Polymers with Pharmacological Activity. 6. Microstructure and Stereochemistry of Hydrophilic Copolymers Prepared from 4-((2-(Methacryloyloxy)ethyl)oxy)acetanilide and 2-Hydroxyethyl Methacrylate

Julio San Román* and Belén Levenfeld

Instituto de Ciencia y Tecnología de Polímeros, Juan de la Cierva 3, 28006 Madrid, Spain

Received March 13, 1991; Revised Manuscript Received June 17, 1991

ABSTRACT: Biocompatible copolymers of 4-((2-(methacryloyloxy)ethyl)oxy)acetanilide (M), an acrylic derivative of paracetamol in which the pharmaceutically active group is separated from the acrylic counterpart by an oxyethylene spacer group, with 2-hydroxyethyl methacrylate (H) were prepared by free-radical copolymerization in *N,N*-dimethylformamide solution at 50 °C, using 2,2′-azobis(isobutyronitrile) as initiator. The methacrylic monomer can also be considered an acrylic derivative of the known pharmacologically active compound phenacetin (4-ethoxyacetanilide), paracetamol being its major metabolite in the living body. The reactivity ratios of this copolymerization system were calculated by the application of linearization and nonlinear least-squares treatments, checking the 95% confidence limits. The most probable values are $r_M = 0.673$ and $r_H = 1.391$. The microstructure of the copolymer chains was analyzed on the basis of the conditional probabilities for the formation of MM, MH, HM, and HH pairs, according to first-order Markov statistics. The stereochemical configuration of monomeric units along the copolymer segments was also analyzed from the ^{13}C NMR spectra of copolymers with different composition on the basis of a Bernoullian trial with the isotacticity parameters $\sigma_{MM} = 0.22$ and $\sigma_{HH} = 0.21$ and coisotacticity parameters $\sigma_{MH} = \sigma_{HM} = 0.21$.

Introduction

The use of hydrogels as biomedical materials has been growing during the past two decades, driven by a progressive understanding of the relationship between the behavior of polymeric hydrogels and their chemical structure.[1-4] From these studies, it has been shown that hydrogels of selected structures may be sensitive to their environment, being useful materials in biomedical applications because of the similarity between their physical properties and those of living tissue.[1,5,6] In this sense, polymers based on 2-hydroxyethyl methacrylate, which are known as typical hydrogels, are useful for the permeation of physiologically active compounds and macromolecules of low or medium molecular mass (<100 000 Da).[7,8] This condition, together with the excellent biocompatibility of poly(2-hydroxyethyl methacrylate), makes the polymeric hydrophilic formulations strong candidates for the preparation of biomedical devices.[9-11]

We have previously reported the preparation of acrylic formulations based on the synthesis and polymerization of methacrylic esters of typical analgesic compounds like salicylic acid (2-(methacryloyloxy)benzoic acid)[12] and of paracetaminophen or paracetamol (4-(methacryloyloxy)-acetanilide)[13] as well as hydrophilic copolymers with 2-hydroxyethyl methacrylate.[14] These systems may be pharmacologically active as a new product or alternatively may be used as a controlled-delivery system, being a temporary carrier from which the pharmacologically active compound or the corresponding metabolite is released upon administration following a hydrolytic process in the physiological medium.[15]

In this article we report the study of the free-radical copolymerization of 4-((2-(methacryloyloxy)ethyl)oxy)-acetanilide (M) with 2-hydroxyethyl methacrylate (H). The acrylic monomer M can be considered as a hydroxyl derivative of the known drug phenacetin (4-ethoxyacetanilide), paracetamol being the major metabolite of this compound in the living body.[16] Phenacetin has been listed as a carcinogen by the Environmental Protection Agency,[17] and therefore the preparation of M–H hydrophilic copolymers may be of interest to improve the durability of pharmacological activity and to reduce the toxicity.

Experimental Section

Monomers and Reagents. 4-((2-(Methacryloyloxy)ethyl)-oxy)acetanilide (M) was prepared by a two-step reaction as described elsewhere.[18] The methacrylic monomer was characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopies.

2-Hydroxyethyl methacrylate (H), kindly supplied by Hydron Europe Ltd., containing <0.05 wt % of ethylene glycol dimethacrylate was distilled under a 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 a reduced pressure of nitrogen. Other reagents (extrapure grade) were used without purification.

Copolymerization. Copolymerization reactions were carried out in DMF solution at 50 °C in Pyrex glass ampules sealed off under high vacuum. A global concentration of monomers of 0.5 mol·L^{-1} and an initiator concentration of 1.5×10^{-2} mol·L^{-1} were used in all experiments. The sealed ampules were shaken vigorously and immersed in a thermostatic bath regulated with an accuracy of ±0.5 °C. After the desired reaction time (see Table I), the reaction mixture was poured into a large excess of diethyl ether–hexane mixture cooled at 0 °C. The isolated polymeric samples were washed twice with the precipitant mixture and dried under vacuum until constant weight was attained.

Copolymer Characterization. The copolymers obtained were analyzed by ^1H NMR spectroscopy with a Bruker AM-200 spectrometer working at 200 MHz and by ^{13}C NMR spectroscopy with a Varian XLR-300 spectrometer operating at 75.5 MHz. The spectra were recorded at 80 °C on 15% (w/v) perdeuterated dimethyl sulfoxide (DMSO-d_6) using TMS as an internal reference standard. To have quantitative response, the ^{13}C NMR spectra were recorded using a flip angle of 80° (pulse width of 13 μs), a relaxation delay of 4 s, and inversed gated decoupling in the acquisition; the spectral width was 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.

0024-9297/91/2224-6083$02.50/0

Table I
Experimental Data and Conditional Probabilities for the Free-Radical Copolymerization of M with H in DMF Solution at 50 °C

F_M (feed)	f_M (copolymer)	polymn time, min	conv, wt %	p_{MH}	p_{HM}
0.150	0.10_0	12.0	4.50	0.89	0.11
0.250	0.20_5	10.0	3.80	0.82	0.19
0.405	0.32_0	11.0	4.20	0.68	0.33
0.500	0.41_0	10.0	3.50	0.60	0.42
0.600	0.51_0	11.0	3.60	0.50	0.52
0.755	0.68_5	10.0	3.20	0.32	0.69
0.855	0.79_0	12.0	3.50	0.21	0.80

Results and Discussion

Over the last few years we have been interested in the preparation of "polymeric drugs", or polymers with potential pharmacological activity, by means of the synthesis and polymerization of acrylic derivatives of traditional pharmacons like salicylic acid[12] or paracetamol.[13,14] According to the theoretical model for pharmacologically active polymers suggested by Ringsdorf in 1975,[19] one of the main advantages of macromolecular systems is the preparation of copolymers assembling molecular units with different properties. In this sense, it is possible to combine segments of chains having a chemical structure that makes the whole copolymer soluble or biocompatible with segments of molecular units where the pharmacon is fixed. Following these criteria, we prepared macromolecular systems based on copolymers of 2-hydroxyethyl methacrylate (hydrophilic and biocompatible component) with the acrylic derivative of paracetamol (4-methacryloyloxy)acetanilide (pharmacologically active supported component). The study of the controlled release of the active pharmacon from copolymers prepared with different amounts of the acrylic derivative revealed interesting kinetic and mechanistic features,[20] demonstrating that these systems act as control release biocompatible devices. Tests in vitro and in vivo revealed that these systems may display by themselves pharmacological activity even in their polymeric form.[21]

In addition, the model suggested by Ringsdorf[19] considers the fixation of the drug (or organic compound that elicits physiological response in the living body) to the polymer backbone through specially designed spacer groups, which, in general, are constituted by oxyalkyl segments, acting as a bridge between the pharmacon and the main polymer chain. In this sense, this paper deals with the preparation of hydrophilic copolymer systems in which the pharmacon (paracetamol) is fixed to the macromolecular backbone by an oxyethylene spacer group.

For the chemical fixation of pharmacons to polymer chains it is necessary to design synthetic conditions mild enough to allow attachment without any adverse effect on the physiological activity of the pharmacon.[19] Therefore, we have undertaken the synthesis of the methacrylic derivative of paracetamol (M) (Scheme I). The first step is a typical Williamson reaction,[22] which gives rise to the intermediate 4-((2-hydroxyethyl)oxy)acetanilide with good yield. The second is a modification of the known Schotten–Bauman process,[23] which permits the preparation of the acrylic derivative M under mild conditions. The spectroscopic characteristics and melting point of this monomer have been reported elsewhere.[18]

The free-radical copolymerization of M with H in dried DMF solution was studied over a wide composition interval with molar fractions of M ranging from 0.15 to 0.85 in the monomer feed. The reaction time was regulated to reach conversions of ca. 5 wt % to keep the composition of

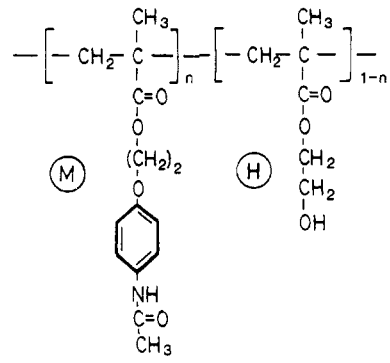
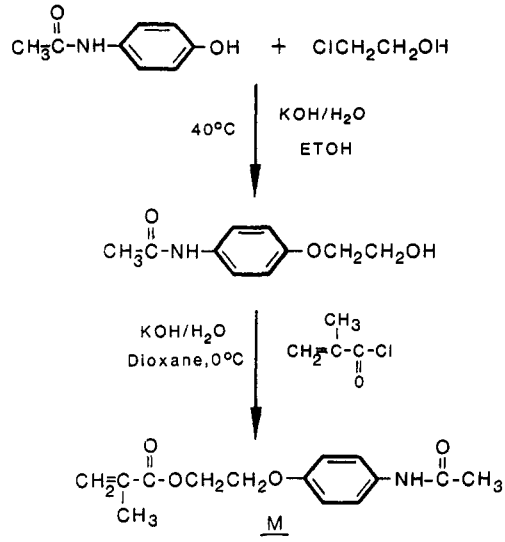


Figure 1. Chemical structure of the repeat comonomeric units in 4-((2-(methacryloyloxy)ethyl)oxy)acetanilide (M)–2-hydroxyethyl methacrylate (H) copolymers.

Scheme I



monomer feed practically constant and therefore to satisfy the differential copolymerization equation.[24] The molar fractions of M in the monomer feed F_M and in the copolymer chains f_M are collected in the first and second columns of Table I, respectively. The conversion of monomers to copolymer was determined gravimetrically after exhaustive drying of the isolated copolymer samples.

The average composition of the copolymer samples was determined from the corresponding ^1H NMR spectra registered in DMSO-d_6 at 80 °C. The assignment of the resonance signals was carried out according to the chemical structure of repeat units in the copolymer chains, drawn in Figure 1, taking into consideration the spectra of the corresponding homopolymers. Thus we considered the integrated intensities of the acetamido (NH) signal at δ 9.47 and the signals of the aromatic protons at δ 7.44 and 6.84 to determine the molar fraction of M in the copolymer chains, whereas for the determination of the H molar fraction we considered the sharp signal at δ 3.85, assigned to the ($COOCH_2$) protons of the H units. Resonance signals at δ 0.86, 1.01, and 1.23, assigned to the α-CH_3 protons of both kinds of units, were also considered. The values of molar fraction collected in the second column of Table I are the average of data obtained from the contribution of the resonance signals mentioned above. The fifth and sixth columns of Table I present the values of the conditional probabilities of monomer addition to polymeric growing chains, p_{ij} (i, j = M, H).[25] These values are useful to determine the statistical distribution and length of monomer sequences along the copolymer chains, considering the classical terminal model of copolymeri-

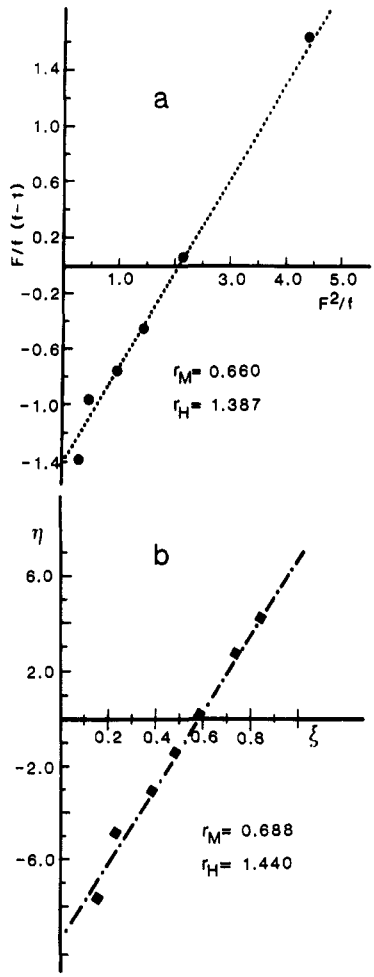


Figure 2. Linearization diagrams for the determination of the reactivity ratios of the M–H system under the experimental conditions reported in the Experimental Section: (a) application of the Fineman–Ross method; (b) application of the Kelen–Tüdös method.

Table II
Reactivity Ratios of 4-((2-(Methacryloyloxy)ethyl)oxy)-acetanilide (M) and 2-Hydroxyethyl Methacrylate (H) for the Free-Radical Copolymerization in DMF at 50 °C

method	r_M	r_H	$r_M r_H$
Fineman–Ross	0.660 ± 0.020	1.387 ± 0.070	0.915
Kelen–Tüdös	0.688 ± 0.035	1.440 ± 0.050	0.991
Tidwell–Mortimer	0.673	1.391	0.936

zation suggested by Lewis and Mayo[24] and Alfrey and Goldfinger.[26]

From the composition data quoted in the first and second columns of Table I we have determined the reactivity ratios of both monomers by the application of the linearization methods of the copolymerization equation suggested by Fineman and Ross[27] (Figure 2a) and Kelen and Tüdös[28] (Figure 2b) as well as the nonlinear least-squares analysis suggested by Tidwell and Mortimer.[29] The values of r_M and r_H determined by these methods are quoted in Table II; errors were derived from the standard deviations of the slope and intercept of the corresponding straight lines. The three methods applied give rather similar values, although the reactivity ratios determined by the nonlinear least-squares analysis are the most probable for this copolymerization system. In this sense, the so-called 95% confidence limits give an idea of the experimental error and of the goodness of experimental conditions used to generate the composition data.[29] The dimensions of the elliptical diagram generated by the application of the

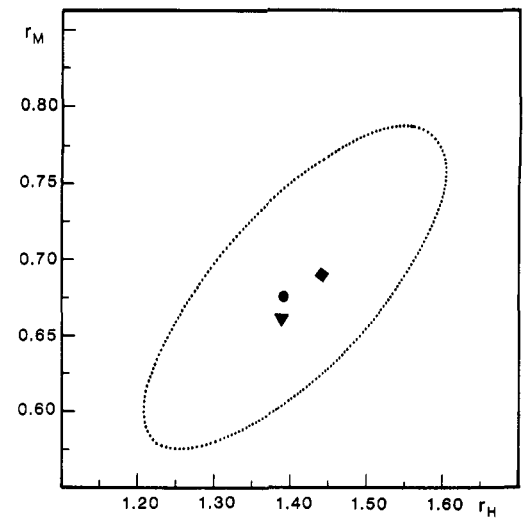


Figure 3. 95% confidence diagram for the reactivity ratios of M and H, determined by the nonlinear least-squares method suggested by Tidwell and Mortimer. Values of reactivity ratios: (♦) Tidwell–Mortimer; (▼) Fineman–Ross; (●) Kelen–Tüdös.

mathematical treatment suggested by Bechnken[30] and Tidwell and Mortimer[29] provide the 95% confidence limits with respect to the true parameters. The diagram drawn in Figure 3 confirms the excellent approximation of the values of r_M and r_H as indicated by the reduced dimensions of the ellipse and makes clear that if there are enough experimental data in the whole interval of compositions and if an appropriate characterization technique for the determination of the composition of copolymer samples is used, the application of the classical linearization methods provides values of the copolymerization parameters rather close to those determined by the application of more sophisticated mathematical treatments.

The values of r_M and r_H quoted in Table II indicate that the M–H system copolymerizes at random, with a statistical distribution of monomeric units along the copolymer chains, as also shown by the proximity to unity of the product $r_M r_H$. On the other hand, the value of r_M is rather different from that of 4-(methacryloyloxy)acetanilide (M′), $r_{M'}$ = 2.15, for the free-radical copolymerization with H, r_H = 0.90, under the experimental conditions outlined in the Experimental Section.[14] Probably, the introduction of the oxyethylene spacer group between the acrylic ester group and the acetanilide residue gives rise to additional steric hindrance to prevent interactions between the acetamido residue with the carbonyl ester group of M neighboring units or incoming monomer molecules. These interactions have been detected in M′ and M′–H systems through the kinetic analysis of the free-radical copolymerization of M′ with H as well as by the high T_g of poly(M′) (471 K) or the relatively high T_g values of M′–H copolymers.[14] The T_g of the homopolymer derived from M is sensibly lower, 385 K, as well as those of the corresponding copolymers with H.[30] The decrease of T_g of poly(M′) respect to poly(M), ΔT_g = 86 K, is much higher than that expected from the increasing flexibility of polymer segments by the introduction of the oxyethylene spacer group in the side substituent without other structural changes in the polymer backbone; for example, poly(methacrylonitrile) has a T_g of 393 K, whereas the T_g of poly(2-cyanoethyl methacrylate) is 364 K, ΔT_g = 29 K, and the T_g of poly(4-cyanophenyl methacrylate) is 428 K, whereas that of poly(4-(cyanomethyl)phenyl methacrylate) is 401 K, ΔT_g = 27 K.[40] Therefore, it can be considered that such a decrease in T_g could be ascribed, at least partially, to the disappearance of the dipolar interactions

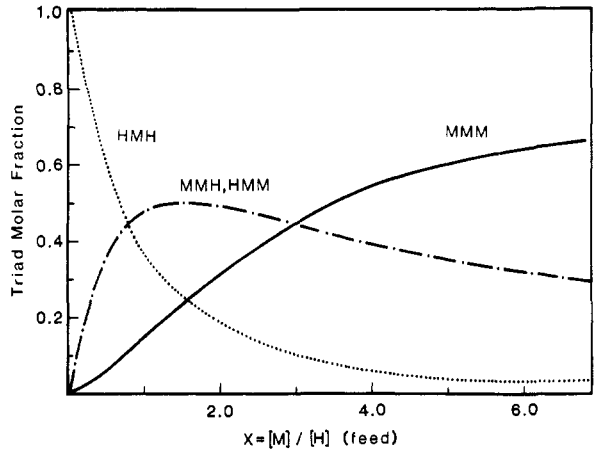


Figure 4. Variation of the molar fraction of 4-((2-(methacryloyloxy)ethyl)oxy)acetanilide-centered triads with the ratio of the concentration of monomers X in the feed.

between the acetamido group and the carbonyl ester function of neighboring units.

These facts explain satisfactorily the predominant random character of the free-radical copolymerization of the M–H system. On this basis, we have determined the statistical distribution of M-centered sequences, considering the equations reported for the first-order Markovian addition probabilities (p_{MH}, p_{MM}, p_{HM}, and p_{HH}) according to the expressions[25]

$$p_{MH} = 1 - p_{MM} = 1/(1 + r_M X)$$

$$p_{HM} = 1 - p_{HH} = 1/(1 + r_H/X)$$

where $X = [M]/[H]$, the ratio of the concentrations of M and H in the monomer feed. Figure 4 shows the diagrams of the statistical distribution of M-centered triads along the copolymer chains as a function of the ratio of the molar concentrations of the monomers in the reaction medium. The concentration of alternating HMH triads decreases dramatically, whereas the concentration of MMM homotriads increases smoothly with increasing X. However, the molar fraction of HMM + MMH heterotriads reaches a maximum of 0.5 for a value of $X = 1.5$, which corresponds to a copolymer with an M molar fraction of about 0.5. These diagrams make clear that the acrylic units supporting the active pharmacon are distributed isolately in segments of H units for copolymers prepared over a relatively wide interval of compositions ($f_H > 0.5$). This conclusion may be of practical interest in preparing biocompatible macromolecular systems with isolated M units separated by H segments to avoid the side effects of hydrolytic processes in neighboring active units.

Stereochemistry. It has been widely demonstrated that the biodegradation of polymer systems in living organisms depends predominantly on their chemical structure,[31] but the hydrolytic or enzymatic degradation of a susceptible bond (i.e., an ester linkage) can also be affected by the conformation of the polymer chain and by the stereochemical configuration of the pseudoasymmetric carbon atoms present in the repeat units of the polymer chains.[32,33] In this regard, it was of interest to us to analyze the stereochemical configuration of copolymers with different compositions. Figure 5 shows the proton-decoupled ^{13}C NMR spectrum of a copolymer with $f_M = 0.320$. The assignment of the resonance peaks to the chemical structures indicated in the figure was carried out according to the resonance signals of the corresponding homopolymers.[34] Copolymer samples with other compositions give spectra similar to that of Figure 5, but

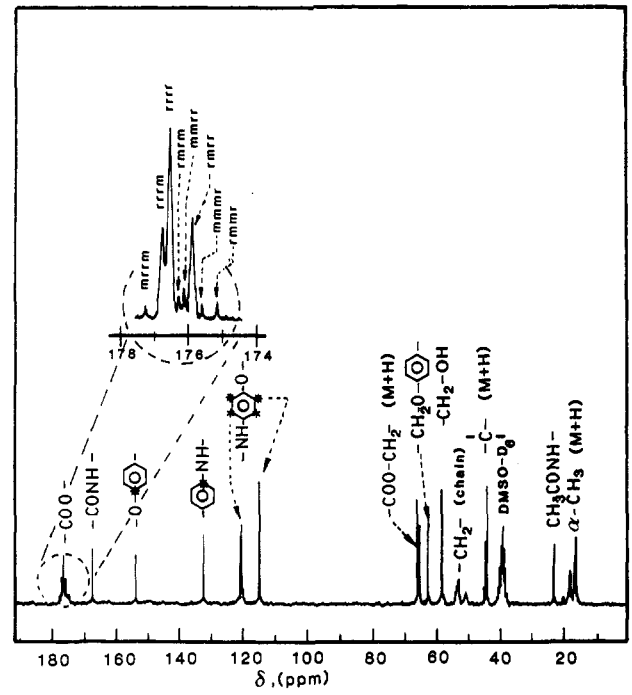


Figure 5. Decoupled ^{13}C NMR (75.5 MHz) spectrum in DMSO-d_6 at 80 °C of an M–H copolymer with $f_M = 0.320$.

logically the intensity of the signals changes with the composition of the copolymer analyzed. However, there are three sets of signals which do not suffer any significant change in the chemical shift or in the intensity with the composition of the copolymer samples. These are the α-CH_3 group of both M and H units, which gives rise to three resonance signals in the interval δ 15–22, the pseudoasymmetric quaternary carbon of both M and H units, which also gives rise to three sharp peaks in the interval δ 43–47, and the carbonyl carbon that presents a rather complex pattern in the interval δ 174–178.

This result indicates that the three chemical groups considered, which are present in the structure of both kinds of monomeric units (see Figure 1), must be magnetically equivalent to give the same chemical shift. Therefore, the appearance of different resonance signals is a consequence of the influence of the relative stereochemical configuration of comonomeric units along the copolymer chains on the shielding of the chemical residues considered. This is better seen in Figure 6, where the different stereochemical triads have been represented schematically. The polymer backbone is the same for both kinds of units, and the structural difference arises from the side group represented by a black circle in the figure. If we take into consideration that the oxyethylene spacer group is also common for both monomeric units, the chemical substitution at the end of this side residue is very far from the organic groups or atoms affected by the stereochemical configuration of units along the macromolecular chains. Therefore, it can be expected that their influence on the stereochemistry is negligible.

Figure 7 shows the expanded ^{13}C NMR decoupled spectrum of the α-CH_3 and quaternary carbon resonances of copolymer samples with different compositions (for clarity the signals of DMSO-d_6 have been drawn with reduced intensity). Both groups present three well-resolved peaks whose relative intensities do not change with the copolymer composition, being the corresponding chemical shifts collected in Table III, together with those of poly(methyl methacrylate) (PMMA). Assignment of these signals to sequences of tactic triads was done

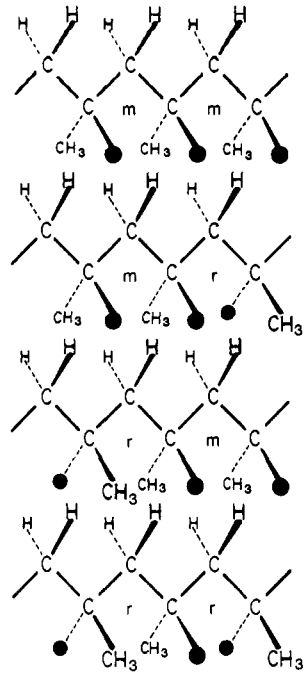


Figure 6. Schematic representation of tactic triads in M–H copolymers. (●) represents the side residue of M (● = $COO(CH_2)_2OC_6H_4HNOCCH_3$) or H (● = $COO(CH_2)_2OH$) units in the macromolecular chains.

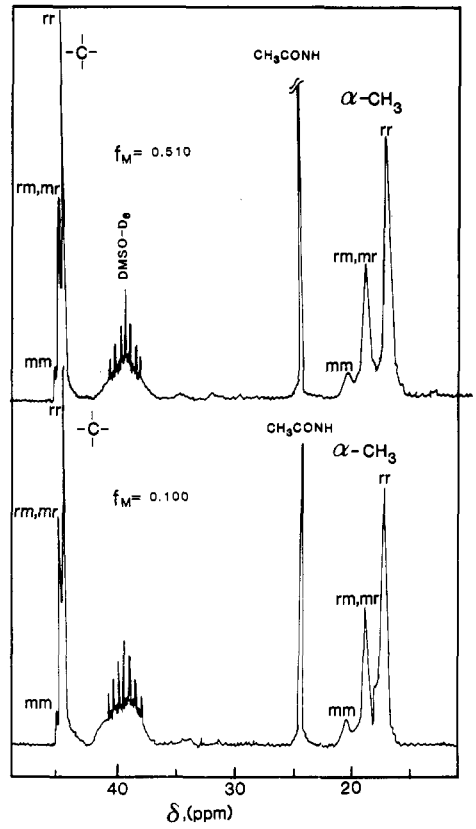


Figure 7. ^{13}C NMR (75.5 MHz) expanded resonance signals of the α-CH_3 and quaternary carbons of M–H copolymers prepared with different compositions.

following the classical assignment of the same groups for pure PMMA[35,36] and poly(M).[34]

As we have reported,[34] it is possible to correlate the molar concentration of M- and H-centered sequences with parameters derived from the statistical analysis of the copolymerization system according to the reactivity ratios quoted in Table II, the conditional probabilities p_{ij} quoted

Table III
Spectroscopic Characteristics of the ^{13}C NMR Resonances of the α-CH_3 and Quaternary Carbons of M–H Copolymers Prepared by Free-Radical Copolymerization in DMF at 50 °C

sequence	δ, ppm	rel intens f_M = 0.100	rel intens f_M = 0.510	PMMA δ, ppm	PMMA mol fract
		α-CH_3 Carbons			
rr	16.90	0.61_5	0.62_3	16.43	0.59
rm + mr	18.61	0.32_4	0.32_0	18.39	0.35
mm	20.41	0.06_1	0.05_7	20.67	0.05
		Quaternary Carbons			
rr	44.30	0.61_2	0.62_6	43.89	0.60
rm + mr	44.58	0.33_8	0.32_4	44.20	0.36
mm	44.86	0.05_0	0.04_9	44.75	0.04

Table IV
Spectroscopic Characteristics and Assignment of ^{13}C NMR Resonances of the Carbonyl Group of the M and H Units in Copolymers Prepared by Free-Radical Copolymerization at 50 °C

δ, ppm	sequence	mol fract exptl	mol fract calcd	δ, ppm	sequence	mol fract exptl	mol fract calcd
177.14	mrrm	0.02_7	0.031	175.85	rmrr	0.20_6	0.200
176.83	mrrr	0.19_0	0.212		mmrm		0.003
176.49	rrrr	0.41_0	0.395	175.55	mmmr	0.02_8	0.024
176.24	rmrm	0.04_0	0.051	175.12	rmmr	0.03_4	0.029
176.10	mmrr	0.06_5	0.055		mmmm		0.000

in Table I, and the average composition of copolymer samples, if the copolymerization reaction is described by the terminal model, and the distribution of comonomeric units along the macromolecular chains fit first-order Markov statistics. Furthermore, the configurational sequence distribution may be described according to a Bernoullian statistics with the isotacticity parameters σ_{MM}, σ_{HH}, and $\sigma^* = \sigma_{MH} = \sigma_{HM}$ as defined by Bovey[37] and Coleman.[38]

The values of σ_{MM} and σ_{HH} correspond to the isotacticity parameters of sequences of M and H units and therefore can be considered in good approximation the values of the corresponding homopolymers prepared under the same experimental conditions,[34] i.e., σ_{MM} = 0.22 and σ_{HH} = 0.21. Taking into consideration these parameters and the average values of the relative intensities of rr, rm + rm, and mm resonances collected in the fourth and fifth columns of Table III, the coisotacticity parameter σ^* was determined by the application of well-known statistical relations,[39] giving a value of $\sigma_{MH} = \sigma_{HM}$ = 0.21.

All of these parameters have practically the same value, as corresponds to the similar stereochemical configuration of both comonomeric units, being very close to that of PMMA,[34,37] σ_{PMMA} = 0.24, which indicates that there is a random distribution of tactic sequences along the copolymer chains, with a clear tendency to form syndiotactic sequences. Finally, we stress here that the complex pattern of the low-field resonances (δ 174–178) assigned to the carbonyl carbon of both M and H units may be analyzed in terms of tactic pentads. The expanded carbonyl carbon resonances have been drawn at the top of Figure 5 for a copolymer sample of f_M = 0.320. As indicated before, other samples with different compositions present practically the same signals. The assignment of the stereochemical pentads indicated in the figure was done on the basis of similar analysis for poly(M)[34] and PMMA.[35,36]

Table IV presents the chemical shifts of the tactic pentads considered together with the molar fraction of the corresponding sequence. The fourth column of this table presents values of pentads, calculated according to the isotacticity parameters σ_{MM} and σ_{HH} and the coiso-

tacticity parameter $\sigma_{MH} = \sigma_{HM}$ indicated above. The good agreement between experimental and calculated values makes clear the random distribution of tactic sequences according to Bernoullian statistics from a stereochemical point of view and supports the assignment of the resonance signals considered.

Acknowledgment. This work was supported by Grant Mat. 88-0579-C02-01. We are also indebted to Dr. J. Guzmán Perote for the computer program to determine the reactivity ratios and confidence limits.

References and Notes

(1) Brannon-Peppas, L.; Peppas, N. A. *Biomaterials* **1990**, *11*, 635.
(2) Peppas, N. A. *Hydrogels in Medicine and Pharmacy*; CRC Press: Boca Raton, FL, 1987.
(3) Dusek, K.; Prins, W. *Structure and Elasticity of Noncrystalline Polymer Networks*; *Adv. Polym. Sci.* **1969**, *6*, 1.
(4) Ishihara, K.; Kobayashi, M.; Shinohara, I. *Polym. J.* **1984**, *16*, 647.
(5) Wisniewski, S.; Kim, S. W. *J. Membr. Sci.* **1980**, *6*, 299.
(6) Folkman, J. *Biomaterials* **1990**, *11*, 615.
(7) Andrade, J. D. *Hydrogels for Medical and Related Applications*; Americal Chemical Society: Washington, DC, 1976.
(8) Ronel, S. H.; D'Andrea, M. J.; Hashiguchi, H.; Klomp, G. F.; Dobelle, W. H. *Biomed. Mater. Res.* **1983**, *17*, 855.
(9) Robert, C. R.; Buri, P. A.; Peppas, N. A. *J. Appl. Polym. Sci.* **1985**, *30*, 301.
(10) Hosaka, S.; Ozawa, H.; Tanzawa, H. *J. Appl. Polym. Sci.* **1979**, *23*, 2089.
(11) Ishihara, K.; Hamada, N.; Kato, S.; Shinohara, I. *J. Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 121.
(12) San Román, J.; Madruga, E. L.; Pargada, L. *J. Polym. Sci., Polym. Chem. Ed.* **1987**, *25*, 203.
(13) San Román, J.; Madruga, E. L. *Polymer* **1989**, *30*, 949.
(14) San Román, J.; Levenfeld, B.; Madruga, E. L.; Vairon, J. P. *J. Polym. Sci., Part A: Polym. Chem.* **1991**, *29*, 1023.
(15) Duncan, R.; Kopecek, J. *Adv. Polym. Sci.* **1979**, *57*, 51.
(16) Presscott, L. F.; Critchley, J. A. J. H. *Annu. Rev. Pharmacol. Toxicol.* **1983**, *23*, 87.
(17) *The Merck Index*, 10th ed.; Merck Co. Inc.: Rahway, NJ, 1983; no. 7064.
(18) Levenfeld, B.; San Román, J.; Madruga, E. L. *Polymer* **1990**, *31*, 160.
(19) Ringsdorf, H. *J. Polym. Sci., Polym. Symp.* **1975**, *51*, 135.
(20) Levenfeld, B.; San Román, J.; Bunel, C.; Vairon, J. P. *Makromol. Chem.* **1991**, *192*, 793.
(21) Burgos, A.; Bravo, L.; Madruga, E. L.; San Román, J.; Rodriguez, A. J.; Tabares, B.; Vivas, J. M. Preprints, XXII Rencontres Internationales de Chimie Therapeutique, Clermont-Ferrand, 1986, p 131.
(22) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1981.
(23) Patai, S., Ed. *The Chemistry of the Carbonyl Group*; Wiley-Interscience: New York, 1966.
(24) Lewis, F. M.; Mayo, F. R. *J. Am. Chem. Soc.* **1944**, *66*, 2050.
(25) Koening, J. L. *Chemical Microstructure of Polymer Chains*; Wiley-Interscience: New York, 1980.
(26) Alfrey, T., Jr.; Goldfinger, F. *J. Chem. Phys.* **1944**, *12*, 205.
(27) Fineman, M.; Ross, S. D. *J. Polym. Sci.* **1950**, *5*, 259.
(28) Kelen, T.; Tüdös, F. *J. Macromol. Sci., Chem.* **1975**, *9*, 1.
(29) Tidwell, P. W.; Mortimer, G. A. *J. Polym. Sci., Part A* **1965**, *3*, 369.
(30) San Román, J.; Levenfeld, B., to be published.
(31) Kopecek, J.; Ulbrich, K. *Prog. Polym. Sci.* **1983**, *9*, 1.
(32) Kim, S. W.; Petersen, R. V.; Feijen, J. Polymeric Drug Delivery Systems. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: London, 1980.
(33) Zierenberg, B. *Med. Res. Ser.* **1989**, *12*, 401.
(34) San Román, J.; Levenfeld, B. *Macromolecules* **1990**, *23*, 423, 3036.
(35) Chûjô, R.; Hatada, K.; Kitamaru, R.; Kitayama, T.; Sato, H.; Tanaka, I. *Polym. J.* **1987**, *19*, 413.
(36) Peat, I. R.; Reynolds, W. F. *Tetrahedron Lett.* **1972**, *14*, 1359.
(37) Bovey, F. A. *J. Polym. Sci.* **1962**, *62*, 197.
(38) Coleman, B. *J. Polym. Sci.* **1958**, *31*, 155.
(39) Bovey, F. A. *Chain Structure and Conformation of Macromolecules*; Academic Press: New York, 1982.
(40) Brandrup, J.; Immergut, E. H., Eds. *Polymer Handbook*, 3rd ed.; Wiley-Interscience: New York, 1989.

Registry No. MH, 135944-78-4.