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Synthesis and stereochemistry of isomeric methacrylic polymers derived from 4- and 5-aminosalicylic acids

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The paper describes the direct synthesis of methacrylamide derivatives of 4-aminosalicylic acid (2-hydroxy-4-*N*-methacrylamidobenzoic acid, 4-HMA) and 5-aminosalicylic acid (2-hydroxy-5-*N*-methacrylamidobenzoic acid, 5-HMA). The monomers obtained present phenolic –OH and carboxylic functional groups in different positions of the side aromatic ring with respect to the methacrylamide group. This structural difference affects slightly the stereochemical structure of the polymers prepared by free radical polymerization at 50°C. From a stereochemical point of view, the polymers are syndiotactic predominantly, with isotacticity parameters $\sigma = 0.17$ for poly(4-HMA) and $\sigma = 0.20$ for poly(5-HMA), and a Bernoullian distribution. The stereochemical configuration of polymers was analysed in terms of triads and pentads based on the ^{13}C nuclear magnetic resonance signals of the α-CH_3, quaternary carbon and amide carbonyl carbon of the polymers. Differential scanning calorimetry gave values for glass transition temperature of 504 K for poly(4-HMA) and 534 K for poly(5-HMA), the difference being explained in terms of the inter- and intramolecular interactions of the polar –OH and –COOH side groups through hydrogen bonding as indicated by Fourier transform infra-red spectroscopy. © 1997 Elsevier Science Ltd.

(Keywords: functional acrylic polymers; stereochemistry; n.m.r. spectroscopy; polymeric drugs)

INTRODUCTION

The main objective of the design of new delivery systems is to optimize the pharmacological response by controlling the drug intake and directing the drug to the targeted biological receptors[1,2]. When the drug is covalently linked to an appropriate polymeric carrier, (systems known as polymeric drugs), the macromolecular systems diffuse more slowly and are adsorbed at distinct pharmacological interfaces. Consequently, the polymeric drugs can prolong therapy at sustained dosages, offering not only a useful depot effect, but in general decreasing the toxicity with respect to the original low molecular weight drug. In addition the polymeric systems offer the possibility of controlling the distribution of the macromolecular conjugates of the polymer drug in the body, by the introduction in systems of specific functional groups, increasing the pharmacological efficacy at the desired location, but avoiding the presence of high concentrations in other points of the organism. The term 'polymeric drug' means that the polymers show their own pharmaceutic activity, and in addition they act as drug carriers if the active residues are linked to the macromolecular chains by means of biodegradable functional groups like ester, amide, carbonate, etc.[3–10].

Water-soluble polymers containing sodium salicylate residues linked at the 5-position by an azo bond to a polysulfonilamine backbone (5-ASA), has been synthesized for the specific metabolic release of 5-ASA in the lower bowel, and is under investigation for the treatment of inflammatory bowel diseases[11]. Ushakov[12] synthesized the *p*-amino salicylate of poly(vinyl alcohol) by reacting *p*-aminosalicylic chloride with poly(vinyl alcohol), and it was shown that the polymeric derivative presented a good antitubercular activity. In this case the aminosalicylic acid residue was linked to a poly(vinyl alcohol) backbone by the partial esterification of the hydroxyl group of PVA chains through the carboxylic function of the salicylic molecules[13]. Callant and Schacht[14] have studied the synthesis and pharmacological behaviour of polymeric drugs based on 5-aminosalicylic acid linked to the polymeric backbone through azo-groups which are reductively cleaned by anaerobic bacteria present in the lower bowel, and Kopeckova and Kopecek[15] have described the preparation of bioadhesive copolymers of *N*-(2-hydroxypropyl) methacrylamide with acrylic derivatives of 5-aminosalicylic acid linked to the polymeric backbone via aromatic azo bonds. Other polyacrylic derivatives of 4- and 5-aminosalicylic acid were prepared earlier by Kennedy *et al.*[16], for the selective extraction of metal cations from aqueous media, profiting by the chelating properties of the salicylic acid[16–18], as well as for the preparation of pharmacologically active polymeric systems[19,20].

We have synthesized acrylic polymers and copolymers by the radical polymerization of a methacrylic ester derivative of salicylic acid, or systems prepared by copolymerization of this monomer with vinyl pyrrolidone or hydroxyethyl methacrylate[21,22]. The polymeric

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derivatives presented low toxicity and good analgesic and anti-inflammatory properties in comparison with aspirin, as well as an interesting behaviour as anti-aggregating agents of platelets, which allows the application of polymeric films as coatings of vascular grafts of Dacron and Goretex, with the improvement of the anti-thrombogenic character of the coated prosthesis in comparison with uncoated ones[23,24].

In the present article we describe the synthesis of methacrylamide derivatives of 4- and 5-aminosalicylic acids and their free radical polymerization, together with the study of the microstructural characterization of polymers by ^{13}C nuclear magnetic resonance (n.m.r.) spectroscopy.

EXPERIMENTAL

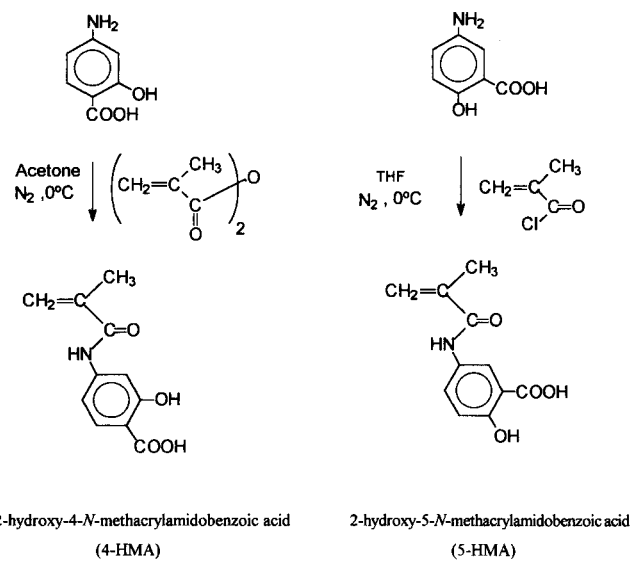
Reagents

4-Amino-2-hydroxybenzoic acid (Merck, 4-AHA) was used as received (m.p. = 140°C). Methacrylic anhydride (Aldrich) was used without purification. 5-Amino-2-hydroxybenzoic acid (Merck, 5-AHA) was used as received (m.p. = 280°C). Methacryloyl chloride (Fluka) was distilled and freshly used (b.p. = 99°C).

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

*Synthesis of 2-hydroxy-4-*N*-methacrylamidobenzoic acid (4-HMA)*

4-HMA was prepared by selective amidation of 4-AHA with methacrylic anhydride at 0°C using acetone as a solvent (*Scheme 1*). To a solution of 20 g (0.13 mol) of 4-AHA in dry acetone (175 ml), a solution of 29 ml (0.19 mol) of methacrylic anhydride in 20 ml of acetone was added dropwise under N_2 atmosphere with magnetic stirring. After reacting for 5 h, the solvent was distilled off at reduced pressure, and the solid residue was washed twice with a water/methanol (4/1) solution. The isolated product was recrystallized twice from methanol/water (2/1) and vacuum dried over phosphorus pentoxide. The yield was 70% (m.p. = 234 ± 1°C).



2-hydroxy-4-*N*-methacrylamidobenzoic acid (4-HMA)

2-hydroxy-5-*N*-methacrylamidobenzoic acid (5-HMA)

Scheme 1

*Synthesis of 2-hydroxy-5-*N*-methacrylamidobenzoic acid (5-HMA)*

5-HMA was prepared by the reaction of 5-AHA with methacryloyl chloride in tetrahydrofuran (THF) solution at 0°C (*Scheme 1*). To a heterogeneous solution of 20 g (0.13 mol) of 5-AHA acid in 200 ml of THF, a solution of methacryloyl chloride (0.19 mol) in 25 ml of THF was added dropwise at 0°C, under N_2 atmosphere with magnetic stirring. After 6 h of reaction, the remaining 5-amino-2-hydroxybenzoic acid was filtered off, and the THF solution was distilled off at reduced pressure. The pale brown solid obtained was recrystallized twice from methanol/water (2/1). The yield obtained was 60% (m.p. = 212 ± 1°C).

Polymerization

Monomers 4-HMA and 5-HMA were homopolymerized at 50°C in a thermostatic bath, using AIBN ($[I] = 1.5 \times 10^{-2}$ mol l^{-1}) and dimethylformamide (DMF) as solvent ($[M] = 1.0$ mol l^{-1}). The experiments were carried out in Pyrex ampoules under oxygen-free N_2 atmosphere.

After the desired time the reaction mixtures were added into a large excess of ethyl ether. The precipitated polymers were filtered off, washed twice with distilled water and vacuum dried at room temperature over phosphorus pentoxide to a constant weight.

Characterization of the products

The methacrylamide derivatives 4-HMA and 5-HMA were characterized by infra-red (i.r.), ^1H and ^{13}C n.m.r. spectroscopy. Fourier transform i.r. (*FT*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 dimethylsulfoxide (DMSO-d_6) solutions on a Varian XLR-300 spectrometer at 70°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 the 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 was 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 temperatures (T_gs) 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 550 K for 30 min and then quenched at −50°C, prior to the measurement run.

RESULTS AND DISCUSSION

4-HMA was selectively synthesized with a good yield by reacting 4-AHA with methacrylic anhydride avoiding the formation of the corresponding methacrylic ester derivative due to the strong tendency of the methacrylic anhydride to react with the basic amine rather than with the acidic phenolic proton. In the conditions described in the Experimental section it is not necessary to protect the hydroxylic phenolic group because the chemical reaction is produced with the 4-amino group exclusively.

5-HMA has been previously synthesized by Lange and Ritter[18] using a procedure in which trimethylchlorosilane was added to protect the phenolic group of 5-AHA to the methacryloyl chloride attack. We consider that the protection of the phenolic group is not necessary if the reaction is carried out under mild experimental conditions. In this sense, the synthesis was carried out decreasing the reaction time and temperature in order to avoid the formation of the ester derivative, being a modification of the Schotten–Bauman scheme[25]. As in the case of 4-HMA, selective amidation reaction is produced in the experimental conditions without protection of the phenolic –OH group.

Physical constants and spectroscopic characteristics of 4-HMA and 5-HMA are given in *Table 1*. *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 distortionless enhancement by polarization transfer (DEPT) spectra, 135°.

The polymerization was carried out according to the experimental conditions mentioned, reaching conversions of 90% for poly(4-HMA) and 85% for poly(5-HMA) after 24 h reaction. The average molecular weight of the polymers prepared, determined by gel permeation chromatography (g.p.c.) with poly(methyl methacrylate) (PMMA) standards, were $\bar{M}_n = 155\,000$ for poly(4-HMA) and $\bar{M}_n = 61\,000$ in the case of poly(5-HMA). According to the g.p.c. curves obtained, the polydispersity of the samples analysed was $\bar{M}_w/\bar{M}_n = 1.7$ and 1.5 respectively, with symmetric g.p.c. diagrams approaching to a Gaussian distribution. A comparative study of the kinetic behaviour of both methacrylic monomers will be reported subsequently.

In the present work we investigate mainly the synthesis and free radical polymerization of the monomers 4-HMA and 5-HMA, as well as the influence of the different position of the carboxylic and phenolic groups of the side residues of these isomeric polymers, on their stereochemistry and chain flexibility. For this purpose, ^{13}C n.m.r. spectra of both polymers have been analysed comparatively. ^{1}H n.m.r. spectra did not show enough information for stereochemical studies.

Figure 2 shows the decoupled ^{13}C n.m.r. spectra of samples of poly(4-HMA) and poly(5-HMA). The resonance signals of the α-CH_3 side groups (16–21δ), and the quaternary carbons of the methacrylic chains (45–48δ) of both polymers, show fine structure, which has been analysed in terms of the content of different stereochemical sequences. *Figure 3* shows the enhanced resolution decoupled ^{13}C n.m.r. spectra of the acrylic carbon atoms of both polymers, giving three well resolved signals which have been assigned to iso (*mm*), hetero (*rm* + *mr*) and syndiotactic (*rr*) triads in order of increasing field, according to similar assignments for PMMA[26,27] and poly(methacrylamide)[28]. From the relative integrated contribution of the signals assigned to the carbon atoms of both polymers (see *Figure 3*), the fractions of tactic sequences were determined (*Table 2*). These indicate that the polymers prepared are predominantly syndiotactic.

The distribution of stereochemical triads is different for the two polymers, the content of *mm* and *mr* + *rm* triads of poly(4-HMA) are slightly lower than those of poly(5-HMA). These data indicate higher selectivity of poly(4-HMA) sequences for the syndiotactic arrangement than those of poly(5-HMA). This behaviour might be ascribed to the higher proximity of the bulky carboxylic groups in poly(4-HMA) in an atactic diad arrangement, than those in poly(5-HMA). Therefore, the side substituents of the repeating units of poly(4-HMA) and poly(5-HMA) will tend to be in a *trans* configuration, predominantly, in order to minimize the relatively high steric hindrance (*Scheme 2*). This effect is even slightly higher for poly(4-HMA) than poly(5-HMA). This point has been studied previously for the acrylic derivatives of 4- and 5-aminosalicylic acid with the same stereochemical structure of the side residues using semiempirical calculations based on the program AM1[30].

From the average values of the molar fractions of the tactic sequences in *Table 2*, the statistical parameters

Table 1 Physical data and spectroscopic characteristics of 4-HMA and 5-HMA

Compound	M.p. (°C)	Functional group	I.r. (cm^{-1})	^{1}H n.m.r. (ppm)
4-HMA	234	–CO*N*H–	3380	10.0
		–COOH–	3200–2500	11–12.2
		Ar–OH	3200	3.2–3.7
		–*C*ONH–	1650	–
		–*C*OOH	1680	–
		$CH_2 = C\langle$	1630	5.83 5.58
			1600, 1540, 1500	7.22–7.75 (eight peaks)
		α-CH_3	–	1.95
5-HMA	212	–CO*N*H–	3380	9.75
		–COOH	3200–2500	11–12.5
		Ar–OH	3200	3.2.–3.7
		–*C*ONH–	1655	–
		–*C*OOH	1675	–
		$CH_2 = C\langle$	1660	5.81 5.50
			1620, 1580, 1540	6.91–8.18 (eight peaks)
		α-CH_3	–	1.95

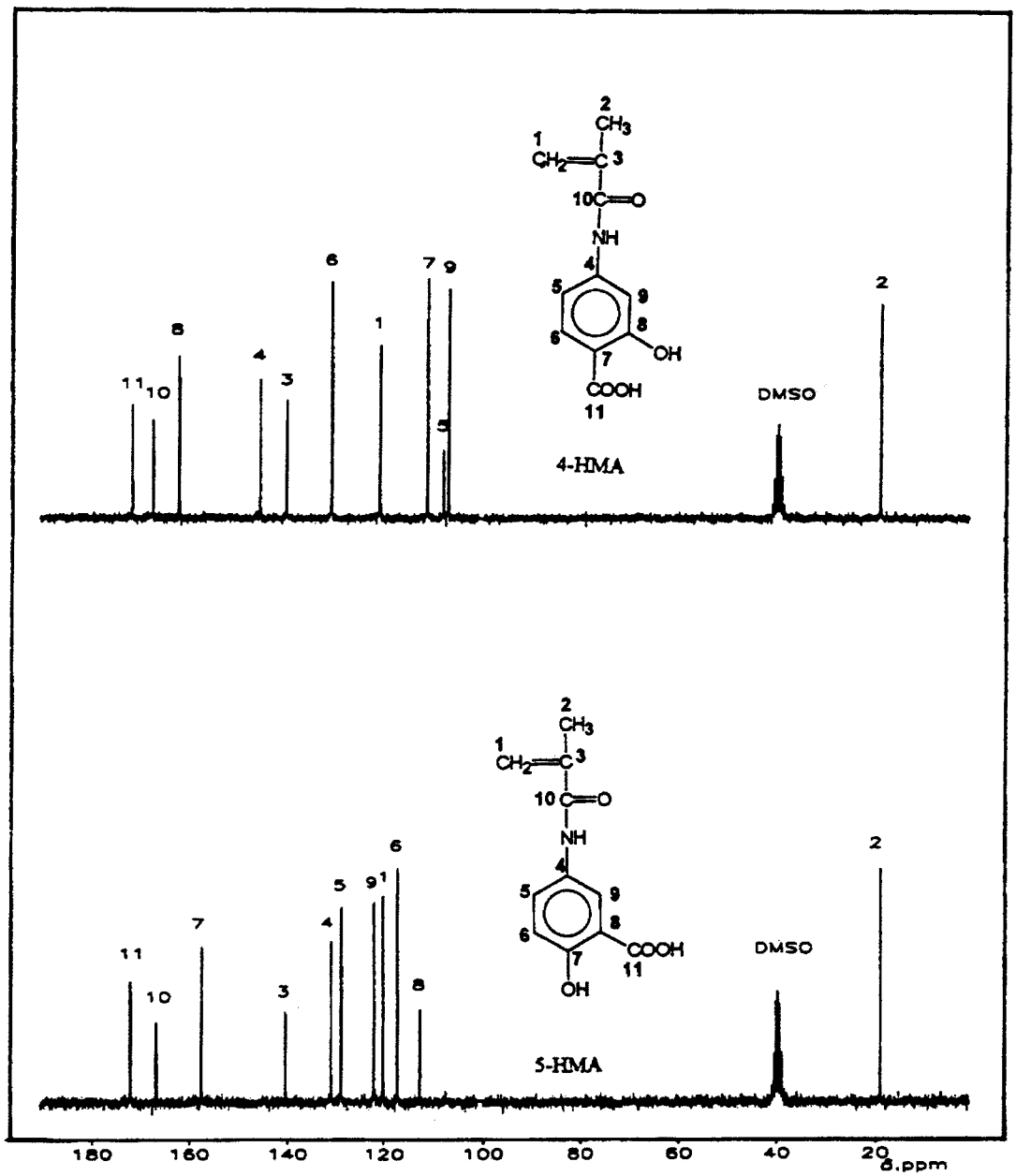


Figure 1 ^{13}C n.m.r. spectra (75.5 MHz) of samples of 4-HMA and 5-HMA recorded in DMSO-d_6

collected in *Table 3* were 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 configuration of the chain end, and j to the adding monomer), indicate a random distribution of the *meso* and *racemic* diads along the polymers chains since the sums $p(m/r) + p(r/m)$ are very close to the unity, closer in the case of 4-HMA[30].

According to these parameters, from the stereochemical point of view, the addition of the monomers 4-HMA and 5-HMA to their respective polymeric growing chains, is consistent with Bernoullian statistics, the isotacticity parameter $\sigma = 0.17$ for 4-HMA being very close to that reported by Hatada *et al.*[28] for the free radical polymerization of methacrylamide ($\sigma = 0.17$), and $\sigma = 0.20$ for 5-HMA close to the reported for MMA ($\sigma = 0.23$) on the basis of Bernoullian statistics.

It can be observed from these data that the statistical parameters which control the formation of isotactic sequences are slightly lower for the polymerization of

Table 2 Molar fractions of isotactic (*mm*), heterotactic (*mr* + *rm*) and syndiotactic (*rr*) triads of poly(4-HMA) and poly(5-HMA), determined from various ^{13}C n.m.r. resonance signals

Signal	*mm*	*mr* + *rm*	*rr*
Poly(4-HMA)			
α-CH_3	0.03_0	0.29_8	0.67_0
–C–	0.02_8	0.29_5	0.67_7
Average	0.02_9	0.29_6	0.67_3
Poly(5-HMA)			
α-CH_3	0.05_6	0.29_2	0.65_0
–C–	0.04_6	0.31_8	0.63_5
Average	0.05_1	0.30_5	0.64_2

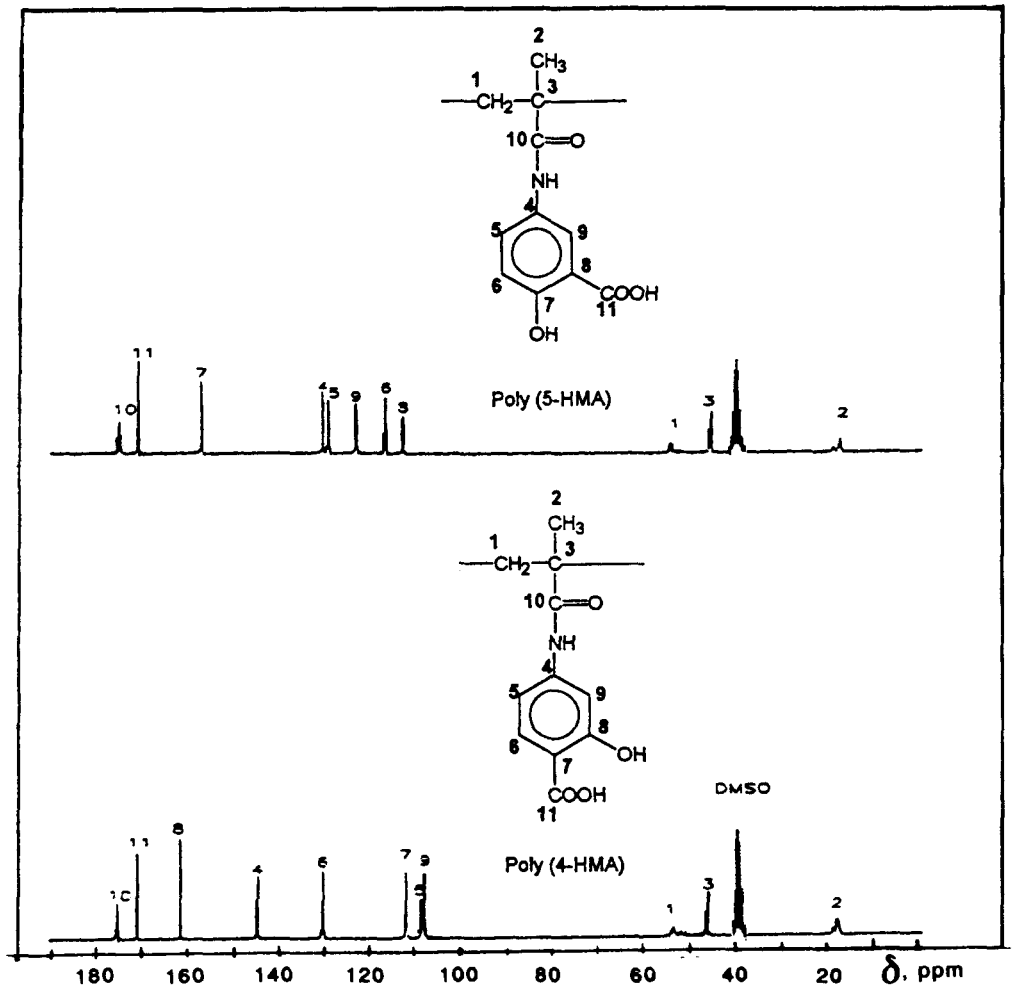
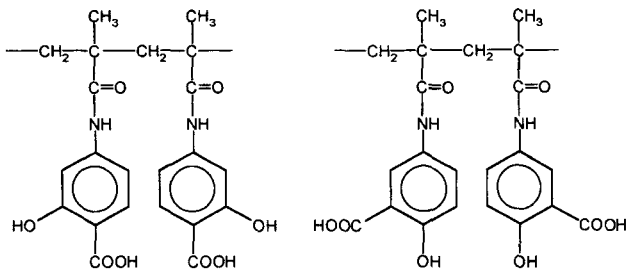


Figure 2 ^{13}C n.m.r. spectra (75.5 MHz) of samples of poly(4-HMA) and poly(5-HMA) recorded in DMSO-d_6



Scheme 2

4-HMA than for the polymerization of 5-HMA. This is a consequence of the isotacticity parameter values, $\sigma = 0.17$ for 4-HMA, 0.03 lower than that of 5-HMA ($\sigma = 0.20$). However, these differences do not modify drastically the random distribution of the stereochemical sequences along the macromolecular chains according to the Bernoullian trial.

Figure 4 shows the ^{13}C n.m.r. pattern of the amide carbonyl of poly(4-HMA) and poly(5-HMA) samples. In both cases, four signals of the ten possible pentad peaks are well resolved, in the interval 176.0–175.0 δ for poly(4-HMA) and 175.8–174.5 δ for poly(5-HMA), and nine sequences have been assigned in a similar way to those for PMMA[29,31,32] and for poly(methacrylamide)[33].

Table 3 Comparative stereochemical parameters of the free radical polymerization of 4-HMA and 5-HMA

Parameter	4-HMA	5-HMA
Additional probabilities		
P_m	0.17_7	0.20_3
P_r	0.82_1	0.79_4
P_{mm}	0.02_9	0.05_1
P_{mr+rm}	0.29_6	0.30_5
P_{rr}	0.67_3	0.64_2
Conditional probabilities		
p(m/m)	0.16_4	0.25_1
p(r/r)	0.82_0	0.80_9
p(m/r)	0.18_0	0.19_2
p(r/m)	0.83_6	0.75_1
p(m/r) + p(r/m)	1.01_6	0.94_3

Poly(4-HMA) signals are shifted downfield about 0.5 ppm than those of poly(5-HMA). However, the splitting and relative intensities of the resonance signals are rather similar in both cases, also showing slightly more syndiotactic character of poly(4-HMA) discussed previously. This is better shown in *Table 4*, which gives the values of the chemical shifts of the pentad signals, as well as the corresponding molar fractions of sequences, together with those calculated considering the Bernoullian statistics for the propagation steps, with the isotacticity parameters $\sigma = p_m$ given in *Table 3*. The excellent agreement between calculated and experimental data supports the assignment suggested in the present work.

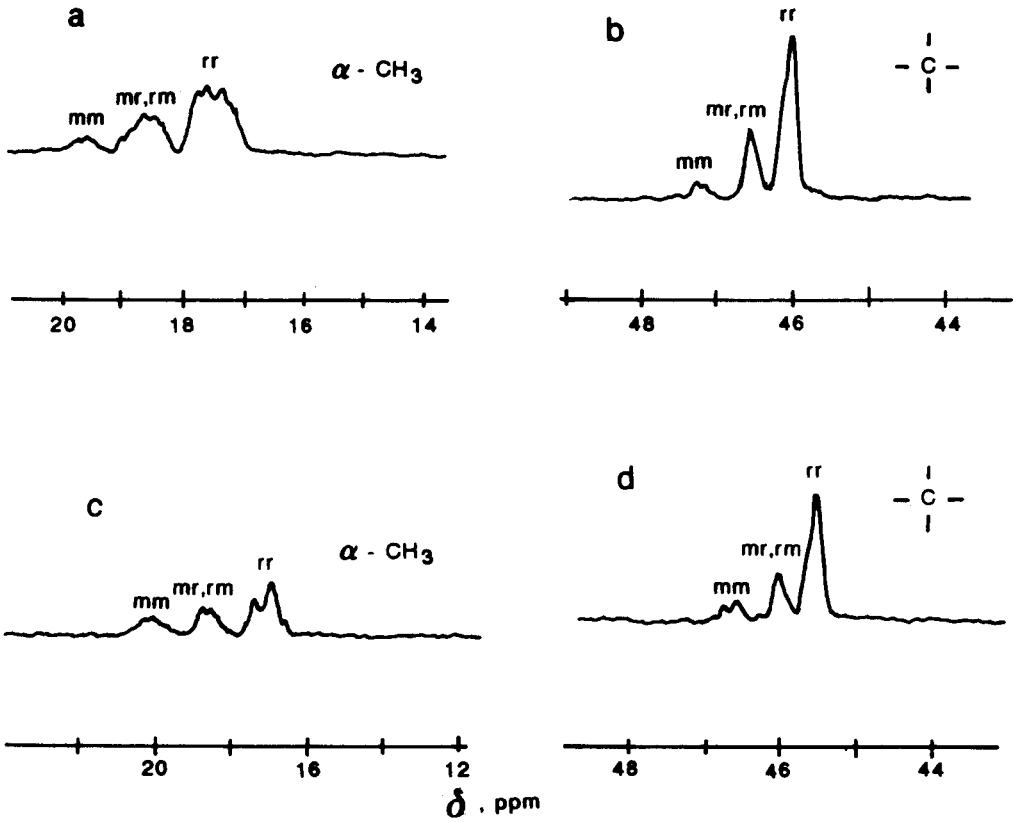


Figure 3 ^{13}C n.m.r. spectra (75.5 MHz) of: (a) α-CH_3 region of poly(4-HMA); (b) quaternary carbon atom region of poly(4-HMA); (c) α-CH_3 region of poly(5-HMA); (d) quaternary carbon atom region of poly(5-HMA)

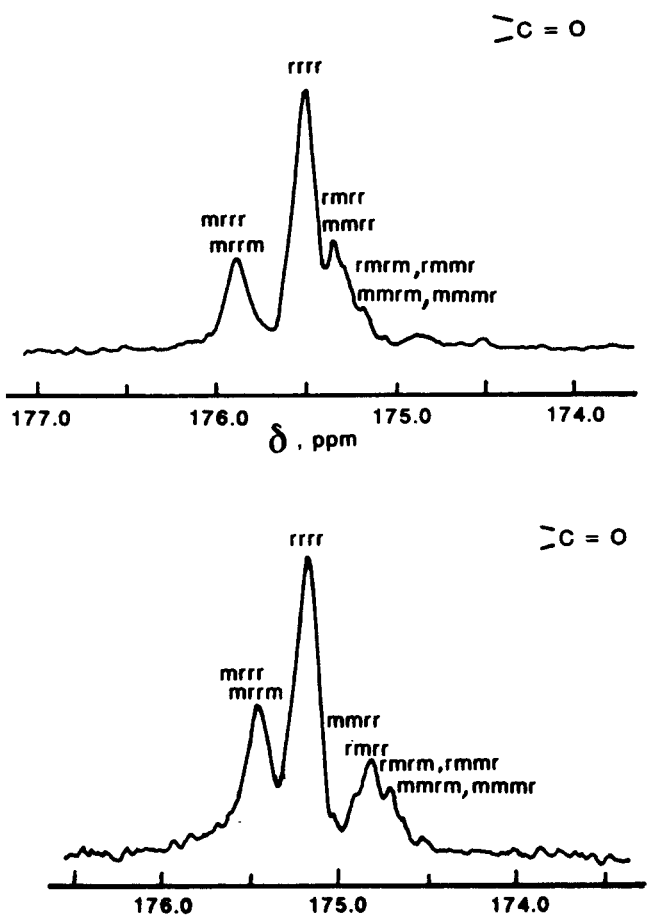


Figure 4 ^{13}C n.m.r. spectra (75.5 MHz) of the amide carbonyl carbon region of: (a) poly(4-HMA); (b) poly(5-HMA)

Table 4 Assignment of the ^{13}C n.m.r. resonance signals of the C=O amide group of both polymers, to sequences of tactic pentads

Sequence	Sequence molar fraction		
	δ (ppm)	Expt.	Calc.[a]
Poly(4-HMA)			
mrrm			
mrrr	175.8	0.20_3	0.21_8
rrrr	175.5	0.45_4	0.45_8
mmrr			
rmrr	175.3	0.25_1	0.23_9
rmrm			
rmmr			
mmrm			
mmmr	175.1	0.09_0	0.08_1
mmmm	–	–	0.00_1
Poly(5-HMA)			
mrrm			
mrrr	175.4	0.26_1	0.23_1
rrrr	175.1	0.41_7	0.40_3
rmrr			
mmrr	174.7	0.24_7	0.25_7
rmrm			
mrmm			
rmmr			
mmmr	174.0	0.07_4	0.10_4
mmmm	–	–	0.00_1

[a] Values calculated according to the Bernoullian trial with $p_m = 0.177$ for poly(4-HMA) and $p_m = 0.203$ for poly(5-HMA)

Another interesting characteristic of these polymers is their relatively low flexibility at room temperature, as is indicated by the relatively high glass transition temperatures, $T_\delta = 504$ K for poly(4-HMA) and $T_g = 534$ K for poly(5-HMA). This behaviour might be ascribed to the stiffness of the methacrylamide side substituent, and also to the intra- and inter-molecular hydrogen bonding between the hydroxy and carboxylic groups along the polymer chains. This is firstly supported by the T_g of the poly(4-hydroxyphenyl methacrylamide), synthesized in our laboratory, $T_g = 391$ K, indicating that the absence of hydrogen bonding between hydroxy and carboxylic groups lowers considerably the T_g in this compound, which also needs less free volume to reach the transition. On the other hand *FT*i.r. data of monomers and polymers, shows a wavenumber decrease of the carbonyl stretching vibration of the carboxylic group from monomer to polymer, supporting the idea of intra- and inter-molecular hydrogen bonding between the hydroxy and carboxylic groups (see *Figure 5*). In fact, it is possible to realise that the minimum at 1689 cm^{-1}, assigned to the carbonyl group of the carboxylic free residue of 4-HMA, is shifted about 17 cm^{-1} (1672 cm^{-1}) for the same group in the polymer (poly(4-HMA)). In the case of the acrylic isomer 5-HMA the carbonyl stretching vibration appears

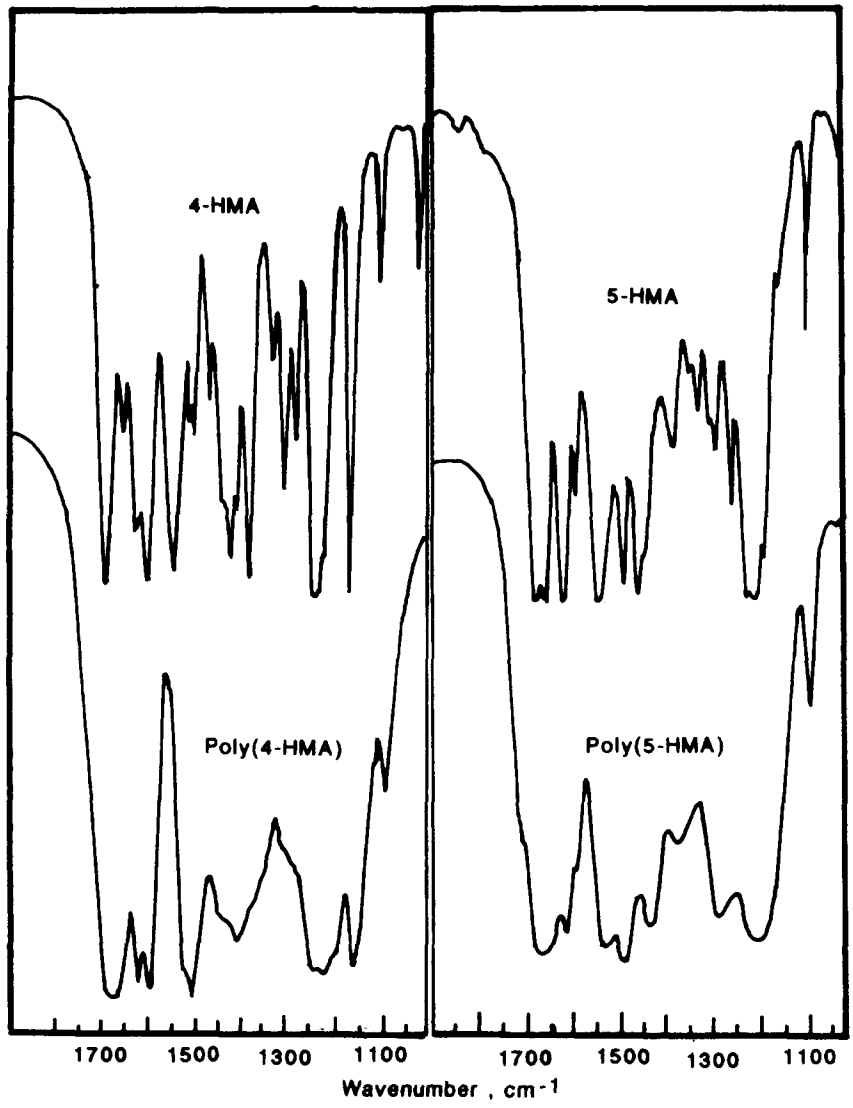


Figure 5 *FT*i.r. spectra of the carbonyl region of 4-HMA, 5-HMA, poly(4-HMA) and poly(5-HMA)

at 1681 cm^{-1} (see *Figure 5*), and it is only shifted 8 cm^{-1} (1673 cm^{-1}) for the polymer poly(5-HMA).

CONCLUSIONS

The methacrylamide derivatives of 4-aminosalicylic acid (4-HMA) and 5-aminosalicylic acid (5-HMA) can be prepared easily by the selective and direct reaction of the corresponding acid isomer with methacrylic anhydride or methacrylic chloride without side reactions under the appropriate experiment conditions.

The isomeric position of the phenolic –OH and carboxylic side groups, has a noticeable influence on the molecular weight of the product of the free radical polymerization, but only a slight effect on its tacticity giving rise to Bernoullian polymers with isotacticity parameters $\sigma = 0.17$ for poly(4-HMA) and $\sigma = 0.20$ for poly(5-HMA).

The stiffness of polymeric chains reflected by the T_g is higher for poly(5-HMA), $T_g = 534$ K, than for poly(4-HMA), $T_g = 504$ K, which can be explained in terms of the intra- and inter-molecular interactions of the polar –OH and –COOH groups of the side residues.

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