Polymers with pharmacological activity: 2. Synthesis and free radical polymerization of an acrylic derivative of phenacetin

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The present work reports the synthesis and free radical polymerization of 4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA), an acrylic monomer derived from paracetamol (4-hydroxyacetanilide), a non-prescription analgesic and antipyretic drug that in recent years has become an increasingly popular substitute for aspirin. The monomer prepared (MOEA) can be also considered an acrylic derivative of phenacetin (4-ethoxyacetanilide) whose major metabolite in the living body is paracetamol. The radical polymerization of MOEA has been carried out in solution of DMF, initiated by AIBN at temperatures in the range 50–140°C. The kinetic behaviour indicates that this compound presents a ceiling temperature of polymerization (T_c) of about 175°C in standard conditions ($|M| = 1$ mol/l). The results obtained are compared with those of the free radical of 4-methacryloyloxyacetanilide (MOA) studied previously. Both acrylic monomers differ only in the presence of an oxyethylenic spacer group in MOEA, which raises the T_c of MOEA by about 38°C with respect to that of MOA ($T_c = 137$°C).

(Keywords: 4-(2-methacryloyloxy)ethyloxyacetanilide; pharmacological polymers; radical polymerization)

INTRODUCTION

Synthetic polymers with biomedical applications are making an interesting contribution to the modern health care and in this sense, the chemical combination of pharmacologically active compounds with polymers is receiving considerable attention. The main objectives are to improve the duration of activity through the controlled release of the pharmacon linked to the polymer backbone[1–3], to obtain a more cell-specific uptake or to reduce the toxicity of the parent drug[4–7]. Macromolecular derivatives of drugs can be prepared by the chemical transformation of the drug into a reactive derivative suitable for polymerization or by binding the drug into an existing natural or synthetic polymer[8]. In most applications, the polymer is considered as a temporary carrier from which the pharmacologically active compound or the corresponding metabolite is released upon administration by the catalytic action of active enzymes[9].

In this connection we have reported in a previous paper[10] the synthesis and free radical polymerization of 4-methacryloyloxyacetanilide (MOA), an acrylic derivative of the well known antipyretic and analgesic compound Paracetamol (4-hydroxyacetanilide) which, in the last ten years, has become an increasingly popular substitute for aspirin. Paracetamol seemed to be remarkably safe in recommended doses but overdoses may have an acute hepatic toxicity[11–15]. The macromolecular systems prepared by the free radical polymerization of MOA were tested *in vivo* according to well known pharmacological methods[16] and the compounds studied (monomer and polymers) present average lethal doses ($DL_{50} > 400$ mg/kg) as well as interesting analgesic and anti-inflammatory activities.

In the present paper we wish to report preliminary studies on the synthesis and free radical polymerization of 4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA), which corresponds to the chemical structure of MOA but with the introduction of an oxyethylene spacer group between the acrylic ester group and the pharmacological active residue. The selection of this spacer group is not by chance, because the 4-(2-hydroxy)ethyloxyacetanilide (R–I), compound isolated as an intermediate in the synthetic route of MOEA, can be considered as an hydroxyl derivative of the drug Phenacetin, Paracetamol being the major metabolite of this compound in the living body[11].

Phenacetin has been listed as a carcinogen by the Environmental Protection Agency[17] and therefore the preparation and study of MOEA and their polymers and copolymers may be of great interest in order to provide the polymeric drug increasing durability, activity and reducing toxicity.

EXPERIMENTAL

Monomer synthesis

4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA) was prepared by a two-step reaction.

Synthesis of 4-(2-hydroxy)ethyloxyacetanilide (R–I). 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 16 g (0.2 mol) of 2-chloroethanol was added slowly. The reaction mixture was refluxed overnight and the solvent was evaporated. The isolated solid product was washed twice with ether, filtered off and dried under vacuum, yield, 90%; m.p. = 107 ± 1°C.

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4-(2-Methacryloyloxy)ethyloxyacetanilide (MOEA). 14.5 g (0.074 mol) of R–I was dissolved in 100 ml of an equimolecular mixture of dioxane/water and 10 g KOH. The solution 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 (0.1 mol) was then added dropwise. The 4-(2-methacryloyloxy)ethyloxyacetanilide precipitated in the reaction medium and after 2 h MOEA was filtered off and crystallized twice with methanol/water; yield, 50%; m.p. = 117 ± 1°C.

The MOEA was characterized by i.r., ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy. The i.r. spectra of the intermediate R–I and monomer MOEA are shown in *Figure 1* and the corresponding ^{1}H and ^{13}C n.m.r. spectra are shown in *Figures 2* and *3*.

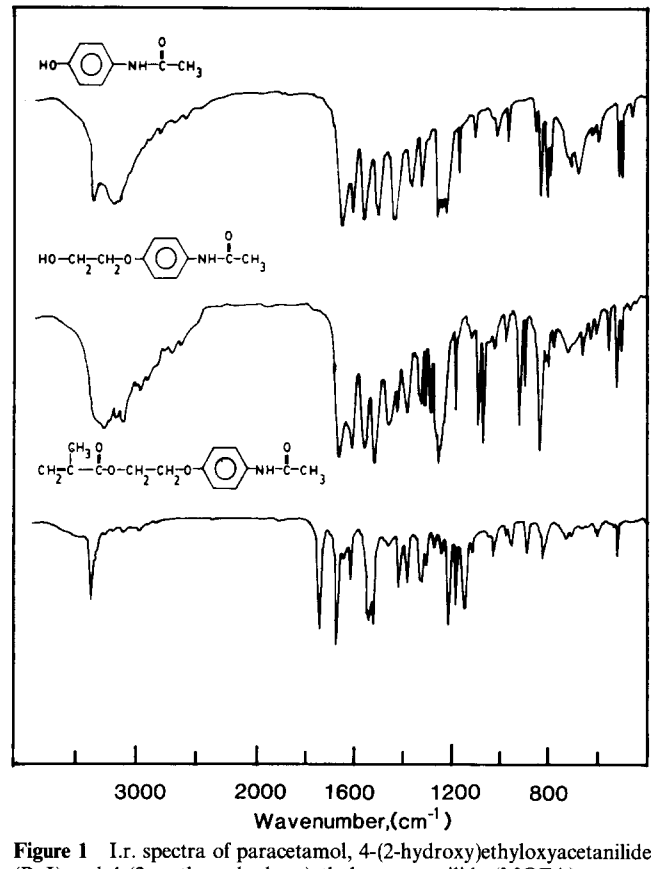


Figure 1 I.r. spectra of paracetamol, 4-(2-hydroxy)ethyloxyacetanilide (R–I) and 4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA)

Polymerization

The monomer, MOEA, was polymerized at different temperatures from 50 to 160°C, in a thermostatic bath regulated with a precision of ±0.1°C, using 2,2′-azobisisobutyronitrile (AIBN), ($|I| = 1.5 \times 10^{-2}$ mol/l), and dimethylformamide (DMF) as solvent ($|M| = 1$ mol/l). All experiments were carried out in Pyrex glass ampules sealed off at high vacuum (10^{-4} mm Hg). 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.

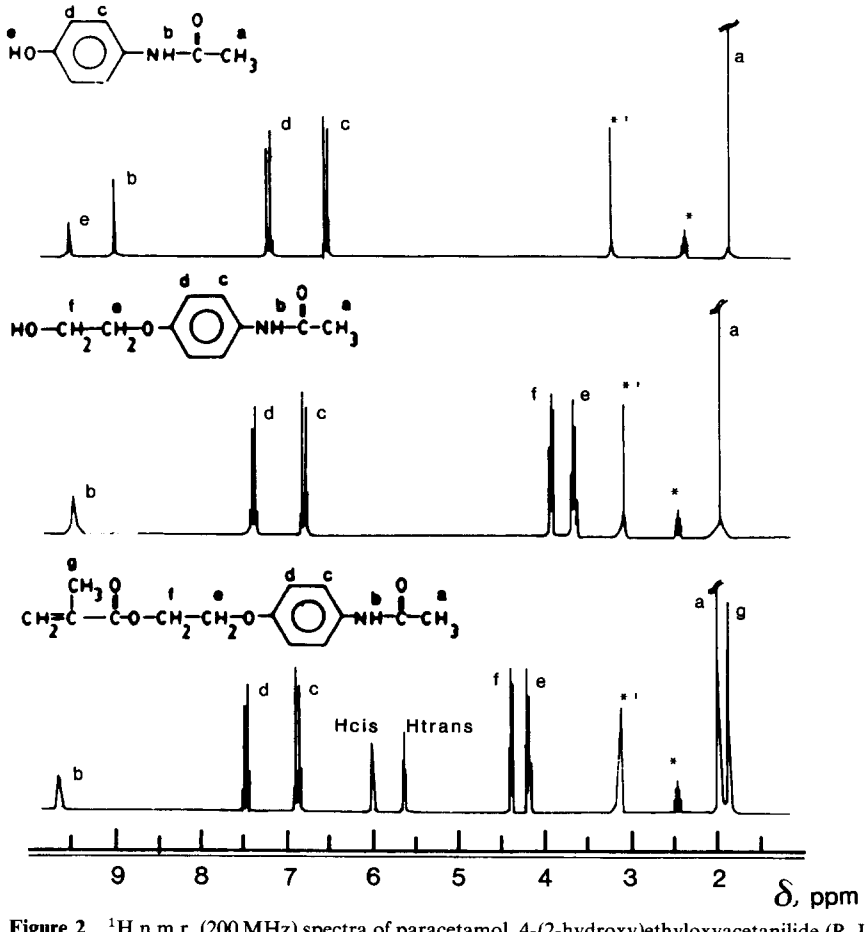


Figure 2 ^{1}H n.m.r. (200 MHz) spectra of paracetamol, 4-(2-hydroxy)ethyloxyacetanilide (R–I) and 4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA) *, DMSO-D_6 resonance signal; *′, H_2O associated with DMSO-D_6

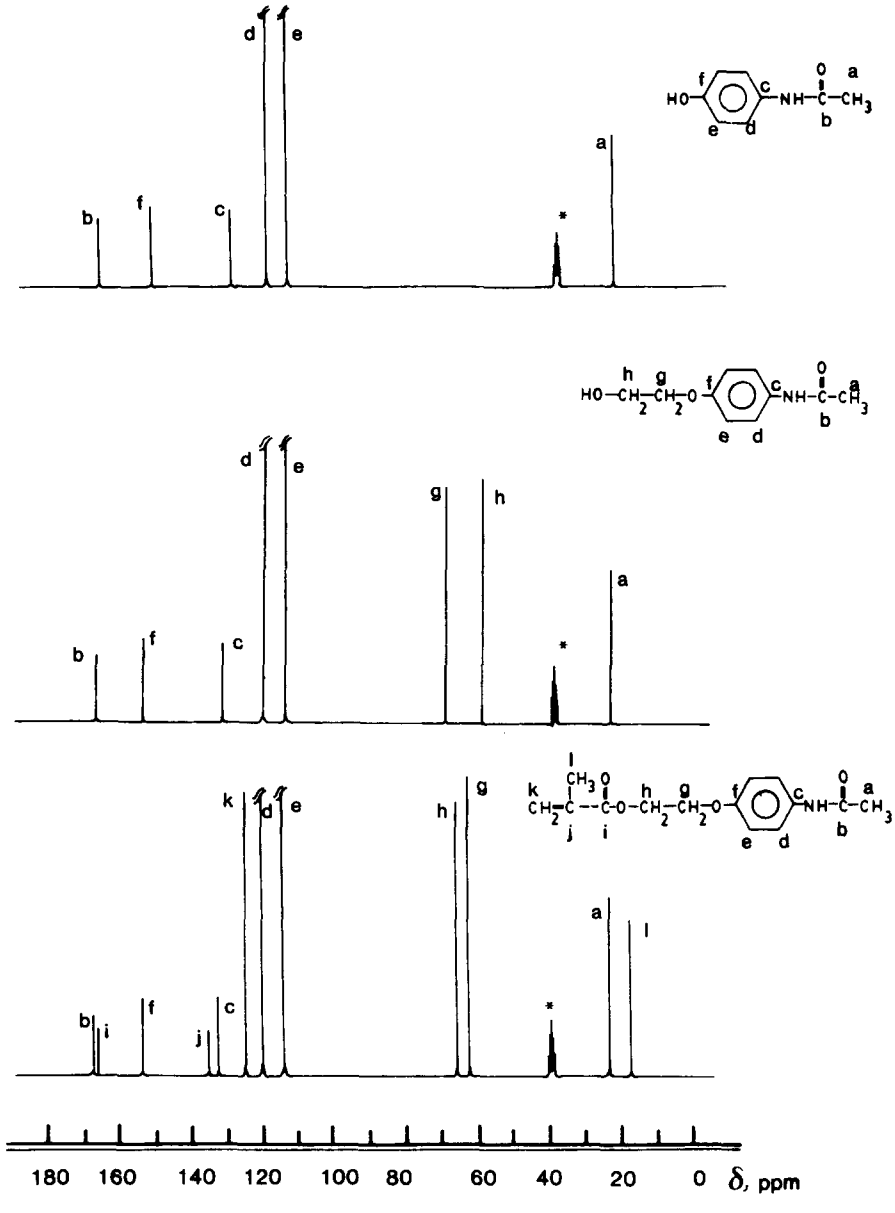


Figure 3 ^{13}C n.m.r. (50.3 MHz) spectra of paracetamol, 4-(2-hydroxy)ethyloxyacetanilide (R–I) and 4-(2-methacryloyloxy)ethyloxyacetanilide (MOEA) *, DMSO-D_6 resonance signal

Characterization of polymers

The monomer and all polymers were characterized by i.r. and n.m.r. spectroscopy. 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 dimethyl sulphoxide (DMSO) solutions on a Bruker AM-200.

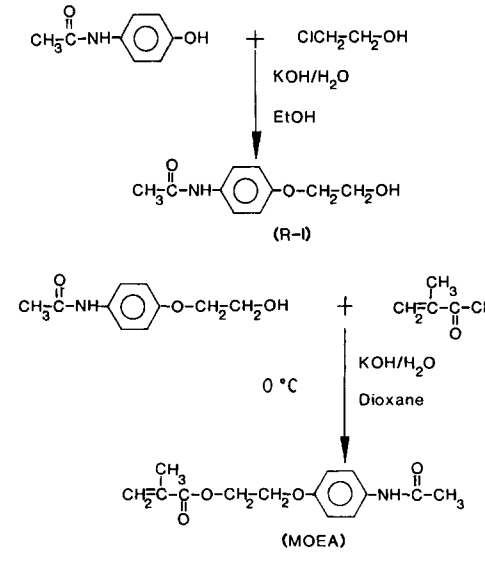
RESULTS AND DISCUSSION

MOEA was prepared according to Scheme 1.

The first step is a typical Williamson's reaction[18] which gives rise to the compound 4-(2-hydroxy)ethyloxyacetanilide (R–I) with good yield. The second is a modification of the known Schotten Bauman scheme[19] which permits the preparation of the acrylic derivative in mild conditions to avoid the uncontrolled polymerization of the double bond.

Figure 1 shows the i.r. spectra of starting product (paracetamol), intermediate (R–I) and acrylic monomer.

Scheme 1



The spectrum of MOEA shows absorption signals at 3300 cm^{-1} (–NH), 1730 cm^{-1} (COO, acrylic esters), 1660 cm^{-1} (–CONH, acetamido) and 1640 cm^{-1} (C=C, acrylic double bond).

Figure 2 shows the ^1H n.m.r. spectra of the products previously mentioned. The shift of the acetamido –NH resonance signal (from 9.1 to 9.6 ppm) by the substitution of the 4-hydroxy group by the ethylene oxide which produces a deshielding effect is noteworthy. This shift is also observed in the resonance signals c and d, which are assigned to the four aromatic protons. The esterification of the 2-hydroxyethylene group with the methacryloyl residue gives rise to a significant deshielding effect on the methylene e and f resonances which are shifted towards lower field by about 0.5 ppm.

Figure 3 shows the ^{13}C n.m.r. spectra of intermediate (R–I) and monomeric (MOEA) compounds. The esterification of the hydroxyethylene group gives rise to an appreciable shift of the monomer signals assigned to methylene carbons C–h and C–g, which are affected by opposite magnetic effects, i.e., the nearest C–h carbon resonance is shifted towards low magnetic field, whereas the C–g carbon resonance is shifted towards the high field by the esterification reaction.

The free radical polymerization of MOEA has been studied in solution of DMF at different temperatures in the interval 50–160°C. The concentrations of monomer and free radical initiator (AIBN) were 1 mol/l and 1.5×10^{-2} mol/l, respectively. *Figure 4* shows the conversion time diagrams at several polymerization temperatures in the interval studied. The free radical polymerization of MOEA in the experimental conditions mentioned above, follows a classical first order kinetic reaction at temperatures of 50 and 70°C, but at higher polymerization temperatures (i.e. 90, 120 and 140°C), the polymerization system tends to reach a relatively low limiting conversion. The level of this conversion degree decreases drastically with increase of the polymerization temperature. Moreover, experiments carried out at 150 and 160°C give apparent conversion degrees lower than 3 and 1 wt% respectively, and the polymeric species isolated by precipitation with cool methanol present the appearance of very viscous liquids. The decrease of the conversion degree with the increasing of polymerization temperature has been reported for the free radical polymerization of several α-substituted vinyl monomers[20] as well as acrylic monomers with different substituents

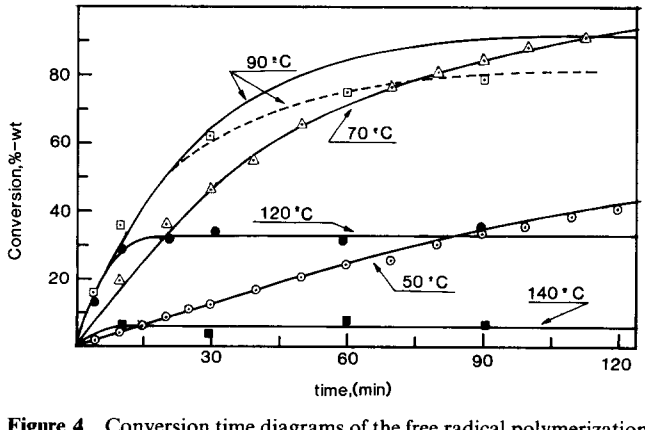


Figure 4 Conversion time diagrams of the free radical polymerization of MOEA at several temperatures. ——, theoretical diagrams according to equation (1); – – – –, curve fitting to the experimental points

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

Polymer temperature (°C)	$k_p/k_t^{1/2}$	k_d (s^{-1})
50	0.613	1.81×10^{-6}
70	0.694	2.90×10^{-5}
90	0.386	3.42×10^{-4}
120	0.197	8.70×10^{-3}
140	0.080	5.80×10^{-2}

of methyl at the α-position[21,22] or bearing alkyl or aryl ester groups with steric hindrance[23]. This behaviour has been ascribed to the existence of relatively low ceiling temperature (T_c) of polymerization for this kind of monomer, in such a way that at reaction temperatures relatively near to the T_c the depropagation process becomes important giving rise to a drastic decrease of the conversion degree.

The experimental results obtained seem to indicate that the MOEA presents a ceiling temperature relatively near to 160°C in the experimental conditions of the present work. This behaviour is rather similar to that of the polymerization of MOA[10], but the temperature interval at which the drastic decrease of the conversion degree is observed is different, and may be ascribed to the influence of the ceiling temperature of this monomer in the kinetic process[23,24].

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 conversion degree (X) with time can be written according to the equation:

$$\ln 1/(1-X) = 2k_p/k_t^{1/2}(f|I|/k_d)^{1/2}|1-\exp(-k_d t/2)| \quad (1)$$

Using the k_d values obtained from the Arrhenius equation of AIBN decomposition reported by Tullig and Tirrel[25] and considering a value of $f = 0.6$, we obtain the diagrams shown in *Figure 4*. The solid lines of this figure were drawn on the basis of equation (1) with a set of kinetic constants quoted in *Table 1*, whereas the broken line corresponds to the best curve fitting of the experimental points for the experiments carried out at 90°C.

It seems apparent from this figure that the free radical polymerization of MOEA in the experimental conditions of the present work deviates from the classical kinetic behaviour when the reaction system reaches conversions higher than 63–65% at a polymerization temperature of 90°C. However, the theoretical curves for the free radical polymerization of MOEA at 50 and 70°C seem to adequately fit the experimental points.

The concordance between theory and experiments observed at polymerization temperatures of 120 and 140°C, might be explained satisfactorily 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 conversion degree, independent of the polymerization time.

The ceiling temperature in free radical polymerization experiments is usually determined by the extrapolation to $R_p = 0$ of the diagram of the overall rate of polymerization (R_p) *versus* polymerization temperature[21]. In order

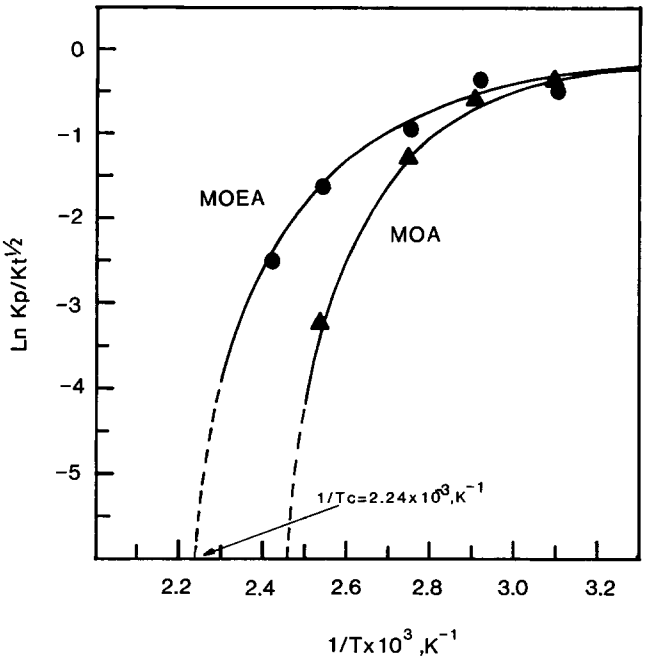


Figure 5 Kinetic diagram for the determination of the ceiling temperature of polymerization (T_c) of MOEA (●) and MOA (▲) according to the treatment suggested by Yamada *et al.*[27]

to avoid the effect of initiation rate on the observed overall polymerization rate, Yamada *et al.*[26] suggested the use of diagrams of $\ln(R_p/k_d^{1/2})$ *versus* polymerization temperature or the more useful $\ln(k_p/k_t^{1/2})$ *versus* the reciprocal of the polymerization temperature[27] (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 that approaches infinity at the ceiling temperature.

According to this treatment, *Figure 5* shows the diagram of $\ln k_p/k_t^{1/2}$ *versus* $1/T$ for the polymerization of MOEA. It is clear that this ratio decreases drastically for temperatures of polymerization beyond 70–80°C and it can be considered that an asymptotic value is reached at a temperature close to 175°C. Thus, the 4-(2-methacryloyloxy)ethyloxyacetanilide presents a T_c of 175 ± 2°C in the experimental conditions used in the present work ($|M| = 1$ mol/l). The diagram obtained for the free radical polymerization of MOA in the same experimental conditions[10] is also shown in this figure.

It is noteworthy that the diagrams are very close at low polymerization temperatures, far from the corresponding ceiling temperature of monomers, but there are clearly observed differences in the kinetic behaviour of both monomers when the reaction temperature approaches to the T_c of MOA. This fact indicates that the introduction of the ethylene spacer group between the polymer backbone and the rigid functional group, gives rise to a drastic increasing of the flexibility of the polymer segments (by the decreasing of the steric hindrance of the rigid aromatic side groups when they are located near to the polymer backbone), but does not appreciably modify the reactivities of the monomer and radicals. The analysis of proton and ^{13}C n.m.r. spectra of the polymer samples obtained[28], makes clear that the introduction of the oxyethylene spacer group also gives rise to a decrease of the dipolar interactions between the acetamido side groups and the acrylic ester groups of neighbouring units of the polymer segments. Therefore, the difference in the kinetic results may be ascribed to the influence of the propagation–depropagation process at each polymerization temperature for both monomers.

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