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Hydrophobically Modified Polycarboxybetaine: From Living Radical Polymerization to Self-Assembly

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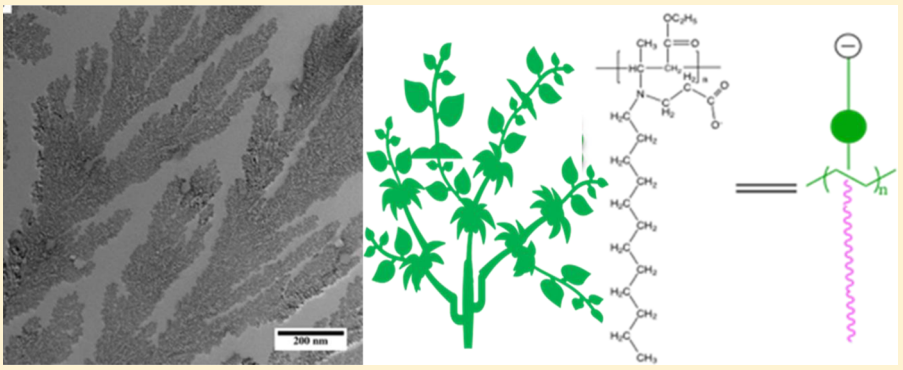
Supporting Information



ABSTRACT: Polybetaines have received widespread attention due to their smart response properties and structures which resemble biological polymers like peptides and DNA. However, few studies have focused on the controlled synthesis and self-assembly of hydrophobically modified polybetaines due to the difficulty of synthesizing these materials. We report the first molecular weight-controlled synthesis of hydrophobically modified polycarboxybetaines (HMPCB). Poly(dodecyl grafted aminocrotonate -methacrylic acid) (P(DACRO-MAA)) was synthesized via the reversible addition−fragmentation chain-transfer (RAFT) polymerization approach. The two different tautomers of the monomer were also successfully identified and separated via thin layer chromatography (TLC) and column chromatography, making it possible to obtain pure polycarboxybetaine via RAFT synthesis. Both the successfully separated enamine form of the monomer and the resulting polycarboxybetaine were confirmed via FTIR and NMR. The polycarboxybetaine was found to have a low polydispersity (PDI) of 1.214, and its molecular weight was determined as 70590 g/mol via gel permeation chromatography (GPC) measurements. Spherical, rodlike, and fractal assembled structures for the P(DACRO-MAA) were observed with pH change using TEM, zeta sizer, and dynamic light scattering (DLS). The unique self-assembled structures of HMPCB synthesized via RAFT provide an opportunity to understand fundamental polymer science and can be engineered for broad applications.

I. INTRODUCTION

Studying the self-assembly of amphiphilic block copolymers is important for both scientific reasons and for applications since the assembled nanostructures provide novel insight into controlling molecular arrangements and understanding fundamental polymer science.[1] Self-assembly of amphiphilic polymers in solution and on the surface has inspired extensive applications ranging from nanomedicine[2] to oil−water separation,[3−6] nanolithography, nanoelectronics, and novel sensors.[7] Fractal or dendritic-assembled morphologies on the surface are an integral part of its application in industrial processes.[8,9] These self-assembled amphiphilic polymers respond to solution conditions, such as pH and temperature, by changing shape and volume as well as developing unique surface characteristics, which are manipulated to develop drug/gene delivery systems and smart response materials.[10,11] Recently, a pH/thermal, dual responsive polyampholyte system was reported.[12] The self-assembly of structures (spherical micelles and fractal aggregate structures) were obtained through self-assembling processes triggered by external stimuli in aqueous solutions.[13,14]

A study of the self-assembly of polybetaines, which carry positive and anionic functional groups on the same repeating unit contrary to polyampholytes, attracts less attention due to the difficulty of synthesis and the presence of active functional groups.[15,16] Polybetaines are considered a synthetic partner of naturally existing biomolecules such as protein and DNA[17−19] and are sensitive to environmental stimuli.[11,20−27] Beyond simple polybetaines, recent research efforts have focused on modifications of polybetaines or amphiphilic polybetaines to

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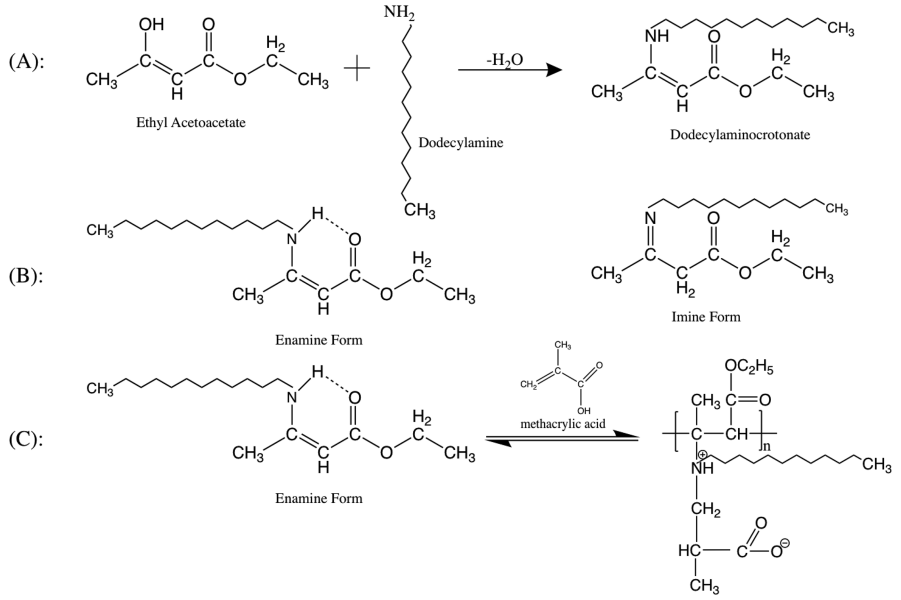

Figure 1. Scheme for the synthesis of (P(DACRO-MAA). (A) Chemical reaction for dodecylaminocrotonate (DACRO) synthesis. (B) Two different tautomers of dodecyl aminocrotonate. (C) Polymerization between dodecylaminocrotonate and methacrylic acid and chemical structure of (P(DACRO-MAA).

achieve better control and versatility.[28−33] Li et al. reported an approach to construct nanocages of hydrophobically modified polybetaine (HMPB), which show promise for applications in pH-responsive drug delivery to tumor tissue.[34−36] The control over nanocage assembly for drug encapsulation and release requires a narrow molecular weight distribution of HMPB. This is possible by using living radical polymerization, a synthesis approach which results in a low PDI and allows for control on molecular weight. Terayama et al. fabricated a sulfonate polybetaine nanobrush with a molecular weight of 10000 g/mol and PDI < 1.2 via atom transfer radical polymerization (ATRP).[37] Unfortunately, this synthesis approach can cause metal contaminants.[38] RAFT polymerization was applied by Skrabania et al. to synthesize carboxybetaine triblock copolymer with a molecular weight of 10000−30000 g/mol and PDI of 1.19−1.34.[39] However, no literature has reported the synthesis of hydrophobically modified polycarboxybetaines (HMPCB) via RAFT.

The aim of this work is to synthesize poly(dodecyl grafted aminocrotonate -methacrylic acid) (P(DACRO-MAA)) with low PDI and controlled molecular weight via the RAFT polymerization approach. This will allow us to study their self-assembly behaviors since previously used methods resulting in random radical polymerization of HMPB provide high PDIs which make the systematic investigation of their self-assembly behaviors difficult.[40] There is speculation that two different monomer structures are present in this polymerization.

More specifically, in the random radical polymerization of the HMPCB reported by our research team,[40] some important questions were not clearly understood yet. One controversy was that the vinyl groups on methacrylic acid may be polymerized with tridecylaminocrotonate as well to form copolymers (or polyampholytes). The tridecylaminocrotonate was also further polymerized without confirming the existence of two different tridecylamincrotonate tautomers. Also, the presence of the two tautomers has not been experimentally confirmed yet. If these two tautomers are present, the polymerization should occur between methacrylic acid and the enamine form of the tautomers since enamine form possesses a carbon−carbon double bond. Therefore, in this work, RAFT polymerization was applied to synthesize P(DACRO-MAA) and explore its self-assembly behaviors by changing pH. It is important to confirm the presence of the two tautomers, which has not been experimentally confirmed so far, and separate the polymerizable monomer for RAFT polymerization to get pure HMPCB.

II. EXPERIMENTAL METHOD

Dodecylamine (99.5%), methacrylic acid (99%), 2,2′-azobies(2-methyl-propionitrile) (98%), 2-cyano-2-propyl dodecyl trithiocarbonate (97%), and fluorescence indicator (manganese-doped zinc silicate green 254 nm) were purchased from Sigma-Aldrich Co.; ethyl acetoacetate (reagent grade) and dichloromethane (HPLC grade) were purchased from Fisher Scientific Co.; a 60 μm TLC silica plate was purchased from Agela Tech Co.; silica gel (40−63 μm) was purchased from the Silicycle Co. Methacrylic acid was purified through distillation to get rid of the inhibitor and stored at 4 °C.

Synthesis of Dodecyl Aminocrotonate. A bulk reaction method was applied to synthesize dodecyl aminocrotonate (Figure 1 A). Dodecylamine was stirred at 60 °C before 1.1:1 molar ratio of ethyl acetoacetate being added into dodecylamine (C-12) dropwise. The required reaction time was 4 h, followed by 24 h of standing at room temperature. The aqueous phase was removed from the mixture via centrifugation. The residue (Figure 1B) was dried in a vacuum oven at 30 °C and 25 in. Hg for 24 h. After dehydration, compositions of the mixture were identified by TLC (a TLC plate with 60 μm silica beads and dichloromethane as solvent). After TLC, all identified components were further separated and collected by flash column chromatography using dichloromethane or a 1% methanol−dichloromethane solution; the latter was used for eluting high polar components. To set up the flash column chromatography, a 4′ × 15″ quartz column was filled up with a mixture of 40−63 μm silica gel with fluorescence indicator at a volume ratio of 1000:1. Then the top of the filled column was loaded with a small amount of products and silica gel at a volume ratio of 1:2. The collected products were further dried by rotary evaporator and dehydrated in the vacuum oven at 30 °C and 25 in. Hg. Dodecylaminocrotonates separated from the reaction mixtures were confirmed by nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR).

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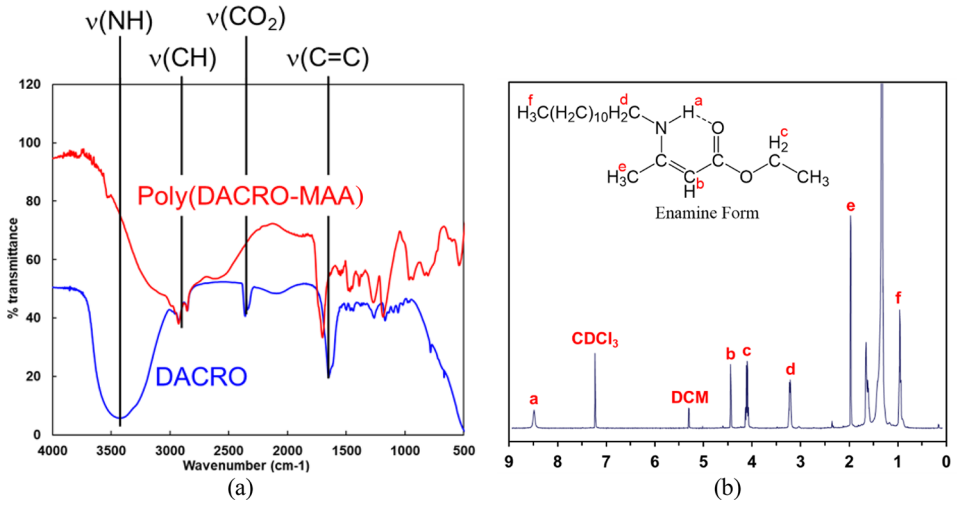

Figure 2. (a) FTIR analysis of DACRO and P(DACRO-MAA). (b) ^{1}H NMR spectra of the first collection from flash column chromatography DACRO.

Synthesis of Poly(dodecyl grafted aminocrotonate-methacrylic acid) (P(DACRO-MAA)). Before the polymerization reaction (Figure 1 C), the obtained dodecylaminocrotonate and methacrylic acid were melted separately at 70 and 25 °C, respectively. A mixture of 2-cyano-2-propyl dodecyl trithiocarbonate (chain transfer agent (CTA)) and 2,2-azobies(2-methyl-propionitrile) (initiator, (AIBN)) was dissolved in 1 mL of benzene. The above prepared solutions were further purged with nitrogen for 10 min. To initiate polymerization, first, methacrylic acid was added into alkylaminocrotonate at a molar ratio of 1.1:1, followed by 1 min of purging. Later, a 1:5 mass ratio mixture of AIBN and CTA was added into the reaction system followed by 30 s of purging. The reaction system was sealed at 70 °C to react for 3 days. The polymer product was finally washed with acetone and dehydrated in the vacuum oven at 30 °C and 25 in. Hg.

H^{1}-NMR was performed on dodecylaminocrotonate (0.5% in deuterated chloroform) with a JEOL ECS 400 MHz NMR spectrometer. ^{13}C-NMR was performed on both dodecylaminocrotonate (2.5% in deuterated chloroform) and P(DACRO-MAA) (2.5% in deuterated dimethyl sulfoxide) with a Varian Unity Inova 500 MHz spectrometer. Peaks of deuterated solvents were used for calibrating chemical shifts. FTIR was used to characterize both the alkylaminocrotonate and polymer products with a VERTEX 70 Fourier transform infrared spectrometer. For solid samples, ground potassium bromide was mixed with ground sample at a mass ratio of 30:1. For liquid samples, one drop of sample was added onto a potassium bromide pellet. All samples and potassium bromide were dehydrated in a vacuum oven at room temperature for 1 day. Nitrogen was purged during the FTIR test to remove any signal noise occurring from air.

GPC was used to measure the molecular weight of poly(dodecyl grafted aminocrotonate-methacrylic acid). The Agilent PLgel Mixed-D column was equipped with a TREOS Wyatt DLS/UV combination detector and a rEX Wyatt refractive index detector. Polymer sample (1%) was prepared in dimethylformamide (DMF) for 12 h. The GPC system was eluted by DMF at a flow rate of 0.5 mL/min and calibrated with polystyrene. Poly(ethylene oxide)s were used as standards.

ζ potentials of the polymer sample at different pH conditions were tested by a Brookhaven NanoBrook Omni Zeta Sizer. Dilute potassium hydroxide and hydrogen chloride solutions were separately prepared in 0.01 M potassium chloride aqueous solution and were filtered with a 0.2 μm syringe filter. The polymer sample (0.015%) was dissolved in a potassium hydroxide solution at pH 12 under ultrasonication. The hydrogen chloride solution was then titrated into the polymer solution to reach selected pH values. In addition, DLS was performed simultaneously to find the size of self-assembled polymers.

A TEM (Hitachi H-8100 scanning transmission electron microscope) equipped with a high resolution camera and an EBD analytical detector was utilized to check micelle structures of self-assembled P(DACRO-MAA). The polymer sample (0.3%) was prepared in a sodium hydroxide solution at different pHs. One drop of the sample solution was dehydrated on a TEM grid at room temperature for 1 h. The sample was tested under a 75 kV beam to avoid drifting or deformation.

III. RESULTS AND DISCUSSIONS

In our previous work,[40] a random radical polymerization approach was developed to synthesize tridecyl grafted poycarboxybetaine with high PDI and low yield without a copolymer or polyampholyte. Even now, there is still speculation over the presence of two tautomers of alkyl aminocrotonate (Figure 1B). Because of this, a systematic investigation into the self-assembly of tridecyl grafted polybetaines was difficult due to high polydispersity. RAFT polymerization was first applied to synthesize P(DACRO-MAA) with a low PDI and to investigate its self-assembly behaviors. To obtain the P(DACRO-MAA), a thin layer chromatography approach was applied to separate the polymerizable monomer (enamine form) from the mixture of the tautomers. In the TLC test, dodecylaminocrotonate mixture, dodecylamine, ethyl acetoacetate, and their pairwise mixtures were dotted on the silica plate. As a result, three distinguishable components appeared under 254 nm UV light exposure or in potassium permanganate solution. Thus, three components were subsequently collected via flash column chromatography. The first collection was verified to be dodecylaminocrotonate by FTIR and ^{1}H NMR as shown in Figure 2. Characteristic peaks corresponding to vinyl and secondary amine groups were present. The second and third collections were also analyzed to find a mixture of dodecylaminocrotonate with unreacted ethyl acetoacetate or dodecylamine. Note that in Figure 2b, the intensity of signal a is relatively low, which is likely due to deuterium exchange with deuterated chloroform. Also in the first collection, the enamine form of dodecylaminocrotonate is more prominent than the imine form due to intramolecular hydrogen bond formation.[28,29] The final yield was 55.67%, which was to a certain degree due to evaporation of volatile ethyl acetoacetate. Also, flash column chromatography purification may cause a

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loss of product or decrease yield but increase purity, which is better for RAFT polymerization and characterization.

The purified dodecyl aminocrotonate, a viscous liquid at room temperature, was polymerized via RAFT method with methacrylic acid. The addition of methacrylic acid into dodecyl aminocrotonate allowed the formation of P(DACRO-MAA) via the Michael reaction.[19,29]

In the synthesis of P(DACRO-MAA), the mass ratio of CTA to initiator was kept at 5:1; the molar ratio was 2.38:1. As the concentration of the initiator (0.1%) was low, no polymerization occurred as shown in Table 1; but as the concentration of the initiator was increased to 1% with reaction time of 72 h, RAFT polymerization occurred. The highest yield for this polymerization was found to be 25%. The resulting P(DACRO-MAA) was separated through the addition of acetone. The purified P(DACRO-MAA) is a yellow powder. To obtain a 25% yield within 3 days, 1.0% initiator was required. The addition−fragmentation rate of CTA on active chains is so fast that the overall rate is too slow. Although the obtained yield was relatively low in contrast to random radical polymerization, CTA agent can be successfully applied to produce HMPCB via RAFT approach. P(DACRO-MAA) synthesized via RAFT polymerization was characterized by FTIR and ^{13}C-NMR, as shown in Figure 2a and Figure 3. The comparison of FTIR results of dodecyl aminocrotonate and P(DACRO-MAA) reveals the disappearance of the N−H bond due to the Michael addition of methacrylic acid on the secondary amine group in Figure 2a. Peaks that show elimination of the C=C bond are covered by peaks that correspond to the C=O bond. Because of this, NMR is needed to confirm the successful addition of methacrylic acid onto dodecylaminocrotonate or a polymerization. Instead of H NMR, ^{13}C-NMR shows a backbone or side chain structures directly based on C−C bonds, as shown in Figure 3. In Figure 3b, the intensity of signals of P(DACRO-MAA) is weak because P(DACRO-MAA) was hardly dissolved in deuterated dimethyl sulfoxide. A comparison of parts a and b of Figure 3 shows a shift of the carboxylic group, indicating a change of environment caused by the disappearance of the C=C bond and the addition of methacrylic acid. Signal b shifts from 162 to 54 because the conjugated carbons in C=C bonds are less shielding than unconjugated carbons in C−C backbones. Signals corresponding to CTA and AIBN also prove the occurrence of polymerization. In Figure 3b, signals b, d, and d' reveal three carbons that are in equivalent environments, indicating the addition of methacrylic acid and the presence of tertiary amine. Therefore, by using a combination of ^{13}C-NMR and FTIR, we were able to confirm the polymerization of alkylaminocrotonate and the Michael reaction.

To verify the Michael addition reaction between methacrylic acid and dodecylaminocrotonate, we intentionally added methacrylic acid into aminocrotonate in the absence of initiator and allowed them to react at 105 °C. As shown in Supporting Figure 1, it was found that poly(dodecyl grafted aminocrotonate-methacrylic acid) was produced. Chemical shifts of characteristic peaks are 3.371, primary alkyl groups connected with tertiary amine; 2.2, primary alkyl group connected with carboxyl group (CH_2COOH); 1.818, secondary alkyl group connected with carboxyl group; and others less than 1.223, other secondary or higher order alkyl groups from ^{1}H NMR spectrum. This result further confirmed the Michael addition reaction carried out before polymerization, which was consistent with results from random radical polymerization of tridecylaminocrotonate and methacrylic acid.[35] Free radical polymerization without methacrylic acid was performed, and this proved that no precipitation shows up in acetone and no corresponding peaks are found in FTIR or NMR results. After confirming the chemical structure of P(DACRO-MAA), GPC was applied to measure the molecular weight and PDI. The number-average molecular weight (M_n) and the weight-average molecular weight (M_w) are 70590 g/mol and 87080 g/mol, respectively, with PDI = 1.214 (Supporting Figure 2). The RAFT polymerization synthesis method and the isolation of the enamine form of

Table 1. Synthesis Protocol of Poly(dodecyl grafted aminocrotonate-methacrylic acid) P(DACRO-MAA)

mass ratio of reactant to benzene	molar ratio of monomer to MAA	mass ratio of initiator to (MMA +monomer) (%)	mass ratio of CTA to initiator	temp. (°C)	reaction time (hr)	yield (%)
1:1	1:1	0.1	5:1	70	24	0
1:0.1	1:1	0.1	5:1	70	24	0
1:0.1	1:1.1	0.1	5:1	70	24	0
1:0.1	1:1.1	0.1	5:1	70	72	~1
1:0.1	1:1.1	1	5:1	70	72	~25

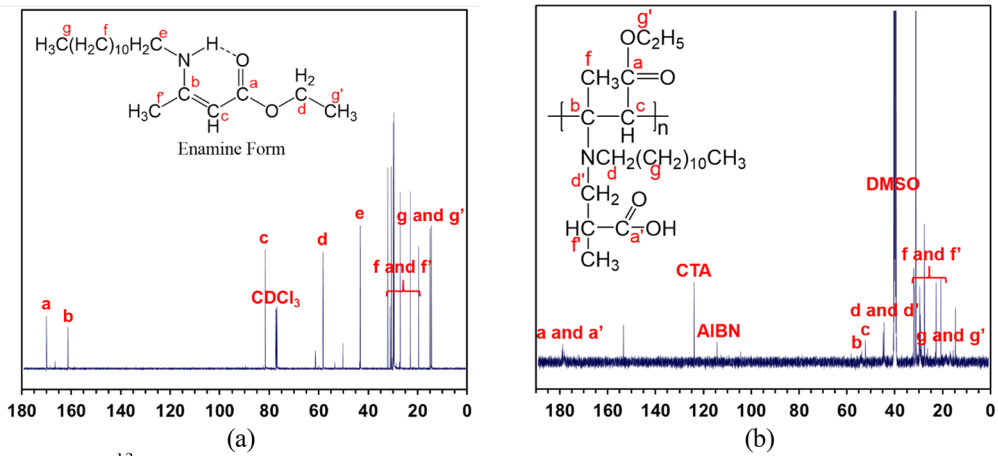

Figure 3. (a) ^{13}C-NMR spectra of the enamine form of dodecylaminocrotonate and (b) poly(dodecyl grafted aminocrotonate -methacrylic acid).

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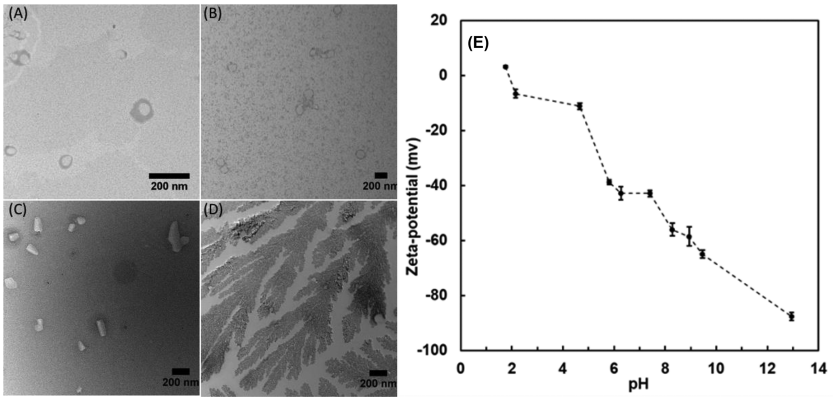

Figure 4. TEM images of the P(DACRO-MAA) formed in the aqueous dispersions at different pH values. Slight contrast change was made in TEM images (A) pH 1.0, (B) pH 3.0, (C) pH 10.0, and (D) pH 12.0. The solution concentration is 10 mg/mL. (E) ζ potential change of P(DACRO-MAA) vs pH.

dodecylaminocrotonate from the tautomers both contributed to the formation of a low polydispersity of molecular weight.

The polymer synthesized via RAFT was further analyzed by ζ potential to find the surface charge evolution in solution. The isoelectric point of the P(DACRO-MAA) was found at pH 1–2, shown in Figure 4 E. Although the DLS measurements for the system using a zeta sizer only yielded a small amount of quantitatively consistent results, some trends were noticed as the pH was changed, as tabulated in Table 2. Some results are not shown for certain pH levels because of lack of reproducibility and technical limits. The largest size, 145 nm, occurred at pH 13. This change is consistent with ζ potential data since the micelle structure swells the most at basic pH and has a large electrostatic repulsion force. Therefore, the micelle structures of P(DACRO-MAA) were analyzed using TEM at pH = 1, 3, 10, 12 based on ζ potential results. For the TEM sample, drops of 10 mg/mL aqueous solution of the P(DACRO-MAA), each with different pH values, were cast onto copper grids coated with carbon film and allowed to dry overnight at room temperature. As shown in Figure 4A,B, spherical micelles were found with average diameters of 60 nm at pH 1 and 150 nm at pH 3. At pH 10, rodlike micelle structures were formed with an average size of 170 nm (Figure 4C). At pH 12, a perfect fractal morphology similar to a

Table 2. DLS Data from ζ Sizer for Polymer at a Certain pH

pH	5.81	8.28	8.94	9.46	12.94
size (nm)	96.8	87.8	85.3	89.6	144.8

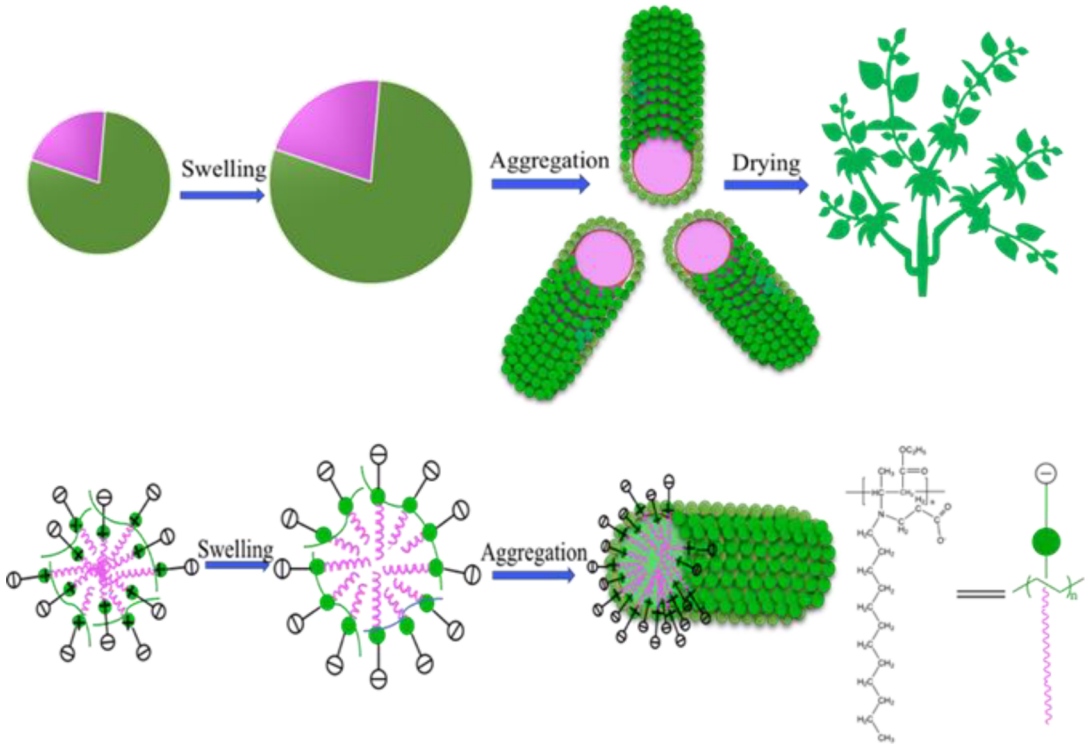

Figure 5. Scheme to illustrate micelle formation. Top: assembly structure transformation from spherical, rodlike, to fractal branch tree structures. Bottom: arrangement of amphiphilic polycaboxybetaines in the assembled structures and a single amphiphilic structure.

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treelike pattern was observed (Figure 4D). The micellar structure's transition from a spherical to a rodlike pattern and finally to fractal morphology was also found for poly(2-(dimethylamino)ethyl methacrylate)-*b*-poly(acrylic acid) (PDMAEMA-*b*-PAA).[41,42]

As illustrated in Figure 5, at pH 1 which is close to the isoelectric point (IEP), the P(DACRO-MAA) molecules interact with each other to form small spherical aggregate structures due to strong inter and intra electrostatic and hydrophobic interactions, a common phenomenon for polybetaines.[11] The polycarboxybetaines were negatively ionized as pH increased, and the spherical micelles swelled to form large spherical micelles due to the strong repulsive electrostatic force. This mechanism was further confirmed by a ζ potential study which indicated that the negative ζ potential became more negative with pH, as shown in Figure 4e. Due to the competition between electrostatic forces among hydrophilic ionized groups and the hydrophobic interaction among dodecyl alkyl chains, as pH approached 10, a hydrophobic interaction lead to the formation of rodlike micelle structures which are commonly found in amphiphilic polymer aggregations. To investigate these micellar structure transformations, dynamic light scattering (DLS) was applied to observe the aggregate structures in aqueous media. Although the size changes in micelles differed from our TEM observations, the trend showed an increase of micelle size with pH. Here, interestingly, we point out that the formations of fractal/dendritic aggregates at a high pH of ~12 were more commonly assembled structures when the polymer contained carboxyl acid groups and the solution had a high concentration of NaOH and NaCI.[41,42]According to the above references, the addition of NaOH causes the ionization of the carboxylic acid groups in the poly methacrylic acid blocks to form sodium-ionized chains and later form cluster structures. The drying process induces cluster deposition on the template of the crystalline NaOH to develop finer brushes.[41] In terms of the detailed study of PDMAEMA-*b*-PAA[41] and PS-*b*-PAA,[42] small electrolytes such as NaOH and NaCI induce fractal aggregation growth since their deposited crystals function as nucleation sites for polyampholyte chains. This mechanistic study strongly supports and explains the fractal/dendritic structure formation of dodecyl grafted polycarboxybetaines at high pH.

IV. CONCLUSIONS

Hydrophobically modified polycarboxybetaine-containing dodecyl groups as hydrophobic side chains were successfully synthesized by RAFT polymerization. The enamine form of the monomer tautomers was successfully separated for the first time and further polymerized to produce poly(dodecyl-grafted amincocrotonate-methacrylic acid) with a MW of 70590 g/mol and a PDI of 1.214. Through ζ potential measurement, the isoelectric point for this amphiphilic polycarboxybetaine was found to be at pH values of 1–2. Self-assembly of the amphiphilic polycarboxybetaines with variable pH resulted in the spherical, rodlike, and fractal aggregate structures. RAFT polymerization of hydrophobically modified polycarboxybetaine offers a new approach to the synthesis of other kinds of polycarboxybetaines with controllable molecular weights and unique assembly structures, allowing for endless potential applications from nanomedicine to nanoelectronics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.8b03561.

^{1}H NMR spectra for the product from reaction between methacrylic acid and aminocrotonate in the absence of initiator, GPC traces of P(DACRO-MAA) PDF)

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Notes

The authors declare no competing financial interest.

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