Synthesis, Characterization, and Kinetic Investigation of Acrylic Monomers Derived from Acetaminophen and ρ-Cresol as Model Drug Molecules

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ABSTRACT: In this work, the synthesis, characterization, and kinetic investigation of the free-radical polymerization of 4-acetylaminobenzene propenoic ester (ABPE) and 4-methylbenzene propenoic ester (MBPE) were studied. The kinetic behaviors of ABPE and MBPE in the polymerization initiated by azobisisobutyronitrile in dimethylformamide solutions at temperatures between 50 and 120°C were investigated, and experimental and theoretical conversion–time curves were compared. Both monomers showed a polymerization ceiling temperature (T_c). T_c was calculated with experimental values of $k_p/k_t^{1/2}$ with a constant concentration of 0.7 mol/L for monomers. T_c was about 141 and 131°C for ABPE and MBPE, respectively. In addition, the solvent effect on the polymerization reaction was investigated via the calculation of the solvent chain-transfer constant (C_s) for the ABPE monomer. Then, C_s was determined from the average degree of polymerization measured with gel permeation chromatography and the calculation of the overall rate of polymerization at 60°C. The results showed that dimethylformamide as a solvent had no effect on the rate of polymerization. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 100: 4369–4374, 2006

Key words: kinetics; synthesis; drug delivery; polymerization; ceiling temperature

INTRODUCTION

Synthetic macromolecules with potential pharmacological activity known as polymeric drugs or polymer-bonded drugs have attracted the considerable attention of a great number of scientific research groups during the last 25 years.[1–3] In this sense, the most interesting investigations are those in which pharmacologically active polymers are used as carriers for pharmaceutical agents widely used in medications.[4] One of the main ideas behind the use of pharmacologically active polymers is the depot effects that can be achieved with such drugs on the basis of the experience acquired with synthetic polymeric blood substituents and plasma expanders.[5] In addition to the properties of individual macromolecular chains, the behavior of pharmacologically active polymers is affected mainly by the nature of the functional groups of the pharmacological side groups. Polymer-bonded drugs avoid the problems of low-molecular-weight drugs, which can produce generalized toxic effects.

In general, the pharmacon is linked to the polymeric matrix via a degradable bond that is quite stable until it is affected by digestive intracellular enzymes or lysosomes.[6] In this sense, the synthesis and free-radical polymerization of *o*-metacryloyloxybenzoic acid and 4-metacryloyloxyacetanilide were previously studied, and they can be considered acrylic derivatives of the popular analgesic and antipyretic drug known as acetaminophen (4-hydroxyacetanilide).[7] The kinetic behavior of this kind of acrylic monomer is characterized by the existence of a relatively low ceiling temperature (T_c) of polymerization, which arises from the dipolar interactions and steric hindrance of aromatic or aliphatic side groups of active growing chain ends and the incoming monomer molecules. Thus, the value of T_c can be dramatically influenced by the flexibility of ester side groups. The main goal of this article is the study of the synthesis and kinetic investigation of the free-radical polymerization of 4-acetylaminobenzene propenoic ester (ABPE) and 4-methylbenzene propenoic ester (MBPE), which differ in the aromatic ester side group.[8–10]

EXPERIMENTAL

Materials

Acrylic acid, benzoyl chloride, ρ-cresol, dimethylformamide (DMF), acetaminophen, sodium hydroxide,

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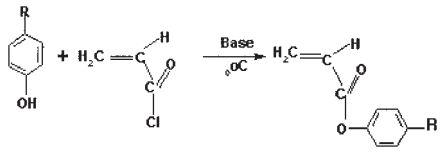


Scheme 1 R = —$NHCOCH_3$:Et_3N; R = —CH_3; base = NaOH.

and other chemicals were obtained from Merck and Aldrich Co. Acrylic acid was vacuum-distilled at 50°C in the presence of hydroquinone to separate the inhibitors.

Monomer synthesis

ABPE and MBPE monomers were prepared via the reaction of acryloyl chloride with acetaminophen and *ρ*-cresol in basic solutions at 0°C according to Scheme 1.

Unique method for the synthesis of acryloyl chloride

First, 141 g (0.7 mol) of benzoyl chloride and 36 g (0.5 mol) of acrylic acid were mixed in a 250-mL, round-bottom flask equipped with a 10-cm partial distillation column filled with 0.5-cm cylindrical packing and connected to a condenser. The entire system was under a vacuum of 10^{-2} mmHg. The mixture was heated to 150°C in an oil bath until the mixture boiled, and the acryloyl chloride gradually evaporated between 74 and 76°C and was collected after condensation in an ice bath. The reaction yield was 80%.

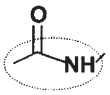
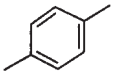
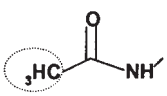
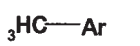
Synthesis of ABPE

First, 10.1 g (0.67 mol) of acetaminophen was dissolved in 200 mL of water and 12.38 g (0.12 mol) of triethylamine. The solution was cooled to 0°C in an ice bath, and then 8.23 g (0.09 mol) of freshly distilled acryloyl chloride was added dropwise with stirring. After 5 h, the precipitated ABPE was filtered off and crystallized twice with a methanol/water mixture. The reaction yield was 70%, and the melting point was 120°C. ABPE was characterized by Fourier transform infrared (FTIR) and ^{1}H-NMR spectroscopy, and the main signals observed in the spectroscopic determinations are listed in Table I.

Synthesis of MBPE

First, 5.42 g (0.05 mol) of *ρ*-cresol was dissolved in 100 mL of water and 5.26 g (0.052 mol) of sodium hydroxide. The solution was then cooled to 0°C, and freshly

TABLE I
Spectroscopic Data for ABPE and MBPE Monomers

	ABPE		MBPE	
Functional group	IR (cm^{-1})	^{1}H-NMR (ppm)	IR (cm^{-1})	^{1}H-NMR (ppm)
	3297	9.3		
	1262			
	1755			
	1661			
	1201		1745	
			1152	
	1504, 1552	7.9,7.74	1454	7.05, 7.1
	857, 802	7.26, 7.11	1507	7.15, 7.2
	1637	6.16		
	904, 998	6.56	1635	6, 6.5
	1300–1400	2.16		
			1404, 2925	2.35

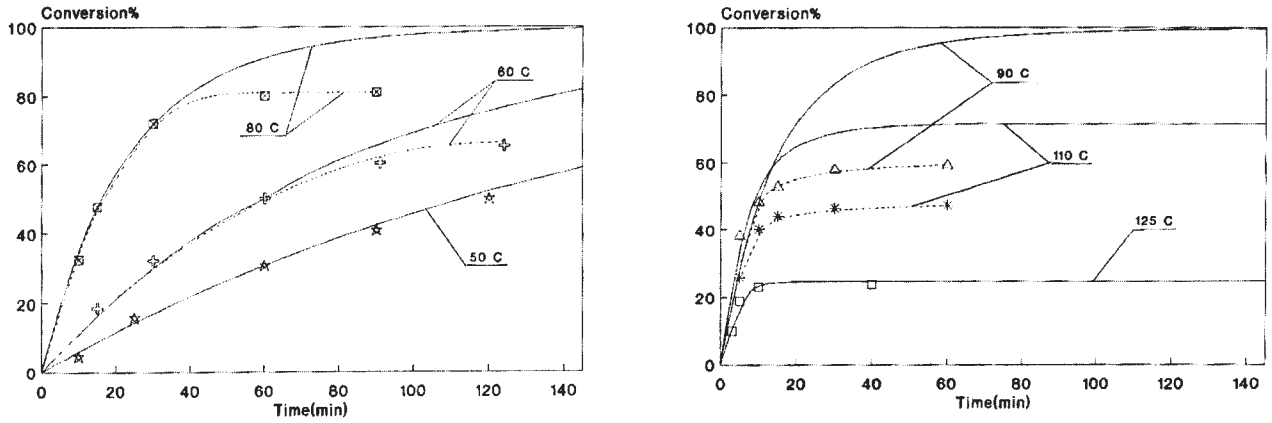


Figure 1 Variation of the conversion percentage against time for ABPE at different temperatures.

distilled acryloyl chloride was added dropwise with stirring. After 3 h, the mixture was warmed to 60°C for 1 h, and the yellow liquid that separated was decanted. It was shaken with 200 mL of a 5% sodium hydroxide solution and then was passed through a 4-cm-diameter and 30-cm-long preparative column packed with 230–400-mesh silica gel and eluted with dichloromethane.

Polymerization

The ABPE and MBPE monomers were polymerized with azobisisobutyronitrile [AIBN; initiator concentration ([I]) = 1.5×10^{-2} mol/lit] at different temperatures from 50 to 125°C in a thermostatic bath regulated with a precision of 0.1°C with a Tronic PTC 1000A temperature controller (Stuttgart, Germany) and with DMF as the solvent. All experiments were carried out in Pyrex glass ampules, which were sealed under a vacuum of 10^{-4} mmHg with a diffusion pump (Leybold Heraeus D2A, Munich, Germany) coupled with a rotary pump after three cycles of cooling and warming in liquid nitrogen. After the reported time, the mixture was added to an extra volume of cold methanol, and the precipitated polymers were filtered and, after being washed with methanol, were dried to a fixed weight at a low pressure.

Characterization

The monomers and polymers were characterized with FTIR and ^{1}H-NMR spectroscopy. FTIR spectra were recorded at room temperature in KBr pills for solid samples and in NaCl cells for liquid samples with a Bruker IFS48 apparatus (Ettlingen, Germany). ^{1}H-NMR spectra were recorded with a PerkinElmer instrument (MA, USA) at 80 MHz and with tetramethylsilane as a reference in a solution of deuterated chloroform $CDCL_3$ and deuterated dimethyl sulfoxide. Gel permeation chromatography (GPC) was used for measuring the average molecular weights of the polymers with a Waters 150C instrument (MA, USA), Styragel columns, and DMF as the mobile phase. For further study on medicine delivery from polymers, spectra were recorded with a Philips PU88co UV spectroscopy instrument (The Netherlands) for the determination of the delivered acetaminophen concentration.

RESULTS AND DISCUSSION

The ABPE and MBPE monomers, as shown in Scheme 1, were synthesized from reactions of acetaminophen and ρ-cresol with acryloyl chloride, respectively, according to the modified Shotten–Bauman method.[11] With this method, acrylic derivative monomers ABPE and MBPE can be produced after the phase transition under moderate conditions.[12,13] The free-radical polymerization of ABPE and MBPE was studied in DMF solutions at different temperatures (50–120°C);[7] the concentrations of the monomer and free radial initiator AIBN were 0.7 and 1.05×10^{-2} mol/L, respectively. Figures 1 and 2 show conversion–time diagrams for ABPE and MBPE polymerizations at different temperatures; comparing the theoretical and experimental data, we can see that the polymerization kinetics at 50 and 60°C obeyed first-order kinetics. However, at a higher temperature, the rate of polymerization was not compatible with a classical first-order kinetic equation. Actually, we were faced with a conversion limit, which was explained for monomers with low T_c's. It could be conceived that the conversion limit decreased dramatically when the reaction temperature increased. For example, just in a few minutes, the conversion limit reached 6–8 wt % at 125°C (Fig. 1). Furthermore, in the experiments, no polymer was separated at a temperature higher than 125°C by precipitating in cool methanol. Similar behavior for monomers with low T_c's such as 4-methacryloyloxy

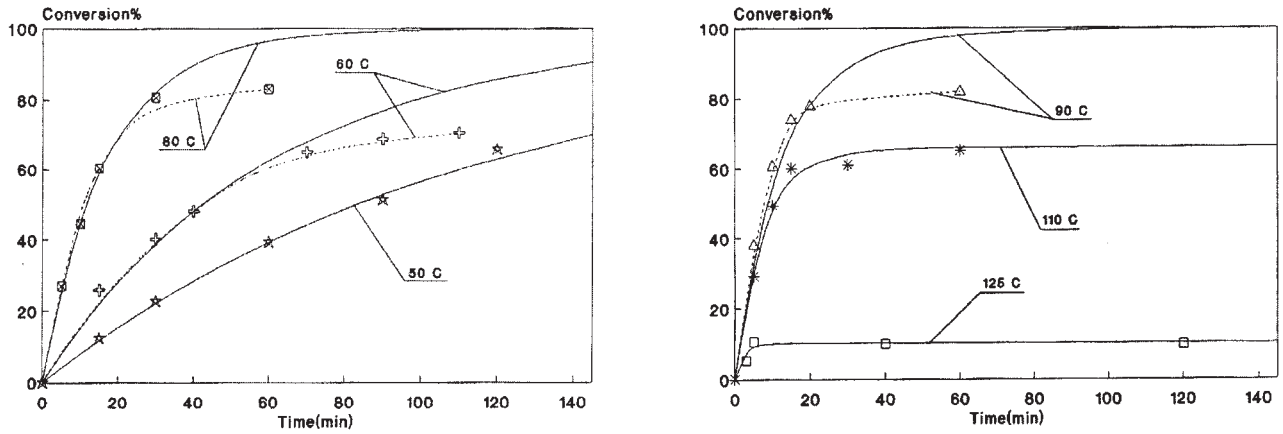


Figure 2 Variation of the conversion percentage against time for MBPE at different temperatures.

acetanilide and 4-methacryloyloxy ethylacetanilide has been reported.[14,15]

Accordingly, in the free-radical polymerization of ABPE and MBPE with respect to first-order kinetics,[16] for the thermal degradation of AIBN, radical addition to the monomer, and propagation and ending reactions, we have eq. (1):

$$\text{in}[1/(1 - x)] = 2(k_p/k_t^{1/2})(f[I]/k_d)^{1/2}[1 - \exp(k_d t / 2)] \quad (1)$$

$$k_d = 8.46 \times 10^{14} \exp(-30{,}439/RT) \quad (2)$$

where k_d is the initiator decomposition constant; R is the universal gas constant; T is temperature; t is time; and $1/(1 - x)$ is $[M_0]/[M]$ proportion of monomer concentration in different times.

With k_d obtained from the Arrhenius equation for AIBN reported by Tulig and Tirrell[17] [eq. (2)] and $f = 0.6$, diagrams were plotted in Figures 1 and 2. The bold curves represent eq. (1), with the calculated kinetic constants listed in Table II, and the dotted curves are the best fitted curves for experimental points. Therefore, the kinetics of polymerization for ABPE and MBPE showed a deviation from first-order kinetics when the reactions reached 40% conversion at 80°C and 15% conversion at 90°C.

The theoretical curves at 125°C were confirmed with experimental points. However, the low conversion limit at this temperature can be described by a comparison of the rate of the initiator concentration decreasing and the rate of the propagation–antipropagation equilibrium being reached.[18]

From these observations, T_c in free-radical polymerization is generally calculated by the extrapolation of the overall rate of polymerization (R_p) against the temperature at $R_p = 0$.[19] To avoid the initial effect on the rate of polymerization, we plotted $\ln(K_p/K_t^{1/2})$ versus T^{-1}.[20,21] In this situation, the diagram had to be a curve with an infinite slope at T_c. Figure 3 shows the diagram of $\text{In}(K_p/K_t^{1/2})$ versus T^{-1} for the free-radical polymerization of ABPE and MBPE; T_c was 141.4 and 131.7°C for ABPE and MBPE, respectively. Alternatively, Schulz[24] reported $T_c = 140$°C for the free-radical polymerization of methyl methacrylate with a monomer concentration [M] = 0.64 mol/L.

Further investigating the kinetic and thermodynamic parameters of the ortho compound substitution of phenyl methacrylates, Otsu et al.[22] showed that the rate of polymerization and numerical mean average

TABLE II
Free-Radical Polymerization Parameters for ABPE and MBPE in DMF at Different Temperatures

Polymerization temperature (°C)	ABPE			MBPE		
	$k_p/k_t^{1/2}$	k_d (S^{-1})	M_n	$k_p/k_t^{1/2}$	k_d (S^{-1})	M_n
50	0.961	1.81×10^{-6}	194976	1.301	1.81×10^{-6}	166234
60	0.9455	7.55×10^{-6}	147749	1.2604	7.55×10^{-6}	104606
80	0.923	1.023×10^{-4}	75926	1.273	1.032×10^{-4}	39085
90	0.8146	3.42×10^{-3}	51302	0.983	3.42×10^{-4}	24327
110	0.4425	3.127×10^{-3}	32833	0.694	3.127×10^{-3}	15754
125	0.1353	1.416×10^{-2}		0.082	1.416×10^{-2}	

M_n = number-average molecular weight.

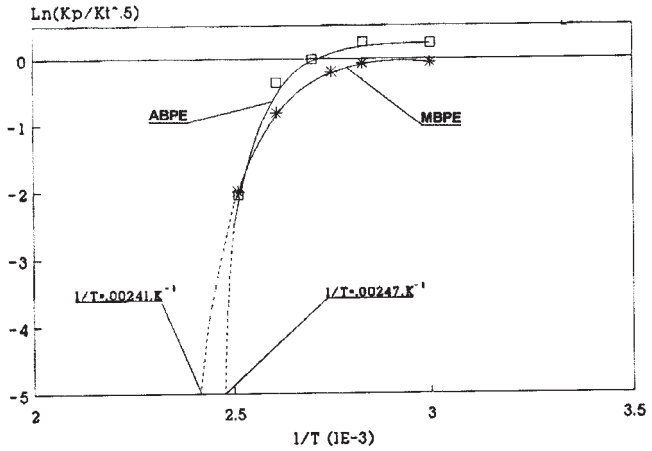


Figure 3 Kinetic diagrams for determining T_c for ABPE and MBPE.

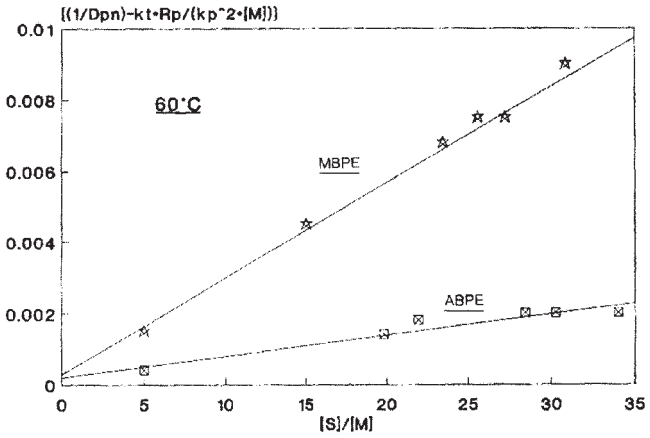


Figure 5 Determination of C_s at 60°C for ABPE and MBPE.

degree of polymerization (DP_n) decreased with an increasing volume of phenyl groups of ester. SanRoman et al.[23] suggested that the addition of substitution in the ρ-aromatic ring position had no effect on T_c, whereas ortho substitution, because of its space hindrance, had a remarkable effect on T_c. Therefore, with respect to T_c's of ABPE and MBPE, the reason for the lower T_c for ABPE was the type of substitution on the aromatic ring, which caused a rapid decrease in $\ln(k_p/k_t^{1/2})$ with the temperature. As a result, the amide group attracted growing radicals and caused $k_p/k_t^{1/2}$ to become smaller. The type of substitution had an effect on T_c even in the para region.

Figure 4 shows the variation in the average molecular weights of ABPE and MBPE as measured by GPC versus the temperature. A rapid reduction in DP_n for MBPE with respect to ABPE was quite obvious.

Solvent effect

Studies on the solvent effect are usually conducted with the Maio relationship,[24] which is written for a small amount of an initiator with a small ring-transition constant such as AIBN:

$$1/\bar{P}_n = k_t R_p/k_p^2[M]^2 + C_M + C_s[S]/[M] \qquad (3)$$

where [S] is the concentration of the solvent, P_n is the number-average degree of polymerization, and C_M and C_s are the transition constants for the solvent and monomer, respectively. A plot of $[1/P_n - K_t R_p/(K_p[M])^2]$ against [S]/[M] is a straight line with a slope of C_s.

Regarding the low value of transfer constant to initiator (C_1 for AIBN) which is negligible,[25] C_s for DMF was measured to be 6.625×10^{-5} and 2.7×10^{-4} for ABPE and MBPE, respectively, at 60°C ; both values are located in the region reported for other solvents.

In addition, a low value of C_s for a monomer containing acetaminophen somehow explains the influence of groups on the benzene ring (Fig. 5).

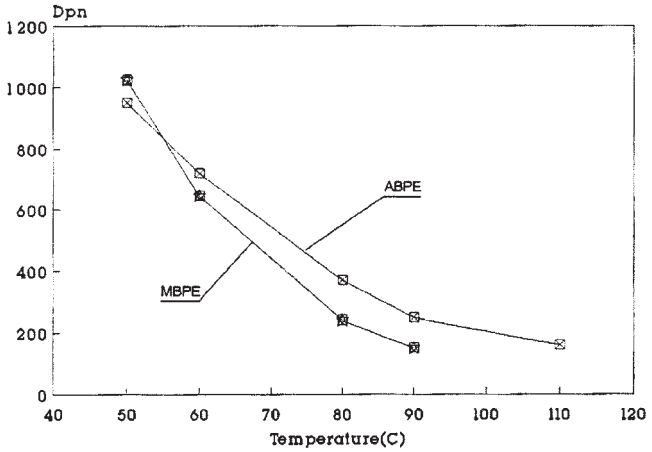


Figure 4 Variation in DP_n against the temperature for ABPE and MBPE.

CONCLUSIONS

A change in the aromatic ring substitution of the ester group in acrylic monomers causes a change in their kinetic properties for polymerization and affects the polymerization T_c value, which is a distinct characteristic of the free-radical polymerization reaction. Although ABPE and MBPE monomers show first-order polymerization kinetics at the low temperature of 50°C, they have T_c's when the temperature increases.

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