Synthesis and characterization of a new poly(methacrylamide) bearing side groups of biomedical interest

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This paper reports the synthesis and polymerization of a new methacrylamide derivative, *N*-[4-(4-methoxyphenylacetyloxy)phenyl]methacrylamide, which supports functional side groups of potential biomedical interest. Polymers obtained by free radical polymerization in a solution of *N*,*N*-dimethylformamide at moderate temperatures were characterized by ^1H and ^{13}C n.m.r., being predominantly syndiotactic, with an isotacticity parameter $\sigma = 0.19$, somewhat lower than that of poly(methyl methacrylate) (PMMA, $\sigma = 0.22$) or poly[*N*-(4-methacryloyloxyphenyl), 2-(4-methoxyphenyl)-acetamide][poly(OM), $\sigma = 0.27$]. This behaviour seems to be a consequence of the stiffness of the methacrylamide side groups with respect to the methacrylic ester function of poly(OM) and PMMA.

(Keywords: synthesis; characterization; poly(methacrylamide))

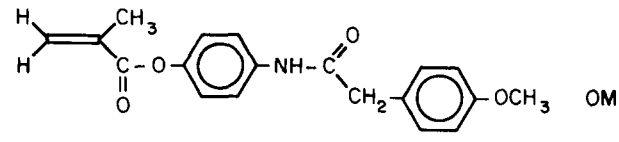
INTRODUCTION

The development of polymeric systems carrying active chemical functions has attracted the interest of different research groups over the past two decades[1–7]. In this sense, controlled release delivery systems are designed to maintain the optimum drug concentration within the therapeutic range. One of the most attractive approaches is the synthesis of new polymeric drugs based on well-known pharmacons or drugs, bound covalently to a macromolecular biodegradable or soluble support[1,8]. The advantage of this kind of system over the delivery system based on a physical property (i.e. transdermal devices or osmotic pump deliveries) is mainly that the 'polymeric drugs' may display pharmacological activity by themselves, but at the same time may be used as carriers for the pharmaceutical agent[8,9]. Therefore, these systems not only offer an interesting way to improve the duration of activity through the controlled release of the drug residue, but also a more cell-specific uptake (targeting effect) and reducing toxicity of the parent drug can be attained[2,10].

In earlier papers we reported the preparation and the study of the pharmacological behaviour of polyacrylic formulations based on the synthesis and polymerization of methacrylate esters of typical analgesic and antipyretic drugs, like salicylic acid[11] and of several derivatives of paracetaminophen or paracetamol[12,13]. More recently, we have been interested in the preparation of polymeric drugs with anti-inflammatory activity, which could be used for the treatment of local inflammatory processes of traumatologic origin (combined with a second hydrophilic biocompatible monomer like hydroxyethyl methacrylate) and also for the treatment of arthritic diseases, the most important being those of rheumatic origin, which are the result of inflammatory processes occurring around and within the joint[14].

Several substituted phenoxypropionic, phenylacetic and propionic acids have been proved to be active in rheumatoid arthritis, in such a way that they are catalogued as a family of anti-inflammatory compounds known as 'non-steroidic anti-inflammatory agents'[15]. In this sense, derivatives of phenylacetic acid have been used extensively as non-steroidic anti-inflammatory agents for the treatment of oedema, erythema and resulting tissue damage associated with inflammatory diseases[16], although this kind of compound presents a considerable hepatic toxicity, as it has been claimed by the Food and Drugs Administration[14]. Particularly, 4-methoxyphenylacetic acid[17] has a lethal dose (LD_{50}) of 1550 mg kg^{-1} and 4-methoxyphenylacetyl chloride has been used for several pharmaceutical and medical applications[18,19].

In this sense, we have reported recently[20] the synthesis and free radical polymerization of *N*-(4-methacryloyloxyphenyl),2-(4-methoxyphenyl)acetamide (OM), a methacrylic ester, derivative of 4-methoxyphenylacetic acid.



OM

As shown by the chemical structure of OM, the phenylacetic residue is linked to the acrylic polymerizable function through a spacer group derived from 4-aminophenol. In addition, we have designed another alternative way to prepare a polyacrylic matrix with rather similar biomedical characteristics but based on the

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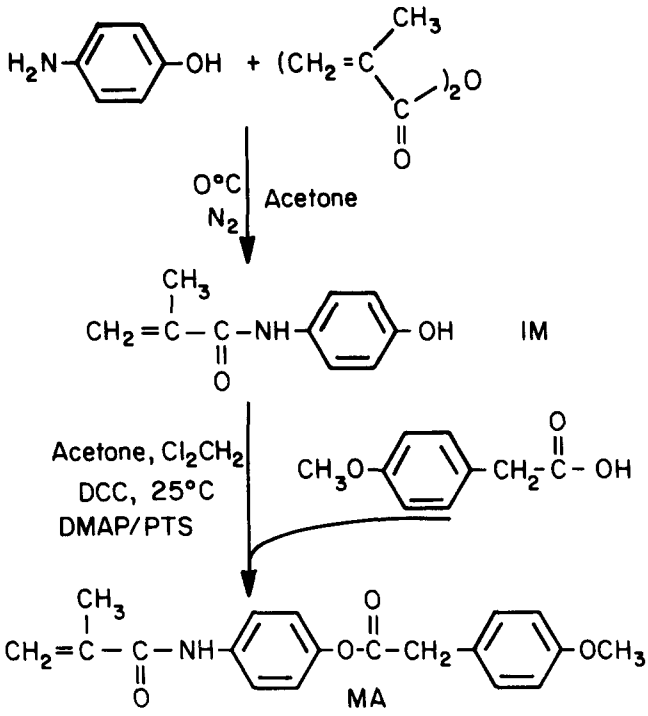


Scheme 1

synthesis of the corresponding methacrylamide derivative (*Scheme 1*). The main aim of this paper is to report the synthesis and the study of the free radical polymerization of the methacrylamide derivative *N*-[4-(4-methoxyphenylacetyloxy)phenyl]methacrylamide (MA). This compound has the same pharmacological residues as the derivative OM, but the bonds of the acrylic and phenylacetic acid residues to the 4-aminophenoxy spacer group are interchanged with respect to the compound OM. Hence, it could be interesting to analyse comparatively the behaviour of both compounds in free radical polymerization, as well as the microstructure of the corresponding polymers.

EXPERIMENTAL

Reagents. 4-Methoxyphenylacetic acid (Fluka AG) was purified by recrystallization from acetone/heptane (m.p. = 87 ± 1°C). 4-Aminophenol (Merck) was twice recrystallized from ethanol/heptane [m.p. = 187 ± 1°C (lit. 184°C)]. Dicyclohexylcarbodiimide (DCC, Merck) was used as received. 4-Dimethylaminopyridine (Fluka AG), was used without purification. *N*,*N*-dimethylformamide (DMF) was dried over anhydrous magnesium sulphate for 2 days and later with phosphoric anhydride overnight. After drying, DMF was distilled under reduced pressure of nitrogen.

2,2′-Azobisisobutyronitrile (AIBN), was purified by fractional crystallization from methanol (m.p. = 104°C). Other reagents (extra-pure grade) were used without purification.

Synthesis of N-(*4-hydroxyphenyl*)*methacrylamide* (*IM*). The intermediate derivative of methacrylamide IM was prepared by the selective amidation reaction of 4-aminophenol with methacrylic anhydride at 0°C using acetone as solvent. To a solution of purified 4-aminophenol (0.15 mol) in dry acetone (100 ml), a solution of methacrylic anhydride (0.20 mol) in 50 ml of acetone was added dropwise under N_2 atmosphere and magnetic stirring. After reacting for 3 h the solvent was distilled off at reduced pressure and the solid residue was washed twice with chloroform. The isolated product was purified by column chromatography (Kiesel-gel 60, Merck), using ethyl acetate as eluent. The yield was 75% and the purity of the isolated compound was tested by h.p.l.c. and i.r. and exceeded 99% (m.p. = 158 ± 1°C).

Synthesis of N-[*4-(4-methoxyphenylacetyloxy)phenyl*] *methacrylamide* (*MA*). The methacrylamide derivative MA was prepared by the reaction of the intermediate IM with 4-methoxyphenylacetic acid in the presence of DCC, 4-(dimethylamino)pyridine (DMAP) and *p*-toluenesulphonic acid (PTS) as catalyst. In a typical experiment, a solution of 4-methoxyphenylacetic acid (0.10 mol), IM (0.10 mol), DCC (0.10 mol), DMAP (0.01 mol) and PTS (0.01 mol) in 50 ml of a mixture of 1:1 dichloromethane/acetone was allowed to stand under N_2 with magnetic stirring at room temperature overnight until sterification was complete. The dicyclohexylurea formed was filtered and the filtrate was concentrated at reduced pressure until crystallization. The isolated product was purified by recrystallization in acetone/methanol, filtered and dried over phosphorus anhydride overnight (yield, 90%; m.p. = 130 ± 1°C).

Polymerization. The methacrylamide derivative MA was polymerized at 50 and 70°C in DMF solution ([MA] = 1 mol l^{-1}) using AIBN as initiator. The reactions were carried out in Pyrex glass ampoules under vacuum over 5 h. The polymer was isolated by pouring the reaction mixture into a large excess of methanol at 0°C. The precipitated polymer was filtered off, washed with methanol and dried at reduced pressure to constant weight.

Characterization of products. The derivatives of methacrylamide IM and MA were characterized by i.r., ^1H and ^{13}C n.m.r. I.r. spectra were recorded in KBr pellets on a Perkin-Elmer 457 spectrometer at room temperature. N.m.r. spectra were recorded in deuterated dimethylsulphoxide (DMSO-d_6) solutions on a Varian XLR-300 spectrometer at 80°C. ^1H n.m.r. (300 MHz) experiments were performed on 5% (w/v) solutions, whereas ^{13}C n.m.r. spectra were recorded on 25% (w/v) solutions with the spectrometer operating at 75.5 MHz. In the case of polymer samples, an inverse gated decoupling sequence pulse with a flip angle of 80° (pulse width of 13 μs) and a relaxation delay of 4 s were used. These conditions ensure the complete relaxation of all the ^{13}C nuclei analysed. The relative peak intensities were measured from the integrated peaks area, calculated by means of an electronic integrator or by triangulation and planimetry.

The melting point and glass transition temperature (T_g) of the products synthesized were determined by d.s.c. using a Perkin-Elmer DSC-4 calorimeter. The samples introduced into the aluminium pan were heated in the calorimeter at 550 K for 30 min and then quenched at −50°C, prior to the measurement run.

RESULTS AND DISCUSSION

According to the model for the design and preparation of pharmacologically active polymeric systems suggested by Ringsdorf in 1975[21], the covalent anchoring of low

molecular weight pharmacons or drugs to a polymer backbone, must be constituted by organic functional groups which can be degraded in the physiological medium. In addition the introduction of a spacer group between the polymer supporting matrix and the active side residue may be of interest in order to minimize the steric hindrance of the rigid macromolecular backbone against the cleavage of the side substituent. The biodegradation in the living body of this kind of system is mainly produced by hydrolytical processes (which can be activated enzymatically) of ester, amide, anhydride, carbonate, carbamate, etc., functions[22,23]. Hence, we have selected the 4-aminophenyloxy residue as the spacer group between the anti-inflammatory component and the polyacrylic matrix, since it provides aromatic ester and amide chemical bonds of relatively low stability in the physiological medium.

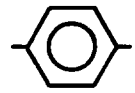
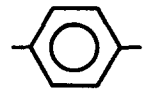
In the last few years there has been increasing interest in the preparation of biomaterials based on derivatives of poly(methacrylamide), because of the excellent biocompatibility and bioadhesion of these kinds of macromolecular systems, as well as in the physico-chemical behaviour of biologically active hydrogels based on poly(methacrylamide) derivatives[24–30]. On the other hand, the anchoring of the pharmacologically active moiety to macromolecular chains must be carried out in synthetic conditions mild enough to allow the linkage without any adverse effect on the future physiological activity of the pharmacon[21]. Therefore, we designed the synthesis of MA following a two-step route according to *Scheme 1*. The first step was the selective synthesis of the methacrylamide derivative of 4-aminophenol, IM. Although the synthesis of this compound was first described by Panarin and Beros in 1968[31], and recently Yasuzawa *et al.*[32] reported the synthesis of IM by the reaction of 4-aminophenol with methacryloyl chloride in a solution of acetic acid at 55°C, we have followed the treatment of 4-aminophenol with methacrylic anhydride in acetone at low temperature reported by Meslard *et al.*[33]. In these experimental conditions, the *N*-(4-hydroxyphenyl) methacrylamide was selectively synthesized, avoiding the formation of the corresponding methacrylic ester derivative, because of the strong tendency of methacrylic anhydride to react with the basic amine centre rather than with the acidic phenolic proton.

The second step is the coupling of the pharmacological active compound to the intermediate IM. This process was carried out on the basis of the condensation reaction at room temperature, of the carboxylic group of 4-methoxyphenylacetic acid with the phenolic group of IM, using PTS and DMAP as catalysts, activated by DCC. It has been demonstrated that the carbodiimides, in the presence of a 1:1 molecular complex of DMAP and PTS, activate the carboxylic function favouring the displacement of the equilibrium reaction to the formation of the amide or ester derivatives[34–36].

Physical constants and spectroscopic characteristics of the intermediate IM and the methacrylamide derivative MA, synthesized as described in *Scheme 1*, are given in *Table 1*. The melting point of the intermediate compound IM is very close to that reported by Yasuzawa *et al.*[32] (m.p. = 155°C).

Figure 1 shows the proton decoupled ^{13}C n.m.r. spectra of both compounds. All the resonance signals have been assigned to the corresponding carbon atoms on the basis of DEPT spectra (Distortionless Enhancement by Polarization Transfer, 135°) and by comparison with the spectrum of OM described previously[20].

Table 1 Physical data and spectroscopic characteristics of IM and MA

Compound	M.p. (°C)	Functional group	I.r. (cm^{-1})	^1H n.m.r.[a] (δ, ppm)
IM	158	*CO*NH–	3280–3300	9.48
		Ar–OH	3200	9.16
		*CO*NH–	1645	–
		$CH_2=C$	1630	5.73, 5.42
			1600, 1585 1540, 1505	7.43, 7.39 6.70, 6.66
		α-CH_3	–	1.92
MA	130	–*CO*NH–	3300	9.60
		–COO–	1745	–
		–*CO*NH–	1655	–
		$-CH_2=C$	1640	5.72, 5.39
			1620, 1600 1530, 1510	7.58–6.91 (8 peaks)
		CH_3O–	1250	3.77
		ArCH_2CO–	–	3.79
		α-CH_3	–	1.99

[a] DMSO-d_6, with TMS reference

The methacrylamide MA was polymerized at 50 and 70°C, by a free radical mechanism in a solution of DMF ([MA] = 1 mol l^{-1}) using AIBN as initiator ([AIBN] = 1.5×10^{-2} mol l^{-1}). Conversions of 87 wt% at a polymerization temperature of 50°C and 90 wt% at 70°C were reached after 5 h of reaction. The average molecular weight of the polymers prepared, determined by g.p.c. with poly(methyl methacrylate) (PMMA) standards, were $M_n = 87000$ and 26000 for reactions carried out at 50 and 70°C, respectively. According to the g.p.c. curves obtained the polydispersity of the samples analysed is $M_w/M_n = 3.1$ and 3.0, respectively, with symmetric g.p.c. diagrams approaching a Gaussian distribution. Comparison with results obtained for the free radical of OM in the same experimental conditions[20], shows that MA seems to achieve slightly lower conversions than the methacrylic ester OM for the same reaction time at a given temperature. However, the molecular weight of the poly(methacrylamide) derivative poly(MA) is approximately two times that of the corresponding polymethacrylate poly(OM), when the polymerization is carried out at 50°C, whereas they are practically equal at a polymerization temperature of 70°C. A study of the comparative kinetic behaviour of both acrylic monomers OM and MA is in progress and will be reported subsequently.

The polymers obtained at different reaction temperatures were characterized by i.r. and n.m.r. spectroscopies, the n.m.r. spectrum giving interesting information on the relative stereochemical configuration of monomeric units along the macromolecular chains of poly(MA). *Figure 2* shows the ^1H n.m.r. spectrum of a polymer sample prepared at 50°C. The resonance of the α-CH_3 side substituent splits into three well resolved peaks at 1.35, 1.18 and 1.05 ppm from TMS, which have been assigned to iso (*mm*), hetero (*mr* + *rm*) and syndiotactic (*rr*) triads,

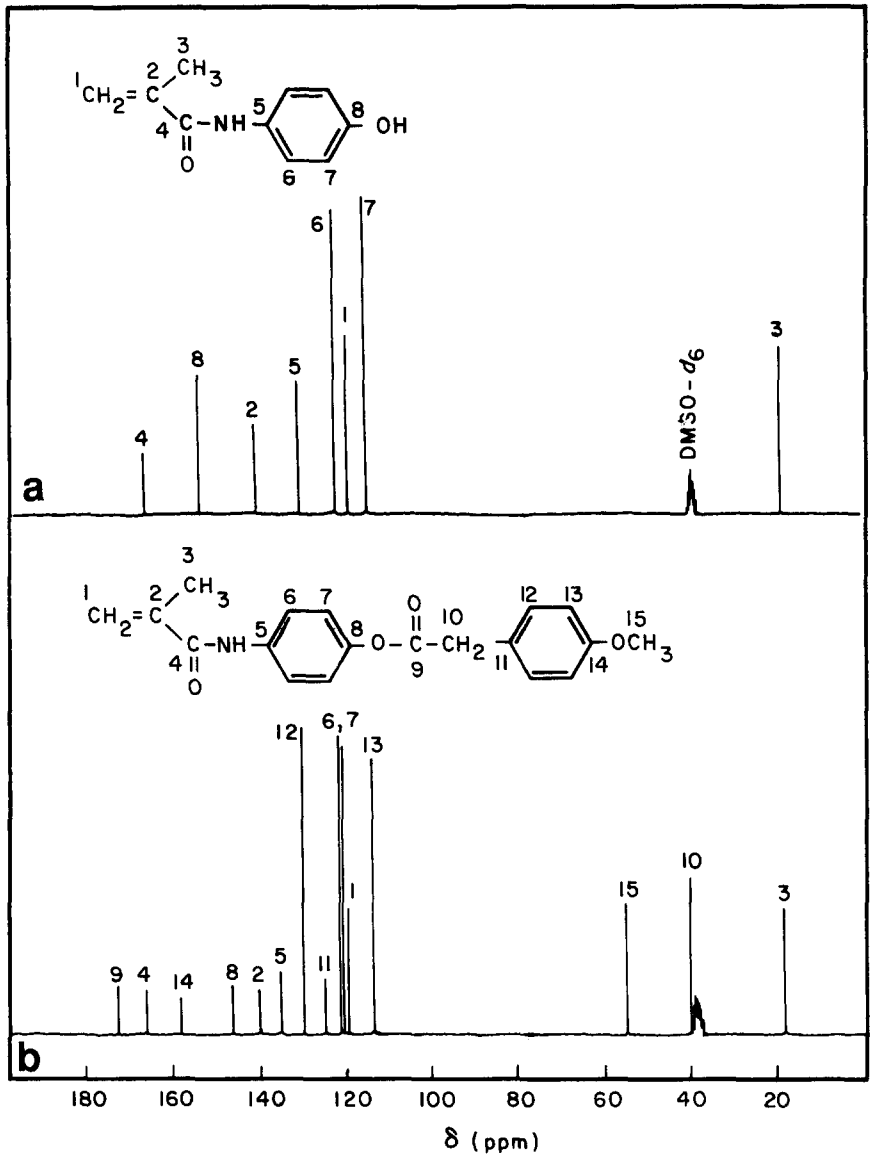


Figure 1 Decoupled ^{13}C n.m.r. (75.5 MHz) spectra of (a) IM and (b) MA, recorded in DMSO-d_6 at 80°C

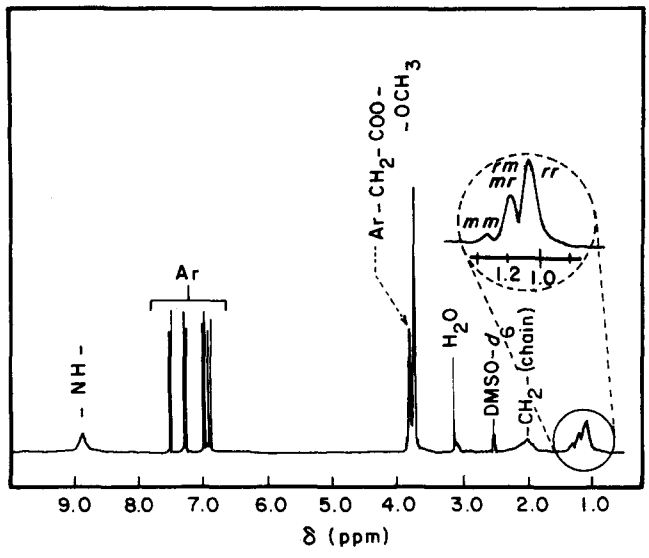


Figure 2 ^1H n.m.r. (300 MHz) spectrum of poly(MA), recorded in DMSO-d_6 at 80°C

in order of increasing field, following the assignment of the α-CH_3 resonances for PMMA[37]. The experimental values of the molar fraction of tactic sequences in the first row of *Table 2* have been determined from the integrated intensities of the signals assigned to the corresponding sequences. It is interesting to stress here that the –NH– proton of the methacrylamide residue is not sensitive to the stereochemistry of monomer units, giving a single resonance signal at 8.95δ, unlike the –NH– proton of poly(OM), which presents three well resolved peaks assigned to the corresponding tactic sequences[20]. However, similar results have been reported for the free radical polymerization of other methacrylamide derivatives[25].

Figure 3 shows the decoupled ^{13}C n.m.r. spectrum of a sample of poly(MA) (the results are independent of the polymerization temperature). The resonances of the α-CH_3 side group (16–21δ), and quaternary carbon of the methacrylic chain (45–47δ), split into several peaks which have been analysed in terms of the content of different stereochemical sequences. *Figure 4* shows the en-

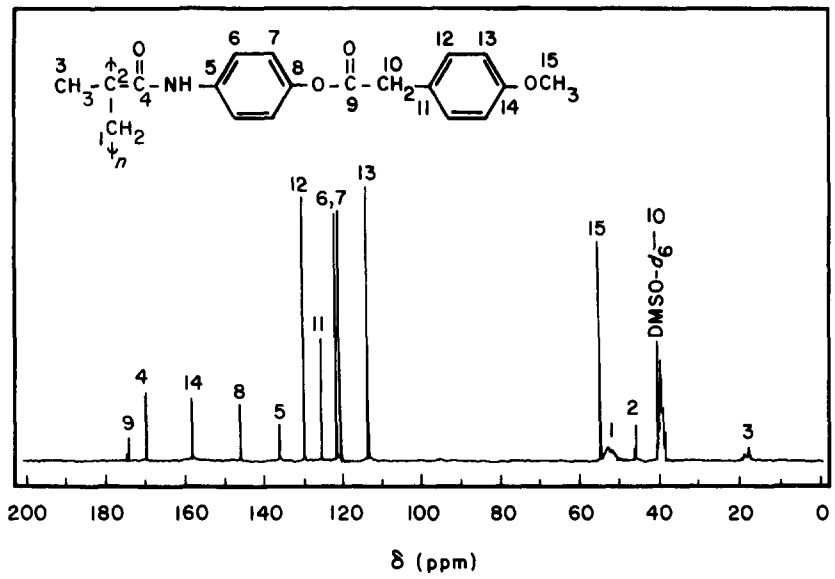


Figure 3 Decoupled ^{13}C n.m.r. (75.5 MHz) spectrum of poly(MA), recorded in DMSO-d_6 at 80°C

Table 2 Molar fraction of isotactic (*mm*), heterotactic (*mr*+*rm*) and syndiotactic (*rr*) triads, and meso (*m*) and racemic (*r*) dyads, of poly(MA), determined from various resonance signals

	Stereochemical sequence		
Signal	*mm*	*mr*+*rm*	*rr*
αCH$_3$ (^{1}H n.m.r.)	0.02_5	0.34_1	0.63_4
α-CH$_3$ (^{13}C n.m.r.)	0.03_5	0.33_3	0.63_2
–C–	0.02_9	0.31_5	0.65_6
Average	0.03_0	0.33_0	0.64_0
Poly(OM)	0.07_2	0.37_9	0.54_9
Dyads	*m*	*r*	
–C(=O)–O–	0.19_1	0.80_9	
Calculated from triads	0.19_5	0.80_5	

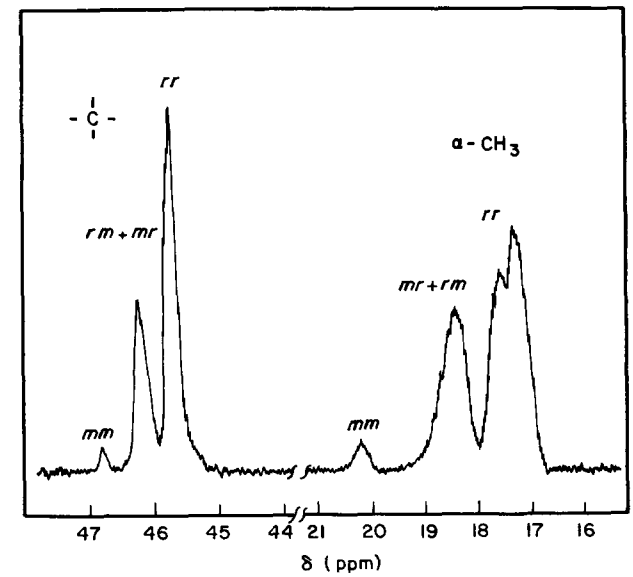


Figure 4 ^{13}C n.m.r. expanded resonance signals of the α-CH$_3$ and quaternary carbons of poly(MA)

hanced resolution decoupled ^{13}C n.m.r. spectrum of both carbon atoms, giving three well resolved signals, which have been assigned to iso (*mm*), hetero (*mr*+*rm*) and syndiotactic (*rr*) triads in order of increasing field, according to similar assignments for PMMA[38,39], poly(OM)[40] and poly(methacrylamide)[41]. It can be observed that the α-CH$_3$ signals present a splitting which probably could be analysed in terms of longer tactic sequences, but the resolution is poor to obtain experimental data with accuracy. Hence, from the relative integrated contributions of the signals assigned to both carbon atoms (see *Figure 4*), the values of the molar fraction of tactic sequences collected in the second and third rows of *Table 2*, have been determined. From the experimental data in *Table 2* the average value of the molar fractions has been obtained of the *mm*, *mr*+*rm* and *rr* tactic triads, the polymer being predominantly syndiotactic, independent of the polymerization temperature. However, the distribution of stereochemical triads is somewhat different from that of poly(OM) (see fourth and fifth rows of *Table 2*), being the content of *mm* and *mr*+*rm* triads of poly(MA), slightly lower than those of poly(OM), and consequently the molar fraction of syndiotactic sequences will be higher. These data indicate a higher selectivity of MA sequences for the syndiotactic arrangement in comparison with poly(OM). This behaviour might be ascribed to the lower flexibility of the amide bond with respect to the methacrylic ester bond of poly(OM), since the –CO–NH– has partial double bond character due to mesomery[40]:

Therefore, the side substituents of repeat units of poly(MA) will tend to be predominantly in a *trans* or syndiotactic configuration to minimize steric hindrance.

From the average values of the molar fractions of the tactic sequences in *Table 2*, the statistical parameters in *Table 3* have been determined. The values of conditional

probabilities for iso- and syndiotactic additions to *meso* or *racemic* growing chain ends, $p(i/j)$, $i,j=m,r$ (i refers to the relative stereochemical configuration of the chain end and j to the adding monomer), indicate a random distribution of the *meso* and *racemic* dyads along the polymer chains, since the sum $p(m/r)+p(r/m)$ is very close to unity[37]. According to these parameters, from a stereochemical point of view, the addition of monomer units to a polymeric growing chain of MA is consistent with Bernoullian statistics with an isotacticity parameter $\sigma=p_m=0.19$, very close to that reported by Hatada *et al.*[41] for the free radical polymerization of methacrylamide ($\sigma=0.17$) on the basis of Bernoullian statistics.

The third and fourth columns of *Table 3* show the statistical parameters determined for the free radical polymerization of OM and MMA for the experimental conditions used. It is clear from these data that the statistical parameters which control the formation of isotactic sequences, are slightly lower for the polymerization of MA than for the polymerization of OM or MMA. This is a consequence of the value of the isotacticity parameter $\sigma=0.19$ of MA, 0.3 lower than that of MMA ($\sigma=0.22$) and 0.8 lower than that of OM ($\sigma=0.27$). However, these differences do not drastically modify the random distribution of stereochemical sequences along the macromolecular chains according to the Bernoullian trial. On this basis, *Figure 5* shows the distribution of stereochemical pentads of polymers prepared from MA, OM and MMA. The diagram gives a clear idea of the strong tendency of MA units to be arranged in a syndiotactic configuration.

On the other hand, *Figure 6* shows the expanded ^{13}C n.m.r. pattern of the carbonyl amide resonance (168.70δ) and carbonyl ester resonances (174.00 and 174.35δ). It is noteworthy that the carbonyl carbon of the methacrylamide functional group gives a sharp single peak, independent of the stereochemical configuration of monomeric units along the polymer chains. This behaviour has been reported for poly(acrylamide)s, but differs from the spectrum of poly(methacrylamide) reported by Hatada *et al.*[41] recorded in glycol-d_6 at 100°C, in which the $-CONH_2$ resonance splits into several peaks assigned to pentads and by Pham *et al.*[42]. Also the carbonyl carbon of the amide group of poly(OM) (although different in nature) gave a ^{13}C n.m.r. pattern with three well resolved peaks assigned to tactic triads[20]. Another interesting fact is the appearance of two resonance signals for the carbonyl ester side group. Although this phenomenon seems to be rather unusual, the integrated intensities of the signals at 174.35 and 174.00δ, are coincident with the molar fraction of *meso* and *racemic* dyads calculated from the experimental concentration of triads, respectively. Also the chemical shift of the *r* resonance signal (174.00δ) is coincident with that of the resonance signal of this group in the spectrum of the monomer (see *Figure 1*, carbon 9 of MA). This means that the carbonyl carbon of the phenylacetic ester side group of a given fraction of MA units of poly(MA) is magnetically equivalent to that of the MA monomer, which is reasonable for sequences having a syndiotactic configuration, since it can be considered that the side groups are oriented in directions of minimum steric hindrance. However, for isotactic sequences the *meso* dyads probably could have the side substituents in parallel directions, with the electronic cloud of the aromatic nuclei oriented in such a way that they produce a little deshielding effect on the carbonyl ester group, in a similar way to the deshielding effect observed in the α-CH_3 or quaternary carbon, as a consequence of the isotactic arrangement.

Finally, another interesting characteristic of this polymer, is the relatively high T_g(=515 K), 97 K higher than that of poly(OM), T_g=418 K, which supports the higher stiffness of the methacrylamide side substituent with respect to the corresponding methacrylic ester. This behaviour has been reported for other substituted

Table 3 Comparative stereochemical parameters of the free radical polymerization of MA, OM and MMA

Parameter	MA	OM	MMA
	Addition probabilities		
P_m	0.19_1	0.26_2	0.23
P_r	0.80_9	0.73_8	0.77
P_{mm}	0.03_0	0.07_2	0.05
$P_{mr}+P_{rm}$	0.33_0	0.37_9	0.35
P_{rr}	0.64_0	0.54_9	0.59
	Conditional probabilities		
$p(m/m)$	0.15_7	0.27_5	0.22
$p(r/r)$	0.79_1	0.74_4	0.77
$p(m/r)$	0.20_5	0.25_7	0.23
$p(r/m)$	0.86_4	0.72_5	0.78
$p(m/r)+p(r/m)$	1.07	0.98	1.01

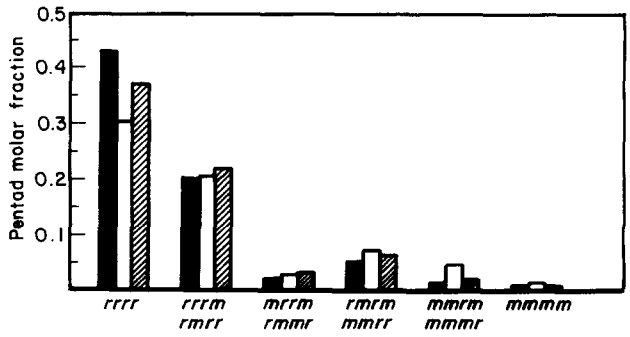


Figure 5 Statistical distribution of stereochemical sequences of pentads: (■) poly(MA) (□) poly(OM); (▨) PMMA

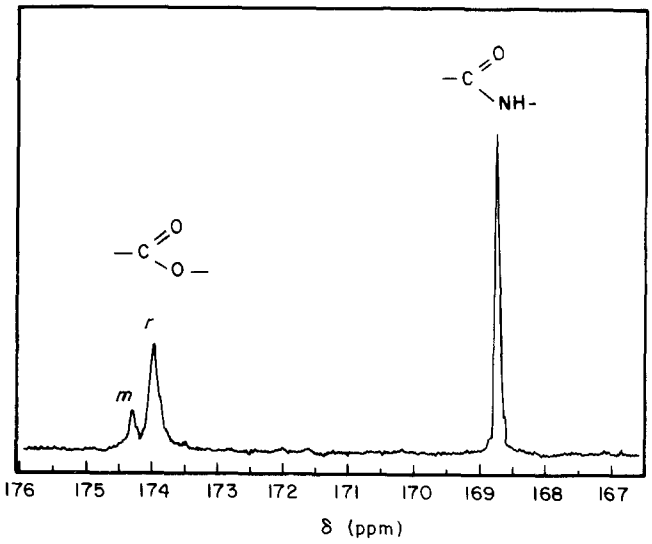


Figure 6 ^{13}C n.m.r. expanded resonance signals of the carbonyl ester group and carbonyl methacrylamide carbon of poly(MA)

poly(methacrylamide)s and poly(alkyl acrylamide)s in comparison with the corresponding poly(methacrylate)s and poly(acrylate)s. For example, the T_g of poly(4-methoxycarbonylphenyl methacrylamide) is 453 K, 74 K higher than that of poly(4-methoxycarbonylphenyl methacrylate), $T_g = 379\,K$[43,44]. In the same way, several poly(alkyl acrylamide)s present T_gs up to 130–140 K higher than the corresponding poly(alkyl acrylate)s[43].

The study of the pharmacological behaviour of these polymers '*in vivo*' is in progress.

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