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Synthesis of multifunctional poly(carbamoyl ester)s containing dual-cleavable linkages and an AIE luminogen *via* Passerini-type multicomponent polymerization†

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We conducted Passerini-type multicomponent polymerizations (P-MCPs) with various monomers and afforded a series of functional poly(carbamoyl ester)s (PCEs). We demonstrated an efficient, diverse, and facile approach through P-MCPs to produce these novel PCEs with dual-cleavable linkages of ester and disulfide groups and the aggregation-induced emission (AIE) luminogen tetraphenylethylene (TPE).

The introduction of new condensation reactions that are so-called "multicomponent reactions (MCRs)", such as Biginelli,[1] Hantzsh,[2] Kabachnik–Fields,[3] Mannish,[4] Passerini,[5] and Ugi[6] reactions, into polymer chemistry has recently been explored to achieve multicomponent polymerizations (MCPs). Among MCPs, Passerini-type MCPs (P-MCPs) have the advantages of being straightforward, high efficiency, mild conditions, and a variety of commercially available monomers. The P-MCR is a three-component reaction of a carboxylic acid (A), an aldehyde (B), and an isocyanide (C) and affords an α-acyloxy carboxamide structure.[7] Interestingly, P-MCPs can be achieved by reacting two difunctional monomers with one mono-functional monomer, such as $A_2 \cap B_2 \cap C$, $A_2 \cap B \cap C_2$, and $A \cap B_2 \cap C_2$ approaches, and have provided diverse designs of novel polymers.[8–11] In 2011, Meier *et al.* excitingly demonstrated the first examples of P-MCPs with diacids, dialdehydes, and isocyanides (*i.e.*, $A_2 \cap B_2 \cap C$) and afforded a series of novel poly(carbamoyl ester)s (PCEs).[12] They further successfully achieved specific macromolecules.[13,14] In the case of the $A_2 \cap B \cap C_2$, the Meier group[15] and Li group[16–19] demonstrated this strategy to afford functional poly(ester-amide)s (PEAs). In the case of the $A \cap B_2 \cap C_2$, the Li group[20] synthesized poly(carbonyl amide)s (PCAs) with various functional side groups. Accordingly, the introduction of functionality to these analogs of polymers prepared *via* P-MCPs remains fascinating and could interestingly expand the fundamental tools and practical applications of polymer science.[21–24]

There have only been limited studies to introduce multifunctionality to these new types of PCEs, PEAs, and PCAs.[25,26] Using the $A_2 \cap B_2 \cap C$ approach, we focus on synthesizing multifunctional PCEs with hydrophilic side groups (*i.e.*, carbamoyl moieties) and hydrophobic backbones (*i.e.*, aliphatic esters). Special functional groups of disulfide bonds and aggregation-induced emission (AIE) moieties (herein, tetraphenylethene (TPE)) are further introduced which correspondingly contribute to redox-triggered cleavage[27] and aggregation-triggered strong emissive[28] properties. As shown in Scheme 1, we conducted P-MCPs with various dialdehydes (A1–A3)/mono-aldehyde (A4),

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Scheme 1 Synthesis of P1–P6 functional PCEs *via* P-MCP of (di)aldehyde A, dicarboxylic acid B, and isocyanide C compounds (TPE: tetraphenylethylene; CA: cyclohexyl amide).

dicarboxylic acids (B1–B2), and mono-isocyanide (C) to afford functional PCEs (P1–P6). We further introduced the fluorescent luminogen TPE into the polymer chains. Applications of the novel PCEs in drug-delivery systems and imaging were investigated.

As depicted in Scheme 1, P-MCPs with various monomer combinations were conducted to afford P1–P6 PCEs. The synthesis and characterization of A3 and A4 monomers are depicted in Scheme S1 and Fig. S1–S5 (see the ESI†). Fig. 1 shows the corresponding kinetic plots of conversion of monomer C *vs.* reaction time in two solvents, dichloromethane (DCM) and methanol (MeOH) (A/B/C = 1/1/2 at 30 °C; $[A]_0$ = 0.5 M). All P-MCPs can attain high conversions (*i.e.*, 80–95%) in about 24–30 h, indicating the high reactivity of P-MCPs. In comparisons of the different solvents, it is obvious that the P-MCPs in DCM (*i.e.*, circles) exhibited faster reaction rates than those in MeOH (*i.e.*, squares). As depicted in Scheme S2 (see the ESI†), the Passerini reaction involves a concerted mechanism in an aprotic solvent whereas it involves an ionic mechanism in a protic solvent.[7,29,30] In the presence of MeOH (*i.e.*, Scheme S2a, ESI†), one issue would come from the strong intermolecular hydrogen bonding between the hydroxyl and carboxylic acid groups. The stable intermediate (*i.e.*, i1) would lead to suppression of the next nucleophilic addition reaction with the aldehyde and isocyanide. Another issue arises from the strong intermolecular hydrogen bonding between the amidated intermediate (*i.e.*, i2) and MeOH. This would hinder the rearrangement reaction for producing ester–amide linkages. In the presence of DCM (*i.e.*, Scheme S2b, ESI†), there is no strong intermolecular interaction between the intermediates and the aprotic solvent during the reaction. The condensation reaction can be accomplished through a cyclization (*i.e.*, forming intermediate i3) and a rearrangement reaction. We estimated the corresponding kinetic results based on the third-order reaction assumption (shown in Fig. S6, see the ESI†). P-MCPs in DCM all displayed higher reaction rates compared to those cases in MeOH. In comparisons of different monomer combinations, the chemical structures of the monomers did not significantly influence the polymerization reactivity. Characterization of P1–P6 is shown in Fig. S7 and S8 (see the ESI†). The P-MCP conditions and characterization of the resulting PCEs are summarized in Table 1.
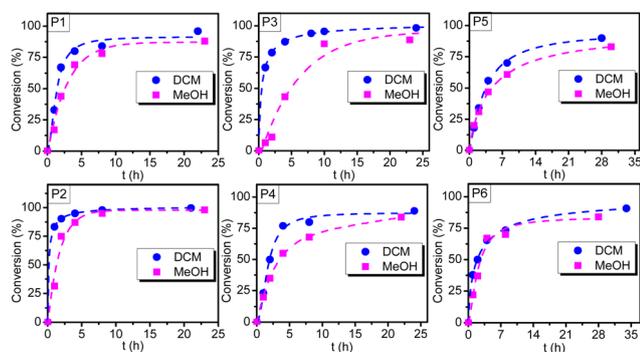
Table 1 Reaction conditions of the P-MCPs and characterization of the resulting PCEs

Comb.[a]	Solvent	t (h)	M_W[b]	PDI[b]	Yield (%)	PCEs[c]
A1B1C	DCM	24	5160	1.43	56	P1
	MeOH	24	3550	1.60	50	
A1B2C	DCM	24	7470	2.09	59	P2
	MeOH	24	5700	1.35	54	
A2B1C	DCM	24	8740	1.61	58	P3
	MeOH	24	5675	1.99	51	
A2B2C	DCM	24	7280	1.64	83	P4
	MeOH	24	5670	1.77	79	
A3B2C	DCM	30	13 490	1.78	74	P5
	MeOH	30	5590	1.34	50	
(A1/A4)B2C	DCM	30	7270	1.98	65	P6
	MeOH	30	5600	1.35	46	

[a] A/B/C = 1/1/2. For P6: (A1/A4)/B/C = (0.9/0.1)/1/2. [b] Characterization of M_W is depicted in the ESI. [c] P2, P4, P5, and P6 have disulfide linkages. P5 and P6 further contain the TPE luminogen.

We thus obtained functional PCEs having disulfide linkages for P2, P4, P5, and P6 and further having the tetraphenylethene (TPE) luminogen, a typical aggregation-induced emission (AIE) structure, on the backbone for P5 and at the chain-end for P6. We examined the aqueous self-assembly behavior of P1–P6 *via* the characterization of the critical micelle concentration (CMC) and showed in Fig. 2A and Fig. S9 (see the ESI†). The CMC values were in a range of around 0.02–0.08 mg mL^{-1}, revealing the amphiphilic nature of the structure. As shown in Fig. 2B, the micelle sizes were approximated to 100 nm with a moderate dispersity measured by DLS. The micelle morphology is further characterized using an SEM. All PCE-based micelles formed globular shaped nano-objects as revealed in Fig. 2C and the nanoparticle sizes and distribution are estimated in Fig. S10 (see the ESI†). Although the PDIs varied from 1.35 to 2.09, the values displayed an insignificant effect on the particle diameters. This is plausibly ascribed to the diluted polymer solutions which led to a minor entropy contribution from the PDI differences to the solution-state self-assembly.

Disulfide bonds were present in P2, P4, P5, and P6 PCEs. With dithiothreitol treatment (10 mM DTT$_{(aq)}$, 0.5 h), we can confirm the cleavage behavior of P1–P6 PMs by using SEM. As shown in Fig. 3A, the P1 and P3 PMs with stable backbones displayed their original globular morphology after the treatment. In the other PM cases, disappearance of the globular morphology and cluttered structures were observed after the treatment, indicating their reduction-triggered cleavage

Fig. 1 Conversion traces of P-MCPs in DCM and MeOH for the preparation of P1–P6.
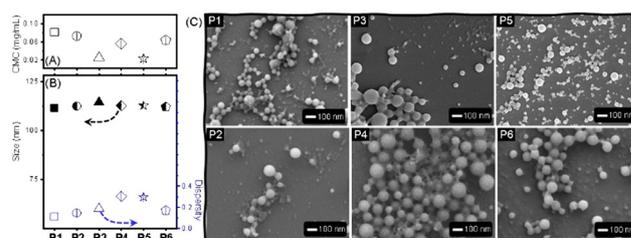
Fig. 2 (A) CMC values, (B) particle size and dispersity, and (C) SEM images of P1–P6.
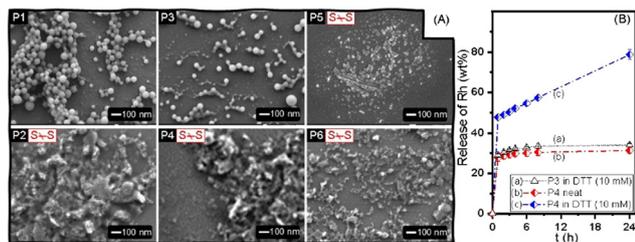
Fig. 3 (A) SEM images of P1–P6 PMs treated with DTT (10 mM$_{(aq)}$, 0.5 h) and (B) release of the model compound Rh.

Fig. 4 Variations of the FL intensity of (A) P2, P5, and P6 in various vol% water and (B) DTT treatment of P5 (10 mM$_{(aq)}$, 0.5 h).

properties. The aggregation might be ascribed to the dismantling of the P2, P4, P5, and P6 PMs through the disulfide bonds and the combination of the fragments into loose and large area disordered morphologies. The behavior was also traced by GPC (Fig. S11, see the ESI†), indicating the corresponding stationary traces in P1 and P3 and decomposition traces in P2, P4, P5, and P6. As shown in Fig. S12 (see the ESI†), when monitored by DLS, the particles showed stable diameters in P1 and P3 PMs and significant aggregation results in P2, P4, P5, and P6. The morphology changes could be effected by many factors, such as concentration, solvents, poly-dispersity, *etc.* By comparing these results, the disulfide linkage-containing PMs treated with small amounts of DTT$_{(aq)}$ can be degraded which leads to the deformation of the original globular nanostructures. Before the next stage of applications, a drug delivery examination with rhodamine B (Rh) was conducted. The appearances of the encapsulated materials are shown in Fig. S14A (see the ESI†). As shown in Fig. 3B, curves a (*i.e.*, P3 PM with DTT treatment) and b (*i.e.*, neat P4 PM) exhibit a low ability in Rh release. In contrast, curve c (*i.e.*, P4 PM treated with DTT$_{(aq)}$) displays a burst of drug accumulation within the initial 1 h and shows a gradual drug accumulation up to around 80%, resulting from the reduction-triggered cleavage and subsequently induced drug release. Besides, all the PMs are composed of ester linkages. As shown in Fig. S13 (see the ESI†), we observed gradual increases in particle sizes and significant decreases in particle numbers (*i.e.*, Kcps), indicating the acid-cleavable polyester behavior. The hydrophobic drug curcumin (Cur) was preliminarily tested and its nano-encapsulation behavior is shown in Fig. S14B (see the ESI†). These results show that the amphiphilic P1–P6 PMs, comprising ester and additional disulfide linkages, possess dual-cleavable features in aqueous environments through hydrolysis and reduction reactions.

We next investigated the photophysical properties of P5 and P6 measured using a UV-vis spectrometer at a concentration of 0.05 mg mL^{-1} in different solvents. Fig. S15 (see the ESI†) displays the UV-vis spectra of P5 and P6 in different solvents, namely THF, DMF, NMP, and DMSO. Both polymers exhibited significant increases in absorption intensity (*A*) with increasing solvent polarity but showed nearly the same characteristic peaks at around 291 and 330 nm. The trends in absorption intensity and polarity index are accordingly illustrated in Fig. S16 (see the ESI†). TPE is a well-known aggregation-induced emission (AIE) luminogen.[31] In comparison, P5 exhibited higher absorption
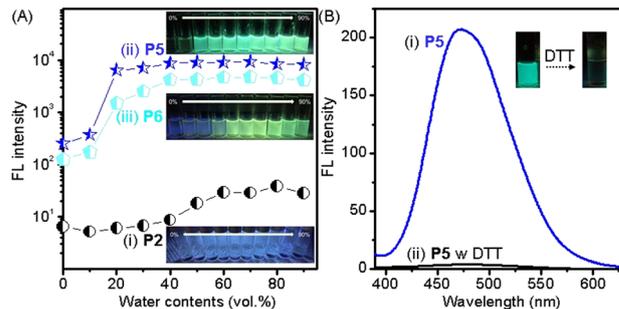
increases (*i.e.*, $\Delta A_{(P5)}/\Delta A_{(P6)}$ = *ca.* 3.2) which were ascribed to the higher number of TPE units in the P5 backbone. We then measured the fluorescence (FL) properties of P2, P5, and P6 in various volume percentage mixtures of DMSO and H$_2$O with a concentration of 0.04 mg mL^{-1} (*i.e.*, PCE/co-solvent) under an excitation wavelength of 330 nm. FL spectra of the three PCEs in various vol% water are shown in Fig. S17 (see the ESI†) which shows the changes in FL intensity (*I*) with increasing water content. The characteristic emission peaks nearly remained at 380 and 490 nm, and the results are summarized in Fig. 4A. All PCEs displayed obvious increases at 488 nm in each case of P2, P5, and P6. We further compared the intensity difference ($\Delta I = I_{max} - I_{sol}$) of the characteristic emission peaks, where I_{max} and I_{sol} are the maximum FL intensity of the PCE aggregates and the FL intensity of the PCEs in the reference solution, respectively. In the P2 case (*i.e.*, Fig. 4A(i)), insignificant apparent luminescence changes (*i.e.*, the inset photo) and a low value of $\Delta I_{(P2)}$ (= *ca.* 30) were obtained. The weak increase in emission might arise from the electron-rich moiety (*i.e.*, phenyl ring) and atoms (*i.e.*, N, O, and S) in the P2 chemical structure and is recognized as a clustering-triggered emission (CTE) behavior.[32] In the P5 case (*i.e.*, Fig. 4A(ii)), significant apparent luminescence increases (*i.e.*, the inset photo) and a large value of $\Delta I_{(P5)}$ (= *ca.* 9200) were attained. In the P6 case (*i.e.*, Fig. 4A(iii)), significant apparent luminescence increases (*i.e.*, the inset photo) and a high value of $\Delta I_{(P6)}$ (= *ca.* 4700) were also acquired. These results illustrated that the TPE-containing P5 and P6 PCEs exhibited significant AIE behavior whether the TPE is linked within the polymer backbones or bonded at the polymer chain ends. The emission intensity difference (ΔI) and normalized intensity difference per unit voltage (*i.e.*, $\Delta I/V$) are summarized in Table S1 (see the ESI†). Furthermore, we examined the influence of the redox reaction on the AIE properties by treating P5 with DTT$_{(aq)}$ (10 mM for 0.5 h). As shown in Fig. 4B, we observed a manifest decrease in FL emission intensity and disappearance of apparent luminescence (*i.e.*, the inset photo) after the treatment. We can anticipate that the extinguishment of AIE behavior was ascribed to the disassembly of the PCE micelles through the cleavage of the disulfide linkages which is consistent with the above-mentioned SEM and GPC results. As revealed from DLS and SEM results, the PDIs showed insignificant effects on the particle diameter and distribution of the solution-state self-assembly properties. Thus, we believe that the PDI difference should also have an insignificant influence

on the AIE behavior. By applying the same conditions to P6, however, we observed an insignificant decrease in FL emission intensity (shown in Fig. S18A (see the ESI†)). We proposed plausible cleavage structures of the TPE-terminated site (shown in Fig. S18B, ESI†). It is rational that the TPE-CASH byproduct could possess a hydrophobic part (*i.e.*, the TPE moiety) and hydrophilic parts (*i.e.*, cyclohexyl amide and thiol groups). This amphiphilic structure can perform self-assembly and retain the AIE behavior.

In summary, through P-MCPs of various monomer combinations, we successfully synthesized a series of poly(carbamoyl ester)s (PCEs: M_w = *ca.* 3500–8700 with PDIs = *ca.* 1.35–2.1). Meanwhile, functional structures of esters, disulfides, and TPE moieties can be facilely introduced. Measuring by SEM and DLS, we detected uniform polymeric micelles (PMs) approximated to 100 nm and attained low CMC values of the obtained PCEs, illustrating their amphiphilic properties. The influences of redox reactions on the PMs were then studied in the presence of DTT, revealing the cleavage properties of P2, P4, P5, and P6 PMs through the disulfide linkages. Besides, hydrolysis of PCEs in acidic aqueous environments was attained. We further demonstrated that such amphiphilic PCEs can be utilized as nano-carriers for more hydrophilic Rh and hydrophobic Cur compounds. By dissolving the PCEs in different ratios of DMSO and H_2O, we found CTE properties for a PCE without the TPE moiety (*i.e.*, P2) but significant AIE behavior for the PCEs with the TPE moiety (*i.e.*, P5 and P6). In the case of PCEs comprising disulfide and TPE moieties (*e.g.*, P5), interestingly, the AIE behavior was "switched off" after DTT treatment which arose from the decomposition of the PCE micelles. We eventually demonstrated the effectiveness of the robust P-MCPs to design functional poly(carbamoyl ester)s.

Conflicts of interest

There are no conflicts to declare.

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