In this case, the overlapping of signals between 175.00 and 174.55 ppm with the more intense

Table V
Stereochemical Configuration of H-Centered Pentads, Determined from the Analysis of the C=O Resonance Signals[a]

tactic pentad	chemical shift, ppm	f_M (copolymer) 0.125	0.261	0.500	0.732	0.889
mrrm	177.10	0.02_6	0.02_7	0.05_3	0.06_6	0.05_4
mrrr	176.90	0.19_6	0.17_9	0.16_8	0.18_9	0.18_6
rrrr	176.60	0.39_3	0.36_8	0.32_8	0.30_3	0.27_3
rmrm	176.40	0.06_3	0.07_2	0.08_8	0.06_6	0.09_8
mmrr	176.20	0.06_8	0.07_6	0.09_8	0.07_6	0.10_9
rmrr	176.00	0.20_4	0.22_5	0.20_4	0.22_8	0.19_7
mmrm						
mmmr	175.55					
rmmr	175.40	0.05_0[a]	0.05_0[a]	0.06_0[a]	0.07_0[a]	0.08_0[a]
mmmm						

[a] These values have been determined statistically.

syndiotactic M-centered sequences (see Figure 6) does not permit us to determine the contribution of isotactic H-centered sequences. Therefore, the values collected in Table V for these sequences have been calculated statistically according to the model described before; nevertheless, their contribution to the whole system can be disregarded in practice.

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