Solution-state self-assembly of novel poly(carbamoyl methacrylate)s synthesized via combining Passerini three-component reactions and free radical polymerizations

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ABSTRACT

Coupling multicomponent reactions (MCRs) with other polymerizations has excellent advantages in inducing multifunctionality and syntheses of complex macromolecular structures. Herein, a straightforward combination method using aqueous Passerini three-component reaction (P3CR$_{(aq)}$) and conventional free radical polymerization (FRP) (termed as P3CR$_{(aq)}$-C-FRP) was applied using mild conditions. Firstly, an environmental-friendly and efficient aqueous P3CR was applied to synthesize various carbamoyl methacrylate (CMA) monomers from methacrylic acid, cyclohexyl isocyanide, and four different aldehydes with high yield (ca. 90 %) and purity. This is plausibly prompted by the key factors of high cohesive energy density of water and facile isolation by the poor solubility of CMAs in aqueous. Then, poly(carbamoyl methacrylate)s (PCMAs) were obtained via FRP with 2,2′-azobis(isobutyronitrile) (AIBN) in dimethylformamide (DMF). Characterizations of both synthesized noble monomers, polymers, solubilities in different solvents, and thermal properties, as well as the solution-state self-assembly behaviors of the polymers by dynamic light scattering (DLS), scanning electron microscope (SEM), and small-angle X-ray scattering (SAXS), including micellized particle sizes, critical micelle concentrations (CMCs), and micelle morphology, were investigated. PCMAs can self-assemble into stable globular micellar nanoparticles (ca. 170–310 nm) with low CMC values (1.6×10^{-5}–4.0×10^{-9} mg/mL).

1. Introduction

Multicomponent reactions (MCRs) have received significant attention by being employed in many disciplines of chemistry and related fields, such as in drug discovery [1] and synthesis of macrocyclic compounds [2], natural products [3], peptidomimetics [4], polymer science [5], and combinatorial chemistry [6]. Their excellent flexibility of products, convergent reactions, and excessive structural and molecular diversity that can be obtained in the final product of the single building blocks in a one-pot manner from at least a three-component reaction arrangement make them widely demanded [7]. Their exclusive features, such as operational simplicity, substrates diversity, and atom and step economy, which fulfill the possible aspects of green chemistry, magnify

their multifold importance in several disciplines [8]. Of the many extensively investigated MCRs, the isocyanide-based, particularly the Passerini three-component reaction (P3CR), is one of the most widely used MCRs in organic chemistry and other files [9]. However, P3CR was introduced into polymer and macromolecular chemistry only recently, yet gaining attention rapidly for the design of new functional polymers, though it can be potentially used as direct polymerization [10], monomer synthesis [11], and post-polymerization modification [12,13]. Some excellent reviews and books have recently appeared to cover the progress of MCRs in polymer science as new synthetic tools [14–16]. As a pioneering work, Meier et al. [17] opened up an innovative insight by operating a P3CR towards synthesizing polymers via Passerini-type multicomponent polymerization (i.e., P-MCP).

Since then, several works have been reported using P3CR as a monomer synthesis tool for combining different polymerization techniques such as nitroxide-mediated polymerization (NMP) [18,19], reversible addition-fragmentation chain transfer (RAFT) polymerization [20,21], atom transfer radical polymerization (ATRP) [18,22], and free radical polymerization (FRP) [11]. Conventional FRP is one of the most widely used techniques for synthesizing polymers due to its versatility, simplicity, and cost-effectiveness. It is commonly applicable in industries for its ease of implementation, wide range of monomers, tolerance to impurities, high reaction rate, high molecular weight, compatibility with other techniques, etc. [11,23–25]. Apart from its versatile advantages, combining MCR and FRP (termed as MCR-*Є*-FRP) is still very limited in the literature [26]. In the previous case, Meier group reported the synthesis of acrylate monomers through P3CR in dichloromethane and aqueous media by tuning substituents on the isocyanide and aldehyde components and further conducted FRPs to obtain novel polyacrylates for the first time [11]. Although a series of acrylate monomers were successfully synthesized, their study presented relatively moderate yields (<75 %) in the P3CR cases using an environmentally friendly water medium.

The P3CR synthetic strategy was purposefully used to induce functionality on the side chains of methacrylic monomers and retained the reactive double bond for further polymerizations. From the literature, amide group-containing methacrylic-type monomers and using proper solutions to polymerize such monomers still need to be expanded and addressed. Herein, we report novel poly(carbamoyl methacrylate)s (PCMAs) synthesized via combinations of P3CR and FRP (named P3CR-*Є*-FRP) for the first time. As shown in Scheme 1, four carbamoyl methacrylate (CMA) monomers were individually synthesized via P3CRs of methacrylic acid (MAA) and cyclohexyl isocyanide (CHI) with different substituent aldehydes in deionized water (DIW) in the first step. CMAs with high purity and yields are obtained with an accelerating reaction rate and avoiding further purification processes. Then, FRPs of the carbamoyl methacrylate monomers were conducted to afford the respective PCMAs. We further examined the thermal and solution-state properties of the synthesized PCMAs by using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic light scattering (DLS), small-angle X-ray scattering (SAXS), and scanning electron microscope (SEM).

2. Experimental section

2.1. Materials and characterization

All the following chemicals were purchased and used as received without further purification: cyclohexyl isocyanide (CHI, 99 %), benzaldehyde (99 %), 4-methoxy benzaldehyde (98 %), methacrylic acid (MAA, 98 %), and 1-butanol (>99 %) all were purchased from Thermo Fisher Scientific. Isobutyraldehyde (97 %) and octanal were purchased from TCI Chemicals and Sigma-Aldrich, respectively. Azobisisobutyronitrile (AIBN, > 99 %) was bought from Aencore Chemicals. All characterization details are depicted in the Supporting Information, including analyses of solubility tests, gas chromatography (GC), gel permeation chromatography (GPC), Fourier transform infrared (FT-IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic light scattering (DLS).

2.2. General synthesis procedure of CMA monomers via P3CR

In a 20-mL scintillation vial, MAA (2 mmol, 169 μL) and an aldehyde (2 mmol) were added to 3 mL deionized water (DIW). An equimolar ratio of CHI was added, and the agitation continued for 5 h at room temperature. After 5 h, the separated solid precipitates were washed with DIW repeatedly and dried under vacuum pressure. All samples were kept in the refrigerator until needed.

2.3. Synthetic procedures of PCMA polymers via FRP

10 mmol of the prepared monomer and 0.05 mmol (8.0 mg) of AIBN were added into a 10-mL round bottom Schlenk flask containing 3 mL of DMF. Then, the sealed solution was stirred under a nitrogen atmosphere for 25 min before allowing the polymerization process at 70 °C in an oil bath for a few hours. The obtained polymer solution was cooled down and transferred into cold DIW and rinsed with diethyl ether and ethyl acetate to remove unreacted monomers and impurities.. After drying to constant weight, the polymer sample was kept for further characterization.
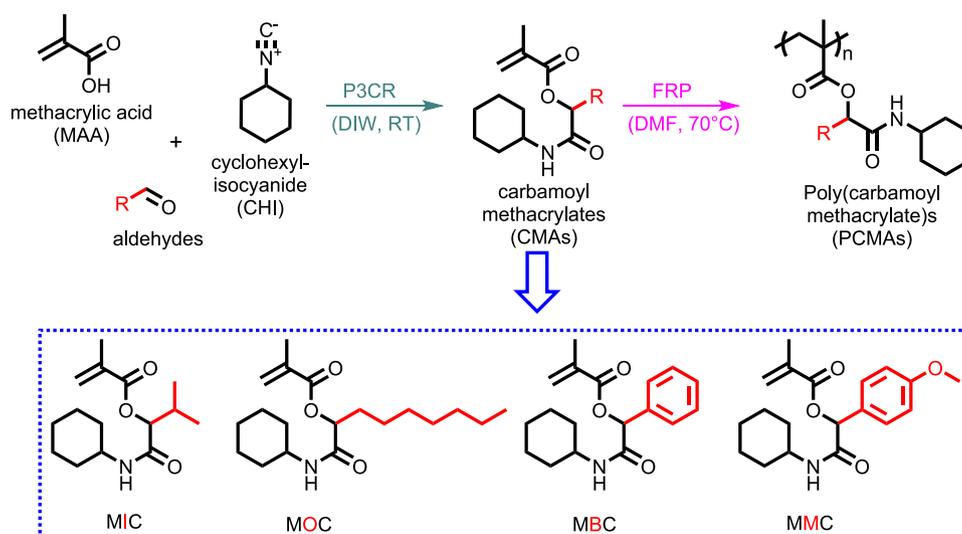
Scheme 1. Synthesis of novel poly(carbamoyl methacrylate)s (PCMAs) via combining aqueous-prompt Passerini three-component reaction and conventional free radical polymerization (P3CR$_{(aq)}$-*Є*-FRP).

3. Results and discussion

3.1. Syntheses and characterizations of carbamoyl methacrylates (CMAs)

Four CMAs namely, methacrylic-isobutyraldehyde-cyclohexyl isocyanide (MIC), methacrylic-octanaldehyde-cyclohexyl isocyanide (MOC), methacrylic-benzaldehyde-cyclohexyl isocyanide (MBC), and methacrylic-4-methoxybenzaldehyde-cyclohexylisocyanide (MMC) were synthesized by P3CR from methacrylic acid, cyclohexyl isocyanide, and aldehydes of different substituents (R) via P3CR in DIW as shown in Scheme 1. The synthesis of these CMA monomers through mild and green methods can facilely keep the integrity of vinyl functionality and is earmarked for further polymerization. P3CR is one of the most versatile and valuable synthetic tools in inducing multifunctionality into the monomers/polymers of desire [27]. Hence, we take these advantages to integrate the ester-amide functionality into the CMAs in this synthesis protocol. DIW water was selected over organic solvents or other aqueous-based solvent systems because of its multiple advantages, including fast reaction rate, relatively easy, green and accessible, and nontoxic, leading to pure and high yields without further purification processes [11,28,29]. The conversions of Passerini reactants were studied by tracking GC trace analyses using n-butanol as a reference and consumption of cyclohexyl isocyanide (CHI) at various times, as shown in Fig. 1. The maximum time taken to reach high conversion for MIC and MOC reactants is 0.5 and 1.5 h, respectively, and the conversion has reached >96 % after 5 h in the case of MMC and MBC. The observed conversion rate differences can be correlated with the structural differences among reactants, i.e., the methoxyphenyl and phenyl substituents on the aldehyde pendant relative to the aliphatic chain of octane and isopropyl groups contribute to the slow rate of conversion in MMC and MBC. Literature supports this phenomenon [11]. The acceleration of multicomponent reactions (MCRs) in water is mainly due to water's high cohesive energy density (CED), the hydrophobic effect, and the enhanced hydrogen bonding transition state during the reaction [30]. Similarly, high product yields of CMAs were obtained in DIW (Table S1; see the Eleronic Supporting Information (ESI)). Figs. S2 and S3 show the resultants' chemical structural assign (see the ESI). The product yields of all monomers are nearly quantitative at over 96 % except MMC, which has a good yield of 87.2 %. This is most likely due to the electron-donating nature of methoxy substituent through resonance, which deactivates the oxonium ion formed from an aldehyde in the
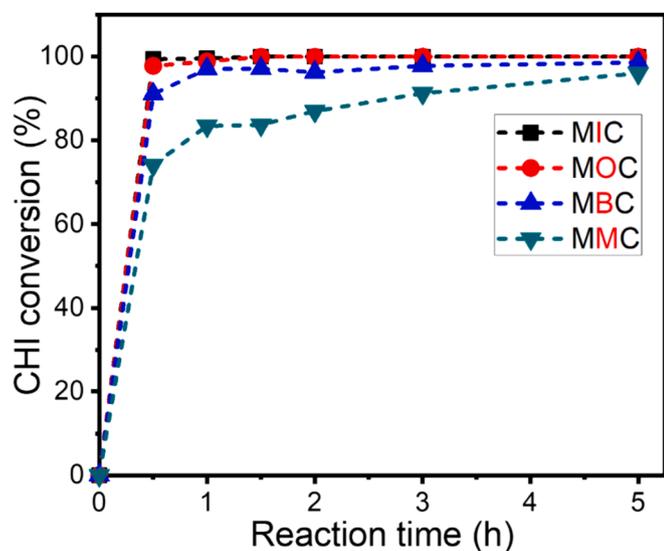
Fig. 1. CHI conversion (traced by GC) via aqueous P3CR at room temperature to the synthesis of carbamoyl methacrylates (CMAs) (MAA/Aldehydes/CHI = 1/1/1; [MAA]$_0$ = 0.67 mM in deionized water (DIW)).

transition state during the reaction, making it less susceptible to the nucleophilic attack from isocyanide [31] (illustrated in Scheme S1 in the ESI). The electron-donating groups, including the benzene ring, are mainly through resonance rather than inductive. Ostaszewski and co-workers reported that MCRs attained higher conversions in DIW than organic or aqueous-based mixtures [32,33]. Herein, using water as a reaction medium for synthesizing CMA monomers surrounded by a specific high cohesive energy density environment from DIW (CED$_{DIW}$ = 550.2 cal/mL at 25 °C) [34] and poor solubilities of CMAs in DIW, leading to effective conducting P3CR, unnecessary time spent, preventing sample loss by extraction and purification, and avoiding utilization of organic solvents.

EA, FT-IR, DSC, ^{1}H NMR, and ^{13}C NMR instruments further confirmed the purity of the obtained CMAs. The quantitative measurements of C, H, and N atoms for CMAs experimentally agree with the high purity theoretical values (EA and FT-IR details are summarized in the experimental section, Table S1, Fig. S1 (see the ESI)). Figs. S2 and S3 show that the resultants' chemical structural assignments of ^{1}H and ^{13}C NMR spectra convey the successful MIC, MOC, MBC, and MMC synthesis. Notably, the appearances of peaks b in ^{1}H NMR spectra (ca. 5.1 ppm/doublet in Fig. S2A (MIC), ca. 5.2 ppm/triplet in Fig. S2B (MOC), ca. 6.1 ppm/singlet in Fig. S2C (MBC), and ca. 6.4 ppm/singlet in Fig. S2D (MMC)] and peaks e in ^{13}C NMR spectra (ca. 75 ppm for each in Fig. S3), resulting from the aliphatic or benzylic/α-amide/α-acetoxy protons and carbons, indicate the foremost characteristic signals via P3CR. Fig. S4 displays a representaive HR-MS spectrum of MMC monomer with high purity.

3.2. Synthesis and characterizations of poly(carbamoyl methacrylate)s (PCMAs)

As illustrated in Scheme 1, FRPs of CMAs were conducted in DMF in the presence of thermal initiator AIBN (CMA/AIBN = 100/0.5 at 70 °C; [CMA]$_0$ = 0.67 M). All the polymers were purified by precipitating out in cold DIW and rinsed with diethyl ether and ethyl acetate to remove unreacted monomers and impurities. Before conducting instrumental characterizations (^{1}H NMR, FT-IR, GPC, TGA, DSC, and DLS analyses), we examined the solubilities of the synthesized polymers in several common solvents. As shown in Table S2 (see the ESI), all PCMAs are entirely soluble in DMAc, EtOH, DMSO, and THF but insoluble in DIW and some other common organic solvents of acetone, ethyl acetate, and dichloromethane. Compared with the solubilities of the corresponding monomers, the poor solubilities of PCMAs might come from the changes in molecular weight, intramolecular hydrogen bonding, hydrophobic effect, and the spacing between the molecular structure of a polymer, which are the most influencing factors for the solubilities of the polymer [35,36]. Thus, the PCMAs with good solubilities in high-polar solvents of DMAc, DMSO, EtOH, and THF are mainly plausible due to the interruptions of strong hydrogen bonding within intra- and inter-chains [37].

As shown in Fig. 2, we assigned the corresponding characteristic of the PCMAs in ^{1}H NMR spectra. Significant disappearances of vinyl signals of CMAs and retained the aliphatic or benzylic/α-amide/α-acetoxy protons with a broadening fashion (i.e., peak b in each spectrum) were delineated. The FT-IR spectroscopy results of CMAs and PCMAs are shown in Fig. S1 (see the ESI). The corresponding absorption peaks are similar and mainly observed at around 3300 (secondary N—H stretching), 2935–2860 (methyl and methylene C—H stretching), 1725 (conjugated ester C═O stretching), and 1660 cm^{-1} (secondary amide C═O stretching). The strong peaks between 1400 and 1000 cm^{-1} mainly indicate methyl C—H rocking, ester C—O stretching, and amide C—N stretching vibrations. As shown in Fig. 3 and summarized in Table 1, the molecular weight characteristics (i.e., number-average molecular weight (M_n) and molecular weight dispersity ($Đ_{mw}$)) of PCMAs are obtained in a range of 44,000–58,000 and 1.6–3.7 by using GPC analysis (THF as the eluent at 35 °C). It is noted that PMIC displays a relatively
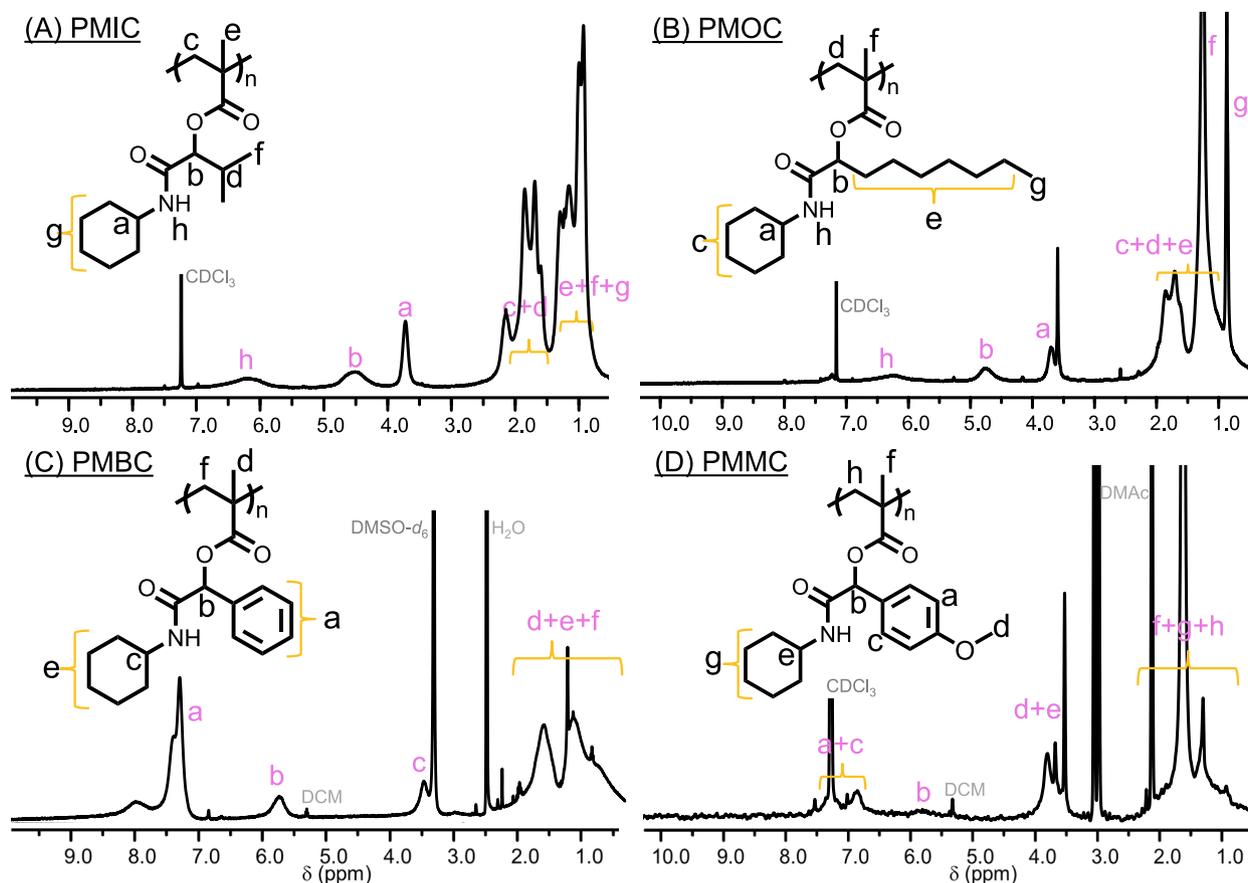
Fig. 2. ^{1}H NMR spectra (400 MHz) of (A) PMIC, (B) PMOC, (C) PMBC, and (D) PMMC (*d*-solvents are illustrated in the spectra).
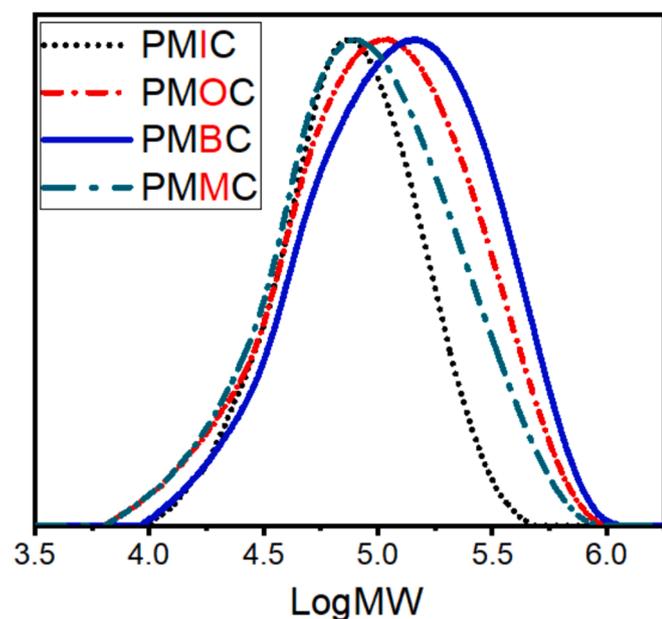
Fig. 3. GPC traces of PMIC, PMOC, PMBC, and PMMC (CMA/AIBN = 100/0.5 at 70 °C; $[CMA]_0$ = 0.67 M in DMF).

Table 1
Characterization and thermal properties of PCMAs.

PCMA	M_n	$Đ_{mw}$[a]	T_g (°C)	$T_{d5\%}$ (°C)[b]	Char yield (%)
PMIC	44,140	1.6	127.8	260.3	2.2
PMOC	48,970	3.7	76.5	226.9	2.0
PMBC	49,300	3.4	131.8	257.4	1.9
PMMC	58,370	2.9	109.5	240.6	0.9

[a] $Đ_{mw}$: molecular weight dispersity ($=M_w/M_n$).
[b] $T_{d5\%}$: decomposition temperature at 5% weight loss.

syntheses of PCMAs by conducting facile conventional FRPs of the CMAs.

3.3. Thermal properties of PCMAs

The thermal properties of PCMA polymers were studied using TGA and DSC thermograms. The thermal decomposition values of PCMAs at 5 wt% loss of weight ($T_{d5\%}$) are given in Table 1. With similar backbone structures of the PCMAs, polymers containing bulky groups on their side chains have higher T_d values and a slow rate of decomposition (Fig. 4A). Therefore, PMIC, PMBC and PMMC have higher $T_{d5}\%$ values than that of PMOC. Because of rigidity and compactness, bulky group-containing polymers have higher thermal stability than their long alky-counterparts of similar molecular weights [38–41]. As displayed in Fig. 4B, the glass transition temperature (T_g) values of PCMAs are identified by DSC traces. No clear and distinct T_m peak was observed in all cases, indicating their amorphous property. The T_g value differences among the polymers are mainly attributed to their various aldehyde substituents. Comparatively, PMOC has a lower T_g value (76.5 °C) due to its long aliphatic hydrocarbon chains on its aldehyde substituent

low $Đ_{mw}$ compared to the other polymers. The relatively shorter hydrocarbon segment on the side chain of PMIC likely allows it to have more intermolecular hydrogen bonding susceptibility, leading to higher uniformity than other PCMAs. Thereby, this contributes to the growing chains with relatively low $Đ_{mw}$. These results indicate successful
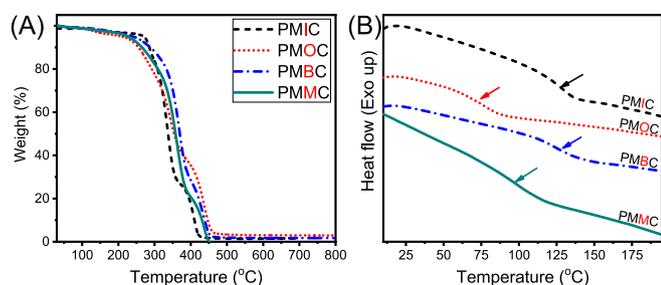
Fig. 4. (A) TGA traces (ramping: 10 °C/min in 30–800 °C) and (B) DSC curves (recorded in 2nd run; ramping: 20 °C/min in 25–200 °C) of PCMAs under $N_{2(g)}$.

sidechains, and PMIC and PMBC have higher T_g values (129 and 132 °C, respectively). PMIC is likely due to its short hydrocarbon chain, which can have more intermolecular hydrogen bonding than PMOC. Nevertheless, the T_g value of PMBC is higher than PMMC, which both have benzene rings in their aldehyde sidechains. This can arise from the flexibility of PMMC, which additionally contains ether functionality. In brief, relatively high T_g values of PCMAs come with small side groups and rigid aromatic rings that increase intermolecular interaction and hinder chain flexibility, respectively [42–46]. The TGA and DSC results are summarized in Table 1.

3.4. Solution properties of PCMAs

It is well-known that micellar polymer nanoparticles, extensively studied for biomedical applications, are generally formed above critical micelle concentration (CMC) through the self-assembly of amphiphilic block polymers [47,48]. However, it is still limited by using a block copolymer-free system to attain nano-scaled polymeric micelles (PMs) [49]. As shown in Fig. 5, excitingly, the PCMA homopolymers can form stable self-assembled micellar having diameter of particle sizes (d_{ps}) in a range of 170–311 nm and dispersity of particle sizes ($Đ_{ps}$) in a range of 0.10–0.23, elucidating their amphiphilic feature. Notably, PMBC (d_{ps} = 226 nm, $Đ_{ps}$ = 0.14) and PMIC (d_{ps} = 170 nm, $Đ_{ps}$ = 0.1), relatively, have lower $Đ_{ps}$ and $Đ_{mw}$ compared to the other PCMAs. These differences arise from the changes in the hydrophobic segment chain length of the hydrophilic pendant among PCMAs. Namely, PMIC and PMBC have shorter hydrophobic segments than PMOC and PMMC, in which the longer hydrophobic chains possess more steric hindrance, resulting in
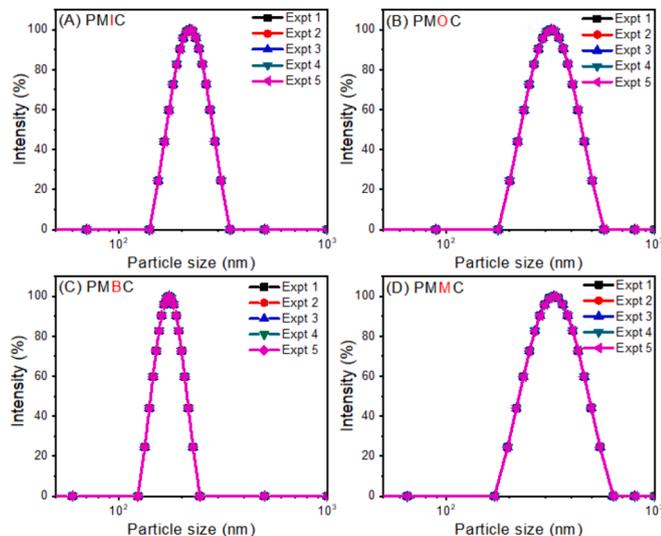
larger particle size aggregates and broader PDI. The high stability of the PCMA-micellized aqueous solutions was further confirmed after one month, observing insignificant changes in d_{ps} and $Đ_{ps}$ (shown in Fig. S2 and Table S3 (see the ESI)). As shown in Fig. 6, PCMA-micellized behaviors demonstrate ultralow CMC values ranging from 1.6×10^{-5} to 4.0×10^{-9} mg/mL (summarized in Table S3 (see the ESI)). A common strategy to attain high-stability micelles is to render or enhance the inter-chain interactions within the forming micelle [48,50,51]. The ultralow CMC values of PCMA micelles are far smaller than those formed from low molecular weight surfactants or conventional small molecule micelles (usually in the ranges of 10^{-3}–10^{-4} mg/mL) [52–54]. The particular ultralow CMC value of PMOC (4.0×10^{-9} mg/mL) could be attributed to its long aliphatic hydrocarbon substituent from the aldehyde reactant. Amphiphilic polymers with long hydrophobic chains have lower CMC values than those with shorter hydrocarbons, which might increase the size of polymeric micelles [48]. This phenomenon can be observed in the cases of PMOC and PMIC micelle sizes (226 and 311 nm in Fig. 5A and B, respectively). Forming a stable dispersion in a highly diluted physiological solution is a challenge [50]. Herein, PCMAs show advanced stable aqueous dispersion at ultralow concentration, making them potential candidates as aqueous carriers in biomedical, catalyst, or relevant applications.

Aqueous solutions with polymer micelles (PMs) are analyzed by small-angle X-ray scattering (SAXS) for further examinations of the microstructures. As shown in Fig. 7, the SAXS scattering profiles do not display periodic aggregations of the microstructures. However, along with the linear behavior of log (I(q)) versus log (q) in the low-q range ($0.03 < q < 0.07$ nm^{-1}), PCMA-based PMs possess the transition fitting slopes of approximated -4, revealing that a distinct Guinier regime of spheres is observable. The morphology of the PMs is then analyzed using an SEM instrument. Fig. 8 displays that solution-states of PCMAs formed globular nanostructures and their corresponding sizes are estimated. The nanoparticle sizes are approximately 100 nm. Based on the chemical structures of PCMAs, the self-assembly behaviors in aqueous are attributed to the presence of their hydrophilic (amide group) and hydrophobic (alkyl and benzyl groups) parts. Compared to Figs. 5 and 8, the particle sizes monitored by DLS are larger than those observed by SEM. The significant shrinkage in the dried state is plausibly ascribed to the strong hydrogen bonding of PCMAs. Several studies have reported that amphiphilic homopolymers with hydrophilic and lipophilic

Fig. 5. Particle sizes of (A) PMIC, (B) PMOC, (C) PMBC, and (D) PMMC in deionized water (0.1 mg polymers/mL DIW) after 1 day (each measured by DLS with five experimental tests).
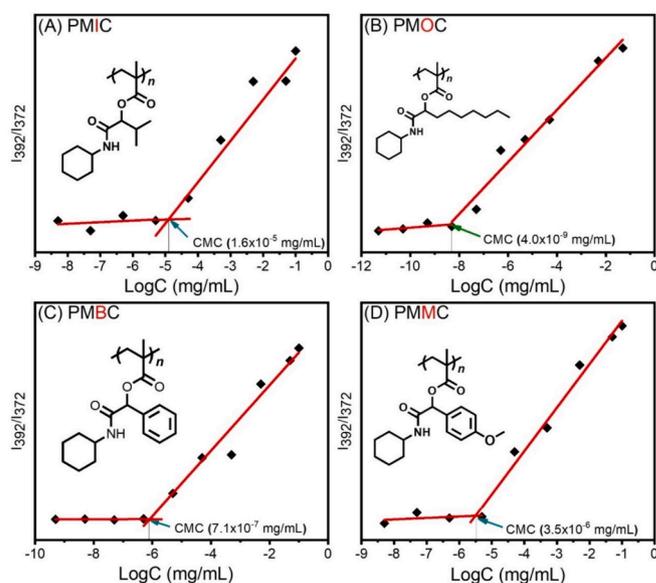
Fig. 6. The FL intensity ratio of I_{392}/I_{372} from pyrene emission spectra versus the log of the concentration (logC (mg/mL), measurements used to determine the CMC for (A) PMIC, (B) PMOC, (C) PMBC, and (D) PMMC.
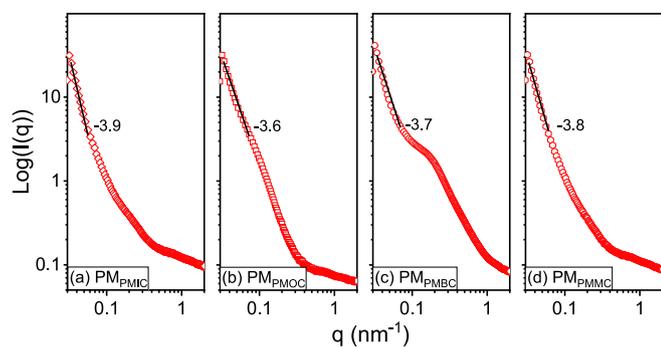
Fig. 7. SAXS of polymer micelle aqueous solutions of (a) PMIC$_{(aq)}$, (b) PMOC$_{(aq)}$, (c) PBMC$_{(aq)}$, and (d) PMMC$_{(aq)}$ (each solution contains ca. 0.05 wt% of PCMA in DIW).

functionalities form chains of surfactants with groups on opposite sides, creating facial amphiphilicity [55–59]. Accordingly, we proposed a plausible solution-state self-assembly of the PCMAs. As shown in Scheme 2, the hydrophilic groups are oriented towards the aqueous, while the lipophilic hydrophobic substituents remain inside the microstructures.

4. Conclusions

P3CR$_{(aq)}$ was demonstrated as a facile tool to efficiently and effectively synthesize various methacrylic ester-amides in water. Water was used as a reaction medium, and a high yield (ca. 90 %) and purity of CMA monomers were acquired. This might be due to a synergistic effect of a high cohesive energy density environment and poor solubilities. We can note that water-insoluble solid substrates will be the limitations in conducting the aqueous-prompted P3CR. One can use surfactants or co-solvents to overcome such limitations and achieve well-dispersions of

water-insoluble substrates. FRP was then used to synthesize poly(carbamoyl methacrylate)s with molecular weights of 44,000–58,000 from various CMAs. Their T_gs range from 76–131 °C and $T_{d5\%}$s are mainly above 225 °C. Interestingly, the synthesized PCMAs can self-assemble into stable micellar nanoparticles (170–311 nm) with good water dispersibility and low CMC (1.6×10^{-5}–4.0×10^{-9} mg/mL) for up to one month. SAXS analysis of solution-states and SEM analyses of dried samples illustrated a globular morphology. Compared to the DLS and SEM measurements, the substantial shrinkage in the dried state is likely attributed to the strong hydrogen bonding present in PCMAs. For more details, investigations and self-assemblies in various solvents, salts, pH, and temperatures are currently underway. In this study, an effective combination of P3CR$_{(aq)}$-ϵ-FRP was demonstrated, making them potential candidates for biomedical applications such as drug carriers.

CRediT authorship contribution statement

Dula Daksa Ejeta: Writing – original draft, Formal analysis, Data curation. **Yi-Shen Huang:** Writing – original draft, Software, Formal analysis, Data curation. **Jun-Rui Hsu:** Methodology, Data curation. **Mária Gurská:** Investigation, Formal analysis. **Shiao-Wei Kuo:** Resources, Methodology. **Jozef Kollár:** Writing – review & editing, Project administration, Methodology. **Jaroslav Mosnáček:** Writing – review & editing, Supervision, Software, Project administration. **Chih-Feng Huang:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
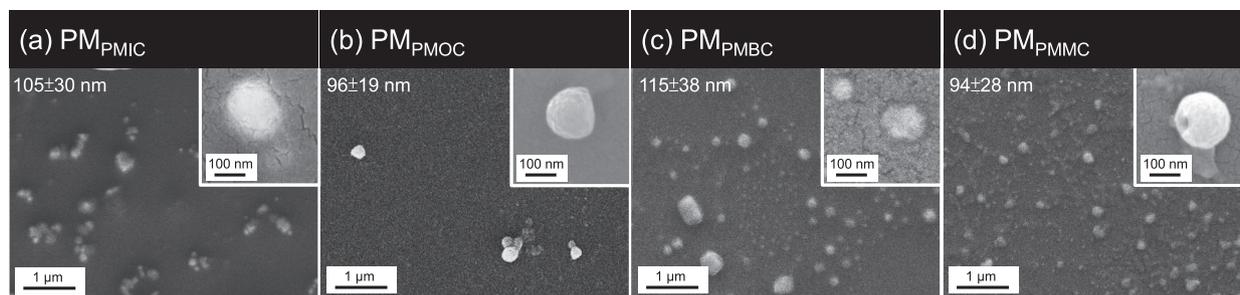
Fig. 8. SEM images of polymeric micelles (PM) for (a) PMIC, (b) PMOC, (c) PMBC, and (d) PMMC (inserted photos: in zoom-in scale; free-dried samples from 0.05 wt % PM solutions).
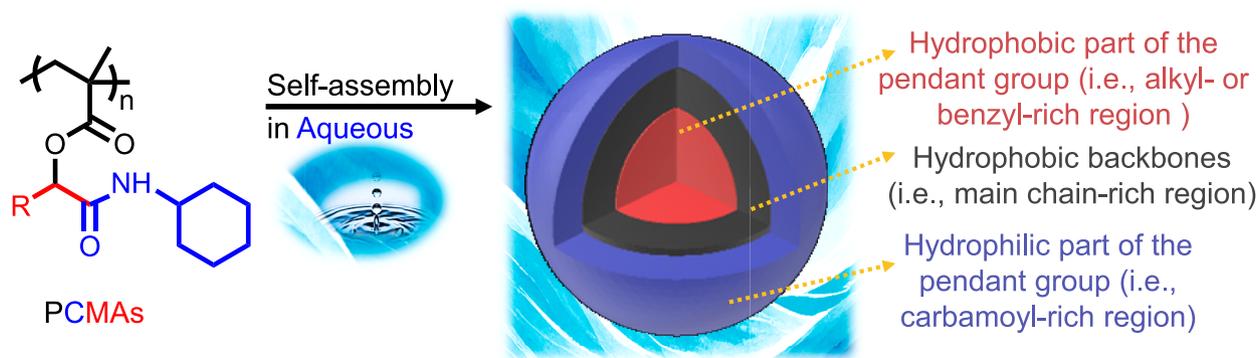
Scheme 2. Proposed self-assembly structures of PCMAs in aqueous.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eurpolymj.2024.113361.

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