# Polymers with pharmacological activity:
# 7. Synthesis and stereochemistry of polymeric derivatives of 4-methoxyphenylacetic acid*

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The synthesis and free radical polymerization of *N*-(4-methacryloyloxyphenyl), 2-(4-methoxyphenyl) acetamide (OM), a methacrylic derivative of 4-methoxyphenylacetic acid (a non-steroidal anti-inflammatory compound) is described. Also the introduction of a residue of 4-aminophenol (an analgesic and antipyretic metabolite) has been designed, in order to obtain macromolecules supporting two pharmacological residues with complementary action per repeat unit. The stereochemical configuration of POM chains has been analysed by $^1$H and $^{13}$C n.m.r. spectroscopies; polymers prepared by a free radical mechanism at temperatures of 50 and 70°C, are predominantly syndiotactic and follow a Bernoullian distribution of tactic sequences, with an isotacticity parameter $\sigma = 0.27$, very close to that of the free radical polymerization of 4-(methacryloyloxy)acetanilide ($\sigma = 0.26$), but slightly different to that of methyl methacrylate ($\sigma = 0.22$). The results are interpreted in terms of the influence of the aromatic character of the side substituents on the pseudoasymmetric quaternary carbon of the methacrylic units.

**(Keywords: polymerization; stereochemistry; pharmacological activity)**

## INTRODUCTION

Although the development of new therapeutic agents based on polymeric formulations is relatively recent, many efforts have been directed to the investigation of novel macromolecular systems and new techniques which could offer a better control of the delivery function and more precise manipulation of the pharmaco-kinetical behaviour of the active drug residue[1–6]. One of the most promising approaches is the synthesis of new polymeric drugs based on well known pharmacons or drugs bound covalently to a macromolecular support[7]. These systems may display pharmacological activity by themselves or alternatively may be used as carriers for the pharmaceutical agent[7,8]. The main objectives are to improve the duration of activity through the controlled release of the drug residue, to obtain a more cell-specific uptake (targeting effect) or to reduce the toxicity of the parent drug[9–11].

We have recently reported the preparation and a study of the pharmacological properties of acrylic formulations based on the synthesis and polymerization of methacrylic esters of typical analgesic and antipyretic drugs like salicylic acid[12] and of several derivatives of paracetaminophen or paracetamol[13,14].

The main aim of this paper is to report the synthesis and the study of the free radical polymerization of the methacrylic derivative of 4-methoxyphenylacetic acid, by introducing between both residues a spacer group, namely 4-aminophenyloxy. Derivatives of phenylacetic acid have been used extensively as non-steroidal anti-inflammatory agents whose major pharmaceutical effect is the reduction of oedema, erythema and resulting tissue damage associated with inflammatory conditions[15], although this kind of compound presents a considerable hepatic toxicity, as claimed by the Foods and Drugs Administration (FDA)[16]. Particularly, the 4-methoxyphenylacetic acid has a lethal dose ($LD_{50}$) of 1550 mg kg$^{-1}$ (ref. 17), and 4-methoxyphenylacetyl chloride has found many pharmaceutical and medicinal applications[18,19]. The introduction of the 4-aminophenoxy spacer group has two results: the hydrolysis of the ester and amido functions of the residue is easier than for the corresponding alkyl residues; and the released compound in physiological conditions (the sodium salt of 4-aminophenol) is an active metabolite of the well known pharmacon paracetamol (*N*-acetyl 4-aminophenol). Since all rheumatic arthritic diseases and inflammatory processes are accompanied by acute pain, it may be interesting to develop a formulation with anti-inflammatory and enhanced analgesic and antipyretic responses.

## 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

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* Dedicated to the memory of Miguel Valero

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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), 2-(4-methoxyphenyl) acetamide (I).* The intermediate derivative of 4-methoxyphenylacetic acid (I) was prepared by the amidation reaction of 4-methoxyphenylacetic acid with 4-aminophenol, 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), 4-aminophenol (0.10 mol), DCC (0.10 mol), DMAP (0.01 mol) and PTS (0.01 mol) in a mixture of 1:1 dichloromethane/acetone (50 ml), was allowed to stand under nitrogen with magnetic stirring at room temperature overnight, until esterification was complete. The dicyclohexyl urea formed was filtered and the filtrate was concentrated at reduced pressure. The concentrated syrup was crystallized in chloroform, filtered and washed with chloroform. The isolated product was recrystallized from ethyl acetate. Yield, 60%; m.p. = 164 ± 1°C.

*Synthesis of* N-*(4-methacryloyloxyphenyl), 2-(4-methoxyphenyl) acetamide (OM).* The methacrylic monomer OM was prepared by the reaction of the intermediate I with methacryloylchloride in 5% aqueous sodium hydroxide solution at 0°C. Then I (0.075 mol) was dissolved in a mixture of 1:1 dioxane/water (100 ml) and sodium hydroxide (5 g). The solution was cooled to 0°C under nitrogen atmosphere and freshly distilled methacryloyl chloride (0.1 mol) was added dropwise. After addition, the reaction was stirred for 3 h at 0°C. The methacrylic monomer precipitated in the reaction medium and was filtered and washed with distilled water. The product isolated was crystallized twice with methanol/water, filtered and dried *in vacuo* over phosphorus anhydride overnight. Yield, 50%; m.p. = 153 ± 1°C.

*Polymerization.* The monomer OM was polymerized at 50 and 75°C in a solution of DMF ($[\mathrm{OM}] = 1\ \mathrm{mol\ l^{-1}}$), using AIBN as free radical initiator. The reactions were carried out in Pyrex glass ampoules sealed at high vacuum. After polymerization for 5 h, the reaction mixture was poured into a large excess of methanol and the precipitated polymer was filtered off, washed with methanol and dried at reduced pressure until constant weight.

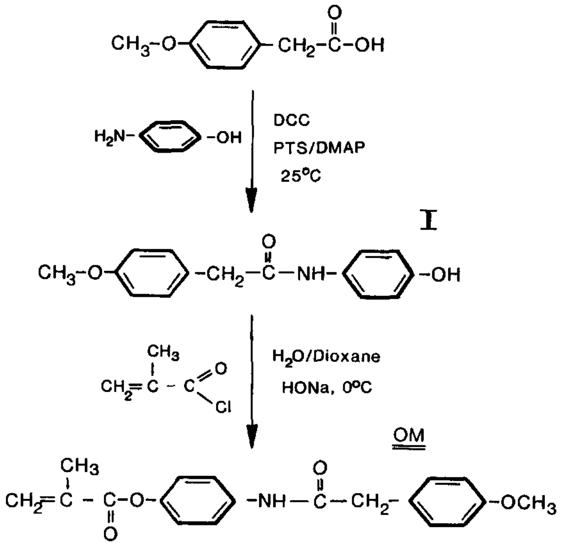
*Characterization of products.* The intermediate compound I, the monomer OM and polymers prepared were characterized by i.r., $^1$H and $^{13}$C n.m.r. spectroscopies. I.r. spectra were recorded in KBr pellets on a Perkin-Elmer 457 spectrometer at room temperature. N.m.r. spectra were recorded in deuterated dimethylsulphoxide (DMSO-$d_6$) solution on a Varian XLR-300 spectrometer. $^1$H n.m.r. experiments were performed at 80°C on 5% (w/v) solutions. $^{13}$C n.m.r. spectra were recorded also at 80°C 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 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 peak areas, calculated by means of an electronic integrator or by triangulation and planimetry.

The melting points and glass transition temperatures of the synthesized products 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 500 K for 30 min, and then quenched at −50°C prior to measurement.

## RESULTS AND DISCUSSION

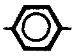
The theoretical model for pharmacologically active polymers suggested by Ringsdorf[20] in 1975 considers the fixation of a drug (or organic compound which elicits a physiological response in the living body) to a polymer backbone, through specially designed spacer groups, which in general are constituted by oxyalkyl segments. The drug moiety must be anchored to the polymer matrix by organic functional groups which can be degraded in the physiological medium. The biodegradation in the living body is produced by hydrolytical processes which can be activated enzymatically. These processes involve the fission of ester, amide, anhydride, carbonate, carbamate, etc., functions through the mediation of esterases or peptidases[21]. Therefore, we have selected 4-aminophenyloxy as the spacer group between the potential anti-inflammatory drug and the polymer matrix, since it provides aromatic ester and amide chemical bonds of limited stability in the biological environment, which can be hydrolysed in mild conditions.

On the other hand, for the chemical fixation of pharmacos to macromolecular chains it is necessary to use synthetic conditions mild enough to allow attachment without any adverse effect on the future physiological activity of the pharmacon[20]. Therefore, we have undertaken the synthesis of OM following a two-step route as shown in *Scheme 1*. The first step is the coupling of the pharmacologically active residue with 4-aminophenol selectively, on the basis of the condensation reaction of the carboxylic group of I with the amino group of the spacer element, using PTS and DMAP as catalyst, activated by DCC at 25°C.



Carbodiimides have been used widely as dehydrating agents in organic reactions and therefore have been applied as condensing agents for the esterification and

**Table 1** Physical data and spectroscopic characteristics of synthesized derivatives of 4-methoxyphenylacetic acid

| Compound | $T_g$ (°C) | Melting point (°C) | Functional group | I.r. (cm$^{-1}$) | $^1$H n.m.r. ($\delta$, ppm) |
|---|---|---|---|---|---|
|  | | | -COO*H* | 3200–3000 | 10.67 |
| | | | -COOH | 1720, 1690 | – |
| | – | 86 |  | 1610, 1580, 1510 | 6.80–7.20 (four peaks) |
| | | | $CH_3O$- | 1240 | 3.70 |
| | | | Ar-$CH_2$-COOH | – | 3.49 |
| | | | -CO*NH*- | 3280–3300 | 9.81 |
| | | | Ar-O*H* | 3200–3300 | 9.14 |
| | | | -CONH- | 1655 | – |
| I | –14 | 164 |  | 1610 | |
| | | | | 1580 | 6.71–7.39 |
| | | | | 1510 | (eight peaks) |
| | | | -$CH_3O$- | 1240 | 3.77 |
| | | | Ar-OH | 1030 | – |
| | | | Ar-$CH_2$-CONH- | – | 3.50 |
| | | | -CO*NH*- | 3310 | 9.85 |
| | | | -COO- | 1735 | – |
| | | | -CONH- | 1660 | – |
| OM | –20 | 153 | $CH_2$=C | 1630 | 6.36, 5.77 |
| | | |  | 1610, 1580 | 6.75–7.45 |
| | | | | 1530, 1510 | (eight peaks) |
| | | | $CH_3O$- | 1250 | 3.80 |
| | | | Ar-$CH_2$-CONH- | – | 3.56 |

amidation of carboxylic acids[22,23], particularly for the synthesis of peptides, nucleotides and oligonucleotides[24]. The usefulness of carbodiimide based reactions including catalysis by the 1:1 molecular complex formed by DMAP and PTS in amidation or esterification reactions has recently been reported[23]. These reagents activate the carboxylic function favouring the displacement of the equilibrium to the formation of the amide or ester derivative.

We have applied this concept to the synthesis of the intermediate compound I, in order to control selectively the amidation reaction, without esterification of the phenolic residue. This has been attained by using the experimental conditions outlined in the Experimental section. Physical constants and spectroscopic characteristics of compound I are given in *Table 1*, together with those of the starting compound, 4-methoxyphenylacetic acid.

The second step is a modification of the known Schotten Bauman reaction[25], which permits the preparation of the acrylic derivative OM in very mild conditions, following a phase transfer process, as indicated in *Scheme 1*. Physical constants and the main spectroscopic i.r. and $^1$H n.m.r. signals of this methacrylic derivative are given in *Table 1*.

*Figure 1* shows the proton-decoupled $^{13}$C n.m.r. spectra of the starting product (4-methoxyphenylacetic acid), the intermediate I and the methacrylic monomer OM. All the resonance signals have been assigned to the corresponding carbon atoms on the basis of distortionless enhancement by polarization transfer (DEPT, 135°).

This monomer was polymerized at 50 and 70°C by a free radical mechanism using the experimental conditions described above, using AIBN as initiator, $[I] = 1.5 \times 10^{-2}$ mol l$^{-1}$ and DMF as solvent, $[OM] = 1$ mol l$^{-1}$. All the experiments were carried out under high vacuum. After reacting for 5 h, at 50 and 70°C, conversions of 95 and 97 wt% were achieved, respectively, giving rise to polymers of relatively high molecular weight, i.e. $\bar{M}_n = 40\,000$ for the polymerization at 50°C and $\bar{M}_n = 25\,000$ for polymerization at 70°C [determined by g.p.c. with poly(methyl methacrylate) (PMMA) standards]. The polymers obtained were soluble in polar solvents like DMSO, DMF, tetrahydrofuran or mixtures of acetone/water, dioxane/water or DMSO/water, with a high content in the organic solvent, except for the DMSO/water system in which the polymer is soluble over a wide range of compositions of the binary mixture. The kinetic behaviour of OM in the free radical polymerization will be analysed in a subsequent paper.

On the other hand, the polymers obtained were also characterized by i.r. and n.m.r. spectroscopies. The i.r. spectrum does not present relevant characteristics apart from those of the monomer, outlined in *Table 1*, but the n.m.r. spectra give interesting information on the stereochemistry of this kind of polymers. *Figure 2* shows the $^1$H n.m.r. (300 MHz) spectrum of a polymer sample prepared at 50°C; similar results were obtained for the sample prepared at 70°C. Apart from the signals assigned to aromatic, methoxy and methylene protons of the side group and the skeleton of the acrylic chain, the resonance signal of the $\alpha$-$CH_3$ substituent, splits into three well-resolved peaks at 1.58, 1.48 and 1.37 ppm from TMS, which have been assigned to isotactic (*mm*), heterotactic (*mr* + *rm*) and syndiotactic (*rr*) triads, in order of increasing field, following the classical assignment of the $\alpha$-$CH_3$ resonances for pure PMMA[26] and poly(4-methacryloyloxyacetanilide) (PMOA)[27].

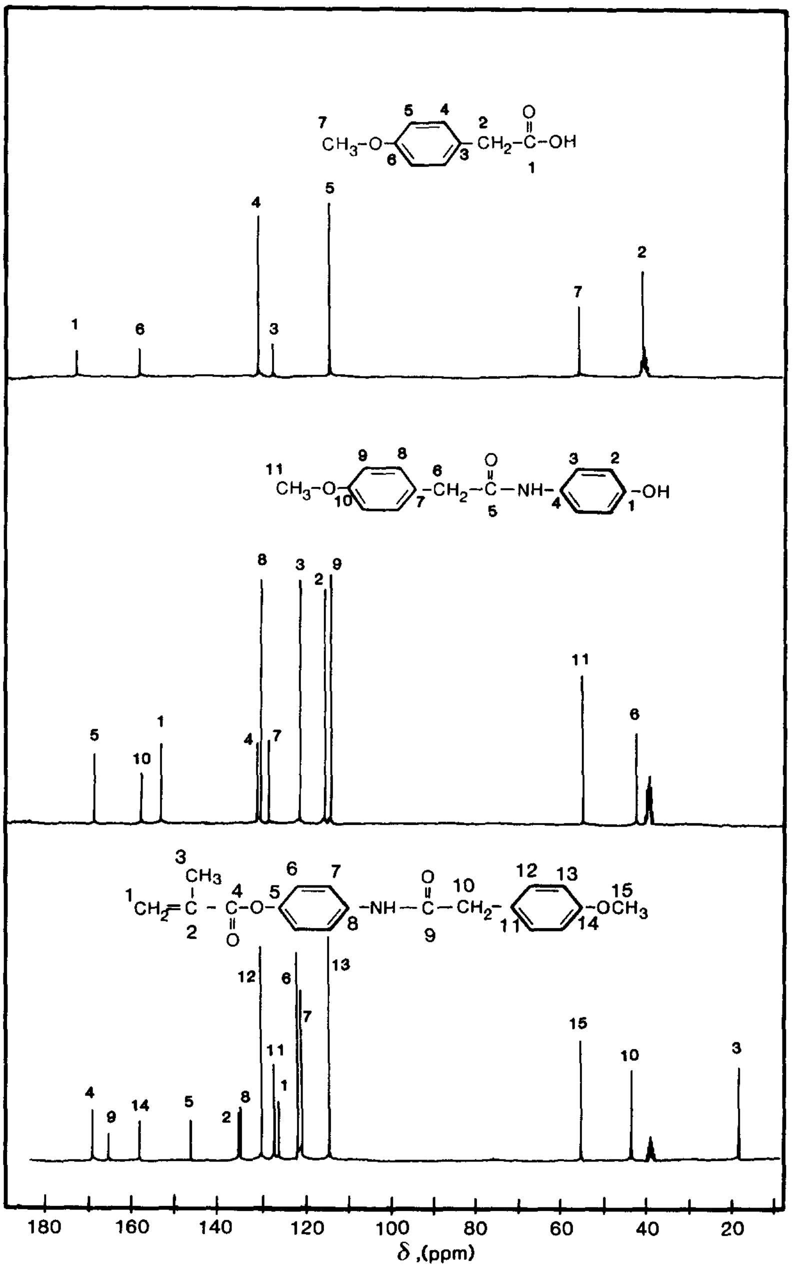


**Figure 1** Decoupled $^{13}C$ n.m.r. (75.5 MHz) spectra of 4-methoxyphenylacetic acid, I and OM recorded in DMSO-$d_6$ at 80°C

It is noteworthy that the chemical shifts of the $\alpha$-$CH_3$ resonances of POM are shifted downfield ~0.5 ppm with respect to those of PMMA or other poly(alkyl methacrylates), but are coincident with those of PMOA[27]. It is a consequence of the aromatic character of the acrylic ester group in POM and PMOA, which makes clear the deshielding effect of the aromatic ring directly bonded to the carboxylic function, compared with the aliphatic character of the ester in PMMA or other poly(alkyl methacrylate)s[27]. Also it can be clearly observed that the differences in chemical shifts between the two signals ($\delta_{mm} - \delta_{mr}$) and ($\delta_{rm} - \delta_{rr}$) is $\simeq$0.11 ppm, somewhat lower than that of PMMA ($\simeq$0.15 ppm). The experimental values of the molar fraction of tactic sequences have been determined from the integrated intensities of the signals assigned to tactic sequences and are given in *Table 2*.

On the other hand, the -NH- proton of the phenylacetamide side residue also seems to be sensible to the stereochemical configuration of the quaternary carbon of methacrylic units, although the acetamide group is rather far from the pseudoasymmetric centre. This behaviour can be explained satisfactorily taking into consideration the strong effect of aromatic nuclei on the diamagnetic character of the carbonyl ester functions of neighbouring units, which enhances the sensitivity of the side substituents with respect to their stereochemical arrangement[13,28,29]. Effectively, the -NH- proton gives three rather well resolved sharp signals at 9.93, 9.88 and 9.84 δ, which have been assigned to *rr*, *mr* + *rm* and *mm* triads in order of increasing field, following the assignment of other side groups in polyacrylic chains[13]. Also the experimental values of the molar fraction of tactic sequences have been determined from the integrated intensities of the signals assigned to tactic sequences and are quoted in *Table 2*, being the corresponding values very close to those determined from the $\alpha$-$CH_3$.

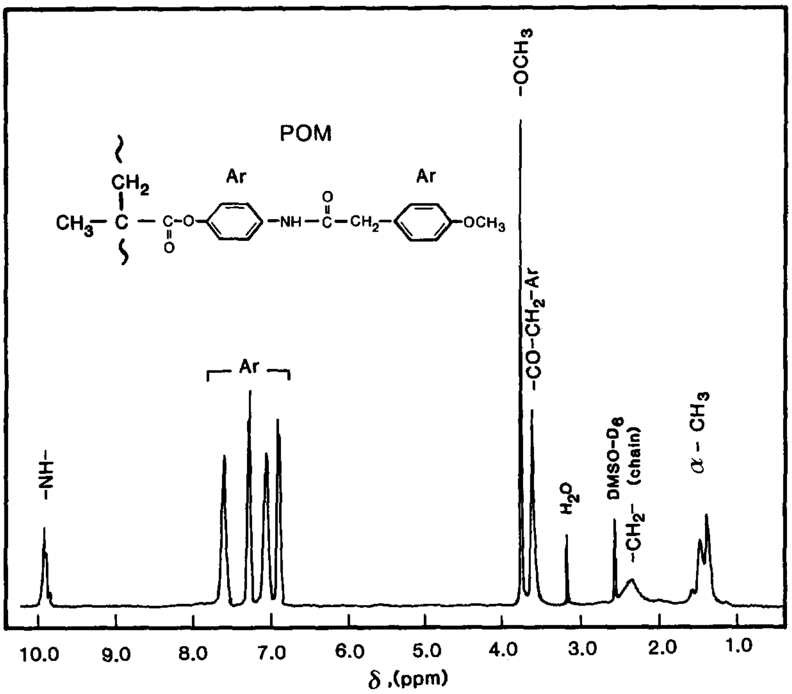


Figure 2 $^1H$ n.m.r. (300 MHz) spectrum of POM recorded in DMSO-$d_6$ at 80°C

Table 2 Molar fractions of isotactic (*mm*), heterotactic (*mr* + *rm*) and syndiotactic (*rr*) triads of POM, determined from different resonance signals

| | | Stereochemical sequence | | |
|---|---|---|---|---|
| Signal | | *mm* | *mr* + *rm* | *rr* |
| $^1H$ n.m.r. | -NH- | $0.07_3$ | $0.37_7$ | $0.55_0$ |
| | α-$CH_3$ | $0.08_1$ | $0.38_8$ | $0.53_1$ |
| $^{13}C$ n.m.r. | α-$CH_3$ | $0.07_2$ | $0.38_0$ | $0.54_8$ |
| | -C- | $0.06_1$ | $0.36_7$ | $0.57_1$ |
| | -CONH- | $0.07_1$ | $0.38_3$ | $0.54_6$ |
| Average | | $0.07_2$ | $0.37_9$ | $0.54_9$ |

As it is known, $^{13}C$ n.m.r. spectroscopy provides excellent and accurate information on the stereochemical configuration of vinyl and acrylic polymers, if the decoupled spectra are registered in the appropriate experimental conditions[30]. *Figure 3* shows the decoupled $^{13}C$ n.m.r. of a sample of POM (synthesized at 50°C), registered in the conditions described in the Experimental section. All the resonance signals have been assigned to the corresponding carbon atoms according to the chemical structure drawn. The α-$CH_3$ group (17–22 δ), quaternary carbon (44–47 δ) and the carbonyl carbon of phenylacetamide (169 δ) and methacrylic ester (174–176 δ) groups, present complex patterns which have been analysed in terms of the content of different stereochemical sequences.

*Figure 4* shows the expanded $^{13}C$ decoupled spectrum of the α-$CH_3$ and quaternary resonances. Both carbon atoms present three signals which have been assigned to isotactic (*mm*), heterotactic (*mr* + *rm*) and syndiotactic (*rr*) triads in order of increasing field, following the classical assignment of the same carbons for pure PMMA[31] and PMOA[13,27]. As in the $^1H$ n.m.r. spectrum, the α-$CH_3$ and quaternary carbons present signals with chemical shifts very close to those of the same carbon in PMOA, but are shifted towards lower field with respect to the corresponding signals of PMMA or other poly(alkyl methacrylate)s[27]. From the relative intensities of the signals assigned to both carbon atoms, the values of molar fraction of tactic sequences collected in *Table 2* have been determined.

*Figure 5* shows the expanded $^{13}C$ n.m.r. decoupled spectrum of the carbonyl phenylacetamide carbon, which gives three well resolved sharp peaks at 169.00, 168.96 and 168.88 δ, assigned to *rr*, *rm* + *mr* and *mm* stereochemical sequences in order of increasing field. The corresponding molar fractions are also quoted in *Table 2*, being very close to those calculated from the α-$CH_3$ and quaternary carbon resonances. All the data collected in this table have been used to calculate the average value of molar fractions of *mm*, *mr* + *rm* and *rr* tactic triads, with the polymer being predominantly syndiotactic, independent of the polymerization temperature, at least for the range of temperatures used in this work. From the average values of the molar fraction of tactic triads quoted in *Table 2*, the statistical parameters collected in *Table 3* have been determined. The conditional probabilities for isotactic 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[26]. Therefore, the stereochemical distribution of monomeric units along the macromolecular chains is consistent with Bernoullian statistics, with a single parameter describing the probability for isotactic placement, defined by Bovey and Tiers[32] as the isotacticity parameter, $\sigma = p_m = 0.27$. *Table 3* also shows the statistical parameters determined for the free radical polymerization of MOA and MMA in the experimental conditions used for the polymerization of OM. It is clear from these data that the statistical parameters for the polymerization of OM are similar to those of the free

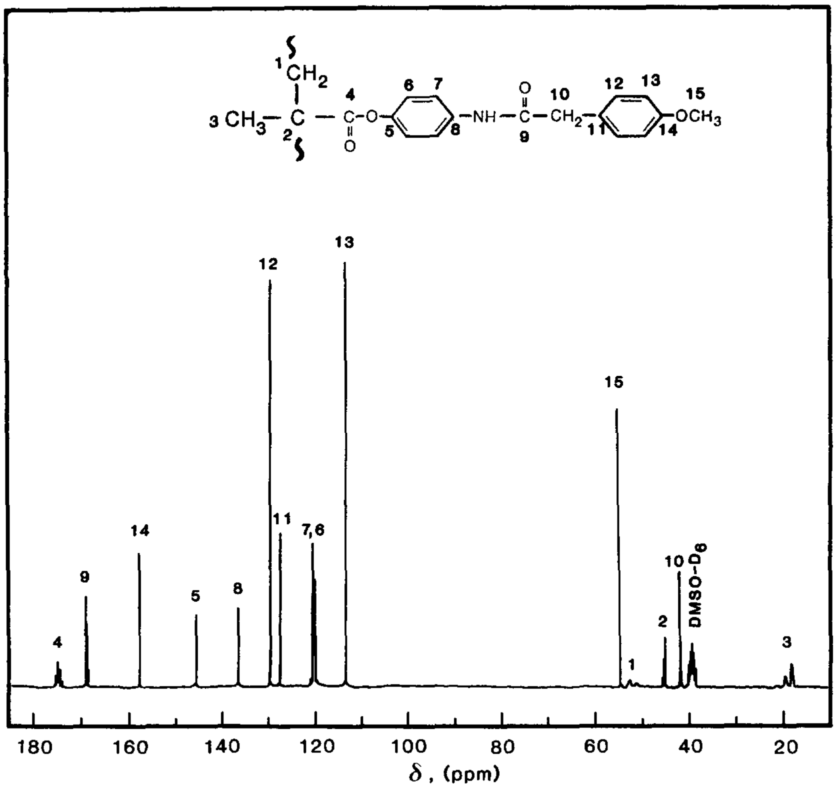


Figure 3 Decoupled $^{13}C$ n.m.r. (75.5 MHz) spectrum of POM recorded in DMSO-$d_6$ at 80°C

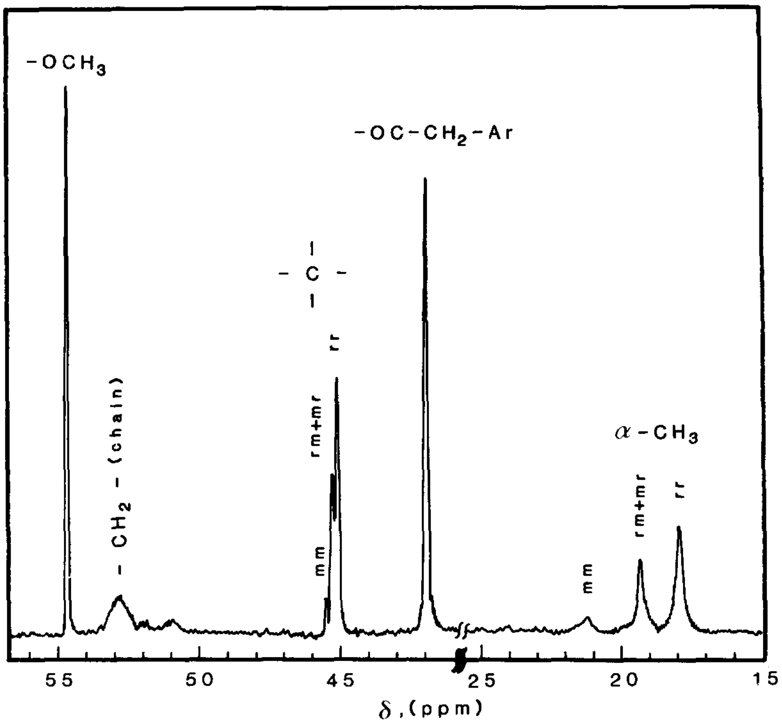


Figure 4 $^{13}C$ n.m.r. enhanced resonance signals of the α-CH$_3$ and quaternary carbons of POM

radical polymerization of MOA, but deviate slightly from those of the classical free radical polymerization of MMA. Moreover, the isotacticity parameter of OM has a value very close to that of MOA[27] ($\sigma = 0.26$), but is five points higher than that of the polymerization of MMA ($\sigma = 0.22$). However, the differences in these parameters do not modify drastically the random distribution of stereochemical sequences along the macromolecular chains on the basis of the Bernoullian character of these systems.

The left-hand side of *Figure 5* shows the expanded $^{13}C$ n.m.r. pattern of the carbonyl ester resonances, which have been analysed in terms of longer stereochemical sequences. As shown in the figure, between 175.40 δ and

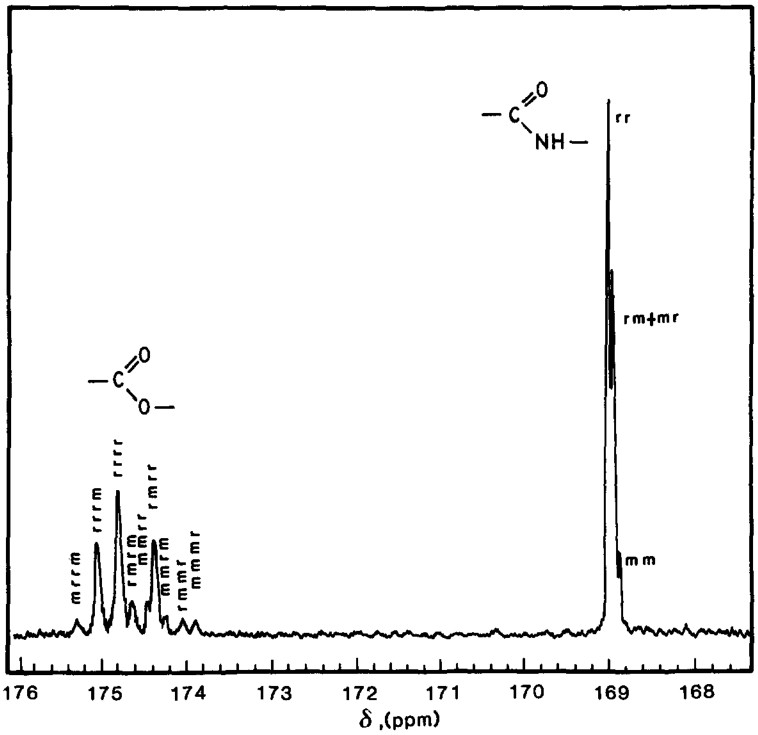


**Figure 5** $^{13}C$ n.m.r. enhanced resonance signals of the carbonyl ester group and carbonyl acetamide carbon of POM

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

| Parameter | OM | MOA[a] | MMA[a] |
|---|---|---|---|
| Addition probabilities | | | |
| $P_m$ | $0.26_2$ | 0.26 | 0.23 |
| $P_r$ | $0.73_8$ | 0.74 | 0.77 |
| $P_{mm}$ | $0.07_2$ | 0.05 | 0.05 |
| $P_{mr} + P_{rm}$ | $0.37_9$ | 0.39 | 0.35 |
| $P_{rr}$ | $0.54_9$ | 0.56 | 0.59 |
| Conditional probabilities | | | |
| $p(m/m)$ | $0.27_5$ | 0.25 | 0.22 |
| $p(r/r)$ | $0.74_4$ | 0.73 | 0.77 |
| $p(m/r)$ | $0.25_7$ | 0.27 | 0.23 |
| $p(r/m)$ | $0.72_5$ | 0.75 | 0.78 |
| $p(m/r) + p(r/m)$ | $0.98_2$ | 1.00 | 1.01 |

[a] Ref. 27

**Table 4** Assignment of the $^{13}C$ n.m.r. resonance signals of the C=O acrylic ester group, to sequences of tactic pentads

| Sequence | δ (ppm) | Sequence molar fraction | |
|---|---|---|---|
| | | Expt. | Calc.[a] |
| *mrrm* | 175.30 | $0.02_8$ | 0.039 |
| *rrrm* | 175.06 | $0.20_3$ | 0.210 |
| *rrrr* | 174.81 | $0.30_5$ | 0.284 |
| *rmrm* | 174.62 | $0.06_8$ | 0.078 |
| *mmrr* | 174.43 | $0.06_9$ | 0.078 |
| *rmrr* | 174.37 | $0.20_3$ | 0.210 |
| *mmrm* | 174.28 | $0.04_5$ | 0.029 |
| *rmmr* | 174.02 | $0.04_5$ | 0.039 |
| *mmmr* | 173.90 | $0.03_4$ | 0.029 |
| *mmmm* | – | – | 0.005 |

[a] Values calculated according to the Bernoullian trial with $\sigma = 0.27$

173.80 δ, nine signals can be distinguished, which have been assigned to sequences of tactic pentads, following the assignment suggested for the C=O resonance signals for PMMA reported by Peat and Reynols[31], Chûjô *et al.*[33], Ferguson and Ovenall[34], and PMOA[27]. *Table 4* presents values of the chemical shifts of signals assigned to pentads, together with the corresponding molar fractions of sequences determined from the relative integrated intensities of the corresponding signals, as well as those calculated considering Bernoullian statistics for the addition step of the free radical polymerization, with the isotacticity parameter $\sigma = 0.27$. The excellent agreement between calculated and experimental data supports the assignment of resonance signals and makes clear the statistical character of the distribution of stereochemical sequences along the macromolecular chains. This result will be useful for interpreting the mechanism of release of the pharmacological active residues in physiological conditions.

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