Polymer 50 (2009) 1270–1280

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Controlled degradation of poly(ethyl cyanoacrylate-*co*-methyl methacrylate) (PECA-*co*-PMMA) copolymers☆

Moon Gyu Han*, Sanghoon Kim

Cereal Products and Food Science Unit, National Center for Agricultural Utilization Research, Agricultural Research Service, United State Department of Agriculture, 1815 N. University Street, Peoria, IL 61604, USA

ARTICLE INFO

Article history:
Received 9 September 2008
Received in revised form
28 December 2008
Accepted 10 January 2009
Available online 18 January 2009

Keywords:
Poly(ethyl cyanoacrylate)
Radical copolymerization
Unzipping degradation

ABSTRACT

Copolymers of poly(ethyl cyanoacrylate-*co*-methyl methacrylate) (PECA-*co*-PMMA) with various compositions were synthesized by free radical bulk polymerization in an effort to control degradation and stability as well as glass transition temperature to overcome intrinsic poor processability of the poly(ethyl cyanoacrylate) (PECA) homopolymer. The copolymers were found to have an alternating random tendency, which was responsible for the efficient inhibition of the unzipping degradation from the polymer chain. Consequently, the stability of the copolymers at elevated temperature and in solution was significantly improved compared to the PECA homopolymer. The glass transition temperatures of the copolymers were lowered by the incorporation of the methyl methacrylate (MMA), thereby further widening the operating temperature range of the polymer. On the other hand, the copolymer films exhibited hydrolytic degradation in phosphate buffered saline (PBS) solution at 37 °C, which is promising for their use as novel biomaterials.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

It is well known that α-alkyl cyanoacrylate monomers are highly susceptible to anionic polymerization, even in the presence of a trace amount of weak bases such as water, alcohol, amines and phosphines [1–5]. Therefore, easy, fast, room temperature, and catalyst-free polymerization characteristic, as well as biodegradability of the monomers, have allowed successful application as nanoparticle drug delivery materials, super glue, or surgical glues [6–11]. Some other applications of these polymer homologues include the detection of latent fingerprints in crime investigations [12], plastic surgery [13], electron beam resists [14], and holographic recording [15].

Despite the above-mentioned merits, there are some limitations of the anionic polymerization of α-alkyl cyanoacrylate monomers over which radical polymerization method offers some attractive advantages. For example, radical polymerization of cyanoacrylate monomers can proceed without any anomalous behavior under suitable conditions and it is easier to control the reaction, compared to anionic polymerization. In addition, there can be more comonomer choices for the copolymerization due to the relatively small difference in reactivity even among structurally different monomers, which is difficult with the anionic polymerization pathway owing to the extremely low activation energy and fast rate of ionic polymerization of the cyanoacrylate monomers [16]. Furthermore, the cyanoacrylate monomers are the only monomers that form biodegradable polymers, among the monomers that are radically polymerizable, which is very promising for the creation of nanoparticle drug delivery systems or other functional colloidal particles through emulsion polymerization [17,18].

There exist considerable demands for functional polymers for various industrial applications. Copolymerization is one of the most successful and powerful methods for effecting systematic changes in polymer properties and endowing functional properties. The incorporation of two different monomers, having diverse physical and chemical properties, in the same polymer chain in varying proportions can lead to the formation of new materials. Therefore, copolymers having desired physical/chemical properties or even unexpected properties that cannot be observed in the individual homopolymers could be obtained by specially designed and controlled copolymerization. In the case of poly(alkyl cyanoacrylate)s (PACAs), there is a special need to prepare more stable polymers, particularly in developing adhesives and polymer composites because these polymers are intrinsically unstable at elevated temperatures, in contact with moisture, or even in dilute

---

☆ Mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.

* Corresponding author. Tel.: +1 309 681 6259; fax: +1 309 681 6685.
E-mail address: mghanm@gmail.com (M.G. Han).

0032-3861/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2009.01.027

solutions [19–22]. For example, the thermal degradation temperature of the poly(ethyl cyanoacrylate) (PECA) homopolymer is only slightly above its glass transition temperature (around 150 °C) [23], which significantly limits the application of this homopolymer due to its limited operating (or service) temperature and processing window. Therefore, the copolymerization of these alkyl cyanoacrylate (ACA) homologues with more stable comonomers would be one way to control the properties and obtain desired polymers. However, owing to the ease of rapid anionic polymerization of the monomer, no detailed study on its free radical copolymerization has been undertaken except for a few reports [17,24–26], even though free radical polymerization can be a viable method for synthesizing PACA copolymers.

To this end, we have developed radical copolymers with controllable degradability by using methyl methacrylate (MMA) as a comonomer for the polymerization of ECA. MMA was chosen based on its radical effectiveness, better thermal stability, structural similarity, and reported compatibility [27]. Poly(methyl methacrylate) (PMMA) is a hard, rigid, and transparent plastic with good weathering resistance, and is relatively easy to process, and therefore finds various industrial applications in opto-electronics. The degradation of the PACA homologues is known to follow an unzipping depolymerization from the chain end [19–22]. Therefore, the unzipping degradation may be suppressed by the presence of MMA units located in the polymer chain, due to the higher stability of PMMA [28]. In addition, the combination of the features of PMMA and PECA would make this functional copolymer an important class of material for advanced application if the properties could be controlled in a desirable manner. Herein, we report our methodology for tailoring the properties of the copolymers through radical copolymerization. The degradation properties as well as glass transition temperatures could be tuned by controlling the copolymer composition, which is important for the application of these materials in the various above-mentioned fields.

2. Experimental section

2.1. Materials

Ethyl cyanoacrylate monomer (E-Z bond, I-1605, contains 0–0.5% hydroquinone as an inhibitor) was purchased from K&R International. Acetone (HPLC grade, >99.9%), methanol (HPLC grade, >99.9%), hydrochloric acid (37%, ACS reagent grade), and methane sulfonic acid (>99.5%) were purchased from Sigma–Aldrich and used without purification. Acetone-d_6 (99.8% D atom, Acros Organics), 2,2′-azobis(2-methylpropionitrile) (AIBN, Sigma–Aldrich), ammonium acetate (molecular biology grade, Sigma–Aldrich), acetyl acetone (Fluka), acetic acid (from EM Science), and phosphate buffered saline (PBS, Sigma–Aldrich) were also used without further purification. Methyl methacrylate (MMA, Sigma–Aldrich) was purified by passing it through a column of activated basic alumina to remove the inhibitor.

2.2. Polymer synthesis

The poly(ethyl cyanoacrylate-*co*-methyl methacrylate) copolymers of various compositions (from 5 to 90 wt% of MMA in the feed) were obtained by bulk radical copolymerization of MMA and ECA monomers using AIBN as a radical initiator at a concentration of 0.3 wt% against total monomer mass at 60 °C in a sealed glass vial after purging the reaction vessel with nitrogen. The reaction vessel was pre-treated with acidified methanol (5 wt% of HCl in methanol) and dried to prevent possible anionic homopolymerization of the ECA monomer. In addition, a small drop of methane sulfonic acid was added to suppress inadvertent anionic polymerization. The reaction was carried out for 18 h to ensure high conversion of monomer to polymer. Homopolymers of PMMA and PECA were also synthesized with the same synthetic recipe. The polymerization of PECA in the absence of AIBN in this system was not occurred after 48 h of reaction in preliminary experiments, which means the anionic polymerization was successfully suppressed and only radical polymerization produced polymers. The homopolymers and copolymers were denoted as M followed by number, in which the number indicates the weight % of MMA used in the synthetic feed. For example, M30 means ca. 30 wt.% of MMA was used in the feed. The polymerized samples were then dissolved in acetone to obtain molecular weight distribution data by Gel Permeation Chromatography (GPC). Portions of the polymers were then isolated by precipitation with large volumes of acidified methanol, filtered with a Buckner funnel, washed twice with methanol and water, and dried under vacuum before conducting other analyses.

2.3. Characterization

2.3.1. Molecular weight

Molecular weights of the polymers were measured with a GPC (Shimadzu, Japan) equipped with auto injector (SIL-10AD VP), column oven (TO-10AS VP), liquid chromatograph pump (LC-10AT VP), and GPC column (Showdex, GF-510 HQ) at 25 °C using acetone as an eluent at a flow rate of 0.3 mL/min. Two detectors, refractive index (Optilab DSP Interferometric Refractometer, Wyatt Technology) and light scattering (DAWN EOS, Wyatt Technology) were used to detect and record GPC output. Poly(methyl methacrylate) (PMMA) standards were used for molecular weight calibration. Specific refractive index increment ($\mathrm{d}n/\mathrm{d}c$) values were measured to be 0.1335 and 0.126, respectively for PECA and PMMA in acetone at 690 nm by refractive index detector. These values were used to determine absolute molecular weights and molecular weight distributions of the copolymers by adopting additive rules of refractive index increment using the following expression [29,30]:

$$\mathrm{d}n/\mathrm{d}c = (\mathrm{d}n/\mathrm{d}c_\mathrm{m})w_\mathrm{m} + (\mathrm{d}n/\mathrm{d}c_\mathrm{e})(1 - w_\mathrm{m}) \tag{1}$$

where $\mathrm{d}n/\mathrm{d}c_\mathrm{m}$ and $\mathrm{d}n/\mathrm{d}c_\mathrm{e}$ are the refractive indices' increment for MMA and ECA, respectively. w_m is the weight fraction of MMA monomer in the copolymer.

2.3.2. NMR spectroscopy

^{1}H NMR spectra of the homopolymers and copolymers were obtained on a Bruker Avance 500 MHz using a 5 mm BBI probe. All polymer samples for NMR experiments were dissolved in acetone-d_6 to prepare an approximately 5 wt% (w/v) solution. The compositions of the copolymers were determined from the areas of the characteristic NMR peak of each component, from which the monomer reactivity ratio was calculated.

2.3.3. Thermal analysis

The glass transition temperatures of the homopolymers and the copolymers were measured with a modulated DCS (DSC 2920, TA Instrument). 30–40 mg of powder sample was placed in a high volume pan and sealed. The samples were heated to 170 °C and cooled down to 5 °C. This heating and cooling cycle was repeated twice at a scan rate of 10 °C/min for all samples. In order to obtain similar thermal histories for each sample, glass transition temperatures (T_gs) were determined from the second scan and the midpoint of the transitions was taken as T_g. Thermal degradation and the resulting weight loss of the samples were obtained by thermogravimetric analysis (TGA). The TGA experiments were carried out under a nitrogen purge from 20 °C to 800 °C at a scan rate of 20 °C/min with a Thermogravimetric Analyzer (TGA 2050, TA Instruments).

2.3.4. Hydrolytic degradation

To carry out hydrolysis experiments, the films of homopolymers and copolymers were prepared by solvent casting on a Petri dish at room temperature after dissolving the polymers in acetone at approximately 5 wt%. After 24 h of slow evaporation of the acetone, freestanding transparent films with ca. 100 μm of thickness were obtained. Specimens with dimensions of 25 mm × 25 mm × 0.1 mm were then cut from the films. The solvent in the films were further evaporated and placed into vials with 20 mL of a phosphate buffer solution (pH = 7.4) and the hydrolytic degradation was allowed to proceed in an incubator at 37 °C with 100 rpm of shaking for 14 days. The released formaldehyde content from the hydrolytic degradation of the polymers was studied by measuring the absorption maximum of the UV–Vis spectra (UV–VIS 1601, Shimadzu) after reaction of the PBS solution containing degraded product with an equal volume of Nash reagent for 2 h. Nash reagent was prepared by dissolving 30 g of ammonium acetate, 0.4 mL of acetyl acetone, and 0.6 mL of acetic acid in de-ionized water to make a total of 1000 mL solution [31]. The color of the mixed solution turned yellow due to the formation of the diacetyldihydrolutidine (DDL). The absorbance at 413 nm was used to calculate the quantity of released formaldehyde using the Lambert–Beer law. The calibration curve was previously obtained by using various concentrations of neat formaldehyde in de-ionized water, covering the concentration range from 0.006 μg/mL to 1.67 μg/mL. A linear plot between the concentration of formaldehyde and the absorption maximum was obtained.

3. Results

3.1. Synthesis of PMMA, PECA, and PMMA-co-PECA copolymers

The synthesis of homopolymers and copolymers with various molar compositions was achieved via bulk free radical polymerization by dissolving 30 mg of AIBN into 10 mL of monomer, or a mixture of comonomers, at 60 °C for 18 h. The average molecular weights and molecular weight distributions of the resulting homopolymers and copolymers are summarized in Table 1. GPC chromatographs show a typical unimodal peak, which indicates the successful preparation of the copolymer. The weight average molecular weights of the copolymers are varied, in the range of 200,000–620,000 (g/mol) depending on the compositions. The polydispersity indices are also varied but show narrower molecular weight distribution when relatively small amounts (up to 30 wt%) of MMA were used. In the radical homopolymerization of MMA or ECA, the growing chains usually undergo chain termination by disproportionation in addition to combination, and the molecular weight may also be limited by the chain transfer to the monomer because of a large transfer constant. Therefore, the polydispersity indices of around 1.5 are acceptable values. Preliminary experiments revealed that the molecular weight distribution was dependent on the AIBN/monomer molar ratios: a higher amount of AIBN decreased molecular weight and increased molecular weight distribution. As a result, 0.3 wt% of initiator to total monomer amount was used for all synthetic protocols reported here.

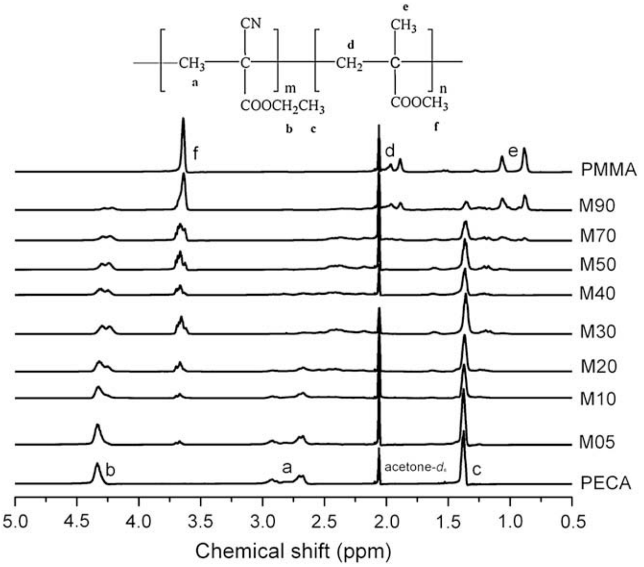


Fig. 1. ^{1}H NMR spectra of PMMA, PECA, and PECA-*co*-PMMA with various compositions.

Fig. 1 displays ^{1}H NMR spectra of homopolymers and copolymers with various compositions. The NMR spectrum of pure PECA is listed at the bottom. Chemical shifts at δ 4.17 and δ 1.38 ppm are due to the protons of ethyl side groups CH$_3$ (b) and CH$_2$ (c), respectively [19,32]. On the other hand, broad peaks located at δ 2.6–3.0 are from backbone CH$_2$ (a). NMR spectrum of the pure PMMA is displayed at the top, which shows characteristic chemical shifts for various proton groups, OCH$_3$ (f), backbone CH$_2$ (d), and α-CH$_3$ (e) [33]. The

Table 1

Copolymerization data of MMA (M_1) and ECA (M_2) as a function of monomer–copolymer composition; weight average molecular weights (M_ws), polydispersity index (PDI, M_w/M_n), mean sequence lengths (μ_1, μ_2) and probability (P_{ij}) for different homo- and heterodiad linkages.

Sample name	[M$_1$] in feed (mol%)	[M$_1$] in copolymer[a] (mol%)	M_w[b]	M_w/M_n[b]	Homodiad[c]		Heterodiad[c]		Mean sequence length[d]	
					P_{11}	P_{22}	P_{12}	P_{21}	μ_1	μ_2
M0	0	0	679,000	1.54	–	–	–	–	–	–
M05	0.062	0.068	308,000	1.69	0.03	0.92	0.97	0.08	1.03	12.60
M10	0.122	0.128	388,000	1.55	0.06	0.85	0.94	0.15	1.06	6.80
M20	0.238	0.246	503,000	1.45	0.12	0.72	0.88	0.28	1.13	3.60
M30	0.349	0.342	629,000	1.33	0.18	0.62	0.82	0.38	1.21	2.63
M40	0.455	0.405	416,000	3.27	0.20	0.59	0.80	0.41	1.24	2.43
M50	0.556	0.485	458,000	1.81	0.28	0.47	0.72	0.53	1.39	1.90
M70	0.745	0.599	180,000	2.62	0.38	0.36	0.62	0.62	1.61	1.57
M90	0.918	0.844	320,000	1.90	0.69	0.14	0.31	0.86	3.21	1.16
M100	1	1	516,000	1.95	–	–	–	–	–	–

[a] Obtained from ^{1}H NMR measurement.

[b] Obtained from GPC analysis.

[c] P_{ij} is the probability for the *ij* diad linkages in the copolymer calculated using equation (8).

[d] Calculated from equations (6) and (7).

comonomer sequence is one of the main factors that influences copolymer properties and can be obtained by tracing the composition of the polymer. Since the NMR signals of f and b are well separated, the ratios of the monomers in the copolymer could be obtained by calculating integrals of the characteristic peaks in the ^{1}H NMR. From the relative areas of proton resonances of the signals, the area of the signals of CH_3 assigned to MMA (A_f) and that of the signals of methylenic protons (CH_2) (A_b) assigned to ECA, the copolymer compositions were calculated using the following equation,

$$\mathrm{MMA(mol\%)} = 2A_f/\left(3A_b + 2A_f\right) \tag{2}$$

The feed monomer compositions and the calculated monomer compositions in the copolymers, using this equation at each feed ratio, are also listed in Table 1. The relationship between feed compositions and polymer compositions is also displayed in Fig. 2. The copolymer is richer in MMA when a relatively smaller amount of MMA was used and is richer in ECA component beyond the crossover point. This composition curve shows that the cross-propagation is favored over homo-propagation. This suggests the tendency towards alternation in this copolymer system. The observed azeotropic composition is around 35 mol% of MMA.

3.2. Thermal transition of the copolymers

The thermal properties of the copolymers are influenced by their chemical structures, compositions, and the monomer sequence distributions. To observe the thermal properties of the polymers, homopolymers and copolymers were subjected to differential scanning calorimetry (DSC) and the results of these experiments are shown in Fig. 3(a). The glass transitions of the polymers are well defined and clearly observable. The glass transition temperature (T_g) of PMMA appears at around 106 °C and that of PECA is located at 145 °C. The observed T_g of PECA is coincident with the previous researcher's results, which report the glass transition in the range of 410–440 K [34,35], and that of PMMA is also in the range of atactic PMMA [36]. With increasing MMA content, the T_g of the copolymer has a tendency to decrease, as is usually observed in the case of general copolymers. These experimental values of T_g were compared with the values predicted by using the well-known Fox equation [37,38], in which the variation of the T_g of the random copolymers, consisting of monomer units MMA and ECA, can be determined with respect to the weight fraction of the monomer units and T_g of the corresponding homopolymers, as is described below.

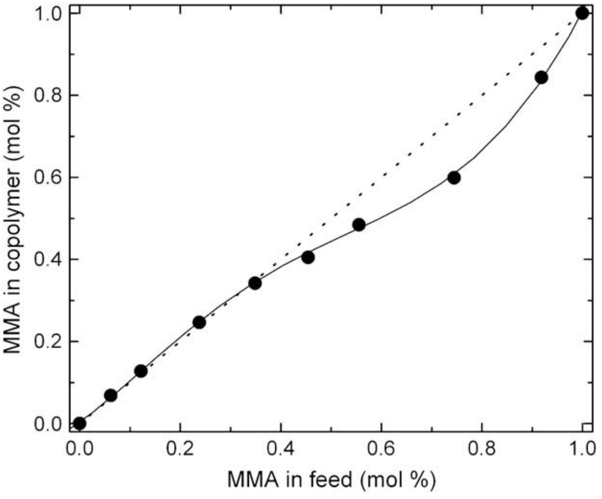


Fig. 2. Mole fractions of MMA in the copolymers versus mole fractions of MMA in the feed. Dotted line is an ideal copolymerization composition plot when the reactivity ratios of both monomers are one ($r_1 = r_2 = 1$).

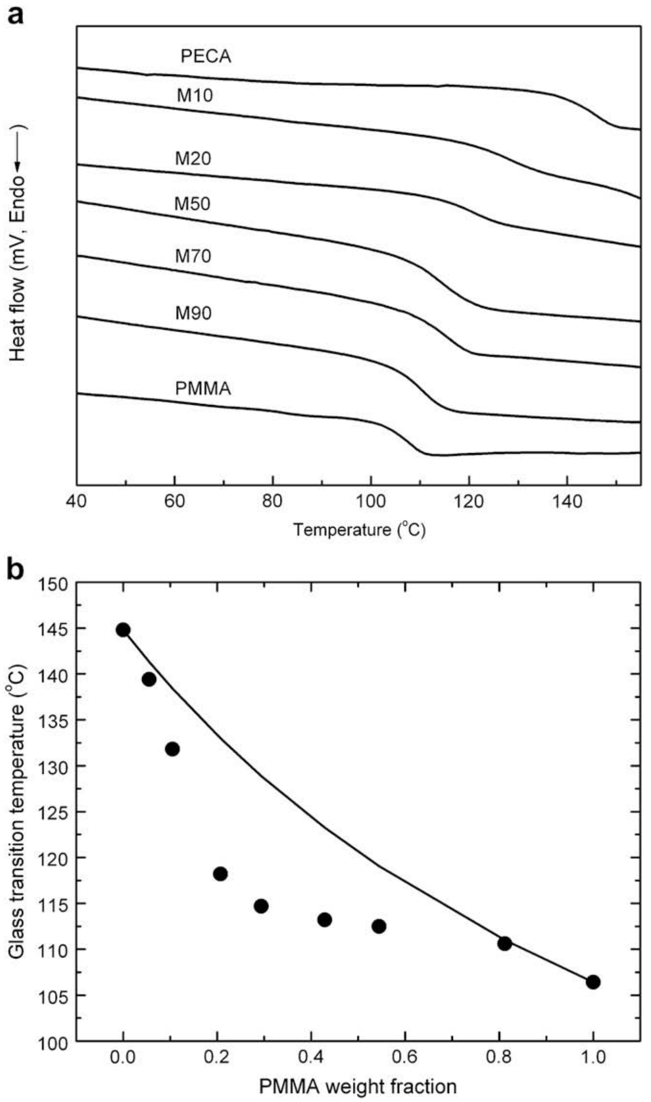


Fig. 3. Representative differential scanning calorimetry (DSC) thermograms of pure PMMA, PECA, and PECA-*co*-PMMA with various compositions (a), and the glass transition temperatures of PMMA, PECA, and PECA-*co*-PMMA as a function of composition (b) (solid line is the fitted curve using Fox equation).

$$1/T_g = W_1/T_{g1} + (1 - w_1)/T_{g2} \tag{3}$$

where T_{g1} and T_{g2} are the T_gs of pure PMMA and PECA, respectively. w_1 is the weight fraction of MMA in the copolymer. There are some variations between experimental results and predicted values, as is shown in Fig. 3(b). The experimental values are lower than the predicted ones, especially in samples containing similar amounts of each component, though they exhibit a general pattern of decrement of T_g with increasing amount of MMA. The Fox equation is known to have limitations because it does not account for factors such as molecular weight, tacticity, chain mobility, steric and energetic interaction between each component, and monomer sequence distribution, but based only on thermodynamic and free-volume theories of the glass transition. In addition, this equation is usually only good for random copolymers. The rapid decrease of the

T_g with the introduction of the MMA component may be explained in terms of an alternating nature of the copolymers. The transition temperature intervals of the copolymers with low MMA content (M05–M20) are a little broad, indicating a possible gradient composition of the copolymers. The deviation of the T_g value from the Fox equation suggests that the copolymer is not totally random and that the interaction between the two components played a major role in the transition temperature. It is worth noting that the sudden drop in the glass transition temperature of the copolymers, induced by introducing a small amount of the MMA, is very promising in regard to overcoming the limited operating temperature of PECA, provided the thermal stability is not deteriorated.

3.3. Thermal degradation

The thermal degradation properties of the homopolymers and the copolymers were investigated by TGA, as is presented in Fig. 4. In Fig. 4(a), PECA starts losing weight at around 220 °C, shows maximum degradation at around 275 °C, and is completely degraded at around 310 °C, which is an enhancement of thermal stability over that of PECA synthesized by the zwitterionic or anionic pathway [19,20]. But, a minor degradation actually starts at around 160 °C as can be observed in the DTG curves in Fig. 4(b), indicating degradation of a small portion of the polymer. This degradation temperature is similar to the temperature of the starting point of the degradation observed in our previous report on anionic/zwitterionic PECA [19]. This is due to the formation of a different chain end, which stems from the diverse termination mechanisms. This will be treated in Section 4 in detail. PECA has been known to have poor thermal stability and it has been suggested that the stability of PACA depends on the nature of the initiator and polymerization method. Drawing from the presented data, it is certain that the radical polymerization method produced PECA with improved thermal stability due to increased thermal stability on the chain end, as compared to the polymer synthesized by the anionic/zwitterionic pathway. The degradation maximum of PMMA observed in the DTG curve is around 384 °C, which is in good agreement with typical radically polymerized PMMA [39]. The coupling and disproportionation reaction may be responsible for the degradation at lower than 320 °C [40]. In the case of copolymers, thermal stability increased with increasing MMA content. Fig. 4(c) presents the relationship between MMA weight fraction in the copolymers and the temperature at degradation maximum as well as at half weight loss. This figure clearly supports that the thermal stability of the polymer was greatly increased by incorporating a small amount of MMA. This sudden rise in the thermal stability may be ascribed to the difference in chain end. Due to an alternating tendency of the copolymer system, the incorporation of the MMA close to the chain end is expected. The higher thermal stability of the MMA unit existing at or near chain end may suppress the unzipping degradation, which is a predominant thermal degradation procedure observed in PACAs [19,20]. It is noteworthy that the incorporation of a small amount of MMA monomer into the polymer chain increases thermal stability and decreases glass transition temperature to a great extent.

3.4. Degradation in solvent (acetone)

It has been reported that PACAs have weak stability and were easily degraded in solutions by unzipping of the monomer from the polymer chain end, and form lower-molecular-weight polymers due to simultaneous repolymerization of the unzipped monomer even at room temperature [21]. The degradation of the anionically synthesized PECA in solvent was found to be due to unzipping of the monomer from the polymer chain end in

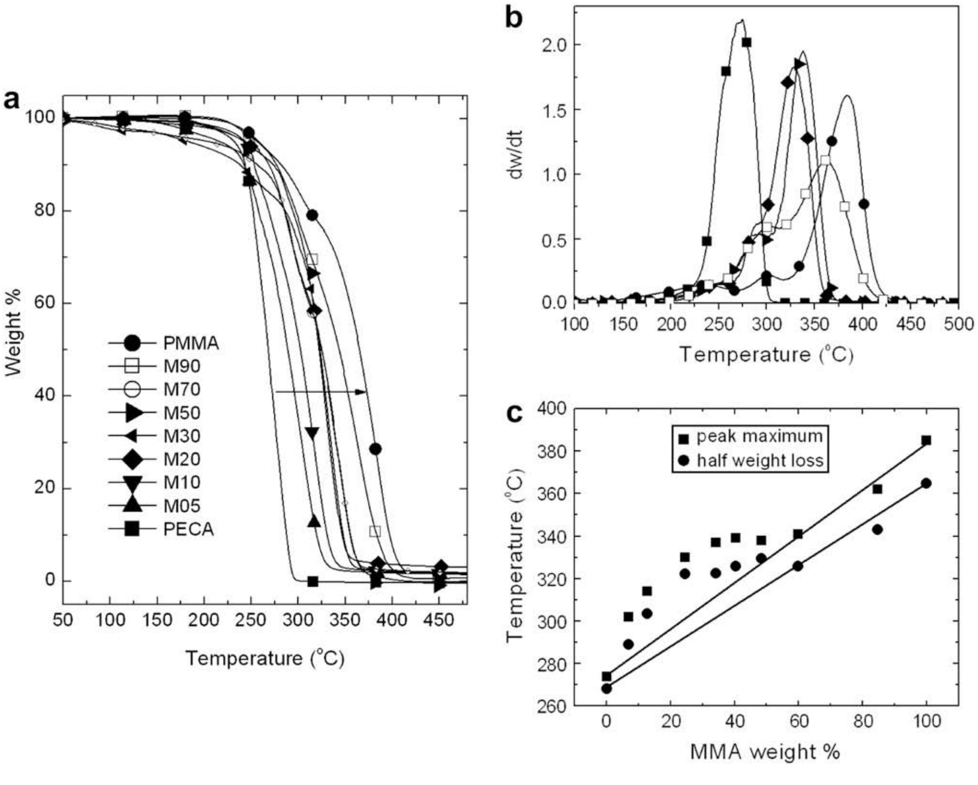


Fig. 4. TGA thermograms of homopolymers and copolymers (a), selected derivative thermogravimetry (DTG) of the homopolymers and copolymers (b), and the temperatures at maximum degradation taken from DTG curves (square) and the temperature at half loss of the weight (circle) as a function of PMMA weight % (c).

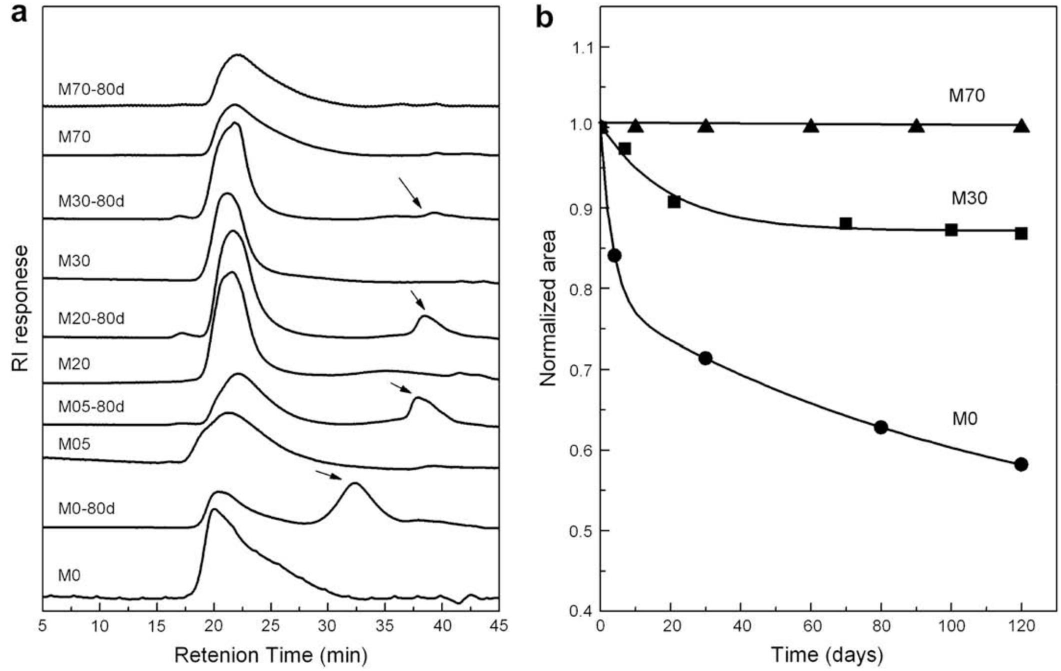


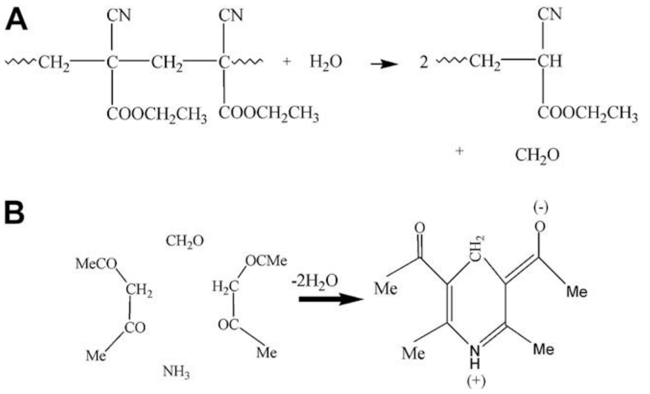
Fig. 5. GPC curves of PECA and selected PECA-*co*-PMMAs before and after 80 days at room temperature in acetone as a mobile phase (a) and the normalized GPC curve areas of the "parent" polymer as a function of time for 120 days (b). Arrows in Fig. 5(a) indicate newly formed "daughter" polymer, from unzipped monomer from "parent" polymer.

response to the chemical stimuli, but the degradation profile could be controlled by temperature, additives, and solvents [19]. Robello and coworkers reported that the use of 5 wt% of MMA as a comonomer in synthesizing PECA greatly reduced the degradation in solution [26]. In order to study the effect of MMA on the degradation in acetone, the degradation behavior of the PECA homopolymer and PECA-*co*-PMMAs of several different compositions was monitored by GPC. Fig. 5(a) shows the changes of the GPC curves of the PECA homopolymer and selected PECA-PMMA copolymers before and after 80 days of aging in a dilute solution of acetone at room temperature. After 80 days at room temperature in a closed system, the intensity of the GPC peak for the originally synthesized PECA homopolymer (M0) decreased, while a new peak corresponding to a lower molecular weight (indicated by arrows in Fig. 5(a)) appeared. The GPC peak position of the originally synthesized PECA did not change noticeably, which supports the unzipping degradation mechanism [19,21]. The appearance of the lower-molecular-weight new peak is due to the repolymerization of the depolymerized monomer to form lower-molecular-weight polymers, which is similar to the case observed in anionically polymerized PECA [19,26]. The unzipping depolymerization and simultaneous repolymerization mechanism of PECA in solvent were confirmed by several evidences: (1) the molecular weight of the pristine high-molecular-weight "parent" polymer observed by GPC peak was not changed after degradation, (2) there was no intermediate GPC peak between pristine high-molecular-weight "parent" polymer and newly produced lower-molecular-weight "daughter" polymer, which should appear if the degradation was random main chain scission, and (3) the addition of a small amount of acid in the solution prevented the formation of the "daughter" polymer. However, the degradation rate is much slower than the anionically synthesized PECA and about half of the originally synthesized polymer still remained without degradation after 120 days.

The degradation of the copolymers in acetone was greatly suppressed with increasing MMA content in the copolymer composition, as can be observed clearly in Fig. 5(a). When 30 wt% of the MMA was used for the copolymer synthesis, the degradation was almost stopped and only a broad GPC output at elution time between 35 and 40 min was detected (indicated by arrow). The degree of the unzipping of the monomer from the polymer chain could be calculated by the change of GPC peak area of the originally synthesized high-molecular-weight polymer. Fig. 5(b) shows the change in calculated GPC area of "parent" polymer of PECA homopolymer and copolymers using 30 wt% and 70 wt% of MMA as a comonomer, during aging at room temperature for 120 days. The unzipping reaction in acetone was greatly suppressed with increasing MMA content and there was no detectable area change in copolymer synthesized using 70 wt% of MMA. This improved stability to solution degradation can also be considered as a comonomer effect. This result confirms that free radical copolymerization of ECA with MMA is a serviceable technique for the preparation of more stable polymers in solution.

3.5. Hydrolytic degradation

The hydrolytic degradation of the polymers generally originates from the hydrolysis of the ester bonds. Therefore, lower-molecular-weight fragments are formed that are converted to water soluble degradation products by progressive hydrolyzation of ester bonds [41]. As a result, a decrease in the molecular weight and a loss of mechanical stability are expected after hydrolytic degradation. Due to their hydrolytic and enzymatic degradability, PACAs have been extensively used as promising drug delivery polymers and surgical glues [6,7]. It has been reported that the degradation of the cyanoacrylate polymer in aqueous media occurred not only by hydrolytic decomposition of the ester but also in the backbone of the polymer, and the hydrolytic degradation mechanism in the presence of water involved the production of formaldehyde as one of the end products [42,43]. The production of formaldehyde via chemical degradation follows a reverse Knoevenagel reaction as



Scheme 1. The production of formaldehyde in aqueous solution through hydrolytic reverse Knoevenagel reaction (A) and the formation of DDL from hydrolytic degradation product containing formaldehyde with Nash reagent (B).

shown in Scheme 1(A) [42,43]. To investigate the hydrolytic degradation behavior, copolymers (M05, M10, and M20) and PECA homopolymers synthesized by radical polymerization and zwitterionic/anionic polymerization [19] were cast on a Petri dish from concentrated acetone solutions. Due to the high molecular weight of the polymers, fairly tractable polymer films were obtained. The *in vitro* degradation behavior in PBS solutions (pH 7.4) of the homopolymers and copolymers at 37 °C were then examined and are compared as a function of degradation time in Fig. 6. The PBS solution containing released formaldehyde as a degradation product was analyzed by UV–Vis absorption spectra after the reaction of this solution with an equal volume of Nash reagent. The amounts of the released formaldehyde for each sample were then calculated based on the calibration curve obtained from pre-measured amounts of neat formaldehyde. Scheme 1(B) describes the formation mechanism of the diacetyldihydrolutidine (DDL) involving the reaction of acetyl acetone and ammonium acetate with produced formaldehyde [44].

The polymers initially release formaldehyde at a fast rate for about 2 days, and then the rate reached a steady state with decreased rate of degradation. Initial faster hydrolysis of the polymer films is may be due to the contact of water with intact surfaces of the films and the presence of polymer chains which are highly vulnerable to hydrolysis. After reaching some level of surface erosion, the surface degradation rate of the polymer decreased. The hydrolytic degradation rate of the cyanoacrylate polymer has been reported to increase with increasing pH [45] and with decreasing molecular weight [43,46]. It was also reported that the degradation rate in PBS was faster with the shorter side chain for poly(alkyl cyanoacrylate) nanoparticles [47,48]. The hydrolytic degradation may also be dependent on the stability of the chemical bonds against hydrolysis. In Fig. 6, the degradation rates of the copolymers, especially M05 and M10 are faster than those of the homopolymers, although the degradation rate was not prominently different. The relatively faster rate of initial hydrolytic degradation of M05 and M10 may be related to the lower molecular weight of these copolymers. The degradation rate of anionically polymerized film was initially slower than any other samples, but the rate was almost similar after 2 days.

The production of formaldehyde is expected to accompany a decrease in number average molecular weight of the polymer [42]. Therefore, the changes of molecular weight before and after hydrolysis for 2 weeks were traced by GPC. As was expected, the decrease in number average molecular weight of M05 and M10 was prominent as is shown in Fig. 7. But the polydispersity indices after degradation were increased. These results indicate that the hydrolytic degradation of the films is predominantly confined to the surface of the films, and that the random scission of the polymer backbone leads to the decrease in molecular weight, although other parameters may also be involved. As a whole, the incorporation of the non-degradable comonomer MMA unit into the PECA polymer chain did not diminish the hydrolytic degradation, and facilitated the degradation in some cases. Therefore, the copolymer is anticipated to be used as materials of biological degradation or as surface materials of biological probes.

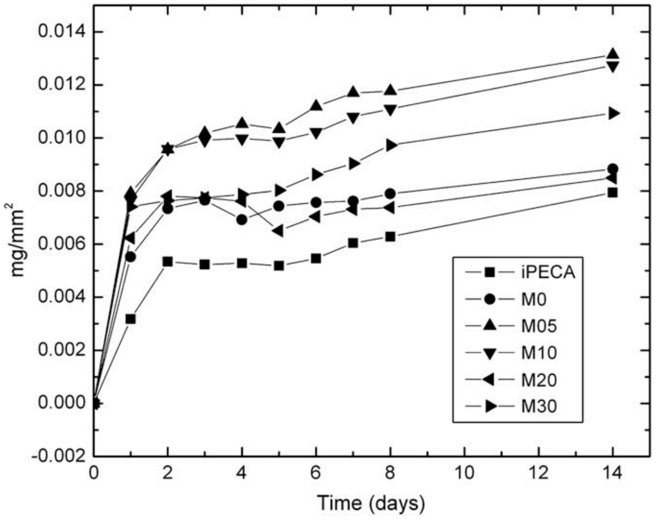


Fig. 6. Amount of formaldehyde as a degradation product released from polymer films after hydrolytic degradation in PBS solution as a function of time. iPECA is anionically synthesized PECA [19].

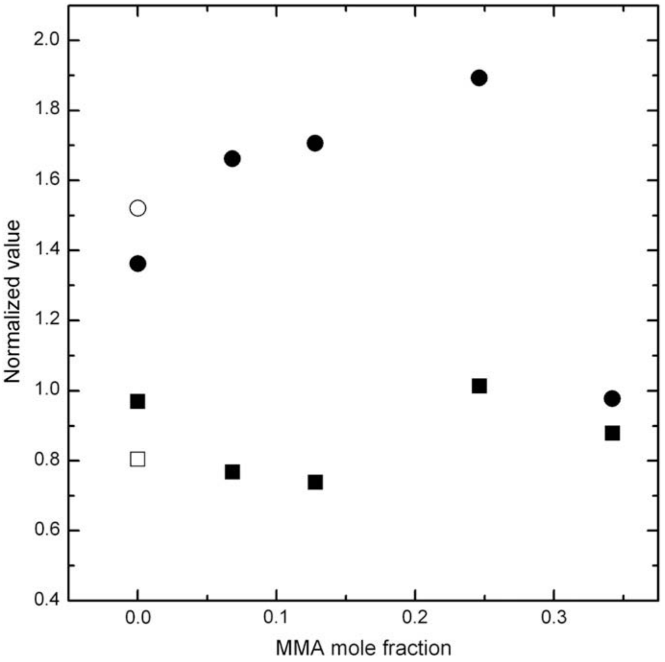


Fig. 7. Molecular weight change of the films after hydrolytic degradation for 2 weeks; the normalized number average molecular weights (M_ns) were calculated by the ratios between before and after hydrolysis (square), and the normalized polydispersity indices (PDIs, M_w/M_n) were calculated by the ratios between before and after hydrolysis (circle). Open symbols are anionically synthesized PECA homopolymer.

4. Discussion

One of the purposes of this research is to develop a more stable polymer system because PACAs are easily degraded by an unzipping mechanism from the polymer chain end [19,46]. This unzipping degradation of PACAs has limited their applications. For example, the sensitivity of PACAs to chain-degradation by basic reagents and even low concentrations of water or amines caused significant reduction in the viscosity of the solutions [22]. The effective copolymerization with more stable comonomer is expected to stop or delay unzipping when the comonomer is located close to the chain end. The controlling of the polymer chain microstructure, therefore, should benefit the final property of the polymer in a favorable way. Alkyl cyanoacrylate monomers are 1,1′-disubtituted olefins with two strong electron withdrawing substituents, ester (COOR) and cyano (CN) groups. Therefore, the copolymerization of these monomers with electron donating monomers such as styrene is expected to yield alternating copolymers after forming a charge–transfer complex as was reported by previous researchers [49], which would satisfy this objective. But, in practice, effective copolymerization with high molecular weight and controllable composition is difficult to achieve [50].

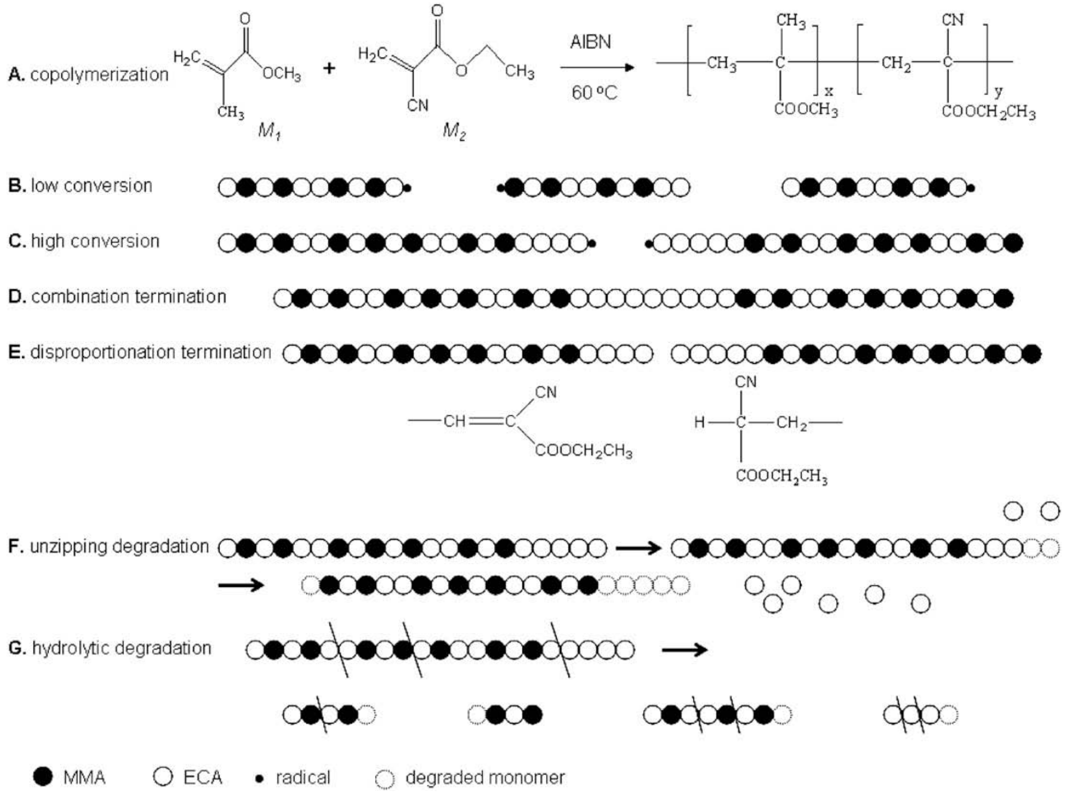
Therefore, copolymers consisting of strong electron-deficient monomer ECA and less electron-deficient monomer MMA were successfully prepared in our experiments. The obtained copolymers exhibited greatly improved stability at elevated temperatures and in solutions, probably due to specific microstructure of the polymer chain, which is related to monomer reactivity ratios. In order to easily calculate monomer reactivity ratios, an Alfrey and Price [51,52] equation has been adopted, using an expression such as the following:

$$r_1 = (Q_1/Q_2)\exp\{-e_1(e_1 - e_2)\} \tag{4}$$

$$r_2 = (Q_2/Q_1)\exp\{-e_2(e_2 - e_1)\} \tag{5}$$

where Q and e are related to the extent of resonance stabilization and the polarity of the monomer. The reported Alfrey–Price Q–e parameters for MMA ($Q = 0.78$, $e = 0.40$) [53] and ECA ($e = 2.48$) [25] are used to calculate r_1 and r_2 values. By modifying the Alfrey and Price equation, the equation of $r_1r_2 = \exp\{-(e_1 - e_2)^2\}$can be deduced. From this equation, the r_1r_2 value can be simply calculated to be 0.013, which means this copolymer has a tendency to be alternating copolymer in the initial stage of copolymerization (at low conversion). In order to determine the monomer sequence length of the final polymer product, the monomer reactivity ratios of the prepared copolymers were also determined using both Finemann–Ross (F–R) and Kelen–Tüdös (K–T) methods [54–56] using the monomer and polymer composition ratios obtained by NMR (from Fig. 2 and Table 1). The calculated monomer reactivity ratios using F–R method were $r_1 = 0.42$ and $r_2 = 0.89$, and those of using K–T method are $r_1 = 0.40$ and $r_2 = 0.81$, respectively, where r_1 is reactivity ratio of MMA. The r_1r_2 values obtained from F–R and K–T methods are 0.374 and 0.324, respectively, which means the copolymers are random copolymers with alternating tendency. Although the values obtained by F–R and K–T may not give exact monomer reactivity ratios, this calculation provides us reasonable polymer microstructure and the opportunity to calculate sequence lengths of the final copolymer products.

The higher tendency for alternating in lower conversion is due to discrepancy between monomer reactivity ratios, causing the more reactive monomer to be depleted before the less reactive monomer; hence an increase of the conversion produces an enrichment of the less reactive monomer. In addition, the



Scheme 2. Schematic illustrations of the procedure for synthesis of the copolymer, termination mechanism, possible compositional structure of the copolymers at azeotropic composition, and the proposed degradation mechanisms.

monomer with a relatively small feed ratio, particularly when the composition ratio is very large, would be depleted before reaching high conversion because the reactivity ratios between two monomers are not significantly different. This will lead to the polymers having a greater alternating tendency in the initial stage of polymerization, whereas more blocky or random structures with increasing conversion before termination. This concept is depicted in Scheme 2(B) and (C). This leads to a high chance of having an MMA unit located at or close to the polymer chain ends. Consequently, the tendency to be alternating, especially in the initial stage of the polymerization, must be the reason for the dramatic increase in the stability of the copolymer in both thermal and solution environments compared to the PECA homopolymer. This is again due to successful prevention of the unzipping depolymerization of the copolymer owing to the presence of MMA. The DSC analysis (Fig. 3(a)) for the copolymers of different compositions presented only one glass transition. This fact establishes that the composition gradient formed in this copolymer system is not large enough to create microphase separation that could be detected by DSC.

The monomer sequence lengths (μ_1 and μ_2) were then calculated from the well-known equations [57] as described in equations (6) and (7) using r_1 (0.41) and r_2 (0.85) values taken from the average values of the F–R and K–T methods,

$$\mu_1 = 1 + r_1 y \tag{6}$$

$$\mu_2 = 1 + r_2/y \tag{7}$$

where μ_1 and μ_2 are mean sequence lengths of MMA unit and ECA unit, respectively.

In addition, probabilities for different homo- and heterodiad linkages were calculated from the equation [58],

$$P_{12} = 1 - P_{11} = 1/(1 + r_1 x),\ P_{21} = 1 - P_{22} = 1/(1 + r_2/x) \tag{8}$$

where P_{ij} is the conditional probability of the addition of monomer j to a growing chain terminated with an active i radical.

The calculated data are listed in Table 1, whereas Fig. 8(a) displays the mean sequence lengths of MMA and ECA units as a function of MMA content. From the values of probability for homo- and heterodiad linkages listed in Table 1, the heterodiad compositions in the copolymer are between 0.53 and 0.63 and the values increased with increasing MMA content.

The radical polymerization method produced more stable PECA than the anionically synthesized counterpart. In addition, the incorporation of the MMA played an important role in further enhancing the stability of the polymer. However, a certain degree of degradation in acetone was observed in radically polymerized PECA homopolymer and the copolymers with low MMA contents. Onyon and coworkers previously reported on the degradation of the poly(methyl cyanoacrylate) synthesized by radical polymerization in various solvents [59]. Nevertheless, the degradation of the radically polymerized PECA has not been studied in detail. The termination mechanism may be involved in the degradation and stability of the radically synthesized PECA and PMMA-*co*-PECA. Scheme 2 summarizes the procedure for synthesizing the copolymer, possible formation of the gradient composition, chain structures formed by a disproportionation termination mechanism, and the degradation mechanisms of the polymer at azeotropic composition (35 mol% MMA). The polymer chain terminated by the combination mechanism (Scheme 2(D)) must have higher stability. On the other hand, the disproportionation termination can induce polymer with some possibility of unzipping (Scheme 2(E)). The degradation of the homopolymer PECA and copolymers with low MMA content may originate from the formation of the same end group as that produced by protonation of the chain end group formed from anionic polymerization, given the disproportionation termination as described in Scheme 2(E). The chemical structure in the right side of Scheme 2(E) is actually the same as the one synthesized by anionic polymerization [26]. Therefore, this chain end should exhibit instability as do those made by the anionic pathway. On the other hand, chains possessing other end groups (left) or chains formed by combination termination (Scheme 2(D)) must have higher stability against unzipping degradation. This fact must be responsible for the incomplete unzipping degradation in radically synthesized PECA homopolymer. Closer inspection of Fig. 5(a) reveals the disappearance of the shoulder-like peak of the GPC curve in sample M0 after 80 days. This indicates that the degradation was predominantly from lower-molecular-weight chains produced by disproportionation termination. In addition, there was a ca. 12% molecular weight decrement in sample M05

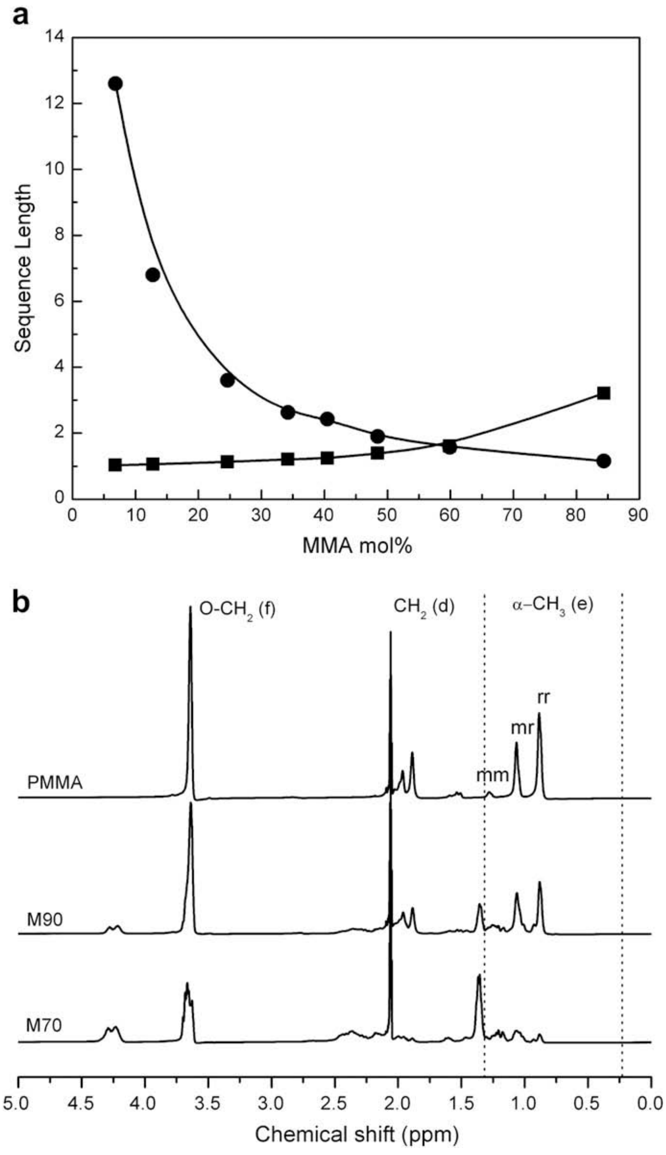


Fig. 8. (a) Monomer sequence length as a function of MMA mol% in the copolymer composition; circle is ECA and square is MMA unit. (b) NMR spectra of PMMA, M90, and M70. The peaks of the triads of syndiotactic (rr), heterotactic (mr), and isotactic (mm) of α-CH$_3$ proton are denoted in the figure.

after 80 days of aging in acetone, which can also be clearly observed in the shifting of the GPC peak. This result originates from the long mean sequence length (12.6) of the ECA unit, which can experience unzipping degradation at each chain. These facts clearly support our proposed scheme and the explanation.

Fig. 8(a) exhibits a dramatic decrease in sequence length of ECA unit with increasing MMA content. On the other hand, the sequence length of MMA unit showed monotonous increase with increasing MMA unit in the copolymers. The sequence length of MMA and ECA units in the copolymer having 0.6 mol fraction of MMA (M70) is similar (ca. 1.6). Accordingly, the complete prevention of the unzipping depolymerization in the M70 sample must be attributed to the short sequence length of the ECA and MMA units due to alternating tendency. Not only the different termination reaction but also the sequence length should affect the thermal stability of the polymers. The weak thermal degradation observed at lower temperature in M05 and M10 (in Fig. 4) must also be due to the formation of the chain end group by disproportionation termination, although the radically synthesized PECA exhibited improved thermal stability compared to the one synthesized by the anionic/zwitterionic pathway [19]. Increasing amount of MMA in copolymer composition induced an abrupt increase in thermal stability (Fig. 4(c)). However, the deviation from a linear increase stops in sample M70 (60 wt% of MMA in copolymers), in which the ECA and MMA units have similar sequence lengths. At or above this composition, the increment of the maximum degradation temperature and temperature at half maximum was linear, which means the end capping effect of the MMA unit was ceased to be valid due to the longer sequence length of MMA units relative to ECA units.

Due to the polar effect of the cyano group, the copolymers may have a marked effect on the radical conformation and the reactivity. This is confirmed by the focused view of NMR spectra of copolymers rich in MMA component presented in Fig. 8(b). The NMR peaks of α-CH_3 were greatly affected by the incorporation of ECA unit; the tacticity of the MMA unit was significantly changed with decreased sequence length of MMA unit, and even discernable when more than 50% of the ECA monomer was used in the feed composition. This high interaction between the two monomer units may be responsible for the significant change in glass transition temperature after incorporating MMA. In terms of hydrolytic degradation, however, the copolymerization with MMA did not affect degradation of the copolymer due to a different degradation mechanism as shown in Schemes 1(A) and 2(G). The copolymerization with more hydrophilic comonomer or lower glass transition temperature would greatly improve the hydrolytic degradation rate. These results are very promising for utilizing the copolymers in various fields including optics, polymer engineering, and biomaterials.

5. Conclusions

A series of copolymers containing ECA and MMA units with various compositions were synthesized by bulk radical copolymerization using AIBN as a radical initiator. These copolymers were characterized by ^{1}H NMR, GPC, DSC, TGA, and UV–Vis spectroscopy in terms of microstructure and its effect on the degradation and stability. The microstructures of the copolymers, which could be estimated by ^{1}H NMR spectra, were tailored by manipulating the feed monomer ratios. The radically synthesized PECA homopolymer exhibited improved stability compared to the anionically synthesized counterpart. The alternating random tendency of the copolymers allows for the incorporation of the more stable MMA unit near the chain end. This feature must be responsible for the further improved stability both at elevated temperature and in solution, by preventing the unzipping depolymerization of the monomer from the chain end. The enhancement of the stability was a function of the MMA content in the copolymer composition. Increasing MMA content in the copolymers not only increased the stability of the copolymers but also lowered the glass transition temperature. For example, the incorporation of 25 mol% of MMA (M20) increased the gap between T_g and the maximum degradation temperature by 85 °C, compared to the PECA homopolymer. As a result, the incorporation of MMA in the polymer chain increased the processing window of the polymer and creates possibility for various applications. In addition, the *in vitro* hydrolytic degradation studies showed that the incorporation of the non-degradable monomer unit, MMA, did not diminish the hydrolytic degradability. The current technology paves the way for new strategies to tune the degradation behavior of the poly(alkyl cyanoacrylate)s by designing macromolecular architectures through judicious choice of comonomer and monomer feed ratios appropriate for the final uses.

Acknowledgment

The authors are grateful to the Biotechnology Research and Development Corporation (BRDC) for the financial support. The assistance of Dr. Abdellatif Mohamed and Mr. Jason Adkins with the TGA and DSC experiments is greatly appreciated. We also thank Dr. Karl Vermillion for his NMR experiment and helpful comments. We are also grateful to Ms. Sheila Maroney for her help in preparing the manuscript. Careful review of this manuscript by Dr. Sean Liu is also appreciated.

References

[1] Johnston DC, Pepper DC. Makromol Chem 1981;182:393–406.
[2] Limouzin C, Caviggia A, Ganachaud F, Hémery P. Macromolecules 2003;36:667–74.
[3] Mankidy PJ, Ramakrishnan R, Foley HC. Chem Commun 2006:1139–41.
[4] Klemarczyk P. Polymer 2001;42:2837–48.
[5] Pepper DC, Ryan B. Makromol Chem 1983;184:395–410.
[6] Koukoubis TD, Gilsson RR, Feagin Jr JA, Seaber AV, Vail TP. J Biomed Mater Res 1995;29:715–20.
[7] Vauthier C, Dubernet C, Fattal E, Pinto-Alphandary H, Couvreur P. Adv Drug Deliv Rev 2003;55:519–48.
[8] Oowaki H, Matsuda S, Sakai N, Ohta T, Iwata H, Sadat A, et al. Biomaterials 2000;21:1039–46.
[9] Simeonovaa M, Antchevab M, Chorbadjiev K. Biomaterials 2003;24:313–20.
[10] Sullivan CO, Birkinshaw C. Biomaterials 2004;25:4375–82.
[11] Couvreur P, Vauthier C. J Control Release 1991;17:187–98.
[12] Exline DL, Wallace C, Roux C, Lennard C, Nelson MP, Treado PJ. J Forensic Sci 2003;48:1047–53.
[13] Toriumi DM, O'Grady K, Desai D, Bagal A. Plast Reconstr Surg 1998;102:2209–19.
[14] Troitsky VI, Matveeva NK. Thin Solid Films 1998;327–329:659–62.
[15] Pinsl J, Gehrtz M, Reggel A, Bräuchle C. J Am Chem Soc 1987;109:6479–86.
[16] Kung E, Lesser AJ, McCarthy TJ. Macromolecules 2000;33:8192–9.
[17] Bertholon I, Lesieur S, Labarre D, Besnard M, Vauthier C. Macromolecules 2006;39:3559–67.
[18] Bravo-Osuna I, Vauthier C, Farabollini A, Palmieri GF, Ponchel G. Biomaterials 2007;28:2233–43.
[19] Han MG, Kim S, Liu SX. Polym Degrad Stab 2008;93:1243–51.
[20] Birkinshaw C, Pepper DC. Polym Degrad Stab 1986;16:241–59.
[21] Ryan B, McCann G. Macromol Rapid Commun 1996;17:217–27.
[22] Donnelly EF, Pepper DC. Makromol Chem Rapid Commun 1981;2:439–42.
[23] Guthrie J, Otterburn MS. J Appl Polym Sci 1985;30:2863–7.
[24] Kinsinger JB, Panchak JR, Kelso RL, Bartlett JS, Graham RK. J Appl Polym Sci 1965;9:429–37.
[25] Yamada B, Yoshioka M, Otsu T. Makromol Chem 1983;184:1025–33.
[26] Robello DR, Eldridge TD, Swanson MT. J Polym Sci Part A Polym Chem 1999;37:4570–81.
[27] Canale AJ, Goode WE, Kinsinger JB, Panchak JR, Kelso RS, Graham RK. J Appl Polym Sci 1960;4:231–6.
[28] Kashiwagi T, Hirata T, Brown JE. Macromolecules 1985;18:131–8.
[29] Netopilík M, Bohdanecký M, Kratochvíl P. Macromolecules 1996;29:6023–30.
[30] Medrano R, Laguna MT, Saiz E, Tarazona MP. Phys Chem Chem Phys 2003;5:151–7.
[31] Nash T. Biochemistry 1953;55:416–21.
[32] Zhou Y, Bei F, Ji H, Yang X, Lu L, Wang X. J Mol Struct 2005;737:117–23.

[33] Brar AS, Singh G, Shankar R. J Mol Struct 2004;703:69–81.
[34] Bykova TA, Kiparisova Y, Lebedev GBV, Mager KA, Gololobov YG. Polymer Science -Series A 1991;33:537–43.
[35] Denchev ZZ, Kabaivanov VS. J Appl Polym Sci 1993;47:1019–26.
[36] Hsu SL. In: Mark JE, editor. Polymer data handbook. Oxford University Press; 1999. p. 656.
[37] París R, de la Fuente JL. J Polym Sci Part B Polym Phys 2007;45:1845–55.
[38] Fox TG, Flory PJ. J Appl Phys 1950;21:581–91.
[39] Demir MM, Castignolles P, Akbey Ü, Wegner G. Macromolecules 2007;40: 4190–8.
[40] Moineau G, Minet M, Dubois P, Teyssí P, Senninger T, Jérome R. Macromolecules 1999;32:27–35.
[41] Gopferich A. Biomaterials 1996;17:103–14.
[42] Leonard F, Kulkarni RK, Brandes G, Nelson J, Cameron JJ. J Appl Polym Sci 1966;10:259–72.
[43] Lenaerts V, Couver P, Christiaens-Leyh D, Joiris E, Roland M, Rollman B, et al. Biomaterials 1984;5:65–8.
[44] Cooper AW, Harris PJ, Kumar GK, Terry JC. J Polym Sci Part A Polym Chem 1989;27:1967–74.
[45] Müller RH, Lherm C, Herbort J, Couvreur P. Biomaterials 1990;11:590–5.
[46] Vezin WR, Florence AT. J Biomed Mater Res 1980;14:93–106.
[47] Olbrich C, Hauff P, Scholle F, Schmidt W, Bakowsky U, Briel A, et al. Biomaterials 2006;27:3549–59.
[48] Hickey A, Leahy JJ, Birkinshaw C. Macromol Rapid Commun 2001;22: 1158–62.
[49] Nagai K, Okada K, Kido J. J Polym Sci Part A Polym Chem 1992;30:1187–92.
[50] Yokozawa T, Ando KD, Endo T. Macromolecules 1994;27:1978–80.
[51] Alfrey T, Price CC. J Polym Sci 1947;2:101–6.
[52] Ameduri B, Bauduin G. J Polym Sci Part A Polym Chem 2003;41:3109–21.
[53] Greenley RZ. In: Brandrup J, Immergut EH, editors. Polymer handbook. 3rd ed. New York: John Wiley; 1989. p. 311.
[54] Finemann M, Ross S. J Polym Sci Part A 1950;5:259–62.
[55] Kelen T, Tüdös F. J Macromol Sci A 1975;9:1–27.
[56] Pugh C, Tang CN, Paz-Pazos M, Samtani O, Dao AH. Macromolecules 2007;40:8178–88.
[57] Pyun CW. J Polym Sci Part B Polym Phys 1970;8:1111–26.
[58] Kuo SW, Kao HC, Chang FC. Polymer 2003;44:6873–82.
[59] Bevington JC, Jemmett JAL, Onyon PF. Eur Polym J 1976;12:255–7.