Polymers with pharmacological activity: 4. Synthesis and free-radical polymerization of an acrylic derivative of 'paracetamol'

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In the framework of the preparation of macromolecular systems with potential pharmacological activity, we have prepared a series of acrylic polymers bearing active pharmacons as side groups. The present paper reports the synthesis and free-radical polymerization of 4-[6-(methacryloyloxy)hexyloxy]acetanilide, which can be considered an acrylic derivative of 'paracetamol' (4-hydroxyacetanilide), a popular analgesic and antipyretic pharmacon. The kinetic results of the free-radical polymerization in solution of dimethylformamide at several temperatures indicate that this compound presents an apparent ceiling temperature of polymerization $T_c = 186$ C in standard conditions, $[M] = 1$ mol l^{-1}. The results obtained are compared with those of the free-radical polymerization of 4-(methacryloyloxy)acetanilide and 4-[2-(methacryloyloxy)ethyloxy]acetanilide, studied previously. The analysis of polymer samples by ^{13}C nuclear magnetic resonance spectroscopy makes it clear that the propagation step fits Bernoullian statistics, from a stereochemical point of view, with an isotacticity parameter $\sigma = P_m = 0.23$. The resonance signals of the carbonyl ester group (C=O) are assigned to tactic sequences in terms of stereochemical pentads.

(Keywords: polymeric drugs; pharmacological activity; synthesis; free-radical polymerization; paracetamol derivative; kinetics; nuclear magnetic resonance)

INTRODUCTION

In the last 20 years the preparation of new formulations with potential pharmacological activity based on macromolecular systems, known as polymeric drugs or polymer-bound drugs, has claimed the attention of a great number of scientific research groups[1-6]. In this sense, in recent papers[7,8] we have reported the synthesis and free-radical polymerization of 4-(methacryloyloxy) acetanilide (MOA) and 4-[2-methacryloyloxy)ethyloxy] acetanilide (MOEA). MOA can be considered an acrylic derivative of the popular analgesic and antipyretic drug known as 'paracetamol' (4-hydroxyacetanilide), whereas MOEA is an acrylic derivative of 'phenacetin' (4-ethoxyacetanilide), whose major metabolite in the living body is paracetamol.

The kinetic behaviour of this kind of acrylic monomer is characterized by the existence of a relatively low ceiling temperature of polymerization T_c, which arises from the dipolar interactions and steric hindrance of the aromatic or aliphatic–aromatic ester side group of the active growing chain ends and the incoming monomer molecules. Thus, the value of T_c will be dramatically influenced by the flexibility of the ester side group.

The main goal of this paper is the study of the synthesis and free-radical polymerization of 4-[6-(methacryloyloxy) acetanilide (MOHA), which presents the chemical structure of MOA, but with the presence of a hexyloxy spacer group between the acrylic ester group and the pharmacologically active residue. The introduction of this hexamethylene segment probably gives rise to an increase of the flexibility of the side group, together with a noticeable decrease of the dipolar interactions between the side groups of neighbouring units or interactions between active chain ends and incoming monomer molecules.

EXPERIMENTAL

Monomer synthesis

The 4-[6-methacryloyloxy)hexyloxy] acetanilide (MOHA) was prepared by a two-step reaction.

Synthesis of 4-[6-hydroxy)hexyloxy]acetanilide (H-I). First, 30 g (0.2 mol) of 4-hydroxyacetanilide (paracetamol) was dissolved in a mixture of 100 ml ethanol and 11.2 g KOH in 50 ml water. A trace of potassium iodide was added and the solution was heated and stirred while 27.3 g (0.2 mol) of 6-chloro-1-hexanol was added slowly. The reaction mixture was refluxed overnight. After elimination of the excess solvent at reduced pressure, the mixture was precipitated with cool water. The isolated solid was washed twice with hexane/ethanol and dried under vacuum: yield, 90%; m.p. = 80 ± 1 C.

Synthesis of 4-[6-methacryloyloxy)hexyloxy]acetanilide (MOHA). First, 10 g (0.04 mol) of H-I was dissolved in toluene, together with 0.5 g of an equimolar mixture of *p*-toluenesulphonic and boric acids. After the addition of a trace of hydroquinone to the reaction medium, the solution was refluxed and 5.2 g (0.06 mol) of methacrylic acid were added slowly under a nitrogen atmosphere. After 4 h of reaction, the crude product was isolated by precipitation into cool hexane, filtered off and crystallized

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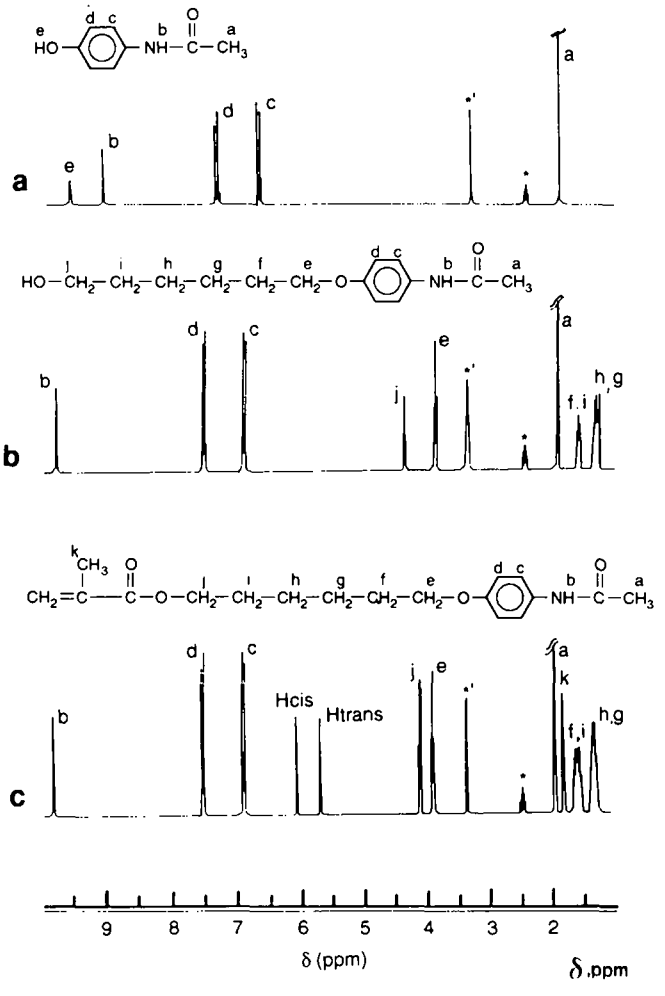


Figure 1 ^{1}H n.m.r. (200 MHz) spectra of (a) paracetamol, (b) 4-[6-(hydroxy)hexyloxy]acetanilide (H-I) and (c) 4-[6-(methacryloyloxy) hexyloxy]acetanilide (MOHA); (*) DMSO-d_6 resonance signal, (*') H_2O associated with DMSO

twice with chloroform/hexane: yield, 70%; m.p. = 65 ± 1 °C.

The MOHA was characterized by i.r., ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopies. The n.m.r. spectra of the intermediate H-I and the acrylic monomer MOHA are shown in *Figures 1* and *2*.

Polymerization

The monomer MOHA was polymerized at several temperatures in the interval 50–160 °C, in a thermostatic bath regulated with a precision of ±0.1 °C, using azobisisobutyronitrile (AIBN) ([I] = 1.5×10^{-2} mol l^{-1}) and dimethylformamide (DMF) as solvent ([M] = 1 mol l^{-1}). All experiments were carried out in Pyrex glass ampoules at high vacuum (10^{-4} mmHg).

After the desired time, the reaction mixture was added to a large excess of methanol, and the precipitated polymer was dried at reduced pressure until constant weight was attained.

Characterization of polymers

Polymer samples 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-d_6) on a Bruker AM-200 (200 MHz, ^{1}H and 50.3 MHz ^{13}C). Proton experiments were performed at 80 °C on 5% (w/v) solutions. Carbon-13 experiments of polymer samples were recorded at 80 °C on 25% (w/v) solutions, by using an inverse gated decoupling sequence pulse with a flip angle of 90° (pulse width of 3.7 μs) and a relaxation delay of 4 s. The relative peak intensities were measured from the integrated peak areas, calculated by means of an electronic integrator or by triangulation and planimetry. Tetramethylsilane (TMS) was used as internal reference standard in all experiments.

RESULTS AND DISCUSSION

MOHA was prepared according to *Scheme 1*. The first step is a typical Williamson's reaction[9], which gives rise to the compound (4-[6-(hydroxy)hexyloxy]acetanilide (H-I) with good yield. The second is an esterification with methacrylic acid catalysed by an equimolar mixture of *p*-toluenesulphonic acid and boric acid[10], which permits the preparation of the acrylic derivative in mild conditions.

The i.r. spectra of MOHA show absorption signals at 3300 cm^{-1} (NH), 1730 cm^{-1} (C=O of acrylic esters), 1660 cm^{-1} (–CONH acetamido) and 1640 cm^{-1} (C=C, acrylic double bond).

Figure 1 shows the ^{1}H n.m.r. spectra of paracetamol, intermediate H-I and acrylic monomer MOHA. It can be clearly observed that a measurable shift of the

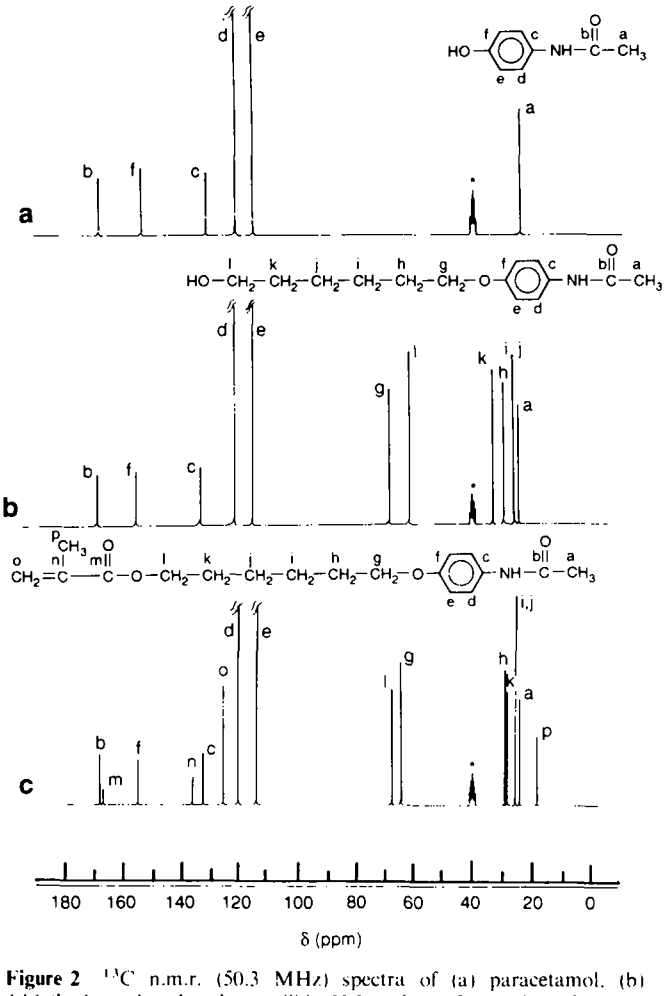
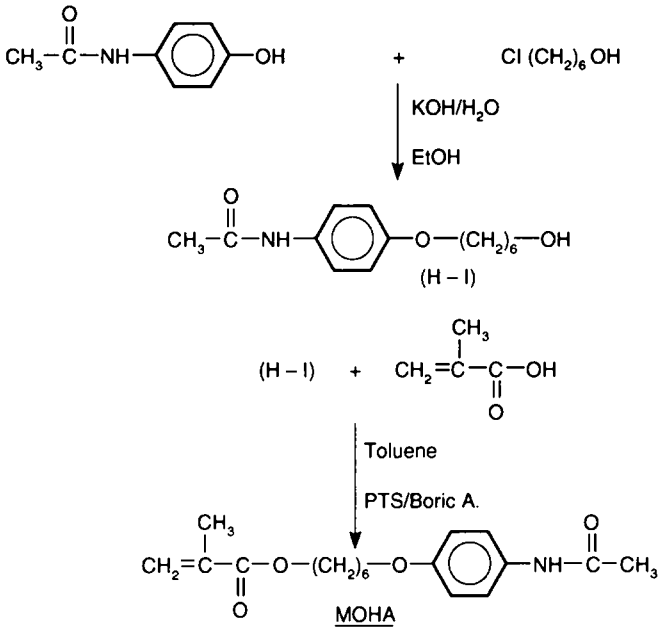


Figure 2 ^{13}C n.m.r. (50.3 MHz) spectra of (a) paracetamol, (b) 4-[6-(hydroxy)hexyloxy]acetanilide (H-I) and (c) 4-[6-(methacryloyloxy) hexyloxy]acetanilide (MOHA); (*) DMSO-d_6 resonance signal



acetamido -NH resonance signal (from $\delta = 9.10$ to 9.65 ppm) is produced by the substitution of the 4-hydroxy group by the hexyloxy residue in the *para* position of the aromatic ring with respect to the acetamido group. Similar shifts are also observed for the resonance signals c and d of *Figure 1*, assigned to the four aromatic protons of the acetanilide residue. Indeed, we found a similar result in the preparation of an acrylic derivative of phenacetin[8] by the substitution of the 4-hydroxy group by the ethyleneoxy residue. However, the esterification of the intermediate H-I with methacrylic acid gives rise to a significant shielding effect on the methylene j protons (see the spectrum of MOHA at the bottom of *Figure 1*), without any other appreciable modification of the resonance signals assigned to the remaining hydrogen atoms of the hexyloxy residue.

Figure 2 shows the ^{13}C n.m.r. spectra of paracetamol, intermediate H-I and monomer MOHA. The methylene carbon signals g and l at both ends of the hexyloxy group change their corresponding position appreciably by esterification with methacrylic acid, the signal l (assigned to the $-CH_2$ carbon) being shifted about 6 ppm downfield with respect to the same group of the intermediate H-I.

The free-radical polymerization of MOHA was studied in solution in DMF at different temperatures in the interval 50–160 C, with concentrations of monomer and initiator outlined in the experimental section. *Figure 3* shows the conversion time diagrams obtained at several polymerization temperatures. These are rather similar to diagrams reported for the free-radical polymerization of MOA[7] and MOEA[8]. In all cases, the kinetic behaviour has been explained in terms of the influence of the so-called ceiling temperature of polymerization of the corresponding acrylic monomer on the reaction process at each temperature. The relatively low ceiling temperature T_c of this kind of monomer accounted for the high polarity and steric hindrance of the acetanilide side group. The introduction of flexible spacer groups between the acrylic ester and acetanilide side group would give rise to the increase of T_c. On this basis, the free-radical polymerization of MOHA in the experimental conditions mentioned above may be described by the classical first-order scheme at low polymerization temperatures (50 and 70 C), but at higher reaction temperatures (90–160°C) the polymerization system tends to reach a relatively low limiting conversion. The level of this degree of conversion decreases drastically with increase of polymerization temperature. Experimentally, we have been able to isolate precipitated species up to a polymerization temperature of 175 C. As indicated above, we have ascribed the anomalous decrease of the degree of conversion with increasing polymerization temperature to the existence of a relatively low ceiling temperature of polymerization for this monomer.

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 according to the equation:

$$\ln\left(\frac{1}{1-x}\right) = \frac{2k_p}{k_t^{1/2}}\left(\frac{f[I]}{k_d}\right)^{1/2}[1-\exp(-k_d t/2)] \quad (1)$$

Using the k_d values obtained from the Arrhenius equation for the thermal decomposition of AIBN, reported by Tulig and Tirrell[11], and considering a value of $f = 0.6$, we obtain the diagrams shown in *Figure 3*. The full curves were drawn on the basis of equation (1), with the set of kinetic constants quoted in *Table 1*, whereas the broken curve corresponds to the best curve fitting of the experimental points for the experiments carried out at 90 C.

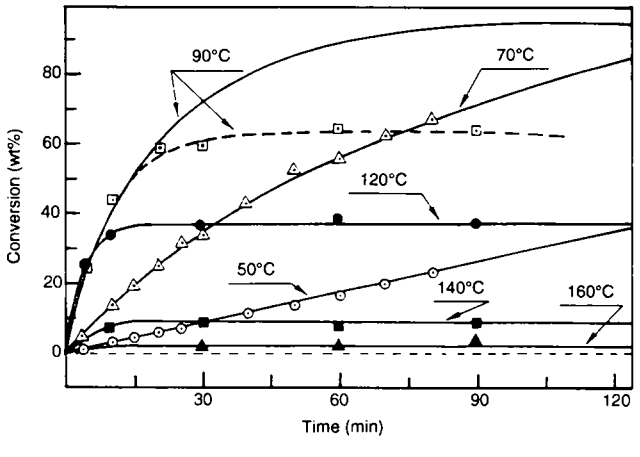


Figure 3 Conversion–time diagrams of the free-radical polymerization of MOHA at several temperatures: ( ) theoretical diagrams according to equation (1); (- - -) curve fitting to the experimental points

Table 1 Kinetic parameters of the free-radical polymerization of MOHA in DMF solution at several temperatures

Reaction temp. (C)	$k_p.k_t^{1/2}$	k_d (s^{-1})
50	0.418	1.81×10^{-6}
70	0.472	2.90×10^{-5}
90	0.480	3.42×10^{-4}
120	0.226	8.70×10^{-3}
140	0.123	5.80×10^{-2}
160	0.067	3.20×10^{-1}

Values of $k_p.k_t^{1/2}$ have been obtained by curve fitting, as shown in *Figure 3*

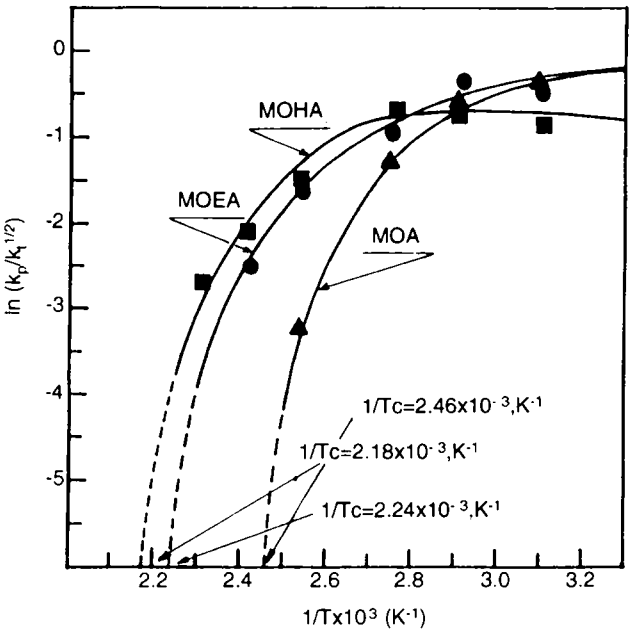


Figure 4 Determination of the ceiling temperature of polymerization T_c of MOHA (■), MOEA (●) and MOA (▲), according to the treatment suggested by Yamada *et al.*[13]

It seems apparent from this figure that the free-radical polymerization of MOHA under the experimental conditions of the present work deviates from the classical kinetic behaviour when the reaction system reaches conversions higher than 60% at a polymerization temperature of 90 C. However, the theoretical curves for the free-radical polymerization of MOHA at 50 and 70 C seem to fit the experimental points adequately. The concordance between theory and experiments observed at 120, 140 and 160 C might be explained satisfactorily by taking into account that the limiting conversion is reached at short reaction times. In view of the relatively high decomposition rate of AIBN at these temperatures, it can be considered that the concentration of initiator becomes so low that the application of equation (1) gives a constant value for the degree of conversion independently of the polymerization time.

The ceiling temperature in free-radical polymerization is usually determined by the extrapolation to $R_p = 0$ of the diagram for the overall rate of polymerization (R_p) *versus* polymerization temperature[12]. However, to avoid the effect of initiation on the observed polymerization rate, Yamada *et al.*[13] have suggested the use of diagrams of $\ln(k_p.k_t^{1/2})$ *versus* the reciprocal of the polymerization temperature (where k_t denotes the rate constant for the termination reaction and k_p the overall rate constant for the propagation depropagation equilibrium reaction). The diagram must give a curve with a slope approaching infinity at the ceiling temperature.

This treatment has two limitations, which can affect the accuracy of the kinetic parameters determined: The values of the ratio $k_p.k_t^{1/2}$ are obtained by considering the classical mechanism of polymerization, but it would be reasonable to consider the influence of the propagation depropagation equilibrium. On the other hand, the extrapolation of the diagram is not a straight line but a curve with the experimental values usually rather far from the extrapolated onset. However, it may be used from a comparative point of view, taking into account apparent values for the T_c determinations.

Figure 4 shows the diagram of $\ln(k_p/k_t^{1/2})$ *versus* $1/T$ for the free-radical polymerization of MOA, MOEA and MOHA, giving apparent values of $T_c = 133 \pm 5$ C for MOA, $T_c = 173 \pm 5$ C for MOEA and $T_c = 186 \pm 5$ C for MOHA. The differences in T_c values may be satisfactorily explained according to the influence of the spacer group on the flexibility of the polymeric growing radicals. In this sense, we have determined by d.s.c. the glass transition temperature of high-molecular-weight polymers prepared from these monomers, giving a value of $T_g = 471$ K for poly(MOA), noticeably higher than that of poly(methyl methacrylate), which reflects the high dipolar and steric interactions associated with the chemical structure of the acetanilide side groups, and values of $T_g = 385$ K for poly(MOEA) and $T_g = 318$ K for poly(MOHA). Thus, the introduction of an ethylene oxide spacer group between the acrylic ester and acetanilide residue gives a decrease of T_g of 86 K and the introduction of the hexylene oxide spacer gives a decrease of 153 K. It can be assumed that the flexibility of the polymeric segments is directly related to the decrease of the glass transition temperature of these acrylic polymers, which present the same macromolecular backbone and differ in the length of the side group.

STEREOCHEMISTRY

It has been widely recognized that the stereochemistry of biologically active compounds affects their biochemical and enzymatic catalysed activity[14]. Thus, it may be of interest to analyse the stereochemical configuration of PMOHA with respect to that of PMOA and PMOEA, in order to discover the influence of the length of the spacer group on the stereochemistry of the corresponding monomer sequences along the macromolecular chains. Therefore we have studied this structural parameter by ^{13}C n.m.r. spectroscopy.

Figure 5 shows the enhanced-resolution high-field spectrum of poly(MOHA), together with that of poly(MOA), recorded in DMSO-d_6 at 80 C (for clarity the signals of DMSO have been drawn with reduced intensity). It is clear from this figure that the α-CH_3 and quaternary carbon resonances of PMOHA are shifted towards higher field with respect to the corresponding signals of PMOA, the chemical shifts being rather similar to those of pure poly(methyl methacrylate)[15]. This is a consequence of the strict alkyl character of the hexyloxy spacer group instead of the aromatic character of the acetanilide group directly linked to the acrylic ester in PMOA. It can be observed that both groups, i.e. α-CH_3 and quaternary carbon, present three main resonances, which have been assigned in terms of triads to isotactic (*mm*), heterotactic (*rm*+*mr*) and syndiotactic (*rr*) sequences, in order of increasing field. This assignment is based on similar results described for PMOA and PMOEA[16] and follows the classical assignment of the same groups for pure poly(methyl methacrylate)[15,17].

The experimental values of relative intensities of the signals assigned to the stereochemical sequences are quoted in *Table 2*, together with those of PMOA and PMOEA. The statistical parameters quoted in *Table 3* have been determined from the tactic triad molar fractions given in *Table 2*. In all cases, the average conditional probabilities for iso- and syndiotactic additions to *meso* or racemic growing chain ends, $p(i\ j)$,

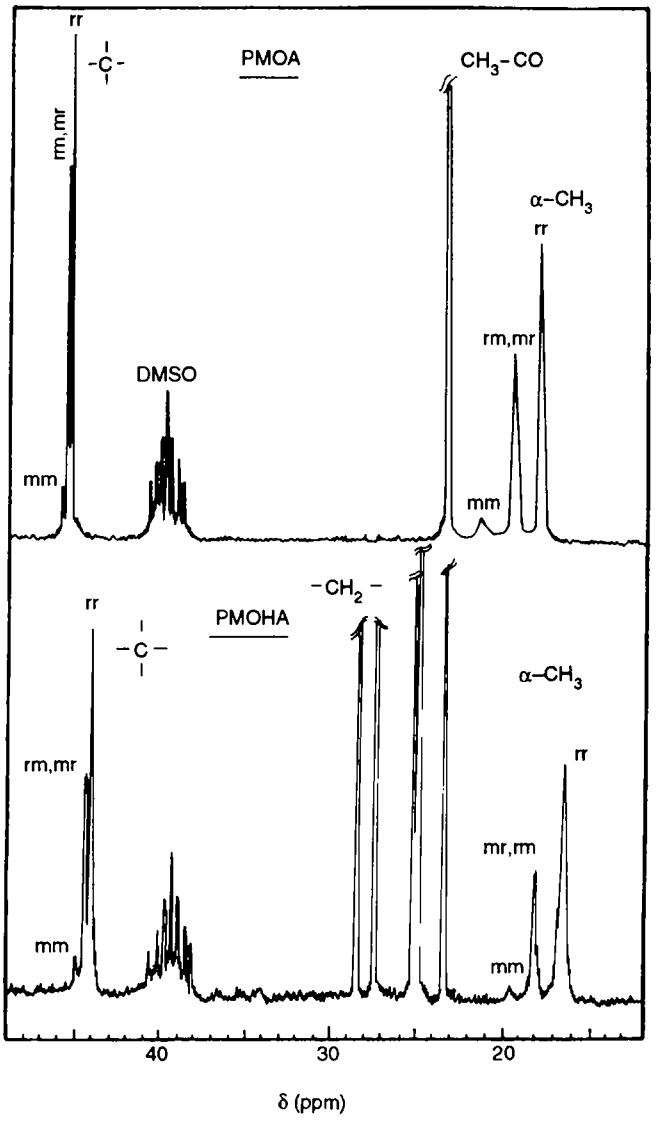


Figure 5 ^{13}C n.m.r. (50.3 MHz) enhanced resonance signals of the aliphatic carbons of PMOHA and PMOA

Table 2 Molar fraction of tactic triads, determined from the resonance signals of α-methyl and quaternary carbons

Signal	Sequence	PMOA[a]	PMOEA[a]	PMOHA
α-CH_3	*rr*	0.56	0.60	0.58
	mr + *rm*	0.39	0.36	0.36
	mm	0.05	0.04	0.06
Quat. C	*rr*	0.55	0.60	0.58
	mr + *rm*	0.40	0.34	0.37
	mm	0.05	0.06	0.05

[a] Data taken from ref. 16

i,j = *m,r* (*i* refers to the relative configuration of the chain and *j* to the adding monomer), indicate a random distribution of the *meso* and racemic diads along the polymer chains, following the classical Bernoullian trial[18,19] with isotacticity parameter $\sigma = P_m$ quoted in *Table 3*. These values indicate the relatively high tendency of monomeric units to form syndiotactic stereosequences. The introduction of spacer groups of different length (two or six methylenes) between the acrylic ester and the aromatic side group does not drastically modify the stereochemical configuration of the monomeric units with respect to that of PMOA.

However, the slight increase of the syndiotactic sequences associated with the introduction of the alkyl spacer segments may arise from the decrease of dipolar interactions between neighbouring units of polymer chains or the interactions between the side groups of chain ends and the incoming monomer, which slightly favours the formation of the apparently more thermodynamically stable syndiotactic arrangement. In any case, the Bernoullian character of the distribution of stereochemical sequences along the polymer chains is evident owing to the proximity to unity of the so-called persistence ratios of syndiotactic sequences (η_s) and isotactic sequences (ρ_i) as defined by Coleman, Reinmoller and Fox[20,21]. These parameters have been calculated from the averaging of experimental data of *rr*, *mr* + *rm* and *mm* tactic triads quoted in *Table 2*.

Figure 6 shows the enhanced resonance signals of the C=O ester group of PMOHA, together with those of the same group of PMOA. The assignment of the different peaks has been carried out on the basis of results previously obtained for PMOA and PMOEA[7,16] and is consistent with assignments suggested by Peat and Reynolds[15], Chûjô *et al.*[17] and Ferguson and Ovenall[22] for the C=O resonances of poly(methyl methacrylate). It is clear from this figure that the resonance signals assigned to tactic sequences of pentads for PMOHA are shifted downfield by about 1.7 ppm with respect to the signals assigned with the same sequence in PMOA. Considering this assignment, the molar fraction of sequences quoted in *Table 4* have been determined. In the last column of this table are quoted the values of the corresponding molar fraction of sequences calculated considering the Bernoullian character of the polymerization by application of the isotacticity parameter $P_m = \sigma = 0.23$ to known statistical relations[19]. The proximity of experimental and statistical data validates the assignment and demonstrates the Bernoullian character of the propagation step from a stereochemical point of view. Also the analysis of samples prepared at different polymerization temperatures makes it clear that this behaviour is independent of the reaction temperature. Thus, we can state that the ceiling temperature of polymerization of these monomers does not apparently affect the relative stereochemical configuration of monomeric units along the macromolecular chains.

Table 3 Stereochemical parameters of the free-radical polymerization of MOA, MOEA and MOHA

Parameter	MOA	MOEA	MOHA
Addition probabilities			
$P_m = \sigma$	0.26	0.22	0.23
P_r	0.74	0.78	0.77
Conditional probabilities			
$p(m/m)$	0.25	0.23	0.26
$p(r/r)$	0.73	0.77	0.75
$p(m/r)$	0.27	0.23	0.23
$p(r/m)$	0.75	0.77	0.78
$\eta_s = (rr)/(r)^2$	0.98	0.98	0.98
$\rho_i = 2(m)/(r)/(mr)$	0.99	0.99	0.98

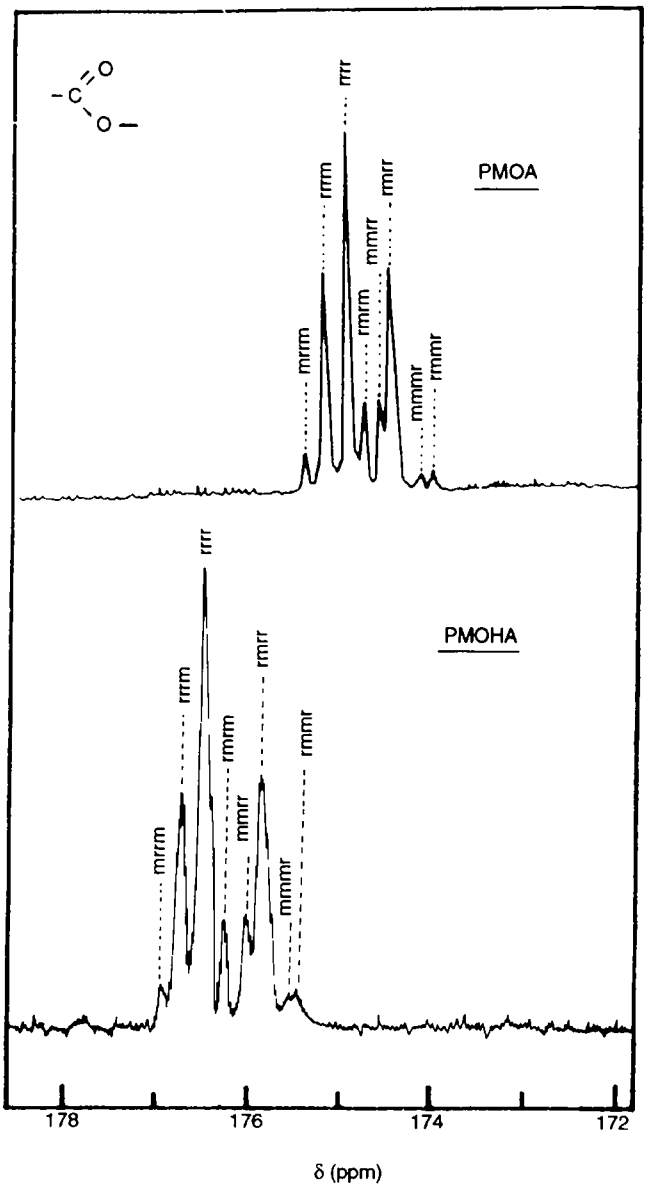


Figure 6 ^{13}C n.m.r. (50.3 MHz) resonance signals of the carbonyl ester group (C=O) of PMOHA and PMOA

CONCLUSIONS

In conclusion, the introduction of alkyl spacer segments into the ester side group of acrylic matrices with acetanilide side groups does not dramatically modify the stereochemistry of monomeric units along the macromolecular chains, but the alkyl character of the methylene segments gives rise to a measurable shift of the resonance signals in the ^{13}C n.m.r. spectrum of PMOHA with respect to that of PMOA.

Table 4 Assignment of pentad sequences to C=O ester group resonance signals of the decoupled ^{13}C n.m.r. spectra in DMSO-d_6

		Molar fraction	
δ (ppm)	Tactic sequence	Expt.	Calc.[a]
176.82	*mrrm*	0.03	0.03
176.58	*mrrr*	0.19	0.21
176.31	*rrrr*	0.35	0.35
176.20	*rmrm*	0.08	0.06
175.85	*mmrr*	0.09	0.06
175.69	*rmrr*	0.18	0.21
–	*mmrm*		0.02
175.30	*mmmr*	0.03	0.02
175.20	*rmmr*	0.04	0.03
–	*mmmm*	–	0.00

[a] According to the Bernoullian trial with $\sigma = 0.23$

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