Polymers with pharmacological activity: synthesis and free-radical polymerization of *P*-methacryloyloxyacetanilide

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(Received 24 March 1988; revised 21 November 1988; accepted 21 November 1988)

The synthesis and free-radical polymerization of *p*-methacryloyloxyacetanilide (MOA), an acrylic monomer derived from paracetaminophen (*p*-hydroxyacetanilide, a non-prescription antipyretic analgesic widely used around the world), has been studied. The kinetic behaviour of MOA in the polymerization initiated by azobisisobutyronitrile in solution of dimethylformamide, at temperatures in the range 50–120°C, seems to indicate a ceiling temperature of polymerization of about 137°C, for a monomer concentration of 1.0 mol l^{-1}. The polymers obtained (PMOA) are predominantly syndiotactic and the stereo-control of the propagation process fits well the Bernoullian statistics, with an isotacticity parameter $P_m = 0.26$, the ^{13}C nuclear magnetic resonance spectrum of C=O ester group being sensitive to the stereochemical configuration of pentads. The hydrolytic behaviour of PMOA at several temperatures in alkaline solution has been tested.

(Keywords: synthesis; free-radical polymerization; *p*-methacryloyloxyacetanilide)

INTRODUCTION

Synthetic macromolecules with functional groups of potential pharmacological activity have attracted considerable interest in the last 10 years[1]. Especially interesting are investigations of pharmacologically active polymers which by themselves may be active as drugs or alternatively may be used as carriers for pharmaceutical agents widely used in medication[2]. One of the main ideas on the use of pharmacologically active polymers is the depot effects that may be achieved with such drugs, based on the experience acquired with synthetic polymeric blood substituents and plasma expanders. However, this depot effect is not the only facet and properties such as controlled polymer degradation or the release of active agents in the living body have been extensively studied[3]. In addition to the properties of the individual macromolecular chains, the behaviour of pharmacologically active polymers is affected mainly by the nature of functional groups of the pharmacological side-group. Such systems avoid the problems of low-molecular-weight drugs which can produce generalized toxic reactions. In general, the pharmacon is linked to the polymeric matrix via a degradable bond which is quite stable until affected by digestive intracellular enzymes or lysosomes[4].

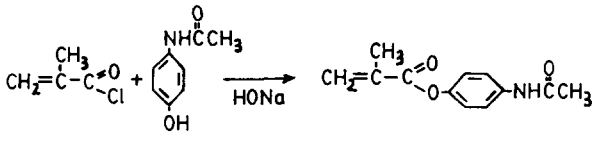
In this sense we have previously reported the synthesis and free-radical polymerization of *o*-methacryloyloxybenzoic acid (an acrylic derivative of salicylic acid)[5] and both monomer and polymer present an interesting pharmacological behaviour, since the release of salicylic acid from the polymer chains is produced easily. The toxicological levels of both compounds determined by well known pharmacological test in mice are rather low (LD50 = 1.28 g kg^{-1} for *o*-methacryloyloxybenzoic acid and LD50 = 103 mg kg^{-1} for poly(*o*-methacryloyloxybenzoic acid), respectively)[6].

The present paper describes the synthesis and free-radical polymerization of *p*-methacryloyloxyacetanilide, which can be considered a methacrylic derivative of paracetaminophen (a non-prescription antipyretic analgesic that was first introduced into clinical medicine towards the end of the last century)[7].

EXPERIMENTAL

Monomer synthesis

p-methacryloyloxyacetanilide (MOA) was prepared by the reaction of paracetaminophen (*p*-hydroxyacetanilide) with methacryloyl chloride in 5% aqueous sodium hydroxide solution at 0°C, according to the scheme:



In a typical experiment a solution of *p*-hydroxyacetanilide (0.1 mol) in 200 ml of 5% aqueous NaOH was placed into a three-necked flask provided with a stirrer, thermometer and dropping funnel. The solution was cooled to 0°C and freshly distilled methacryloyl chloride (0.12 mol) was then added dropwise. The *p*-methacryloyloxyacetanilide precipitated in the reaction medium and after 2 h MOA was filtered off and crystallized twice with methanol/water. Yield, 65–70%; m.p. = 126°C. The MOA was characterized by i.r., ^1H n.m.r. and ^{13}C n.m.r. spectroscopies. The main signals observed in the spectroscopic determinations are quoted in *Table 1*.

0032-3861/89/050949-06$03.00

Table 1 Spectroscopic characteristics of *p*-methacryloyloxyacetanilide (MOA)

Functional group	I.r. (cm^{-1})	^1H n.m.r.[a] (ppm)	^{13}C n.m.r.[a] (ppm)
$CH_3-C(=O)-NH-$	3300 1175	8.10 (s)	166.35
$-C(=O)-O-Ar-$	1730 1140	–	169.03
	1610 1530 1510	7.50 (s) 7.40 (s) 7.05 (s) 6.95 (s)	146.94 135.79 121.78 121.16
$CH_2=C<$	1635	6.35 (m) 5.75 (m)	136.00 127.46
$=C(CH_3)-C(=O)$	1400–1300	2.04 (m)	18.29
$CH_3-C(=O)-NH-$	1400–1300	2.05 (m)	24.11

[a] Solvent, $CDCl_3$

Polymerization

The monomer, MOA, was polymerized at different temperatures from 50 to 120°C, in a thermostatic bath regulated with a precision of ±0.1°C, using 2,2'-azobis-isobutyronitrile (AIBN) ($[I]=1.5\times10^{-2}$ mol l^{-1}) and dimethylformamide (DMF) as solvent ($[M]=1.0$ mol l^{-1}). All experiments were carried out in Pyrex glass ampoules sealed off at high vacuum (10^{-4} mmHg). After the desired time the reaction mixture was added into a large excess of methanol and the precipitated polymer was filtered off, washed with methanol and dried at reduced pressure until constant weight was attained.

Hydrolysis of poly(p-methacryloyloxyacetanilide) (PMOA)

Polymers were hydrolysed by dissolving 0.5 g (2.28×10^{-3} mol of monomeric units) samples in 50 ml aliquots of dimethylsulphoxide/water (40/60) and adding to each 0.5 g (1.25×10^{-2} mol) of sodium hydroxide dissolved in 10 ml of distilled water. The solutions were stirred at several temperatures and, at desired times, 10 ml aliquots of the reaction medium were analysed by volumetric titration with 0.1 N HCl.

Samples completely hydrolysed were recovered by precipitation in cool water acidified with HCl to ensure that the hydrolysed polymer was recovered as the carboxylic acid rather than as the sodium salt. The precipitate was filtered, washed with water and dried in vacuum at 50°C. The infra-red spectrum of poly-(methacrylic acid) in the form of a solid film was checked.

Esterification of poly(methacrylic acid)

The poly(methacrylic acid) obtained from polymers was transformed to poly(methyl methacrylate) (PMMA) according to the method of Katchalsky[8] by treating 0.1 g of dried poly(methacrylic acid) with 50 ml of a saturated benzene solution of diazomethane. The reaction mixture was kept standing overnight at room temperature and precipitated with a large excess of methanol. Crude poly(methyl methacrylate) was purified by reprecipitation from a benzene/methanol system.

Characterization of polymers

Monomer and all polymers were characterized by i.r. and 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) solutions on a Bruker WP80SY operating at 80 MHz for ^1H and at 20.15 MHz for ^{13}C nuclei, respectively.

The molecular weights of poly(methyl methacrylate)s were determined by measuring the intrinsic viscosity in benzene solutions at 30±0.1°C; the equation given by Fox *et al.*[9] for unfractionated poly(methyl methacrylate) was applied:

$$[\eta]=8.69\times10^{-3}\bar{M}_v^{0.76}\ \mathrm{cm^3\,g^{-1}}$$

RESULTS AND DISCUSSION

The free-radical polymerization of MOA has been studied in solution of DMF at different temperatures in the interval 50–120°C. The concentrations of monomer and free-radical initiator (AIBN) were 1.0 mol l^{-1} and 1.5×10^{-2} mol l^{-1}, respectively. *Figure 1* shows the conversion–time diagrams at different polymerization temperatures in the interval studied. The free-radical polymerization of MOA under the experimental conditions mentioned above follows classical first-order kinetics at a temperature of 50°C, but at higher polymerization temperatures (i.e. 70, 90 and 120°C) the polymerization system tends to reach a limiting conversion at relatively short reaction times. The level of this degree of conversion decreases drastically with increasing polymerization temperature. It should be noted that a limiting conversion of only 6–8 wt% is reached at a reaction temperature of 120°C, for a reaction time as short as 4 min, remaining constant in the whole interval of time studied, and that at polymerization temperatures higher than 125°C, no polymeric species can be isolated from the reaction medium by precipitation with cool methanol. This behaviour has already been described in the literature for monomers that present a relatively low or moderate ceiling temperature of polymerization[10,11].

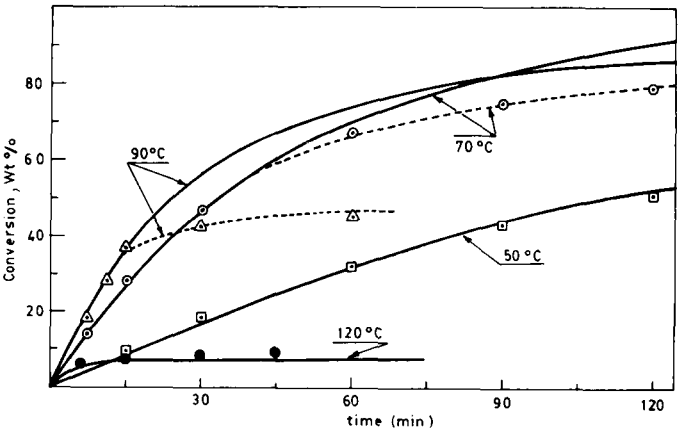


Figure 1 Conversion–time diagrams of the free-radical polymerization of MOA at several temperatures: (——) theoretical diagrams according to equation (1); (– – – –) curve fitting to the experimental points

Considering a simple kinetic scheme with first-order thermal decomposition of initiator, addition of primary radicals to monomer, propagation and termination reactions, the variation of the degree of conversion (X) with time can be written as:

$$\ln[1/(1-X)] = 2(K_p/K_t^{1/2})(f[I]/K_d)^{1/2}[1-\exp(-K_d t/2)] \quad (1)$$

Using K_d values obtained from the Arrhenius equation of AIBN decomposition reported by Tulig and Tirrell[12] and considering a value of $f=0.6$, we obtain the diagrams shown in *Figure 1*. The full curves of this figure were drawn on the basis of equation (1) with a set of kinetic constants quoted in *Table 2*, whereas the broken curves correspond to the best curve fitting the experimental points. It seems apparent from this figure that the free-radical polymerization of MOA under the experimental conditions of the present work deviates from the classical kinetic behaviour when the reaction system reaches conversions higher than 50 wt% at a polymerization temperature of 70°C and 37–38 wt% when the temperature of polymerization is 90°C. Although the theoretical curve for the free-radical polymerization at 120°C fits the experimental points, it is necessary to take into account that the limiting conversion at this temperature is very low. It is probable that the influence of decreasing initiator concentration with the time of polymerization could be higher than that of the equilibrium propagation–depropagation at this temperature, which explains satisfactorily the results obtained. *Figure 2* shows the diagram of $\ln(K_p/K_t^{1/2})$ *versus* $1/T$ for the polymerization of MOA according to the treatment suggested by Yamada *et al.*[13]. It is clear that this ratio decreases drastically for polymerization temperatures above 70–80°C and it can be considered that an asymptotic value is reached at a temperature close to 137°C. (According to the treatment proposed by Yamada *et al.*[13], T_c can be determined as the temperature at which the slope of the curve drawn in *Figure 2* becomes infinite.) Thus, *p*-methacryloyloxyacetanilide presents a T_c of 137 ± 2°C under the experimental conditions used in the present work ($[M]=1.0\,mol\,l^{-1}$).

Table 2 Kinetic parameters of the free-radical polymerization of MOA in DMF solution at several temperatures

Polym. temp. (°C)	$K_p/K_t^{1/2}$	K_d (s^{-1})	$\bar{M}_n$[a]
50	0.70	2.28×10^{-6}	183000
70	0.59	3.74×10^{-5}	94000
90	0.28	4.51×10^{-4}	30000
120	0.04	1.17×10^{-2}	16000

[a] Calculated by transformation of PMOA into PMMA

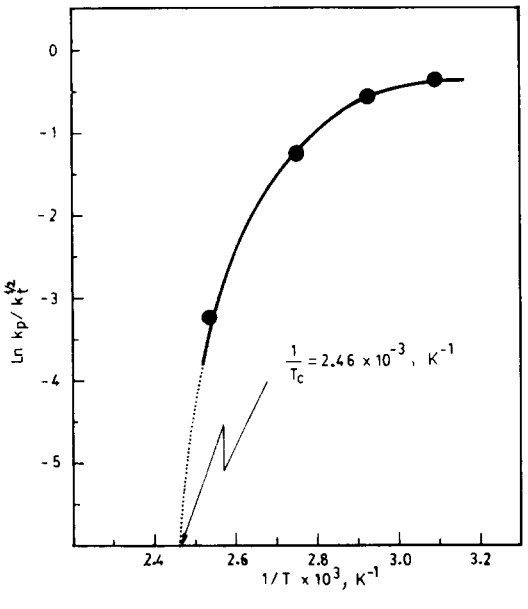


Figure 2 Kinetic diagram for the determination of the ceiling temperature of polymerization (T_c) of MOA, according to the treatment suggested by Yamada *et al.*[13]

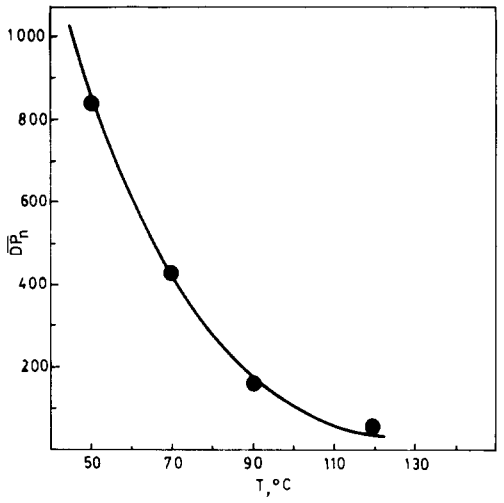


Figure 3 Variation of the average degree of polymerization with reaction temperature for the free-radical polymerization of MOA

In this sense, Schulz and Wittmer[14] have reported a ceiling temperature of 145°C and Yamada *et al.*[13] reported a $T_c=140$°C for the free-radical polymerization of methyl methacrylate when the monomer concentration is $[M]=0.64\,mol\,l^{-1}$ in both cases. Otsu *et al.*[15], in an interesting study of the effects of *ortho*-substituents on the kinetics and thermodynamic parameters of the free-radical polymerization of several phenyl methacrylates, show that the rate of polymerization and the number-average degree of polymerization decrease with increasing bulkiness of the ester phenyl group, the ceiling temperature of phenyl methacrylate being somewhat higher than 140°C for a monomer concentration of $[M]=0.64\,mol\,l^{-1}$. These authors suggest that the introduction of substituents in the *para*-position of the aromatic ring does not affect T_c, whereas *ortho*-substitution causes a significant decrease in T_c, because of the steric hindrance associated with substitution in the *ortho*-position.

In order to find out the average degree of polymerization and thus the molecular weight of the polymers prepared at different temperatures, they were transformed into the corresponding poly(methyl methacrylate)s by means of hydrolysis of PMOA to the corresponding poly(acrylic acid) using the potassium hydroxide/methanol system and subsequent methylation of the polyacids with diazomethane. It has been widely demonstrated that this treatment does not modify either the stereochemical configuration or the molecular weight of the polymer chains for acrylic polymers[16,17].

The molecular weight of poly(methyl methacrylate) samples was determined by measuring the intrinsic viscosity in benzene solution at 30°C. *Figure 3* shows the

variation of the average degree of polymerization determined from the molecular weight of PMMA samples, plotted against the polymerization temperature. The drastic decrease of the average degree of polymerization with increasing temperature is clear.

STEREOCHEMISTRY

The stereochemical configuration of monomeric units along the macromolecular chains has been analysed by ^1H and ^{13}C n.m.r. spectroscopies. *Figure 4* shows the ^1H n.m.r. spectrum of the methyl groups. The resonance signal of the α-CH_3 splits into three well resolved peaks at 1.32, 1.43, 1.54 ppm from tetramethylsilane (TMS), which have been assigned to iso- (mm), hetero- (mr + rm) and syndiotactic (rr) triads in order of increasing field, in a similar way to the classical assignment of the α-CH_3 resonance signals for pure poly(methyl methacrylate)[18]. The peak area was measured by electronic integration as well as by the cutting and weighing method and the corresponding values were averaged to give the results quoted in *Table 3*. It is interesting to stress the fact that the resonance pattern of the acetyl protons (CH_3CO–) also splits into three rather well resolved peaks at 1.98, 2.01, 2.04 ppm from TMS which have been assigned to syndiotactic, heterotactic and isotactic triads in order of increasing field. This assignment is based on the comparison of the relative intensity of these signals with those of the α-CH_3 resonances and also corresponds to the assignment of the resonance signals of acetyl protons for poly(vinyl acetate)[18]. However, we wish to stress that the sensitivity of the acetyl side-group resonance signals to the stereochemistry of the polymer segments is rather surprising, since this group is relatively far from the

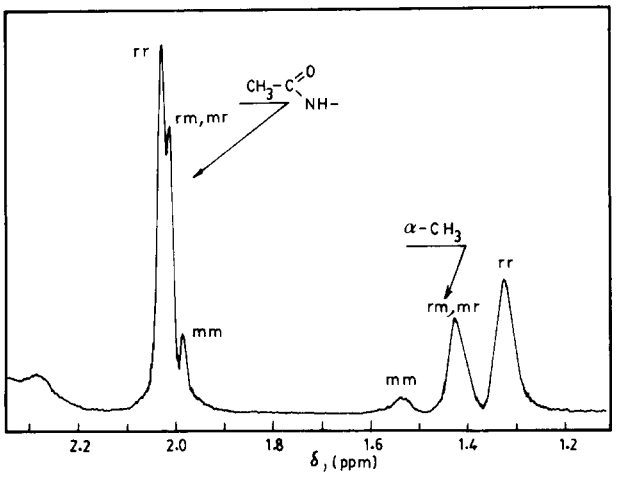


Figure 4 ^1H n.m.r. of the methyl groups of PMOA. Spectrum recorded in DMSO solution at 90°C

Table 3 Triad and dyad molar fractions of PMOA synthesized by free-radical polymerization. The experimental data have been obtained from the analysis of ^1H n.m.r. spectra

		α-CH_3	CH_3CONH–	Average
Triad	mm	0.06_3	0.06_8	0.06_5
	mr + rm	0.39_6	0.39_4	0.39_5
	rr	0.54_1	0.53_8	0.54_0
Dyad	m	0.25_9	0.26_5	0.26_2
	r	0.74_1	0.73_5	0.73_8

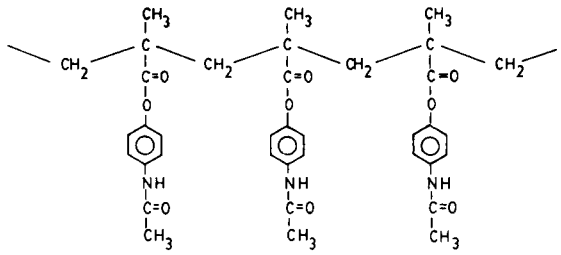


Figure 5 Repeat mesomeric unit in sequences of PMOA

pseudo-asymmetric quaternary carbon, as is drawn in the scheme of *Figure 5*. This behaviour can be accounted for satisfactorily by taking into consideration the effect of aromatic solvents and the presence of polar groups on the splitting of the resonance signals of methoxy groups in poly(methyl methacrylate)[19,20]. It is widely demonstrated that the resonance signal of methoxy protons is sensitive to the stereochemical configuration of the polymer segments when the spectra are recorded in aromatic solvents like benzene or more polar nitrobenzene[21]. In the case of PMOA the ester side-group presents a rigid 1,4-disubstituted aromatic nucleus together with the polar amido group. It seems justified that the interactions of these groups with the carbonyl groups of neighbouring units would be responsible for the stereochemical effect on the pattern of the acetyl-proton resonance signals. In this regard, we have verified that the sensitivity of the signal of the acetyl group disappears when a flexible segment is introduced into the side-group. This is the case for the introduction of an oxyethylene spacer group between the ester group and the aromatic nucleus (–COO–CH_2–CH_2–O–C_6H_4–), which gives rise to the appearance of only a sharp singlet for the acetyl protons, independent of the tacticity of the polymer chains[22].

In this way, the experimental values of the molar fraction of tactic triads are quoted in *Table 3*, being independent of the polymerization temperature in the range 50–120°C, together with the calculated molar fraction of dyads and the corresponding average values. The triad molar fraction estimated from CH_3–CO–NH– resonances agree closely with those obtained from the analysis of the α-CH_3 peaks. It is clear that PMOA presents a stereochemical configuration predominantly syndiotactic in the range of temperatures used in the present work (50–120°C). From the values quoted in *Table 3* the statistical parameters collected in *Table 4* have been determined. The values of the conditional probabilities for iso- and syndiotactic additions to meso or racemic growing chain ends, $p(i/j)$, $i, j = m, r$, as well as the persistence ratios for isotactic (ρ_i) and syndiotactic placements (η_s) as defined by Coleman, Reinmoller and Fox[23,24], strongly suggest that the stereosequence distribution of the monomer units in the macromolecular chains is consistent with the Bernoullian statistics with a single parameter describing the probability for isotactic placements as defined by Bovey[25], $\sigma = P_m = 0.26$. The analysis of the so-called Z-parameter[26] stresses this behaviour, since it is very sensitive to variation of the propagation mechanism from Bernoullian statistics, principally when the polymers obtained are predominantly syndio- or isotactic[27]. The fact that this parameter has a value very close to unity makes it clear that the propagation mechanism of the stereo-control of the polymerization process is Bernoullian.

Table 4 Stereochemical parameters of the free-radical polymerization of MOA

$p(m/m)=(mm)/(m)=0.25$	$\rho_i=2(m)(r)/(mr)=0.98$
$p(r/r)=(rr)/(r)=0.73$	$\eta_s=(rr)/(r)^2=0.99$
$p(m/r)=\frac{1}{2}(mr+rm)/(r)=0.27$	$Z=4(mm)(rr)/(mr)^2=0.90$
$p(r/m)=\frac{1}{2}(mr+rm)/(m)=0.75$	

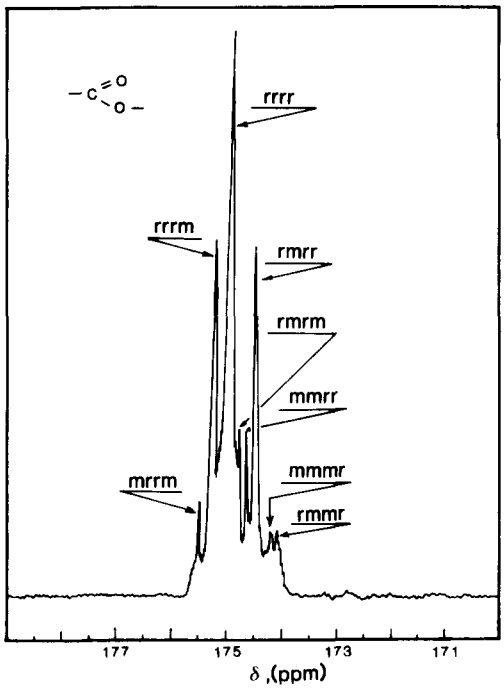


Figure 6 Expanded ^{13}C n.m.r. spectrum of the C=O acrylic ester group resonances. Solvent, DMSO; temperature, 90°C

Table 5 Pentad molar fractions of PMOA determined from the analysis of the ^{13}C=O resonance signals

Pentad	Experimental	Calculated[a]
mmmm	–	0.00_5
mmmr	0.03	0.02_6
rmmr	0.04	0.03_8
mmrm	–	0.02_6
mmrr	0.07	0.07_5
rmrm	0.08	0.07_5
rmrr	0.19	0.21_1
mrrm	0.05	0.03_8
rrrm	0.18	0.21_1
rrrr	0.29	0.29_7

[a] According to Bernoullian statistics with $P_m=0.26$

On the other hand, it has been widely recognized that ^{13}C n.m.r. can give more information than ^{1}H n.m.r. on the tacticity of stereoregular polymers, since the ^{13}C resonance signals may be sensitive to the stereochemical configuration of longer sequences, i.e. tetrads, pentads, etc., than the proton-resonance signals. This fact may be ascribed in general to specific γ and δ effects, which are not observed in proton n.m.r.[28]. *Figure 6* shows the decoupled ^{13}C spectrum of the C=O ester group, in which eight of the 10 possible pentad peaks are rather well resolved, whereas the C=O acetamido group (not shown in the figure) presents a single sharp peak which is not sensitive to the stereochemical configuration of the monomer units along the macromolecular chains. The assignment of the eight peaks of the C=O ester group has been carried out on the basis of triad probabilities determined from the ^{1}H n.m.r. spectra, considering that the polymers fit Bernoullian statistics with $P_m=0.26$, and by comparison with the assignment of the C=O resonance signals for PMMA reported by Hatada *et al.*[26] and Peat and Reynolds[28]. The results obtained are quoted in *Table 5*, together with those calculated considering the Bernoullian character of the propagation step with an isotacticity parameter $P_m=0.26$. The good agreement between calculated and experimental data supports the assignment suggested in the present work and makes clear that the pure syndiotactic pentads (rrrr) and the heterotactic pentads (rmrr and rrrm) are formed preferentially during the propagation step of the free-radical polymerization of MOA, independently of polymerization temperature in the range 50–120°C.

HYDROLYTIC BEHAVIOUR

In order to study possible applications of this kind of polymer as a pharmacologically active compound, we have studied from a chemical point of view the hydrolysis of PMOA in aqueous medium using sodium hydroxide as catalyst at several temperatures. I.r. spectra of the isolated products of hydrolysis indicate the release of paracetaminophen during the process and the modification of the corresponding polymers into poly(methacrylic acid).

The degree of modification of the original polymers was determined by volumetric titration with hydrochloric acid and the results obtained are quoted in *Table 6*. At physiological temperatures (37°C), the hydrolytic process is very slow, reaching only a modification of 21–22 mol% after five days of treatment, whereas if the reaction is carried out at 50°C, only two days is necessary to reach total conversion, which indicates a great influence of temperature on the rate of the process. The relatively low cleavage of the paracetaminophen residues from the macromolecular chains at physiological temperatures seems to indicate a potential depot effect which would be interesting from a practical point of view. However, it would be necessary to obtain a deeper insight into the hydrolytic behaviour from a mechanistic point of view as well as the study of enzymatic hydrolysis. These are in progress.

On the other hand, the activity of the monomer and polymer *in vivo* has been studied from a pharmacological point of view using several series of mice. The results obtained are reported elsewhere[29] but we stress here that both compounds present mean lethal doses (LD50 > 400 mg kg^{-1}) as well as interesting analgesic and anti-inflammatory activities. Also both compounds are powerful agents against the aggregation of platelets.

Table 6 Hydrolytical modification of PMOA in aqueous media

Reaction temp. (°C)	Time (h)	Modification (mol%)
37	90	10.1
37	120	21.6
50	24	73.0
50	48	100

ACKNOWLEDGEMENTS

The authors thank M. Victoria Lopez Moyano for technical assistance and are grateful for the financial support provided by the 'Comision Asesora de Investigación Cientifica y Técnica'.

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