Microstructural analysis of copolymers of hydroxyethylmethacrylate and methacrylic esters of biomedical interest by n.m.r. spectroscopy

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Copolymers of *N*-(4-methacryloyloxyphenyl), 2-(4-methoxyphenyl) acetamide, M, a methacrylic derivative of 4-methoxyphenylacetic acid, and 2-hydroxyethylmethacrylate, H, prepared by free-radical polymerization in solution at low conversion, were analysed by ^1H (300 MHz) and ^{13}C (75.5 MHz) nuclear magnetic resonance spectroscopy, in terms of sequence distribution and stereochemistry of monomeric units along the copolymer chains. The concentration of M- and H-centred sequences was determined experimentally from the analysis of the α-CH_3 resonance signals of M and H units, which gave a relatively complex pattern assigned to M and H centred triads with specific composition and stereochemical configuration. The carbonyl carbon group of M and H gave resonance signals with different chemical shift sensitive to sequences of tactic pentads, independently of the chemical composition. The experimental results 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} and P_{ii} determined from the reactivity ratios $r_M = 1.49$ and $r_H = 0.61$ and the stereochemical parameters $\sigma_{MM} = 0.27$, $\sigma_{HH} = 0.21$ and $\sigma^* = \sigma_{MH} = \sigma_{HM} = 0.30$.

(Keywords: polymeric drugs; acrylic copolymer; n.m.r. spectroscopy)

INTRODUCTION

The design and preparation of polymeric drugs for pharmacological applications are among the most interesting fields of research of new polymeric systems as biomaterials, mainly since Ringsdorf suggested a practical model of active polymeric systems in 1975[1,2]. In this context, we have recently reported the preparation and study of the pharmacological properties of acrylic formulations based on the synthesis of polymethacrylic esters bearing as side substituents typical analgesic and anti-inflammatory drugs such as salicylic acid and several derivatives of paracetamol[3–6]. On the other hand, the biodegradative or hydrolytic behaviour of these systems in physiological conditions depends predominantly on their chemical structure[7] but it has been widely recognized that the microstructure of polymer chains, i.e. the distribution of monomeric sequences along copolymeric chains and the stereochemical configurations of the pseudoasymmetric carbons present in the repeat methacrylic units along the macromolecular chains, drastically affects the kinetics and mechanism of the biodegradation process, which in addition can be controlled enzymatically[7–9].

The main goal of this paper is to describe the study of the microstructure and the stereochemical analysis by ^1H (300 MHz) and ^{13}C (75.5 MHz) nuclear magnetic resonance (n.m.r.) spectroscopy of biocompatible acrylic copolymers with controlled hydrophilic character, prepared by the free-radical copolymerization of a methacrylic derivative of 4-methoxyphenylacetic acid and 2-hydroxyethylmethacrylate.

EXPERIMENTAL

Materials

N-(4-methacryloyloxyphenyl),2-(4-methoxyphenyl) acetamide, M, was synthesized in two steps as described elsewhere[10]. An intermediate derivative of 4-methoxyphenylacetic acid was prepared by the selective amidation of 4-methoxyphenylacetic acid with 4-aminophenol. The acrylic monomer M was then prepared by the reaction of this intermediate with methacryloyl chloride in aqueous sodium hydroxide solution at 0°C. The methacrylic ester was purified by fractional crystallization with methanol/water and by column chromatography (Kieselgel 60, Merck) using ethyl acetate as eluent. Other experimental details are given elsewhere[10,11].

2-Hydroxyethylmethacrylate (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 b.p. 87–89°C/0.5 mmHg was collected. The purity of the monomer and the absence of dimethacrylate were tested by high-performance liquid chromatography (h.p.l.c.), being higher than 99.95%.

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2,2'Azobisisobutyronitrile (AIBN) was purified by fractional crystallization from methanol, to give a melting point of 104°C.

N,N-dimethylformamide (DMF) was exhaustively dried over anhydrous magnesium sulfate for 2 days and later with phosphoric anhydride overnight. DMF was finally distilled and stored over 4 Å molecular sieves. Other reagents were of extra pure grade and used without purification.

Copolymerization

The polymerization reactions were carried out in DMF solution at 50 ± 0.1°C, in Pyrex glass ampoules sealed off under high vacuum. Monomer and initiator concentrations were 1 mol l^{-1} and 1.5×10^{-2} mol l^{-1}, respectively. The sealed ampoules were shaken and immersed in a water bath held at the required temperature of polymerization. After the proper reaction time, the content of the ampoules was poured into a large excess of a 1/1 mixture of diethylether and chloroform at low temperature. The precipitated samples were washed and dried under vacuum until constant weight was attained.

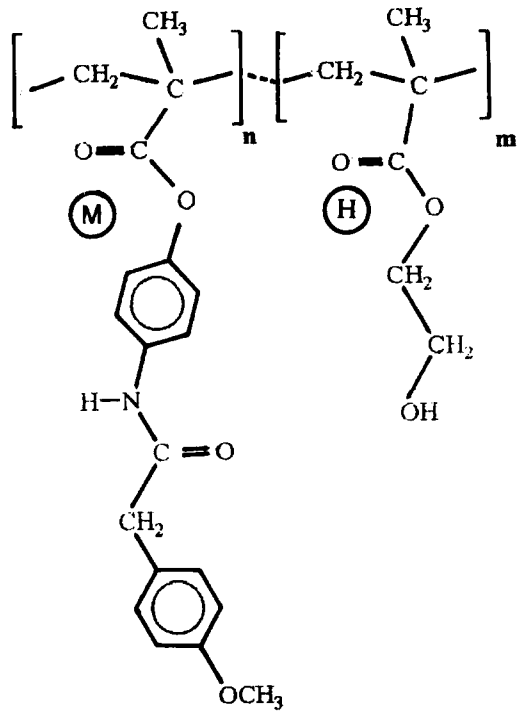
Characterization

The copolymers obtained with different composition were characterized by ^{1}H and ^{13}C n.m.r. spectroscopy. The spectra were recorded at 80°C on 5% (for ^{1}H) or 15% (for ^{13}C) w/v solutions in perdeuterated dimethylsulfoxide (DMSO-d_6) with a Varian XLR-300 spectrometer operating at 300 MHz for ^{1}H n.m.r. experiments and 75.5 MHz for ^{13}C n.m.r. experiments. Tetramethylsilane was used as an internal reference. In order to have a quantitative response, the ^{13}C n.m.r. spectra were recorded by using a flip angle of 90° (pulse width of 13 μs) and a relaxation delay of 4 s, with inverse-gated decoupling in the acquisition and a spectral width of 16 K data points. These conditions ensured the complete relaxation of all the ^{13}C nuclei analysed. The relative peak intensities were measured from peak areas calculated by means of an electronic integrator or by triangulation and planimetry.

RESULTS AND DISCUSSION

The chemical structure of M and H units is represented in *Scheme 1*. Both units, M and H, are methacrylic esters with very different side groups since the 4-methoxyacetamidophenoxy residue of M is rather hydrophobic, with a practically planar structure but having dipolar groups (methoxy, amido) which give rise to strong dipolar interactions, whereas the ester residue of H units is very flexible, with a clear hydrophilic character because of the hydroxy side group. These characteristics provide copolymers with very different properties determined not only by the average composition of the copolymer chains but also by the microstructural and stereochemical parameters. These have been determined statistically from the kinetic data of the copolymerization and experimentally by the analysis of ^{1}H and ^{13}C n.m.r. spectra of copolymer samples prepared with different monomer composition.

Figure 1 shows the ^{1}H n.m.r. spectra of several copolymer samples prepared with different feed composition. The average molar composition of copolymers was determined from the integrated intensities of (–NH–) at $\delta = 9.93$ ppm and aromatic protons ($\delta = 6.4$–7.8 ppm) of



Scheme 1

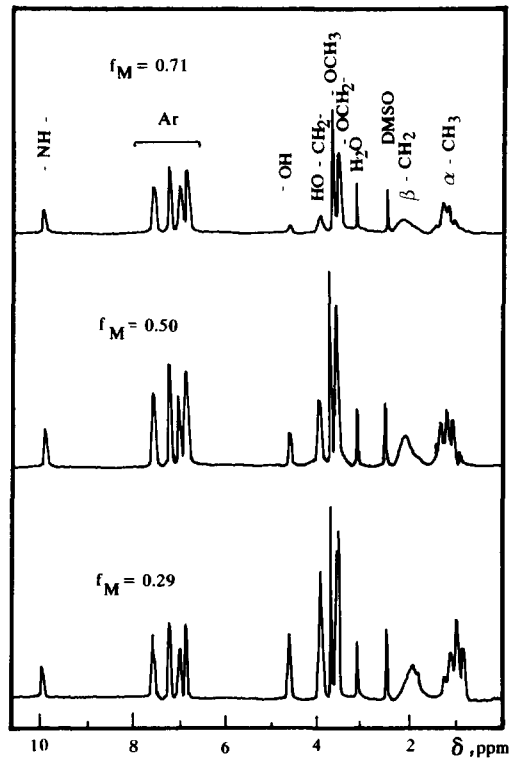


Figure 1 ^{1}H n.m.r. (300 MHz) spectra of M–H copolymers prepared by free-radical copolymerization in solution at 50°C. f_M is the molar fraction of M in the copolymer

M units and the $-CH_2-OH$ protons $\delta = 3.9$ ppm of H as well as α-CH_3 of both M and H units. The composition data of the feed and copolymers isolated at low conversion are collected in the first and second columns of *Table 1* respectively. The reaction time was regulated to obtain copolymers with a conversion degree lower than 0.1. This was necessary to guarantee an homogeneous distribution of comonomeric units without the possible influence of the conversion in the distribution of sequences. *Figure 2* shows the composition diagram for

Table 1 Average molar composition of M–H copolymers and conditional probabilities, P_{ij}, for the free-radical copolymerization of the acrylic monomers in DMF solution at 50°C

Feed F_H	Copolymer f_H	Conversion degree	P_{HM}	P_{MH}
0.20	0.15	0.078	0.868	0.143
0.30	0.22	0.063	0.793	0.223
0.40	0.29	0.056	0.711	0.309
0.50	0.39	0.046	0.621	0.402
0.60	0.50	0.040	0.522	0.502
0.70	0.60	0.043	0.413	0.610
0.80	0.71	0.045	0.291	0.729

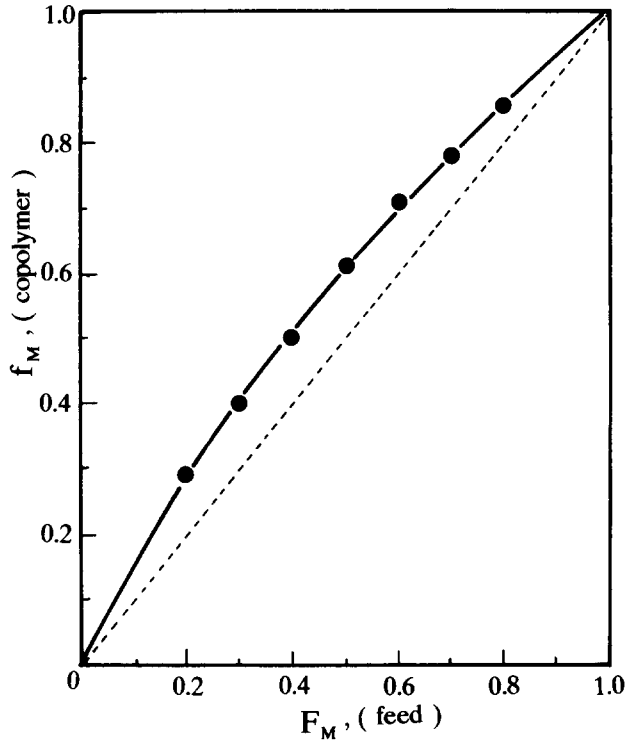


Figure 2 Average composition diagram for the free-radical copolymerization of M and H in solution at 50°C, initiated by azobisisobutyronitrile

the free-radical copolymerization of this system in the experimental conditions mentioned above. It apparently corresponds to a random process with a statistical distribution of comonomeric sequences. The points are the experimental data quoted in *Table 1* and the curve is the variation of the composition according to the classical terminal model of Mayo–Lewis[11]. The kinetic parameters for the copolymerization of this system were determined as reported in a recent paper, the most probable reactivity ratios being $r_M = 1.49$ and $r_H = 0.61$, with excellent confidence limits[12].

Columns 4 and 5 of *Table 1* present data of the statistical parameters $P_{HM} = 1 - P_{HH}$ and $P_{MH} = 1 - P_{MM}$, which represent the conditional probabilities of addition of monomer units to copolymeric growing chains, according to the first-order statistics of Markov. These parameters are related to the reactivity ratios by the expressions:

$$P_{MH} = 1 - P_{MM} = \frac{1}{1 + r_M X}$$

$$P_{HM} = 1 - P_{HH} = \frac{1}{1 + r_H / X}$$

where $X = [M_M]/[M_H]$ is the ratio of the concentration of M and H in the monomer feed.

From the values of P_{MH} and P_{HM} collected in *Table 1*, the molar fraction of M- and H-centred sequences can be determined by the application of well known statistical relationships[13]. *Figure 3a* shows the variation of the molar fraction of H-centred triads with the average content of H in the copolymer chains, whereas *Figure 3b* shows the diagrams corresponding to M-centred triads. In both cases, the diagrams obtained correspond to statistical sequences with a random distribution of comonomeric units in the sequences considered. Therefore, the concentration of an individual sequence, i.e. *iii*, *jii* or *iij* and *jij* ($i,j = M, H$) can be regulated by controlling the composition of the monomer feed. According to the relative proximity of r_M and r_H to unity, it can be expected that the average composition of the monomer feed does not change drastically with conversion and therefore the distribution diagrams of M- and H-centred sequences drawn in *Figures 3a* and *b* are valid as a first approximation for copolymers prepared in a wide interval of conversions.

On the other hand, the repeating M and H units of copolymer chains have a quaternary carbon that can be considered as a pseudoasymmetric centre sensitive to the stereochemical configuration of the corresponding side substituents, i.e. α-CH_3 and carboxylic ester functions.

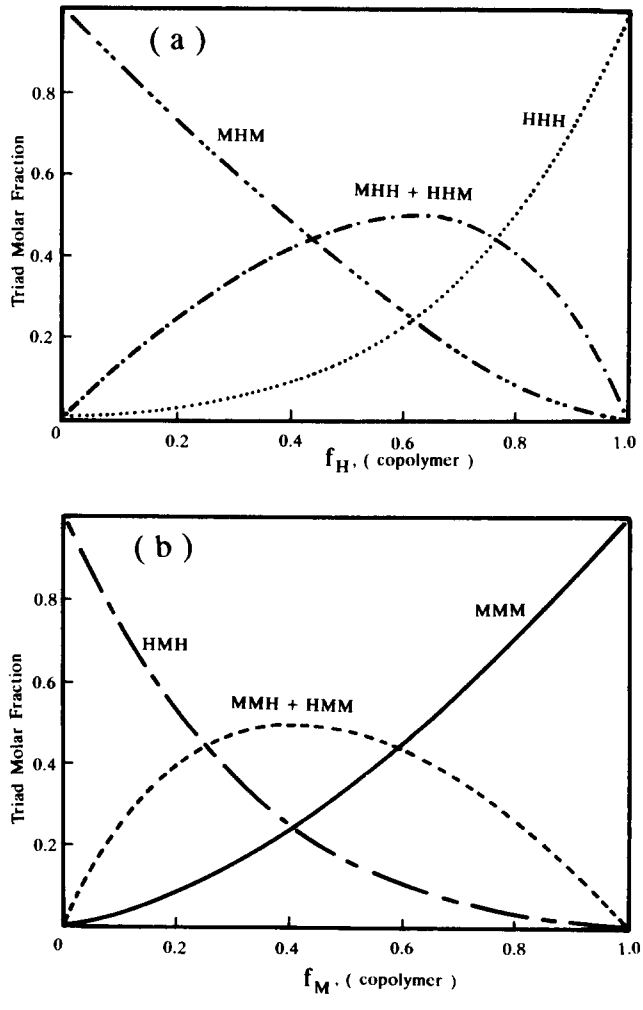


Figure 3 Variation of the molar fraction of H-centred triads (a), and M-centred triads (b) with the composition of copolymer chains, according to the conditional probabilities quoted in *Table 1*

Therefore, for a complete description of the monomer sequence distribution and relative stereochemical configuration in terms of M- and H-centred sequences, it is necessary to take into consideration as many as 10 different triads with a central M unit, magnetically distinguishable, as shown in the scheme of *Figure 4*. Similarly, 10 triads with a central H unit must also be considered.

The complete statistical analysis of this kind of system includes the study of the sequence distribution, i.e. the arrangement of M and H units along the macromolecular chains, as well as the stereochemical configuration of the side substituents of both M and H units with respect to the chemical arrangement of M and H. As we have mentioned above, it can be considered that the free-radical copolymerization reaction of M with H follows the classical terminal model of copolymerization of Mayo–Lewis[12,14].

We have found that, in general, the stereochemical distribution of the side groups of acrylic monomers in free-radical copolymerizations follows Bernoullian statistics[15,16]. On this basis, we assume that the configurational sequence distribution of H–M copolymers may be described according to Bernoullian statistics with the isotacticity and co-isotacticity parameters σ_{MM}, σ_{MH}, σ_{HM}, σ_{HH}, defined by Bovey[17,18] and Coleman[19], where σ_{ij} is the probability of generating a meso dyad between an i ending growing radical and incoming j monomers. σ_{MM} and σ_{HH} correspond to the isotacticity parameters of the free-radical polymerization of M and H in the experimental conditions used for the preparation of copolymers giving values of $\sigma_{MM}=0.27$ (ref. 10) and $\sigma_{HH}=0.21$ (ref. 16). The co-isotacticity parameters σ_{MH} and σ_{HM} are not accessible directly but in good approximation it can be assumed that $\sigma_{MH}=\sigma_{HM}=\sigma^*$ as has been considered for many other systems[15,16,20,21]. This parameter can be determined from the analysis of the stereochemical configuration distribution derived from n.m.r. data. The equations necessary to determine the concentration of M- and H-centred triads with a particular stereochemical configuration are collected in *Table 2*. The statistical parameters are the co-isotacticity parameters σ_{MM}, σ_{HH} and $\sigma_{MH}=\sigma_{HM}=\sigma^*$ as well as the conditional probabilities given in *Table 1*.

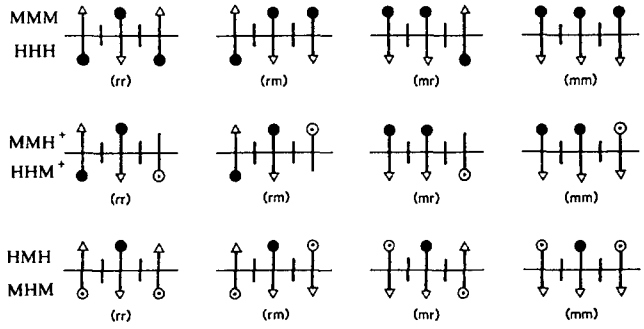


Figure 4 Schematic arrangement of side groups in M- and H-centred sequences of triads, considering the chemical composition and the relative stereochemical configuration of neighbouring units. ●, ⊙ = –COOR, △ = $-CH_3$

From the equations quoted in the second column of *Table 2* it is easy to derive the equation:

$$[mm]=[(P_{MH}P_{HM})^{1/2}\sigma^*+\sigma_{MM}P_{MM}]^2 \quad (1)$$

This gives the whole concentration of co-isotactic triads, independently of their chemical composition. Similarly, the whole concentration of co-syndiotactic triads is given by:

$$[rr]=[(P_{MH}P_{HM})^{1/2}(1-\sigma^*)+(1-\sigma_{MM})P_{MM}]^2 \quad (2)$$

These equations are valid for a composition interval in the copolymer in which $(P_{ij}P_{ji})^{1/2}=1/2(P_{ij}+P_{ji})$. For the copolymerization of M with H, this condition is attained in a wide interval of feed composition with $F_M\simeq 0.30$ to $F_M\simeq 0.60$.

Equations (1) and (2) can be expressed as follows:

$$\sigma^*=\frac{(mm)^{1/2}-\sigma_{MM}P_{MM}}{(P_{MH}P_{HM})^{1/2}} \quad (3)$$

and

$$(1-\sigma^*)=\frac{(rr)^{1/2}-P_{MM}(1-\sigma_{MM})}{(P_{MH}P_{HM})^{1/2}} \quad (4)$$

Dividing both equations and operating, the following expression is obtained:

$$\frac{1}{\sigma^*}=\frac{(rr)^{1/2}+(mm)^{1/2}-P_{MM}}{(mm)^{1/2}-\sigma_{MM}P_{MM}} \quad (5)$$

which gives the co-isotacticity parameter σ^* as a function of the whole concentration of isotactic (*mm*) and syndiotactic (*rr*) triads, the isotacticity parameter of the free-radical polymerization of M, σ_{MM}, and the probability of monomer addition to growing M chains, P_{MM}.

The concentration of (*mm*) and (*rr*) stereochemical triads can be determined from the analysis of the ^1H and ^{13}C n.m.r. spectra of copolymers prepared with feed composition in the interval $F_M=0.30$ to $F_M=0.60$. The appropriate selection of n.m.r. resonance signals was possible after the assignment of the ^1H and ^{13}C n.m.r. resonances of the α-CH_3 side groups of both kinds of repeating units, giving an average value of $\sigma^*=0.30$.

^1H n.m.r., α-CH_3 resonance signals

The proton n.m.r. spectra of statistical M–H copolymers prepared with different composition (*Figure 1*) provide interesting information not only on the average composition, but also on the distribution of M and H units along

Table 2 Statistical correlation between the molar fraction of M- and H-centred triads (M, H = i,j) and the co-isotacticity parameters σ_{ii}, σ_{ij}, σ_{ji} and conditional probabilities P_{ii}, P_{ij}, P_{ji}

	Stereochemical configuration			
Sequence	*mm*	*mr*	*rm*	*rr*
iii	$\sigma_{ii}^2P_{ii}^2$	$\sigma_{ii}(1-\sigma_{ii})P_{ii}^2$	$(1-\sigma_{ii})\sigma_{ii}P_{ii}^2$	$(1-\sigma_{ii})^2P_{ii}^2$
iij	$\sigma_{ii}\sigma_{ij}P_{ii}P_{ij}$	$\sigma_{ii}(1-\sigma_{ij})P_{ii}P_{ij}$	$(1-\sigma_{ii})\sigma_{ij}P_{ii}P_{ij}$	$(1-\sigma_{ii})(1-\sigma_{ij})P_{ii}P_{ij}$
jii	$\sigma_{ji}\sigma_{ii}P_{ji}P_{ii}$	$\sigma_{ji}(1-\sigma_{ii})P_{ji}P_{ii}$	$(1-\sigma_{ji})\sigma_{ii}P_{ji}P_{ii}$	$(1-\sigma_{ji})(1-\sigma_{ii})P_{ji}P_{ii}$
jij	$\sigma_{ji}\sigma_{ij}P_{ji}P_{ij}$	$\sigma_{ji}(1-\sigma_{ij})P_{ji}P_{ij}$	$(1-\sigma_{ji})\sigma_{ij}P_{ji}P_{ij}$	$(1-\sigma_{ji})(1-\sigma_{ij})P_{ji}P_{ij}$

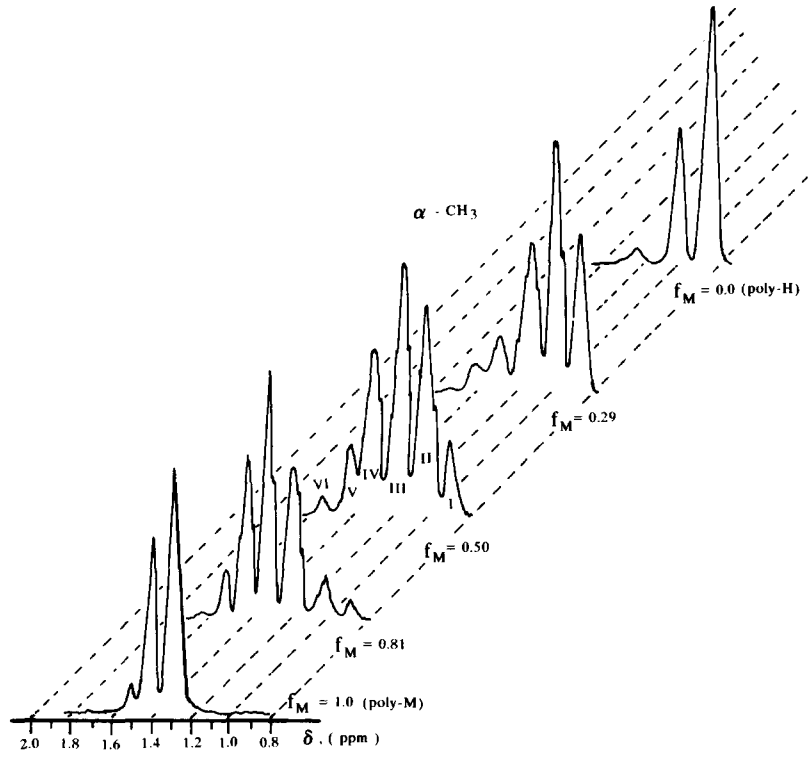


Figure 5 ^{1}H n.m.r. resonance signals of the α-CH_3 side groups of H and M units of random copolymers prepared by free-radical copolymerization

the copolymer chains and the relative stereochemical configuration of the pseudoasymmetric centre of each kind of unit. Particularly, the resonance signals of the α-CH_3 side groups present a rather complex pattern with at least six well defined peaks whose intensities change drastically with composition, as shown in the spectra in *Figure 5*. The parent homopolymers, poly-H and poly-M give three well resolved peaks, assigned to *mm*, *mr*+*rm* and *rr* stereochemical sequences in order of increasing field. However, two important differences between the M and H signals have to be considered.

First, the chemical shift of the α-CH_3 signals of poly-M at 1.55, 1.45 and 1.36 ppm, assigned to isotactic (*mm*), heterotactic (*mr*+*rm*) and syndiotactic (*rr*), respectively, are approximately 0.5 ppm higher than the corresponding α-CH_3 signals of poly-H (see *Figure 5*), i.e. 1.16, 1.00 and 0.85 ppm for *mm*, *mr*+*rm* and *rr* sequences, respectively. This is a consequence of the aromatic character of the ester group of poly-M and the aliphatic character of poly-H. We have found this behaviour for other poly(methacrylic esters) with aromatic side groups, such as poly(4-methacryloyloxy) acetanilide[16], which shows the deshielding effect of the aromatic ring directly bonded to the carboxylic ester group, compared with the aliphatic character of the ester in poly-H, poly(methyl methacrylate) or other poly(alkyl methacrylate)s[16].

The second noticeable difference is the separation between peaks assigned to different stereochemical sequences, since it seems that the change of a racemic dyad by a meso gives rise to a deshielding effect about 0.11 ppm for poly-M, i.e. $(\delta_{mm}-\delta_{mr})$ or $(\delta_{mr}-\delta_{rr})$ is $\simeq$0.11 ppm, whereas in the case of poly-H and in general in poly(alkyl methacrylates) the deshielding effect is somewhat higher, i.e. $(\delta_{mm}-\delta_{mr})$ or $(\delta_{mr}-\delta_{rr})$ is $\simeq$0.15 ppm. These two characteristics are very useful to obtain valuable information on the distribution of monomer units and the relative stereochemical configuration of the repeating units along the macromolecular chains.

It is well known that the sensitivity of the α-CH_3 resonances to the stereochemical configuration arises from the diamagnetic effects of the carbonyl ester group of the neighbouring units on the α-CH_3 residue of the methacrylic ester central unit[18,22]. This means that the resonance signal of the α-CH_3 of a particular H or M unit depends on the character M or H of its neighbours and the meso or racemic stereochemistry of the corresponding units (see the scheme drawn in *Figure 4*); taking into consideration this fact and the contribution to the deshielding effect provided by the aromatic character of the M units as well as the configurational meso effect described above, we suggest the assignment presented in the scheme of *Figure 6*. At the bottom of the scheme are indicated the H- and M-centred triads, being $HHM^+ = HHM + MHH$ and $HMM^+ = HMM + MMH$. The expected chemical shift of the α-CH_3 group of the central unit in the triads represented, is the contribution of the aromatic or aliphatic character of the unit, as well as that of the neighbouring units, and the meso or racemic stereochemistry of the corresponding units.

Values of the contribution of the concentration of sequences assigned to peaks I to VI according to the scheme of *Figure 6* for copolymers with different average composition are collected in *Table 3*, together with the corresponding contributions calculated statistically by the application of equations collected in *Table 2*, with the isotacticity parameters σ_{MM}, σ_{HH} and σ^* mentioned above. The good agreement between the experimental and statistical values indicates that the assignment suggested is correct, and supports the validity of the model under consideration to determine the parameter that controls the addition of monomers to growing chain ends and the stereochemistry of comonomeric units.

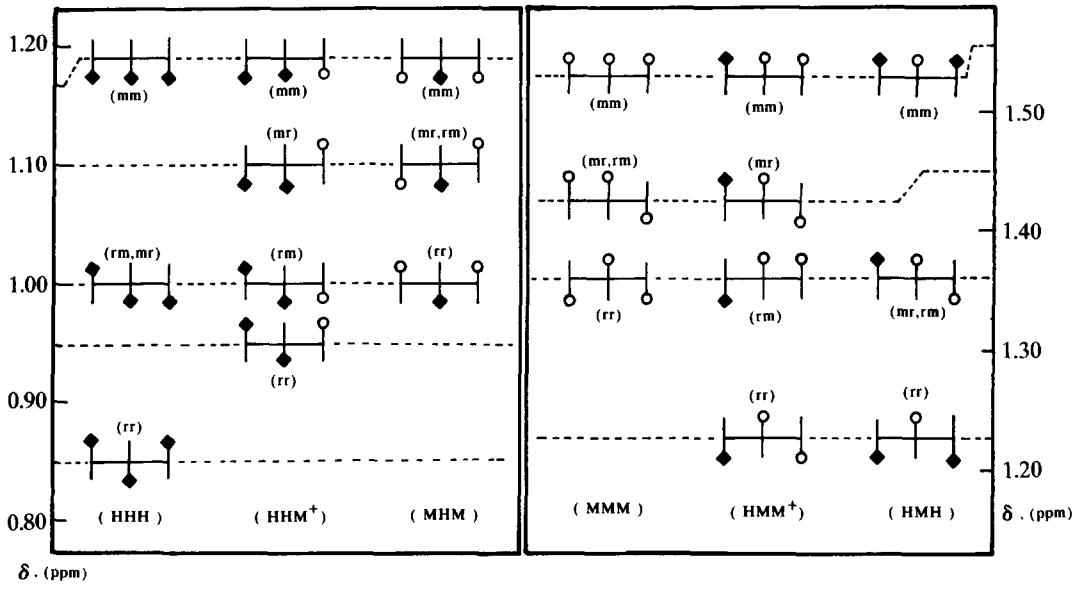


Figure 6 Schematic assignment of the α-CH_3 resonance signals to H- and M-centred triads considering the chemical composition and the relative stereochemistry of sequences

Table 3 Contribution of sequences assigned in the scheme of *Figure 6* to the relative intensity of the ^1H n.m.r. α-CH_3 resonance signals. Experimental values correspond to the contributions determined from the spectra. Statistical values correspond to the contribution of the molar concentration of sequences calculated according to the equations collected in *Table 2*

f_M (copolymer)						
0.29		0.50		0.81		N.m.r.
Expt	Stat.	Expt	Stat.	Expt	Stat.	signal
0.24	0.22	0.09	0.07	0.02	0.04	I
0.38	0.37	0.27	0.30	0.07	0.10	II
0.23	0.24	0.31	0.32	0.22	0.22	III
0.10	0.10	0.23	0.17	0.38	0.35	IV
0.05	0.03	0.08	0.10	0.25	0.26	V
0.02	0.02	0.03	0.04	0.08	0.06	VI

^{13}C n.m.r., α-CH_3 signals

Figure 7 shows the α-CH_3 resonance pattern of both homopolymers and those of three copolymer samples with different composition. The α-CH_3 groups of poly-M and poly-H are sensitive to the stereochemical configuration in sequences of triads, giving three well resolved peaks assigned to *mm*, *rm*+*mr* and *rr* tactic sequences in order of increasing field, following the trend observed for the same carbons in poly(aryl methacrylates) and poly(alkyl methacrylates)[16].

As in the ^1H n.m.r. spectra, there are several interesting differences between the corresponding resonance signals, since the (*rr*) and (*rm*+*mr*) resonances of poly-M (18.00 and 19.30 δ), appear at somewhat lower field than those of the poly-H, (*rr*) at 16.40 δ and (*rm*+*mr*) at 18.50 δ. However, the resonance signal assigned to isotactic (*mm*) sequences has practically the same chemical shift for both polymers, 20.50 δ. This means that the α-CH_3 side group in isotactic sequences shows very little sensitivity to the aliphatic or aromatic character of the ester groups, which is reasonable since, as represented schematically in *Figure 4*, the diamagnetic carbonyl centres are as far as possible from the α-CH_3 group of the central unit in the triad. On the other hand, it is easily seen in the spectra drawn in *Figure 7* that the separation between tactic signals of poly-H is noticeably higher, $(\delta_{mm}-\delta_{mr})\simeq(\delta_{mr}-\delta_{rr})\simeq 2.10$ ppm, than that of poly-M, $(\delta_{mm}-\delta_{mr})\simeq(\delta_{mr}-\delta_{rr})\simeq 1.30$ ppm. This means that except for (*mm*) sequences, the chemical shift of M and H units is sensitive to the composition and the stereochemical configuration of the neighbouring units in sequences of triads. We found a similar behaviour for copolymers of 4-methacryloyloxyacetanilide with 2-hydroxyethylmethacrylate[16], and this is the origin of the relatively complex splitting of the α-CH_3 resonances for statistical M–H copolymers. As indicated in *Figure 7*, at least seven complex signals can be distinguished, even with a poorly resolved fine structure.

On the basis of the assignment considered for the signals of the corresponding homopolymers and taking into consideration the effect of the chemical structure M or H of the neighbouring units and their stereochemical configuration with respect to the central unit of triads, we suggest the assignment presented in *Figure 8* in which different groups with similar magnetic characteristics has been considered to give a resonance signal in a very narrow interval represented by the dimension of the bars. The intensity of these bars represents the expected contribution of the sequences considered for copolymers with $f_m=0.81$ and 0.29 respectively, according to the terminal model of copolymerization with a Bernoullian distribution of the tacticity. The profile of the expected spectra is rather similar to the experimental ones, shown in *Figure 7*.

One interesting feature of these signals with the assignment suggested in *Figure 8* is that all the (*mm*) triads centred in M and H give a typical small but well resolved resonance centred at 20.50 δ and all the (*rr*) sequences contribute to the signals labelled I, II and III at high field. This means that it is possible to determine accurately the concentration of (*mm*) and (*rr*) sequences to calculate the parameter $\sigma^*=\sigma_{MH}=\sigma_{HM}$ by the application of equation (5) from the data of copolymers prepared in the composition interval indicated above. This results in an average value $\sigma^*=0.30$. In *Table 4* are collected the normalized experimental values of signals I

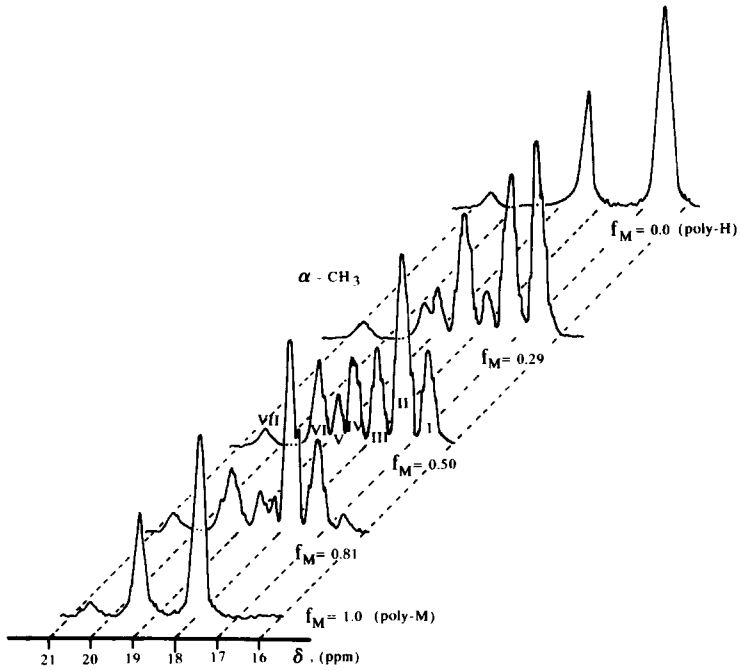


Figure 7 ^{13}C n.m.r. resonance signals of the α-CH_3 side group of H–M copolymer samples with the composition indicated by the value of f_M

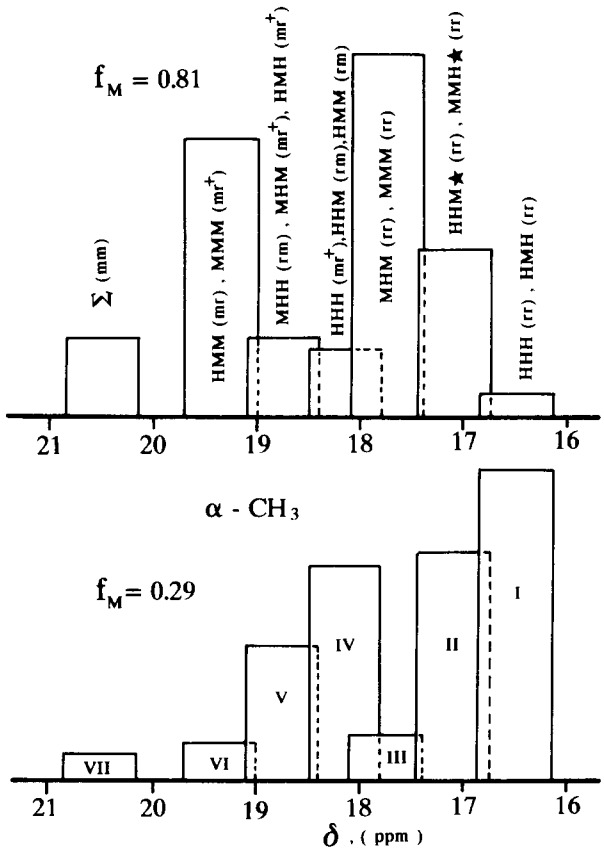


Figure 8 Schematic representation of the α-CH_3 resonance signals drawn in *Figure 7*, with the assignment to M- and H-centred sequences according to the criteria reported in the text. HHM* = HHM + MHH; MMH* = MMH + HMM; $mr^+ = mr + rm$

to VII determined by averaging the integrated intensities and the curve fitting by planimetry, together with the statistical contributions according to the assignment of sequences indicated in the scheme, with the conditional probabilities reported in *Table 1* and the stereochemical

Table 4 Contribution of sequences assigned in the scheme of *Figure 8* to the relative intensity of the ^{13}C n.m.r. α-CH_3 resonance signals. Experimental and statistical values have been determined as before

f_M (copolymer)						
0.29		0.50		0.81		
Expt	Stat.	Expt	Stat.	Expt	Stat.	N.m.r. signal
0.29	0.30	0.14	0.13	0.05	0.02	I
0.25	0.22	0.29	0.27	0.17	0.16	II
0.07	0.04	0.15	0.13	0.35	0.35	III
0.19	0.21	0.13	0.14	0.05	0.06	IV
0.10	0.13	0.09	0.14	0.09	0.07	V
0.06	0.03	0.13	0.10	0.24	0.26	VI
0.04	0.02	0.08	0.07	0.07	0.08	VII

parameters $\sigma_{MM} = 0.27$, $\sigma_{HH} = 0.21$ and $\sigma^* = 0.30$. The good agreement between statistical and experimental values supports the assignment suggested and provides a useful experimental way to determine the relative concentration of copolymer sequences for many methacrylic systems. *Figure 9* shows the variation of the molar fraction of tactic M- and H-centred sequences as a function of the composition of copolymer samples expressed as f_M.

The concentration of isotactic M- and H-centred sequences is fairly constant for all the composition intervals studied, with values rather near to classical polymethacrylic systems (6–8 mol%), but the concentration of co-heterotactic $mr + rm$ and co-syndiotactic sequences seems to be rather sensitive to the average composition of copolymer chains, the difference being more noticeable for H-rich copolymers. This behaviour is easily explained if we consider the strong polarity of the aromatic side substituent of M units which gives rise to dipolar interactions or even hydrogen bonding between M and H neighbouring units. Logically these interactions are favoured for H-rich copolymers in which the probability of having sequences with a central M unit

surrounded by H units is relatively high, as shown in *Figure 3b*. It is necessary to consider that the amide group conjugated with the ester aromatic ring has a planar and very rigid geometry, which provides steric hindrance to adopt a co-isotactic stereochemical configuration.

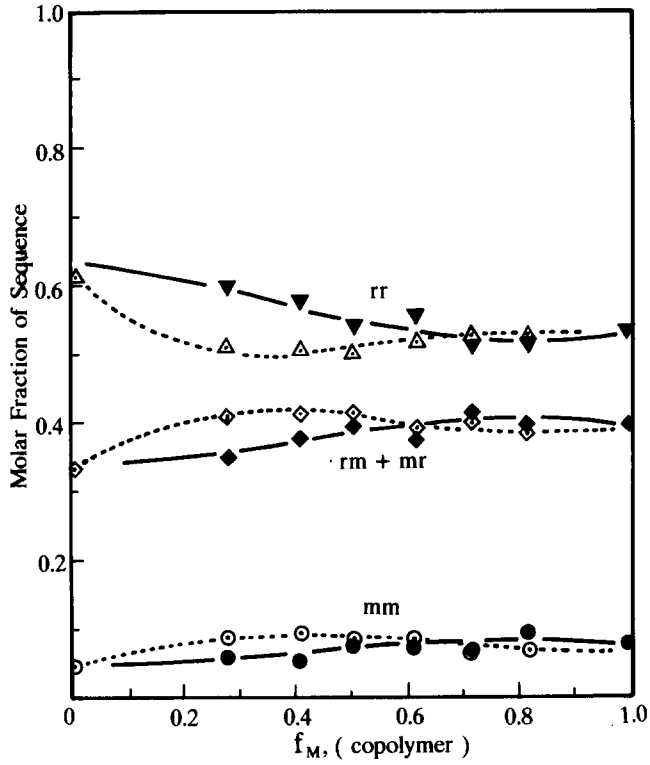


Figure 9 Variation of the global concentration of tactic sequences for M–H copolymers. (●, ◆, ▼), M-centred sequences; (⊙, ◇, ▽), H-centred sequences

Carbonyl ester resonance signals

The analysis of the splitting of the carbonyl carbon resonances is very interesting because of the sensitivity of the carbonyl carbon of H and M units to the stereochemical configuration of surrounding units in terms of pentads. *Figure 10* shows the spectra of the C=O resonances for three copolymer samples with different f_M, together with those of poly-H and poly-M. Both C=O groups give a rather complex pattern in the interval 174–178 δ, but the C=O group of the aromatic acrylic ester units, M, is shifted to higher field with respect to those of the H units. The assignment of these signals has been reported in earlier papers[10,16] and it has been considered that they are sensitive to stereochemical pentads for poly(alkyl methacrylates)[23–25].

If the spectra of copolymers with different composition drawn in *Figure 10* are compared with those of the homopolymers M and H, it is easily seen that they correspond to the superposition of both spectra, with intensities depending on the average molar composition of copolymer chains. This means that the C=O resonances of M- and H-centred sequences are not sensitive to the chemical composition and distribution of monomeric units, but are sensitive to the relative stereochemical configuration of monomeric units in terms of sequences of tactic pentads. We also have found this behaviour for copolymers prepared by the copolymerization of 2-hydroxyethyl methacrylate with 4-methacryloyloxy acetanilide[16]. *Table 5* presents values of the chemical shifts of signals assigned to tactic pentads centred in M units as well as the experimental and statistical molar fraction of the stereochemical sequences indicated in the first column of this table for copolymers with different average composition. Similarly, *Table 6* reports the corresponding data for H-centred sequences. The good agreement between statistical and experimental

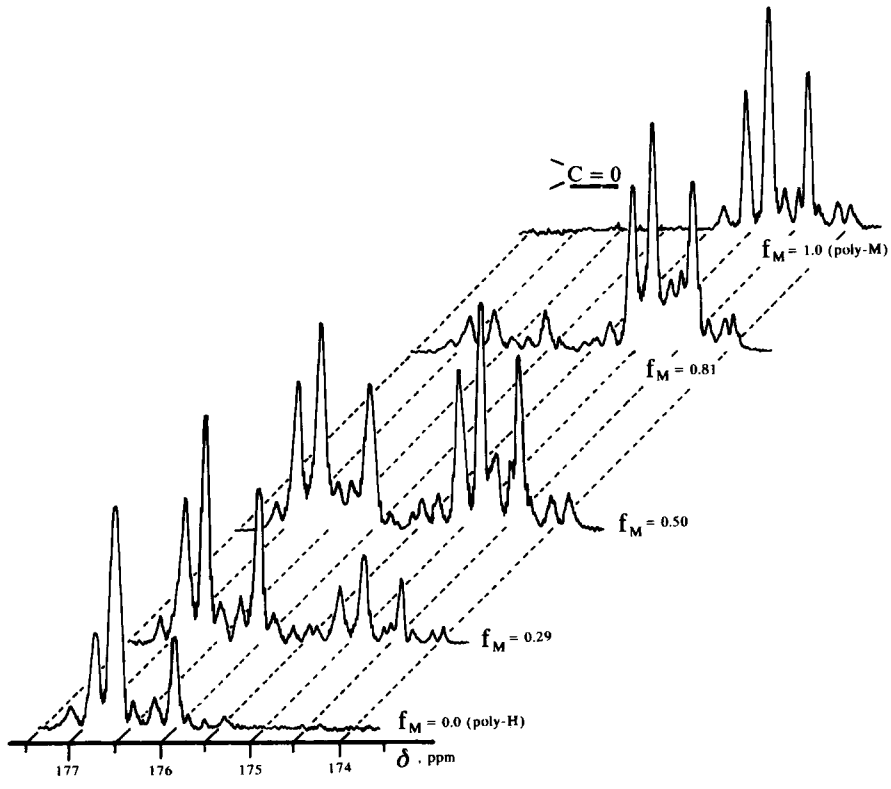


Figure 10 ^{13}C n.m.r. signals of the C=O ester group of H and M units of M–H random copolymers

Table 5 Molar fraction of tactic M-centred pentads determined from the analysis of the C=O resonance signals

Sequence and δ(ppm)	Sequence molar fraction, f_M					
	0.29		0.50		0.81	
	Exp.	Stat.	Exp.	Stat.	Exp.	Stat.
mrrm 175.30	0.02_9	0.031	0.04_5	0.038	0.05_7	0.041
mrrr 175.06	0.18_8	0.186	0.18_6	0.206	0.18_9	0.212
rrrr 174.81	0.29_0	0.276	0.26_9	0.277	0.26_3	0.278
rmrm 174.62	0.05_8	0.076	0.09_0	0.082	0.08_6	0.081
mmrr 174.43	0.07_2	0.076	0.07_7	0.082	0.09_6	0.081
rmrr 174.37	0.21_7	0.228	0.20_5	0.221	0.19_2	0.210
mmrm 174.28	0.04_3	0.026	0.03_8	0.030	0.03_7	0.031
mmmr 174.02	0.04_3	0.031	0.03_8	0.033	0.03_5	0.031
rmmr 173.90	0.05_8	0.047	0.04_5	0.044	0.04_3	0.040
mmmm–	–	0.005	–	0.006	–	0.006

Exp., Experimental; Stat., statistical

Table 6 Molar fraction of tactic H-centred pentads determined from the analysis of the C=O resonance signals

Sequence and δ(ppm)	Sequence molar fraction, f_M					
	0.29		0.50		0.81	
	Exp.	Stat.	Exp.	Stat.	Exp.	Stat.
mrrm 177.10	0.03_8	0.037	0.04_0	0.040	0.04_9	0.037
mrrr 176.90	0.20_1	0.221	0.21_6	0.214	0.19_4	0.195
rrrr 176.60	0.31_3	0.329	0.30_4	0.288	0.28_1	0.253
rmrm 176.40	0.06_9	0.068	0.07_2	0.074	0.06_5	0.076
mmrr 176.20	0.06_9	0.070	0.080	0.074	0.06_5	0.079
rmrr 176.00	0.21_3	0.202	0.20_0	0.198	0.23_8	0.200
mmrm 175.80	0.04_4	0.023	0.02_4	0.028	0.03_2	0.030
mmmr 175.60	0.04_3	0.021	0.02_4	0.026	0.03_2	0.031
rmmr 175.40	0.058	0.031	0.04_0	0.034	0.04_3	0.040
mmmm–	–	0.004	–	0.005	–	0.006

Exp., experimental; Stat., statistical

results supports the assignment suggested and the validity of the statistical parameters considered, according to the model of copolymerization and stereochemical distribution described above.

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